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4 Reflection paper on ethical and GCP aspects of clinical  
5 trials of medicinal products for human use conducted in  
6 third countries and submitted in marketing authorisation  
7 applications to the EMA

8 Draft

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## 16 **Table of contents**

17	<b>1. Glossary .....</b>	<b>4</b>
18	<b>2. Introduction .....</b>	<b>5</b>
19	<b>3. Clarification of the practical application of ethical standards for clinical</b>	
20	<b>trials on medicinal products for human use in the context of the European</b>	
21	<b>Medicines Agency activities .....</b>	<b>7</b>
22	3.1. Local ethics committee and national regulatory authority oversight .....	8
23	3.2. Information/Consent procedure.....	11
24	3.3. Confidentiality .....	13
25	3.4. Fair compensation.....	15
26	3.5. Vulnerable populations.....	16
27	3.6. Placebo and active comparator.....	18
28	3.7. Access to treatment post trial .....	19
29	3.8. Applicability of data to EEA population.....	21
30	<b>4. Determine the practical steps to be undertaken during the provision of</b>	
31	<b>guidance and advice in the drug development phase .....</b>	<b>22</b>
32	4.1. Assessment of therapeutic needs in the EEA and relationships with its drug development	
33	plan.....	23
34	4.2. Issues related to feasibility of clinical trials .....	24
35	4.3. General measures to assure data quality when conducting trials outside the EU .....	24
36	4.4. Considerations for designing clinical trials: .....	25
37	<b>5. Determine the practical steps to be undertaken during the marketing</b>	
38	<b>authorisation phase.....</b>	<b>26</b>
39	5.1. Points to consider during the assessment process: identify assessment issues and	
40	processes .....	26
41	5.2. Inspections: Triggers for inspection to be identified by assessor.....	28
42	5.3. Actions available in response to non compliance .....	30
43	5.4. Transparency, including improvement of EPAR content and consistency .....	32
44	<b>6. International cooperation in the regulation of clinical trials, their review</b>	
45	<b>and inspection and capacity building in this area .....</b>	<b>34</b>
46	6.1. Identification of priorities .....	35
47	6.2. Identification of opportunities and partners.....	36
48	6.2.1. Identification of other initiatives .....	36
49	6.2.2. Categories of initiatives and actions .....	36
50	6.2.3. Establishment of contact with key initiatives.....	37
51	6.3. Action plan.....	37

52	6.3.1. Core activities .....	37
53	6.3.2. Short Term activities: .....	38
54	6.3.3. Long Term activities: .....	39
55	6.4. Resource considerations.....	40
56	6.5. Example of initiatives.....	40
57	<b>7. Regulatory action overview .....</b>	<b>42</b>
58	7.1. Clarify the practical application of ethical standards for clinical trials, in the context of	
59	EMA activities .....	42
60	7.1.1. Local Ethics Committee and national Regulatory Authority oversight .....	42
61	7.1.2. Information/Consent Procedure .....	42
62	7.1.3. Confidentiality.....	43
63	7.1.4. Fair Compensation.....	43
64	7.1.5. Vulnerable populations .....	43
65	7.1.6. Placebo and Active Comparator .....	44
66	7.1.7. Access to treatment post trial.....	44
67	7.2. Determine the practical steps undertaken during the provision of guidance and advice in	
68	the drug development phase. ....	44
69	7.3. Determine the practical steps to be undertaken during the Marketing Authorisation	
70	phase .....	45
71	7.3.1. Points to consider during the assessment process: identify assessment issues and	
72	processes .....	45
73	7.3.2. Inspections: triggers for inspection to be identified by assessor.....	45
74	7.3.3. Actions available in response to non compliance .....	45
75	7.3.4. Transparency, including improvement of EPAR content and consistency .....	45
76	7.4. International cooperation in the regulation of clinical trials their review and inspection	
77	and capacity building in this area .....	46
78	7.4.1. Identification of Priorities.....	46
79	7.4.2. Identification of Opportunities and partners.....	46
80	7.4.3. Action Plan .....	46
81	7.4.4. Resource considerations .....	46
82	<b>8. References .....</b>	<b>47</b>
83		

84 **1. Glossary**

85 AR, Assessment Report

86 COE, Council of Europe

87 CHMP, Committee for Medicinal Products for Human Use

88 COMP, Committee for Orphan Medicinal Products

89 EEA, European Economic Area

90 EMA, European Medicines Agency

91 EPAR, European Public Assessment Report

92 GCP, Good Clinical Practice

93 ICH, International Conference on Harmonization

94 IMP, Investigational Medicinal Product

95 MAA, Marketing Authorisation Application

96 NGOs, Non-governmental organisations

97 PDCO, Paediatric Committee

98 SAE, Serious Adverse Event

99 SAG, Scientific Advisory Group

100 Third Country. In this document the term "Third Country" means any country that is not a member  
101 state of the European Union or European Economic Area.

## 103 2. Introduction

104 The European Medicines Agency (EMA) is a decentralised body of the European Union. Its main  
105 responsibility is the protection and promotion of public and animal health, through the evaluation and  
106 supervision of medicines for human and veterinary use. The EMA is responsible for the scientific  
107 evaluation of applications for European marketing authorisation for medicinal products (centralised  
108 procedure). The EMA provides the Member States and the institutions of the EU the best-possible  
109 scientific advice on any question relating to the evaluation of the quality, safety and efficacy of  
110 medicinal products for human or veterinary use referred to it in accordance with the provisions of EU  
111 legislation relating to medicinal products. In addition article 58 of Regulation (EC) No. 726/2004  
112 provides that the European Medicines Agency can give a scientific opinion, in the context of  
113 cooperation with the WHO, for the evaluation of certain medicinal products for human use intended  
114 exclusively for markets outside the EU. Such opinions are drawn up by the Committee for Medicinal  
115 Products for Human Use (CHMP), following a review of the Quality, Safety and Efficacy data, analogous  
116 to the review undertaken via the centralised procedure, after consultation with the WHO. The  
117 standards applicable to both types of application (MAA or Article 58 Opinion) are the same and set out  
118 in Annex 1 to Directive 2001/83/EC.

119 In the context of this document the term "Third Countries" means countries that are not member  
120 states of the European Union/European Economic Area (EEA).

121 The revisions to the pharmaceutical legislation which came into place in 2004 increased emphasis on  
122 the ethical standards required of clinical trials conducted outside the European Economic Area (EEA)  
123 and included in Marketing Authorisation Applications (MAAs) submitted in the EEA for medicinal  
124 products for human use. The number of patients recruited in countries outside of the EEA is substantial  
125 (<http://www.ema.europa.eu/Inspections/GCPgeneral.html>). Some clinical trials are conducted across  
126 several regions, including Europe, whereas many others are conducted solely outside of the EEA.

127 Regulation (EC) No EC/726/2004 states in recital 16:

128 "There is also a need to provide for the ethical requirements of Directive 2001/20/EC of 4 April  
129 2001 of the European Parliament and of the Council on the approximation of the laws,  
130 regulations and administrative provisions of the Member States relating to the implementation  
131 of good clinical practice in the conduct of clinical trials on medicinal products for human use to  
132 apply to medicinal products authorised by the Community. In particular, with respect to clinical  
133 trials conducted outside the Community on medicinal products destined to be authorised within  
134 the Community, at the time of the evaluation of the application for authorisation, it should be  
135 verified that these trials were conducted in accordance with the principles of good clinical  
136 practice and the ethical requirements equivalent to the provisions of the said Directive."

137 Paragraph §8 of the Preamble – Introduction and General Principles of Annex 1 to Directive  
138 2001/83/EC states:

139 "All clinical trials, conducted within the European Community, must comply with the  
140 requirements of Directive 2001/20/EC of the European Parliament and of the Council on the  
141 approximation of the laws, regulations and administrative provisions of the Member States  
142 relating to the implementation of good clinical practice in the conduct of clinical trials on  
143 medicinal products for human use. To be taken into account during the assessment of an  
144 application, clinical trials, conducted outside the European Community, which relate to  
145 medicinal products intended to be used in the European Community, shall be designed,  
146 implemented and reported on what good clinical practice and ethical principles are concerned,  
147 on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They

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148 shall be carried out in accordance with the ethical principles that are reflected, for example, in  
149 the Declaration of Helsinki.”

150 The EMA Work Programme for 2008 ([http://www.ema.europa.eu/pdfs/general/direct/emeawp/](http://www.ema.europa.eu/pdfs/general/direct/emeawp/EMEA_Work_Programme_2008_full.pdf)  
151 [EMEA\\_Work\\_Programme\\_2008\\_full.pdf](http://www.ema.europa.eu/pdfs/general/direct/emeawp/EMEA_Work_Programme_2008_full.pdf)) set out a number of objectives relating to the acceptance, in  
152 MAAs submitted to the EMA, of clinical trials conducted in countries outside the EEA on medicinal  
153 products for human use. All such trials are required to meet internationally agreed ethical and data  
154 quality standards. These objectives need to be built into the process of clinical development. They  
155 need to be addressed before and during the conduct of the clinical trials and not only by assessment  
156 and inspection at the time of MAA by which point the trials have been completed, in some cases  
157 several years earlier.

158 Actions to meet this objective therefore need to encompass EMA processes having an impact on clinical  
159 trials commencing prior to early phase clinical development. These processes include development of  
160 guidelines, Scientific Advice, Orphan Product Designation and Paediatric Investigation Plans and  
161 continue through to the finalisation of the CHMP opinion on the MAA, and post-authorisation activities.

162 In Dec 2008 the EMA published a strategy paper “Acceptance of clinical trials conducted in third  
163 countries for evaluation in Marketing Authorisation Applications” ([http://www.ema.europa.eu/](http://www.ema.europa.eu/Inspections/docs/22806708en.pdf)  
164 [Inspections/docs/22806708en.pdf](http://www.ema.europa.eu/Inspections/docs/22806708en.pdf)) outlining four areas for action. These are:

- 165 1. Clarify the practical application of ethical standards for clinical trials, in the context of European  
166 Medicines Agency activities.
- 167 2. Determine the practical steps undertaken during the provision of guidance and advice in the drug  
168 development phase.
- 169 3. Determine the practical steps to be undertaken during the Marketing Authorisation phase
- 170 4. International cooperation in the regulation of clinical trials, their review and inspection and capacity  
171 building in this area.

172 In 2009 the EMA established a Working Group on third country clinical trials on medicinal products for  
173 human use. This working Group has been asked to develop practical proposals for tasks and  
174 procedures or guidance to address the four action areas set out above. The present document reflects  
175 the results of the discussion of this Working Group.

176 The best approach to achieving these objectives is to ensure that a robust framework exists for the  
177 oversight and conduct of clinical trials, no matter where in the world the clinical investigators’ sites are  
178 located and patients recruited. An international network of regulators from all countries involved,  
179 working together to share best practices, experiences and information and working to standards  
180 agreed and recognized by all, can provide an effective platform for such a robust framework. The EMA  
181 will seek to build and extend its relationship with regulators in all part of the world and with  
182 international organisations in order to work to achieve this.

183 The Reflection Paper highlights and emphasizes the need for cooperation between Regulatory  
184 Authorities involved in the supervision of clinical trials and the need to extend and link networks to  
185 support these activities.

186 The specific scope of this Reflection Paper extends to clinical trials conducted in third countries and  
187 submitted in marketing authorisation applications to the EMA in respect of medicinal products for  
188 human use.

### 3. Clarification of the practical application of ethical standards for clinical trials on medicinal products for human use in the context of the European Medicines Agency activities

For the purpose of research, three ethical principles should be adhered to: a) respect for persons, b) beneficence/non-maleficence and c) justice, where respect for persons includes the respect for autonomy and the protection of dependent and vulnerable persons, beneficence/non-maleficence is defined as the ethical obligation to maximize benefits and to avoid or minimize harms, and justice is a fair distribution of the burdens and benefits of research<sup>1</sup>.

*“The rights safety and wellbeing of the trials subjects are the most important consideration and should prevail over the interests of science and society”.*<sup>2</sup>

Clinical trials conducted in third countries and used in Marketing Authorisation Applications in the EEA or in applications for a Scientific Opinion under article 58 of the Regulation (EC) No. 726/2004, must be conducted on the basis of principles equivalent to the ethical principles and principles of good clinical practice applied to clinical trials in the EEA<sup>3</sup>.

Ethical principles have been established mainly by intergovernmental organisations such as the Council of Europe or WHO, or by professional bodies such as the World Medical Association, as well as in national or regional legislation or guidance. The latter often refer directly or indirectly to the internationally established principles.

Ethical principles governing the conduct of clinical trials in the EEA are set out in the Charter of Fundamental Rights of the European Union (2000)<sup>i</sup> the Council of Europe’s Convention on Human Rights and Biomedicine (1997)<sup>ii</sup> and its Additional Protocol on Biomedical Research (2005)<sup>iii</sup>, the Universal Declaration of Human Rights (1948)<sup>iv</sup>, the Convention for the protection of Human Rights and fundamental Freedoms (1950)<sup>v</sup>, the United Nations’ Convention on the Rights of the Child (1989)<sup>vi</sup>, the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005)<sup>vii</sup>, the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997)<sup>viii</sup>, the International Declaration on Human Genetic Data (UNESCO, 2003)<sup>ix</sup>, the CIOMS-WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects (Geneva 2002)<sup>x</sup>, the Declaration of Helsinki of the World Medical Association (2008)<sup>xi</sup>, Opinion 17 of the European Group on Ethics (2003)<sup>xii</sup> and the EU Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (2008)<sup>xiii</sup>. Practical steps to implement ethical requirements are set out in the CPMP/ICH/135/95 guideline on Good Clinical Practice (1995) (ICH E6)<sup>xiv</sup> and ICH E11 Note for guidance on clinical investigation of medicinal products in the paediatric population (2001)<sup>xv</sup>.

The European pharmaceutical legislation sets out the ethical requirements for the conduct of clinical trials in Directive 2001/20/EC<sup>xvi</sup>, Directive 2005/28/EC<sup>xvii</sup> and Directive 2001/83/EC<sup>xviii</sup>. Provisions of the European Paediatric Regulation 1901/06/EC are equally taken into consideration<sup>xix</sup>.

Provisions for the protection of personal data are laid down in Directive 1995/46/EC<sup>xx</sup>,

The extent to which these various documents pertinent to clinical trials (both legal and ethical instruments) are taken into account in National or regional legislation within or outside EU is variable. They overlap in many areas, but some given greater precision on certain points whilst on others there

1 WHO (CIOMS) Guidelines 2

2 Paragraph 2.3 of ICH-E6

3 Paragraph 8 of the Preamble of Annex 1 to Directive 2001/83/EC

230 are differences in approach. The aim of the present document is not to establish a new, additional, set  
231 of principles but rather to describe how the regulatory processes of the EMA can take these into  
232 account in a practical way.

### 233 **3.1. Local ethics committee and national regulatory authority oversight**

234 Most countries now have a regulatory authority to which application should be made before a clinical  
235 trial may commence. These requirements must be met in each country in which a clinical trial is  
236 conducted. It is an important element of international cooperation that regulators support compliance  
237 with local requirements in each country as well as reinforcing international ethical and good clinical  
238 practice standards.

