

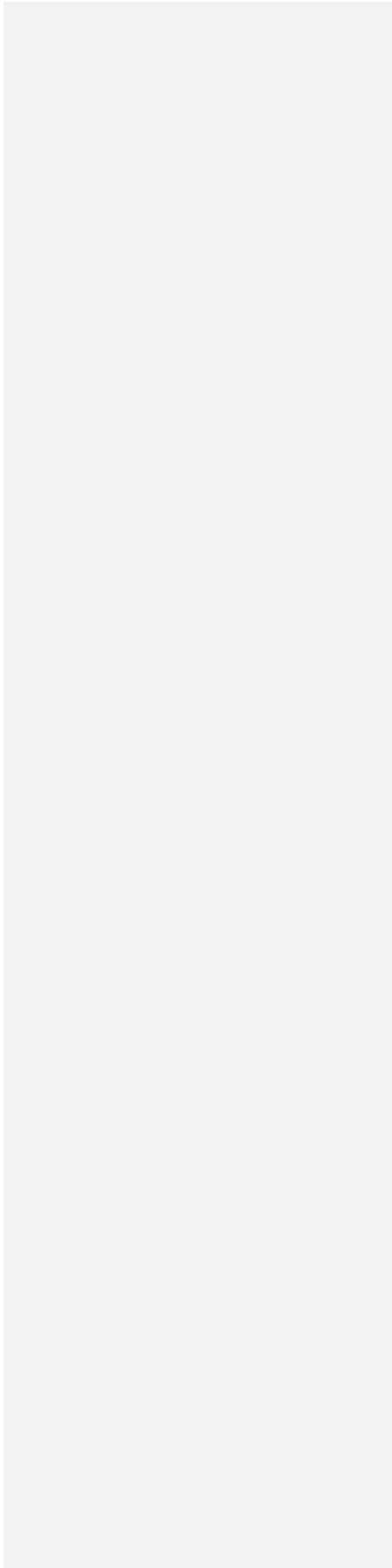
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Consultation document

**Risk proportionate approaches in clinical trials**

**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**

*This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area*



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45

46 **1. Introduction**

47 The legislation for clinical trials has seen significant changes during the last decade, starting with  
48 the implementation, in 2004, of the Clinical Trials Directive 2001/20/EC ('Directive'), continuing  
49 with the publication of the Good Clinical Practice Directive 2005/28/EC<sup>i</sup> in 2005 and more  
50 recently with the Clinical Trials Regulation (EU) No. 536/2014 ('Regulation')<sup>ii</sup>.

51 Despite the relative flexibility of the legislation and guidelines (for e.g. ICH Guideline E6 for  
52 Good Clinical Practice<sup>iii</sup>), it has been observed that in general a 'one size fits all' approach to the  
53 design and conduct of clinical trials has been followed to comply with the ethical and scientific  
54 standards of Good Clinical Practice (GCP). Many clinical trials, however, pose only a minimal  
55 additional risk to subject safety compared to normal clinical practice. A proportionate approach to  
56 the design and conduct of clinical trials is therefore supported by the Regulation. This approach  
57 should be adapted to the risk to the subject of the research carried out.

58 Different, proportionate approaches can be taken with regard to the rules to which a clinical trial  
59 is designed, conducted, evaluated and reported, depending on a number of factors that may affect  
60 the risk posed to a subject, such as the status and nature of the investigational medicinal product  
61 (IMP), the indication, the trial population in which it is to be used, the level of difference of the  
62 trial-related intervention from normal clinical practice, the complexity of the protocol, and the  
63 specific operational aspects of the planned clinical trial or the clinical development project.

64

65 **2. Scope**

66 The goal of the Regulation is to foster innovation whilst ensuring the protection of the  
67 participants in clinical trials and the quality and integrity of the trial outcomes.

68 The Regulation provides the basis for developing a guideline on risk proportionate approaches in  
69 clinical trials. The present recommendations build on the reflection paper prepared in 2013 by the  
70 European Medicines Agency (EMA), in collaboration with the Clinical Trial Facilitation Group  
71 (CTFG) and the GCP Inspectors Working Group, on risk based quality management in clinical  
72 trials, and on the ICH E6 GCP R2 addendum.<sup>iv</sup>

73 This document, based on the requirements of the Regulation, provides further information on  
74 how such a risk proportionate approach can be implemented and also highlights the areas  
75 identified in the Regulation which support and facilitate such adaptations. This guideline applies  
76 to all sponsors, commercial as well as academic and all types of clinical trials, from early  
77 development of unauthorised products to clinical research conducted in the post-authorisation  
78 phase. Thus it is addressed both to those clinical trials that are intended to be included in the  
79 application for a marketing authorisation for the medicinal product under investigation, clinical  
80 trials with novel IMPs and to trials using only IMPs with a marketing authorisation, within or  
81 outside the terms of their marketing authorisation.

