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Draft proposal for an addendum, on transparency, to the “Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014”

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Comments should be provided using this [template](#). The completed comments form should be sent to: ctreg@ema.europa.eu



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26 1. Executive summary

27 The new European Clinical Trial Regulation (EU) No 536/2014 aims to foster innovation through
28 simplification of the clinical trial application process, and to increase transparency and availability of
29 information on clinical trials and their results.

30 The key instrument to ensure transparency of clinical trials is the new clinical trial portal and database
31 that will be used for submission and maintenance of clinical trial applications and authorisations within
32 the European Union. The database will serve as the source of public information on clinical trial
33 applications assessed, and clinical trials conducted in the EU, from the time of decision to authorise a
34 trial up to the finalisation of those trials and inclusion of their results in the database. The Regulation
35 gives EMA responsibility for its development and maintenance.

36 The Regulation states that the EU database “shall be publicly available unless one or more exceptions
37 apply”. These are:

- 38 • to protect personal data;
- 39 • to protect commercially confidential information, in particular taking into account the marketing
40 authorisation status of the medicinal product, unless there is an overriding public interest;
- 41 • to protect confidential communication between Member States in preparing their assessment;
- 42 • to protect the supervision of clinical trials by Member States.

43 This consultation document sets out proposals and options on the application of these exceptions in
44 relation to the transparency provisions of the European Clinical Trial Regulation. Once finalised, this
45 addendum will complement the [functional specifications for the EU portal and database to be audited](#),
46 which were drawn up by the Agency and endorsed by its Management Board in December 2014.

47 The aim of this consultation is to seek stakeholders’ views on the application of these exceptions, so
48 that they strike the right balance between respecting patients’ and doctors’ needs and the publics’
49 entitlement to extensive and timely information about clinical trials and developers’ and researchers’
50 need to protect their investments. A balanced approach is needed to protect public health and also
51 foster the innovation capacity of European medical research, thus supporting the EU as a location for
52 innovative, cutting edge research that results in development of novel products and research into new
53 and better uses of existing products.

54 The information that will be made public for all clinical trials registered in the system will include:

- 55 • the main characteristics of the trial comprising design, scientific and, where applicable, therapeutic
56 intent, title, identification of the investigational medicinal products (IMPs), treatment arms,
57 treatment population and number of subjects, inclusion and exclusion criteria and main objectives
58 and endpoints;
- 59 • conclusion of the assessment and decision on the trial;
- 60 • information updated during the trial to indicate the start and end dates of recruitment;
- 61 • substantial modifications to the trial;
- 62 • the end date of the trial and 12 months later the summary of results and a summary in lay
63 language;
- 64 • clinical study reports for medicines for which a marketing authorisation has been granted, the
65 procedure completed or the marketing authorisation application withdrawn.

66 **Commercially confidential information**

67 Sponsors have a legitimate economic interest in the trial they conduct, either because they seek a
68 marketing authorisation for the investigational medicinal product or because they need to obtain
69 research funding for this and future trials. The legislation does not distinguish between different types
70 of sponsor. The consideration of what might be commercially confidential is therefore based on the
71 nature of the trial and the status of the medicinal product being studied.

72 Certain documents which are entered into the database are considered to contain significant
73 confidential information, particularly for trials on medicines without a marketing authorisation. These
74 documents include the clinical trial protocol and the related subject information sheet, the
75 investigational medicinal product dossier, and the investigator brochure. A number of proposals are
76 presented for the timing of when these documents should be made public. The time of publication is
77 linked to key time points of the clinical trials and the status of the marketing authorisation as well as to
78 the development stage of the product (Phase I¹, II², III³ and IV⁴ trials and low-intervention trials).

79 Stakeholders are asked to comment on these proposals and to indicate which, according to their view,
80 best meets the requirements and objectives of the Regulation. Phase I trials are commercially
81 particular sensitive and it is proposed to allow for these trials a deferral of publication of information
82 until 12 months after the end of the trial, when the summary of results is published. Phase IV and low-
83 intervention trials carry fewer concerns in relation to the economic interest of the sponsor and a
84 specific proposal is made with respect to those trials.

85 Additional proposals concern the publication of inspection reports, union control reports, reports of
86 serious breaches, corrective measures and also urgent safety measures.

87 **Protection of personal data**

88 The rules on personal data protection are addressed in relation to trial subjects, investigators, and
89 personnel responsible for the authorisation and supervision of clinical trials in Member States, as well
90 as sponsors and marketing-authorisation holders. The European Clinical Trial Regulation states that no
91 personal data of trial subjects shall be made public nor should such data be included in the database.
92 Consequently the database will not contain any individual patient data listings from clinical trials.

93 **How to use this document**

94 Chapter 2 to 4 describe the purpose, legal background and interpretation of the transparency
95 requirements of the Regulation. They propose how the exceptions to the transparency requirements
96 listed by the European Clinical Trial Regulation should be applied. Stakeholders are invited to comment
97 on the proposed application of the transparency rules.

98 Section 4 is structured through a set of direct questions for stakeholders, which support the present
99 consultation. The actual addendum to be added to the functional specifications is set out in Section 5

¹ Phase I: Phase I is the first stage of a clinical trial. It is to test whether a treatment is safe for people to take, rather than to try to treat a condition, and to study pharmacokinetics and pharmacodynamics (where possible). These trials are very small, (typically around 30 people), and usually involve healthy volunteers or sometimes patients. Ref:

<http://www.mssociety.org.uk>

² Phase II: The second phase in clinical trials aims to investigate the safety and effectiveness of a potential therapy, and to investigate potential dose regimes. Usually between 100 and 300 people will be enlisted to take part with the aim of determining whether the treatment will be safe and effective to treat a condition.

³ Phase III: If previous trials have indicated a treatment is safe and that it also shows promise in being able to treat a condition, Phase III clinical trials begin. These involve large numbers of participants usually from several hundred to several thousand subjects, and are often spread between different hospitals and countries. If these trials show that a drug is safe and effective, the sponsor can apply for a marketing authorisation.

⁴ Phase IV: Post marketing studies to delineate additional information including the drug's risks, benefits, and optimal use. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use. They are carried out in accordance with the terms of the marketing authorisation (indication, route of administration and formulation).

100 including the table in that section. Appendices to this document illustrate how the data and documents
101 in the EU clinical trial database may be made public. These, however, are included for illustration
102 purposes only, since the exact data fields of the database are subject to this consultation and have
103 therefore not yet been finalised. The appendices will not be part of the functional specifications.

104 Stakeholders are invited to send comments using the attached [template](#) to ctreg@ema.europa.eu by
105 end of day on 18th February 2015.

106 **2. Background and introduction**

107 1. Clinical trials are performed in many different contexts. They are conducted to generate data to
108 support applications for marketing authorisation and to expand scientific knowledge on medicines
109 through publications in medical journals. Therefore, clinical trials are an indispensable part of
110 clinical research which, in turn, is essential to develop medicinal products and improve medical
111 treatment. Without clinical trials, there would be no new medicines, no further development of
112 existing medicines, and no evidence-based improvement of treatments with medicines.

113 2. The EU Clinical Trial Regulation (EU) No 536/2014 has a number of objectives and aims amongst
114 others:

- 115 • To protect the rights, safety, dignity and well-being of subjects and the reliability and
116 robustness of the data generated. The interests of the subjects should always take priority
117 over all other interests. To this end clinical trials are subject to prior authorisation.
- 118 • Foster innovation and simplify the clinical trial application process, in particular for multistate
119 trials.
- 120 • To provide publicly available information from the EU database, increasing transparency of
121 clinical trials and their results - this should contribute to protecting public health and fostering
122 the innovation capacity of European medical research, while recognising the legitimate
123 economic interests of sponsors.