239 In every case the trial must receive a positive opinion or approval from an ethics committee with  
240 appropriate jurisdiction for the investigator sites and trial concerned.

241 Research may only be undertaken if the research project has been approved by an ethics committee  
242 (or other bodies authorised to review clinical research on human beings) after independent  
243 examination of its scientific merit, including assessment of the importance of the aim of research, and  
244 multidisciplinary review of its ethical acceptability.<sup>4</sup> Ethics committees have to be pluralist,  
245 multidisciplinary and independent.<sup>5</sup>

246 *"Ethical review committees may be created under the aegis of national or local health administrations,  
247 national (or centralised) medical research councils or other nationally representative bodies".<sup>6</sup>*

248 The ethics committee must be independent of the research team and sponsor, and any direct financial  
249 or other material benefit they may derive from the research should not be contingent on the outcome  
250 of their review<sup>7</sup>, and should be declared.

251 All the information which is necessary for the ethical assessment of the research project shall be given  
252 in written form to the ethics committee.<sup>8</sup> The ethics committee, in preparing its opinion shall consider  
253 amongst others the points set out in art. 3, 4, 5 and 6 of the Directive 2001/20/EC, the Appendix to  
254 the Additional protocol on biomedical research (COE- Information to be given to the ethics committee),  
255 and chapters 2 and 3 of ICH E 6 and WHO (CIOMS) guidelines 2. The ethics committee must be  
256 satisfied that no undue influence, including that of a financial nature (or limiting or increasing access to  
257 medical care), will be exerted on persons to participate in research. In this respect, particular attention  
258 must be given to vulnerable or dependent persons.<sup>9</sup>

259 The ethics committee shall give clearly stated reasons for its positive or negative conclusions.<sup>10</sup>

260 *"The ethics committee should also check that the content of the protocol is scientifically sound with  
261 respect to paediatric subjects protection<sup>11</sup>. "No change to the protocol may be made without  
262 consideration and approval by the ethics committee".<sup>12</sup> Directive 2001/20/EC specifies this should*

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4 Art. 6 (2) and Art. 9 (2) of Directive 2001/20/EC, Art.9 and 10 Additional Protocol on biomedical research (COE), Paragraph 15 of Declaration of Helsinki, WHO (CIOMS) guidelines 2.

5 Art.19 International Declaration on Bioethics (UNESCO); ICH E6 paragraphs 1.27 and 3

6 WHO (CIOMS) guideline 2.

7 WHO (CIOMS) guideline 2.

8 Art. 11 of Additional Protocol on biomedical research (COE).

9 Art.12 of Additional Protocol on biomedical research (COE).

10 Art. 6 (5) of Directive 2001/20/EC; Art.9 Additional Protocol on biomedical research (COE) Explanatory report paragraph 42.

11 Paragraph 8.2 of EU Ethical Considerations for clinical trials on medicinal products conducted with the paediatric population

12 Paragraph 15 of Declaration of Helsinki



263 apply to substantial amendments.<sup>13</sup> Research projects shall be re-examined if this is justified in the  
264 light of scientific developments or events arising in the course of the research.<sup>14</sup>

265 *“The ethics committee must have the right to monitor ongoing studies”<sup>15</sup> “and to report to institutional*  
266 *or governmental authorities any serious or continuing non-compliance with ethical standards as they*  
267 *are reflected in protocols that they have approved or in the conduct of the studies”<sup>16</sup>.*

268 Where a clinical trial is to be conducted in countries that have limited frameworks for ethical review or  
269 regulatory oversight, the sponsor should consider submitting the study protocol for ethical and  
270 scientific review to an ethics committee(s) that operates within an established regulatory framework  
271 with ethical standards equivalent to those applying in the EU, in addition to doing to in the country  
272 concerned by the trial. This would be particularly relevant where the study design (e.g. choice of  
273 comparator) or the vulnerability of the proposed patient population might give rise to additional  
274 concerns. The deliberations and conclusions of that committee(s) should be made available to the local  
275 ethics committee and regulatory authority, making clear to what extent the committee has considered  
276 the location and circumstances in which the trial is to be conducted. Such an approach does not  
277 substitute for the need to apply to, and follow the requirements of, a local ethics committee or to  
278 submit to the regulatory authority of the country where the trial is to be conducted. The local ethics  
279 committee(s) and competent authority in the country where the trial is to be conducted should review  
280 the trial, ensuring that the proposed research is ethical, takes into account the local conditions, that  
281 the local sites are suitable and that circumstances and arrangements for the conduct of the research  
282 are appropriate for that country and the study population concerned. In multicentre studies, a central  
283 ethics committee could review the study from a scientific and ethical standpoint, and the local ethics  
284 committee could verify the practicability of the study in their communities, including the  
285 infrastructures, the state of training, and ethical considerations of local significance.<sup>17</sup> It should be  
286 remembered that ethical review in one country or region will usually be focussed on their own local  
287 conditions and requirements unless they have been specifically asked to consider other countries and  
288 have the knowledge, expertise and capacity to do so.

289 It should be clear that any ethics committee reviewing the trial at an international level, and the ethics  
290 committee(s) and the National Regulatory Authority in the country where the trial is to be conducted,  
291 should be able to withhold approval of research proposals. When there are objective grounds for  
292 considering that the conditions in the request for this authorisation are no longer met, or there is  
293 information raising doubts about the safety or scientific validity of the clinical trial, it should be possible  
294 to suspend or prohibit the trial notifying the sponsor thereof.<sup>18</sup>

295 The ethics committee in the country where the trial is to be conducted should have, as either members  
296 or consultants, persons with understanding of the community's customs and traditions.” *Such persons*  
297 *should be able, for example, to indicate suitable members of the community to serve as intermediaries*  
298 *between investigators and subjects and to advise on whether material benefits or inducements may be*  
299 *regarded as appropriate in the light of a community's gift-exchange and other customs and traditions”.*  
300 <sup>19</sup>

301 There should be assurance that the review is independent and that there is no conflict of interest that  
302 might affect the judgment of members of the ethics committee in relation to any aspect of the  
303 research. Any members with a special or particular, direct or indirect, interest in a proposal should not  
304 take part in its assessment if that interest could subvert the member's objective judgment.

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13 Art. 10 (a) of Directive 2001/20/EC

14 Art. 24 of Additional Protocol on biomedical research (COE)

15 Paragraph 15 of Declaration of Helsinki

16 WHO (CIOMS) guideline 2

17 WHO (CIOMS) Guideline 2.

18 Art. 12 of Directive 2001/20/EC

19 WHO (CIOMS) Guideline 3.

305 A declaration of possible conflict of interest should be provided by any of the ethics committee  
306 members.<sup>20</sup>

307 When the sponsor is an international organisation, its review of the research protocol must be in  
308 accordance with its own independent ethical-review procedures and standards and the research  
309 protocol should be submitted for ethical and scientific review in the country of the sponsoring  
310 organisation and the ethical standards applied should be no less stringent than they would be for  
311 research carried out in that country.<sup>21</sup>

312 National or local ethics committee should be so composed as to be able to provide complete and  
313 adequate review of the research proposals submitted to them. Membership should include physicians,  
314 scientists and other professionals such as nurses, lawyers, ethicists, clergy, as well as lay persons  
315 including patients' representatives, qualified to represent the cultural and moral values of the  
316 community and to ensure that the rights of the research subjects will be respected. *"When uneducated  
317 or illiterate persons form the focus of a study they should also be considered for membership or invited  
318 to be represented and have their views expressed"*<sup>22</sup>

319 Ethics committees shall include appropriate paediatric expertise or take advice in clinical, ethical and  
320 psychosocial problems in the field of paediatrics when reviewing protocols involving paediatric  
321 population. Similarly relevant expertise should be included where studies involve subjects with mental  
322 health disorders or other vulnerable populations. Paediatric expertise may be defined on the basis of  
323 education, training and experience on the various aspects of child development, ethics and  
324 psychosocial aspects as well as on the basis of the experience in paediatric care and direct experience  
325 of clinical trials with children. *"Expertise used should be documented and recorded by the ethics  
326 committee"*.<sup>23</sup>

#### 327 **Regulatory action/ action plan**

- 328 1. *Failure to submit a protocol to an independent ethics committee is a serious violation of ethical*  
329 *standards.*
- 330 2. *EU Competent authorities should refuse to consider data obtained in such an unethical manner,*  
331 *when submitted in support of a MAA in accordance with Directive 2001/83 EC or Regulation EC*  
332 *726/2004.*
- 333 3. *Requirements for submission to the national regulatory authority of each country in which the trial*  
334 *is conducted and to the ethics committee(s) in those countries must be complied with, and*  
335 *evidence of both submissions and approvals provided.*
- 336 4. *The applicant for a MAA should provide EU Competent Authorities with a summary of ethics*  
337 *committee, and National Regulatory Authority approvals of each clinical trial supporting the MAA.*  
338 *This information should form part of the clinical study report in accordance with ICH E3.*
- 339 5. *EU Competent Authorities should identify those studies that may give rise to special ethical*  
340 *concern (e.g. arising from their design, the local regulatory framework within which they are*  
341 *conducted, the vulnerability of the study subjects) and where applicable to seek additional*  
342 *assurance that the trials have been ethically conducted.*
- 343 6. *Where clear serious concerns are identified the EU competent Authority should communicate these*  
344 *concerns to the National Regulatory Authority of the Country (ies) concerned.*

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20 WHO (CIOMS) Guideline 2.

21 WHO (CIOMS) Guideline 3.

22 WHO (CIOMS) Guideline 2.

23 Art. 4 of Directive 2001/20/EC and Paragraph 8 of EU Ethical Considerations for clinical trials on medicinal products conducted with the pediatric population

### 345 **3.2. Information/Consent procedure**

346 Scientific research as well as any preventive, diagnostic or therapeutic medical intervention involving  
347 human subjects is only to be carried out with the prior, free, express, specific, documented and  
348 informed consent of the person concerned, based on adequate and comprehensible information<sup>24</sup>  
349 provided both in writing and orally. Furthermore, consent should, be given, and may be withdrawn, by  
350 the person concerned at any time and for any reason without disadvantage or prejudice.<sup>25</sup> *"Informed*  
351 *consent is documented by means of a written, signed and dated informed consent form"*.<sup>26</sup> Refusal to  
352 give consent or withdrawal of consent to participation in research shall not lead to any form of liability  
353 (particularly of a financial nature) and/or to any form of discrimination against the person concerned,  
354 in particular regarding the right to medical care<sup>27</sup>. The same level of care and information should be  
355 maintained during treatment or investigations.

356 The informed consent of each subject shall be renewed if there are significant changes in the  
357 conditions or procedures of the research or if new information becomes available that could affect the  
358 willingness of subjects to continue to participate, and in long-term studies at pre-determined intervals,  
359 even if there are no changes in the design or objectives of the research.<sup>28</sup>

360 In particular studies alternative ways of documenting the informed consent may need to be established  
361 as described below. For persons who are not capable of exercising autonomy, special measures are to be taken to  
362 protect their rights and interests. Research on a person without the capacity to consent (children, adults with severe  
363 mental disability,<sup>29</sup> or behavioural disorders<sup>30</sup> and research in emergency situations may be undertaken  
364 only if the necessary authorisation has been given specifically and in writing by the legal representative or an authority,  
365 person or body provided for by law and having received adequate information, taking into account the person's previously  
366 expressed wishes or objections.

367 An adult not able to consent shall as far as possible take part in the information/authorisation procedure.<sup>31</sup> In proportion to  
368 age and degree of maturity, the child should participate in the (informed) consent process together with the  
369 parents and provide assent. The process of informed consent should be conducted with enough time  
370 and at the same time as obtaining consent from the parent(s) or the legal representative, so that the  
371 informed consent reflects the presumed will of the minor or of the adults who don't have the capacity  
372 to consent. The information process provided to the child and the child's response should be  
373 documented. *"Strong and definitive objections from the child should be respected"*.<sup>32</sup>

374 *"If a subject is unable to read or if a legally acceptable representative is unable to read an impartial*  
375 *witness should be present during the entire informed consent discussion. After the written informed*  
376 *consent form and any other written information to be provided, is read and explained to the subject or*  
377 *the subject's legally acceptable representative, and after the subject or the subject's legally acceptable*  
378 *representative has orally consented to the subject's participation in the trial and, if capable of doing so,*

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24 Art.2 (j), art. 3.2 (b) and art. 4-5 of Directive 2001/20/EC; Art. 5-6, 16 (iv) (v)-17 of Convention on Human Rights and Biomedicine of the Council of Europe (COE); Art. 13-16 of Additional protocol on Biomedical research (COE), 2005; Art. 5 and 9 of Universal declaration on Human genome and Human Rights; Art. 8-9 of International Declaration on Human Genetic Data (2003); Paragraphs 22,24,26,27,28 and 29 of Declaration of Helsinki (2008); Art. 3 (2) of Charter of Fundamental Rights of the European Union (2000); Art. 5 of Universal Declaration on Bioethics and Human Rights (UNESCO, 2005); Paragraph 1.28 and 2.9 of ICH E6

25 Art. 3.2 (e) of Directive 2001/20/EC; Art. 6 of Universal Declaration on Bioethics and Human Rights (Unesco,2005); Art. 14 Additional Protocol on Biomedical research (COE), 2005

26 Art. 2 (j) of Directive 2001/20/EC; Paragraph 1.28 of ICH E6, 1995

27 Art. 14 section 2 of the Additional Protocol on Biomedical Research to the Convention on Human Rights and Biomedicine and section 80 of its Explanatory report

28 WHO(CIOMS) Guideline 6

29 Art. 3.2 (d), 4 and 5 of Directive 2001/20/EC; Art. 6 of Convention on Human Rights and Biomedicine of the Council of Europe (COE)

30 WHO (CIOMS) International guidelines n. 15

31 Art. 4 (a), (b) and (c) and art. 5 (a), (b) and (c) of Directive 2001/20/EC; Art. 14 and 15 of Additional protocol on Biomedical research (COE), 2005

32 Paragraphs 7- 7.2 of Ethical considerations for clinical trials on medicinal products conducted with the pediatric population.

379 *has signed and personally date the informed consent form, the witness should sign and personally date*  
380 *the consent form. By signing the consent form, the witness attests that the information in the consent*  
381 *form and any other written information was accurately explained to, and apparently understood by, the*  
382 *subject or the subject's legally acceptable representative, and that informed consent was freely given*  
383 *by the subject or the subject's legally acceptable representative*<sup>33</sup>. Mechanisms should be put in place  
384 to ensure that the trial subject has understood the information and process being entered into.