82 In this document, more explanations and examples of the areas for potential adaptation are  
83 provided, when sponsors follow a risk proportionate approach in the design and conduct of  
84 clinical trials.

85 The Regulation however, contains detailed information on (reduced) requirements for the  
86 following aspects of a clinical trial, which are not repeated in this document:

87

**Comment** [REDACTED] The document relates exclusively to clinical trials on medicinal products, it remains a general document which states that the details explained in the directive are not included in this document

This text lacks legal and regulatory framework and does not deal with the common tools to implement for the application of this Directive. While some examples of tools are available, they are however not suitable for clinical research. A different interpretation by country or site is possible. There is no clear description and formulation of the criteria for classifying a study in the "low intervention", except the use of experimental drug according its marketing authorization or not; that is not sufficient as a criterion. This classification is left to the discretion of the sponsor

Risk proportionate approaches in clinical trials

Area	Sections of the Regulation
<p><b>Content of the application</b></p> <ul style="list-style-type: none"> <li>Investigator’s Brochure (IB)</li> <li>IMP dossier (IMPD) and simplified IMPD (Summary of Product Characteristics (SmPC))</li> <li>Insurance</li> </ul>	<p>Annex I, Section E. INVESTIGATOR’S BROCHURE (IB) (28), (29)</p> <p>Annex I, Section G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD), 1.2. Simplified IMPD by referring to other documentation</p> <p>Article 76(3), Annex I, Section O. PROOF OF INSURANCE COVER OR INDEMNIFICATION (INFORMATION PER MEMBER STATE CONCERNED)</p>
<p><b>Labelling of the IMP</b></p>	<p>Annex VI. LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCTS AND AUXILIARY MEDICINAL PRODUCTS</p>
<p><b>Informed consent</b></p>	<p>Article 30</p>

88

89 The risk to subject safety in a clinical trial mainly stems from two sources: the IMP and the trial  
90 procedures.

91 The Regulation provides for less stringent rules or adaptations with regards to monitoring,  
92 traceability of the IMP and content of the TMF, to those clinical trials which pose only a minimal  
93 additional risk to subject safety (as defined in Article 2(3) of the Regulation) compared to normal  
94 clinical practice.

95 Some risk adaptations apply in particular to low intervention clinical trials, however, depending  
96 on the circumstances, risk adaptations may be applied to any type of clinical trial. In practice all  
97 clinical trials determine procedures which are in various respects risk adapted and therefore these  
98 considerations are relevant in all cases.

99 The determination of whether a clinical trial is low intervention or not, is largely based on the  
100 marketing authorisation status of the IMP and its intended use in the trial. The IMP risk category  
101 has implications for other trial related risks, however it does not determine all of them. For  
102 example, if a clinical trial is considered low intervention from an IMP perspective, it does not  
103 mean that all other risks associated with this trial are low as well. Other risks could be related to  
104 the trial design, the clinical procedures specified in the protocol, the patient population, the  
105 informed consent process etc. These risks should be also assessed and mitigated where  
106 appropriate (see section 4.1.)

107 Equally if a trial is not low intervention, this does not mean that risk proportionate procedures  
108 cannot or should not be applied.

109 **3. Low intervention clinical trials**

110 Some clinical trials pose only a minimal additional risk to subject safety compared to normal  
111 clinical practice and within this scenario these trials can be risk adapted.

**Comment** This is to be highlighted and developed more, as the objective – and then the design and the implemented methods – is an important consideration

### Risk proportionate approaches in clinical trials

112 Such clinical trials, defined in Article 2(3) of the Regulation as low intervention clinical trials, are  
113 those trials which fulfil all of the following conditions:

114 (a) the investigational medicinal products, excluding placebos, are authorised;

115 (b) according to the protocol of the clinical trial,

116 (i) the investigational medicinal products are used in accordance with the terms of the  
117 marketing authorisation; or

118 (ii) the use of the investigational medicinal products is evidence-based and supported by  
119 published scientific evidence on the safety and efficacy of those investigational medicinal  
120 products in any of the Member States concerned; and

121 (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional  
122 risk or burden to the safety of the subjects compared to normal clinical practice in any Member  
123 State concerned.

124 The published scientific evidence supporting the safety and efficacy of an IMP which is not used  
125 in accordance with the terms of the marketing authorisation could include evidence based  
126 treatment guidelines and health technology assessment reports, and clinical trial data published  
127 in scientific peer-reviewed journals or other appropriate evidence.