124 3. The Regulation foresees transparency on the conduct of trials in the European Union⁵ from the
125 point of their authorisation to the publication of the results of those clinical trials. Published
126 information should be updated, where applicable, if it changes during the trial. The application of
127 the proposed transparency rules should ensure that all of the following requirements are met.
128 Public access to clinical trial information is provided to:

- 129 • Ensure that a public record exists of all clinical trials conducted in the EU and their outcome,
130 thus, providing the EU contribution to the global objective of ensuring that all clinical trials in
131 human subjects are publicly registered. The Regulation requires that all clinical trials used in
132 support of a clinical trial application are publicly registered in a providing data to the WHO
133 ICTRP (WHO International Clinical Trials Registry Platform).
- 134 • Support public confidence in the clinical trial process and in the EU medicines regulatory
135 system. This confidence is important to ensure that EU citizens are willing to participate or
136 support participation in clinical trials as an essential part of medical progress. Public
137 information on clinical trials also reinforces public trust in clinical trial outcomes and the
138 decisions taken by regulators based on those outcomes.
- 139 • Provide patients, trial subjects, their legally designated representative, and healthcare
140 professionals:

⁵ References in this document to the EU should also be read as references to the EEA (European Economic Area).

- 141 – with access to information on clinical trials, as of their beginning, to facilitate their
142 participation in suitable trials where possible,
- 143 – who have participated in clinical trials with a summary of the results of those trials once
144 they have been completed,
- 145 – with a summary of the results of all completed EU clinical trials, for their reference,
146 regardless of the marketing authorisation status of the medicinal products involved.
- 147 • Provide the public, in particular patients and their carers as well as healthcare professionals
148 and academia, with information on clinical trials conducted in the EU that relate to medicines
149 available on the market and on the data used to support decisions on marketing
150 authorisation, or use in practice.
- 151 • Act as a knowledge management resource to foster innovation and stimulate and accelerate
152 further research by building on accumulated knowledge and technical ability. This aims to
153 avoid unnecessary duplication of clinical trials, and repetition of trials that have been
154 terminated due to major safety or efficacy failures, or have demonstrated such failures even
155 if the trial was completed.
- 156 • The information made available to the public under the Regulation should be freely viewable,
157 searchable and downloadable from the portal without entering into any further agreement, or
158 intervening restrictions being required.
- 159 • Innovation and development also need investment in research. To ensure that such
160 investment is attracted to the EU and is sustained investors and researchers have to be able
161 to benefit from their engagement. It is therefore important to recognise the legitimate
162 economic interests of sponsors.
- 163 • The transparency aimed for needs to balance the public interests set out above with the need
164 to stimulate and attract investment in innovation thus contributing to the growth and
165 development of commercial and academic research centres, medical facilities and expertise.
- 166 4. This document sets out proposals for the application of the transparency rules of the Regulation in
167 order to achieve a correct balance that respects both, the patients' and public's entitlement to
168 extensive and timely information on clinical trials, and developers' and researchers' need to benefit
169 from investments thus enhancing the EU as a destination for innovative, cutting edge research and
170 development of novel products and research into new and better uses of existing products.

171 **3. Legal basis**

172 ***3.1. The transparency requirements of the Clinical Trial Regulation***

173 The Regulation sets out requirements for increased transparency of EU clinical trials. These
174 requirements apply specifically to information contained in the EU database but not to information held
175 outside of the EU database. The Regulation specifies what information should be held in the EU
176 database.

177 Any data and documents submitted via the EU Clinical Trial Portal (hereinafter "the portal") defined in
178 Article 80 of Regulation (EU) No 536/2014 (hereinafter "the Regulation") are held in the EU Clinical
179 Trial Database (hereinafter "the database"). Only data and information defined in the Regulation as
180 being submitted via the portal and/or stored in the database shall be held in that database and subject
181 to the transparency rules set out in the Regulation. Article 81(4) of the Regulation states that the EU

182 database shall be publicly accessible unless, for all or part of the data and information contained
183 therein, confidentiality is justified on any of the following grounds:

- 184 a) protecting personal data in accordance with Regulation (EC) No 45/2001;
- 185 b) protecting commercially confidential information, in particular through taking into account the
186 status of the marketing authorisation for the medicinal product, unless there is an overriding public
187 interest in disclosure;
- 188 c) protecting confidential communication between Member States in relation to the preparation of the
189 assessment report;
- 190 d) ensuring effective supervision of the conduct of a clinical trial by Member States.

191 No data from the clinical trial application dossier can be made public before the decision on the clinical
192 trial has been taken (Article 81(5) of the Regulation), unless there is an overriding public interest to do
193 so earlier for a particular clinical trial. Although not explicitly stated in the legislation, in principle only
194 information on validated applications should be made public, since invalid applications may contain
195 incomplete or erroneous information.

196 Every clinical trial should, as a minimum, be registered in a public register prior to its start and its
197 results summary also made public. This standard for public registration at the start of the trial is
198 reinforced by the requirement in Article 25(6) that data from a clinical trial shall only be submitted in
199 an application dossier (in support of a new clinical trial application), if that clinical trial has been
200 registered prior to its start in a public register which is a primary or partner registry of, or a data
201 provider to, the WHO ICTRP. Therefore if EU clinical trials (which are registered in the EU database) as
202 well as non-EU clinical trials (which are registered in other registers) are to be acceptable in support of
203 an EU clinical trial application, they must also meet the public registration standard set out in Article
204 25(6) (for trials started before the Regulation comes into application this can also be achieved by
205 publication of the results in an independent peer reviewed scientific journal).

206 In accordance with Article 93(2) of the Clinical Trial Regulation, Regulation (EC) No 45/2001 applies to
207 the processing of personal data by the Agency. The Agency is the controller of the EU database (Article
208 81(1) of the Clinical Trial Regulation - "data controller" is defined in Article 2 (d) of Regulation (EC)
209 45/2001. In accordance with Regulation (EC) No 45/2001 the processing of personal information and
210 its publication on the website will be limited to the information that is justified as a necessary
211 interference into the private sphere of the persons involved.

212 The EU database shall contain personal data only insofar as this is necessary for the purposes of Article
213 81(2) of the Regulation (i.e. to enable cooperation between the competent authorities of the Member
214 States for the application of the Regulation and to facilitate communication with sponsors).

215 Article 81(7) of the Regulation requires that no personal data of subjects (participating in a clinical
216 trial) shall be publicly available and Recital 67 provides further clarification that no personal data of
217 trial subjects should be recorded in the EU database. Article 37(4), final paragraph, of the Regulation
218 further reinforces this point by setting out that for cases where the sponsor decides to share raw data
219 on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those
220 data.

221 The Regulation provides further details on how these provisions should be applied in Recital 67 which
222 sets out that publicly available information contained in the EU database should contribute to
223 protecting public health and fostering the innovation capacity of European medical research, while
224 recognising the legitimate economic interests of sponsors. Recital 68 sets out what as a minimum
225 should be public on each trial (on the basis that it is not in general confidential) - the main

226 characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorisation
227 of a clinical trial, the decision on the authorisation of a clinical trial, the substantial modification of a
228 clinical trial, and the clinical trial results including reasons for temporary halt and early termination. In
229 addition for clinical trials included in a marketing authorisation application in the EU, Article 37(4)
230 requires that the applicant for a marketing authorisation submit the clinical study report to the EU
231 database within 30 days after the day the marketing authorisation has been granted, the procedure for
232 granting marketing authorisation has been completed, or the applicant has withdrawn the application.
233 Recital 68 provides further clarification stating that for the purposes of this Regulation the data
234 included in a clinical study report, in general should not be considered commercially confidential once
235 one of the conditions set out above for submission of the clinical study report to the EU database has
236 been met.

237 The importance of providing and maintaining public information is further reinforced by Article 94 of
238 the Regulation which requires Member States to make provisions for penalties to be imposed in cases
239 of non-compliance with its provisions on submission of information to be made publicly available to the
240 EU database.

241 The EU portal and database will be updated in accordance with the experience acquired during the
242 implementation of the Regulation (Article 84) and the functional specifications revised, accordingly, in
243 preparation for each update.