385 *"In appropriate cases of research carried out on a group of persons or a community, additional agreement of the legal*  
386 *representatives of the group or community concerned may be sought. In no case should a collective community agreement*  
387 *or the consent of a community leader or other authority substitute for an individual's informed consent*<sup>34</sup>. *"In some*  
388 *cultural context an investigator may enter a community to conduct or approach prospective subjects*  
389 *for their individual consent only after obtaining permission from a community leader, a council of*  
390 *elders, or another designated authority. Such customs must be respected. In no case, however, may*  
391 *the permission of a community leader or other authority substitute for individual informed consent*<sup>35</sup>

392 The consent process and the information provided should take into account the needs of persons who  
393 are unfamiliar with medical concepts and technology<sup>36</sup>. All documentation (information and  
394 consent/assent) must be written in a lay-friendly language, wording appropriate to age, psychological  
395 and intellectual maturity and must be designed to protect vulnerable and poorly educated subjects  
396 involved in research.

397 Sponsors and investigators should develop culturally appropriate ways to communicate information  
398 that is necessary for adherence to the standard required in the informed consent process. *"Also, they*  
399 *should describe and justify in the research protocol the procedure they plan to use in communicating*  
400 *information to subjects*<sup>37</sup>

401 *"For collaborative research in developing countries the research project should, if necessary, include*  
402 *the provision of resources to ensure that informed consent can indeed be obtained legitimately within*  
403 *different linguistic and cultural settings*<sup>38</sup>.

404 Where appropriate, a cultural mediator, familiar with medical terminology, independent from the  
405 sponsor and investigator, experienced in the language<sup>36</sup>, social habits, culture, traditions, religion and  
406 particular ethnic differences should be available to provide help in the process of obtaining informed  
407 consent, but should not consent on behalf of the subject.<sup>39</sup>

408 Nevertheless, cultural diversity and pluralism are not to be invoked to infringe upon human dignity, human rights and  
409 fundamental freedoms or to limit their scope.<sup>40</sup>

410 *"Sponsors and investigators have a duty to refrain from unjustified deception, undue influence, or*  
411 *intimidations*<sup>41</sup> *and "to renew the informed consent of each subject if there are significant changes in*  
412 *the conditions or procedures of the research or if new information becomes available that could affect*  
413 *the willingness of subjects to continue to participate"*<sup>42</sup>

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33 Paragraph 4.8.9 of ICH E6

34 Art. 6 of Universal Declaration on Bioethics and Human Rights (UNESCO, 2005)

35 WHO (CIOMS) Guideline 4

36 WHO (CIOMS) Guideline 4

37 WHO(CIOMS) Guideline 4

38 WHO (CIOMS) Guideline 4

39 Paragraph 6.3 of Ethical considerations for clinical trials on medicinal products conducted with the pediatric population

40 Art. 12 of Universal Declaration on Bioethics and Human Rights (UNESCO, 2005)

41 WHO (CIOMS) Guideline 6

42 WHO (CIOMS) Guideline 4 and 6

416 **Regulatory action/ action plan:**

- 417 1. *Failure to obtain informed consent (and/or assent where applicable) is a serious violation of ethical*  
418 *standards.*
- 419 2. *EU Competent Authorities should refuse to consider data obtained in such an unethical manner,*  
420 *when submitted in support of a MAA in accordance with Directive 2001/83 EC or Regulation EC*  
421 *726/2004.*
- 422 3. *The applicant for a MAA should provide EU drug regulatory authorities with a summary of the*  
423 *consent processes used and any variations of those processes in the clinical trials supporting the*  
424 *MAA. and include sample information sheets on consent forms. This information should form part*  
425 *of the clinical study report in accordance with ICH E3.*
- 426 4. *EU Competent Authorities should identify those studies that may give rise to special ethical*  
427 *concern regarding the consent process (e.g. arising from the patient population included and their*  
428 *capacity to provide informed consent, the regulatory framework within which they are conducted,*  
429 *the vulnerability of the study subjects) and where applicable to seek additional assurance that*  
430 *consent was properly obtained.*
- 431 5. *Additional good practice guidelines on the communication of the information to the potential*  
432 *participants in research may be required to better describe some research situations and should be*  
433 *developed, with input from patients' organisations and community groups as well as other experts*  
434 *in ethics and clinical trials.*

435 **3.3. Confidentiality**

436 Any information of a personal nature collected during biomedical research shall be considered as  
437 confidential and treated according to the rules relating to the protection of individuals with regard to  
438 the processing of personal data<sup>43</sup>.

439 *"To the greatest extent possible, such information should not be used or disclosed for purposes other*  
440 *than those for which it was collected or consented to, consistent with international law, in particular*  
441 *international human rights law".<sup>44</sup>*

442 Any participant in research shall be entitled to know any information collected on his/her health. Other  
443 personal information collected for a research project will be accessible to him/her in conformity with  
444 the applicable laws on the protection of individuals with regard to processing of personal data<sup>45</sup>.

445 In accordance with European Directive 95/46/EC on the protection of individuals with regard to the  
446 processing of personal data and on the free movement of such data, data must be<sup>46</sup>: fairly and lawfully  
447 processed; processed for limited purposes; adequate; relevant and not excessive; accurate; not kept  
448 longer than necessary; processed in accordance with the data subject's rights; secure; not transferred  
449 to countries without adequate protection.

450 *"An investigator who proposes to perform genetic tests of known clinical or predictive value on*  
451 *biological samples that can be linked to an identifiable individual must obtain the informed consent of*  
452 *the individual or, when indicated, the permission of a legally authorised representative. Conversely,*  
453 *before performing a genetic test that is of known predictive value or gives reliable information about a*  
454 *known heritable condition, and individual consent or permission has not been obtained, investigators*

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43 Art. 3.2(c) of Directive 2001/20/EC

44 Art. 9 of Universal Declaration on Bioethics and Human Rights (UNESCO, 2005); art. 14 International Declaration of Human Genetic Data; art 8 Charter of fundamental rights of the European Union

45 Art. 26 of Additional Protocol on Biomedical research (COE), 2005

46 Art. 6 of Directive 95/46/EC

455 *must see that biological samples are fully anonymized and unlinked; this ensures that no information*  
456 *about specific individuals can be derived from such research or passed back to them".*<sup>47</sup>

457 If research gives rise to information of relevance to the current or future health or quality of life of  
458 research participants, this information must be offered to them. That shall be done within a framework  
459 of health care or specific counselling<sup>48</sup>, most of all in the case of predictive genetic tests. *"In*  
460 *communication of such information, due care must be taken in order to protect confidentiality and to*  
461 *respect any wish of a participant"* [including the minor and/or his/her legal representative] *"not to*  
462 *receive such information"*, in accordance with national law.<sup>49</sup>

463 *"During the process of obtaining informed consent the investigator should inform the prospective*  
464 *subjects about the precautions that will be taken to protect confidentiality".*<sup>50</sup>

465 The written information and informed consent form to be provided to subjects should include  
466 explanations:

467 a) of the extent to which the monitor(s), the auditor(s), the ethics committee and the regulatory  
468 authority(ies) will be granted direct access to the subject's original medical records for verification of  
469 clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent  
470 permitted by the applicable laws and regulations and that, by signing a written informed consent form,  
471 the subject or the subject's legally acceptable representative is authorising such access.

472 b) *"that records identifying the subject will be kept confidential and, to the extent permitted by the*  
473 *applicable laws and/or regulations, will not be made publicly available. If the results of the trial are*  
474 *published, the subject' identity will remain confidential".*<sup>51</sup>

475 Biobank sample retention and the need for consent to such use (and reuse) should be described in the  
476 protocol.

477 The trial documents should be archived for a duration that takes into consideration the potential need  
478 for long-term review of trials performed in children (long-term safety).

479 Where personal information is collected, stored, accessed, used, or disposed of, a researcher should  
480 ensure that the privacy, confidentiality and cultural sensitivities of the subject and/or the collectivity  
481 are respected, most of all when children are involved<sup>52</sup>.

482

483 **Regulatory action/ action plan:**

484 1. *EU Competent Authorities will refuse to consider reports which fail to properly protect the*  
485 *confidentiality of the trial subjects, when submitted in support of a MAA in accordance with*  
486 *Directive 2001/83 EC or Regulation No (EC) 726/2004. These reports should be returned to the*  
487 *applicant and the breaches of confidentiality rectified prior to eventual resubmission.*

488 2. *The applicant for a MAA should provide EU Competent Authorities with a summary of the steps*  
489 *taken to protect confidentiality and the consent obtained to enable the use of and access to the*  
490 *subjects' data. This information can form part of the clinical study report section on ethical*  
491 *considerations and informed consent in accordance with ICH E3.*

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47 WHO (CIOMS) Guideline 18

48 Art 27 of additional Protocol on Biomedical research (COE), 2005

49 Art. 10 of Convention on Human Rights and Biomedicine of the Council of Europe (COE); Art. 27 of Additional Protocol on Biomedical research (COE), 2005

50 WHO (CIOMS) Guideline 18

51 Paragraph 4.8.10 of ICH E6

52 Paragraph 18 of Ethical considerations for clinical trials on medicinal products conducted with pediatric population.

492 3. *EU Competent Authorities should identify those studies that may give rise to special concern*  
493 *regarding confidentiality (e.g. arising from the use of genetic information or bio banked samples)*  
494 *and where applicable seek additional assurance that confidentiality has been properly maintained.*

### 495 **3.4. Fair compensation**

496 Article 3.2 (f) of Directive 2001/20/EC requires that provision is made for insurance or indemnity.

497 Art 31 of the Additional Protocol on Biomedical research of Council of Europe states that "*The person*  
498 *who has suffered damage as a result of participation in research shall be entitled to fair compensation*  
499 <sup>53</sup> *according to the conditions and procedures prescribed by law*"

500 The WHO-CIOMS Guideline 19 recommends that research subjects who suffer injury as a result of their  
501 participation should be entitled to free medical treatment for such injury and to such financial or other  
502 assistance as would compensate them equitably for any resultant impairment, disability or handicap.  
503 In the case of death as a result of their participation, their dependants are entitled to compensation.

504 "*Subjects must not be asked to waive the right to compensation or required to show negligence or lack*  
505 *of a reasonable degree of skill on the part of the investigator in order to claim free medical treatment*  
506 *or compensation. The informed consent process or form should contain no words that would absolve*  
507 *an investigator [or sponsor] from responsibility in the case of accidental injury, or that would imply*  
508 *that subjects would waive their right to seek compensation for impairment, disability or handicap.*  
509 *Prospective subjects should be informed that they will not need to take legal action to secure the free*  
510 *medical treatment or compensation for injury to which they may be entitled. They should also be told*  
511 *what medical service or organisation or individual will provide the medical treatment and what*  
512 *organisation will be responsible for providing compensation".*<sup>54</sup>

513 Before the research begins, the sponsor, whether a pharmaceutical company or other organisation or  
514 institution, should agree to provide compensation for any physical injury for which subjects are entitled  
515 to compensation, or come to an agreement with the investigator concerning the circumstances in  
516 which the investigator must rely on his or her own insurance coverage (for example, for negligence or  
517 failure of the investigator to follow the protocol, or where government insurance coverage is limited to  
518 negligence). In certain circumstances it may be advisable to follow both courses.

519 "*Sponsors should provide insurance or should indemnify (legal and financial coverage) the*  
520 *investigator/the institution against claims arising from the trial, except for claims that arise from*  
521 *malpractice and/or negligence".*<sup>55</sup>

522 "*Both the informed consent discussion and the written informed consent form and any other written*  
523 *information to be provided to subjects involved in research should include explanations of the*  
524 *compensation and/or treatment available to the subject in the event of trial-related injury".*<sup>56</sup>

525 Information shall be provided to the ethics committee on details of any insurance, indemnity or  
526 compensation to cover damage arising in the context of the research project<sup>57</sup> (in particular "*provision*  
527 *for indemnity or compensation in the event of injury or death attributable to a clinical trial, and any*  
528 *insurance or indemnity to cover the liability of the investigator and sponsor").*<sup>58</sup>

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53 Art. 31 of Additional Protocol on Biomedical research (COE) 2005

54 WHO (CIOMS) Guideline 19

55 Paragraph 5.8 of ICH-E6

56 Paragraph 4.8.10 of ICH-E6

57 Art 11 juncto appendix of Additional Protocol on Biomedical research (COE)2005; Paragraph 3.1.2 of ICH-E6.

58 Art. 6.3 (h) and (i) of Directive 2001/20/EC

529 In preparing its opinion, the ethics committee (and where required the National Regulatory Authority)  
530 should consider these provisions<sup>59</sup> and should pay careful attention to waivers of liability in the  
531 insurance contract, in particular with respect generally to long term effects and on development for  
532 children included in research. However, *“unrecognised congenital defects are generally excluded”*.<sup>60</sup>

### 533 **Regulatory action/action plan**

- 534 1. Failure to provide fair compensation by insurance or indemnity is a serious violation of ethical  
535 standards
- 536 2. The applicant for a MAA should provide EU Competent Authorities with a summary of the  
537 provisions made to provide for the fair compensation of subjects for trial related injury. This  
538 information can form part of the clinical study report section on ethical considerations and informed  
539 consent in accordance with ICH E3.
- 540 3. EU Competent Authorities should identify those studies that may give rise to special concern  
541 regarding insurance, indemnity or compensation for research related injury and where applicable  
542 to seek additional assurance that trial subjects' interest have been protected.

### 543 **3.5. Vulnerable populations**

544 “Vulnerability” is defined as susceptibility of being wounded. Vulnerability is applied both to individuals  
545 and to populations. *“Vulnerable persons are those who are relatively (or absolutely) incapable of*  
546 *protecting their own interests”*,<sup>61</sup> that means *“individuals whose willingness to volunteer in a clinical*  
547 *trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with*  
548 *participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to*  
549 *participate”*<sup>62</sup> *“More formally, vulnerable persons may have insufficient power, intelligence, education,*  
550 *resources, strength, or other needed attributes to protect their own interests”*<sup>63</sup>

551 Example of vulnerable subjects are patients with incurable diseases, persons in nursing homes,  
552 unemployed or impoverished persons, patients in emergency situations, homeless persons, nomads,  
553 refugees, prisoners, minor and those incapable of giving consent. Other groups or classes may also be  
554 considered vulnerable (e.g. elderly persons, people receiving welfare benefits or social assistance some  
555 ethnic and racial minority groups and individuals who are politically powerless). *“Vulnerable subjects*  
556 *include “members of a group with a hierarchical structure, such as medical, pharmacy, dental, and*  
557 *nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical*  
558 *industry, members of the armed forces, and persons kept in detention”*.<sup>64</sup> *“Persons who have serious,*  
559 *potentially disabling or life-threatening diseases are highly vulnerable”*.<sup>65</sup>

560 *“Children represent a vulnerable population with developmental, physiological and psychological*  
561 *differences from adults, which make age- and development- related research important for their*  
562 *benefit”*.<sup>66</sup> Clinical research on children should be ethical and of high quality and should be carried out  
563 under conditions affording the best possible protection for these subjects, without subjecting paediatric  
564 population to unnecessary trials.<sup>67</sup> To this aim an application for Marketing Authorisation for medicinal  
565 products be regarded as valid only if requirements of the article 7 of Regulation No (EC) 1901/2006 on  
566 medicinal products for paediatric use are complied with.