128 In terms of the level of additional risk or burden to the safety of the subjects posed by additional  
129 diagnostic or monitoring procedures as compared to normal clinical practice in the Member State  
130 concerned, the following are some examples of what may be accepted as minimal additional  
131 burden, thus rendering the clinical trial a low intervention one:

132 • weighing, height measuring, questionnaires, analysis of saliva, urine, stool samples, EEG  
133 and ECG measurements, blood withdrawal through a pre-existent catheter or with  
134 minimal additional venipuncture.

135 The limit for an acceptable burden could be exceeded when these interventions are conducted in a  
136 significantly more frequent manner or on a considerably larger scale than in normal clinical  
137 practice. However, it should be noted that additional risk or burden might include non-invasive  
138 procedures as well as invasive procedures, as described above, if these are performed with a  
139 significantly higher frequency or significantly greater intrusiveness, or a larger number of  
140 assessments are undertaken compared to normal clinical practice, during a higher number of  
141 visits to the clinic/hospital.

142 The Regulation specifies that sponsors should indicate in the cover letter of the clinical trial  
143 application if they consider a clinical trial to be a low intervention clinical trial and also, a  
144 detailed justification thereof should be included.

145 The Regulation explains the term 'low intervention clinical trial' also in the light of the  
146 provisions of the Recommendation of the Organisation for Economic Cooperation and  
147 Development (OECD), which introduces different risk categories for clinical trials. Low  
148 intervention clinical trials, as defined in the Regulation correspond to the OECD categories A and  
149 B(1)<sup>V</sup>.

150 The OECD framework introduces a risk-based oversight and management methodology for  
151 clinical trials, combining a stratified approach that is based on the marketing authorisation status  
152 of the medical product being investigated, with a trial-specific approach that considers other  
153 issues such as the type of populations concerned by the trial, or the informed consent of the  
154 patients.

**Comment** For instance, do additional CT-Scans increase the risks even if each CT-Scan does not increase the risks in standard practice ?

**Comment** Guidance should be developed on this aspects, as some procedures like questionnaires, samples are subject to different interpretation from CA / Ethics Committees

## Risk proportionate approaches in clinical trials

155 In order to ensure subject safety, low-intervention clinical trials are subject to the same  
156 assessment process as any other clinical trial, however with adapted dossier requirements.

157

### 158 4. Risk proportionate approaches in clinical trials

#### 159 4.1. Risk based quality management

160 Risks in clinical trials should be considered at the system level (e.g. facilities, standard operating  
161 procedures, computerised systems, personnel, vendors), as well as at the trial level (e.g. IMP, trial  
162 design, data collection and recording).

163 Apart from the risks associated with the IMP, there are also risks that can arise from the protocol  
164 and study procedures i.e. the intervention. Such risks can have an impact on the clinical trial  
165 subjects (e.g. risks associated with the clinical procedures specified by the protocol, failure to  
166 obtain fully informed consent, or failure to protect personal data), on data integrity, on the  
167 reliability of the results or their scientific use or validity.

168 A risk based quality management system for clinical trials should include the following steps:

- 169 • risk identification
- 170 • risk evaluation
- 171 • risk control
- 172 • risk review
- 173 • risk communication
- 174 • risk reporting

#### 175 Risk identification and evaluation

176 Risk identification and evaluation should be conducted, as this is key to managing and mitigating  
177 risks.

178 The risk evaluation process covers the assessment of: the likelihood of potential hazards  
179 associated with the trial, the impact, if they would occur, of these hazards on subjects' safety and  
180 data integrity and the extent to which such hazards would be detectable<sup>VI</sup>.

181 For each risk identified, an appropriate mitigation strategy (for e.g. monitoring) should be  
182 implemented or a determination made that the risk can be accepted.

183 Risks should be considered in proportion to its potential impact and the likelihood of its  
184 occurrence. The risk identification and risk evaluation should take into account the whole  
185 spectrum of risk determinants for defining trial management and operations, including, but not  
186 limited to: informed consent, insurance coverage, safety reporting, monitoring, trial master file  
187 content, data management, computer systems, traceability of investigational medicinal products,  
188 clinical sample management and analysis, data processing, analysis (statistics) and reporting<sup>VI</sup>.

189 The risk evaluation should commence prior to the finalisation of the protocol as the risk  
190 assessment and mitigation may influence the trial design and procedures, as well as the financing  
191 or funding of the clinical trial or development project.