244 ***3.2. The transparency requirements of the Paediatric Regulation (EC) No*** 245 ***1901/2006***

246 Article 41 of the Paediatric Regulation (EC) No 1901/2006 stipulates requirements for the publication of
247 results of paediatric clinical trials conducted in the EU and in third countries. As the Clinical Trial
248 Regulation fulfils all of the requirements previously set by the Paediatric Regulation regarding clinical
249 trials conducted in the EU, this aspect loses its practical relevance. However, additional requirements
250 with regard to non-EU trials included in a paediatric investigation plan (PIP), as per Article 41 or
251 reported in accordance with Article 46 of the Paediatric Regulation continue to apply. Those additional
252 requirements are not part of this document. They will be addressed in the detailed requirements for
253 the EU portal and database, but outside of the present functional specifications and outside of the audit
254 foreseen by Article 82 of the Regulation.

255 ***3.3. Application of Regulation (EC) No 1049/2001***

256 The implementation of the transparency rules of the Clinical Trial Regulation is without prejudice to the
257 application of Regulation (EC) No 1049/2001 and citizens' right to request documents under that
258 Regulation.

259 ***3.4. Status of clinical trials made public under the current clinical trial*** 260 ***legislation in the EU Clinical Trial Register***

261 Clinical trials conducted under the current legislation – Directive 2001/20/EC – are registered in the
262 EudraCT database and summary information on the protocols of those trials, and summaries of their
263 results are included in EudraCT and made public in the EU Clinical Trials Register. Those clinical trials
264 will continue to be subject to the current rules on data to be included in EudraCT and made public via
265 the EU Clinical Trials Register. Once the existing legislation has been repealed and no further trials or
266 their result summaries remain to be registered, the EudraCT and EU CTR data content will be retained
267 as a reference for the competent authorities of the Member States, the Agency and the Commission on
268 the one hand and for the public on the other. The transparency rules of new Regulation (EU) No

269 536/2014 will apply only to new trials authorised under that Regulation, or trials authorised under the
270 old legislation but still ongoing 3 years after the Regulation comes into application. Provisions will have
271 to be made, for these “transition” trials to have relevant information entered into the EU portal and
272 database, in time before those 3 years have elapsed.

273 **4. Application of the transparency requirements - Data and** 274 **documents to be made public and timing of publication**

275 **4.1. Background**

276 All of the data and documents that are explicitly designated by the Regulation to be submitted via the
277 EU portal, and/or stored in the EU database shall be public, by default, unless one or more of the
278 exemptions set out in Article 81(4) apply. This rule includes all of the data and documents listed in
279 Annexes I, II, IV and V of the Regulation which set out the content of the application dossier for the
280 initial application, the application dossier for substantial modification, the content of the summary of
281 results of the clinical trial and the content of the summary of results of the clinical trial for lay persons.
282 The assessment reports of the Member States, their questions to the sponsor (and sponsor responses
283 to these) and the decisions of the Member States are included in the database. In addition the
284 Regulation also stipulates that further information is submitted via the portal and or to the database by
285 the sponsor including notifications from the sponsor on the start and end of recruitment, the end of the
286 trial, unexpected events which affect the risk-benefit of the trial, urgent safety measures, third country
287 inspection reports, serious breaches of the Regulation or the protocol, or by Member States on the
288 planning of inspections, inspection reports, corrective measures required by the Member States,
289 reports on Union controls by the Commission and clinical study reports submitted by the applicant/MAH
290 [provisional lists of data and documents are provided as appendices to this paper to illustrate the
291 practical impact of the proposals set out below, the details of the data fields of this list may change as
292 the database is developed, so the appendices should not be taken as a definitive list].

293 In order to establish rules for the public access to the database, rules for the application of the
294 exceptions, set out in Article 81(4), need to be established. These rules will need to operate in an
295 automatic way which means that there should be fields in the data or metadata that enable the system
296 software to determine if and for how long a particular data element or document should not be made
297 public. Automatic rules are necessary because there will be 4-5000 clinical trial applications and
298 multiple additional processes per trial taking place in the system every year. The rules need to be
299 applied in a fair and systematic way, in accordance with established rules, and not based on repeated
300 human judgment and intervention, which would be impossible to control and create a very large
301 burden on authorities and on sponsors. The rules must be designed in order that the system produces
302 a consistent and predictable outcome so that those submitting data and documents and those viewing
303 them benefit from legal certainty as to what is made public and when.

304 The exceptions to publication set out in Article 81(4) are each considered below and where relevant
305 different proposals are considered in section 4.3. below.

306 Section 4.2. below summarises the information to be made available for every clinical trial.

307 **4.2. What will be made public for every clinical trial**

308 Recital 68 refers to “the main characteristics of a clinical trial” – these can be considered to be its main
309 design characteristics, its scientific and where applicable, therapeutic intent, title, identification of the
310 IMPs (Investigational Medicinal Products), treatment arms, treatment population characteristics and
311 number of subjects, inclusion and exclusion criteria and main objectives and endpoints (see Appendix 1
312 to this document).

313 The current EU CTR (EU Clinical Trials Register) is a primary registry of the WHO ICTRP, and the new
314 database should make public a similar level of information and provide it to the WHO ICTRP.

315 Information should also be equivalent in nature (though may be differently arranged, with different
316 fields) to that already made public for Phase II-IV adult and all paediatric clinical trials under the
317 present EU legislation in the EU Clinical Trial Register.

318 For every clinical trial, regardless of the marketing authorisation status of the medicinal product and
319 regardless of the phase of the trial, the following information will be made public, as soon as it is
320 available, once the decision on the trial has been made:

321 **At the time of decision on the trial:**

- 322 • the main characteristics of the trial (as set out in the clinical trial application form - being in effect
323 a structured synopsis of the clinical trial protocol),
- 324 • the protocol summary,
- 325 • the conclusion on the assessment of Part I of the trial,
- 326 • the decision on the trial including reasons for refusal if the trial is not authorised (or where
327 applicable the reason for its withdrawal),
- 328 • the start of the trial,

329 **During the trial:**

- 330 • the first visit of the first subject in the trial in each MS concerned,
- 331 • substantial modification of the trial (the fact that a substantial modification has been submitted
332 and assessed, the conclusion on Part I (if applicable) and the decision on the substantial
333 modification, as it relates to the major characteristics of the trial, or the sponsor or investigators
334 involved at the time of the decision on the substantial modification, or other modifications to
335 previously published information),
- 336 • notification on the temporary halt or early termination of the trial for reasons affecting the risk-
337 benefit,
- 338 • notification on the end of recruitment in each MS concerned,
- 339 • notification on the end of the trial (per MS concerned, in all MS concerned and global),
- 340 • other documents and notifications set out in the Regulation and its annexes (unless other
341 exceptions below apply to them – see details in the appendices to this paper). Refer to the
342 appendices 2, 3 and 4 to this document for listing of potential items that may be made public.

343 **After the end of the trial:**

- 344 • the summary clinical trial results as set out in Annexes IV and V of the Regulation.

345 In the case of Phase I clinical trials in healthy volunteers there is particular sensitivity about the
346 commercial confidentiality of information on the trial. Section 4.4.3., part 7, contains a proposal for an
347 option for the sponsor to defer the publication of information from the start of the trial to the point at
348 which the summary of results is included 12 months after the end of the trial.

349 The clinical trial protocol and related subject information sheet will be made public for all clinical trials
350 but this publication may be deferred (see proposals in section 4.4.3.).

351 The investigational medicinal product dossier (IMPD) safety and efficacy sections will be made public
352 for all clinical trials but this publication may be deferred (see proposals in section 4.4.3.).

353 The IMPD quality section will not be made public as it contains detailed information on manufacturing
354 processes and related information which remain commercially confidential even after the marketing
355 authorisation has been given (see section 4.4.3.).

356 **4.3. Protecting personal data in accordance with Regulation (EC) No**
357 **45/2001**

358 The data retained in the database and made public are there to provide public information on
359 medicines and support the further development of these and other medicines. Personal data (other
360 than trial subject data which are not included in the database) included in the database are made
361 public only to the extent required for the application of the Regulation (Article 81(6)). Data subjects
362 have the right to have personal information corrected and incorrect personal information deleted in
363 accordance with Regulation (EC) No 45/2001. Data protection rules set out that personal data should
364 not be retained for longer than is necessary. The rules supporting the WHO ICTRP require that
365 information published in a clinical trial registry should not be removed from the public domain, even
366 where a particular piece of information is superseded by new information. The Regulation imposes a
367 minimum 25-year retention rule on trial master files, which should therefore serve as a minimum.
368 Clinical investigators names and site information are however integral to the authorisation of the trial
369 and should be retained for as long as data on the clinical trials is retained in the system.

