Diversified harmony: Supranational and domestic regulation of pediatric clinical trials in the European Union

Wim Pinxten *, Kris Dierickx, Herman Nys

Centre for Biomedical Ethics and Law, K.U. Leuven, BE-3000 Leuven, Belgium

Abstract

Over the past decades, considerable legislative effort has been made to facilitate and encourage clinical research in the European Union (EU). Hereby, specific attention has been paid to the urgent need to conduct research in minors. In this article, we will analyze the regulation that currently governs pediatric clinical research conduct at the supranational level of the EU and at the level of individual EU member states. Our analysis will focus on the way in which the national and supranational legal frameworks address five ethical issues that are specific to pediatric clinical research: (a) informed consent, (b) the necessity to conduct research in minor subjects, (c) the interests of the subject concerned, (d) the risks and burdens involved, and (e) the pediatric expertise of protocol review committees. We conclude by discussing the harmonization and diversification of the legal requirements that govern pediatric clinical research in the EU.

Keywords: Medical ethics; Health law; Clinical trials; Minors; 2001/20/EC

1. Introduction

Safe and efficacious drugs cannot be provided to those in need without the conduct of clinical research. Over the past decades, considerable legislative effort has been made to facilitate and encourage the conduct of clinical research in the European Union (EU). Hereby, specific attention has been paid to the urgent need to conduct research in small and vulnerable populations in general and minors in particular.

At present, pediatrics is still hampered by a stringent lack of licensed drugs that are labeled for pediatric use. Although minors have been designated as therapeutic orphans ever since this phenomenon was first described in 1968 [1], the gamut of approved medicines for use in children remains considerably smaller than that available to adults [2–4]. Nonetheless, catching up with pediatric research is a precarious enterprise, and several constraints render the conduct of clinical studies in minor subjects complicated and expensive [5].

In the specific case of cystic fibrosis, the conduct of clinical research in minor subjects is particularly valuable for several reasons. First, starting with preventive and therapeutic measures at an early stage of the disease is an important asset because the pathology of cystic fibrosis develops over time. Therefore, the disease will have caused less irreversible damage to the body in young children than in adults, and early intervention may open up additional therapeutic opportunities. Second, the treatment of CF involves considerable drug intake, also for minors. The availability of safe and efficacious drugs is thus of great importance to minors suffering from CF. In addition, clinical trials may result in a reduction of the number of drugs that CF patients need to take, and thus reduce the burden of the – often harsh – therapeutic scheme. Third, the number of patients with CF is relatively large, rendering the population a good candidate for the conduct of pediatric clinical research. The population of CF minors is not too small to compound representative samples of research subjects, and the market for newly tested medicines can be large enough to make research financially viable.

* Corresponding author: Wim Pinxten, Centre for Biomedical Ethics and Law, K.U. Leuven, Kapucijnenvoer 35, Box 7001, BE-3000 Leuven, Belgium. Tel.: +32 16 332926; fax: +32 16 336952.
E-mail address: wim.pinxten@med.kuleuven.be (W. Pinxten).
Obviously, the conduct of clinical research in the vulnerable population of minors generates abundant, diverse, and specific ethical issues. Nonetheless, these issues have increasingly been addressed in the ethical and legal frameworks that currently govern clinical research in the EU [5].

In this article, we will analyze the regulation that currently governs pediatric clinical research conduct at the supranational level of the EU and at the level of individual EU member states. Our analysis will focus on the way in which the national and supranational legal frameworks address five ethical issues that are specific to pediatric clinical research: (a) informed consent, (b) the necessity to conduct research in minor subjects, (c) the interests of the subject concerned, (d) the risks and burdens involved, and (e) the pediatric expertise in committees that review research protocols for pediatric studies. Our analysis concludes with a discussion of the harmonization and diversification of the legal requirements that govern pediatric clinical research in the European Union.

2. Scope, materials and methods

In this article, the supranational and national legal frameworks that govern pediatric clinical research in the EU are investigated. Several criteria were used to determine the scope of our analysis. First, our analysis is limited to legislation that was issued under the responsibility of either the European Union, the Council of Europe, or by a legislative body of an individual EU Member State. Second, only legal regulations fall within the scope of our analysis. Ethical codes that were not promulgated by a legislative body, such as the Declaration of Helsinki, are thus not taken into account, even though these codes may have considerable (moral) authority. Third, to be part of our analysis, regulation must concern the ethics of pediatric research conduct, and thus be related to good clinical practice in pediatric research conduct or the encouragement and facilitation of pediatric clinical research. Therefore, purely administrative requirements fall outside the scope of our analysis, even when they are specific to pediatric research. Likewise, the general requirements for good clinical practice in research conduct that are also applicable to other patient populations will not explicitly be part of our analysis, even though these requirements are often applicable to research in minor subjects. Also the general procedures of protocol approval by ethics committees or competent authorities in individual EU member states will not be the subject of our analysis, as such analysis was already published elsewhere [6,7].

At the supranational level, the Clinical Trial Directive (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of laws, regulations and administrative provisions of the member states in relation to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use) functions as the centerpiece of a wider regulatory framework [8]. In addition to the Clinical Trial Directive, the Pediatric Regulation (Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 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) is highly relevant for the conduct of pediatric clinical research in EU Member states [9]. This regulation discusses the conduct of ethical research and aims to encourage and reward the conduct of pediatric clinical research. Third, the Council of Europe Convention on Human Rights and Biomedicine (European Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, Oviedo 1997, further the European Convention) is binding upon the EU member states that respectively signed and ratified the Convention [10]. In 2005, the European Convention was supplemented with an additional protocol on biomedical research (Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Strasbourg, 25.1.2005), which is binding upon the member states that signed and ratified this additional protocol [11].

In addition to our analysis of supranational regulation, we analyzed the domestic legislation that implements the Clinical Trial Directive into the national law of individual EU member states. Table 1 offers an overview of national laws implementing the Clinical Trial Directive. The original texts of domestic laws, acts, decrees, or regulations that implement the Clinical Trial Directive into national law entail different legal systems (civil law and common law) and are issued in no less than 22 different languages. Our analysis covers original texts in four languages (English, French, German, and Dutch). In addition, (most often unauthorized) English translations of national laws were consulted, and in one case, a native speaker was called upon to gather information where no translation was accessible.

For 24 EU Member States, the text of the national law that implements the Clinical Trial Directive could be analyzed in its original language or via an (unauthorized) English translation. Specific regulations arranging the operational implementation of national laws (e.g. (royal) decrees, orders, circulars), however, were often difficult or impossible to access in English. Therefore, these documents will not exhaustively be part of the analysis presented in this article. For three countries, there was no English translation of the national law implementing the European Clinical Trial Directive available (Cyprus, Hungary, and Slovenia). For these countries, the analysis in this article is based on secondary sources, in so far that such information could be traced.

