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Consultation document

**Ethical considerations for clinical trials on medicinal products
conducted with minors**

**Recommendations of the expert group on clinical trials for the implementation of
Regulation (EU) No 536/2014 on clinical trials on medicinal products for human
use**

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

21 **Note for Public consultation**

22 The main objective of updating these recommendations is to align them with the requirements
23 of the Clinical Trials Regulation (EU) No 536/2014 and with the latest (scientific) insights on
24 research with children.

25 Main changes were made on the following:

- 26 • More emphasis on the evolving maturity of children, underlying the requirement of
27 the Regulation to respect the explicit wish of a minor to refuse participation in, or to
28 withdraw from, a clinical trial at any time;
- 29 • Recommendations on the requirement of participation of the minor in the informed
30 consent process;
- 31 • Introduction of the term ‘agreement’, equivalent to the term ‘assent’ in medical
32 literature, since the Regulation reserves the term ‘assent’ to have legal value in some
33 Member States;
- 34 • More emphasis on informed consent as a continual process;
- 35 • More emphasis on burden, next to risk, its subjective nature and the importance to
36 involve children in the assessment and minimisation of burden;
- 37 • Assessment of the relationship between benefit, risk and burden, in particular when
38 there is no direct benefit for the participant, only benefit for the population, and the
39 risk and burden should be minimal in comparison to the standard treatment;
- 40 • Additional recommendations for emergency situations;
- 41 • Addition of the latest insights on trial designs and sampling methods;
- 42 • Additional recommendations on trials with female adolescents;
- 43 • Updates on data protection;
- 44 • Updates on GCP compliance.

45

Specific feedback on the following topics would be highly appreciated:

Q1: The table of Annex 3 (previously Annex 4) has not been changed. Is the proposed categorisation of these procedures still adequate?

Q2: Which insights may lead to changes in categorisations (in particular those indicated in yellow)?

F1: General feedback on clinical trials in minors in emergency situations (within the meaning of article 35 of the clinical trials Regulation) is welcome.

F2: If you are aware of any other relevant references you are invited to put them forward.

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48	TABLE OF CONTENTS	
49	EXECUTIVE SUMMARY	5
50	1. INTRODUCTION - RATIONALE FOR THE DEVELOPMENT OF	
51	RECOMMENDATIONS	5
52	2. SCOPE	6
53	3. ETHICAL PRINCIPLES AND FUNDAMENTAL RIGHTS	7
54	4. LEGAL CONTEXT	7
55	4.1 LEGAL CONTEXT	7
56	4.2 RELEVANT GUIDELINES	8
57	5. DEFINITIONS/ GLOSSARY	9
58	5.1 AGE GROUPS	9
59	5.2 ASSENT	9
60	5.3 AGREEMENT	9
61	5.4 CHILD	10
62	5.5 ETHICAL REVIEW	10
63	5.6 INFORMED CONSENT	10
64	5.7 LEGALLY DESIGNATED REPRESENTATIVE OF THE MINOR	11
65	5.8 MINOR	11
66	5.9 PAEDIATRIC POPULATION	11
67	6. THE PROCESS OF INFORMED CONSENT	11
68	6.1 INFORMED CONSENT FROM THE LEGALLY DESIGNATED REPRESENTATIVE	11
69	6.2 PARTICIPATION OF THE CHILD IN THE INFORMED CONSENT PROCESS	13
70	6.3 INFORMED CONSENT OF FAMILIES WITH DIFFERENT CULTURAL BACKGROUND	13
71	6.4 CONSENT AT THE BEGINNING OF A TRIAL AND CONTINUED CONSENT DURING TRIAL	13
72	6.5 WITHDRAWAL OF THE CONSENT	13
73	6.6 CONSENT, ASSENT AND AGREEMENT IN EMERGENCY SITUATIONS	14
74	7. PARTICIPATION OF MINORS IN THE INFORMED CONSENT PROCESS AND	
75	AGREEMENT	15
76	7.1 ASSENT	16
77	7.2 PARTICIPATION AND AGREEMENT ACCORDING TO AGE GROUPS AND LEVEL OF MATURITY	16
78	7.2.1 <i>Newborns and infants (from birth to 2 years of age)</i>	16
79	7.2.2 <i>Pre-schoolers (2-5 years of age)</i>	17
80	7.2.3 <i>Schoolers (6-9 years of age)</i>	17
81	7.2.4 <i>Adolescents (10-18 years of age)</i>	17
82	7.3 DIFFERENCE OF OPINION BETWEEN THE CHILD AND THE PARENTS/LEGALLY DESIGNATED	
83	REPRESENTATIVE	18
84	8. EXPERTISE REQUIRED FOR ASSESSMENT	18
85	8.1 PAEDIATRIC EXPERTISE	18
86	8.2 METHODOLOGICAL EXPERTISE	19
87	8.3 OPINION ON THE APPLICATION DOSSIER	19
88	9. DESIGN OF CLINICAL TRIALS CONDUCTED WITH THE PAEDIATRIC	
89	POPULATION	20
90	9.1 DESIGN AND ANALYSIS	20
91	9.2 PAEDIATRIC CONTROL GROUPS	21
92	9.2.1 <i>Use of placebo</i>	21
93	9.2.2 <i>Superiority versus non-inferiority trials</i>	22
94	9.2.3 <i>Controlled trials using (reference) medicinal products without a marketing authorisation</i>	
95	<i>in children</i>	22
96	9.2.4 <i>Clinical trials using medicinal products containing radio-isotopes</i>	23
97	10. THE CONCEPT OF BENEFIT	23

Ethical considerations for clinical trials on medicinal products conducted with minors

98	10.1 PROSPECT OF DIRECT BENEFIT FOR THE MINOR CONCERNED	23
99	10.2 PROSPECT OF SOME BENEFIT FOR THE POPULATION REPRESENTED BY THE MINOR	24
100	10.3 CLASSIFICATION OF TRIAL PROTOCOLS	24
101	11. IDENTIFYING, MINIMISING AND MONITORING RISKS AND BURDEN	24
102	11.1 ASSESSMENT OF RISK	25
103	11.2 ASSESSMENT OF BURDEN	26
104	11.3 MONITORING THE LEVEL OF RISKS AND BURDEN	27
105	12. ASSESSMENT OF THE RELATIONSHIP BETWEEN BENEFIT, RISKS AND BURDEN	28
106	12.1 ASSESSING TRIALS WITH PROSPECT OF DIRECT BENEFIT FOR THE MINOR CONCERNED	28
107	12.2 ASSESSING TRIALS WITH PROSPECT OF SOME BENEFIT FOR THE POPULATION REPRESENTED BY	
108	THE MINOR	28
109	12.2.1 <i>Standard treatment</i>	31
110	12.2.2 <i>Assessment of risks and burden for individual children</i>	31
111	13. ASSAYS IN RELATION TO AGE/BODYWEIGHT AND BLOOD SAMPLING	31
112	13.1 TYPE OF ASSAYS AND SAMPLE COLLECTION	31
113	13.2 VOLUME OF BLOOD	32
114	14. TRIALS WITH NEONATES (TERM AND PRE-TERM)	32
115	15. TRIALS WITH HEALTHY MINORS	33
116	16. TRIALS WITH ADOLESCENT FEMALES	33
117	17. PAEDIATRIC FORMS AND FORMULATIONS TO BE USED IN PAEDIATRIC TRIALS	33
118	18. INDIVIDUAL DATA PROTECTION	34
119	19. UNNECESSARY REPLICATION OF TRIALS	34
120	19.1 PUBLICATION OF PAEDIATRIC TRIALS AND RESULTS	35
121	19.2 INTERNATIONAL DATABASE AND AVAILABILITY TO THE PUBLIC	35
122	20. ADVERSE EFFECTS REPORTING	35
123	21. INDUCEMENTS VERSUS COMPENSATION FOR CHILDREN	35
124	22. INSURANCE ISSUES	36
125	23. TRIALS WITH CHILDREN IN NON-EU COUNTRIES	36
126	24. ETHICAL VIOLATIONS AND NON-COMPLIANCE WITH GCP	36
127	25. ANNEX 1: LIST OF ISSUES TO BE CONSIDERED IN A CLINICAL TRIAL	
128	INVOLVING MINORS	38
129	26. ANNEX 2: INFORMATION FOR INFORMED CONSENT	40
130	27. ANNEX 3: EXAMPLES FOR LEVELS OF RISKS AND BURDEN	42
131	28. REFERENCES	44
132	28.1 GENERAL GUIDANCE	44
133	28.2 NATIONAL GUIDANCE ON ETHICS	45
134	○ RESEARCH AND CLINICAL TRIALS IN CHILDREN	45
135	28.3 INVOLVEMENT, COMPETENCE, CONSENT AND ASSENT	46
136	28.4 NEONATES IN CLINICAL TRIALS	47
137	28.5 INFORMATION MATERIAL	48
138	28.6 PLACEBO USE AND CLINICAL TRIAL DESIGN	48
139		
140		

141 **EXECUTIVE SUMMARY**

142 This document has been revised by the European Commission expert group on Clinical Trials
143 in preparation for the implementation of **Regulation (EU) No 536/2014**¹ on clinical trials on
144 medicinal products for human use. The objective of the revision is to update these
145 recommendations to bring them in line with the changed legal context of the new regulation.
146 The document provides recommendations on various ethical aspects of clinical trials
147 performed in minors from birth up to the legal age of competence to provide informed
148 consent. This will contribute to the protection of all minors who participate in clinical trials.
149 The protection against the risks of research in such a vulnerable population is paramount,
150 whilst this should not lead to denying them the benefits of research, both from participation in
151 clinical trials and from access to the resulting evidence based medicinal products (recital 8).
152 As the authorisation of clinical trials, including ethical approval, is performed by the Member
153 States, any recommendations on ethical aspects of clinical trials in minors will also facilitate a
154 harmonised approach to the application of the clinical trials Regulation across the EU, thereby
155 facilitating the conduct of clinical trials across the EU, in whichever country the clinical trial
156 in minors occurs.

157 Minors are not small adults and there is a need to carry out specific trials that cannot be
158 performed in adults in order to obtain evidence specifically attuned to the needs of children.
159 By definition, children (minors) are unable to consent (in the legal sense), but they should be
160 involved in the process of informed consent as much as is possible, using age appropriate
161 information. In the ethical review, paediatric expertise is required to balance the benefits,
162 risks and burden of research in minors. The difference between minors and adults as research
163 participants has implications on the design, conduct and analysis of trials, which should also
164 include paediatric expertise. Pain, fear, discomfort and parental separation should be
165 prevented and minimised when unavoidable. The neonate represents the most vulnerable of
166 all paediatric age groups and requires even more careful review Finally, various other aspects
167 relating to the performance of trials in children are discussed.

168 **1. INTRODUCTION - RATIONALE FOR THE DEVELOPMENT OF**
169 **RECOMMENDATIONS**

170 Off label use of medicinal products in children without proper evidence poses an ethical
171 problem. That is why the need for clinical trials with children has now been widely
172 recognised and is stimulated by European legislation, e.g. by requiring Paediatric
173 Investigation Plans². At the same time, children are a vulnerable population, relatively
174 incapable of protecting their own interests, and therefore they deserve protection against the
175 risks and burden of research. It is the duty of all involved in paediatric research to minimise
176 and mitigate any risks and burden while doing research with children. That is why in
177 Regulation (EU) No 536/2014 (hereinafter the Clinical Trials Regulation) an appropriate
178 balance is sought between protecting children (i.e. minors in the meaning of the Clinical
179 Trials Regulation) and enabling research that provides evidence for good medical care. Trials
180 are necessary and should aim at progressing the wellbeing and treatment, prevention and
181 diagnosis of ill health of patients, including children. Furthermore, clinical trials facilitate the
182 development of appropriate drug dosage forms. Although the same ethical principles apply
183 across age ranges, from children to the elderly, additional protection should be defined for
184 research performed in minors, at all stages and ages.

¹ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance)

² Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use

Ethical considerations for clinical trials on medicinal products conducted with minors

185 The reasons why medicinal products need to be studied in minors have been detailed in
186 various publications. In summary, minors are not small adults. Data on effectiveness and
187 safety cannot reliably be derived from data in adults. Major changes in pharmacokinetics and
188 pharmacodynamics occur with increasing age, due to changes in body composition, drug
189 metabolism and transport and renal function. Growth and maturation processes, as well as
190 certain specific diseases are unique to children. Specific consequences of medical
191 interventions may be seen in minors if no appropriate clinical trials are conducted and may
192 only appear long after exposure. Unfortunately this has been demonstrated by previous
193 calamities with the use of medicinal products. Trials are therefore necessary in the paediatric
194 population to develop a better knowledge of drugs' effects in children (safety and efficacy).

195 Because of the special protection they deserve, minors should not be the subject of clinical
196 trials when the research can be done in legally competent subjects (i.e. adults capable of
197 informed consent). If research with minors proves necessary, in line with Article 32(1e) of the
198 Clinical Trials Regulation, the least vulnerable among them should usually be included.
199 However, a 'staggered approach' (starting by the older and going sequentially to the younger
200 age groups), has not been shown to protect younger study participants but leads to delays in
201 data availability, and is therefore not recommended. Such an approach will ultimately result
202 in prolonged off-label use for the younger age groups (especially neonates) and the
203 impossibility of conducting any trial to provide age specific evidence for these groups. If
204 there is a necessity to subject minors to a clinical trial, the choice of subsets of the paediatric
205 population to be included should be made on the basis of the likely real-life target population
206 for the medicine being tested, the possibility of extrapolation, and the scientific validity of
207 such an approach.

208 The recommendations in this document aim to bring together ethical principles from the
209 various documents that already exist (cf. section 4.2), as they are understood currently. In
210 addition, the European Network of Paediatric Research (Enpr-EMA) has recognised expertise
211 in performing clinical studies with children and has the main objective to foster high-quality,
212 ethical research on the quality, safety and efficacy of medicines for use in children. Over time,
213 with changing legislation or progressing insights, e.g. by Enpr-EMA, the need for further
214 revision of this document may emerge.