370 There are several categories of personal data that need to be considered:

371 **4.3.1. Clinical trial subjects being evaluated for or participating in a trial**

372 The Clinical Trial Regulation makes clear that no personal data of trial subjects may be included in the
373 database and no personal data of trial subjects should be publicly available, from the database. It
374 follows that individual patient data listings (sometimes referred to as raw data) which form some of the
375 appendices included in clinical study reports may neither be included in the database nor made public.

376 It should be noted that the reporting of SUSARs and annual safety reports which contain individual trial
377 subject data in pseudo-anonymized form are not part of the EU database but are submitted to the
378 separate EudraVigilance system, and are therefore out of scope of this document.

379 The clinical trial result summaries (as per Annex IV and V of the Regulation) are structured in such a
380 way that even where an individual element of data relating to a single subject (most likely a single
381 adverse reaction) is presented it does not include trial subject identifiers.

382 **4.3.2. Clinical trial investigators and their staff**

383 Annex I M of the Regulation requires that a list of the clinical trial sites, the name and position of the
384 investigator or principal investigator in charge of the trial at a site, their qualification and CV and
385 description of GCP training and any conditions such as economic interests and institutional affiliations
386 that might influence the impartiality of the investigators shall be presented, as part of the application
387 dossier. The (principal) investigator is a key actor identified in the Regulation (and internationally in all
388 rules and guidelines on good clinical practice, ethics of clinical trials, national legislation in non EU
389 countries etc.) with a legally assigned responsibility for conduct of the clinical trial at a given site and
390 for the care and treatment of the trial subjects in the context of the trial. The (principal) investigators
391 are responsible for ensuring the protocol is followed at their site, and for the collection and reporting to
392 the sponsor of the data required by the trial protocol which form the basis of the clinical study report,
393 which they or a chosen reporting investigator is required to sign where it is prepared for potential
394 submission in a marketing authorisation application.

- 395 1. Therefore it is considered an integral part of the clinical trial authorisation of every trial that the list
396 of principal investigators and their sites is made public as part of that authorisation.
- 397 2. The (principal) investigators' CVs, containing only professional information relevant to the conduct
398 of clinical trials, are part of the application dossier and therefore the database. It is considered that
399 these should be public, as they document the qualification of the investigator to conduct the trial. A
400 template or list of information that should be included in the CV will be made available.
- 401 3. Any conditions such as economic interests and institutional affiliations that might influence the
402 impartiality of the investigators which are submitted, as part of the application dossier should be
403 made public. A template or list of information that should be included will be made available.
- 404 4. A written statement issued by the head of the clinic/institution or some responsible person
405 testifying to the suitability of the facilities and human resources available for the trial is part of the
406 application dossier. It is proposed that when the statements are made public the name of the
407 signatory of the statement is included, on the basis that they are fulfilling a specific role in signing
408 a statement required by the Regulation.

409 **Question 1: Please comment on whether these proposals meet the**
410 **requirements and objectives of the Regulation (EU) No 536/2014.**

411 **4.3.3. Member State experts (mainly scientific assessors, regulatory** 412 **officials, ethics committee members, inspectors)**

413 In general, the names of Member State experts will not be included in the database. To the extent that
414 personal information identifying them is collected in the database at all, it will not be made public.

415 **Question 2: Please comment on whether this proposal meets the**
416 **requirements and objectives of the Regulation (EU) No 536/2014.**

417 **4.3.4. Personnel of the clinical trial sponsor or other parties acting on their** 418 **behalf**

419 In general, personal information identifying sponsor staff (or consultants, contractors, agents or staff
420 of those acting on behalf of the sponsor) will not be included in the database. To the extent that
421 information is included it will not be made public except for those persons with certain legal roles such

422 as the legally designated representative of the sponsor, or where the sponsor is a natural person (e.g.
423 an investigator who is also the sponsor).

424 **Question 3: Please comment on whether this proposal meets the**
425 **requirements and objectives of the Regulation (EU) No 536/2014.**

426 **4.3.5. Personnel or experts of the marketing-authorisation**
427 **holder/applicant for MA, or of the sponsor or the investigators, laboratory**
428 **personnel or other actors in the conduct of a trial named in or signing**
429 **clinical study reports**

430 Personal information identifying MAH/applicant personnel (or consultants, contractors, agents or staff
431 of those acting on behalf of the sponsor or MAH, investigators or other parties) identified in the clinical
432 study report that is loaded into the database by the MAH/applicant will be made public. As a minimum
433 the signatories of the clinical study report and the investigator(s) who conducted the trial should be
434 identified.

435 **Question 4: Please comment on whether this proposal meets the**
436 **requirements and objectives of the Regulation (EU) No 536/2014.**

437 **4.3.6. Contact details of clinical investigators, sponsor or MAH personnel**

438 It is proposed that no direct contact details such as direct telephone number or email address is
439 provided for any natural person. Two exceptions to this are the possibility to include a sponsor contact
440 point for information on the trial and a sponsor contact point for information on the scientific aspects of
441 the trial required for public registration of the trial. These may be provided as functional roles, but if
442 they are provided as contact details of natural persons these will in any event always be made public.

443 An option will also be provided for investigator sites to provide a contact point for trial subjects or their
444 healthcare providers or carers, to enable them to seek further information about trial participation.

445 **Question 5: Please comment on whether this proposal meets the**
446 **requirements and objectives of the Regulation (EU) No 536/2014.**

447 ***4.4. Protecting commercially confidential information, in particular through***
448 ***taking into account the status of the marketing authorisation for the***
449 ***medicinal product, unless there is an overriding public interest in disclosure***

450 The Regulation has two key objectives, to promote the EU as a location for clinical research
451 (encouraging innovation), and to provide extensive public information on clinical trials conducted in the
452 EU. These two objectives, need to carefully balanced, as reflected in Recitals 67 and 68 and in Article
453 81(4)(b) of the Regulation.

454 **4.4.1. What should be considered to be commercially confidential**
455 **information?**

456 ***4.4.1.1 Definitions***

457 Commercially confidential information can be considered as meaning any information contained in the
458 data or documents submitted to the database that is not in the public domain or publicly available and
459 where disclosure may undermine the legitimate economic interest of the sponsor.

460 Sponsors have a legitimate economic interest in the trial they conduct which may derive from their
461 intention to seek a marketing authorisation for the investigational medicinal product or because they
462 need to obtain research funding for that and future trials. The legislation does not distinguish between
463 different types of sponsor organisation (e.g. commercial, non-commercial or academic). The
464 consideration of what might be commercially confidential is therefore based on the nature of the trial
465 and status of the medicinal product being studied, rather than the nature of the sponsor organisation
466 conducting the trial.

467 By having a legitimate economic interest in their trial the sponsor can claim that certain information
468 relating to the trial should be considered commercially confidential, at least for a certain time period.
469 Information may be commercially confidential because the clinical trial forms part of the development
470 of a medicinal product for commercialisation of that product (i.e. seeking a marketing authorisation or
471 variation). Alternatively it may be commercially confidential because the clinical trial is conducted to
472 further basic or applied research on medicines and as such may be part of a process for which research
473 funds have been obtained or may contribute to the obtaining of future research funds. The sponsor
474 may need to retain some confidentiality of research plans in order to sustain their ability to conduct
475 original research and maintain funding for that research, the ability to publish that research in journals
476 and to pursue their research programme in the future. Since these concepts are necessary to research
477 funding they can also be considered to represent legitimate economic interests and fulfil the definition
478 of commercial confidentiality expressed in the first paragraph of this section, for the purposes of
479 application of this Regulation.

480 Overriding public interest can be considered, in this context, as meaning that the general public
481 interest in having information made publically available may outweigh considerations that the same
482 information should remain confidential. The public interest per se is multifactorial, but includes access
483 to information that supports the objectives for transparency set out in chapter 2 part 3 of this
484 document.