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1 For an overview of countries that signed and ratified the European Convention, see: http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=5&DF=5&CL=ENG (accessed 1 December 2009)

2 For an overview of countries that signed and ratified the European Convention’s Additional Protocol concerning Biomedical Research, see: http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=195&CM=7&DF=313/12/2009&CL=ENG (accessed 1 December 2009)

3 The authors are grateful to Zuzanna Osewska for the analysis and translation of the Polish law.
Table 1
Overview of the national laws implementing the European Clinical Trial Directive

<table>
<thead>
<tr>
<th>Country</th>
<th>Domestic implementation of Directive 2001/20/EC*</th>
<th>Article</th>
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<tbody>
<tr>
<td>Belgium</td>
<td>Law concerning experiments on the human person (7 May 2004)</td>
<td>Art. 7</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Medicinal Products in Human Medicine Act (13 April 2007). Regulation No. 31 on the Rules for GCP (12 August 2007) is applicable.</td>
<td>Art 97, 100</td>
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<tr>
<td>Cyprus</td>
<td>–</td>
<td>Section 52</td>
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<tr>
<td>Czech Republic</td>
<td>Act on Pharmaceuticals and on Amendments to Some Related Acts (the Act on Pharmaceuticals, 6 December 2007). Decree on good clinical practice and detailed conditions of clinical trials on medicinal products (23 June 2008).</td>
<td>Section 8 (5)</td>
</tr>
<tr>
<td>Denmark</td>
<td>Act on a Scientific Ethical Committee System and the Processing of Biomedical Research Projects (28 May 2003).</td>
<td>Art. 17, Art. 19</td>
</tr>
<tr>
<td>Estonia</td>
<td>Medicinal Products Act (16 December 2004).</td>
<td>§91</td>
</tr>
<tr>
<td>Germany</td>
<td>Medicinal Products Act (12 December 2005).</td>
<td>Chapter 6, Section 40(4) and 41(2)</td>
</tr>
<tr>
<td>Finland</td>
<td>Medical Research Act No. 488/1999 (23 April 2004).</td>
<td>Section 8</td>
</tr>
<tr>
<td>France</td>
<td>Law no. 2004-806 of 9 August 2004 concerning public health policy</td>
<td>1121–1122</td>
</tr>
<tr>
<td>Hungary</td>
<td>Health Ministry Decree EüM24/2002 on the clinical trial of medicinal products for human use and on Good Clinical Practice</td>
<td></td>
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<tr>
<td>Ireland</td>
<td>Statutory Instrument No. 190 of 2004 (European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations (29 April 2004).</td>
<td>Part 4</td>
</tr>
<tr>
<td>Italy</td>
<td>Legislative Decree no. 211 concerning the transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use (24 June 2003)</td>
<td>Section 4</td>
</tr>
<tr>
<td>Latvia</td>
<td>Cabinet Regulation No 172 Regulations on Conducting Clinical Trials and Non-interventional studies and Labeling of Investigational Medicinal Products, and Procedure for Conducting Inspections on Compliance with the Requirements of Good Clinical Practice (28 February 2006).</td>
<td>Art. 30</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>Grand Ducal Regulation concerning the application of good clinical practice in the conduct of clinical trials of medicines for human use (Clinical Trials of Medicines for Human Use, 30 May 2005).</td>
<td>Art. 4, Art. 6</td>
</tr>
<tr>
<td>Malta</td>
<td>Amended Medicines Act (Medicines act to make provision for matters connected with the manufacture, preparation and assembly, wholesale distribution, storage, destruction, disposal, advertising and authorization of medicinal products and any activity connected therewith and the regulation of the sale of medicinal products, pharmacies and related pharmaceutical activities and for any other matters ancillary thereto or connected therewith, 21 November 2003)</td>
<td>Art. 18.2</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Amended Medicinal Research involving Human Subjects Act (Regulations on medical research involving human Subjects, 1 March 2006).</td>
<td>Section 6</td>
</tr>
<tr>
<td>Poland</td>
<td>Resolution of the Senate of the Republic of Poland of 16 April 2004, amending the Pharmaceutical Law and the Act on the Profession of the Medical Doctor</td>
<td></td>
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<tr>
<td>Portugal</td>
<td>Law no. 46/2004 concerning Clinical Trials on Medicinal Products for Human Use (19 August 2004).</td>
<td>Art. 7</td>
</tr>
<tr>
<td>Romania</td>
<td>Ministry of Health order No. 904/25.07.2006 on approval of rules relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use</td>
<td></td>
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<tr>
<td>Slovakia</td>
<td>Ministerial Decree on clinical trials and Good Clinical Practice (1 May 2004).</td>
<td>Art. 15b</td>
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<tr>
<td>Slovenia</td>
<td>–</td>
<td></td>
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<tr>
<td>Sweden</td>
<td>Act concerning the Ethical Review of Research Involving Humans (5 June 2003).</td>
<td>Section 18</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Medicines for Human Use (Clinical Trials) Regulations (Statutory Instrument 2004 No. 1031, 31 March 2004).</td>
<td>Part 4</td>
</tr>
</tbody>
</table>

*The document named in the list is the main law, act or regulation implementing the Clinical Trial Directive into the national law of the member state concerned, that has explicitly been drafted to implement the Clinical Trial Directive. It is important to acknowledge that other laws, acts or regulations that are complementary to the named document(s) in the regulation of pediatric research may exist.*
3. Ethical issues addressed in the legal frameworks

Five major ethical issues in pediatric clinical research conduct are addressed in the European legal frameworks governing pediatric research: (a) informed consent, (b) the necessity to conduct research in minors, (c) the interests of the research subject in the study concerned, (d) the risks and burdens involved, and (e) the pediatric expertise of ethics committees reviewing protocols for clinical studies in minors.

3.1. Informed consent

Ever since the research scandals during the Second World War and its aftermath, the principle of respect for persons has been adopted steadfastly in influential ethical guidelines and legal regulations. Traditionally, this principle has been made operational in the ethical and legal doctrine of informed consent.

The current paradigm of informed consent for research participation is voluntary consent provided by a legally competent adult after being duly informed about all relevant aspects of the clinical trial concerned. For several reasons, this paradigm has serious workability problems in the case of pediatric clinical studies. First, due to age restrictions, most minors are not capable of granting legally valid consent, as they may not have reached the age of medical majority (which is not necessarily the same as the age of legal majority) [12]. Second, the capacity to understand and assess information is often still underdeveloped in minor research subjects. As a result, minors may lack the competence necessary to make rational decisions and it may be difficult to inform minors duly. Third, most minors are largely dependent upon their parents in numerous aspects of their lives. It is widely recognized that parents enjoy considerable discretion in educational matters, and therefore they may, to a large extent, decide autonomously whether and to what extent their minor children can participate in decisions about clinical trial participation.

Due to the incompetence of minors to provide legally valid informed consent, the involvement of a competent adult acting as a surrogate decision maker is most often required to enroll a minor in a clinical trial. Obviously, such involvement of a proxy does not preclude minors from playing an active role in decisions about clinical trial participation. Quite the reverse, several decision making strategies, including (i) dual consent, (ii) consent by the proxy and assent by the child, and (iii) respect for the dissent of the child, aim at encouraging shared decision making and a fair differentiation of decision authority between the proxy decision maker and the minor research subject.