215 2. SCOPE

216 This document is intended to provide recommendations on various ethical aspects related to
217 the conduct of interventional clinical trials and studies falling under the provisions of the
218 Clinical Trials Regulation on medicinal products for human use.

219 The document is intended as recommendations for all persons involved in any stage of a
220 clinical trial, including sponsors of clinical trials, assessors, regulatory authorities,
221 pharmaceutical companies, insurance companies (regarding trial subjects), investigators
222 (including all trial-related staff) of clinical trials performed in children of all ages (minors, cf.
223 section 5.8), families, and participants. This document is without prejudice to the obligations
224 created by the Clinical Trials Regulation and other European and Member State legislation.

225 This document focuses on the ethical specificities of clinical trials with minors and should
226 therefore be read in conjunction with the relevant legal texts and guidelines. In particular, the
227 specific legislation of the Member States may differ. These recommendations do not
228 distinguish between non-commercial and commercial research.

229

230 **3. ETHICAL PRINCIPLES AND FUNDAMENTAL RIGHTS**

231 The Clinical Trials Regulation and these underlying recommendations should be applied in
232 line with the Charter of Fundamental Rights of the European Union (2012). In particular
233 Article 24 on the rights of the child is relevant in this context (see also recital 83 of the
234 Clinical Trials Regulation).

235 In addition, ethical principles referred to in this document are those expressed, for example, in
236 the Declaration of Helsinki published by the World Medical Association (2008)³, the
237 International Ethical Guidelines for Biomedical Research Involving Human Subjects of the
238 Council for International Organizations of Medical Sciences (CIOMS) in collaboration with
239 the World Health Organization (WHO (Geneva 2002), the United Nations' Convention on the
240 Rights of the Child, the Universal Declaration on Bioethics and Human Rights (UNESCO,
241 2005), the Universal Declaration on the Human Genome and Human Rights (UNESCO,
242 1997), the International Declaration on Human Genetic Data (UNESCO, 2003), the Universal
243 Declaration of Human Rights of 1948, and the Council of Europe's Convention for the
244 Protection of Human Rights and Dignity of the Human Being with regard to the Application
245 of Biology and Medicine: Convention on Human Rights and Biomedicine and its additional
246 protocol concerning biomedical research. These principles are also echoed and referred to in
247 the ICH E6 guideline on Good Clinical Practice and in the ICH E11 guideline on the Clinical
248 Investigation of Medicinal Products in the Paediatric Population.

249 Although the above mentioned documents might differ and emphasize specific ethical
250 requirements, they share a common ground. They all build on four important ethical
251 principles that should be adhered to when performing research with children: Beneficence,
252 non-maleficence, respect for persons and justice. Beneficence is defined as the ethical
253 obligation to secure/promote well-being and non-maleficence is the obligation to avoid harm.
254 Respect for persons is defined as the obligation to treat individuals as autonomous agents and
255 protect those with diminished autonomy. Justice is defined as a fair distribution of risk,
256 burden and benefits of research. These are fully applicable to clinical trials in children.

257 The Clinical Trials Regulation underlines the importance of taking account of the wishes of
258 children with regard to their participation in clinical trials. The Regulation requires their full
259 engagement with the aim to treat children as developing autonomous beings, whose maturity
260 gradually evolves with age and experience, and whose will should be taken seriously.
261 Although it is acknowledged that children form a vulnerable group, the focus should be on
262 their capacities and the shared goal of enabling them to participate in decision making
263 processes.

264 **4. LEGAL CONTEXT**

265 **4.1 Legal context**

266 – Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April
267 2014 on clinical trials on medicinal products for human use, and repealing Directive
268 2001/20/EC (herein the 'Clinical Trials Regulation').

269 – Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001
270 on the Community code relating to medicinal products for human use.

271 – Directive 2003/94/EC of the European Commission of 8 October 2003 laying down the
272 principles and guidelines of good manufacturing practice in respect of medicinal products

³ This version of the Declaration of Helsinki is referenced in the Clinical Trials Regulation.

Ethical considerations for clinical trials on medicinal products conducted with minors

- 273 for human use and investigational medicinal products for human use. [Note: this will be
274 repealed – reference to the new legislation will be included after the public consultation]
- 275 – Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down
276 Community procedures for the authorisation and supervision of medicinal products for
277 human and veterinary use and establishing a European Medicines Agency.
- 278 – Regulation (EC) No 1901/2006 of the European Parliament and the Council, on medicinal
279 products for paediatric use and amending Regulation (EEC) No 1768/92, Directive
280 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (herein the
281 ‘Paediatric Regulation’).

282 **4.2 Relevant guidelines**

- 283 – Clinical Investigation of Medicinal Products in the Paediatric Population (E 11),
284 CPMP/ICH/2711/99 (addendum E11(R1) under preparation)
- 285 – Concept paper on the involvement of children and young people at the Paediatric
286 Committee (EMA/PDCO/388684/2012)
- 287 – Guideline for Good Clinical Practice (E 6), CPMP/ICH/135/95, CPMP
- 288 – Choice of Control Group in Clinical Trials (E 10), CPMP/ICH/364/96, CPMP
- 289 – Guideline on clinical trials in small populations, CHMP/EWP/83561/05, CHMP
- 290 – Guideline on conduct of Pharmacovigilance for medicines used by the paediatric
291 population (June 2006) EMA/CHMP/PhVWP/235910/2005- rev.1, CHMP
- 292 – Guidelines on Good pharmacovigilance practices (GVP)⁴, EMA
- 293 – Detailed guidance on the European database of Suspected Unexpected Serious Adverse
294 Reactions (EudraVigilance – Clinical Trial Module) ENTR/F2/BL D(2003) [note: this
295 reference will be updated].
- 296 – The rules governing medicinal products in the European Union. Volume 10 – Guidance
297 documents applying to clinical trials. Questions & Answers, Version 11.0 [note: update of
298 this document is ongoing].
- 299 – Standards and operational guidance for ethics review of health-related research with
300 human participants, World Health Organization (WHO)_(Geneva, 2011)
- 301 – International Ethical Guidelines for Biomedical Research Involving Human Subjects,
302 Council for International Organizations of Medical Sciences (CIOMS) in collaboration
303 with the World Health Organization (WHO). (Geneva 2002).
- 304 – Management of Safety Information from Clinical Trials. Report of CIOMS Working
305 Group VI, Council for International Organizations of Medical Sciences (CIOMS)

4

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

306 **5. DEFINITIONS/ GLOSSARY**

307 **5.1 Age groups**

308 When referring in these recommendations to a specific subset of the paediatric population, the
309 age range will be given for clarity. This age range is meant to provide guidance regarding the
310 proper involvement of minors of different ages in the informed consent process. With the
311 exception of the age range of 2 to 11 years, subsets of the paediatric population as defined in
312 ICH E11 are adopted, and the age group of 2 to 11 years is redefined. This leads to the
313 following age groups: preterm newborn infants (gestational age less than 37 weeks, post-natal
314 age up to one month), term newborn infants (gestational age 37 weeks or more, post-natal age
315 up to one month), infants (1-23 months), preschoolers (2-5 years), schoolers (6-9 years) and
316 adolescents (from the age of 10 up to but not including 18 years). Of note, in some Member
317 States not all adolescents are regarded as minors (see section 5.8)

318 It should be noted that these age groups only partly correlate with maturation especially from
319 the developmental point of view. Where it is necessary to set some boundaries, the definition
320 of the different age groups should be viewed as a practical instrument. Maturity rather than
321 age should be the starting point for the way a trial is discussed with children. Each individual
322 child should be involved in a way that matches his or her maturity and ability to take part in
323 the decision making process. Although this may be difficult, as ‘maturity’ is not a clear-cut
324 criterion in contrast to age, such an approach will foster more attention to differences between
325 children and will support that they are properly involved in decisions that concern them.

326 It is important to distinguish the above mentioned age groups from ‘physiological or
327 metabolic’ definitions of age groups, which will be used for other purposes, for example to
328 define dose, or to establish inclusion criteria.

329 **5.2 Assent**

330 The term assent in the context of the Clinical Trials Regulation has a different meaning from
331 that in medical literature and therefore also in this document, since it has legal value
332 depending on Member State law (cf. Section 5.3).

333 The notion of assent is explicitly included in article 29(8) of the Clinical Trials Regulation:
334

335 “This Regulation is without prejudice to national law requiring that, in addition to the
336 informed consent given by the legally designated representative, a minor who is
337 capable of forming an opinion and assessing the information given to him or her,
338 shall also assent in order to participate in a clinical trial.”

339 In this document, “assent” should be understood as a legally required expression of the
340 minor’s will to participate in a clinical trial, dependent on Member State law. Usually the
341 legal requirement of assent only applies to minors of a certain age. Assent is a statement of
342 will with legal value, required at the same time as the consent of the parents/legally
343 designated representative. The minor’s assent is not sufficient to allow participation in
344 research unless supplemented by informed consent of the parents/legally designated
345 representative.

346 **5.3 Agreement**

347 The Clinical Trials Regulation provides a number of conditions for participation of minors in
348 clinical trials, one of which is for investigators to respect the explicit wish of a minor, who is
349 capable of forming an opinion and assessing information, to refuse participation in, or to
350 withdraw from, the clinical trial at any time.

Ethical considerations for clinical trials on medicinal products conducted with minors

351 Agreement in this document is used in accordance with the term "assent" in the medical
352 literature. It means the expression of the minor's will to participate in a clinical trial. This
353 document supports a systematic request for agreement, and recommends that the investigator
354 obtains agreement from the child in addition to informed consent of the parents/legally
355 designated representative, even when this agreement is not mandatory by law.

356 The way in which the minor participates in the informed consent process, leading to the
357 potential agreement, depends on his or her maturity. So agreement is not age-dependent, in
358 contrast to legally required assent. In addition, whereas lack of legal assent mostly means the
359 minor's refusal to participate (depending on Member State law), lack of agreement does not
360 necessarily mean the child will not participate, since it may be evaluated that the child is not
361 mature enough to express agreement.

362 Dissent however, meaning the expression of the minor's will not to participate, should be
363 respected, in line with Article 32(1c) of the Clinical Trials Regulation on condition that the
364 minor is capable of forming an opinion and assessing the information given.

365 The Clinical Trials Regulation requires the following involvement of the minor in the
366 informed consent procedure (Article 32):

367 "1(b) the minors have received the information referred to in Article 29(2) in a way
368 adapted to their age and mental maturity and from investigators or members of the
369 investigating team who are trained or experienced in working with children;
370 1(c) the explicit wish of a minor who is capable of forming an opinion and assessing
371 the information referred to in Article 29(2) to refuse participation in, or to withdraw
372 from, the clinical trial at any time, is respected by the investigator;
373 2. The minor shall take part in the informed consent procedure in a way adapted to
374 his or her age and mental maturity."

375 The notion of agreement recognises the evolving autonomy of minors. The capacity of a
376 minor to make voluntary, informed decisions i.e. to agree to participate in a clinical trial,
377 evolves with age, maturity and previous experience of life and illness.

378 The recommendations provided in this document refers both to (legally-required) assent and
379 to agreement, which were covered by the term "assent" in the previous version of this
380 document as referred to in the Declaration of Helsinki (2008).

381 5.4 Child

382 When the term "children" is used within these recommendations, it is used consistently with
383 the provisions of the Clinical Trials Regulation to mean minors, in contrast to ICH E11
384 guideline which refers to children as individuals aged from 2 to 11 years.

385 5.5 Ethical review

386 The ethical review shall be performed in accordance with the Clinical Trials Regulation and
387 the law of the Member State concerned. Member State law will define the body performing
388 the ethical review. In the case of paediatric clinical trials, there is a requirement to include
389 paediatric expertise during the assessment of applications for the authorisation of clinical
390 trials.

391 5.6 Informed consent

392 Article 2(2.21) of the Clinical Trials Regulation defines:

393 "Informed consent means a subject's free and voluntary expression of his or her
394 willingness to participate in a particular clinical trial, after having been informed of

Ethical considerations for clinical trials on medicinal products conducted with minors

395 all aspects of the clinical trial that are relevant to the subject's decision to participate
396 or, in case of minors and of incapacitated subjects, an authorisation or agreement
397 from their legally designated representative to include them in the clinical trial."

398 Articles 29 and 32 of the Clinical Trials Regulation provide additional requirements related to
399 informed consent. In this document, "consent" refers to the legal definition of informed
400 consent, as stated above. The Clinical Trials Regulation states that the child should be
401 involved in the process of informed consent.

402 Some Member States use the concept of assent, meaning that minors of a certain age are
403 required to assent, in addition to the consent given by the parents/legally designated
404 representative.

405 5.7 *Legally designated representative of the minor*

406 Article 2(2.20) of the Clinical Trials Regulation defines a legally designated representative as
407 "a natural or legal person, authority or body which, according to the law of the
408 Members State concerned, is empowered to give informed consent on behalf of a
409 subject who is an incapacitated subject or a minor."

410 For most minors, the legally designated representative will be one or both parents, depending
411 on national law. Although national law may allow written consent from only one parent, both
412 parents should be encouraged to participate in the informed consent process. Legally
413 designated representatives may be other family members, guardians or local authorities.
414 Parents/legally designated representative have the duty to protect their child, the child's
415 interests, and the child's point of view based on their knowledge of the child during the child's
416 life up to that time.

417 5.8 *Minor*

418 Article 2(2.18) of the Clinical Trials Regulation defines:

419 "Minor means a subject who is, according to the law of the Member State concerned,
420 under the age of legal competence to give informed consent."

421 Of note, in the case of multinational trials the age of legal competence may differ across
422 Member States.

423 5.9 *Paediatric population*

424 According to Regulation (EC) No 1901/2006, the term "paediatric population" refers to the
425 part of the population aged between birth and 18 years. This term is used throughout these
426 recommendations to cover all paediatric age groups. Exposure to medicinal products may
427 occur before birth in the context of clinical trials with pregnant women; this topic is not
428 covered in this document.

429 6. The process of informed consent

430 6.1 *Informed consent from the legally designated representative*

431 As the child (minor) is unable to provide legal consent, informed consent must be sought
432 from the parents/legally designated representative (see definition above) on the child's behalf.
433 Articles 29 and 32 of the Clinical Trials Regulation require that the specific and written
434 informed consent of parents/legally designated representative must be sought prior to
435 enrolling a child in a trial.