192 Following a risk identification and evaluation in each trial, a risk proportionate approach can be  
193 applied. The risk assessment and mitigation should be described and implemented. The

**Comment** It could be useful to separately identify the risks for the patients and the risks for the studies

**Comment** this paragraph covers only the identification step and not the evaluation step. The evaluation is realized only after identifying the risks from the spectrum of risk determinants

**Comment** Examples or reference to papers could help: « for example through preidentified risk area (= "Quality Critical factor" according to CTII guide: "Quality by Design and Quality Risk Management in Clinical Trials" or through preidentified checklist (Transcelerate tool "Risk assessment and Categorization tool")

**Comment** Following items could also be listed:  
-personnel (expertise, training),  
-management providers  
-type of study participants,  
-study governance and organization  
-planning

## Risk proportionate approaches in clinical trials

194 documentation should include the rationale and the responsible functions for any specific actions  
195 required (e.g monitor, investigator etc).

196 For example, as part of the risk identification and risk assessment of the safety reporting process  
197 described in the protocol, the sponsor should ensure adequate and tailored training for the  
198 investigators and trial staff for those specific adverse events anticipated to occur in the trial  
199 subjects due to the nature of the IMP or the disease

200 Careful consideration should also be given to the adequacy of the measures to protect the privacy  
201 of trial subjects and confidentiality of their personal data, taking into account applicable  
202 European laws on data protection and the Declaration of Helsinki.

203 Examples on performing risk assessments are available on the websites of some national  
204 authorities, academic and non-commercial organisations' initiatives<sup>vii, viii</sup>.

### 205 Risk control

206 The purpose of risk control is to reduce the risk to an acceptable level or determine that the risk  
207 can be accepted. The main components of risk control are risk mitigation, adaptations and risk  
208 acceptance actions.

209 The resource allocated for risk control should be proportionate to the significance of the risk and  
210 the importance of the process or outcome exposed to the identified risk.

211 The risk assessment and risk mitigation would typically involve multiple functions able to  
212 consider all the various aspects of the trial, and may include various personnel such as data  
213 managers, statisticians, trial managers, monitors and/or auditors and personnel who would have  
214 more direct involvement with patients such as clinical experts and investigators with an  
215 understanding of the therapeutic area and use of the proposed IMP, as well as pharmacists and  
216 research nurses.

217 Examples of mitigations could involve implementation of risk mitigation steps in procedural  
218 documents or manuals (e.g. SOPs, pharmacy manuals, (e)CRF manual, (e)TMF manual), plans  
219 (monitoring plan, data management plan, statistical analysis plan), training material, parameters  
220 used for site and vendor selection and planning of performance metrics, contractual quality  
221 agreements.

222 Table 1 below highlights the specific areas where the Regulation sets out possibilities to apply  
223 risk adaptations ("less stringent rules") in the design and conduct of clinical trials.

### 224 **Table 1 Areas where risk adaptations can be applied**

Risk Adaptations	Areas impacted	Section of the CT Regulation
1. Safety reporting	Safety profile of IMP Data integrity of safety information	Article 41(2) Annex III(2.5, 21)
2. IMP Management	Traceability and accountability	Article 51(1)
3. Trial management	Monitoring	Article 48
4. Trial documentation	Content of the Trial Master File (TMF)	Article 57

225

**Comment** The example could be developed a little bit more: the identified risk can be for example "the lack of declaration of SEA by the investigator"  
The risk evaluation including cause analysis, the cause is "the lack of training for the investigator for those specific adverse event"  
And the risk mitigation is "improve the training slide about this SAE"  
The comprehension of this paragraph can be better if you describe an example using the steps of the risk management

**Comment** Add tool example :  
-Transcelerate tool "Risk assessment and Categorization tool"  
- CTTI guide: "Quality by Design and Quality Risk Management in Clinical Trials"

**Comment** Add "and should take into account existing control, the definition of new actions plans and the preparation and implementation of this actions plans"

**Comment** Add department responsible of risk management for example the QA people

## Risk proportionate approaches in clinical trials

### 226 Risk review

227 An on-going reassessment of the risks should be performed, by review of new information  
228 emerging during the conduct of the trial (e.g. new pre-clinical data, new safety data, updated  
229 Investigator Brochure, protocol amendments) and the outputs of trial management activities (e.g.  
230 monitoring output, data management, DSMB meeting output, audit reports). The risk review also  
231 assesses the impact of the new information on the risk assessment and mitigations. These should  
232 be reviewed on an ongoing basis and updated, if necessary. The implementation, effectiveness  
233 and need for mitigations should be periodically reviewed.

**Comment** [REDACTED] The risk review also includes the effectiveness evaluation of action plans

### 234 Risk communication

235 There should be a process to ensure that the risk assessment and mitigation plan and any  
236 subsequent updates, as well as changes that may impact on trial conduct e.g. protocol  
237 amendments, serious breaches, safety reporting, protocol deviations etc. are shared with the  
238 relevant personnel.