3.2. Necessity to involve minors

Minors are widely regarded as a vulnerable population that deserve extensive protection against harm and abuse. Therefore, it is a generally accepted principle that minors should not be exposed to the risks to harm and abuse that are inherent to any clinical trial, unless this is strictly required to generate relevant research results that will be of benefit to minor patients. In this respect, the large majority of ethical codes and legal rules prohibit research from being conducted in minors whenever alternative research methods or (non-vulnerable) populations are available.

3.3. Interest in the research

To preclude human subjects who participate in clinical trials being used as a means to procure a scientific end, two principles of research conduct are generally adopted in the ethical codes and legal regulations governing clinical research. First, the principle that the interests of science and society never prevail over the interests of individual research subjects is widely endorsed in ethics and law. Second, it is widely assumed that research should comply with the interests of the subjects involved. However, it is important to emphasize that these interests can be very broad and diverse, as they may range from mere altruism to becoming one of the very first beneficiaries of a newly developed safe and efficacious treatment.

In the specific case of pediatric research, there exists a considerable consensus that clinical research in the pediatric population should only be undertaken in so far that the research serves the interests of minors, either by generating a direct benefit for the minor research subject concerned, or by yielding an indirect benefit to a larger group of beneficiaries, such as the population of minors or the group of patients to which the minor belongs.

3.4. Risks and burdens

Research participation never comes without burdens, and most often accepting a certain degree of risk is essentially part of participating in a clinical trial. Deciding upon the acceptability of the risks and burdens inherent to research participation, however, is often a complex and difficult issue, particularly when research is conducted in a vulnerable population such as minors.

Throughout the recent history of pediatric clinical research, the ethical acceptability of research risks has been the subject of considerable debate [13]. Excluding minors from research participation altogether may be considered the most effective way to protect minors from research risks. However, the practical outcome of such a stance is devastating, because it leads minors to become therapeutic orphans [1]. Therefore, alternate ways have been sought to keep minors from unacceptable research risks. At the present time, risk thresholds often play a prominent role in the assessment of the ethical acceptability of pediatric clinical trials [14–17]. As a general rule, research in minors will increasingly be considered to be acceptable as the risks involved decrease. In addition, it is a widely supported premise that, to a considerable extent, the benefits generated by clinical research justify the risks involved.

Several principles guide the assessment of this risk–benefit
ratio. First, a principle of proportionality is used to determine whether the risks inherent to a clinical trial are deemed acceptable. The greater the benefit to a person or group of individuals the research is expected to yield, the more the risk will be considered acceptable. Second, a direct benefit to the subject concerned is preferred over a benefit to more remote beneficiaries, such as the population of minors, the group of patients to which the minor belongs, or a group of future patients. As a result, the more remote the beneficiary, the higher the risk threshold. Third, also the physical condition of research subjects relates to the acceptability of research risks. The worse the condition of a patient, the higher the risk that will be deemed acceptable. In severe conditions, such as life threatening diseases at an advanced stage, decision-makers, including ethics committees, clinicians, parents, or a minor subject will be generally prepared to accept higher risks in research participation.

3.5. Pediatric expertise of ethics committees

Before research in minor subjects can start, the research protocol must be reviewed and endorsed by the competent authority and at least one ethics committee. To guarantee an adequate assessment of issues that are specifically related to the conduct of clinical research in minors, ethics committees require expertise to assess rigorously research protocols. This pediatric expertise can be achieved in various ways, such as fostering pediatric expertise within the ethics committee (e.g. by having a pediatrician among the committees members), or by consulting external expertise.

4. Regulation at the supranational level

At present, clinical research is to a considerable extent regulated at the supranational level. At the European supranational level, the European Convention on Human Rights and Biomedicine, the European Clinical Trial Directive, and the Pediatric Regulation together constitute the legal framework governing pediatric clinical trials.

4.1. European Convention on Human Rights and Biomedicine

In 1997, the European Convention was denounced by the Council of Europe. In 2005, this Convention was supplemented with an additional protocol on biomedical research. To date, the European Convention is binding upon the 14 EU Member States (and 10 countries outside the EU) that signed and ratified it, and its additional protocol is binding upon the 4 EU Member States (and 1 country outside the EU) that signed and ratified it.

The European Convention specifically addresses the issue of pediatric research in art. 17. Also art. 6 and 16 are of some relevance, as they provide details on the protection of persons not able to consent to research (be it not specifically in the setting of clinical research), and the protection of persons undergoing research (be it not specifically minors), respectively. The additional protocol on biomedical research touches the subject of pediatric research in art. 17.

The European Convention’s provisions on the involvement of minors in clinical research are related to the provision of informed consent, the necessity to involve minors, the interest of the research subject and the risks and burdens involved in the study.

4.1.1. Informed consent

The European Convention provides in art. 17,1iv that the representative of the minor must grant his or her informed consent for the enrollment of a minor subject in a clinical trial. This authorization must be provided specifically and in writing. According to the European Convention, it is not required that minor research subjects provide informed consent or assent in addition to the proxy consent provided by the parents or another legal representative. However, the active participation of minors in decisions is hereby not precluded. Quite the reverse, the European Convention does not create any hurdles to the active participation of minors in consent discussions, and even grants minors clear decision making
powers in the form of a veto right, as art 17,1iv provides that research can only be carried out if the minor research subject does not object. In addition, the European Convention provides that the opinion of minors must be taken into consideration as an increasingly important factor in relation to age and degree of maturity regarding therapeutic interventions (art. 6,2). Although this requirement is provided with regard to therapeutic interventions and is not highlighted in the section on research intervention, respect for this requirement is recommended in the research setting.

4.1.2. Necessity to involve minors

The European Convention endorses the principle that minors should only take part in clinical research if similar results cannot be obtained without their involvement, i.e. by research not involving humans (art. 16,i) or research in individuals capable of informed consent (art. 17,1iii).

4.1.3. Interest of the research subject

As a general rule, art. 17,1ii of the European Convention provides that research on a person who lacks the capacity to provide legally valid consent may only be undertaken if “the results of the research have the potential to produce real and direct benefit to his or her health”. In absence of a real and direct benefit to the research subject concerned, the risks and burdens are only deemed acceptable if two additional requirements are met. First, research must aim at generating benefit to persons sharing the same age category, disease, disorder, or condition with the participating research subject (art. 17,2i). Second, research may only entail a minimal risk and minimal burden to the research subject involved (art. 17,2i).

4.1.4. Risks and burdens

The European Convention explicitly links the acceptability of risks and burdens to the benefit involved. In the absence of a direct benefit to the research subject, only minimal risk and minimal burden are deemed acceptable. The additional protocol clarifies the notions “minimal risk” and “minimal burden”, as according to art. 17 of the additional protocol, a research intervention only entails minimal risk if the results of that intervention generate at most a very slight and temporary negative impact on the health of the person concerned and entails only minimal burden if it is to be expected that the discomfort to the research participants will be, at most, temporary and very slight. The explanatory report illustrates minimal risk as taking a single blood sample from a child (Explanatory Report, §111), which implies that many clinical trials, especially those with investigational medicinal products and in relatively early stage of the research, are outlawed by the European Convention.