Ethical considerations for clinical trials on medicinal products conducted with minors

436 The person providing the information – usually the investigator or his adequately trained
437 delegate – should be experienced in providing such information and in working with children.
438 The information should be given to each parent, or the legally designated representative, both
439 in oral and written form. Article 29.2(a) describes the information that should be provided.
440 The parents/legally designated representative should be given sufficient time and necessary
441 information to consider their decision to endorse participation of their child. When providing
442 such information, it is important to take into consideration the fear and uncertainty of parents,
443 especially when they are inexperienced with respect to the child's condition.

444 Regarding the information given to the parents/legally designated representative, items for
445 review by the ethics committee are proposed in Annex 1.

446 When seeking informed consent, the investigator should not put undue pressure on the
447 parents/legally designated representative. In particular:

448 – Parents/legally designated representative should be explicitly informed of their right to
449 refuse to have the child participate and the right to withdraw their child from the clinical
450 trial at any time without any resulting detriment for the child and without having to
451 provide any justification, in line with Article 29(2aii) of the Clinical Trials Regulation.

452 – According to Article 32(1d) of the Clinical Trials Regulation there must not be financial
453 inducement to enrol the child in the trial; no financial incentive should be offered except
454 compensation for expenses and loss of earnings of the parents directly related to the
455 participation in the clinical trial.

456 In the complex relationship between parents and physician(s), especially in case of chronic
457 diseases and of rare diseases, but also in acute serious illnesses, or in the situation of less
458 educated parents, there is a risk of perceived obligations and emotional subordination on the
459 side of the parents. Moreover, this may not be perceived by either party. Therefore, the
460 investigator should not put undue pressure or be the one to make the decision on participation,
461 but should ensure that the information has been understood and that there has been enough
462 time allowed to come to a decision. Provision of information is a continual process.

463 If an adolescent is no longer a minor as defined by the Clinical Trials Regulation, or is an
464 “emancipated minor”⁵, then written informed consent is required from these individuals as for
465 any adult capable of giving consent. Under these conditions, informed consent is no longer
466 required from the parents/legally designated representative. As soon as a minor becomes
467 legally competent to give informed consent during the course of the trial, no trial-related
468 procedures may be performed until informed consent is provided.

469 Considering that the age when a person is considered to be an adult is highly variable across
470 Member States, a multi-state trial may include at the same time minors of the same age who
471 are still minors in one Member State and "adults" i.e. those able to consent in another Member
472 State. Adolescents may still have some elements of vulnerability, even though they are legally
473 allowed to provide their own consent. In practice, the adolescent with the legal capacity to
474 consent may decide to involve his or her parents in the informed consent process. The
475 information given to adolescents should therefore recognize the potential situation of
476 vulnerability.

⁵ This is a legal term and applies under exceptional conditions: Minors can become emancipated through certain actions, such as marriage.

477 **6.2 *Participation of the child in the informed consent process***

478 Consent in line with Article 29 of the Clinical Trials Regulation should be obtained from the
479 parents/legal representative and, in line with Article 32, the child should be involved
480 throughout this process and receive the information adapted to their age and mental maturity.
481 Participation of minors is addressed in section 7.

482 **6.3 *Informed consent of families with different cultural background***

483 It is important that the language skills of the child and consenting parents/legal representative
484 are sufficient for them to understand the provided information. Also cultural differences may
485 lead to misunderstandings. Where appropriate, a translator and/or a cultural mediator, familiar
486 with medical terminology, experienced in the language, social habits, culture, traditions,
487 religion and particular ethnic differences should be available in the process of obtaining
488 informed consent. A translated informed consent form could also be an appropriate way to
489 provide trial related information adapted to the specific needs of families with a different
490 cultural background.

491 **6.4 *Consent at the beginning of a trial and continued consent during trial***

492 As discussed above, investigators should devote sufficient time to provide information and
493 seek the parents'/legally designated representative's consent as well as the child's
494 assent/agreement prior to trial enrolment. It is important to realise that consent is a dynamic,
495 continual process, and should therefore not only be obtained prior to enrolling a child in a trial
496 but should be maintained during the trial on a continual basis. The child should be involved in
497 this (cf. Section 7). This could be done, for example, by a brief discussion during each repeat
498 visit. It is recommended to document this process in the medical records or equivalent. The
499 discussion is part of the ongoing dialogue between children, parents and investigators and
500 should focus on all aspects of the trial but in particular on any new information that arises in
501 relation to the trial and that might affect the willingness of the parents and child to continue.

502 During the progress of the trial, especially in long-term trials, the investigator should check
503 the progressing maturity of the child and his or her ability for assent/agreement. This should
504 be documented.

505 In the rare event of a change in legally designated representative during the trial, informed
506 consent should be sought again as soon as possible.

507 **6.5 *Withdrawal of the consent***

508 In all circumstances, parents/legally designated representative should be made aware of the
509 right to refuse participation in a clinical trial and are entitled to freely withdraw their informed
510 consent at any time, without giving reasons. Parents/legally designated representative should
511 be reassured that the withdrawal from the trial will not prejudice the child, will not result in
512 any detriment and will not affect the provision of normal clinical practice⁶. In addition, refusal
513 to give consent or withdrawal of consent to participation in research must not lead to any
514 liability or discrimination (e.g., with regard to insurance or employment) against the person
515 concerned. The parents/legally designated representative need to be informed about the risks
516 that premature termination of the trial would present to the subject's health, if applicable.

⁶ Normal clinical practice is defined by the Clinical Trials Regulation as the treatment regime typically followed to treat, prevent, or diagnose a disease or disorder.

Ethical considerations for clinical trials on medicinal products conducted with minors

517 Parents/legally designated representative who give informed consent for a child to participate
518 in clinical trials should have the opportunity to follow the research as it proceeds (unless
519 clinically inappropriate, e.g., during an operation under general anaesthesia), so as to be able
520 to decide on whether to withdraw the child from the research at any time. In the event of
521 withdrawal from a blinded trial, if the parents/legally designated representative wish to
522 continue to follow the progress of the trial, and it should be stated that the summary of the
523 results, including a summary that is understandable to a layperson, will be available in the EU
524 database.

525 When consent is withdrawn during a procedure, for example, during anaesthesia, it may not
526 always be possible to stop the procedure immediately, as this might jeopardize the health of
527 the child. If this possibility can be envisaged beforehand, due to the trial design or a specific
528 intervention, this should be clearly explained as part of the initial consent process, to manage
529 expectations before the situation arises.

530 It must be emphasised that after a child withdraws from a trial, the investigator is still
531 responsible for reporting trial-related events. In addition, the investigator needs to assure
532 appropriate treatment and follow-up.

533 6.6 Consent, assent and agreement in emergency situations

534 Research involving children in rapidly evolving, life-threatening situations is necessary to
535 advance outcomes and treatments. Emergency situation trials may concern children with
536 various conditions, including some that are specific, or relatively frequent, in children (e.g.
537 initial manifestations of metabolic diseases, status epilepticus, acute trauma). In some
538 emergency situations, consciousness may be altered and/or treatment or intervention is
539 required within minutes, thus the parents/legally designated representative may not be
540 available to provide prior informed consent and children cannot be informed, nor express
541 assent or agreement.

542 Article 35 of the Regulation provides for derogation from prior informed consent
543 requirement, including for paediatric trials in emergency situations, with some restrictions.
544 However, in all cases, informed consent should be sought as soon as possible after the
545 decision to include the child into the trial or after the first intervention (sometimes called
546 deferred consent). Of note, there is no derogation for such clinical trials from the requirement
547 to respect the child's explicit wish to refusal to participate.

548 Recruitment and inclusion procedures for such trials should be scrutinised from the ethical
549 perspective, in particular the time lag until consent is obtained, how and by whom the
550 decision to include the child in the trial will be taken, information given to the legally
551 designated representative, highlighting the right to object to the use of the data obtained in
552 these circumstances, and the assent or agreement process.

553 Various approaches to obtain informed consent in particular situations have been used or
554 should be considered according to national law. It is sometimes possible to identify
555 participants before the emergency situation arises (known risk of worsening, for example,
556 sepsis in immune-compromised children). This provides opportunities to inform parents, and
557 even early informed consent and assent/agreement (pre-consent). In other cases, awareness of
558 a trial recruiting within a community can be ensured through schools, medias, or outpatient

Ethical considerations for clinical trials on medicinal products conducted with minors

559 clinics.⁷ Emergency situations described in this paragraph are not to be confused with those
560 referred to under article 35 of the Clinical Trials Regulation.

561 Some Member States recommend that a third party is involved (if available in such a
562 timeframe, a healthcare provider knowing the child) with the responsibility to protect the
563 child's best interest. Conversely, other Member States prohibit to ask third parties (for
564 example teachers) to substitute for the legally designated representative.

565

Feedback requested:

General feedback on clinical trials in minors in emergency situations (within the meaning of article 35 of the Clinical Trials Regulation (EU) No 536/2014) is welcome.

566

567 **7. Participation of minors in the informed consent process and agreement**

568 The child should participate in the informed consent process together with the parents (article
569 32(2)), in a way that is appropriate to his or her age and maturity (Article 32(1b) of the
570 Clinical Trials Regulation). The aim is to treat children as persons who, in the context of their
571 own family and social environments, have the potential from an early age to play an active
572 role in determining their own lives and in engaging with others. Involving children in
573 discussions and the decision-making process respects their emerging maturity. This process
574 should be conducted with enough time and at the same time as obtaining consent from the
575 parents/legally designated representative, so that the child is optimally involved in the
576 informed consent process and the minor has the opportunity to dissent (in line with Articles
577 32(2) and 32(1c) of the Regulation). The central role of parents in the protection of their child
578 should be recognised. The parents might also wish to discuss with the child on their own,
579 after having been informed on the trial, and before meeting with the investigator and
580 consenting to participation of their child.

581 This document supports a systematic request for agreement, and recommends that the
582 investigator obtains agreement from the child in addition to informed consent of the
583 parents/legally designated representative, even when this agreement is not mandatory by law.
584 If the child's agreement is not obtained, it is recommended that this be documented with
585 justification in the consent form which is signed by the parents/legally designated
586 representative and investigator.

587 The evaluation to what extent a child is able to provide agreement should not solely be based
588 on chronological age, but should also depend on other factors such as developmental stage,
589 intellectual capacities (especially in children with special needs and/or learning difficulties),
590 life/disease experience, etc. The contribution of these other factors to the child's maturity and
591 the extent to which the child is able to participate in the informed consent process need to be
592 established after discussions between the investigator, the parents/legally designated
593 representative, and the child.

⁷ Wellcome Trust, MRC Hubs for Trials Methodology Research: Research without Prior Consent (Deferred Consent) in Trials Investigating the Emergency Treatment of Critically Ill Children: CONNECT Study Guidance. Version 2 July 2015, available at <https://www.liverpool.ac.uk/psychology-health-and-society/research/connect/>

Ethical considerations for clinical trials on medicinal products conducted with minors

594 Refusal of a minor to participate, i.e. dissent, should be respected, in line with Article 32(1.c)
595 of the Clinical Trials Regulation, stating:

596 “the explicit wish of a minor who is capable of forming an opinion and assessing the
597 information referred to in Article 29(2) to refuse participation in, or to withdraw
598 from, the clinical trial at any time, is respected by the investigator”.

599 It is important to note that “forming an opinion” should not be understood to only apply to
600 children that have reached a certain age or level of maturity, as even young children are able
601 to form and express their opinion in one way or another. Therefore, any objections raised by a
602 child at any time during a trial should be analysed, including those of very young children.
603 The child’s will should be respected. The child does not have to provide reasons. The child
604 should be informed of the possibility to freely withdraw from the trial, at any time for any
605 reason, without any disadvantage or prejudice (cf. section 6.5). This also means that
606 investigators should be able to recognize signs of resistance in children. They should evaluate
607 whether these signs are part of the anticipated burden (e.g. distress or fear), consult with the
608 parents/legally designated representative, and appropriately respond to the child’s worries,
609 e.g. by trying to decrease the burden. This behaviour may lead to the understanding that the
610 child dissents, and that therefore the child should not be enrolled in or should be withdrawn
611 from the trial.

612 Separate information material for adults and children should be used in order to provide age
613 appropriate information, in visuals, language and wording appropriate to age and
614 psychological and intellectual maturity. The information material should be ethically
615 approved by the Member State concerned. The information material should have been tested
616 in the relevant population, and should include provision of information on all the relevant
617 aspects of the trial, in terms that are honest, but not frightening, using visual such as
618 drawings, cartoons etc. See also Annex 2 for recommended contents. In addition, separate
619 consent and agreement forms (where applicable, cf. Section 7.2) should be used, satisfying
620 the above mentioned criteria for the information material.

621 Agreement, like consent, is a continual process and should be sought during the trial as well,
622 e.g. during repeat trial visits. The processes for informing the child and seeking agreement
623 should be clearly defined in advance of the research and documented for each child. While
624 agreement may not be possible in all age groups (e.g., neonates), the information process
625 provided to the child and the child’s response should be documented. In any case, the
626 investigator should report on the agreement procedure in writing, even if the agreement could
627 not be given in writing.

628 **7.1 Assent**

629 Some Member States have a legal requirement to obtain assent. Any specific requirements for
630 assent are defined by national law, recognised by Article 29(8) of the Clinical Trials
631 Regulation. Recommendations on participation of the minor in the informed consent process,
632 leading to the possible assent, are given in this section. The recommendations provided for
633 various age groups (section 7.2) to seek agreement to participate in a clinical trial should be in
634 accordance with national law.

635 **7.2 Participation and agreement according to age groups and level of maturity**

636 **7.2.1 Newborns and infants (from birth to 2 years of age)**

637 In this age group, it is not possible to obtain agreement, and understanding of research is not
638 expected. Providing information to the child is mostly aimed at preparing the child for the
639 procedures to come. Although these children are not able to raise verbal objections, any signs

Ethical considerations for clinical trials on medicinal products conducted with minors

640 of resistance or protest should be identified and lead to a discussion with the parents/legally
641 designated representative.