**Comment** [REDACTED] Risk communication include also the development of procedure and tool on the risk management to the operational personnel

### 239 Risk reporting

240 In accordance with the ICH guidelines E3- Structure and Content of Clinical Study Reports and  
241 E6- Good Clinical Practice, the sponsor should describe the implemented risk adaptations in the  
242 clinical study report.

**Comment** [REDACTED] It should be taken into account the risk of excessive communication of risks !

243

**Comment** [REDACTED] Refer to the use of a excel table tool summarizing each step of risk management (for example FMECA (Failure Modes, Effects and Criticality Analysis))

## 244 4.2. Safety reporting

245 The Regulation includes provisions for applying a risk proportionate approach for safety  
246 reporting. Any such adaptation should be clearly stated and justified in the protocol, which will  
247 be submitted to the Member States for clinical trial authorisation.

248 Risk adaptations to safety reporting according to the Regulation refer to recording of adverse  
249 events in the CRF (and hence reported to the sponsor) and to the requirements of immediate  
250 reporting from the investigator to the sponsor.

251 As a general rule, any adverse event considered by the investigator as being potentially related to  
252 the IMP, and therefore representing an adverse reaction, should be reported to the sponsor, unless  
253 justified in the protocol and supported by the risk assessment outcome.

254

255 Article 41 of the Regulation refers to two possible risk adaptations to safety reporting:

256

257 • selective recording and reporting of adverse events,

258 and

259 • adaptations to expedited reporting from the investigator to the sponsor, for certain serious  
260 adverse events.

261

262 Risk adaptations to adverse event recording, collection and reporting should be detailed in the risk  
263 assessment and mitigation plan that is produced in conjunction with the protocol development  
264 and prior to the start of the trial.

265 Detailed collection and reporting of adverse events (serious and non-serious) is particularly  
266 important where data about the safety profile of an IMP from available pre-clinical and clinical  
267 trials is scarce. As the knowledge of a medicine and its use evolve and increasing amounts of data  
268 become available in order to determine the benefits and risks of an IMP, the level of detail and  
269 reporting requirements for adverse events may be adapted in the protocol, in line with the scope



## Risk proportionate approaches in clinical trials

270 and type of a clinical trial and the level of knowledge on the safety profile of the IMP tested and  
271 the disease profile of the trial subjects. This means in practice that the protocol may select only  
272 certain (and not all) adverse events to be recorded and reported to the sponsor. This applies in  
273 particular, but not only, to marketed products, with a known safety profile, which are tested  
274 within the framework of low-intervention clinical trials. In this regard, the following situations  
275 apply:

- 276  
277 • IMPs are used according to the conditions of the marketing authorisation:  
278 In this case, a reduced or targeted safety data collection may be appropriate if supported  
279 by data from post-marketing use and if the number of subjects exposed during clinical  
280 development was sufficient to adequately characterize the medicinal product's safety  
281 profile (even in terms of rare adverse drug reactions), and if the occurrence of expected  
282 adverse drug reactions was similar across multiple trials in terms of seriousness and  
283 severity.
- 284  
285 • IMPs are marketed, but used differently to the conditions of the marketing authorisation:  
286 In such cases, any adaptation to safety reporting should be based on a trial-specific risk  
287 assessment. The risk assessment should consider whether the clinical trial under  
288 evaluation includes a new population (e.g. in terms of age, gender or other patient  
289 characteristics), or using a new combination therapy or a different concomitant  
290 medication), a new indication, a different dose or dosage regime or a different route of  
291 administration, compared to the conditions of use in the SmPC that may lead to more  
292 severe or more frequent adverse drug reactions, new adverse drug reactions or new drug-  
293 drug interactions.

294  
295  
296 In both scenarios described above, expected IMP and anticipated disease or population related  
297 adverse events may be waived from recording in the CRF by the investigator and reporting to the  
298 sponsor. For example, in oncology indications, where the toxic nature of the marketed medicinal  
299 products causes many well-known adverse events, such as nausea, vomiting, headache, or in  
300 COPD patients experiencing disease-related adverse events like breathlessness etc., there might  
301 be no added value to record these adverse events and report them to the sponsor. Such a risk  
302 adaptation should be described in the protocol.