4.2. Clinical Trial Directive

The Clinical Trial Directive mainly aims at the harmonization of the provisions on good clinical practice and the facilitation of multicentre clinical trials across the borders of individual EU Member States. All EU Member States were bound to implement this directive into national law before the deadline of 1 May 2004. In the national implementation of the European Directive, EU Member States were free to adopt stricter provisions than those set down in the European Directive, as long as the standards of protection and time limits captured in the Clinical Trial Directive were not violated (art. 3,1). As a result, there exists considerable diversity in the national provisions on the conduct of pediatric clinical research across the EU. Nevertheless, several EU member states opted for an almost verbatim implementation of the text of the Directive6. The Clinical Trial Directive addresses the specific issues of pediatric research in its art. 4 (Box 2).

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**Box 2**

**Clinical Trial Directive (Directive 2001/20/EC)**

**Article 4 – Clinical trials on minors**

In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

(a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor’s presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

(f) the corresponding scientific guidelines of the Agency have been followed;

(g) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

(h) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and

(i) the interests of the patient always prevail over those of science and society.

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6 Italy, Luxembourg, Malta, Portugal and Romania opted for a (nearly) verbatim implementation of the text of the Clinical Trial Directive.
In addition to the provisions of the European Directive, the scientific guidelines of the European Medicines Agency (EMEA) have to be followed. In this respect, specific guidance on the implementation of the Clinical Trial Directive in pediatric research practice was provided in the guideline “Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population” [18]. This guideline addresses a number of important issues involving minors in clinical trials. First, the participation of minors in decisions on their enrollment in clinical research is addressed. In this respect, assent, a term that is not used in the European Directive, is recommended as a means to enable the participation of minors in decisions. Notwithstanding this provision, the responsibility of parents to protect the interests of their child is emphasized.

Second, the grey zone in between legal incapacity to consent and factual capacity to consent is addressed. It is acknowledged that certain minors are mature enough to provide valid consent, even when they have not reached the legal minimum age. In this respect, the guideline acknowledges that “emancipated minors” must give written consent to research participation, and that the consent of the parents or another legal representative is not required for mature minors. Notwithstanding this provision, it is emphasized that mature minors can be vulnerable, and may require additional discussions and explanations.

Like the European Convention, the Clinical Trial Directive captures specific provisions on the involvement of minors in clinical research (art. 4), in which the ethical concerns of informed consent, the necessity of involving minors, the interests of the research subject, the risks and burdens involved, and the review of research protocols are addressed.

4.2.1. Informed consent

Art. 4a of the Clinical Trial Directive requires that consent for research participation is given by the parents or a legal representative. It is specified that consent “must represent the presumed will of the minor, and may be revoked at any time without repercussions to the minor”. In addition, the Clinical Trial Directive serves to involve minors in decisions on research participation by stating in art. 4b that minors must receive information “regarding the trial, the risks, and the benefits of the trial”, in accordance with their capacity of understanding and provided by staff with experience with minors. Further, art. 4c provides that the (principal) investigator must consider the explicit wish to refuse or discontinue participation formulated by a minor who is capable of assessing information and forming an opinion. In the Dutch version of the Directive, however, it is stated that the will of the minor to discontinue participation must be respected by the principal investigator [19].

4.2.2. Necessity to involve minors

The Clinical Trial Directive provides in art. 4e that minors should not be involved in research whenever similar results can be obtained by research in competent adults or by other research methods.

4.2.3. Interests of the research subject

The Clinical Trial Directive requires that the research generates a direct benefit. In art. 4e, this direct benefit is defined broadly as “some direct benefit” that either can be an individual benefit (to the research subject) or a group benefit (to the group of patients). In case of a group benefit, no additional requirements are applicable. In addition, this article requires that research is related directly to “a clinical condition from which the minor concerned suffers or be of such nature that it can only be carried out on minors”. The Clinical Trial Directive explicitly guards minors and their parents against financial persuasions, as art. 4d prohibits all incentives or financial inducements to stimulate research participation, except for compensation.

4.2.4. Risks and burdens

In art. 4g, the Clinical Trial Directive provides that clinical trials must be designed to “minimize pain, discomfort, fear, and any other foreseeable risk in relation to the disease and developmental stage”. The requirement that the degree of distress and risk threshold have to be constantly monitored, captured in the same article, demonstrates the importance of this provision, as conformity with most requirements in the Clinical Trial Directive is only assessed at a single moment in time. In addition, the well known general principle that the interests of the patient always prevail over those of science and society is adopted in art. 4i of the Directive. Somewhat notable, this provision is subsumed in the specific provisions on clinical trials on minors.

4.2.5. Pediatric expertise

According to art. 4h of the Clinical Trial Directive, ethics committees that assess studies involving minor research subjects must include a member with pediatric expertise, or gain advice about the clinical, ethical, and psychosocial problems in the field of pediatrics before deciding upon the research protocol.

4.3. Pediatric regulation

Even though the Clinical Trial Directive was a milestone in the facilitation of clinical trials, further legislative initiatives were needed to address the poor interest in developing drugs for the young. To correct the disinterest of industry in developing and marketing drugs for children, the Pediatric Regulation requires that clinical trials in minors are planned and conducted for all new products entering the market. In addition, the Pediatric Regulation offers considerable rewards for the conduct of clinical trials in minors, in the form of prolongation of market exclusivity.

In contrast to the European Convention and the European Directive, the Pediatric Regulation is entirely dedicated to clinical research in minors. In art. 2.1 of the Regulation, minors are defined as the population aged between birth and 18 years of age.

The Pediatric Regulation does not specifically address ethical issues related to the involvement of minor subjects in
clinical research, but focuses on facilitation and encouragement of pediatric drug development. The regulation requires that for every request for marketing authorization, a Pediatric Investigation Plan (PIP) is negotiated early in research (art. 7). This PIP is to ensure that the necessary data to use a drug in all subsets of the pediatric population are gathered in the clinical research preceding marketing authorization. However, waivers and deferrals to this general rule are possible under certain conditions. In addition, the conduct of pediatric research is stimulated with strong incentives, as drugs tested in children obtain an extension of market exclusivity of six months (art. 36). Also for off-patent drugs, research in minors is rewarded by means of the ‘pediatric use marketing authorization’ (PUMA). To organize the assessment of PIPs, waivers, and deferrals, art. 3 of the Pediatric Regulation mandated the establishment of a Pediatric Committee (PDCO), having as its main tasks the assessment of PIPs, waivers, and deferrals, and to support and advise the Agency and Commission.

5. Regulation at the national level of EU member states

At the level of EU member states, national regulation sets out the conditions in which pediatric clinical research can be conducted in the territory of the nation in question. The requirements captured in the national legislation of an EU member state, however, can diverge from the requirements captured in the regulatory framework at the supranational level or be applicable supplementary to the provisions in the directive.

The analysis of domestic regulatory requirements will focus on the implementation of the Clinical Trial Directive in the national legislation of EU member states. Like the analysis of the regulation at the supranational level, the analysis of the domestic legislation of EU Member States will focus on the five major ethical issues in pediatric clinical trials that are regulated: (a) informed consent, (b) the necessity to involve minors in research to obtain relevant results, (c) the interests of minors in research participation, (d) the potential risks and burdens related to clinical trial participation, and (e) the pediatric expertise of ethics committees.