642 *7.2.2 Pre-schoolers (2-5 years of age)*

643 Within this age group there is the emergent capacity to provide agreement. Where the child
644 has some capacity of understanding, age- and maturity-appropriate information is still needed
645 even if after giving information, agreement is evaluated not to be obtainable. Since
646 information in text is not helpful for most of these children, other ways of providing visual
647 information should be sought, e.g. videos, pictograms, cartoons or drawings, which can be
648 taken home and discussed with the parents/legally designated representative, in order to
649 ensure that the child is properly informed.

650 Research on cognition shows that younger children have significant ability to provide
651 agreement. It is recognised that children from the age of 3-4 years can express altruism and
652 have an emerging capacity to form an opinion. At the same time, these children have
653 significant ability to express fundamental resistance and protest, beyond the usual signs of
654 discomfort during or after unpleasant procedures. These expressions should be taken seriously
655 and discussed with both the child and the parents/legally designated representative. When it is
656 evaluated that these are expressions of dissent, this should be respected.

657 *7.2.3 Schoolers (6-9 years of age)*

658 Within this age group there is a growing capacity to provide agreement, and this group is
659 known to be able to express altruism. From the age of 7, children may be able to understand
660 benefits and risks of research and start to understand conflicting or abstract information. This
661 should be taken into consideration when developing information material and agreement
662 forms (if applicable) aimed at children. Most children and parents are not familiar with the
663 concept of randomisation, making it a complex notion to understand. However, it has been
664 shown that children with chronic illness may have developed an increased capacity to make
665 independent judgements based on previous life experience. These judgments and the child's
666 point of view should be taken into account. The dissent should be respected, as these children
667 are capable of forming an opinion of their own.

668 In any case, it is of major importance to inform the child and obtain agreement as described
669 above, preferably in writing, and to keep track of the procedures to seek agreement as well as
670 of such agreement. Even though the child is of 'school age', i.e. able to read and write, proper
671 understanding can be enhanced by making use of visuals such as videos, pictograms, cartoons
672 and drawings.

673 *7.2.4 Adolescents (10-18 years of age)*

674 In some Member States a subgroup of adolescents are no longer minors, since they have the
675 legal right to give informed consent. This section therefore does not apply to that particular
676 subgroup. In addition, in some Member States (part of) this group is legally required to
677 assent.

678 Conducting research in this group remains difficult although many threats to adolescent
679 health continue to be evident. Adolescents belong to the paediatric age group, although they
680 may have the capacity to make adult decisions in many other areas of life. Seeking agreement
681 should put in balance the emerging capacity of an adolescent for independent decision-
682 making with the need for continued special protection as provided by the parents/legally
683 designated representative. Most guidelines and publications recognise that adolescents are,
684 under certain circumstances, able to make independent judgements, and this should be
685 respected according to Article 32 of the Clinical Trials Regulation. As in the younger age

Ethical considerations for clinical trials on medicinal products conducted with minors

686 groups, the individual maturity and capacity to understand and agree is also linked to
687 developing cognition and previous life/disease experiences.

688 Agreement from an adolescent who is a minor should be sought and respected, but does not
689 suppress the need for informed consent from the parents or legally designated representative
690 (see Article 32(1.a)). The information about the clinical trial needs to be provided to the
691 adolescent according to their level of understanding and maturity. If the adolescent dissents,
692 this should be respected.

693 An additional issue of trials in adolescents is the protection of confidentiality, especially for
694 research on socially sensitive issues such as illicit drugs, sexuality and violence. In some
695 Member States, discretion and professional secrecy vis-à-vis parents when dealing with
696 adolescents may bind health professionals. The specific aspects of disclosure to parents of
697 information concerning adolescents should therefore be taken into consideration for clinical
698 trials in this age group and should be transparent to the adolescent concerned.

699 7.3 *Difference of opinion between the child and the parents/legally designated* 700 ***representative***

701 Every effort should be made to understand and respect differences of opinion between the
702 child and his/her parents/legally designated representative. Objections from the child should
703 be respected, as was clarified in section 7.2. A different situation arises if a child wishes to
704 participate while the parents//legally designated representative oppose. In any case, the will
705 and motives of the minor should be taken seriously. This means that the investigator should
706 aim to reconcile the differences of opinion, in order to do justice to the (growing) capacity of
707 children to make adult-like decisions. If the child and parents/legally designated
708 representative are not able to come to a consensus, the dissent of either party is decisive. A
709 minor's agreement is not sufficient to allow participation, as it should always be
710 supplemented by the informed consent of the parents/legally designated representative.

711 8. Expertise required for assessment

712 8.1 *Paediatric expertise*

713 The Clinical Trials Regulation includes the need for appropriate expertise in the assessment of
714 a clinical trial to be performed in children of any age group (Article 10(1)).

715 The expert(s) may be permanent members of the assessment body (e.g. an ethics committee),
716 or experts providing advice and consulted on an *ad-hoc* basis. All members participating in
717 the ethical review, including paediatric experts consulted on an ad hoc basis, should be
718 independent of the sponsor, the investigator and the research proposed (Article 9 of the
719 Clinical Trials Regulation). The qualifications and expertise of the experts used should be
720 documented and annexed to its opinion.

721 The paediatric expertise should be available for the assessment of the application dossier, as
722 well as for any subsequent substantial amendments. Ethics committees specialised in
723 paediatrics could be considered for the evaluation of application dossiers that are complex or
724 in serious paediatric diseases. As required by the Clinical Trials Regulation, lay persons
725 should participate in the assessment of the applications for the authorisation of clinical trials,
726 some of whom may be parents.

727 Paediatric expertise goes beyond having professionally worked with children and could be
728 defined on the basis of a combination of education, training and experience on the various
729 aspects of child development, ethics and psychosocial aspects. Paediatric expertise is
730 preferably provided by a paediatrician with at least some years of experience in paediatric
731 care, some years of direct experience of clinical trials with children in similar age groups,

Ethical considerations for clinical trials on medicinal products conducted with minors

732 expertise in clinical pharmacology and expertise in ethics. If this cannot be found in one
733 individual, two or more paediatric experts could contribute to the expertise needed. In
734 addition, other types of expertise may be provided by nurses, health practitioners, paediatric
735 clinical pharmacologists, and bio-statistical experts. Expertise used should be documented.

736 8.2 Methodological expertise

737 In paediatric trials minimising the number of subjects and the level of risk and burden is
738 especially important. This may require smart trial designs, advanced statistical methods, and
739 assays (cf. Sections 9.1 and 13.1). To guarantee that these designs and assays are of sufficient
740 quality, contribute to valid and significant outcomes, and meet all relevant scientific
741 requirements (e.g. regarding the use of placebo), methodological expertise is required in the
742 scientific and ethical review processes.

743 8.3 Opinion on the application dossier

744 Considering the need for additional protection of children involved in trials and with a view to
745 providing an opinion on the application dossier, the content of the dossier should be carefully
746 checked with respect to protection of minors. All requirements are specified in the Clinical
747 Trials Regulation.

748 Moreover, for paediatric trials, the following points should be examined:

- 749 – Whether the trial replicates similar trials based on an identical hypothesis (which should
750 be avoided)
- 751 – Protection and safety of children is ensured (including minimisation of risks, fear, pain
752 and distress) and appropriate paediatric expertise is available at all trial sites.
- 753 – A description is provided of the way procedures are explained to the child during the
754 conduct of the trial, including ways to comfort the child in case of distress.
- 755 – A justification is provided for the inclusion of children and the choice of age groups to
756 achieve the trial objectives. Depending on age groups, inclusion/exclusion criteria may
757 need to include the use of contraception and the outcome of a pregnancy test. Explanation
758 of this should be clear in the information provided, including appropriate contraceptive
759 advice.
- 760 – Appropriate non-clinical data are available before the use of the product in children. Such
761 data are defined, for example, in the ICH E11 guideline. This may include data from
762 juvenile animal studies, modelling or other predictive studies.
- 763 – Appropriate evidence is available to provide sufficient scientific ground to expect either
764 direct benefit for the minor concerned, or benefit for the population represented by the
765 minor according to article 32(1)(g) of the clinical trials Regulation.
- 766 – Extensive and comprehensive review of available evidence (including relevant
767 publications) and experimental work on the investigational medicinal product should be
768 available and should be reviewed to justify the initial hypothesis, the safety and the
769 evaluation of expected benefit, and the age ranges of children to be included.
- 770 – The protocol has been designed with and reviewed by parents and patients (if applicable,
771 based on age and level of understanding).
- 772 – The quality of the performance of the trial is such that it is likely that the results will be
773 interpretable and robust; monitoring, audit and quality assurance are described in the
774 dossier.

Ethical considerations for clinical trials on medicinal products conducted with minors

- 775 – The trial uses age-appropriate forms and formulations of the medicinal product(s).
- 776 – An independent Data and Safety Monitoring Board (DSMB) with appropriate expertise in
777 the conduct of clinical trials in children is identified in the protocol, if appropriate.
- 778 – There are provisions in the protocol for systematic independent publications of results,
779 within the timeframe required by both the Clinical Trials Regulation and the Paediatric
780 Regulation, including when results are unfavourable.
- 781 – The protocol may include a provision for the medicinal products to be given to patients
782 involved in trials after the completion of the trial where appropriate, unless the benefit to
783 risk balance of the medicinal product tested proves negative.
- 784 – The protocol should justify the duration of follow up in the given paediatric population.
785 Follow up must include assessment of physical development (e.g. Tanner staging) where
786 appropriate.
- 787 – The Member States should ensure that the sponsor regularly monitors and re-examines the
788 balance of risk and benefit of the research so that the health and wellbeing of the children
789 enrolled are safeguarded.
- 790 – For randomised trials there should be equipoise (“genuine uncertainty within the expert
791 medical community [...] about the preferred treatment”) at the beginning of the trial and
792 no participants should receive care known to be inferior to existing treatments.
- 793 To help assessors in reviewing paediatric trials, Annex 1 provides a list of the aspects to be
794 taken into consideration when reviewing a clinical trial to be performed in children.

9. Design of clinical trials conducted with the paediatric population

9.1 Design and analysis

797 The clinical trial design depends on the objective(s) of the trial and the scientific question(s)
798 to be answered. Reference should be made to scientific guidelines for drug development in
799 children, including EU and EMA guidelines.

800 To ensure feasibility of trials to be performed, the investigator and protocol writer should
801 ensure that there is involvement of children (suffering from the relevant condition) and of
802 families in the development of information material, and where feasible also in the design,
803 analysis and conduct of the trial. Exceptions to this recommendation should be justified.

804 The trial should be designed to minimise risk and burden for subjects. The size of the trial
805 conducted in children should be as small as possible but large enough to demonstrate the
806 appropriate efficacy with sufficient statistical power and to provide a robust safety database.
807 In conjunction with the analysis of risks and benefit, trials involving fewer children should be
808 weighed against trials involving more children but using less invasive procedures or advanced
809 data analysis methods.

810 To this end, it is in any case suggested to use "smart" trial designs, and advanced statistical
811 techniques for analysis of paediatric data. Examples of designs are adaptive designs and proof
812 of concept in combination with a randomized controlled trial (seamless approach). Advanced
813 data analysis methods, for instance pharmacometric techniques such as population
814 pharmacokinetic/pharmacodynamic (PK/PD) modelling and/or physiologically based
815 pharmacokinetic (PBPK) modelling may be used to predict the behaviour of a medicinal
816 product in children, and should be used to design the study, select the doses and analyse the
817 data. Investigators should strive to use improved trial designs and statistical techniques that
818 optimally protect children's interests while also ensuring scientific quality and validity.

Ethical considerations for clinical trials on medicinal products conducted with minors

819 Alternative (less conventional) designs and/or analyses should be justified and it is
820 recommended that they are agreed with competent authorities when used with a view to
821 provide data for regulatory purposes.

822 In addition to the selection of the age group(s) of children to be included in the trial, particular
823 attention should be paid to the inclusion (and possibly detection) of certain ethnic subgroups,
824 or subgroups with certain genetic characteristics (e.g. G6PDH deficiency) or syndromes. Like
825 in adults, genetic variations may produce significant and informative differences in medicines
826 metabolism, in clinical response to drugs, and in adverse reactions that are to be expected.
827 One should therefore be alert to prevent harm. However, minorities should not be
828 systematically excluded, leading to lack of evidence for their treatments.

829 Adequate dose rationale should be included in the protocol. A scientific justification has to be
830 provided for the dose and dose regimen proposed in the trial.

831 As is the case for trials in adults, all measures to avoid bias should be included in trials
832 performed in children. For example, unblinded and/or uncontrolled trials for the
833 demonstration of efficacy are subject to increased bias and should be avoided whenever
834 possible.

835 Whenever possible (e.g., when differences in product mode of administration are impossible
836 to mask), open trials should include provisions for blinding of assessment. Most aspects of
837 assessment, i.e. a systematic evaluation and documentation, are usually carried out by
838 professionals, to ensure accuracy, precision, standardisation etc. of measurements. Ideally,
839 these professionals should also be blinded to allocation. Reporting adverse events in many
840 cases will be based on the assessment by parents, or other carers. Whenever possible, the
841 evaluation by the child should additionally be obtained. Patient-reported outcomes (PROs) are
842 important to understand health status and changes with an intervention. Instruments to
843 document PROs and health-related quality of life in children are increasingly available.

844 Trials performed in children affected by rare diseases should aim to follow the same
845 methodological standards as those performed in more common diseases, although this will not
846 always be feasible (for example, the power of a controlled trial in a rare disease may be
847 reduced). These trials are generally based on increased uncertainty: for example less-known
848 mechanism of disease, lack of validated endpoints. In addition, they have more complex
849 logistical issues, as participants are fewer and more dispersed (this is a higher burden to
850 children and their families), and require often more trial sites.

851 **9.2 Paediatric control groups**

852 The use of control groups, including the use of placebo, should be based on equipoise, should
853 be appropriate to the condition(s) under investigation in the trial, and should be justified
854 scientifically.