303  
304 Article 41 of the Regulation gives the possibility for the investigator not to report certain serious  
305 adverse events to the sponsor, if provided for in the protocol. In cases of blinded clinical trials  
306 carried out in high morbidity or high mortality diseases, in which efficacy or safety endpoints  
307 meet the criteria of serious adverse events, the sponsor may determine in the protocol that these  
308 outcome events are exempted from the rules of expedited reporting. In this case, an independent  
309 Data Safety Monitoring Board (DSMB)<sup>1</sup> should be appointed for the evaluation of the safety data  
310 from the ongoing trial in an unblinded manner and in regular, adequate intervals. If in such cases,  
311 another Committee is also appointed, the sponsor should put procedures in place to ensure that  
312 the assessment by this Committee on whether an event qualifies as a serious adverse event or an  
313 efficacy or safety endpoint and the communication of this outcome to the DSMB is performed  
314 in a timely manner and delays in serious adverse events reporting are minimised. After each DSMB  
315 meeting, the DSMB should advise the sponsor whether to continue, modify or terminate the  
316 trial<sup>ix</sup>. The functional roles and operational procedures of the DSMB, as well as its trial-specific

Comment: What is the justification for unblinding data for the DSMB ?

<sup>1</sup> In line with the provisions of the Regulation, the terms Data Safety Monitoring Board and Data Safety Monitoring Committee are synonymous

## Risk proportionate approaches in clinical trials

317 tasks (i.e. how frequently the DSMB will meet, what data will be assessed under which  
318 viewpoints, description of the decision making process and range of decision) should be  
319 described in summary in the protocol and in more detail in the DSMB charter.

320 The safety reporting rules from the investigator to the sponsor should be described in detail in the  
321 protocol. The risk assessment and mitigation plan may identify adverse events and/or laboratory  
322 abnormalities that are critical to safety evaluations and require expedited reporting from the  
323 investigator to the sponsor. These requirements should be included in the protocol.

324

### 325 4.3. IMP management

#### 326 Traceability and accountability

327 Investigational medicinal products shall be traceable. Drug accountability refers to maintaining  
328 documentation that ensures traceability of investigational medicinal products used in a clinical  
329 trial.

330 As set forth in Article 51, paragraph 2 of the Regulation, information on the provisions for  
331 traceability should be contained in the application dossier.

332 The level of accountability needed may vary depending on several factors, such as the  
333 authorisation status of the investigational medicinal product(s), whether its/their use in the  
334 clinical trial is within the authorised indication, the trial design (e.g. population, blinding,  
335 complexity of the dosing regimen), who is administering the trial product(s) and the toxicity of  
336 the IMP(s) and its/their supply chain. The risk assessment and mitigation plan should include  
337 justifications for the documentation used to reconstruct drug traceability and the doses  
338 administered.

339 If allowed in the concerned Member State, in clinical trials where marketed products are used in  
340 accordance with the terms of the marketing authorisation, IMPs may be sourced from normal  
341 stock of the community or hospital pharmacy. The IMPs could also be provided directly to the  
342 sites by the trial sponsor. For these IMPs, the risk assessment and mitigation plan should define  
343 the level of accountability of the IMP(s) that is required based on the risk assessment and the  
344 requirements in the Member States.

345 For low-intervention clinical trials, where authorised medicinal products in the concerned  
346 Member State are used as IMPs, the sponsor could decide that normal prescribing practice and  
347 documentation would apply and if specific documentation of prescribed amounts and doses taken  
348 in the patient's medical chart or other source documents other than normal practice is required,  
349 e.g. the patient's diary or the case report form (CRF) or the routinely maintained pharmacy  
350 documentation on receipt, storage and handling.

351 In the case of low intervention clinical trials, if a marketed product is re-labelled or repackaged  
352 for blinding purposes or distributed outside of normal supply chains, sufficient traceability and  
353 documentation should be available to allow for a recall of the IMP or its inclusion in a more  
354 general recall of a marketed product, to the extent that recall applies.

355 Where unlicensed medicinal products are used as IMPs and especially in those clinical trials with  
356 high complexity of dosing regimen and used in certain populations, full accountability records of  
357 receipt, use and return/destruction is usually required, unless justified in the risk assessment and  
358 mitigation plan.

**Comment** There is a possibility for the investigator to not report certain SAEs in the appropriate time and give to the DSMB a role in the later interpretation of AE and SAE This can result on information shortcomings in terms of pharmacovigilance, especially for phases IV, and particularly the framework of the safety, in real time, for patients included in the research. There are enough difficulties to have the information relative to the SAE and we do not recommend allowing the non-declarations in time

**Comment** This paragraph let the possibility the investigator not to report certain SAEs on time and let a DSMB role in interpreting posterior AEs and SAEs. This can result information errors in terms of pharmacovigilance, especially for phases IV trial, and especially the security framework, in real time, for patients who are suitable for research. Actually there are enough difficulties for information on serious adverse events to allow authorized non declaration

**Comment** The objective of the trial (which entails the design and the procedures)

**Comment** Including street /retail pharmacy ?

## Risk proportionate approaches in clinical trials

359 In all cases, the risk assessment and mitigation plan should include justifications for the level of  
360 IMP accountability undertaken.