5.1. Informed consent

Article 4 of the Clinical Trial Directive addresses the specific issue of informed consent to enroll a minor in a clinical study and sets down several requirements for the consent to enroll a minor in a clinical trial. First, proxy consent must be provided by the parents or another legal representative. This consent may be revoked at any time without negative consequences to the minor concerned, and must represent the presumed will of the minor. Second, the minor concerned must receive information regarding the trial, the risks and the benefits, appropriate to his/her capacity of understanding, and provided by staff with experience with minors. Third, the explicit dissent to start or continue research participation expressed by a minor who is capable of forming an opinion and assessing the information relevant to participation in the clinical trial, must be considered by the (principal) investigator at any time. Fourth, no incentives or financial inducements may be provided except for compensation.

Among the different domestic laws that implement the Clinical Trial Directive into the national law of individual member states, diversity exists regarding all four requirements for valid informed consent. In addition, several EU Member States specifically define age criteria or an age cut-off with regard to the decision making capabilities of minor research subjects.

5.1.1. Age criteria

The Clinical Trial Directive does not specify an age cut-off for medical majority. However, as a general rule, all individuals who have not reached the age of 18 years can be regarded as minors in decisions concerning their participation in a clinical trial. Nonetheless, several EU member states define specific age criteria that deviate from this general rule (Table 2 provides an overview of the age cut-offs that are applicable in different EU Member States). For example, in Ireland, Lithuania and the United Kingdom, all individuals who have not yet reached the age of 16 years are considered minors. Alternately, several EU Member States distinguish between two age groups, each of which is subjected to specific requirements for informed consent. The age criterion that is used to distinguish age groups varies significantly, ranging from 7 to 15 years of age. For example, in Estonia, the group of minors up to 6 years of age is differentiated from minors aged 7–17 years. In the Netherlands and Spain, the age of 12 is used as an age cut-off. The Bulgarian act differentiates between “children” (being minors up to 14 years of age) and “young persons” (being minors aged 14 to 18 years old). Also in Hungary, an age cut-off of 14 years of age is applicable. Persons under the age of 14 are considered as legally incompetent, persons aged 14 and older have a “limited competency”, similar to adults that are placed under limited guardianship [6]. The Finnish act distinguishes minors up to 14 years of age from minors aged 15 and older. Also Denmark distinguishes minors under the age of 15 from minors aged 15 to 17 years old. In Poland, the age of 16 is used as an age cut-off.

5.1.2. Proxy consent representing the presumed will of the minor

The Clinical Trial Directive requires that proxy consent has been obtained from the parents or another legal representative prior to enrolling a minor subject in a clinical trial. This consent can be withdrawn at any time without detriment to the minor (e.g. by a decrease in the current level of care), and must represent the presumed will of the minor. This last requirement, however, is very confusing, as it is neither clear what constitutes the presumed will of the minor, nor how this presumed will (or violations to it) can be determined.

Within the domestic law of EU Member States, considerable variation in requirements regarding proxy consent representing the presumed will of the minor can be found.
First, several member states specify who must grant informed consent. The Bulgarian act emphasizes that consent must be provided by both parents or the legal representatives. In Latvia, the informed consent of at least one of the parents or another legally acceptable representative of the minor and the children’s rights protection agency of a district or a city is required. However, when the parents of a minor are divorced, the consent of one of the parents or of the legally acceptable representative and of the district or city children’s rights protection agency suffices.

Depending on the age cut-off defined in domestic legislation, the consent of a minor may be required in addition to the proxy consent granted by the parents. According to the Estonian implementation of the Clinical Trial Directive, minors aged 7 to 17 years old must provide their informed consent in addition to the consent of the parents or another legal representative. In Hungary, minors aged 14 to 18 years old must provide their informed consent in addition to the consent of the parents or another legal guardian. In Spain, minors aged twelve or older must give their consent to take part in the trial. In Bulgaria, young persons (aged 14 to 18 years old) must provide their informed consent in addition to (both) parents or the custodian. In Hungary, minors with limited competency (aged 14 and older) must not grant their informed consent in addition to the consent provided by a close relative or a legal guardian. Thus, the age cut-off used in Hungary to discern incompetent minors from minors with limited competency does not have any impact on the consent process [6]. In Finland, minors under the age of 15 years who are capable of understanding the importance of the research procedure to be carried out on them must
provide written consent in addition to the proxy consent given by their guardian or legal representative. For minors aged 15 and older surrogate consent is not required, provided that the minor is capable of understanding the importance of the research procedure (taking account of the age and maturity of the minor) and the research is likely to be of direct benefit to the minor’s health. Here, the written consent of the minor is sufficient, although the guardian must be informed about the participation of the minor in the clinical trial. In Denmark, the ethics committee may grant exemptions from surrogate consent for minors aged 15 and older. It is emphasized that this exemption shall be granted with due regard to the nature, risk and harmfulness of the project. The exemption of surrogate consent does not rule out the holder of the custody, as it is emphasized that the holder of the custody must receive the same information and must be involved in the decision of the minor. In Poland, minors aged 16 or older must grant written consent in addition to the consent of the parents or another legal representative, in so far that the minor concerned is capable of expressing a conscious opinion about participation in the research concerned.

The Greek law does not use a fixed age cut-off, but requires that minors who are capable of comprehending the essence of the clinical trial grant their written consent in addition to the consent of the parents or the legal representative. This is also the case in Germany, where minors who are capable of understanding the nature, significance and implications of the clinical trial and who are capable of forming a rational opinion regarding participation in the trial must grant their informed consent in addition to the proxy consent granted by the legal representative. In addition, the German law clarifies that consent must only represent the presumed will of the minor whenever such a will can be ascertained. In the Czech implementation of the Clinical Trial Directive, it is stated that consent must be respectful to the minor’s age and/or intellectual capacity.

The Austrian act requires that consent has been obtained from minor research subjects in so far the minor concerned is capable of making rational decisions and of understanding the importance, scope, and risks of the trial. This consent is complementary to the consent provided by the legal guardian. In France, minors must be consulted according to their capacity of understanding and their assent for research participation must be sought. Finally, the Estonian Act provides that proxy consent must not always be respected. For minors who have not reached the age of 7, the proxy consent to enroll the minor in a clinical study must not be adhered to by researchers if the decision of the legal representative clearly violates the interests of the child concerned. This provision however, seems completely redundant, as there are no valid reasons for involving minors in research that clearly violates their interests, even if the parents would be prepared to consent to such research. In addition, parental consent never obliges researchers to enroll a minor in a study, since there is no such thing as a generally recognized right to be in a clinical trial.

5.1.3. Information provided to the minor

The Clinical Trial Directive stipulates that minors must receive information according to their capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits. Obviously, this general formulation leaves much to the discretion of those implementing the provisions of the Clinical Trial Directive, including the legislators of the 27 EU member states. Member states vary considerably with regard to age criteria, the content of the information, the person providing the information and the verification of understanding.

First, several EU Member states relate requirements to provide information to the age of minor subjects. In Estonia, children aged 6 or younger must, to a reasonable extent, be informed about the clinical trial and the decisions made. In the Netherlands, minors under the age of twelve and other minors that are not capable of consenting to research participation must be told what is to happen in a way they are able to understand. According to Swedish law, minor subjects who have reached the age of 15 must be provided with information about the trial and consent to research participation in so far that they realize what their part in the research entails.