855 *9.2.1 Use of placebo*

856 Placebo should not be used when it means withholding effective treatment, particularly for
857 serious and life-threatening conditions. However, the use of placebo may be warranted in
858 children as in adults when evidence for any particular treatment is lacking or when the
859 placebo effect is known to be very variable (e.g. pain, hay fever). As the level of evidence in
860 favour of an effective treatment increases, the ethical justification for placebo use weakens.
861 Long-term use (beyond 3-6 months) of placebo is known to create difficulties in acceptance
862 of the trial by participants and to increase drop-out rates.

Ethical considerations for clinical trials on medicinal products conducted with minors

863 Placebo use is not equivalent to absence of treatment, for example placebo could be used on
864 top of standard care. In the placebo arm, participants are protected against the (potential)
865 harms of the test product.

866 In all cases, placebo use should be associated with measures to minimise exposure and avoid
867 irreversible harm from the disease, especially in serious or rapidly evolving diseases. As
868 appropriate, rescue⁸ treatment and escape procedures⁹ should be set up (ICH E10). Other
869 situations where the use of placebo should be scrutinised and challenged include run-in
870 periods where a protocol requires active treatment to be withheld.

871 Situations in which placebo only may be considered as a comparator, for example, might be
872 when there is no commonly accepted therapy for the condition and the investigational
873 medicinal product is the first one that may modify the course of the disease process, or when
874 the commonly used therapy for the condition is of questionable efficacy or carries with it a
875 high frequency of undesirable adverse reactions and the risks may be significantly greater
876 than the benefits.

877 Other trial designs should be considered if appropriate. Active-control trials without a placebo
878 arm may be more difficult to interpret than placebo-controlled ones but may provide useful
879 information on comparative benefit/risk balance. Reference is made to the ICH E6 guideline,
880 and other relevant guidelines. The 2011 EMA “Reflection paper on the need for active control
881 in therapeutic areas where use of placebo is deemed ethical and one or more established
882 medicines are available”¹⁰ can also be consulted.

883 Therefore, it is as important to discuss the exclusion of placebo, as it is to discuss its inclusion
884 for paediatric clinical trials.

885 9.2.2 Superiority versus non-inferiority trials

886 Equivalence and non-inferiority trials, and in particular the choice of equivalence or non-
887 inferiority margins in relation to sample sizes in the paediatric population, raise several issues,
888 and should be fully justified when used instead of superiority trials. In addition, inconsistent
889 trial conduct may further blur differences between treatments in equivalence or non-
890 inferiority trials. Some equivalence and non-inferiority trials may be acceptable. For example,
891 new dosing regimens using drugs with a longer half-life with dosing intervals of once per day
892 versus three times per day may offer an advantage, if side effects are comparable. Existing
893 guidelines on methodology issues and/or specific EMA guidelines per therapeutic area should
894 be consulted and regulatory advice should be obtained.

895 9.2.3 Controlled trials using (reference) medicinal products without a marketing 896 authorisation in children

897 As many medicines used in children have not been fully assessed and authorised, the choice
898 of active control products should be discussed thoroughly. Medicinal products not having a

⁸ Rescue medications are medicines identified in the protocol as those that may be administered to the patients when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation. As the provision of rescue treatment may undermine the efficacy measured in the trial, the number of patients receiving rescue treatment should be documented and analysed in the trial.

⁹ Escape refers to prompt removal of subjects whose clinical status worsens or fails to improve to a defined level, who have a single event that treatment was intended to prevent, or who otherwise require rescue treatment (see ICH E10 for further detail).

¹⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/01/WC500100710.pdf

Ethical considerations for clinical trials on medicinal products conducted with minors

899 marketing authorisation may be considered suitable as controls if they represent evidence-
900 based standard of care. Appropriate justification for use needs to be included in the protocol
901 and requirements for investigational medicinal products should be followed. Definitions of
902 standard of care may vary, which should be respected in trial design and analysis.

903 *9.2.4 Clinical trials using medicinal products containing radio-isotopes*

904 Except when radio-isotopes are required for therapy, the use of stable isotopes should be
905 considered to avoid irradiation.

906 **10. The concept of benefit**

907 The Clinical Trials Regulation distinguishes between trials with the prospect of direct benefit
908 for the participating minors which outweighs the risks and burdens involved, and research
909 with the prospect of some benefit for the population represented by the minor (Article
910 32(1g)). This distinction is essential because during trials that only offer the prospect of
911 benefit for the population, the participating minors cannot expect a personal health benefit,
912 whereas they do have to face the research risks and burdens.

913 Benefit can be defined as progress in treatment, diagnosis, or prevention for the children. It is
914 a tangible outcome that may be experienced by the child or the population. This may be
915 obtained through either increased efficacy or safety resulting in a better benefit-risk balance,
916 or through the provision of an alternative to existing treatment with at least similar expected
917 benefit-risk balance. Benefit can also be obtained through contribution to patient care, for
918 example, better route of administration, decreased frequency of dosing, improvement in
919 relation to potential medication errors or compliance, reduced treatment duration, or a
920 clinically relevant age-appropriate formulation.

921 *10.1 Prospect of direct benefit for the minor concerned*

922 One may speak of a prospect of a direct benefit in cases where the clinical trial is expected to
923 play a clinically relevant role in the treatment, diagnosis, or prevention of the disease of the
924 participants. For example, the medicinal product changes or replaces the standard treatment,
925 or forms an addition to normal clinical practice (or to options for care, in those cases where no
926 standard treatment exists yet).

927 The estimation of whether there is a 'prospect of direct benefit' for the participating minors is
928 based on a scientific hypothesis made at the inception of the trial. A controlled trial should be
929 based on equipoise (cf. Section 9), meaning that at the outset of the trial there is genuine
930 uncertainty in the expert medical community about the most beneficial treatment. As a
931 consequence, it is unknown in which of the arms (intervention versus control) participants
932 will experience the highest net benefit (in case of superiority trials: the highest efficacy; in
933 case of equivalence trials: the least adverse events). Furthermore, at the start of a randomised
934 controlled trial, all participants have an equal chance to be allocated to either arm. Therefore,
935 at the outset of a trial, all participants have an equal chance to experience the highest net
936 benefit. The same holds for trials that use a placebo control (obviously these must be
937 superiority trials). That is why a randomised controlled trial, even when the control is a
938 placebo, may be regarded to have a prospect of direct benefit for the minor concerned.

939 Therapeutic confirmatory ("phase III") drug trials are the best-known examples of research
940 belonging to this category. However, depending on the design, early phase drug trials may
941 also offer the prospect of direct benefit. During the benefit-risk assessment of the trial, the
942 expected direct benefit of the intervention(s) should outweigh the risks and expected burdens.

943 **10.2 Prospect of some benefit for the population represented by the minor**

944 When a trial does not offer the prospect of direct benefit to the minor, there should be the
945 prospect of some benefit for the population represented by the minor. However such a clinical
946 trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned
947 in comparison with the standard treatment of the minor's condition. Benefit for the population
948 includes increased knowledge of the medicine and/or of the condition, which is expected to
949 result in better diagnostic tools, better prevention or better treatment strategies for the
950 condition at stake. Examples of research falling in this category are observational studies and
951 some PK studies.

952 Even though all research should produce scientific value (increased knowledge), it is
953 important to note that the Clinical Trials Regulation requires the trial to be valuable for the
954 population represented by the minors concerned, and that this benefit expected from the trial
955 should be identified in the protocol. The magnitude of expected benefit for the population is
956 determined by a variety of factors, such as the severity of the condition, its prevalence, the
957 relevance of the data to be obtained, and the likelihood that the trial will succeed in producing
958 these data.

959 **10.3 Classification of trial protocols**

960 Classification of trial protocols regarding the presence or absence of a prospect of direct
961 benefit for the minor concerned may be a difficult task, both for investigators and for
962 assessors. Since the level of risk and burden that may be justified in a trial depends on its
963 classification (trial with direct benefit for the minor concerned or some benefit for the
964 population) it is important that classification of trial protocols is consistent within and
965 between Member States.

966 Whether a clinical trial provides a prospect of direct benefit for the children that participate
967 depends on the intervention and the additional procedures that are part of it. Several factors
968 may contribute to the decision to consider the clinical trial as providing a prospect of direct
969 benefit for the minor concerned:

- 970 - intention of direct benefit, that is clear from the trial design (by the presence of
971 clinical efficacy and end-points) and duration;
- 972 - existing knowledge from (pre)clinical studies with the medicinal product or
973 comparable products in other subjects;
- 974 - indications for efficacy of the medicinal product for the condition under study or in
975 the population under study;
- 976 - in case of existing knowledge on dosage, the plausibility that in a dose-escalating
977 study the begin dose is effective.

978 However, clinical trials may consist of a combination of the two research categories described
979 above. For example, early phase drug trials in minors often involve different aspects,
980 including components that may be regarded as treatment options, offering direct benefit for
981 the participants, alongside components such as PK sampling, which may or may not generate
982 direct benefit (for example PK sampling for therapeutic drug monitoring may provide direct
983 benefit).

984 **11. Identifying, minimising and monitoring risks and burden**

985 Assessment of risks and burden is a crucial step in evaluating a protocol and conducting the
986 trial. The child's interest should always prevail over that of science and society. This is
987 paramount when assessing and monitoring risks and burden. Both risks and burden may be
988 physical, psychological, or social, may be immediate or delayed, and may vary according to
989 age groups.

Ethical considerations for clinical trials on medicinal products conducted with minors

990 Risks and burden are to be viewed in relation to the benefit (cf. Section 12). Article 28(1e) of
991 the Clinical Trials Regulation requires that the clinical trial is designed to involve as little
992 pain, discomfort, fear and any other foreseeable harm as possible. In other words, risk and
993 burden should be prevented as much as possible and procedures causing risk and/or burden
994 should be justified. Where possible within the limits of both the trial and the clinical setting,
995 procedures should be combined, for example opportunistically taking study samples at the
996 same time as venipunctures required for usual clinical care.

997 Risk is defined as the probability and magnitude of harm or discomfort anticipated in the
998 clinical trial.

999 Burden is defined as the subjective load that affects a participant, parents and family, due to
1000 elements of the trial that cause pain, discomfort, fear, disturbances of their lives and personal
1001 activities, or otherwise unpleasant experiences.

1002 *11.1 Assessment of risk*

1003 To evaluate the total risk a trial carries for the minors involved, risks and harms should not
1004 only be assessed in terms of probability and magnitude, but also in terms of duration and
1005 repetition. Paediatric trials should be analysed for potential risks, including those that may not
1006 usually be of concern in adults because medicines or procedures may cause adverse effects in
1007 children that have not been identified in adults. A thorough analysis of the risks in a trial
1008 should be described in the application dossier, in order to be assessed by the Member State
1009 and to be able to conclude on the approvability.

1010 Risk assessment is difficult in practice as probabilities are unknown. Sometimes it will be
1011 difficult to pre-identify risks or harm arising in a particular clinical trial, for example if a very
1012 novel treatment is to be tested or if participants suffer from serious conditions or if standard
1013 treatment is liable to cause multiple adverse effects. Therefore, the elements that influence the
1014 risks should be identified in the application dossier. Finally, any identified risk should be
1015 associated to measures to prevent, minimise, and monitor such risks as much as possible.

1016 Risk assessment also includes the evaluation of the invasiveness and intrusiveness of research
1017 procedures; the risks of the medicinal product tested or the control, which includes the
1018 reversibility of harm, adverse effects and reactions, and their preventability; and the risk of
1019 withholding active treatment in some cases. The accumulation of research projects in the
1020 same population (over-studied population) is another potential harm in addition to raising
1021 methodological issues. For both reasons, concurrent clinical trials using investigational
1022 medicinal products in an individual should be discouraged.

1023 The timing of paediatric studies in relation to the information obtained from preclinical data
1024 and in adults may also be related to the levels of risk, either when studies are performed ‘too
1025 early’ or when the study of potentially effective medicinal products in children is delayed by
1026 obtaining irrelevant adult data.

1027 The unavailability of age-appropriate paediatric forms and formulations may also incur a risk.

1028 Disclosure of a risk for a serious or an incurable disease following a pre-symptomatic
1029 diagnosis (e.g., genetic diagnosis) might also incur a risk, such as decrease in opportunities
1030 and freedom of choice. Similarly, violation of privacy is considered as a risk.

1031 In case of emerging issues during a trial with potential conflict between the children’s interest
1032 and research interest, the protocol should envisage the management of such issues. In addition
1033 to the risks inherent to the trial, there is a need for evaluation of external risks, for example
1034 linked to the centres involved with variable level of expertise and/or experience.

1035 **11.2 Assessment of burden**

1036 Burden should be assessed in terms of magnitude, duration and repetition, and is by definition
1037 determined by the experience of the person bearing the burden. It is important to realise that
1038 the burden of a clinical trial is added to the burden associated with the child's disease and
1039 routine care. Efforts should be made to avoid or minimise this additive effect. A thorough
1040 analysis of the burden in the trial (for the minors and their parents) should be described in the
1041 application dossier, in order to be assessed in the ethical review and to be able to conclude on
1042 the approvability. Since the magnitude of burden is (at least partly) a subjective experience,
1043 assessment of burden is difficult. Not only are there differences between age groups, there are
1044 also differences between individuals, due to patient age, nature and severity of the condition,
1045 previous experiences as part of the disease, experience with the intervention, and
1046 circumstantial factors. The variability of response to pain, discomfort and fear between
1047 children should be taken into consideration. Different reactions may be expected, when
1048 children are affected by a chronic or acute disease. Coping mechanisms alter with age and
1049 maturation, changing the burden experiences, for example when medical procedures are not
1050 considered any more as 'punitive'. As a consequence of its subjective nature, it seems that the
1051 assessed magnitude of burden during ethical review does not always match the burden as
1052 experienced by children. Therefore, obtaining knowledge on the burden that children
1053 experience while undergoing certain procedures is highly important and such knowledge
1054 should be used to evaluate application dossiers. In this context, also taking into consideration
1055 the burden experience of parents and families is relevant (see below).