361 Risk adaptations performed on drug accountability should take into account the impact of not  
362 performing drug accountability, on the reliability of that particular clinical trial results and should  
363 be documented in the risk assessment and mitigation plan. The level of accountability should  
364 correspond to what is necessary for the scientific validity of the trial outcome or the safety to the  
365 trial subjects.

366 Other risk factors, like the stability of the active ingredient that impact the management of IMP  
367 should also be considered in the risk assessment and for example, temperature monitoring or  
368 light-protection if applicable, should be adapted depending on the outcome of that risk-  
369 assessment.

370

### 371 4.4. Trial management

#### 372 Monitoring

373 The Regulation makes provision for a risk proportionate approach to be applied to monitoring.  
374 According to Article 48 of the Regulation, the extent and nature of monitoring should be  
375 determined by the sponsor on the basis of an assessment, i.e. the risk assessment, that takes into  
376 consideration all characteristics of the clinical trial, such as whether the trial is a low intervention  
377 trial, the methodology and objective of the clinical trial, and how the intervention deviates from  
378 normal clinical practice and the operational peculiarities of the clinical trial. The outcome of  
379 assessments of sites, staff, facilities, and training needs may also influence monitoring methods  
380 utilised. The resulting monitoring strategy should take the identified study-specific risks into  
381 account and be proportionate in nature and scope.

382 There are several risk proportionate approaches that can be applied to monitoring. The type and  
383 combination of monitoring activities can be adapted and tailored to suit a particular clinical trial.  
384 Examples include on-site monitoring and centralised monitoring. These can be supported by  
385 statistical tools, trial steering committees and data monitoring committees.

386 Centralised monitoring processes provide additional monitoring capabilities that can complement  
387 and justify adaptations to the extent and/or frequency of on-site monitoring or may replace them  
388 for some types of trial. On-site monitoring remains relevant in certain types of clinical trials, as it  
389 is instrumental for the verification of several critical aspects at the trial site, for e.g. the informed  
390 consent process, source data verification and IMP handling on site.

391 In defining the monitoring strategy based on the risk assessment performed, the intensity and  
392 focus of the monitoring may vary. The level of on-site monitoring activities may vary from  
393 frequent and or detailed monitoring to low levels of visit and activity, or targeted visits to certain  
394 sites only or there may be no on-site visits in certain trials.

395 The risk assessment and mitigation plan should contain the identified risks that are mitigated by  
396 monitoring and the type and intensity of monitoring undertaken. A monitoring strategy plan  
397 should be put in place based on the risk assessment and mitigation plan.

398 The trial-specific risks may be such that reduced or no on-site monitoring is justified or that a  
399 particular area is not monitored. Centralised and/or on-site monitoring can be used with the  
400 flexibility to adapt the requirements throughout the life cycle of a trial. The monitoring strategy  
401 may involve central tools to identify the need for targeted monitoring visits based on assessment

Comment: Advantages of centralized monitoring, (as described in section 5.18.3 of ICH E6 R2) could be more detailed

Comment: This is too restrictive

Comment: Adequation of the premises, document filing,

## Risk proportionate approaches in clinical trials

402 (statistical or other) of centrally accrued data and information. The strategy may need to be  
403 reviewed during the trial, for example if the protocol is amended, new risks may be identified that  
404 require adjusted monitoring methods and strategy. In that case the risk assessment and mitigation  
405 as well as the monitoring strategy plan should be updated accordingly.

406 In order to ensure that any monitoring that is carried out is sufficiently focused, escalation  
407 procedures should be built in to follow-up and correct identified non-compliance at an early  
408 stage. Such escalation procedures will have different processes and actions when using  
409 centralised monitoring, in which the data management and/or biostatistician are involved in the  
410 identification of issues, and processes other than onsite monitoring may be used for follow-up.

411 Centralised monitoring enables the review of reported data / information, remote contact,  
412 communication and training where relevant and can be used to set certain actions in motion when  
413 pre-determined tolerance limits for processes or data have been exceeded.

414 Monitoring activities (whether they are on-site or done centrally) need to be sufficiently well  
415 documented to demonstrate that the monitoring plan has been followed and actions have been  
416 taken as a result of the outcome of the monitoring activities. Failure to adhere to the plan can  
417 result in ineffective monitoring and potentially compromised data, and also lead to a situation  
418 where the sponsor is not in control of the trial. As unanticipated risks may emerge in the course  
419 of a trial, resulting in a change to the risk assessment and mitigation plan, the monitoring plan  
420 should be reviewed and modified as necessary.