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59 Art. 6.3 of Directive 2001/20/EC

60 Paragraph 22 of Ethical considerations for clinical trials on medicinal products conducted with paediatric population.

61 WHO (CIOMS) Guideline 13

62 Paragraph 1.61 of ICH-E6,

63 WHO (CIOMS) Guideline 13

64 Paragraph 1.61 of ICH-E6

65 WHO (CIOMS) Guideline 13

66 Recital 3 of Directive 2001/20/EC

67 Recital 4 and art. 1 of Regulation EC/1901/2006 and art. 4 of Directive 2001/20/EC.



567 Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the  
568 institutionalized may continually be sought as research subjects, owing to their ready availability in  
569 settings where research is conducted, or the conditions they suffer from (e.g. renal insufficiency).  
570 *"Given their dependent status and their frequently compromised capacity for free consent, they should*  
571 *be protected against the danger of being involved in research solely for administrative convenience, or*  
572 *because they are easy to manipulate as a result of their illness or socioeconomic condition".*<sup>68</sup>

573 To the extent that these and other classes of people have attributes resembling those of classes  
574 identified as vulnerable, the need for special protection of their rights and welfare should be reviewed  
575 and applied, where relevant. *"Medical research involving a disadvantaged or vulnerable population or*  
576 *community is only justified if the research is responsive to the health needs and priorities of this*  
577 *population or community and if there is a reasonable likelihood that this population or community*  
578 *stands to benefit from the results of the research".*<sup>69</sup>

579 Chapter V of the Additional protocol on Biomedical Research of the Council of Europe titled "Protection  
580 of persons not able to consent to research Chapter" discusses research in certain populations where  
581 particular vulnerabilities exist – in particular in articles 15 (Protection of persons not able to consent to  
582 research), 18 (Research during pregnancy or breastfeeding) and 20 (Research on persons deprived of  
583 liberty). Research should only be undertaken in such groups when particular conditions are met.

584 Such consideration include whether the results of the research have the potential to produce real and  
585 direct benefit to the trial subject (or to that of the embryo, foetus or child after birth in the case of  
586 pregnant women), whether research of comparable effectiveness cannot be carried out on individuals  
587 capable of giving consent (or on women who are not pregnant, or on persons who are not deprived of  
588 liberty), whether the person undergoing research has been informed of his or her rights and the  
589 safeguards prescribed by law for his or her protection, unless this person is not in a state to receive  
590 the information, whether the necessary authorisation has been given specifically and in writing by the  
591 legal representative, and the person (or pregnant woman) concerned does not object.

592 Exceptionally and under the protective conditions prescribed by law, where the research may not have  
593 the potential to produce results of direct benefit to the health of the person concerned, such research  
594 may be authorised, if it can contribute to the benefit of the group concerned whilst fulfilling the other  
595 conditions described above. The research should have the aim of contributing, through significant  
596 improvement in the scientific understanding of the individual's condition, disease or disorder, to the  
597 ultimate attainment of results capable of conferring benefit to the person concerned or to other  
598 persons in the same age category or afflicted with the same disease or disorder or having the same  
599 condition (or conferring benefit to other women in relation to reproduction or to other embryos,  
600 foetuses or children, or benefit to persons deprived of liberty) The research should entail only minimal  
601 risk and minimal burden for the individual concerned; and any consideration of additional potential  
602 benefits of the research shall not be used to justify an increased level of risk or burden.

603 Benefit for the group (e.g. children affected by the same disease, or a disease which shares similar  
604 features and for which the medicinal product could be of benefit) could be defined by increased  
605 knowledge of the condition and/or treatment, which would eventually result in better diagnosis,  
606 treatment or prevention.

607 *"Measures of such benefit would include the importance of knowledge gained, severity of the issue to*  
608 *be addressed, commonality of the issue, likelihood of obtaining results from proposed research, and*  
609 *usefulness of benefits obtained".*<sup>70</sup>

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68 Belmont Report: ethical principles and guidelines for the protection of human subjects of research, Section D 3.

69 Art. 17 of Declaration of Helsinki (2008).

70 Paragraph 12 of Ethical considerations for clinical trials on medicinal products conducted with pediatric population

610 In addition vulnerable subjects should not be recruited into a trial where this was not explicitly  
611 foreseen in the trial protocol or other information provided to and approved by the ethics committee.  
612 Any special consent procedures or other precautions required should have been explicitly described to  
613 the ethics committee and approved by them.

614 The decision to include vulnerable subjects in a trial should be fully justified by the sponsor.

615 **Regulatory action/action plan:**

- 616 1. *The inclusion of vulnerable subjects in a clinical trial without the approval of the ethics committee*  
617 *and without implementation of the appropriate consent processes is a serious violation of ethical*  
618 *standards.*
- 619 2. *EU Competent Authorities should refuse to consider data obtained in such an unethical manner,*  
620 *when submitted in support of a MAA in accordance with Directive 2001/83 EC and Regulation No (*  
621 *EC) 726/2004.*
- 622 3. *The applicant for a MAA should provide drug regulatory authorities with an adequate and*  
623 *appropriate justification for inviting vulnerable individuals or groups to serve as research subjects*  
624 *and the description of the specific measures and means implemented to protect their rights and*  
625 *welfare. This information can form part of the clinical study report in accordance with ICH E3.*
- 626 4. *EU Competent Authorities should identify those studies that may give rise to special ethical*  
627 *concern regarding the inclusion of vulnerable populations and where applicable to seek additional*  
628 *assurance that the inclusion of such populations was justified and their rights and welfare*  
629 *protected.*

630 **3.6. Placebo and active comparator**

631 “Research shall neither delay nor deprive trial participants of medically necessary preventive,  
632 diagnostic or therapeutic procedures”.<sup>71</sup> A clinical trial cannot be justified ethically unless it is capable  
633 of producing scientifically reliable results. “In some circumstances it may be acceptable to use an  
634 alternative comparator, such as placebo or “no treatment”,<sup>72</sup> whilst taking into account that “the  
635 rights, safety and wellbeing of the trials subjects are the most important considerations and should  
636 prevail over the interests of science and society”.<sup>73</sup>

637 The use of placebo is permissible in accordance with principles foreseen in the Directive 2001/20/EC,  
638 Directive 2005/28/EC, the WHO (CIOMS) Guidelines 8 and 11, paragraph 32 of the Declaration of  
639 Helsinki (2008), article 23 of the Additional Protocol on Biomedical Research of the Council of  
640 Europe(2005), paragraph 2.1; 2.2; 2.3 and 2.12 of the Note for Guidance on Good Clinical Practice  
641 (CPMP/ICH/135/95), paragraphs 9.2.1 and 9.2.3 of the guideline on ethical considerations for clinical  
642 trials on medicinal products conducted with the paediatric population (2008) and ICH E10 (Choice of  
643 Control Group). The CPMP position statement on the use of placebo in clinical trials (28 June 2001  
644 EMEA/17424/01) should also be taken into account.<sup>74</sup>

645 Studies carried out in third countries should meet the same ethical principles and standards applied to  
646 studies performed in the EEA. Derogation from these principles should not be accepted in particular in  
647 the context of the marketing authorisation procedure.

648 EU Competent Authorities should neither require nor expect study designs, involving placebo or other  
649 comparator, which would not be ethically acceptable in the EEA.

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71 Article 23 of Additional protocol on biomedical research (COE), 2005

72 WHO (CIOMS) Guideline 11

73 Paragraph 2.3 of ICH-E6

74 <http://www.ema.europa.eu/pdfs/human/press/pos/1742401en.pdf>

650 “Economic [or logistical] reason for the unavailability of an established effective intervention cannot  
651 justify a placebo-controlled study in a country of limited resources when it would be unethical to  
652 conduct a study with the same design in a population with general access to the effective intervention  
653 outside the study”.<sup>75</sup>

654 Lack of access of patients in community within, or outside of, the EEA, to the EEA-licensed (or  
655 equivalent) comparator cannot be a justification to withhold this treatment option to those patients  
656 when participating in a trial regardless of the reasons for the lack of access (e.g. no reimbursement, no  
657 national marketing authorisation). Regardless of the location of the trial, all patients participating in  
658 these trials should receive the same or a similar standard of care and comparable treatment options as  
659 trial participants within the EEA.

660 EU Competent Authorities should verify that the study has been reviewed by the ethics review  
661 committees and that they have determined: whether the use of placebo or other comparator is  
662 ethically acceptable in the context of that trial; whether the safety and rights of the subjects have been  
663 fully protected and whether prospective subjects would be fully informed about the use of placebo  
664 and/or other comparators and available alternative treatments, in accordance with above cited ethical  
665 principles.<sup>76</sup>

666 **Regulatory action/action plan:**

- 667 1. Sponsors should describe in detail in the protocol and in the clinical study report the justification  
668 for the use of placebo and/or choice of active comparator in accordance with the ethical principles  
669 referred to above. This information can form part of the clinical study report in accordance with  
670 ICH3 and protocol in accordance with ICH E6.
- 671 2. EU Competent Authorities will identify those studies that may give rise to special ethical concern  
672 regarding the use of placebo or other comparators and where applicable to seek additional  
673 assurance that the design was appropriate and ethically acceptable.
- 674 3. Where it is determined that a study design was not acceptable in accordance with the  
675 aforementioned criteria, it should not be accepted in support of a MAA in accordance with Directive  
676 2001/83 EC and Regulation No (EC) 726/2004.
- 677 4. Sponsors should seek scientific advice on study design before carrying out the trials.

678 **3.7. Access to treatment post trial**

679 The availability of an intervention shown to be successful to the participants in the research once the  
680 research is complete is a question that researchers, sponsors ethics committees, and regulatory  
681 Authorities/Governments have to consider in research related to healthcare concerns. Because  
682 resources for healthcare are scarce in developing countries, this issue is often particularly difficult to  
683 address. For many impoverished people, participation in a trial may offer access to significantly better  
684 medical care and treatment than would otherwise be available to them. The cessation of such care and  
685 treatment, once a trial is over, has been widely criticized as exploitation of vulnerable people who will  
686 seldom be in a position to negotiate the extended provision of better medical care and treatment at the  
687 termination of a clinical trial.

688 The nature of access to treatment post trial has proved to be a controversial topic. Whilst there are  
689 many common considerations there are also inconsistencies of emphasis or expectation in the  
690 recognized documents

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75 WHO (CIOMS) Guideline 11

76 WHO (CIOMS) Guideline 11

691 When considering whether it is appropriate to conduct a specific research study within a low to middle  
692 income country one issue that should be considered by the sponsor, ethics committee and National  
693 Regulatory Authority is whether the intervention being studied is likely to be available in that country if  
694 it is shown to be effective.

695 Paragraph 14 of the Declaration of Helsinki requires that the research protocol describes arrangements  
696 for post-study access by study subjects to interventions identified as beneficial in the study or access  
697 to other appropriate care or benefits.

698 If a product developed or knowledge generated by research is unlikely to be reasonably available to, or  
699 applied to the benefit of, the population of a proposed host country or community after the conclusion  
700 of the research, and if the sponsor doesn't foresee arrangements to make it available, the ethics of  
701 conducting the research in that country or community need to be carefully considered, reflecting on  
702 the need for access to treatment and on the risks and benefits that would apply to those participating  
703 in the trial and to their community (including the medical care environment of that  
704 country/community).

705 Before undertaking research in a population or community with limited resources, every effort should  
706 be taken by the Sponsor, ethics committees and Competent to ensure that : a) the research is  
707 responsive to the health needs and the priorities of the population or community in which it is to be  
708 carried out; and b) there is a reasonable likelihood that this population or community stands to benefit  
709 from the results of the research and that any intervention or product developed, or knowledge  
710 generated, will be made reasonably available for the benefit of that population or community.<sup>77</sup>

711 *"At the conclusion of the study, patients entered into the study are entitled to be informed about the*  
712 *outcome of the study and to share any benefits that result from it, for example, access to interventions*  
713 *identified as beneficial in the study or to other appropriate care or benefits".<sup>78</sup>*

714 Before consenting, subjects must be informed, whether, when and how any products or interventions  
715 proven by the research to be safe and effective will be made available to them after they have  
716 completed their participation in the research, and whether they will be expected to pay for them.<sup>79</sup>

717 Obligations of sponsors to provide health-care services will vary with the circumstances of particular  
718 studies and the need of host countries. The sponsor's obligations in particular studies should be  
719 clarified before the research is begun. The research protocol should specify what health care services  
720 will be made available during and after the research, to the subjects themselves, to the community  
721 from which the subjects are drawn, or to the host country, and for how long. The details of these  
722 arrangements should be agreed by the sponsor, officials of the host country, other interested parties,  
723 and, when appropriate, the community from which the subjects are to be drawn. The agreed  
724 arrangements should be specified in the consent process and documentation.

725 Although sponsors are, in general, not obliged to provide health-care services beyond that which is  
726 necessary for the conduct of the research, it is morally praiseworthy to do so.

727 Finally, sponsors should ensure the availability of:

- 728 • *"health-care services that are essential to the safe conduct of the research;*
- 729 • *treatment for subjects who suffer injury as a consequence of research interventions; and,*

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77 WHO(CIOMS) Guideline 10 and art. 17 of Declaration of Helsinki (2008)

78 Art.33 of Declaration of Helsinki (2008)

79 WHO (CIOMS) Guideline 5

- 730 • *services that are a necessary part of the commitment of a sponsor to make a beneficial*  
731 *intervention or product developed as a result of the research, reasonably available to the*  
732 *population or community concerned*".<sup>80</sup>

733 **Regulatory action/action plan:**

- 734 1. *Sponsors should describe in the protocol and in the clinical study report the provisions made with*  
735 *respect to access to treatment post trial. This information can form part of the clinical study report*  
736 *in accordance with ICH E3.*
- 737 2. *EU Competent Authorities should identify those studies that may give rise to special ethical*  
738 *concern regarding access to treatment post trial and where applicable to seek additional assurance*  
739 *that the solution was appropriate and ethically acceptable.*
- 740 3. *The applicant should explain in the MAA how the medicinal product has been/will be made*  
741 *available in the countries where the trials were conducted and this information should be*  
742 *summarised in the European Public Assessment Report (EPAR).*

743 **3.8. Applicability of data to EEA population**

744 There are several issues relating to the applicability of third country trials to European populations.  
745 These involve factors both intrinsic and extrinsic to the study population and EEA population.<sup>81</sup>

746 These are discussed in the "Reflection Paper on the extrapolation of results from clinical studies  
747 conducted outside the EU to the EU population"<sup>xxi82</sup> (Doc. Ref. EMEA/CHMP/EWP/692702/2008) and  
748 the ICH 1998 E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data  
749 (<http://www.ich.org/LOB/media/MEDIA481.pdf>).<sup>83xxii</sup>

750 The choice of active comparator should be relevant to the EEA population and made in accordance with  
751 EEA guidelines and take into account the peculiarities of paediatric population.<sup>84</sup>

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80 WHO (CIOMS) Guideline 21

81 ICH 1998 E5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

82 Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population  
EMEA/CHMP/EWP/692702/2008

83 ICH 1998 E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

84 ICH E10 Choice of Control Group in Clinical Trials

752

753 **4. Determine the practical steps to be undertaken during the**  
754 **provision of guidance and advice in the drug development**  
755 **phase**

756 The European Medicines Agency plays a role in stimulating innovation and research in the  
757 pharmaceutical sector. The Agency gives scientific advice and protocol assistance to companies for the  
758 development of new medicinal products and draws up scientific guidelines aimed at helping applicants  
759 develop medicinal products in order to support marketing-authorisation applications for medicinal  
760 products for human use. The tasks and responsibilities of the Agency under the Paediatric Regulation  
761 include the provision of objective scientific decisions on the development plan for medicines for use in  
762 children.