Second, several EU member states provide detailed requirements about the content of the information provided. In Germany, both minors and their legal representative should be offered a counseling session with an investigator about conditions surrounding the conduct of the clinical trial. According to the Irish statutory instrument, informed consent must be preceded by an interview with the investigator (or another member of the investigating team) in which he or she has been given the opportunity to understand the nature, objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. In Ireland and the UK, the person with parental responsibility must have been provided with a contact point where further information about the trial can be obtained prior to granting informed consent. The Czech Decree on Good Clinical Practice specifies that the information provided to the minor must include information about possible discomfort and potential problems, be provided in writing and be specifically tailored to the level of understanding of the minor whenever possible.

Third, details on the person providing the information are given in the domestic implementation of the Clinical Trial Directive of several EU member states. In this respect, the Danish law stipulates that the information be provided by a person that is familiar with the trial and possesses the educational qualifications to communicate with minors of the age group in question. The Irish legislation requires that consent is given in consultation with the registered medical practitioner who has been treating the minor.

Finally, several EU member states require that the understanding of information is verified. In the Netherlands, the party conducting the research must ensure that the person from whom consent is requested is informed of (a) the aim, nature and duration of the research, (b) the risk of participating in the trial and of withdrawing participation prematurely, and (c) the burdens involved in research participation before
the consent is granted. In addition, this information must be provided in such a way that there is no reasonable doubt that it has been understood by the recipient, and the recipient must be given sufficient time to consider the information properly and to reach a reasoned decision. According to the Slovak implementation of the Clinical Trial Directive, the investigator must verify that (a) the minor has expressed the will to participate in the trial and is aware of his/her right, (b) is capable of forming an opinion and evaluating the information provided, and (c) is aware of the right to refuse or withdraw participation at any time, without negative consequences.

5.1.4. Explicit dissent

According to art. 4(c) of the Clinical Trial Directive, the explicit wish of a minor to refuse participation in a clinical trial or to be withdrawn from a clinical trial is to be considered at any time during the trial by the (principal) investigator, in so far the minor concerned is capable of forming an opinion and assessing the information provided. Obviously, the obligation to “consider” the explicit dissent of the minor is open to various interpretations. Several EU Member States, however, narrow this broad formulation.

In Belgium, the Czech Republic, Germany, France, Finland, Greece, the Netherlands, and Sweden, the explicit dissent of a minor must be considered and respected. However, the Finnish law nuances that the age and maturity of the minor must be taken into account in this matter. The Swedish law explicitly adds that the dissent of a minor must also be respected in the case that informed consent has been obtained from the minor’s guardians.

The Bulgarian law requires that the expressed dissent of young persons (i.e. minors aged 14 to 18 years old) is taken into account by the (principal) investigator. However, since according to the Bulgarian law, young persons must provide their informed consent prior to research participation, the function of this provision is unclear.

5.1.5. No incentives other than compensation

The EU has a clear policy with regard to the payment of minor research subjects. In conformity with art. 4(d) of the Clinical Trial Directive, no incentives or financial inducements except for compensation may be granted to reward research participation. This requirement is adopted (nearly) verbatim in all domestic implementations of the Clinical Trial Directive.

Latvia adds in its domestic implementation of art. 4(d) of the Directive that also compensation in the event of injury or death attributable to research participation may be provided to the minor. However, such compensation cannot be regarded as an incentive, and therefore this addition is not relevant and rather confusing. Likewise, in the Slovak implementation of art. 4(d) of the Clinical Trial Directive, it is stipulated that financial motives, financial or other material advantages apart from indemnification are forbidden.

5.2. Necessity to involve minors

Minors are widely regarded as a vulnerable population that deserve extensive protection against harm and abuse. Therefore, minors should not be exposed to the risks to harm and abuse that are inherent to any clinical trial, unless this is strictly required to generate relevant research results for the benefit of minor patients (cf. infra).

In art. 4(e), the Clinical Trial Directive requires that the involvement of minors be absolutely necessary to validate data obtained in clinical trials on persons able to give informed consent or by other research methods, and that research in minor subjects either relates directly to a clinical condition from which the minor concerned suffers, or be of such a nature that it can only be carried out on minors.

Although, theoretically, necessity is a term that is open to various interpretations, the term appears to be understood uniformly in the European legislative landscape, as no significant variation in domestic provisions regarding the necessity of involving minors in clinical research can be found in the legislation of individual EU member states.

5.3. Interests of minor research subjects

Two provisions of the Clinical Trial Directive incorporate the requirement to serve the interests of minor research subjects. First, it is required that the clinical research generates “some direct benefit for the group of patients”. The interpretation of this puzzling requirement is hampered by the many ambiguities it entails, as a direct benefit is by definition a benefit to the research subject concerned and thus not to a group of individuals, and because research subjects are not necessarily patients, and patients are not necessarily minors [19]. Unfortunately, these ambiguities are not cleared up in the domestic implementations of the Clinical Trial Directive of EU member states. Second, it is required that research either relates directly to a clinical condition from which the minor concerned suffers, or be of such nature that it can only be carried out on minors.

Several member states specify the requirements captured in the Clinical Trial Directive. In Austria, investigational medicinal products must be used in accordance with the latest state of the art of medical science, diagnose, cure, alleviate, or prevent minors from illnesses. Likewise, the Bulgarian act stipulates that the tested medicinal product must be designed for diagnosis, treatment or prevention of diseases that is specific to children and young persons. The Czech Health Act provides that research in minors must be expected to generate preventive or therapeutic benefits for the participating subjects and generate a direct benefit for a group of patients. According to the French Public Health Code, research can only be conducted in minors when the expected benefit to the participating subjects is likely to justify the foreseeable risks. Alternately, also a benefit for other minors may justify the risk that the research entails. In Germany, medicinal products can only be tested in minors if they are intended to facilitate diagnosis or prevention of
diseases in minors. In addition, the German act requires that investigational medicinal products are indicated according to the findings of medical science to save the life of the person concerned, to restore a subject’s health, or to alleviate his or her suffering, unless the trial is of direct benefit to the group of patients suffering from the same disease as the subject concerned.

In Estonia, the broad and unclear requirement to generate some direct benefit for the group of patients is narrowed as, according to the Estonian act, pediatric clinical trials of investigational medicinal products must be expected to generate a direct benefit to the research subject. Also in Lithuania, it is required that the research results have the potential to produce a real and direct benefit to the health of the research subjects themselves, rather than a group of patients. In the Netherlands and Hungary, clinical research may not be conducted in minors under 18 years of age unless the research is of direct benefit to the subjects. However, the requirement to generate a direct benefit is linked to a specific risk threshold: research with negligible risks and minimal burden for the minor subject concerned may be conducted, also in the absence of a direct benefit to the research subject.

5.4. Risks and burdens

In art. 4(g), the Clinical Trial Directive requires that clinical trials must be designed to minimize pain, discomfort, fear, and any other foreseeable risk in relation to the disease and developmental stage. In addition, the risk threshold and degree of distress must be specially defined and constantly monitored.