1056 Burden should not only be defined in terms of pain, discomfort and fear experienced by the
1057 child. It has been shown that other factors of burden provide reasons for minors and parents to
1058 withdraw from a clinical trial. For minors these are factors such as missing out on social
1059 activities, sports and even normal schooldays. For parents these are factors like finding the
1060 time to fill out questionnaires, missing work days, driving their child to appointments,
1061 collecting samples, and recording measurements or diary entries. In particular for trials
1062 without a prospect of direct benefit for the child, burden (both for the child and for parents) is
1063 an important factor for children and parents in their decision whether to enrol in a clinical
1064 trial, and also impacts their subsequent compliance. For both investigators and assessors
1065 performing the ethical review it is important to be aware that these types of burden may be
1066 crucial, and that factors such as logistics should be included in the assessment of burden of a
1067 clinical trial. Even though only the burden of the child is of importance for assessment of risk
1068 and burden in relation to benefit (Article 32 of the Clinical Trials Regulation and cf. Section
1069 12), burden affecting compliance and participation may impact scientific soundness of the
1070 trial and as such deserves an independent assessment.

1071 Physical and emotional pain should be prevented as much as possible, and effectively treated
1072 when unavoidable. This requires that physical pain and discomfort intensity is assessed and
1073 regularly monitored according to guidelines and age- and condition-appropriate validated
1074 scales, particularly in preterm, newborn and other children who cannot verbally express it.
1075 Effective treatment in relation to the intensity of pain should be administered and reviewed
1076 regularly on the basis of the assessments performed. Patient-controlled analgesia may be used
1077 where appropriate, i.e. in children of sufficient understanding. Pain may be due to the disease
1078 or condition itself, and directly or indirectly related to the medical interventions. Painful
1079 procedures should be minimised. This may be achieved for example by using indwelling
1080 catheters introduced under topical anaesthesia if repeated blood sampling is necessary. Non-
1081 invasive procedures should be preferred, if validated. Population approaches and sparse
1082 sampling for pharmacokinetic data should be applied to reduce the number of blood samples
1083 required to be taken for each child. In all situations, investigations/interventions should be
1084 limited to the minimum required for obtaining valid data and performed using size-/age-

Ethical considerations for clinical trials on medicinal products conducted with minors

1085 appropriate material and devices, including limiting in advance the number of attempts for
1086 sampling.

1087 The parents/legally designated representative should be informed of which procedure is part
1088 of the usual care and which is performed in relation to the trial. In addition, they should be
1089 informed of the nature of the trial procedures, i.e. whether a direct benefit may be expected or
1090 not. Age-appropriate explanation should be given to the child prior to any investigation or
1091 procedure, in order to decrease anxiety and anticipation of pain, in honest, but not frightening
1092 terms. Any procedures that might lead to humiliation of the child (such as undressing),
1093 therefore causing emotional pain, should be avoided or explained. Examples of painful
1094 procedures include, but are not limited to, physical discomfort (exposure to cold, heat or light,
1095 noise), positioning and immobilisation, invasive procedures such as blood sampling
1096 (capillary, venous and especially arterial) and vascular access, biopsies, lumbar puncture,
1097 sampling, repeat examination of injured or traumatised limbs or part of the body, endotracheal
1098 intubations and airways clearance, oral or nasal tubing. In addition, if sedation is needed,
1099 monitoring should be set up (cf. Section 11.3) and the appropriate level of sedation needed for
1100 the procedure(s) should be maintained.

1101 In order to minimise pain, discomfort, and fear, facilities should be appropriate to childcare,
1102 and the personnel should be trained to look after children and supervised by experienced
1103 health care professionals. Staff should be trained to communicate with both the
1104 parents/legally designated representative and the children. Children in a trial should be hosted
1105 in a familiar environment - including appropriate furniture, toys, activities, and where
1106 appropriate, school attendance - and their concerns should be addressed by skilled personnel.

1107 Fear should be prevented if possible, or if not, minimised; the need of the child for comfort
1108 and reassurance, preferably by someone the child is already familiar with, should be attended
1109 to. Changes in the procedures should be explained to the child. Separation of the child from
1110 parents or familiar persons should be avoided whenever possible. If unavoidable, the child
1111 should always be accompanied by a trial-related staff member, known to the child, who could
1112 provide reassurance. At the sign of distress and/or dissent the trial procedure should be
1113 stopped; a short pause to allow the child to feel in control, further explanation and an
1114 assessment of the situation may be needed to reassure the child, or to decide to definitely
1115 abandon the procedure and perhaps even withdraw from the trial.

1116 ***11.3 Monitoring the level of risks and burden***

1117 The level of risks and burden may evolve over time, during the trial and with evolving
1118 knowledge. Risks and burden should be continuously monitored and monitoring should be
1119 pre-specified in the protocol. Burden monitoring may involve carefully observing the child
1120 and proactively checking the child's perception. It is valuable to find ways to have the child
1121 and the parents directly reporting to the investigator on the levels of burden they experience,
1122 for example through an online tool.

1123 Stopping rules should be included in the protocol, e.g. in case of unexpected high levels of
1124 burden for (individual) children, and especially for unscheduled or scheduled analyses in
1125 relation to safety or non-compliance. The use of a Data and Safety Monitoring Board
1126 (DSMB) is recommended. The DSMB should include paediatric experts. If a DSMB is not
1127 used, for example in certain pharmacokinetic studies, this should be justified.

1128 In line with the Clinical Trials Regulation (Articles 28.1(a) and 28.1(e)), the sponsor of the
1129 clinical trial should identify, assess and monitor the burden, risks and harms induced by the
1130 investigational medicinal products. Article 43 requires annual reporting on safety to the EMA
1131 throughout the duration of the clinical trial, or on request, for assessment by the concerned

Ethical considerations for clinical trials on medicinal products conducted with minors

1132 Member States. In this report the sponsor should perform a specific analysis of the subjects'
1133 safety in the paediatric population enrolled in the clinical trial.

1134 12. Assessment of the relationship between benefit, risks and burden

1135 The determination of the benefits in relation to the levels of risks and burden are the basis for
1136 ethical approvability. As the assessment of benefit, risks, and burden may be based on
1137 probabilities and assumptions, this should also be balanced with the severity of the condition
1138 or disease to be studied and the benefit, risks, and burden of alternative treatments.

1139 The Clinical Trials Regulation describes the following relationships between risks and
1140 burden on the one hand and benefit on the other hand (Article 32(1g)). When there are
1141 scientific grounds for expecting that participation in the clinical trial will produce:

1142 - a direct benefit for the minor concerned: then risks and burdens should be outweighed by
1143 the benefits;

1144 - some benefit for the population represented by the minor concerned: then the clinical trial
1145 will pose only minimal risk to, and will impose minimal burden on, the minor concerned in
1146 comparison with the standard treatment of the minor's condition.

1147 12.1 Assessing trials with prospect of direct benefit for the minor concerned

1148 For clinical trials having the prospect of direct benefit for the minor concerned, the
1149 assessment concerns the balance of benefits with risks and burden for the participants in the
1150 proposed clinical trial. In such trials, the expected benefits for the participants should always
1151 outweigh the risks and burdens of the trial (Article 32.1(g)). The crucial consideration in the
1152 ethical review is which level of benefit justifies certain levels of risk and burden.

1153 If a clinical trial involves a prospect of direct benefit for the minor, there is a realistic
1154 possibility that their health or wellbeing will be improved by participating in the trial,
1155 including for example through additional safety monitoring. However, it is important to keep
1156 in mind that direct benefit for the minor concerned may not materialise. After all, it is a trial
1157 with an investigational medicinal product that may prove to be less effective than the
1158 standard treatment and/or may come with more adverse reactions.

1159 12.2 Assessing trials with prospect of some benefit for the population represented by the 1160 minor

1161 For clinical trials with a prospect of benefit for the population, there is no benefit for the trial
1162 participants. As a result, balancing benefit versus risks and burden is not appropriate because
1163 participants can only experience the risks and burden, and not any direct benefit. Directive
1164 2001/20/EC¹¹ did not formulate a threshold for acceptable risks and burden for trials with
1165 "some direct benefit for the population" (i.e. without the prospect of direct benefit for the
1166 participant). As an extra protective measure, the Clinical Trials Regulation introduces a new
1167 criterion for the assessment of risks and burden, in addition to general safeguards such as
1168 ethical review, consent of the parents/legally designated representative, and subsidiarity. This
1169 new criterion demands that for trials with some expected benefit for the population
1170 represented by the minor, the risks and burden should be minimal in comparison with the

¹¹ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Repealed by the Clinical Trials Regulation.

Ethical considerations for clinical trials on medicinal products conducted with minors

1171 standard treatment of the minor's condition. This means that in the situation where no direct
1172 benefit is expected for the trial participants, the levels of risks and burden for participants are
1173 assessed relative to that of the standard treatment they receive. In such trials the procedures
1174 are limited to those that present experiences of risk and burdens that are reasonably
1175 commensurate with those that are part of the minor's standard treatment. Overall, the level of
1176 exposure to risks and burden should be assessed with the participants' interests in mind, in
1177 line with Article 3 of the Clinical Trials Regulation.

1178 Minimal risk can be defined as the probability and magnitude of harm or discomfort similar
1179 to risks ordinarily encountered in a child's daily life, or during the performance of routine
1180 physical or psychological examinations, or simple tests in a child. Examples of
1181 investigations, tests or procedures which could be considered minimal risk (or not) are
1182 provided in Annex 3. Given that the regulation has put 'minimal risk and burden' in direct
1183 relation to the standard treatment, there is no set definition that will apply to all clinical trials
1184 with minors without the prospect of direct benefit. As a result, in each specific trial 'minimal
1185 risk and burden' will have to be viewed in the context of the disease, health status, prior
1186 experiences and related standard treatment for the participants.

1187 Ethical review needs to establish whether the level of risk and burden is minimal in
1188 comparison with the standard treatment of the minor's condition. It is important to bear in
1189 mind that even if the answer is affirmative, this does not necessarily mean that the trial, with
1190 accompanying risk and burden, is ethically acceptable. In any case, the foreseeable risks and
1191 burden should be justified by the expected benefit for the population represented by the
1192 minor and risks and burden should be minimised as much as possible (Articles 28(1a) and
1193 28(1e) of the Clinical Trials Regulation respectively). Therefore, the sum of elements in the
1194 ethical review regarding assessment of benefit, risks and burden, schematically shown in box
1195 1, should guarantee appropriate protection of children.

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Box 1. Guide to assessing acceptable levels of risk and burden in relation to the benefit

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Relevance

- Does the clinical trial address an important question?
- Does the clinical trial answer a question that has not yet been answered?

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Subsidiarity

- Is it necessary to conduct a clinical trial with *human subjects* to answer the research question?
- Is it necessary to conduct the clinical trial with (this particular group of) *children*?
- Can the clinical trial be conducted in a way that is less risky or burdensome?

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Classification I

- Does the clinical trial provide a prospect of direct benefit for the minor concerned?

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No

Yes

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Classification II

- Does the clinical trial provide a prospect of some benefit for the population represented by the minor

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Standard treatment

- What is/are the standard treatment(s) for the condition under study?
- Can the risks and burdens of the clinical trial be considered as minimal in comparison to the standard treatment(s)?

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General proportionality

- Do the anticipated benefits to the subjects or public health justify the foreseeable risks and burdens of the clinical trial?

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1246 *12.2.1 Standard treatment*

1247 Where possible, standard treatments used as comparators should be evidence based. Since in
1248 paediatric medicine the level of evidence may be poor, in those cases best practices qualify
1249 as standard treatment. Importantly, the baseline of evidence will improve with every new
1250 trial that is conducted and results that are obtained. When there is no evidence based,
1251 professionally accepted standard (therapeutic) treatment available for the minor's condition,
1252 the standard treatment should be regarded as the health care delivered for the child's
1253 condition. This may include interventions to reduce pain, discomfort or fear, such as cleaning
1254 of wounds, pain medication, and oxygen therapy.

1255 When there are multiple standard treatments, an ethics committee should assess the risks and
1256 burdens of the clinical trial in comparison to each of the different standard treatments that are
1257 common for the paediatric population under study. The risks and burden should be minimal
1258 in comparison to either standard treatment.

1259 Furthermore, the standard treatment of the minor's disease may vary over time, depending on
1260 the condition of the minor or the phase of the disease. For instance, when the minor no
1261 longer has a prospect for cure, standard treatment is palliative care. The risks and burden that
1262 the minor is exposed to during this phase of treatment may differ substantially from the risks
1263 and burden in the previous phases. This change of standard treatment therefore has
1264 consequences for the level of risks and burden that the minor may be subjected to in the
1265 clinical trial.

1266 *12.2.2 Assessment of risks and burden for individual children*

1267 In the ethical review it is only possible to assess the context and circumstances of the
1268 population under study, not of individual minors. Therefore, investigators are responsible for
1269 assessing (advisably in consultation with a child's treating physician) whether the risks and
1270 burden of a trial are minimal for an individual child in comparison with the standard
1271 treatment the child receives for his or her condition, before enrolment in the trial. This
1272 evaluation should be carried out together with the parents/legally designated representative
1273 and where possible minorsn themselves, to ensure that the burden the child may be able to
1274 bear is taken into account in the evaluation of acceptable risk and burden. Some children who
1275 have prior experience with certain procedures know what to expect and may consider that
1276 these procedures entail minimal burden. Other children may have developed fear or distress
1277 due to the same procedures, and this will result in subjecting them to an unacceptable level of
1278 burden. These experiences should be discussed with the children and their parents/legally
1279 designated representative. Experience and knowledge of what certain procedures entail may
1280 also have a positive impact on the informed consent procedure, because parents and children
1281 understand what they agree to.

1282 **13. Assays in relation to age/bodyweight and blood sampling**

1283 Assays, investigations and blood sampling volumes related to the trial should be described
1284 and justified in the protocol.

1285 *13.1 Type of assays and sample collection*

1286 The number and type of assays and investigations should take into consideration the age
1287 and/or bodyweight (body surface area if appropriate) of the children to be included in the

Ethical considerations for clinical trials on medicinal products conducted with minors

1288 trial: appropriate facilities and material should be used. Alternatives to blood sampling (e.g.
1289 urine or saliva sampling) for pharmacokinetic studies should be preferred when possible.