763 The European pharmaceutical legislation (and that in other regions of the world also) requires clinical  
764 trials to be performed prior to the granting of a marketing authorisation. The analytical,  
765 pharmacotoxicological and clinical requirements in respect of testing of medicinal products are set out  
766 in the Annex 1 of Directive 2001/83/EC. Additional requirements and incentives apply to encourage the  
767 conduct of clinical trials for the development of medicines for the treatment of children and for the  
768 treatment of patients with rare (orphan) diseases. These requirements increase the number and scope  
769 of clinical trials being conducted, not all of which can or need to be carried out in Europe. Clinical trials  
770 conducted in the EEA will need to comply with applicable laws and regulations. In addition, future  
771 applicants in the EEA are recommended to consult with EEA regulators about the design and ethical  
772 conduct of clinical trials prior to their commencement when those trials are planned to be conducted in  
773 third countries. EEA regulators should ensure that every opportunity is taken prior to the  
774 commencement of clinical trials to influence their design and ensure their ethical conduct.

775 Several operational or technical considerations lead to the conduct of clinical trials in a widening range  
776 of countries:

- 777 • Availability of patients willing to participate in clinical trials, and with the relevant disease profile,  
778 • Availability of qualified investigators willing and available to conduct the trials,  
779 • Preparation for marketing authorisation application, in those other countries,  
780 • Lower costs in some countries,  
781 • More rapid approval of trials,  
782 • Willingness of patients to participate in trials due to the trial facilitating access to higher standard  
783 of care and / or medication(s) not otherwise available to them,  
784 • Small number of relevant patients existing in Europe,  
785 • Availability of patients who are naïve to treatment,  
786 • Difficulty in recruiting patients due to differences in standard of care across developed countries.

787 The identification of these issues or other circumstances influencing the location of clinical trials outside  
788 the EEA should be identified.

789 The applicant should provide appropriate justification for the location of a clinical trial and detail its  
790 plan for addressing ethical and operational issues related to its proposed development plan.

791 Agency working groups should take into consideration the circumstances driving the location of trials  
792 when considering requests for advice, establishing requirements for the conduct of trials or developing  
793 guidelines and should:

- 794 • highlight these circumstances and their related risks
- 795 • try to minimize the risk by recommending some corrective actions or other alternatives for the  
796 drug development plan or clinical trials proposals
- 797 • make the applicant aware of those potential issues before the trial is conducted whenever possible,  
798 or before the MA application
- 799 • clearly identify the potential impact on the ethical aspects of trials and the quality of clinical data to  
800 be generated.

#### 801 ***4.1. Assessment of therapeutic needs in the EEA and relationships with its*** 802 ***drug development plan***

803 When addressing the targeted indication(s) and its applicability to the European population, both the  
804 applicant and European Medicines Agency parties/ committees should specifically consider the following  
805 issues that could influence the decision to conduct trials outside the EU:

- 806 • Condition(s) less frequent in the EEA than in other non-EEA countries
- 807 • Small number of affected subjects worldwide due to the rarity of the condition (e.g. orphan  
808 diseases)
- 809 • Applicability of the targeted drug claim in the European population when the disease is  
810 predominant mainly outside Europe (e.g. tropical diseases)
- 811 • Different therapeutic needs in the European population
- 812 • Clinical data to be generated may be of little relevance to the European population (e.g. notable  
813 difference in disease management).

814 When applicable according to the procedure applied for, the applicant should consider the relevance of  
815 its clinical program, in relation to:

- 816 • Applicability of the proposed indication and the therapeutic needs of the European population
- 817 • Prevalence of the condition in non-EEA countries and in EEA countries.

818 The consequences of drug development with clinical trials conducted outside the EEA (completely or  
819 partially) should be considered with regards to:

- 820 • Limitations of data extrapolation from non-EU patients to the EEA
- 821 • Impact of the geographic source of patients on the efficacy and safety results and their  
822 extrapolation the European population in the context of disease management (e.g. national  
823 characteristics of disease management and patient care)
- 824 • Validity of the selected comparators (active or placebo) for enabling assessment of the Risk/Benefit  
825 balance of the product for the European population
- 826 • Pre-specified subgroup analyses based on ethnicity and/or regions of the world
- 827 • Evaluation of the level of adherence to standard background treatment regimes for a specific  
828 disease

- 829 • Take into consideration possible differences in genetic profiles which could influence the drug  
830 response.

831 Where a scientific advice, guidance or assessment relates to an application for a scientific opinion in  
832 the context of article 58 of Regulation No (EC) 726/2004 the considerations should relate to the  
833 population for which the medicinal product is to be used, rather than the EU population.

#### 834 **4.2. Issues related to feasibility of clinical trials**

835 The applicant should provide available information on its development plan:

- 836 • Details on the locations of the trials planned in the EEA and outside

- 837 • Criteria for the selection of the non-EEA countries

838 A feasibility assessment for recruiting the targeted number of patients in a clinical trial should be  
839 provided in order to allow consideration of the possible consequences on the future MAA and results  
840 interpretation. This feasibility assessment should include as a minimum:

- 841 • Recruitment plan for patients in the EEA and outside

- 842 • Selection criteria and numbers of centres per country or regions outside the EU

- 843 • Duration of trial recruitment and expected impact of comparability of results over time in case of  
844 very long recruitment (e.g. duration of recruitment longer than 3 years for rare disease).

#### 845 **4.3. General measures to assure data quality when conducting trials** 846 **outside the EU**

847 Issues that may have an impact on the quality of data to be generated should be clearly identified and  
848 minimised when appropriate:

- 849 • Duration of the study

- 850 • Complexity of the trial design, e.g.: requirement for blinding / shipments of samples (e.g. tissues)/  
851 specific or high level of technology platforms required (e.g. MRI)/ frequency of  
852 biological/radiological monitoring

- 853 • Restricted access to specific tests and laboratory with possible impact on final data quality (e.g.  
854 testing of HIV resistance)

- 855 • Access to active comparators/ placebo/ age-appropriate formulation at the national level or when  
856 provided by the applicant

- 857 • Differences in Patients-Reported Outcomes

- 858 • Limitations for long term follow up of patients after treatment (active comparator and study drug)  
859 discontinuation

- 860 • Anticipated quality of data monitoring and training of investigators

861 Specific measures to be taken into consideration in order to assure the quality of results should  
862 include:

- 863 • Identification of limitations in extrapolating data from non-EU patients to the EEA populations, such  
864 as different ethnicities, underlying specific conditions

- 865 • Appropriateness of study design in accordance with the European guidelines and the most up to  
866 date scientific recommendations and ethical requirements
-



- 867 • Choice of claim for superiority versus non inferiority in relation to a proper identification of  
868 therapeutic needs and respective recruitment capacity in the EEA and outside
- 869 • Identification of standards of care for the targeted disease among countries
- 870 • Drug and study acceptability by the patients in the targeted countries and by the national ethics  
871 committees
- 872 • Research responsive to the health needs and priorities of the population or community in which it  
873 is carried out.

874 **4.4. Considerations for designing clinical trials:**

875 The applicant should pay particular attention when designing trials outside the EEA in order to avoid  
876 generating data not relevant for the intended purpose:

- 877 • Study design:
- 878 – Risk of futility when efficacy assessment based on an inaccurate statistical hypothesis (e.g.  
879 inappropriate claim of superiority due to an underestimation of disease outcome in the  
880 countries outside the EEA )
  - 881 – Choice and access to active comparators and availability of other therapeutics required for best  
882 disease management in the selected countries
  - 883 – Level of overall management care in the targeted countries
  - 884 – Stopping rules in case of lack of efficacy or safety issue
  - 885 – Existence and responsibilities of the independent Data and Safety Monitoring Board and/ or  
886 Data Monitoring Board
  - 887 • Analysis of factors potentially impacting on the ability to extrapolate the clinical trial results to the  
888 EU population, such as:
    - 889 – Sources of data variability
    - 890 disease outcome and management
    - 891 parameters impacting the drug effect variability
    - 892 standards of patients management care
    - 893 specific measures for assessment of treatment adherence in some specific cases
    - 894 – Validation of assessment scale to be used in the non- EEA population (e.g. Quality Of Life  
895 scoring)
    - 896 – Implementation and interpretation of biomarkers and surrogate end-points

897 **Regulator action/action plan:**

- 898 1. Clinical trials are conducted not only for submission to the EEA but also to many other regulators  
899 worldwide. In order to minimise risk of non-approvability of the application due to the choice of  
900 study populations not applicable to the EEA population or trial designs not acceptable in the EEA  
901 sponsors should seek EU scientific advice prior to the conduct of those trials.
- 902 2. EMA Committees and working Parties (and assessors) evaluating requests for Scientific Advice,  
903 Orphan designation, and Paediatric Investigation Plans should systematically consider the issues

904 raised in this reflection paper and apply the proposals during their assessments and  
905 recommendations/opinions provided to the applicants.

906 3. Applicants should clearly explain why data from the patient populations selected are applicable to  
907 the EEA population unless the product is intended to be used outside the EEA.

## 908 **5. Determine the practical steps to be undertaken during the** 909 **marketing authorisation phase**

### 910 **Submission, validation, assessment and inspection of the clinical trials contained in the** 911 **Marketing Authorisation Application**

912 Recital 16 of Regulation (EC) No 726/2004 states that, with respect to clinical trials conducted outside  
913 the Community on medicinal products destined to be authorised within the Community, at the time of  
914 the evaluation of the application for authorisation, it should be verified that these trials were conducted  
915 in accordance with the principles of good clinical practice and the ethical requirements equivalent to  
916 the provisions of the said Directive.

917 Article 6(1) of the same regulation requires that the application include a statement to the effect that  
918 clinical trials carried out outside the European Union meet the ethical requirements of Directive  
919 2001/20/EC.

920 Article 56 (4) of the same regulation foresees that the Committee for Medicinal Products for Human  
921 Use may, if they consider it appropriate, seek guidance on important questions of a general scientific  
922 or ethical nature.

923 As a consequence, the Marketing Authorisation evaluation should ensure that these GCP principles  
924 have been applied to all submitted clinical trials, and, that ethical guidance is sought if required.

925 Furthermore, an application for Marketing Authorisation for medicinal products for any population shall  
926 be regarded as valid only if requirements of the art.7 of the European Paediatric Regulation are also  
927 complied with.

### 928 ***5.1. Points to consider during the assessment process: identify assessment*** 929 ***issues and processes***

#### 930 **Background**

931 Three scenarios are considered:

- 932 • The first relates to acceptability of foreign data for the EU, from a scientific viewpoint. This is  
933 already adequately covered elsewhere (see section 3.8).
- 934 • The second relates to concern over the conduct of the study, and data reliability – this should  
935 trigger requests for clarification from the applicant, and also discussion with inspectors as to  
936 whether a GCP inspection may be appropriate or required (see 5.2).
- 937 • The third relates to concern over the design of studies in relation to acceptability in Europe. Such  
938 concerns may relate to the use of placebo or duration of use of placebo, poorly optimised  
939 background therapy, use of inappropriate comparator, inappropriate investigations, lack of consent  
940 etc. Many of these issues include ethical concerns. This aspect is addressed below.

941

942

943 **Review procedures**

- 944 • At the time of the application, information should be provided on where each clinical trial was  
945 performed and on how ethical requirements were met.
- 946 • As part of the review of the MAA, assessors should determine whether or not there are ethical  
947 concerns relating to the studies that have been included in the dossier to support the MAA.  
948 Assessors should confirm in the Assessment Report that they have not identified any ethical issues  
949 in their assessment of the studies, that the studies have been approved by the concerned ethics  
950 committee and by the National Regulatory Authority, that the sponsor has provided the statement  
951 that the studies have been conducted as set out in Annex 1 of Directive 2001/83, and that there  
952 are no concerns identified regarding the conduct of the study. Particular attention should be given  
953 where vulnerable patients are included within the trial population, and/or trials are conducted in  
954 low to middle income countries, and/or where no EEA ethics committee has reviewed and approved  
955 the study/studies for trials performed outside the EU.
- 956 • In considering the design of studies, assessors should be aware of international guidelines for  
957 biomedical research involving human subjects where the recommendations are that research is  
958 responsive to the health needs and priorities of the population or community in which it is carried  
959 out and any intervention or product developed or knowledge generated will be made reasonably  
960 available for the benefit of that population or community. Whilst it is not possible for assessors to  
961 conclude definitively, questions or concerns in relation to this area should also be included in the  
962 List of Questions to the applicant to request further information about the conduct of the trials.

963

964 *The EU assessment report should reflect:*

- 965 1. That steps have been taken to determine that all clinical trials were conducted in accordance with  
966 the principles of good clinical practice and the above mentioned ethical requirements ,
- 967 2. The ethical concerns that have been raised, if any.
- 968 3. How these ethical concerns have been solved and whether they had an impact on the assessment  
969 of the quality, safety and efficacy of the product,
- 970 4. Whether the CHMP has sought additional ethical expertise,
- 971 5. The reasons for and outcome of any GCP inspections requested (these may be routine or  
972 triggered),
- 973 6. Discussion of applicability of data to the EEA population

974

975 *Actions to take if there are concerns over the ethics of studies*

- 976 1. Where the assessor is concerned that a study may not have been conducted ethically, the  
977 assessors should seek further clarification from the applicant who should be given the opportunity  
978 to justify their position.
- 979 2. In addition the CHMP should develop appropriate links with those with expertise in ethics who  
980 could advise on these aspects as appropriate. A proposal for the establishment of a pool of experts  
981 supporting the CHMP in its assessment of the ethical aspects of CTs submitted with the MAA could  
982 be set up. A structure similar to a SAG might be envisaged. It is essential that if actions were to  
983 follow CHMP's assessment of a study as 'not conducted in accordance to the appropriate ethical  
984 requirements', the justification for the assessment should be robust.

985 *Consequences of a study being considered unethical*

986 1. If, (after taking appropriate advice if necessary), the CHMP concludes that a study has not been  
987 carried out in accordance with the appropriate ethical requirements then the CHMP must conclude  
988 upon additional steps. No single solution will be applicable to all situations, and issues are likely to  
989 be complex.

990 2. Therefore the European Medicines Agency /CHMP must have a number of possible tools at its  
991 disposal. These may include the following:

992 2.1. Assessment of the application without data from the studies or part of the studies deemed  
993 unethical. Additional analyses may be required. This may result in an application that is not  
994 approvable.