485 Specific situations may occur where the "overriding public interest" would prevail in ad hoc situations
486 over and above the general transparency rules established for the database and documents and data
487 not usually made public may be published or made public at an earlier time point than would be usual.
488 The database would have to provide functionality to enable non-public documents or data to be made
489 public on such occasions. Outside of the database a decision making process will need to be
490 established in order to invoke use of the overriding public interest in such ad hoc cases.

491 Documents and data included in the EU database can be grouped in two broad categories for this
492 purpose – study specific and (active substance/medicinal product) specific documents.

493 These documents are complex and mixtures of commercially confidential and non-confidential
494 information are present together in different sections. In many multicentre trials they will be in use in
495 the EU and outside of the EU. To require that they be structured in confidential and non-confidential
496 parts would impose a significant burden on sponsors who would have to prepare them for input into
497 the portal in a very different way for the EU compared to elsewhere. It would also impose on sponsors
498 of EU trials a more detailed structure, as different information would need to be entered in different
499 fields, whereas at present it is included in a single document. Such an approach would increase the
500 administrative burden of the clinical trial application process.

501 **4.4.1.2 Categories of documents**

502 **a) Study specific documents:**

503 **Protocol:** The protocol is defined in Article (2)(22) of the Regulation as: *“Protocol’ means a document*
504 *that describes the objectives, design, methodology, statistical considerations, and organisation of a*
505 *trial. The term ‘protocol’ encompasses successive versions of the protocol and protocol modifications.”*

506 The protocol contains extensive detailed information on the IMP, its mode of action and plans for its
507 testing at least in the authorised trial. Such details can involve the scientific hypotheses being tested,
508 and the test methods and endpoints being used. The details in the protocol which can be commercially
509 confidential are not confined to any particular part of the document but may be entered in many
510 different sections, so it should be treated as one entity for the purpose of transparency rules.

511 Summarised elements of the protocol are to be found in the clinical trial application form (“the major
512 characteristics of the trial”) and result summaries, which are made public.

513 The protocol can therefore contain extensive detail of a commercially confidential nature, especially for
514 clinical trials conducted before a marketing authorisation has been granted, or for new indications or
515 formulations of a product already on the market.

516 **Subject information sheet:** The subject information sheet is a detailed description of the trial
517 subject’s rights and of the details of the potential risks and benefits of participation in the trial, details
518 of the trial purpose and methodology and of any tests, sample collection or other impositions on the
519 trial subject due to their participation in the trial. As such it will contain details, albeit possibly in lay
520 terms, of the medicinal product, the purpose of the trial and its objectives and the tests that will be
521 undertaken. It will also contain up to date information on the safety of the product based on preclinical
522 testing and on any earlier clinical trial data that is available.

523 The subject information sheet can therefore contain extensive detail of a commercially confidential
524 nature, for clinical trials conducted before a marketing authorisation has been granted, or for new
525 indications or formulations of a product already on the market.

526 **Related list of questions, responses and assessment reports:** Assessment reports contain a
527 detailed analysis and critique of the protocol, subject information and the purpose, design and
528 supporting data of the trial. These will contain information from the documents submitted by the
529 sponsor both in the initial application and additional information provided in response to questions from
530 the Member States.

531 The list of questions, responses and assessment reports related to the protocol and subject information
532 sheet can therefore contain extensive detail of a commercially confidential nature, particularly for
533 clinical trials conducted before a marketing authorisation has been granted, or for new indications or
534 formulations of a product already on the market.

535 **b) Product specific documents:**

536 **Investigator brochure:** The investigator brochure is defined in Article 2((23) of the Regulation as:
537 *“Investigator’s brochure’ means a compilation of the clinical and non-clinical data on the*
538 *investigational medicinal product or products which are relevant to the study of the product or*
539 *products in humans”*. The investigator brochure contains extensive detail on the pre-clinical and clinical
540 testing and development of the IMP as well as further lines of investigation for future development.
541 These details are often not trial specific but cover all trials, as generally there is one investigator
542 brochure for each active substance in development. The details include extensive scientific background
543 on the toxicology, safety and efficacy of the IMP, detailed information on pharmaceutical development,
544 pharmacokinetic and pharmacodynamic testing and methods, results of absorption, distribution and

545 metabolism and excretion tests, the mode of action of the product, discussion of endpoints and clinical
546 development methods. The investigator brochure includes the reference safety information (RSI).
547 Investigator brochure are frequently provided in confidence to investigators to thoroughly acquaint
548 them with the IMP being tested, and are regularly (at least annually) updated, so provide a detailed
549 update on the development of an IMP.

550 The investigator brochure therefore contains extensive detail of a commercially confidential nature,
551 particularly for clinical trials conducted before a marketing authorisation has been granted, or for new
552 indications or formulations of a product already on the market.

553 **Investigational Medicinal Product Dossier (IMPD):** The IMPD is a detailed technical and scientific
554 description of the investigational medicinal product. According to Annex I(G)(36) of the Regulation
555 *“The IMPD shall give information on the manufacture and control of the investigational medicinal*
556 *product, and data from non-clinical studies and from its clinical use.”* It is regularly updated, and these
557 updates will be submitted to the EU database in accordance with the Regulation, so long as there are
558 related trials ongoing in the EU.

559 For the purposes of the present document the IMPD is considered to have three sections one each on
560 quality (IMPD-Q), safety (IMPD-S) and efficacy (IMPD-E).

561 The IMPD-Q section provides extensive detail on the manufacturing methods and controls, the
562 chemical or biological characterisation of the product, its stability, stage of pharmaceutical
563 development and further plans in that respect.

564 The IMPD-S and E sections provide extensive non-clinical and clinical trial data, plans for future trials
565 and details of the current risk benefit assessment. They include extensive details relevant not only to
566 the trial applied for but for any anticipated trials, including those in other indications or formulations
567 that may be developed further in the future.

568 The IMPD is regularly updated to support all ongoing trials so individual updates may be more relevant
569 for some trials than others, it provides a detailed updated review of the current state of knowledge
570 and plans for the active substance/product.

571 The IMPD therefore contains extensive detail of a commercially confidential nature, particularly for
572 clinical trials conducted before a marketing authorisation has been granted, or for new indications or
573 formulations of a product already on the market., and the IMPD-Q section can always have extensive
574 commercially confidential information.

575 **Related list of questions, responses and Assessment Reports:** Assessment reports contain a
576 detailed analysis and critique of the information in the investigator brochure and IMPD Q, S and E
577 sections. These will contain information from the documents submitted by the sponsor both in the
578 initial application and additional information provided in response to questions from the Member
579 States.

580 The list of questions, responses and assessment reports related to investigator brochure and IMPD
581 therefore contain extensive detail of a commercially confidential nature, particularly for clinical trials
582 conducted before a marketing authorisation has been granted, or for new indications or formulations of
583 a product already on the market.

584 **4.4.2. How should the status of marketing authorisation of the medicinal**
585 **product be applied in the context of Article 81(4)(b) of the Regulation?**

586 The status of the marketing authorisation for the medicinal product shall be taken into account in
587 deciding which information/documents in the EU database shall be publicly accessible, and at what
588 time point, unless there is an overriding public interest in disclosure (Article 81 (4)(b)).

589 1. Article 81(4)(b) of the Regulation states the commercially confidential information should be
590 considered taking account, in particular, of the marketing authorisation status of the medicinal
591 product. In order to apply this exclusion it is necessary to determine how the concept of marketing
592 authorisation will be applied. Three proposals are made below (1.1, 1.2 and 1.3 but only one will
593 be selected for inclusion in the final rules):

594 1.1. once a marketing authorisation has been issued, by at least one Member State, for the
595 active substance contained in that medicinal product,

596 or:

597 1.2. once a marketing authorisation has been issued, by at least one Member State, for a
598 medicinal product using that active substance and for the indication under study,

599 or:

600 1.3. once a marketing authorisation has been issued, by at least one Member State, for a
601 medicinal product using that active substance and for the indication and formulation/route of
602 administration under study.