Several EU member states provide additional details concerning the risks and burdens involved in pediatric clinical research. In this respect, the Belgian law provides that research risks may not be disproportionate to the expected benefits. More generally, the Finnish Medical Research Act requires that the risks involved in research are limited. Likewise, the Lithuanian law requires that biomedical research does not pose risks to the health or life of vulnerable research subjects.

Germany has a more restrictive policy than the Clinical Trial Directive. The German act specifies that clinical research may only cause minimal risk and minimal burden to the minor concerned. Moreover, the German act stipulates that a research intervention only entails (i) minimal risk if this intervention will result, at most, in a very slight and temporary impairment of the minors’ health, and (ii) minimal burden when it is to be expected that the discomfort for the minor will be, at most, temporary and very slight. Also in the Netherlands, pediatric clinical research that does not generate a direct benefit to the subjects participating in the trial may not cross the thresholds for minimal risk and minimal burden. The Austrian act requires that the benefits to the subject concerned outweigh the risks involved, unless when the trial (i) aims at generating a substantial progress in scientific understanding of the condition, disease, or disorder from which the minor suffers and therefore is likely to benefit the patient or group of patients to which the minor belongs, and (ii) only entails minimal risk and minimal burden.

5.5. Pediatric expertise of Ethics Committees

The legislator has assigned research ethics committees an essential task in checking the compliance of research protocols with the ethical legal requirements captured in the Clinical Trial Directive. For the assessment of pediatric research protocols, the Clinical Trials Directive explicitly requires in art. 4(h) that ethics committees either have pediatric expertise, or take advice in clinical, ethical and psychosocial problems in the field of pediatrics.

Several EU member states provide specific requirements with regard to this pediatric expertise. In France, pediatric expertise in ethics committees is required in so far research concerns subjects aged 16 years or less, and only when the ethics committee concerned has no pediatrician among its members. In Italy, it is required that ethics committees include a pediatrician among their members. The Belgian law stipulates that Ethics committees that assess and endorse pediatric protocols must include at least two doctor-specialists in pediatrics, or take advice from two doctor-specialists in pediatrics on the clinical, ethical, and psychosocial aspects of the protocol. In Bulgaria, the consultation of external experts in pediatrics by the ethics committee is mandatory for all clinical trials in children or young persons. Likewise, in Denmark, it is required that ethics committees that assess protocols for pediatric clinical trials take advice from an expert in pediatrics. The Czech Decree Good Clinical Practice requires that ethics committees perform their supervision in at least six-monthly intervals. Ethics committees lacking experience in pediatrics must involve a specialist qualified in pediatrics for the purposes of this supervision. Four member states, Finland, Slovakia, the Netherlands, and Italy, have ethics committees that are specifically devoted to minors [7].

6. Discussion

Throughout the past decades, considerable effort has been made to harmonize the legal framework governing clinical trials in the EU. Hereby, attention has been paid to the specific issues in pediatric research. Particularly the European Clinical Trial Directive is a milestone in the harmonization of good clinical practice guidelines and legal requirements for conducting clinical research in minors. As such, the European Clinical Trial Directive is an important instrument in efforts to facilitate pan-European multicentre pediatric research. Nonetheless, the harmonizing capacity of the European Clinical Trial Directive is profoundly compromised by three factors. First, apart from the Clinical Trial Directive, also the European Convention and the Pediatric Regulation govern the conduct of pediatric clinical trials in Europe at the supranational level. This supranational legal framework in its entirety, however, contains various unclear and contradictory provisions, which complicate the implementation of this legal framework. Second, a Directive, in contrast to a European
Regulation, must be implemented into domestic law by all EU Member States. As such an implementation is not necessarily a servile copy of the original text of the Directive, the implementation process may create diversity within the European legal landscape. Third, not everything in the law is arranged by law, and the legal frameworks, both at supranational and at national level, leave a lot of the interpretation and implementation of the legal frameworks to those who are actually involved in the conduct of pediatric research.

First, a comparative analysis of the three main documents of the European legal framework at the supranational level reveals that this framework lacks internal consistency. Contradictory provisions between the different documents, for example with regard to provisions on the conduct of non-beneficial research and the veto-power of minors in decisions about research participation, render it difficult to interpret and implement the European supranational legal framework. Regarding non-beneficial research, art. 17,2 of the European Convention requires that in the absence of a direct benefit to the individual research participant, a minor can only be involved in research if the study only entails minimal risks and minimal burden, while art. 4e the Clinical Trial Directive only requires “some direct benefit” to the research subject or a related group of beneficiaries. This indicates that the European Convention endorses a more restrictive policy than the European Directive. As a consequence, early stage drug development may be compromised in Member States that have signed and ratified the European Convention. Also in relation to the power of a minor to veto participation in clinical research, contradictory provisions exist. While art. 4c of the Clinical Trial Directive provides that the (principal) investigator must consider the explicit wish of a minor to refuse or discontinue participation (in the case of a minor that is capable of assessing information and forming an opinion), art. 17,1v of the European Convention provides that minors cannot be involved in a study whenever they object to research participation. Thus, theoretically, the European Convention grants minors more extensive decision making powers than the European Directive. In addition to these contradictory provisions, the European legal framework also contains numerous contingencies that require extensive interpretation. It is for example not clear what must be understood as an acceptable risk–benefit ratio, what it means to “consider” the explicit dissent of a minor, how the capacity of minors to make decisions can be assessed, or why the Clinical Trial Directive designates minor research participants as “patients” and links benefits to the “group of patients”.

Second, to a certain extent, the domestic implementation of the clinical trial directive works against harmonization, as Member States are free to vary the original text and stipulate additional legal requirements, provided the standards of protection and time limits captured in the European Clinical Trial Directive are not violated.

The analysis of the domestic implementation of the Clinical Trial Directive in the 27 member states of the EU presented in this article shows that the domestic implementation creates considerable legislative diversity. However, despite these variations in national provisions, few of the domestic implementations of the Clinical Trial Directive appear to be a major obstacle to pediatric clinical trials. In general, research protocols can be tailored to comply with national legal requirements of a Member State relatively easily, provided that one takes notice of the domestic provisions of an individual Member State. Nonetheless, there is still a long way to go in making all national requirements of individual EU member states accessible, due to a lack of authorized translations and easily accessible compilations of all legal requirements.

Third, not everything in the law is arranged by law. Particularly the role of individual decision makers in the interpretation and implementation of European legal frameworks can hardly be overestimated. These decision makers can be institutional bodies (for example ethics committees, or competent authorities) or persons (for example clinicians, minors and their parents or legal representatives).

As the European legal framework leaves considerable discretion in the interpretation and application of regulatory requirements individual and institutional decision-makers, the implementation of this legal framework becomes largely dependent upon the bodies and/or individuals who actually decide on the involvement of an individual minor in a clinical trial. Applying the same set of rules does not guarantee a similar interpretation or application of these rules, and therefore the discretionary freedom of decision-makers in the setting of pediatric clinical research provokes a certain diversification of the regulatory landscape. The diversity in implementation of regulatory requirements, however, entails harsher consequences than the diversity of legal provisions itself because of their practical impact. Rendering the implementation of regulation dependent upon the discretion of individuals that decide upon the accessibility and execution of a research protocol, tends to make the implementation of legal requirements a poorly intelligible process, the outcome of which often appears hard to predict.