995 2.2. The possibility to making public the circumstances and details of studies which were found  
996 not to have been conducted in accordance with ethical requirements.

997 2.3. A graded system of potential actions should be developed (see 5.3).

998 3. Regulatory authorities should have some degree of discretion over how, when and if to take action,  
999 taking into account the circumstances of the trial, and the nature and severity of the issues that  
1000 have been identified.

1001 **Regulatory action/action plan**

1002 1. *The European Medicines Agency should establish a pool of experts to advise the CHMP in its*  
1003 *assessment of the ethical aspects of clinical trials submitted with the MAA, and define their*  
1004 *membership, required expertise, mandate and procedures, and the process by which the CHMP,*  
1005 *EMA or other agency scientific committee, may consult them. Such consultation may be on general*  
1006 *matters of principle involved in establishing requirements and guidance, or specific cases involving*  
1007 *particular trials and products.*

1008 2. *EU Competent Authorities should develop a system for review of MAA dossiers, and identification of*  
1009 *studies of potential ethical or GCP concern, involving review at the time of validation by the EMA*  
1010 *product team, and during the assessment by the assessment team and CHMP, supported by the*  
1011 *EMA product team.*

1012 **5.2. Inspections: Triggers for inspection to be identified by assessor**

1013 GCP inspection is an important tool for monitoring compliance with requirements. A programme of  
1014 routine inspections is required to ensure that information is available to the regulator on a regular  
1015 basis and in the absence of any particular concern triggering a specific inspection to investigate the  
1016 issues giving rise to concern. In addition to GCP inspections conducted by EU inspectors, the possibility  
1017 for communication and exchange of information with the regulators in the countries concerned, should  
1018 be expanded.

1019 **Inspection triggers:**

1020 During the review of an application for a marketing authorisation, concerns can be raised by CHMP  
1021 related to the compliance of the study conduct with current local and international legal and regulatory  
1022 provisions, and to the reliability of the data submitted.

1023 During the review several criteria may act as triggers for a GCP inspection. Some of these criteria are  
1024 study-related aspects while others relate to the fact that the study was conducted in countries outside  
1025 the EU.

- 1026 Study-related triggers for an inspection are in general focused around four main issues:
- 1027 1. Existence and characteristics of trial subjects, distribution of subjects.
- 1028 1.1. Rate of inclusion in a specific centre
- 1029 1.2. Centres involved late during the course of the study in order to boost the recruitment)
- 1030 1.3. Centres with a burst of fast recruitment following a long period of inactivity
- 1031 1.4. Unusual trends in analysis/efficacy data, enrolment, drop-out rate, SAE
- 1032 1.5. Study data suggesting attendance on the required day on every occasion
- 1033 1.6. Compliance with entry criteria
- 1034 1.7. Study data indicating specific centre effects
- 1035 2. Quality and administration of investigational medicinal products.
- 1036 2.1. Identity of the IMP and treatments unclear
- 1037 2.2. Any modification of the product during the study
- 1038 2.3. Any concern identified with treatment compliance and treatment duration
- 1039 2.4. Any concern identified with treatment blinding or un-blinding
- 1040 2.5. Concerns regarding concomitant medications
- 1041 3. Efficacy and safety evaluation criteria and data.
- 1042 3.1. Unclear definition of the variables used in the study
- 1043 3.2. Method of measurement unclear
- 1044 3.3. Inconsistent, inaccurate or incomplete data recording and reporting
- 1045 3.4. Major changes to the protocol (e.g. change in primary endpoints or in statistical methods)
- 1046 during the study
- 1047 3.5. Data with abnormal variation or distribution
- 1048 3.6. Unexpectedly low levels of (S)AE reporting.
- 1049 4. Ethical and regulatory aspects of study and trial team.
- 1050 4.1. Lack of information about regulatory requirements followed in conducting the trials, in the
- 1051 clinical study report
- 1052 4.2. Information about review by an Independent ethics committee is missing
- 1053 4.3. Adequacy and completeness of the written information given to the patients is questionable
- 1054 If a study has been conducted in third country(ies), additional triggers may be identified during the
- 1055 review process. Some of these triggers may be:
- 1056 1. Design of the study raises ethical concerns. Whilst these specific points relate to trial design,
- 1057 which is apparent from the review process without inspection, they may sometimes raise a more
- 1058 general concern about the conduct of the trial.
- 1059 1.1. Inadequate justification of the use or duration of use of placebo
- 1060 1.2. Poorly optimised background therapy

- 1061 1.3. Use of inappropriate comparator
- 1062 1.4. Use of inappropriate investigations
- 1063 2. Conduct of the study raises ethical concerns
- 1064 2.1. Inclusion of vulnerable patients, e.g. children, women, unconscious patients
- 1065 2.2. High incidence of illiteracy in the study population
- 1066 2.3. Specific requirement for witness
- 1067 3. Lack of familiarity or concerns with/unawareness of the local legislative regulatory or ethical  
1068 framework on the part of EU Regulators
- 1069 4. Lack of previous or recent inspections by EEA inspectors in the country concerned
- 1070 5. The study was conducted mainly/solely outside EEA
- 1071 6. Concern about the stability of IMP in a non-temperate climate

1072 The list of triggers is by no means complete, but in case of concerns identified during the review of an  
1073 application for Marketing Authorisation, questions should be addressed to the sponsor, as well as  
1074 discussed between assessors and inspectors, and an inspection triggered whenever required.  
1075 Inspections may also be requested as part of a programme of routine inspections.

1076 **Regulatory action/action plan**

- 1077 1. *The criteria used as the basis for both routine and triggered GCP inspections should be further*  
1078 *developed.*
- 1079 2. *The processes for identifying triggers for GCP inspections should be further developed and*  
1080 *systematised.*
- 1081 3. *Frameworks for contact with National Regulatory Authorities, to gain information on the GCP*  
1082 *compliance and local inspection, in the countries where clinical trials take place should be*  
1083 *developed.*

1084 **5.3. Actions available in response to non compliance**

1085 The underlying philosophy of this reflection paper is that pro-active steps should be taken to reinforce  
1086 the regulatory framework for the conduct of ethical, scientifically valid clinical trials, and the protection  
1087 of trial subjects. Ideally such measures would ensure that significant non-compliance would not occur.  
1088 The processes available to address situations where requirements have not been followed, should  
1089 strive to further refine and reinforce the framework for the conduct of trials and the understanding of  
1090 requirements by all involved. The range of actions available should recognise this need and include  
1091 activities that involve communication, education and refinement as the preferred course. In some  
1092 circumstances this will not always be possible, or appropriate, not least because by the time the  
1093 Marketing Authorisation Application is made, the clinical trials in question are generally completed and  
1094 little can be done to remedy deficiencies in the conduct of those particular trials.

1095 Trial subjects and their communities also need to be assured that their rights and welfare will be  
1096 supported and reinforced by regulators, both locally, and internationally. That assurance is a central  
1097 requirement as the entire process of development of medicines relies on the willingness of individuals  
1098 to participate in clinical trials.

1099

1100 Particular emphasis should be given to trials conducted in third countries. There is a need to ensure  
1101 that the role and authority of the ethics committees and National Regulatory Authorities in the  
1102 countries where the trials are conducted are supported. when non compliance with GCP regulatory  
1103 obligations and ethical concerns is detected, action should be taken in this context, and include  
1104 communication with the National Regulatory Authority concerned. The action to be taken should be  
1105 proportionate to the consequences of the observed violation of the rights and welfare of the trial  
1106 subjects and of the deficiencies of the data integrity.

1107 There is the need to define and to make public the consequences of non compliance with GCP and  
1108 above mentioned ethical concerns in designing, conducting, recording and reporting of the clinical trials  
1109 included in the MAA.

1110 Non compliance which significantly affects the rights, safety or well being of the subjects or the quality  
1111 and integrity of the data reported is not acceptable, and will result in rejection of data and/or other  
1112 regulatory actions.

1113 Regulatory Actions/Action Plan:

1114 Regulatory options include the following:

1115 *Information and possible action by third country regulators*

1116 Information on non-compliance should be available to the Regulatory Authority in the country in which  
1117 the trial non-compliance has been identified and to other regulators in the international network,  
1118 (subject to appropriate confidentiality arrangements if applicable).

1119 *Request for additional information or action by the sponsor*

1120 The sponsor may be asked to supply additional information or explanation, conduct further analyses or  
1121 data collection/review, or to commission further monitoring or independent audits of a wider range of  
1122 sites.

1123 *Inspection or re-inspection*

1124 (Further) sites involved in the same trial/and or further trials and/or sponsor site/Marketing  
1125 Authorisation Holders may be inspected to determine the extent of non-compliance.

1126 The COMP or PDCO might request an inspection of a clinical trial at the time of their evaluation in  
1127 coordination with the Clinical Trial Facilitation Group (where the trial is conducted in the EU) and the  
1128 EEA GCP IWG (Inspectors Working Group) where concerns arise about the conduct of a trial(s).

1129 *Rejection of data/exclusion of trial/negative opinion*

1130 Data obtained from clinical site(s) or from a trial found to be seriously non compliant with GCP and/or  
1131 ethical requirements should be excluded from use in support of the Marketing Authorisation  
1132 Application.

1133 *Education and Facilitation*

1134 Applicants and/or Marketing Authorisation Holders may be informed of non-compliance and advised on  
1135 how this can be remedied for future trials, and in some cases action may be possible for the trial in  
1136 question.

1137 *Warning*

1138 The European Medicines Agency may issue a formal warning reminding Applicants and/or Marketing  
1139 Authorisation Holders of their GCP obligations in conducting clinical trials in accordance with above  
1140 mentioned ethical requirements

1141 *Transparency regarding clinical trial conduct and compliance including non-compliant Marketing  
1142 Authorisations*

1143 The European Public Assessment (EPAR) report should describe any serious non-compliance

1144 encountered and discuss the steps taken as a consequence. This should be done whether the CHMP  
1145 opinion is positive or negative or the application is withdrawn prior to the opinion.

#### 1146 *Suspension of the Marketing Authorisation/Urgent Safety restriction /Revocation of the Marketing* 1147 *Authorisation*

1148 Suspension/Urgent safety restriction/revocation of the Marketing Authorisation should be considered  
1149 where the non-compliance is identified after the MA has been granted in accordance with the  
1150 legislation, guidance and rules applicable.

#### 1151 *Penalties*

1152 The possibility of applying specific penalties should be considered and the mechanism for application of  
1153 those penalties identified.

#### 1154 **Regulatory action/action plan**

1155 1. EU Competent Authorities should develop a system for regulatory action in case of non compliance  
1156 with ethical and GCP requirements.

1157 2. Where clear serious concerns are identified the EU competent Authority should communicate these  
1158 concerns to the National Regulatory Authority of the Country (ies) concerned.

#### 1159 **5.4. Transparency, including improvement of EPAR content and** 1160 **consistency**

1161 The European Public Assessment Report (EPAR) summarises the quality, safety and efficacy data  
1162 evaluated and the outcome of that evaluation during the marketing authorisation process in order to  
1163 ensure that consistent and appropriate information is provided to the public on the clinical trials  
1164 included in the Marketing Authorisation Application. The EPAR is produced to a standard format and its  
1165 content based on the CHMP Assessment Report (AR) after deletion of commercially confidential  
1166 information.

1167 The CHMP assessment report is obtained from the assessments at the different phases of the CHMP  
1168 review. The application of GCP and ethical requirements and steps taken to confirm this, or any related  
1169 issues should be reflected in the EPAR.

1170 The guidance to assessors outlines the kind of clinical trial information that should be included in the  
1171 assessment report at Day 80 and in the CHMP assessment report/EPAR. (see Guidance Document –  
1172 Day 80 Clinical Assessment Report [http://www.ema.europa.eu/pdfs/human/chmptemplates/CHMP-  
1173 D80-AR-Guidance/D80AR\\_Clinical\\_Guidance\\_rev10\\_09.pdf](http://www.ema.europa.eu/pdfs/human/chmptemplates/CHMP-D80-AR-Guidance/D80AR_Clinical_Guidance_rev10_09.pdf) ).

1174 Inclusion in the guidance of the items listed below, and the consistent application of this, will  
1175 substantially improve the content of assessment reports and hence the EPAR in respect of ethical and  
1176 GCP compliance.

1177 The assessment report and the EPAR should address the following aspects:

- 1178 • The standard GCP review which should be summarised in an annex to the Assessment Report and  
1179 to the EPAR, should list, for each clinical trial submitted the protocol identification and title, start  
1180 and end date, identification of the sponsor, of the countries where each trial was conducted and  
1181 the numbers of subjects recruited in each country. The nature of the patient population should  
1182 also be described (age and gender and any particular considerations of vulnerability). The  
1183 standards to which the trials were conducted should be identified. This summary should be based  
1184 on information to be supplied, electronically, by the applicant.



1185 • During the course of the assessment, any relevant ethical issue such as access to treatment post  
1186 trial, use of placebo or treatment interruptions, choice of active comparators, treatment of  
1187 vulnerable populations and applicability of data to EEA population should be highlighted as part of  
1188 the assessment of the individual trial.

1189 • GCP inspection. When performed, the reason(s) for inspection should be described. The outcome  
1190 and consequences on the assessment of marketing authorisation application should be further  
1191 elaborated. Relevant information from the inspection report may be made publicly accessible.

1192 • When GCP/ethical concerns have been raised, the assessment report should present the issue,  
1193 describe any external expertise sought and the advice received, and discuss the ethical aspects  
1194 and their consequences on the assessment of the quality, safety and efficacy of the product.

1195 • The actions taken should be reflected in the EPAR.

1196 The EPAR should describe the justifications for the study designs, choice of comparators and selection  
1197 of study populations, with particular emphasis on those studies that involve increased ethical  
1198 sensitivity due to their design, indication, patient population or location of conduct. The applicability of  
1199 the trial to the EEA population should be demonstrated where relevant.

1200 The steps taken to evaluate and provide assurance regarding the ethical conduct of the trials should be  
1201 described as should any significant deficiencies and how they have been addressed

1202 A comment that “no ethical issues were identified” may be sufficient where applicable.

1203 **Regulatory action/action plan**

1204 1. The CHMP assessment report and the European Public Assessment Report should describe clearly  
1205 the clinical trials included in the Marketing Application dossier, listing the trials and details  
1206 concerning their conduct. The applicant should provide tabular listings of this information to  
1207 facilitate this process.

1208 2. The EPAR should describe the assessment of the ethical issues and GCP compliance of the trials in  
1209 the Marketing Authorisation Application, steps (including inspection) taken to confirm this and  
1210 expert advice sought. The EPAR should confirm that the trials have are considered to have fulfilled  
1211 requirements, or, if that is not the case should describe the circumstances and details of studies  
1212 which have been found not conducted in accordance with ethical requirements and GCP, and the  
1213 actions taken as a consequence.