1290 Advanced statistical techniques such as population approaches and optimal design techniques
1291 should be applied to reduce the number of samples required. For blood and tissue assays,
1292 micro-volumes and micro-assays should be used. Not using micro-assays should be justified
1293 in the protocol. In principle, general and/or local anaesthesia should be used as appropriate for
1294 painful and/or invasive procedures in accordance with the outcome of the risk assessment.

1295 Timing of sampling should be co-ordinated with daily activities as far as possible to avoid
1296 repeat procedures in order to minimise pain and distress, and the risk of iatrogenic
1297 complications. Sampling should be performed by trained staff. The number of attempts for
1298 sampling should be limited. For example, it is recommended that after one unsuccessful
1299 attempt, another experienced person take over the procedure. Timing of sampling and number
1300 of sampling attempts should be defined in the protocol.

1301 ***13.2 Volume of blood***

1302 Preterm and term neonates have very limited blood volume, and are often anaemic due to age
1303 and frequent sampling related to pathological conditions. The fact that children, especially in
1304 this age group, receive blood transfusions (or iron or erythropoietin supplementation) should
1305 not be used as a convenience for increased volume or frequency for blood sampling.

1306 In addition to advanced statistical techniques, micro-methods (on dry spots and scavenged
1307 blood remnants) should be used whenever possible since they allow less trial-related blood
1308 loss. Innovative sampling methods, for example opportunistic or sparse sampling methods,
1309 methods which can be applied when population approaches are used, could also reduce the
1310 volume of blood needed and the number of times blood needs to be collected from children.
1311 The following blood volume limits for sampling are recommended (although are not
1312 evidence-based). Per individual, the trial-related blood loss (including any losses in the
1313 manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks
1314 and should not exceed 1% at any single time. In the rare case of simultaneous trials, the
1315 recommendation of 3% remains the maximum. The total volume of blood is estimated at 80
1316 to 90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight. When blood sampling is
1317 also needed for normal health care, these indicated trial-related blood volumes may be too
1318 high, especially in (preterm newborn) infants. Trial-related blood sampling should always be
1319 justified.

1320 Monitoring of actual blood loss is routinely required in preterm and term neonates. Expected
1321 blood loss should be detailed in any trial protocol, and should be detailed also in the patient
1322 information sheet.

1323 **14. Trials with neonates (term and pre-term)**

1324 Neonates, be they preterm or term, represent the most vulnerable group of the paediatric
1325 population. When affected by serious diseases, they are multi-drug users with potential
1326 interactions to be taken into consideration. This paediatric age group may suffer from diseases
1327 that are specific to them and also differ pharmacologically from older ones. They should be
1328 considered as a very heterogeneous group of patients (for instance weight may vary between
1329 0.5 and 5 kg). Sponsors should take into account the complexity of the situation and the
1330 potential for long-term effects, including developmental effects when designing trial protocols
1331 in this population.

1332 **15. Trials with healthy minors**

1333 In principle, healthy minors should not be enrolled in clinical trials as healthy volunteers,
1334 because usually a trial does not benefit them or the population of healthy minors. Moreover,
1335 they cannot consent and are still considered to be a vulnerable population in the same way as
1336 children with a disease or condition. Studies should not be performed in children when they
1337 can be performed in adults. Exceptions could be where healthy children participate in
1338 palatability testing such as swill and spit taste testing for a new flavoured medicine. The
1339 desire to help others has been cited as a factor influencing the participation decisions of some
1340 children and young people. In any case, Article 32 of the Clinical Trials Regulation should be
1341 adhered to, meaning that healthy children may only be enrolled in trials when they may
1342 expect a direct benefit or when the population of healthy children may expect some benefit of
1343 the trial.

1344 In some situations, studies need to be performed in children who are healthy at the time of the
1345 trial. Prevention trials or paediatric vaccine trials, including immunogenicity studies, will fall
1346 into this category but should include the target population likely to benefit. Trials in children
1347 with intermittent diseases (e.g., flare-ups or seizures) may be acceptable because even in the
1348 “healthy” phase the children are affected. Proof of concept should first be obtained in relevant
1349 animal models and/or in adults whenever possible. Studies such as pharmacokinetic studies,
1350 which cannot be performed in adults, should be done in the intended population as far as
1351 possible, i.e. the one affected by the disease, although it is recognised that data obtained in
1352 affected children may have increased variability.

1353 **16. Trials with adolescent females**

1354 Young females who have developed the capacity to become pregnant should be offered the
1355 opportunity to participate in clinical trials, despite the possibility that they might become
1356 pregnant during the trial, because data are needed in this group and their access to the benefits
1357 of research should not be delayed. Therefore, inclusion with the use of contraception should
1358 be made possible by the investigator for this group of participants. There should be thorough
1359 explanation of this as part of the informed consent process.

1360 **17. Paediatric forms and formulations to be used in paediatric trials**

1361 Forms and formulations used in a trial should be described in the protocol.¹² Additionally,
1362 forms and formulations used in paediatric clinical trials should be reported in publications.

1363 Age-appropriate forms should be used to avoid the risk of adverse reactions, invasive
1364 administration procedures (for example, intramuscular injectables or young children choking
1365 on large tablets), and the high risk of dosing errors or inaccuracy. When they exist, paediatric
1366 formulations should be used. If extemporaneous preparations are used as a consequence of a
1367 lack of appropriate formulation, the conditions for preparing them and the dose should be
1368 indicated and should follow appropriate and proportionate requirements of Good
1369 Manufacturing Principles, as required by the Clinical Trials Regulation and the Commission
1370 Directive 2003/94/EC¹³ [note: the reference will be updated once this is repealed]. Conditions
1371 e.g. to avoid bacterial contamination, degradation of the medicinal product, and to protect
1372 from light, should be specified in the protocol or Investigational Medicinal Product Dossier as
1373 appropriate.

¹² ICH E6, section 6.4.4

¹³ Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

Ethical considerations for clinical trials on medicinal products conducted with minors

1374 In addition, bridging PK data to the marketed pharmaceutical form may be required.

1375 Excipients used for the formulation should take into consideration the age of the children
1376 included in the trial (e.g., benzyl alcohol is contraindicated in neonates).¹⁴

1377 **18. Individual Data protection**

1378 The processing of private data in any clinical trial, including paediatric, shall in light of
1379 Article 93 of Clinical Trial Regulation comply with the Directive 95/46/EC (as of 25 May
1380 2018 with Regulation (EU) 2016/679 on the protection of natural persons with regard to
1381 processing of personal data and free movement of such data, repealing Directive 95/46/EC
1382 (the General Data Protection Regulation – GDPR).¹⁵

1383 The specificity of data protection in children also relates to future (unknown) use of data
1384 obtained in children. The use of the data beyond the protocol, e.g. for the purpose of future
1385 research, should be subject to informed consent, and conform with Article 28(2) of the
1386 Clinical Trials Regulation. Biobank samples retention and the need for consenting to such use
1387 should be discussed in the protocol. It may be difficult to reach a minor participant of a trial
1388 after several years to obtain consent after the participant has reached the age of consent. In
1389 such cases, yearly check-ups regarding the contact data of the patient and his/her parents are
1390 advisable. The law of Member States determines how to act when the participant who has
1391 reached the age of consent, cannot be contacted, e.g. samples may have to be destroyed. The
1392 trial documents should be archived for a duration of 25 years after the end of the trial and
1393 medical files of the subjects shall be archived in accordance with national law (Article 58).

1394 Children are less likely to challenge records about themselves. Therefore there is an additional
1395 duty for sponsors to protect confidentiality and access to data. Protocols should specify the
1396 level of protection of educational performance records contained in trial documents when
1397 studies are performed in schools (access, amendments and disclosure), and the information
1398 given to parents/legally designated representative. This is also particularly important when
1399 trials include adolescents and address issues of sexuality, illicit drug use, or violence.

1400 Where personal information on a child is collected, stored, accessed, used, or disposed of, the
1401 investigator should ensure that the privacy, confidentiality and cultural sensitivities of the
1402 subject and the community are respected. Children participating in a trial are entitled to have
1403 access to any information collected on their health. Other personal information collected for a
1404 clinical trial will have to be made accessible to them in conformity with national laws on the
1405 protection of individual data. Disclosure of genetic findings, which may be regarded as a risk
1406 in clinical trials, requires expert counselling in an adequate setting.

1407

1408 **19. Unnecessary replication of trials**

1409 It is considered unethical to replicate trials in children unnecessarily. This can only be
1410 avoided by ensuring that information gained in any trial is made rapidly available to sponsors
1411 and the public, as is provided for in Article 41 of Regulation (EC) No 1901/2006 on
1412 medicinal products for paediatric use and Article 81 of the Clinical Trials Regulation.

¹⁴ Commission guideline on excipients, guideline for excipients in the dossier for application for marketing authorisation of a medicinal product (EMA/CHMP/QWP/396951/2006) and the guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2)

¹⁵ OJ L 119/2016, p 1-88

1413 **19.1 Publication of paediatric trials and results**

1414 The Clinical Trials Regulation provides for public access to the data held in the EU database.
1415 In principle within 6 months from the end of the trial¹⁶, a summary of the results is submitted
1416 to the database. The summary of the results should be accompanied by a summary of the
1417 results that is understandable by laypersons. In case of paediatric trials, the summary should
1418 be understandable by the children that have participated in the trial. The summary of the
1419 results, including a summary that is understandable to a layperson, will be available in the EU
1420 database.

1421 The clinical trials Regulation provides for systematic registration of paediatric clinical trials
1422 and publication of results, including unfavourable ones. Together with a thorough analysis of
1423 the literature this should allow detection of similar trials, with similar aims, and thus prevent
1424 unnecessary duplication of trials in children.

1425 Protocols that restrict independent publication by investigators should not be accepted, and
1426 the timeline for publication should be reasonable and specified in the respective protocols.

1427 **19.2 International database and availability to the public**

1428 There is an ethical duty to check whether existing knowledge is available to modify the initial
1429 hypothesis for the trial. Public access to ongoing and completed trials through existing
1430 systematic reviews and databases will facilitate avoiding replicating unnecessarily trials in
1431 children. This is supported by the general provisions on transparency in the Clinical Trials
1432 Regulation and by the Paediatric Regulation, which demand that information on the results of
1433 studies in the paediatric population, as well as on the status of the paediatric investigation
1434 plans, waivers and deferrals, should be included in product information.

1435 **20. Adverse effects reporting**

1436 Rules and obligations for adverse events and adverse reactions reporting in paediatric trials
1437 are identical to the Clinical Trials Regulation requirements for adults. This includes the
1438 notification of serious adverse reactions observed in clinical trials (articles 41-43 of the
1439 Clinical Trials Regulation).

1440 As adult data are poorly predictive of safety in children, reporting may cover target organs
1441 and types or severity of reactions differing from that known in adults. A specific assessment
1442 of the adverse reactions associated with the administration of the investigational medicinal
1443 product in children should be performed in the annual safety report.

1444 Parents/legally designated representative and carers should be strongly encouraged and
1445 carefully instructed to report adverse reactions and events to the investigators in a prospective
1446 and timely manner. This is particularly important for younger children, who may not be able
1447 to identify adverse reactions.

1448 **21. Inducements versus compensation for children**

1449 Articles 28(1.h) and 32(1.d) of the Clinical Trials Regulation require that there must be no
1450 inducement to enter a trial, either for the parents, legally designated representative or children.
1451 Parents/legally designated representative can only be compensated for expenses and loss of
1452 earnings directly related to participation in the clinical trial.

¹⁶ As provided for by the Paediatric Regulation No 1901/2006 of the European Parliament and the Council, on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, which is *lex specialis* to the clinical trial Regulation

1453 **22. Insurance issues**

1454 Coverage ensuring that damages will be compensated is mandatory according to the Clinical
1455 Trials Regulation (Article 76(1)) and Member States should ensure there is a system for
1456 damage compensation, e.g. insurance. Obtaining insurance for trials performed in children, in
1457 particular those in neonates, may be difficult, for example, because insurance companies
1458 invoke issues of long-term liability. Insurance companies' contracts should not waive
1459 liabilities regarding long-term effects, or limit the liability period, and Member States should
1460 pay careful attention to the insurance contract regarding this issue, in particular with respect
1461 to long-term effects on development. Unrecognised congenital defects are generally excluded.
1462 Suspected unexpected serious adverse reactions that can be related to these unrecognized
1463 congenital defects should be covered in insurance contracts.

1464 Medical records should be protected by the privacy requirements of the applicable national
1465 laws in order not to pose a risk of labelling individuals with pre-existing conditions by
1466 insurance companies.

1467 **23. Trials with children in non-EU countries**

1468 According to Directive 2001/83/EC, clinical trials submitted in a marketing authorisation
1469 application in the EU, which were performed in third countries (non-EU countries), should be
1470 conducted in accordance with the principles of good clinical practice and the ethical
1471 requirements equivalent to the provisions of Clinical Trials Directive (to be repealed by the
1472 Clinical Trials Regulation) and should comply with equivalent good manufacturing practices
1473 of EU countries. The same requirements apply to Paediatric Use Marketing Authorisations
1474 (PUMA), as introduced by Regulation (EC) No 1901/2006, as well as the same being applied
1475 to paediatric trials where the medicinal product is not studied with a view to obtaining a
1476 marketing authorisation.

1477 Similarly, ethical standards should be no less exacting than they would be for research
1478 carried out in EU countries and that, in addition, the trial protocol should be submitted for
1479 ethical and scientific review in the EU Member State in which the sponsor or its legally
1480 designated representative resides.

1481 The trial should ensure that it responds to the public health needs and priorities of the country
1482 in which it is carried out. It is the responsibility of all involved parties to ensure that this is
1483 respected and that the paediatric specificities, including assent/agreement are obtained for
1484 children.

1485 The recommendations in this document should be followed by EU investigators and sponsors
1486 carrying out trials in third countries, as well as by ethics committees reviewing such trials or
1487 their results. In addition, the laws and regulations of the countries in which the trials are
1488 carried out should be respected.