421 A risk adaptive approach to monitoring should include utilisation of one of or a combination of  
422 approaches listed below:

- 423 • On site monitoring activities;
- 424 • Trial oversight structures such as Data Monitoring Committee, Trial Management Group,  
425 Trial Steering Committee;
- 426 • Monitoring activities that do not require visits to individual sites such as: telephone  
427 contact with the site, web-enabled training;
- 428 • Centralised monitoring of the trial data.

429

### 430 4.5. Trial documentation

#### 431 *Content of the Trial Master File (TMF)*

432 According to preamble 52 of the Regulation, in order to be able to demonstrate compliance with  
433 the clinical trial protocol and with the Regulation, a clinical trial master file, containing relevant  
434 documentation to allow supervision (monitoring and auditing by the sponsor and inspection by  
435 Member States) shall be kept by the sponsor and the investigator. Guidance on the content of the  
436 TMF is provided in the guideline on GCP compliance in relation to the trial master file (paper  
437 and/or electronic) for content, management, archiving, audit, and inspection of clinical trials and  
438 the ICH Guideline for Good Clinical Practice<sup>iii</sup>

439 Article 57 of the Regulation states that the essential documentation in the TMF shall take into  
440 account all characteristics of the clinical trial including in particular whether the clinical trial is a  
441 low-intervention clinical trial.

Comment Use ?

### Risk proportionate approaches in clinical trials

442 Risk proportionate approaches applied to a trial therefore may affect the content of the TMF. The  
443 extent of these changes would be directly related to the type of clinical trial and the outcome of  
444 the trial risk assessment, with more adaptations likely to be possible for low intervention clinical  
445 trials.

446 Examples of how the TMF could be affected include the following:

- 447 • Combining of documents: one document serves multiple purposes (job descriptions,  
448 curriculum vitae);
- 449 • Objectives achieved by other means;
- 450 • Absence of documents, as a result of implementation of other risk \_\_\_proportionate  
451 measures, for example:
  - 452 ○ Specific on-site monitoring reports, as there may not be on-site visits as a  
453 consequence of the implementation of a risk adapted monitoring strategy plan
  - 454 ○ IMP related documentation: investigational medicinal products with a marketing  
455 authorisation and supplied to the patients via a routine medicines supply chain  
456 (i.e. from the pharmacy, based on a medical prescription) may not require any  
457 additional accountability records or only limited recording of consumption of the  
458 IMP e.g. in the CRF or patient diary. Therefore, the following documents may not  
459 be needed to be included in the TMF: instructions for handling, shipping records,  
460 certificates of analysis of IMPs or trial-related materials, drug accountability  
461 documentation (see also Section 4.3), temperature monitoring records (if the IMP  
462 is used as per normal clinical practice and stored in the usual place, for those that  
463 do not have temperature monitoring – e.g. ambient storage in hospital theatre),  
464 sample of labels as these may just be the normal hospital dispensing label;
  - 465 ○ Hospital laboratory accreditation certificates and reference ranges (when these  
466 laboratories are not providing information that is critical to the reliability of the  
467 trial results) or where the data values are used in their own right, where  
468 accreditation certificates are not applicable (or not available) and other measures  
469 such as population statistics in large trials account for divergences;
  - 470

Comment: This should be clarified. Can be a telephone report

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478 5. References

- i. [Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products](#)
- ii. [Regulation \(EU\) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC](#)
- iii. [ICH Guideline E6 - Good Clinical Practice](#)
- iv. [Reflection paper on risk based quality management in clinical trials, EMA/269011/2013, 18 November 2013](#)
- v. [OECD Recommendation on the Governance of Clinical Trials, OECD website, 2013](#)
- vi. ICH Guideline Q9 – Quality Risk Management
- vii. <http://forums.mhra.gov.uk/showthread.php?1678-Examples-of-risk-assessments>
- viii. Brosteanu O., Houben P., Ihrig K., Ohmann C., Paulus U., Pfister B., Schwarz G., Strenge-Hesse A., Zettelmeyer U., Risk analysis and risk adapted on-site monitoring in non-commercial clinical trials, *Clinical Trials* 2009; 6: 585-596
- ix. [Guideline on Data Monitoring Committees, EMEA/CHMP/EWP/5872/03, January 2006](#)
- x. [Transcelerate tool “Risk assessment and Categorization tool”](#)
- xi. [CTTI guide: “Quality byDesign and Quality Risk Management in Clinical Trials”](#)
- xii. [FMECA tool \(Failure Modes, Effects and Criticality Analysis\)](#)

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