603 2. For the purposes of the proposals 1.2 and 1.3 medicinal products containing active substances
604 which are bio-similar should be considered separately from the originator products (i.e. as not
605 having a marketing authorisation until that is granted for the biosimilar product in question).

606 **Question 6: Please comment on which of proposals 1.1. or 1.2. or 1.3.**
607 **above best meets the requirements and objectives of the Regulation.**

608 **Please provide a brief rationale for your choice of proposal and explain**
609 **briefly disagreement with the other proposals.**

610 **4.4.3. When should information that may be considered commercially**
611 **confidential, be made public taking into account the marketing**
612 **authorisation status of the medicinal product and unless there is an**
613 **overriding public interest?**

614 **General considerations**

615 1. In applying the concepts of protecting commercially confidential information, in particular taking
616 account of the marketing authorisation status of a product, and of overriding public interest, a
617 graduated approach could be taken to the release of information on clinical trials. Thus, the extent
618 of information made public could progressively increase during the development period to the
619 marketing authorisation of a medicine from first in human Phase I trials to post-authorisation
620 Phase IV and low-intervention trials.

621 2. Currently there is no structured codification of the indications and formulations that would allow
622 these to be determined automatically. The sponsor would have to indicate the marketing
623 authorisation status of the medicinal product, in response to questions in the clinical trial

624 application form. As part of the assessment of the dossier the Member States would have to assess
625 this status and decide whether or not the clinical trial is using the IMP within or outside the labelled
626 indications/formulations/routes of administration or established therapeutic guidance (for low-
627 intervention trials). The decision of the Member States should be final. This also relates to the
628 determination of the low-intervention trial status of some trials so both aspects could be
629 considered together.

630 3. There are many clinical trials carried out on non-authorized medicines, in the early phases of
631 development prior to marketing authorisation, which are never later used in a marketing
632 authorisation as the development of the medicines is discontinued (approximately 80% of
633 medicines which enter trials in human subjects are discontinued) or indeed the trials may not have
634 been conducted in preparation for a future marketing authorisation, but rather as basic research.

635 **Publication of study specific and product specific documents (see 4.4.1.2)**

636 4. Regardless of marketing authorisation status the IMPD-Q section on IMP quality and the related
637 lists of questions, responses and assessment report sections should be considered to be
638 commercially confidential and not be made public for any trial at any time, as this deals with the
639 manufacturing and related pharmaceutical development information which continues to be CCI,
640 indefinitely, post marketing authorisation.

641 **Question 7: Please comment and give a brief rationale for your support or**
642 **disagreement with this proposal regarding the IMPD-Q section.**

643 5. Clinical trials on products with a marketing authorisation:

644 Taking into account the general considerations under 1, 2 and 3 the following should apply to trials
645 of products with a marketing authorisation (the so called Phase IV trials and low-intervention
646 trials⁶) with respect to the publication of study specific and product specific documents. The study
647 and product specific documentation should be made public at the time of the decision on the trial.
648 However, the sponsor will be given the option to defer this publication until the time that the
649 summary of trial results is loaded into the database and made public (i.e. 12 months after the end
650 of the trial), in cases where protection of commercially confidential information would be required.
651 The sponsor should indicate in the clinical trial application form if they are opting for this deferral.

652 **Question 8: Please comment and give a brief rationale for your support or**
653 **disagreement with this proposal regarding clinical trials on products**
654 **without a marketing authorisation.**

655 6. Clinical trials on products without a marketing authorisation:

656 Taking into account the general considerations under 1, 2 and 3 above, the following should apply
657 to trials of products without a marketing authorisation (the so called Phase I, II and III trials) with
658 respect to the publication of study specific and product specific documents. Four proposals are
659 made but only one will be selected for inclusion in the final rules:

⁶ Low-intervention trial – defined in Article 2(2)(3) of the Regulation. Low-intervention clinical trials are carried out with IMPs which have a marketing authorisation (placebos excepted), and are used in accordance with the terms of the marketing authorisation or where the use is evidence-based and supported by published scientific evidence on their safety and efficacy. The additional diagnostic or monitoring procedures do not pose more than a minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

660 6.1. **Proposal One:** The study specific and product specific documents are made public at the
661 time of the decision on the trial, and the exception set out in Article 81(4)b would only apply
662 to the IMPD-Q section, which would not be made public at any stage.

663 6.2. **Proposal Two:** The study specific and product specific documents (with the exception of the
664 IMPD-Q section, which would not be made public at any stage) should only be made public
665 after the earlier of the conditions set out in paragraph 6.5 below are met.

666 6.3. **Proposal Three:** A differential approach is taken equivalent to different stages of
667 development – i.e. conservatively for Phase I and II trials, but then less conservatively for
668 Phase III trials. This can be justified by interpreting that the degree of commercial
669 confidentiality diminishes during development as information on the product and active
670 substance and related clinical trials are more and more available in the public domain.
671 Conversely the concept of overriding public interest increases due to the wider availability of
672 the IMP/active substance and its use in larger subject populations for therapeutic/prophylactic
673 purposes.

674 The study specific and product specific information (with the exception of the IMPD-Q section,
675 which would not be made public at any stage) for Phase I and II trials should only be made
676 public when the earlier of the conditions set out under paragraph 6.5 below are met.

677 For Phase III trials the study specific information should be made public at the time the
678 summary of trial results is loaded into the database and made public (i.e. 12 months after the
679 end of the trial) and the product specific information (with the exception of the IMPD-Q
680 section, which would not be made public at any stage) should only be made public when the
681 earlier of the conditions set out in paragraph 6.5. below are met.

682 6.4. **Proposal Four:** A differential approach is taken during different stages of development – i.e.
683 conservatively for trials without therapeutic (or prophylactic) intent, but then less
684 conservatively for trials with therapeutic (or prophylactic) intent (a question in the clinical
685 trial application form would ask if the trial has a therapeutic (or prophylactic) intent for the
686 participating subjects. This can be justified by interpreting that the degree of commercial
687 confidentiality diminishes during development as information on the product and active
688 substance and related clinical trials are more and more available in the public domain.
689 Conversely the concept of overriding public interest increases due to the wider availability of
690 the IMP/active substance and its use in larger subject populations. Article 81(4)(b) requires
691 that both the marketing authorisation status, and overriding public interest be considered
692 when establishing the exception on the basis of commercial confidentiality.

693 For trials without therapeutic⁷ or prophylactic⁸ intent the study specific and product specific
694 information (with the exception of the IMPD-Q section, which would not be made public at
695 any stage) should only be made public when the earlier of the conditions set out under
696 paragraph 6.5. below are met.

⁷ Clinical trial without “therapeutic intent” - a clinical trial carried out in healthy volunteers, or in patients who do not suffer from the disease to be treated or where the dose regime does not have the potential to have a therapeutic effect (e.g. a single dose trial).

⁸ Clinical trial without “prophylactic intent” - a clinical trial carried out in healthy volunteers, or in patients who would not normally be considered for such prophylaxis, or would not usually benefit from it or where the dose regime does not have the potential to have a prophylactic effect (e.g. a single dose trial).

697 For trials with therapeutic⁹ or prophylactic¹⁰ intent the study specific information should be
 698 made public at the time that the summary of trial results is loaded into the database and
 699 made public (i.e. 12 months after the end of the trial) and the product specific information
 700 (with the exception of the IMPD-Q section, which would not be made public at any stage)
 701 should only be made public when the earlier of the conditions set out in paragraph 6.5. below
 702 are met.

703 **Table 1.** Description of proposals 1 - 4 and optional deferral for Phase IV trials

	Clinical trials on medicinal products without marketing authorisation				Clinical trials on medicinal products with marketing authorisation
	Proposal One	Proposal Two	Proposal Three	Proposal Four	Phase IV and low-intervention trials
Study specific documents – protocol and subject information sheet	Time of decision on trial	Time of MA or 9 years after first summary results posted	Phase I and II time of MA or 9 years after first summary results posted Phase III – time when first summary results are posted	Non therapeutic trials – time of MA or 9 years after first summary results posted Therapeutic trials – time when first summary results are posted	Time of decision on trial, but sponsor may opt to defer to time when first summary results are posted
Product specific documents – IMPD S and E sections and investigator brochure	Time of decision on trial	Time of MA or 9 years after first summary results posted	Time of MA or 9 years after first summary results posted	Time of MA or 9 years after first summary results posted	Time of decision on trial, but sponsor may opt to defer to time when first summary results are posted on trial

⁹ Clinical trial with “therapeutic intent” - a clinical trial carried out in subjects suffering from the condition which the investigational medicinal product is intended to treat and where at least one of the treatment arms is carried out with a dose regime that has the potential to have a therapeutic effect. The trial may still involve placebo, or standard of care arms.