1489 **24. Ethical violations and non-compliance with GCP**

1490 In order to ensure GCP compliance, the sponsor of a clinical trial and the investigator have to
1491 take appropriate account of the ICH guidelines on Good Clinical Practice. Article 52 of the
1492 Clinical Trials Regulation requires sponsors to notify the Member States concerned by the
1493 conduct of a trial about serious breaches of the Regulation or of the protocol applicable at the
1494 time when the breach occurred via the EU portal. Although this requirement is not specific to
1495 paediatric trials, monitoring and appropriate reporting of serious breaches, including ethical
1496 violations as well as GCP non-compliance are particularly important as children are a
1497 vulnerable population. The assessment of these serious breaches will be performed by the
1498 Member States.

Ethical considerations for clinical trials on medicinal products conducted with minors

1499 All parties involved in protocol assessment and supervision of clinical trials in their territory
1500 should be kept informed of such violations or non-compliance. These serious breaches may
1501 fall into different categories of issues according as to whether and to which extent rights,
1502 safety and well-being of trial participants and scientific value are compromised. The preferred
1503 option to avoid such violations is education, training and implementation, and adherence to an
1504 effective quality system for clinical trials activities performed.

1505 Compliance with GCP should be made explicit in publications. The clinical trial Regulation
1506 mandates that results of all studies, including those conducted unethically are made public.
1507 Information on such trials is needed to avoid repetition of similar errors and to protect future
1508 trial subjects. Public information with warnings on the unethical aspects also contributes to
1509 education on how to conduct paediatric trials ethically. Unethical aspects in trials are not
1510 limited to fraud and scientific misconduct. A wide range of ethical violations may occur in
1511 trials, and therefore a detailed explanation is warranted (Points to consider on GCP inspection
1512 findings and the benefit-risk balance, EMA/868942/2011).¹⁷

1513 If a study is found to be non GCP-compliant during an inspection of a marketing authorisation
1514 application (MAA), or Paediatric Use Marketing Authorisation (PUMA), the quality of the
1515 data, the study results, and consequently the validity of the marketing authorisation
1516 application should be scrutinised. Sensitivity analysis should be performed within the GCP-
1517 compliant full data set, and in some cases also in comparison with all GCP-non compliant
1518 data. The overall reliability of the trial should be questioned. Subsequent measures (including
1519 initial review) should be taken in accordance with legislation, if appropriate.

1520

¹⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/01/WC500137945.pdf

Ethical considerations for clinical trials on medicinal products conducted with minors

25. ANNEX 1: List of issues to be considered in a clinical trial involving minors

List of issues to be taken into consideration for planning and assessing a paediatric trial:

1. Identification and scientific validity of the study question to be answered
2. Justification of the study to be performed in children and in the proposed age groups
3. Evidence of direct benefit for the child, or benefit for the population
4. The competence of the responsible study investigator and his/her team
5. The infrastructure of the institution or primary care practice that should be qualified and experienced in paediatric research in general and in particular in the field of the applied project.
6. The pre-clinical safety and efficacy data (investigator's brochure, available literature) that are preconditions for a paediatric clinical trial
7. The clinical results of adult studies (literature, investigator's brochure), if any.
8. Type and phase of the study
9. Use of placebo or active control, or other design
10. Age-appropriate forms and formulations of medicinal products
11. Validated age-appropriate scales or measures of end-points (e.g., pain scale)
12. Study design and biometric planning in relation to the trial question
13. Design feasibility trial burden checked with children / patient and family representatives
14. Inclusion and exclusion criteria
15. Statistical methods
16. Criteria for the termination of the study
17. Safety measures including the set-up of a Data Safety and Monitoring Board (DSMB)
18. The option of sperm and oocyte cryopreservation if the child's fertility has the potential to be affected by participation in the trial
19. Appropriate pharmacovigilance procedures are put in place by the sponsor
20. Identification of benefits in trials without a prospect of benefit for participants.
21. Identification of benefits in trials with a prospect of benefit for participants.
22. Study risk for participants
23. Study burden for participants (including pain, fear discomfort, time investment and logistical aspects)
24. Study burden for parents and siblings (including time investment and logistical aspects)
25. The potential risks and burden have been weighed against the expected benefits for the children enrolled in the clinical trial with prospect of direct benefit. The balance of expected benefit versus risks and burden should be positive for the clinical trial.

Ethical considerations for clinical trials on medicinal products conducted with minors

26. Comprehensive, understandable Informed Consent and Information sheets for parents/legally designated representatives (as appropriate)
27. Consent, assent/agreement and information sheets: illustrated and understandable age-specific for children
28. Anonymity of the data, as well as confidentiality of personal information related to the child involved in the research, and to his/her family
29. The system for damage compensation in place in the relevant country
30. If available, opinions of other ethics committees for international multicentre studies
31. Publication of trial results and timelines, and informing participants and their families
32. Continuation of trial medication for participants, beyond the end of the trial, where appropriate

26. ANNEX 2: Information for informed consent

Information material should be specific for parents and children: It should be concise in content, precise in language (e.g., use of non-technical terms), and appropriate for the age of children (e.g., avoid abstract concepts, multiple options)¹⁸. Separating the information sheet in 2 parts (one with a summary, and the other with more detailed information) may help to prevent providing children and their parents/legally designated representative with an overload of information. Based on reading the first part, they can decide whether they are interested in the study and read the full information sheet. In addition, splitting the information into smaller chunks increases attractiveness of the information and ease of reading. The use of visual help is encouraged (drawings, pictures, cartoons), but also other media and formats (such as DVD's, computer programmes) may be used, for example to provide general information explaining what research is.

The number of age-specific variations of sets of information material should be kept to a minimum number required to include substantially different wording or presentation. In addition, information sheets should not cause unnecessary distress. They should be designed with input from participants, affected children or parents.

Information material should be harmonised throughout sites in multi-centre trials, and address similar age groups in multinational trials.

If the primary language of the child or parents/legally designated representative is not covered by that of the trial documents, the information sheets should be translated in writing, or there should be a (certified and medically) competent translator during trial-related discussions of the investigator and the parents/legally designated representative. These aspects also need to be documented (cf. section 7).

List of items recommended to be covered in the information sheets:

1. What is the purpose of the trial?
2. How long is the trial going to take?
3. Will I have the same doctor or investigator from start to finish?
4. Why have I been chosen?
5. Do I have to take part?
6. What will happen to me if I take part?
7. What are the compensations?
8. What will I have to do? What will my parents have to do?
9. What is the medicine that is being tested?
10. What are the alternatives for diagnosis or treatment?
11. What are the possible disadvantages and risks of taking part?
12. What are the side effects of any treatment received when taking part?
13. Is ionising radiation to be received, and which regulations are respected?
14. Is there possible harm to an unborn child?
15. What are the possible benefits of taking part?

¹⁸ For examples of age-specific variations in information material, see <http://www.hra-decisiontools.org.uk/consent/examples.html>. For an example of age-specific assent forms, see <http://www.finpedmed.fi/index.php?page=1255&lang=2>

Ethical considerations for clinical trials on medicinal products conducted with minors

16. What happens when the research study stops?
17. What if there is a problem?
18. Will my taking part in the trial be kept confidential?
19. What will happen if I don't want to carry on with the trial?
20. What are the options if I stop taking part in the trial?
21. How is my General Practitioner/Family doctor involved?
22. What will happen to any samples taken from my body?
23. Will any genetic tests be done?
24. What will happen to the results of the research trial?
25. Who is organising and funding the research?
26. Who has reviewed the trial and what are the results?
27. Contact details for information or complaints

Trial alert and information cards (comprising of trial essentials and especially of contact information) should be handed to the child, if appropriate, and the parents/ legally designated representative.

27. ANNEX 3: Examples for levels of risks and burden

The following table provides examples of risk and burden evaluation of procedures carried out for the purpose of a trial. This evaluation is not fixed, because the circumstances of the child influence the evaluation of risks and burden. For example, an existing central venous line may reduce the pain and invasiveness of blood sampling, but also increases the risk of infection and of excess blood losses with line handling. The evaluation of some of the procedures (including, but not limited to those marked *) is very much dependent on such circumstances and on the context of its use in the trial. In addition, the level of risks and burden increases with the increase in frequency of the procedures and with susceptibility to harm of involved/exposed organs. The categorisation proposed in the table applies to single or very infrequent use of the procedure. The examples presuppose that the procedures are carried out to the highest professional standards.

It must be noted that the table should function as the starting point for the evaluation of risks and burden: It should not be used dogmatically, and critical and careful assessment in the ethical review is always necessary. In addition, new or changing scientific insights into how children experience certain procedures may lead to further revision of the table.

The three categories of procedures present an increase in evaluated risks and burden.

For trials with expected direct benefit for the minor involved, the benefit should outweigh the risk and burden. Therefore, trials that involved procedures in category 2 should provide a prospect of direct benefit greater than trials only containing procedures in category 1, and so on for trials containing procedures in category 3.

For trials with some benefit for the population, the risks and burden should be minimal in comparison with the standard treatment. In general, minimal risks and burden can be defined as the probability and magnitude of harm or discomfort similar to risks and burden ordinarily encountered in daily life. By consequence, minimal risk and burden for children with a disease or disorder, who undergo routine examinations, tests and treatments, may be different from minimal risk and burden for healthy children. The procedures presented in category 1 may in general be considered as minimal in risk and burden (for example also for healthy children). Trials with only such procedures can therefore often be regarded as minimal in risk and burden (unless there are many of those procedures in the trial and/or these are frequently applied, see above). Risks and burden of procedures in category 2 might be regarded as minimal, only if the standard treatment of the child involves these or comparable procedures and the child perceives them as sufficiently minimal in burden. In addition, ethical review should determine whether in such situations the sum of risks and burden can indeed be regarded as minimal for the particular group of children involved. Trials with procedures in category 3 should never be approved when there is no prospect of direct benefit for the child involved, since the risks and burden of these procedures cannot be evaluated as minimal, regardless of the context of the child.

Ethical considerations for clinical trials on medicinal products conducted with minors

No or minimal risk and burden	Risks and burden that might be regarded minimal, dependent on the standard treatment	More than minimal risks and burden, regardless of the standard treatment
Category 1	Category 2	Category 3
<ul style="list-style-type: none"> - History taking - Clinical examination - Auxological measurements - Tanner staging - Behavioural testing - Psychological testing* - Quality of Life assessment - Venipuncture* - Heel prick* - Finger prick* - Subcutaneous injection - Urine collection with bag* - Breath condensate collection - Collection of saliva or sputum - Collection of hair sample - Collection of tissue removed from body as part of medical treatment* - Topical analgesia* - Stool tests - Bio-impedancemetry - Transcutaneous oxygen saturation monitoring (pulse oxymetry)* - Blood pressure monitoring - Electroencephalography - Electrocardiography - Vision or hearing testing - Ophthalmoscopy - Tympanometry - Lung function tests (peak flow, exhaled NO, spirometry) - Oral glucose tolerance test - Ultrasound scan - Digitally amplified chest or limb X-ray* - Stable isotope examination 	<ul style="list-style-type: none"> - Urine collection via endoluminal or suprapubic catheter - Arterial puncture - Umbilical catheter - pH metry - Nasogastric tube insertion and use - Transcutaneous oxygen or carbondioxide tension monitoring - Electrophysiological measurements (using stimulation) - Exercise testing (ergometry, spiroergometry) - Raised volume pulmonary function testing (infants) - Peripheral venous lines - Polysomnography - Fasting (≥ 1 meal) - Spinal CSF tap - Bone marrow aspiration - MRI scan - X-ray other than digitally amplified chest or limb X-ray - CT scan* - X-ray DEXA bone density measurement - Use of contrast media - Paracentesis - Skin punch biopsy - Airways or skin hyper-reactivity challenge test 	<ul style="list-style-type: none"> - Heart catheterisation - Endoscopy - Biopsy - Surgery or modification of standard surgical procedure carried out as part of medical treatment - Sedation - Anaesthesia - Systemic analgesia - Hypoglycaemia test - Unstable isotope usage - PET scanning

Feedback requested:

Q1. Is the proposed categorisation of these procedures still adequate?

Q2. Which insights may lead to changes in categorisations (in particular those indicated in yellow)?

28. REFERENCES

Feedback requested:

If you are aware of any other relevant references you are invited to put them forward.

28.1 General guidance

- Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (Strasbourg 2005)
<http://conventions.coe.int/treaty/en/treaties/html/195.htm>
- Charter of Fundamental Rights of the European Union (2012)
http://www.europarl.europa.eu/charter/default_en.htm
- Clinical investigation of medicinal products in the paediatric population. ICH E11. CPMP/ICH/2711/99. <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/clinical-investigation-of-medicinal-products-in-the-pediatric-population.html>
- Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. European Treaty Series – No 164. Oviedo, 4 IV 1997
<http://www.coe.int/nl/web/conventions/full-list/-/conventions/treaty/164>
- Convention on the Rights of the Child. United Nations (1990)
<http://www.ohchr.org/Documents/ProfessionalInterest/crc.pdf>
- EuroSOCAP-Project: European Guidance for Healthcare Professional on Confidentiality and Privacy in Healthcare (2006)
<http://www.aemh.org/aemh/Documents/2006/06-019%20Eu-Guidance-for-Healthcare-Prof-on-Confidentiality-and-Privacy-in-Healthcare.pdf>
- Gill D. Ethical principles and operational guidelines for good clinical practice in paediatric research. Recommendations of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). Eur J Pediatr 2004; 163: 53-57
- Mason S, Megone C. European Neonatal Research: Consent, Ethics Committees, and Law. Ashgate, Aldershot 2001.
- National Institute for Health Research (NIHR). Young persons' advisory group. (2014) <https://www.crn.nihr.ac.uk/children/pcpie/young-persons-advisory-group/>
- UNESCO. Universal Declaration on Bioethics and Human Rights (2005)
http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html
- United Nations High Commissioner for Human Rights: Convention on the Rights of the Child (20/11/1989). <http://www.ohchr.org/english/law/pdf/crc.pdf>
- World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Revision 2008.
<http://www.wma.net/en/30publications/10policies/b3/17c.pdf>

28.2 National guidance on Ethics

- American Academy of Pediatrics. The committee on Drugs and Committee on Pediatric Research. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics* 2010;125(4): 850-60
- Ethical conduct of clinical research involving children. MJ Field and R Behrman Eds. Institute of Medicine. 2004. The National Academies Press.
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