RQA GCP-PV Committee Comments on GL_4

Risk Proportionate Approach in Clinical Trials

Comment no.	General Comment (if any)	Outcome (if any)
1	There are existing regulatory post marketing requirements regarding collection of adverse event data. How can the new guideline's guidance to only report certain adverse events be reconciled with this? The GVP modules VI and VIII require clarification of what is to be reported in the protocol and overt reasons as to why you are not going to collect all data. It is considered that there may be confusion over what should be collected and this may therefore constitute an increased risk of organisations not reporting anything. Additionally, how will the limited reporting be monitored? Consistency of reporting will be required.	
2	Is the risk assessment and mitigation plan separate to the protocol? What approval and control processes would be expected for this document? Is it approved as part of the protocol? Will the EEA QPPV be required to review and approve this? There is no reference in the guidance to the EEA QPPV, who should be included in the discussions relating to trial design for a product that has a license in the EEA or where a MAA has been submitted.	
3	There are no references to Risk Management Plans or Adverse Events of Special Interest. We would recommend these are considered when developing the protocol and how/what data is to be collected. It will lead to issues if they are not aligned. There must be communication by clinical teams with the safety team.	
4	As specified in the next section, it would be helpful to align the general structure of how risk management is described with the equivalent text in the proposed addendum to ICH GCP (R2) Section 5.	
Line Number(s)	Comment and rationale; proposed changes If changes to the wording are suggested, they are highlighted	
132 – 134	Do these examples present any opportunities for reduced documentation burden in relation to the issues discussed in 4.5 Trial Documentation, e.g. where they do not relate to the main objectives of the trial?	
168 – 242	It would be logical and helpful to align the structure of these sections with the final text of the proposed addendum to ICH GCP (R2), as the content is largely consistent albeit organised slightly differently.	
194 – 199	This text seems to relate to aspects of risk control, which is covered in the subsequent section.	
205 – 225	More emphasis could be given to linking the outcome of risk evaluation and any aspects to which risk adaptations (i.e. "less stringent rules") could be applied, which was one of the themes in the Regulation. As it is, the text mixes the concepts of risk adaptations to drive more effective quality management and adaptations that are acceptable because of the agreed (low)	

	risk status of a trial ("less stringent rules"). The two considerations could be more clearly distinguished.	
211 – 216	There are aspects of risk evaluation overlapping with this text under risk control.	
273	What constitutes "a known safety profile"? How is a safety profile considered known? Signals are still coming out from products that have been on the market for years. It may perhaps be better to quantify e.g. no significant changes to the safety profile in the last x years?	
421 – 428	This section repeats most but not all of the points made in 382 – 385. Suggest to rationalise the information between these two places for clarity.	
447 – 448	This might not be the best example as it does not seem to come from a risk assessment, i.e. if this could be acceptable, it would apply in any risk scenario.	
449	This is not clear as an example.	
452 - 453	This is not a risk adaptation in itself, rather a consequence of a different risk-based decision regarding the type of monitoring. If there were no on-site monitoring and this was justified then there would be no expectation of on-site monitoring visit reports. In contrast, the subsequent examples about documentation for IMP and laboratory aspects do give more insight as to what could be acceptable in making some reductions in documentation burden. More examples would be welcome. Documentation of IMP destruction could also be among the list of items not necessarily required for certain IMPs in a low intervention/risk category.	