1214 **6. International cooperation in the regulation of clinical**  
1215 **trials, their review and inspection and capacity building in**  
1216 **this area**

1217 International cooperation has been clearly identified as a key foundation in developing a robust  
1218 international framework for the conduct of clinical trials.

1219 As more and more clinical trials on medicinal products marketed in the EU are performed in countries  
1220 outside of the EU, enhanced international cooperation is seen as essential to ensure that, as far as  
1221 possible, there is a common international approach to the oversight of clinical trials. In addition the  
1222 clinical trials are conducted, increasingly in countries, with which EU regulators have limited formal  
1223 contacts or experience in the domain of clinical trials. Building contact with, and between, the National  
1224 Regulatory Authorities in these countries, their regional networks and associations, and the  
1225 establishment of an international network of clinical trial regulators should therefore be a fundamental  
1226 objective.

1227 The scope of this section is to specifically reflect on how to enhance international cooperation in the  
1228 regulation of clinical trials performed including countries outside the EEA, including considerations for  
1229 information exchange, capacity building and interaction with, and coordination between existing  
1230 initiatives.

1231 The ultimate objective should be to ensure that wherever clinical trials are performed, at least the  
1232 following instruments are in place:

- 1233 1. Regulations that permit trials of medicinal products only if the trial is authorised by the national  
1234 regulatory authority and by the concerned ethics committee(s) in that country and that sanction  
1235 violations;
- 1236 2. Ethics committees that are truly independent , professionally sound and adequately resourced;
- 1237 3. Systems of follow-up of clinical trials by the National Regulatory Authority and concerned ethics  
1238 committee(s), with power to suspend or/and stop clinical trials when needed.
- 1239 4. Systems of control of clinical trials before, during and after their conduct, through the use of GCP  
1240 Inspection by the National Regulatory Authority ;
- 1241 5. Regulations that permit the marketing of medicinal products only if authorised and that sanction  
1242 any non compliance;
- 1243 6. Regulations that allow the possibility of refusal by Regulatory Agencies of the marketing  
1244 authorisation of medicinal products when safety and efficacy have not been shown through trials  
1245 conducted in accordance with GCP and ethical requirements.

1246 Such an approach will promote confidence among ethics committees and Regulatory Authorities, avoid  
1247 unnecessary duplication and multiplication of on site inspections, and allow exchange of valuable  
1248 information.

1249 It is recognised that achieving this objective is a long-term goal; nonetheless in order to reach that  
1250 goal it is necessary to identify and take steps , in a phased manner, .towards its achievement.

1251 In order to set priorities and identify the possible steps to be taken in achieving the objective described,  
1252 a number of concerns and opportunities have been considered.

1253 **6.1. Identification of priorities**

1254 It is recognised that with limited resources, there is be a need to prioritise particular activities and/or  
1255 interaction with particular regions/countries. A first step is to identify the countries where growing  
1256 number of clinical trials are performed, followed by communication with the National Regulatory  
1257 Authorities and the sharing of information on the regulatory systems in these countries.

1258 **The following criteria have been considered:**

1259 ***Countries that recruit a significant number of patients.***

1260 The European Medicines Agency has prepared statistics on the numerical distribution of patients  
1261 participating in pivotal trials included in Marketing Authorisations Applications (MAA) submitted to the  
1262 Agency during the period January 2005 to December 2009, it has been noted that certain non-EU  
1263 countries (excluding USA/Canada/EFTA) have contributed about 26% of patients:

- 1264 • Africa: South Africa (2.6%)
- 1265 • Middle East/Asia/Pacific: India (1.5%), Israel (1.3%), Philippines (0.9%), China (0.7%) and  
1266 Thailand (0.7%)
- 1267 • Australia/New Zealand: Australia (1.2%)
- 1268 • Central/South America: Brazil (2.6%), Argentina (2.2%), Mexico (1.3%), Costa Rica (0.7%) and  
1269 Peru (0.6%).
- 1270 • Commonwealth of Independent States: Russia (2.9%) and Ukraine (0.8%)
- 1271 • Eastern Europe-non EU: Croatia (0.5%).

1272 Therefore some of these countries and others where there is an increase in the number of clinical trials  
1273 or patient participation in trials, should be considered as a priority. Since the European Medicines  
1274 Agency information is limited to centrally authorised products, collecting equivalent information from  
1275 Member States and other regulatory partners, including WHO, and non-EU regulatory agencies, and  
1276 form sponsor associations (in particular on ongoing trends) should also be considered.

1277 ***Type of Regulatory System in place***

1278 Those countries that have a limited regulatory system or one that is still under development should  
1279 also be considered as a priority. It will be useful to obtain high level information from all countries from  
1280 which clinical trials are submitted to the EU in order to identify these countries.

1281 Information available on the regulation and conduct of biomedical research activities: Countries where  
1282 there is little information available and/or where information suggests that ethics committees may not  
1283 be properly established should also be identified as priorities.

1284 In order to evaluate the level of priority in the context of the aforementioned criteria, it is proposed  
1285 that a high level "mapping" of information be established and maintained in relation to:

- 1286 • the level of activity in the field of clinical trials, identifying subcategories of those clinical trials (e.g.  
1287 Phase I, Bioequivalence studies, phase II and III in specified therapeutic areas);
- 1288 • the established and functional regulatory framework for clinical trial authorisation (competent  
1289 authorities and ethics committees), GCP inspections.
- 1290 • the infrastructure for and levels of investigator support and training.

1291 This 'mapping' should identify the strengths and weaknesses of the national systems, should identify  
1292 whether capacity building or related development activities are ongoing and should help to select areas

1293 for possible cooperation: the selection of the areas for cooperation (i.e. GCP inspections, strengthening  
1294 of Regulatory Systems or Ethics Committees (strengthened cooperation, capacity building and/or  
1295 focussed, joint, training)) will depend on the needs identified in the countries included in the priority  
1296 list and should be oriented to avoid duplication with other initiatives in the same area of intervention.

1297 This mapping should also identify the opportunities for cooperation with all countries including those  
1298 where the systems are already developed, and authorities already exist and functional (see section  
1299 6.2.).

#### 1300 **Regulatory action/action plan**

1301 1. The EMA will prioritise the third countries with which it will focus its interaction based firstly on the  
1302 numbers of trial subjects recruited there as part of clinical trials submitted to EMA and secondly on  
1303 a review of the regulatory systems in place for the supervision of clinical trials in those countries.

### 1304 **6.2. Identification of opportunities and partners**

#### 1305 **6.2.1. Identification of other initiatives**

1306 In order to avoid duplication of effort, any work performed by the European Medicines Agency Working  
1307 Groups should be complementary to the other numerous initiatives being carried out by international,  
1308 European, regional and national organisations in this field. The aim should be to look for synergies and  
1309 avoid duplication of effort and activities.

1310 Existing initiatives in many instances are implemented without having a clear picture of what has been  
1311 done already, what the results have been and what is being done in the same geographical area, in the  
1312 same field of study etc.. As a consequence, there may be little knowledge of:

- 1313 • neglected areas of intervention;
- 1314 • the necessity for complementary interventions that can be more effective;
- 1315 • previous initiatives with favourable or unfavourable results;
- 1316 • the risk of duplication of initiatives.

1317 The group is aware of different initiatives at different levels carried out by different organisations.  
1318 These initiatives can be categorised as follows:

#### 1319 **6.2.2. Categories of initiatives and actions**

- 1320 • Assessment of National Regulatory Authorities and systems
- 1321 • Strengthening National Regulatory Authorities
  - 1322 – Competent authority
  - 1323 – Ethics committee
  - 1324 – Other stakeholders

1325 Examples of initiatives are provided in section 6.5.

1326

1327

1328 **6.2.3. Establishment of contact with key initiatives**

1329 Relevant contact points for these different initiatives and countries of interest should be identified and  
1330 good communication established in order to obtain:

- 1331 • updated knowledge of the situation in each of the priority countries
- 1332 • an evaluation on what has already been done to date;
- 1333 • reciprocal knowledge of what is being done in this field;
- 1334 • a continuous update on what is going to be done.

1335 This will facilitate the identification of partnerships for joint, common or coordinated activities.

1336 **Regulatory action/action plan**

- 1337 1. The EMA will identify other initiatives that are being carried out in the area of clinical trials  
1338 supervision, mapping of regulatory systems in place and capacity building.
- 1339 2. EMA will identify contact points with the other initiatives in order to identify partnerships for joint,  
1340 common or coordinated activities.

1341 **6.3. Action plan**

1342 Three major directions are identified:

- 1343 • Increasing the efficiency and effectiveness of GCP inspection
- 1344 • Improving the capacity of National Regulatory Authorities
- 1345 • Motivating sponsors, Marketing Authorisation applicants to ensure adequate levels of control of  
1346 their own clinical trials.

1347 The proposed action plan addresses the first two of these.

1348 **6.3.1. Core activities**

1349 The core set of actions consists in ensuring planned and coordinated contribution of GCP inspectors,  
1350 clinical trial assessors and experts in the following areas of intervention depending on the needs  
1351 identified in conjunction with the priority countries and based on the information obtained on the  
1352 existence of other initiatives carried out by other organisations:

- 1353 • GCP Inspection:
  - 1354 – Increase the number of inspections in the priority countries
  - 1355 – Encourage observed and joint inspections with National Regulatory Authorities
  - 1356 – Develop frameworks and priority topics for information exchange
- 1357 • Regulatory authorities (evaluation and inspection sectors):
  - 1358 – Assistance with the establishment and operation of National Regulatory Authority systems for  
1359 review and oversight of clinical trials, and evaluation of the processes established
  - 1360 – Training (courses, workshops, support in the preparation of guidelines/SOPs etc.)
  - 1361
  - 1362

- 1363 – Scientific / technical support:
- 1364 Protocol assistance/Scientific Advice
- 1365 Support for Assessment of clinical trials. Seek the contribution of the Clinical Trial Facilitation  
1366 Group.
- 1367 – Explore and establish frameworks for different types of information exchange.
- 1368 • Ethics committees:
- 1369 – Assistance with the establishment and operation of ethics committees, and evaluation of their  
1370 processes
- 1371 – Training (courses, workshops, support in the preparation of guidelines/SOPs etc.)
- 1372 – A registry of ethics committees and documentation on their composition and activity could be  
1373 established
- 1374 – Evaluation of clinical trials by ethics committees – the cooperation of EU ethics committees can  
1375 be sought
- 1376 – Investigation of systems for accreditation
- 1377 – Explore and establish frameworks for different types of information exchange
- 1378 This core set of actions should be refined in accordance with the results and will contribute to the  
1379 update of the short term and long term activities, described hereunder.

### 1380 **6.3.2. Short Term activities:**

- 1381 In the following context, regional groups and associations of national regulatory authorities or ethics  
1382 committee bodies will often facilitate activities and improve the efficiency and effectiveness of the  
1383 activities involved.
- 1384 • Establishing and maintaining high level information on:
- 1385 – the established regulatory frameworks for clinical trial authorisation (National Regulatory  
1386 Authorities and ethics committees), GCP inspections, and investigator support and training in  
1387 priority countries in order to identify and prioritise the areas for increased cooperation; this  
1388 action can be done by assessment of the available systems, partly as a collaborative work with  
1389 other established initiatives.
- 1390 – the level of activity in the field of clinical trials (numbers, types and purpose [national  
1391 market/'export'] of clinical trials), in order to identify the interest of the country. This action  
1392 requires identification of other sources of information (e.g. registries of clinical trials, National  
1393 Regulatory Authorities etc).
- 1394 – information on relevant activities underway by other regulatory authorities or international  
1395 organisations/initiatives/partnerships.
- 1396 • Establishing, sharing and maintaining a list of relevant contact points for the organisations ,  
1397 authorities and initiatives (international, regional, national etc.) involved in these areas including  
1398 the priority countries
- 1399 • Establishing links – formal and informal – with other projects and initiatives in relation to the  
1400 priority countries:

- 1401 – Inventory of all organisations and initiatives (international, regional and national e.g. WHO  
 1402 mediated groups, ASEAN, African initiatives such as Health Organization (WAHO) and ECOWAS  
 1403 etc.) and training and other capacity building initiatives already implemented and ongoing by  
 1404 these organisations.
- 1405 – Inventory of the models of initiatives implemented and their real efficacy
- 1406 – Information on relevant activities underway by other regulatory authorities and international  
 1407 partners.

1408 **6.3.3. Long Term activities:**

1409 The establishment of a “Service” or “Centre” that could enable sharing - through continuous links with  
 1410 the international organisations, the European Union Member States and institutions and those of third  
 1411 countries, as well as NGOs (non-governmental organisations) - the following (and other) information  
 1412 for each country where a relevant number of clinical trials are conducted:

- 1413 1. the laws and regulations governing this field;
- 1414 2. Information on National Regulatory Authorities, ethics committees and GCP Inspectorates;
- 1415 3. Centres or Research Groups with experience on conducting trials according to the above  
 1416 mentioned ethical and GCP requirements, as shown by favourable reports from GCP Inspectorates;
- 1417 4. models of initiatives implemented and information on obstacles encountered and their real efficacy.

1418 This could provide a useful support for implementing interventions that can be more targeted to the  
 1419 real needs, more selective, complementary and avoiding duplication. The interventions should be  
 1420 defined on the basis of the results of experiences already carried out with success, to contribute to the  
 1421 process of ensuring that research on medicinal products respects GCP and ethical requirements in  
 1422 accordance with the international human rights law.

1423 In this way, such a “Service” would allow the participating partner countries and international  
 1424 organisations to be up to date on the latest developments in the field could be particularly useful for in  
 1425 the following contexts:

- 1426 1. when the European Medicines Agency and National Regulatory Agencies need to verify compliance  
 1427 to the principles of GCP for a certain clinical trial;
- 1428 2. when the European Medicines Agency and other international, regional and national organisations  
 1429 or NGOs want to support a country through capacity building initiatives, such as training  
 1430 programmes for investigators or for members of ethics committees or GCP inspectors;
- 1431 3. when a scientific institution or a pharmaceutical company wants to conduct a clinical trial;
- 1432 4. when a qualified institution wants to provide advice on the preparation of regulations or procedures  
 1433 in this field.

1434 **Regulatory action/action plan**

- 1435 1. Refer to the Action Plan outlined in section 6.3 of the Reflection paper for detailed actions.

1436

#### 1437 **6.4. Resource considerations**

1438 It is recognised that additional resources will be needed to address these objectives, both short and  
1439 long-term. Liaison and communication with the actors identified below will help to establish possible  
1440 funding and collaboration opportunities.

- 1441 • The European Medicines Agency
- 1442 • Interested EU Member States
- 1443 • EU Commission
- 1444 • National Regulatory Authority partners interested or concerned by such initiatives
- 1445 • International and regional organisations:
  - 1446 – Organisations responsible for funding projects
  - 1447 – Organisations responsible for organizing the activities (without funding): to be categorized for  
1448 areas of activity (e.g. training, legislation, GCP, etc.)
  - 1449 – Organisations that fall under both categories

1450 In this context it is recognised that WHO in particular has a range of activities ongoing that are of  
1451 particular relevance and interest.