¹⁰ Clinical trial with “prophylactic intent” - a clinical trial carried out in subjects where at least one of the treatment arms is carried out with a dose regime that has the potential to have a beneficial prophylactic effect in the trial subjects receiving it. The trial may still involve placebo, or standard of care arms.

704 **Question 9: Please comment on proposals one, two, three or four regarding**
705 **clinical trials on products with a marketing authorisation indicating which**
706 **proposal best meets the requirements and objectives of the Regulation.**
707 **Please provide a brief rationale for your choice of proposal and explain**
708 **briefly disagreement with the other proposals.**

709 6.5. **Triggers for timing of publication** (in relation to proposals two, three or four above
710 regarding clinical trials on products without a marketing authorisation):

711 6.5.1. The granting, refusal, or the withdrawal of the marketing authorisation application
712 has triggered the loading into the EU database (and therefore publication) by the
713 marketing authorisation applicant of the clinical study report for the same trial.

714 6.5.2. Nine years have elapsed from the date on which the first summary of results of the
715 trial should have been published and therefore at least 10 years after the end of the
716 trial, taking into account that for some trials an extension of the time limit for
717 publication of the summary of results can be justified (for scientific reasons) in
718 accordance with Article 37(4) of the Regulation). The period of 10 years have been
719 chosen to give a reasonable period after the trial has been completed, before
720 publication, 10 years corresponding, by analogy, though not actually linked to, the
721 data protection period provided for in the EU.

722 **Question 10: Please comment on the proposed time points in paragraphs**
723 **6.5.1 and 6.5.2 and indicate whether they meet the requirements and**
724 **objectives of the Regulation. Please provide a brief rationale for your**
725 **support or disagreement.**

726 **Information to be made public at the time of decision on the trial – possible deferral for**
727 **Phase I trials in healthy volunteers (see 4.2.).**

728 7. Section 4.2. above describes the information to be made public, as soon as it is available, once the
729 decision on the trial has been made. That information will be made public for all trials regardless of
730 their marketing authorisation status or of the phase of the trial.

731 For Phase I trials (in healthy volunteers), the default information made public at the start of the
732 trial, and during the course of the trial, will remain that described in section 4.2. "What is made
733 public for every trial".

734 However, the sponsor will be given the possibility to opt (by indicating this in the clinical trial
735 application form) to have only a very minimal public information at the time of decision on the
736 trial. In this case the minimum information made public at the time of decision on the trial would
737 be a subset of the fields of the WHO ICTRP, in particular the EU number of the trial, the sponsor,
738 the investigator site, the phase of the trial (i.e. Phase I), the number of trial subjects and the
739 population under study (i.e. healthy volunteers). The decision on the trial would also be made
740 public, but identifying the trial only by this minimum set of information. The information that would
741 usually have been made public at the start of the trial and during the trial will, in case of a
742 deferral, be made public at the point when the summary of trial results is published 12 months
743 after the end of the trial. This option for deferral will not apply to Phase I trials conducted in
744 paediatric populations.

745 **Question 11: Please comment and give a brief rationale for your support or**
746 **disagreement with this proposal regarding Phase I trials.**

747 The arrangements for payment of investigators and sites as set out in Annex I (P) (69-71) of the
748 Regulation, should not be published as they relate in all cases to the commercial financial
749 arrangements between the parties and the exception set out under Article 81(4)(b) should apply in all
750 cases, because this information can be considered to be commercially confidential.

751 **Question 12: Please comment on whether this proposal meets the**
752 **requirements and objectives of the Regulation.**

753 ***4.5. Protecting confidential communication between Member States in***
754 ***relation to the preparation of the assessment report***

755 The confidentiality of communication between Member States in relation to the preparation of the
756 assessment report is required to enable the preparation and drafting of assessment reports to be
757 conducted in confidence to ensure that the assessment and hence where applicable the decision
758 making process is not subject to interference.

759 The Regulation does not require the draft assessment reports to be submitted through the portal to the
760 database and therefore they will not be made public.

761 **Question 13: Please comment on whether this proposal meets the**
762 **requirements and objectives of the Regulation.**

763 ***4.6. Ensuring effective supervision of the conduct of a clinical trial by***
764 ***Member States***

765 Supervision of a clinical trial by the Member States encompasses the planning, conduct, reporting and
766 follow-up of inspections conducted in accordance with Article 78 of the Regulation. Article 78 also
767 includes certain inspection coordination activities of the Agency, and the taking of corrective measures
768 by the Member States in accordance with Article 77 of the Regulation. Supervision also includes the
769 Union controls foreseen by Article 79 of the Regulation. The receipt, evaluation and follow-up of reports
770 of serious breaches reported in accordance with Article 52 of the Regulation, are also part of the
771 supervision of clinical trials.

772 In the context of supervision of clinical trials it will be necessary for certain documents to contain
773 personal data or commercially confidential information in order to fulfil their scientific and regulatory
774 purpose.

775 In this context the exception under Article 81(4)(a),(b) and (d) should be taken into account in the
776 publication of inspection reports, Union Control reports, serious breach reports and their follow-up and
777 corrective measures.

778 **4.6.1. Inspection reports**

- 779 1. Information on the planning of an inspection, its conduct, reporting and follow-up should remain
780 confidential until the final inspection report has been issued.
- 781 2. Inspection reports should be made public once the inspection process is completed and the final
782 inspection report signed off and issued by the Member State(s) inspectorate. This may be deferred
783 where its publication would be prohibited by ongoing legal proceedings in the Member State.

- 784 3. Where an inspection has been requested as part of the assessment of a marketing authorisation
785 application, the final inspection report should be released at the time point set out for inclusion of
786 clinical study reports in the database, or later if the inspection process is not yet completed for that
787 inspection, in which case paragraph 2 above applies.
- 788 4. The inspection report made public should be redacted, by the responsible inspectorate, in line with
789 the principles set out in accordance with exceptions under Article 81(4) (a) and (b). The report
790 should nonetheless identify the relevant clinical trials by their EU number and or protocol number
791 (for third country trials) and the site of the inspection, including where applicable the name of the
792 investigator, and the name of the institution, or for other facilities the name of the facility (e.g.
793 laboratories). Redacted and un-redacted versions should be submitted to the database but only the
794 redacted version made public. No personal data of trial subjects should appear.

795 **Question 14: Please comment on whether these proposals meet the**
796 **requirements and objectives of the Regulation.**

797 **4.6.2. Union Control reports**

798 The final report of a Union Control submitted by the European Commission through the portal should
799 be made public at the time it is submitted via the portal. Redaction of personal data or commercially
800 confidential information, if applicable, will be carried out by the Commission.

801 **Question 15: Please comment on whether this proposal meets the**
802 **requirements and objectives of the Regulation.**

803 **4.6.3. Serious breaches and corrective measures**

- 804 1. Serious breaches reported in accordance with Article 52 should not be made public until they have
805 been investigated and a conclusion reached by the Member State to whom the breach has been
806 reported or in whose territory the breach occurred if different. Where the same serious breach is
807 reported to several Member States, they may decide to agree on one Member State taking the lead
808 in evaluating the case, and preparing text to support the following notices in the database.
- 809 1.1. If the Member State concludes that there is no case to answer a notice should be included in
810 the database and published, to the effect that a serious breach reports was received but that
811 the Member State concluded that no serious breach had been substantiated, thus closing the
812 process. No details of the reported breach would be published as none had been
813 substantiated.
- 814 1.2. If the Member State concludes that there is a serious breach without requiring further action
815 by the Member State, then a final notice should be included in the database and published,
816 describing the serious breach and the conclusion of the Member State.
- 817 1.3. If an inspection is initiated then the serious breach notice should be included in the database
818 and published, at the same time as the associated inspection report (or after corrective
819 measures have been taken in accordance with Article 77(see below) whichever is later).
- 820 1.4. If the Member State decides to take corrective measure in accordance with Article 77, then
821 the notice detailing the serious breach should be included in the database, and published, at
822 the same time as the notice of corrective measures is issued.