While it is true that the European legal frameworks that govern pediatric clinical research by their nature generate a considerable diversity in their actual interpretation and implementation, this diversity need not become an enemy to be defeated. Quite the reverse, the diversity in interpretation and application of the legal frameworks governing pediatric clinical research can be regarded as a considerable asset for several reasons. First, research is not an impersonal enterprise. Taking the personal concerns of clinicians, minors and their parents seriously, however, can hardly be done in a regulatory environment that fails to tolerate a certain level of diversity. Second, research is not a universal enterprise. The demographic, institutional, economic, and cultural particularities of individual member states are relevant to the design and conduct of pediatric clinical studies. Apparently uncomplicated environmental factors, such as research infrastructure may deeply affect the conduct of pediatric research. Consequently, locality matters.

Therefore, the way forward in pediatric clinical research rather seems one of dealing with diversity than one of seeking
Further operational harmonization. Nonetheless, certain contradictory provisions should be rectified urgently. In particular, the contradiction in the stance towards non-beneficial research between the European Convention and the Clinical Trials Directive should be resolved. This should be feasible, because now that the Clinical Trial Directive has been governing pediatric clinical trials for more than five years, we should be able to assess whether the more tolerant approach of the Clinical Trial Directive in comparison to the European Convention has permitted unethical research conduct. To our knowledge, no incidences have been reported in this respect. Therefore, it is doubtful whether abolishing the minimal risk and minimal burden thresholds would impair ethical research conduct or decrease the level of protection of research subjects. If the minimal risk and minimal burden threshold, however, do not contribute to increased ethical standards in pediatric clinical research, they may be considered an obstacle that works against the key objective of encouraging and facilitating clinical studies in children.

Although further harmonization can solve certain issues, handling diversity will be indispensable in a landscape as diverse as the EU. Operational strategies to manage this diversity, however, remain largely unexplored to date.

7. Recommendations for the conduct of clinical trials in minor CF patients

7.1. A shared responsibility

The ethical conduct of clinical research is a shared commitment of all those involved. Obviously, the approval of a research protocol is by no means a full guarantee for clinical research to be ethically sound. Therefore, all parties involved have a responsibility in assessing the acceptability and appropriateness of the research, in general, and for the subject concerned, from their own, unique perspective.

Although the European legal framework only draws explicit attention to permission in the form of protocol approval and informed consent, clinicians have an important role. They must assess whether research participation is medically recommended to the subject concerned. When the researcher is also the patient’s physician, their knowledge of the patients’ medical and personal background aids greatly this assessment.

7.2. Walking the thin line

The regulations that govern pediatric clinical research in the EU address ethical issues in research participation detached from the therapeutic context in which clinical trial participation is often discussed. In practice, however, the dividing line between research and therapy is often extremely thin. Therefore, dealing with the ambiguous distinction between research and therapy is essential for good clinical practice.

While framing clinical research in the therapeutic context of the minor concerned offers unique opportunities to clarify the relevance of the proposed research for the individual minor, integrating research in a therapeutic framework may at the same time blur the dividing line between research and therapy. Therefore, it is of key importance that research is also distinguished from therapy, even when it is discussed against a therapeutic background. In this respect, it is particularly important to communicate what the patient is to expect after the trial has been terminated.

7.3. It’s all about the minor

Conducting research in minors is all about minors. Therefore, minors who are eligible research subjects should have a central position and sometimes also an active role in the consent discussion, reflecting their personal desire to take part in the decision, and their maturity and developmental stage.

Notwithstanding this central role of the minor, the main responsibilities in deciding upon the enrollment of a minor in a clinical trial are in the hands of the adults surrounding them. These are in the first place the parents or legal guardians that hold the legal capacity to grant informed consent for research participation, but also their physicians and the researchers that invite them to participate in the clinical trial. All involved should strive to move beyond their personal convictions, and aspire to decide in the interests of the minor concerned.

7.4. Validate experience

In the specific case of clinical research on CF patients, it should be taken into account that due to the chronic nature of this disorder and its impact on their lives, young CF patients may already have developed above-average decision making skills. Therefore, they should not be underestimated in their capacity to participate. Moreover, the experience that minor patients already have and will create in the near future should be taken into account.

It should be acknowledged that throughout the years, CF patients are frequently invited to participate in studies. Clinicians should therefore guard against individual CF patients participating too frequently in clinical studies to prevent them from becoming research guinea pigs. On the other hand, inordinate enthusiasm for clinical trials may create the impression that research subjects are elected to be the first beneficiaries of novel and important medical breakthroughs. This should also be avoided.

7.5. In between the lines

The supranational and national legal frameworks that govern pediatric clinical trials set down general requirements for the conduct of studies in minor research subjects. To a large extent, the interpretation and implementation of these frameworks, however, is not arranged by law but left to the discretion of those who are directly involved in the conduct of clinical trials. Here, obviously, clinicians hold an expertise and experience that is disproportionately large in comparison to that of minors and their parents. Therefore, they have a vital role in the realization of good clinical practice.
Giving shape to poorly defined ethical and legal requirements is a complex task, that should not be reduced to the responsibility of a single individual. Therefore, it is recommended that ethical issues in the conduct of clinical research are discussed among colleagues, and that the created expertise in dealing with these issues is shared over individual trials.

7.6. Incorporate trust

The fact that clinicians, minors, and their parents (or another legal representative) are assigned a considerable role in the interpretation and implementation of the legal framework renders the relationships between these actors of vital importance. Within these relationships, trust is essential, from the moment of recruitment to the termination of the trial, to bridge the asymmetry in knowledge, expertise, and commitment of the different parties involved.

However, despite the fundamental importance of trust in the mutual relationships between clinicians, minors, and their parents (or other legal representative), also the downside of trust must be acknowledged. Trust is not infallible, can be very naive, and may open minor research subjects to the possibility of coercion and abuse. Therefore, it is necessary that safeguards against inordinate loyalty, deception, therapeutic misconception and other ethical digressions are incorporated in clinical practice. Rather than having outsiders bringing in such safeguards, expertise should be created both in clinicians who communicate about the trial and in minors and parents who consider enrollment into a clinical trial.

7.7. Pediatric expertise

The ethical and legal frameworks that govern pediatric research in the EU formally require that ethics committees foster pediatric expertise, either by including a pediatrician among their members or by calling in external advice. Although it is clear that individual pediatricians are to embody this pediatric expertise (who), it is neither clear what such pediatric expertise entails contentwise (what), nor what added value such expertise should bring to the assessment of research protocols (why). Therefore, both the content and the aims of pediatric expertise in pediatric research should be cleared out. Hereby, it must be acknowledged that the individual pediatricians who embody the pediatric expertise of ethics committees may lack specific knowledge on certain ethical and legal aspects of their practice, no matter how experienced they are. Therefore, it is essential that pediatricians who act as an expert in ethics committees are provided with up to date, clear and relevant research results on the ethical, legal, and social issues in pediatric clinical research practice.

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Conflict of interest

The authors have no conflicts of interest to declare.

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