#### 1452 **Regulatory action/action plan**

- 1453 1. EMA will identify resource requirements and budget to support EMA participation to capacity  
1454 building activities, as part of its work programmes for 2011 and onwards.
- 1455 2. EMA will identify and work with other funding bodies in order to benefit from potential funds to  
1456 support EMA or EU Member State experts contribution to capacity building exercises.
- 1457 3. EMA will identify and work with other funding bodies in order to identify funds that may help  
1458 delegates from concerned third countries to participate and benefit from capacity building  
1459 exercises.

#### 1460 **6.5. Example of initiatives**

##### 1461 **GCP Inspections:**

- 1462 • Increase the number of inspections in developing countries
- 1463 • Encourage observed and joint inspections with local authorities  
1464 The EMA and FDA have agreed to launch an initiative on GCP, with the following key objectives:
  - 1465 1. To conduct Periodic Information Exchanges on GCP-Related Information
  - 1466 2. To conduct collaborative GCP
  - 1467 3. To share information on interpretation of GCP
- 1468 • Harmonization of practice  
1469 The European Medicines Agency, through its GCP IWG (Inspectors Working Group) organises every  
1470 year specific training for EU inspectors. Since 2007 it has included representation from WHO  
1471 (2007, 2008 and 2009), and other non EU regulatory authorities (e.g. Argentina, Brazil, Ghana,



1472 South Africa and USA were involved in the 2008 training course, and Argentina, Australia, Canada,  
1473 India, Japan, Mexico and USA in 2009), in order to contribute to increase the communication and  
1474 sharing of best practices and expertise among regulatory authorities from within the EU and from  
1475 third countries in relation to GCP inspection activities.

1476 • About joint inspections, harmonisation of practice and information exchange, the EMA and FDA  
1477 have agreed to launch an initiative on GCP, with key objectives including:

- 1478 – Periodic Information Exchange on GCP-Related Information
- 1479 – To conduct collaborative GCP inspections
- 1480 – To share information on interpretation of GCP and best practice

1481 **Regulatory authorities (evaluation and inspection sectors):**

- 1482 • Assessment of / assistance in implementing National Regulatory Authorities  
1483 WHO, Immunization standards, strengthening national regulatory authorities,  
1484 [www.who.int/immunization\\_standards/vaccine\\_regulation/nra\\_rp\\_info/en/index](http://www.who.int/immunization_standards/vaccine_regulation/nra_rp_info/en/index)
- 1485 • Training (courses, workshops, support in the preparation of guidelines/SOPs etc.)
- 1486 • EDCTP training course on GCP, Gambia, 7-11 May 2007

1487 Scientific / technical support:

- 1488 • Protocol assistance/Scientific Advice
- 1489 • Assessment of clinical trials and clinical data
- 1490 • The European Medicines Agency is working, in cooperation with the European Commission DG  
1491 Development and with WHO on a project to help regulators from less well developed National  
1492 Regulatory Authorities, to develop their expertise in the review of Marketing Authorisation  
1493 Applications.

1494 **Ethics Committees:**

- 1495 • Assessment of / assistance in implementing ethics committees
- 1496 • FERCAP initiative, [www.fercap-sidcaer.org](http://www.fercap-sidcaer.org)
- 1497 • Training (courses, workshops, support in the preparation of guidelines/SOPs etc.)
- 1498 • Evaluation of clinical trials.
- 1499 • Investigation of systems for accreditation
- 1500 • Information exchange

## 1501 **7. Regulatory action overview**

1502 Regulatory actions described in the text are summarised in this chapter.

### 1503 **7.1. Clarify the practical application of ethical standards for clinical trials,** 1504 **in the context of EMA activities**

#### 1505 **7.1.1. Local Ethics Committee and national Regulatory Authority oversight**

- 1506 • Failure to submit a protocol to an independent ethics committee is a serious violation of ethical  
1507 standards.
- 1508 • EU Competent authorities should refuse to consider data obtained in such an unethical manner,  
1509 when submitted in support of a MAA in accordance with Directive 2001/83 EC or Regulation EC  
1510 726/2004.
- 1511 • Requirements for submission to the national regulatory authority of each country in which the trial  
1512 is conducted and to the ethics committee(s) in those countries must be complied with, and  
1513 evidence of both submissions and approvals provided.
- 1514 • The applicant for a MAA should provide EU Competent Authorities with a summary of ethics  
1515 committee, and National Regulatory Authority approvals of each clinical trial supporting the MAA.  
1516 This information should form part of the clinical study report in accordance with ICH E3.
- 1517 • EU Competent Authorities should identify those studies that may give rise to special ethical concern  
1518 (e.g. arising from their design, the local regulatory framework within which they are conducted,  
1519 the vulnerability of the study subjects) and where applicable to seek additional assurance that the  
1520 trials have been ethically conducted.
- 1521 • Where clear serious concerns are identified the EU competent Authority should communicate these  
1522 concerns to the National Regulatory Authority of the Country (ies) concerned.

#### 1523 **7.1.2. Information/Consent Procedure**

- 1524 • Failure to obtain informed consent (and/or assent where applicable) is a serious violation of ethical  
1525 standards.
- 1526 • EU Competent Authorities should refuse to consider data obtained in such an unethical manner,  
1527 when submitted in support of a MAA in accordance with Directive 2001/83 EC or Regulation EC  
1528 726/2004.
- 1529 • The applicant for a MAA should provide EU drug regulatory authorities with a summary of the  
1530 consent processes used and any variations of those processes in the clinical trials supporting the  
1531 MAA. and include sample information sheets on consent forms. This information should form part  
1532 of the clinical study report in accordance with ICH E3.
- 1533 • EU Competent Authorities should identify those studies that may give rise to special ethical concern  
1534 regarding the consent process (e.g. arising from the patient population included and their capacity  
1535 to provide informed consent, the regulatory framework within which they are conducted, the  
1536 vulnerability of the study subjects) and where applicable to seek additional assurance that consent  
1537 was properly obtained.
- 1538 • Additional good practice guidelines on the communication of the information to the potential  
1539 participants in research may be required to better describe some research situations and should be

1540 developed, with input from patients' organisations and community groups as well as other experts  
1541 in ethics and clinical trials.

### 1542 **7.1.3. Confidentiality**

- 1543 • EU Competent Authorities will refuse to consider reports which fail to properly protect the  
1544 confidentiality of the trial subjects, when submitted in support of a MAA in accordance with  
1545 Directive 2001/83 EC or Regulation No (EC) 726/2004. These reports should be returned to the  
1546 applicant and the breaches of confidentiality rectified prior to eventual resubmission.
- 1547 • The applicant for a MAA should provide EU Competent Authorities with a summary of the steps  
1548 taken to protect confidentiality and the consent obtained to enable the use of and access to the  
1549 subjects' data. This information can form part of the clinical study report section on ethical  
1550 considerations and informed consent in accordance with ICH E3.
- 1551 • EU Competent Authorities should identify those studies that may give rise to special concern  
1552 regarding confidentiality (e.g. arising from the use of genetic information or bio banked samples)  
1553 and where applicable seek additional assurance that confidentiality has been properly maintained.

### 1554 **7.1.4. Fair Compensation**

- 1555 • Failure to provide fair compensation by insurance or indemnity is a serious violation of ethical  
1556 standards
- 1557 • The applicant for a MAA should provide EU Competent Authorities with a summary of the provisions  
1558 made to provide for the fair compensation of subjects for trial related injury. This information can  
1559 form part of the clinical study report section on ethical considerations and informed consent in  
1560 accordance with ICH E3.
- 1561 • EU Competent Authorities should identify those studies that may give rise to special concern  
1562 regarding insurance, indemnity or compensation for research related injury and where applicable to  
1563 seek additional assurance that trial subjects' interest have been protected.

### 1564 **7.1.5. Vulnerable populations**

- 1565 • The inclusion of vulnerable subjects in a clinical trial without the approval of the ethics committee  
1566 and without implementation of the appropriate consent processes is a serious violation of ethical  
1567 standards.
- 1568 • EU Competent Authorities should refuse to consider data obtained in such an unethical manner,  
1569 when submitted in support of a MAA in accordance with Directive 2001/83 EC and Regulation No (   
1570 EC) 726/2004.
- 1571 • The applicant for a MAA should provide drug regulatory authorities with an adequate and  
1572 appropriate justification for inviting vulnerable individuals or groups to serve as research subjects  
1573 and the description of the specific measures and means implemented to protect their rights and  
1574 welfare. This information can form part of the clinical study report in accordance with ICH E3.
- 1575 • EU Competent Authorities should identify those studies that may give rise to special ethical concern  
1576 regarding the inclusion of vulnerable populations and where applicable to seek additional assurance  
1577 that the inclusion of such populations was justified and their rights and welfare protected.

### 1578 **7.1.6. Placebo and Active Comparator**

- 1579 • Sponsors should describe in detail in the protocol and in the clinical study report the justification  
1580 for the use of placebo and/or choice of active comparator in accordance with the ethical principles  
1581 referred to above. This information can form part of the clinical study report in accordance with  
1582 ICH3 and protocol in accordance with ICH E6.
- 1583 • EU Competent Authorities will identify those studies that may give rise to special ethical concern  
1584 regarding the use of placebo or other comparators and where applicable to seek additional  
1585 assurance that the design was appropriate and ethically acceptable.
- 1586 • Where it is determined that a study design was not acceptable in accordance with the  
1587 aforementioned criteria, it should not be accepted in support of a MAA in accordance with Directive  
1588 2001/83 EC and Regulation No (EC) 726/2004.
- 1589 • Sponsors should seek scientific advice on study design before carrying out the trials.

### 1590 **7.1.7. Access to treatment post trial**

- 1591 • Sponsors should describe in the protocol and in the clinical study report the provisions made with  
1592 respect to access to treatment post trial. This information can form part of the clinical study report  
1593 in accordance with ICH E3.
- 1594 • EU Competent Authorities should identify those studies that may give rise to special ethical concern  
1595 regarding access to treatment post trial and where applicable to seek additional assurance that the  
1596 solution was appropriate and ethically acceptable.
- 1597 • The applicant should explain in the MAA how the medicinal product has been/will be made available  
1598 in the countries where the trials were conducted and this information should be summarised in the  
1599 European Public Assessment Report (EPAR).

## 1600 ***7.2. Determine the practical steps undertaken during the provision of*** 1601 ***guidance and advice in the drug development phase.***

- 1602 • Clinical trials are conducted not only for submission to the EEA but also to many other regulators  
1603 worldwide. In order to minimise risk of non-approvability of the application due to the choice of  
1604 study populations not applicable to the EEA population or trial designs not acceptable in the EEA  
1605 sponsors should seek EU scientific advice prior to the conduct of those trials.
- 1606 • EMA Committees and working Parties (and assessors) evaluating requests for Scientific Advice,  
1607 Orphan designation, and Paediatric Investigation Plans should systematically consider the issues  
1608 raised in this reflection paper and apply the proposals during their assessments and  
1609 recommendations/opinions provided to the applicants.
- 1610 • Applicants should clearly explain why data from the patient populations selected are applicable to  
1611 the EEA population unless the product is intended to be used outside the EEA.

1612 **7.3. Determine the practical steps to be undertaken during the Marketing**  
1613 **Authorisation phase**

1614 **7.3.1. Points to consider during the assessment process: identify**  
1615 **assessment issues and processes**

- 1616 • The European Medicines Agency should establish a pool of experts to advise the CHMP in its  
1617 assessment of the ethical aspects of clinical trials submitted with the MAA, and define their  
1618 membership, required expertise, mandate and procedures, and the process by which the CHMP,  
1619 EMA or other agency scientific committee, may consult them. Such consultation may be on general  
1620 matters of principle involved in establishing requirements and guidance, or specific cases involving  
1621 particular trials and products.
- 1622 • EU Competent Authorities should develop a system for review of MAA dossiers, and identification of  
1623 studies of potential ethical or GCP concern, involving review at the time of validation by the EMA  
1624 product team, and during the assessment by the assessment team and CHMP, supported by the  
1625 EMA product team.

1626 **7.3.2. Inspections: triggers for inspection to be identified by assessor**

- 1627 • The criteria used as the basis for both routine and triggered GCP inspections should be further  
1628 developed.
- 1629 • The processes for identifying triggers for GCP inspections should be further developed and  
1630 systematised.
- 1631 • Frameworks for contact with National Regulatory Authorities, to gain information on the GCP  
1632 compliance and local inspection, in the countries where clinical trials take place should be  
1633 developed.

1634 **7.3.3. Actions available in response to non compliance**

- 1635 • EU Competent Authorities should develop a system for regulatory action in case of non compliance  
1636 with ethical and GCP requirements.
- 1637 • Where clear serious concerns are identified the EU competent Authority should communicate these  
1638 concerns to the National Regulatory Authority of the Country (ies) concerned.

1639 **7.3.4. Transparency, including improvement of EPAR content and**  
1640 **consistency**

- 1641 • The CHMP assessment report and the European Public Assessment Report should describe clearly  
1642 the clinical trials included in the Marketing Application dossier, listing the trials and details  
1643 concerning their conduct. The applicant should provide tabular listings of this information to  
1644 facilitate this process.
- 1645 • The EPAR should describe the assessment of the ethical issues and GCP compliance of the trials in  
1646 the Marketing Authorisation Application, steps (including inspection) taken to confirm this and  
1647 expert advice sought. The EPAR should confirm that the trials have been considered to have  
1648 fulfilled requirements, or, if that is not the case should describe the circumstances and details of  
1649 studies which have been found not conducted in accordance with ethical requirements and GCP,  
1650 and the actions taken as a consequence..

1651 **7.4. *International cooperation in the regulation of clinical trials their***  
1652 ***review and inspection and capacity building in this area***

1653 **7.4.1. Identification of Priorities**

- 1654 • The EMA will prioritise the third countries with which it will focus its interaction based firstly on the  
1655 numbers of trial subjects recruited there as part of clinical trials submitted to EMA and secondly on  
1656 a review of the regulatory systems in place for the supervision of clinical trials in those countries.

1657 **7.4.2. Identification of Opportunities and partners**

- 1658 • The EMA will identify other initiatives that are being carried out in the area of clinical trials  
1659 supervision, mapping of regulatory systems in place and capacity building.
- 1660 • EMA will identify contact points with the other initiatives in order to identify partnerships for joint,  
1661 common or coordinated activities.

1662 **7.4.3. Action Plan**

- 1663 • Refer to the Action Plan outlined in section 6.3 of the Reflection paper for detailed actions.

1664 **7.4.4. Resource considerations**

- 1665 • EMA will identify resource requirements and budget to support EMA participation to capacity  
1666 building activities, as part of its work programmes for 2011 and onwards.
- 1667 • EMA will identify and work with other funding bodies in order to benefit from potential funds to  
1668 support EMA or EU Member State experts contribution to capacity building exercises.
- 1669 • EMA will identify and work with other funding bodies in order to identify funds that may help  
1670 delegates from concerned third countries to participate and benefit from capacity building  
1671 exercises.

## 8. References

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