823 1.5. For corrective measures issued for other reasons (unrelated to a serious breach) the
824 Member State should include in the database, for publication a notice of corrective measures
825 in accordance with Article 77(3). That notice should be published in line with the same
826 conditions set out in 1.6.

827 1.6. The information provided by the sponsor should include a summary, for publication, of the
828 serious breach with personal data or commercially confidential information redacted. The
829 detailed data supporting the notice serious breach should not be published in order to allow
830 the sponsor to provide all relevant details which may include information on individuals
831 other than the investigator, or commercially confidential information. The notice of serious
832 breaches and/or corrective measures made public by the Member State should use the
833 summary provided by the sponsor. The Member State should redact that part of the notice
834 the Member State generated prior to its publication, in line with the principles set out in
835 accordance with exceptions under Article 81(4)(a) and (b). The notice should nonetheless
836 identify the relevant clinical trials by their EU number and or protocol number (for third
837 country trials) and the sites involved, including where applicable the name of the
838 investigator, and the name of the institution, or for other facilities the name of the facility
839 (e.g. sponsor site, CRO, laboratories). Redacted and unredacted versions should be
840 submitted to the database but only the redacted version made public. No personal data of
841 trial subjects should appear.

842 **Question 16: Please comment on whether these proposals meet the**
843 **requirements and objectives of the Regulation.**

844 ***4.7. Reporting of unexpected events in accordance with Article 53 and***
845 ***urgent safety measures in accordance with Article 54***

846 1. A report of an unexpected event made in compliance with Article 53 should be made public at the
847 time it is reported, unless one of the supervision measures itemised in section 4.6.3 is taken, in
848 which case it should be made public in line with the measure concerned.

849 2. A report of urgent safety measures made in accordance with Article 54 should be made public at
850 the time it is reported.

851 3. The report made public in accordance with Articles 53 and 54 should be redacted, by the sponsor,
852 in line with the principles set out in accordance with exceptions under Article 81(4)(a) and (b). The
853 report should nonetheless identify the relevant clinical trials by their EU number and or protocol
854 number (for third country trials). Redacted and unredacted versions should be submitted to the
855 database but only the redacted version made public. No personal data of trial subjects should
856 appear.

857 **Question 17: Please comment on whether these proposals meet the**
858 **requirements and objectives of the Regulation.**

859 ***4.8. Clinical study reports submitted by the marketing-authorisation***
860 ***applicant/holder***

861 1. Clinical study reports including all appendices except those listing individual patient data, will be
862 submitted to the database by the marketing-authorisation applicant/holder and made public within
863 30 days after the day the marketing authorization has been granted, the procedure for granting
864 the marketing authorisation has been completed or the applicant has withdrawn the application.

865 2. The preparation of the content of the reports prior to being loaded into the system should be part
866 of separate guidance to be developed by the appropriate EU expert group, taking account of
867 considerations on what may constitute commercially confidential information, and their redaction,
868 published by the EMA in its Policy 70 on access to clinical study data, and need not be set out here
869 as it is not necessary to the structure of the EU database and therefore need not be specified in the
870 functional specifications.

871 **Question 18: Please comment on whether these proposals meet the**
872 **requirements and objectives of the Regulation.**

873 **5. Proposed addendum to the “Functional specifications for**
874 **the EU portal and EU database to be audited -**
875 **EMA/641479/2014”**

876 The following text including the part of Table 2 Section 4.3 will be revised following the consultation
877 and added to the “Functional specifications for the EU portal and EU database” as an addendum.

878 Below is the text to be added to Section 6 as published in the functional specification document, as an
879 addendum:

880 **“6. Functional Specifications to be audited (addendum)**

881 The functional specifications of the EU portal and the EU database and associated workspace are
882 outlined below and are considered necessary to enable the EU portal and the EU database to be fully
883 functional.

884 In accordance with the Regulation, the EU database shall be publicly accessible unless, for all or part of
885 the data and information contained therein, confidentiality is justified on any of the grounds outlined in
886 Article 81(4).

887 **Additional principles and details to apply based on the outcome of this consultation should**
888 **be inserted here describing application of the exceptions, to the rule that the database**
889 **content is public, set out in Article 81(4).**

890 Any type of document/data that fall under the grounds for exception described in Article 81(4) of the
891 Regulation will not be made publicly available, or only after a particular event/timeframe has
892 occurred/elapsed.”

893

894 **Below is the text to be added to Table 2 Section 4.3 as previously published in the functional**
895 **specification document, as an addendum:**

4.3	Publication of CT data and information	<p>The clinical trial data and information is to be made publicly available through a publication module of the database according to detailed rules to be defined taking into consideration the workflow of the trial.</p> <p>The rules are to be automated and implemented through the publication module of the database.</p> <p>The publication of clinical trial related documents and/or information will be an automatic process operated in accordance with predefined rules and criteria, set out in the present document, with no manual intervention and taking into consideration the workflow of the trial and its status.</p> <p>A manual override will be made available to enable publication in exceptional circumstances where an overriding public interest applies, as provided in the Regulation. The override may also be used to remediate errors where information has been published contrary to the established rules, or where data processing errors have occurred.</p> <p>The system should identify all data and documents in the EU database regarding their public or non-public status and any timeframe/event to trigger that publication, and include the necessary rules to ensure their availability at the required time. For each data field (or set of related fields) or document the system will have metadata and rules to support their publication status and timing publication.</p> <p>For each of these sets of information the database will have a structure to contain a document (or data such as names and addresses in the case of the investigator/trial sites list, sponsors etc.), but the content of the related documents should be defined outside of the design of the database and taking into account whether or not the information should be made public. The appropriate expert group of the EU should develop guidance and/or templates for the content of documents to be included in the database.</p> <p>The IMPD should be structured to enable each section (Q, S, E) to be separate and have different publication rules applied to each.</p> <p>The protocol synopsis and protocol should be separate and have different publication rules applied to each.</p> <p>The application form will contain questions that will provide data points on which to base certain of the publication rules, which are not driven by other actions or data in the database. These questions (to be adjusted based on the final outcome of the consultation on publication rules) will include items such as:</p> <ol style="list-style-type: none">1. Does the trial have a therapeutic (or prophylactic) intent?2. Does the active substance appear in any marketing authorisation already granted in the EU?
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3. Does the indication(s) under study in this trial appear in any marketing authorisation already granted in the EU for that active substance?
4. Do the formulation(s)/route(s) of administration appear in any marketing authorisation already granted in the EU for that active substance?
5. Is this trial being carried out for commercial purposes?
6. If this trial is not being carried out for commercial purposes can the study specific (protocol etc.) and product/active substance specific (IMPD (S&E sections), IB etc.) be released at the time of the decision on the trial?
7. What is the phase of the trial?
8. Additional questions as required.

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Question 19: Please comment on whether the proposed addendum to the functional specifications meets the requirements and objectives of the Regulation.

899

900 **Appendices:**

901 The appendices are to be added describing the data and documents that may be made public and
902 when. They can be accessed at the following [link](#).

903 **NB These appendices are provided for indicative purposes**
904 **only to illustrate how the implementation of these proposals**
905 **might work and will be further refined as the data model for**
906 **the database is refined.**

907 Appendix 1: The clinical trial application form, and those elements considered to be the “major
908 characteristics of the trial”, as referred to in Recital 68 including WHO ICTRP data elements.

909 Appendix 2: The contents of the clinical trial initial application dossier.

910 Appendix 3: The contents of the clinical trial substantial modification application dossier.

911 Appendix 4: Other data and documents submitted to the database.

912 Appendix 5: The summary of results of the trial.

913 Appendix 6: The laypersons summary of the trial.

914 Appendix 7: The clinical study report including its appendices.