

# Pediatric clinical research: The regulatory landscape

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Ethical aspects of clinical research with minors.  
Eur J Pediatr. 2013;172(7):859-866  
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## ABSTRACT

Over the past decades, clinical research has increasingly been subjected to ethical requirements and legal regulation. The specific focus of ethical and legal frameworks on competent adults (which serve as the paradigmatic research subject), however, has created an ambivalent attitude towards pediatric clinical research. On one hand, minors are regarded as a vulnerable population that deserves additional protection against the risks and burdens involved in clinical research. On the other hand, the population of minors should not be denied (or not get timely) access to the benefits of clinical research.

In this chapter, we will explore the legal regulation and ethical guidance that currently governs pediatric clinical research in the European Union and discuss the future challenges in this field. In addition, we will discuss major ethical concerns in pediatric clinical research, with a focus on the acceptability of research risks and the informed consent process. In the discussion, we will address key concerns in both regulating pediatric clinical research and implementing ethical and legal requirement in the actual pediatric research conduct.

## INTRODUCTION

Over the past decades, clinical research has increasingly been subjected to ethical requirements and legal regulation. Since the Second World War, landmark codes of ethical research conduct have been drafted and legal regulation has been issued in the US, the European Union (EU), and many other countries. Despite the considerable diversity in ethical and legal requirements, there has always been consensus on the cornerstones of ethical research conduct. For example, the doctrine of informed consent, the premise that the interest of science and society should not prevail over those of the individual, and the fact that human subjects should never be exposed to unnecessary risks in clinical research have been widely endorsed from the very start.

The historical efforts to secure an adequate protection of human subjects in clinical research have been grafted on a paradigmatic research subject: the competent adult. This specific focus, however, has created an ambivalent attitude towards pediatric clinical research. On the one hand, minors are regarded as a vulnerable population that deserves additional protection against the risks and burdens involved in clinical research. Such a protection could not be maximized further than in a full exclusion of minors from clinical research. On the other hand, the population of minors should not be denied (or not get timely) access to the benefits of clinical research. The impressive share of drugs that are prescribed off-label or off-license in pediatric practice,<sup>1</sup> however, clearly indicates that research in competent adults does not automatically generates timely advancements in the diagnosis, care, and treatments for minors. Minors are not just small adults, and omitting to conduct clinical trials in the population of minors turns minors into 'therapeutic orphans.'<sup>2,3</sup> By consequence, the conduct of pediatric clinical trials is indispensable to catch up with the lack of licensed drugs that are labelled for pediatric use.

From an ethical and legal point of view, however, the conduct of pediatric clinical trials is a precarious enterprise, as it often remains difficult to balance scientific advancement with the adequate protection of minors.<sup>4,5</sup> In addition, several hurdles such as difficult recruitment, market issues (e.g., a problematic return on investment for pediatric clinical research), and restrictive regulation (e.g., risk thresholds for non-beneficial research) may be hard to surpass.

In this chapter, we will explore the legal regulation and ethical guidance that currently governs pediatric clinical research and discuss the future challenges in this field. In this respect, it must be emphasized that the applicable ethical and legal frameworks are often formulated in general terms, while pediatric research is a very heterogeneous landscape. As such, these frameworks may fail to respond directly to the specific ethical

issues that come to the surface in practice. Certain issues therefore call for an appropriate ethical approach, which cannot be derived easily from the available ethical and legal guidance. Table 1 lists a number of such issues.

**Table 1:** Recognized problems from a clinical point of view in critically ill minors

Recognized problems from a clinical point of view in critically ill minors	
1.	The compassionate use at an individual base as a last resort drug (Imatinib) for pulmonary hypertension original labelled as an anti-cancer drug.
2.	The conduction of first in men studies such as new amino acid composition for parenteral nutrition in extreme low birthweight infants in the absence of adult data.
3.	The application of a therapeutic modality (for instance liquid ventilation with an organ preservation substance) in the absence of safety data.
4.	Invasive fetal treatment modalities guided by industrial progress and not supported by properly designed RCTs.
5.	Opportunistic sampling of residual blood samples from routine laboratory test, as well as dry blood spot sampling with the aim to determine drug levels.
6.	Diagnostic procedures such as PET-scans to obtain normal values for the age-dependent distribution of opioid receptor isoforms in the central nervous system needed radioactive labelled substance.

## THE REGULATION OF ETHICAL ISSUES IN PEDIATRIC CLINICAL RESEARCH IN THE EU

### THE LEGAL REGULATION GOVERNING PEDIATRIC CLINICAL RESEARCH IN THE EU

In the EU, various supranational and national regulations that have been promulgated by diverse legislative bodies over the past 15 years aim to harmonize existing standards of good clinical practice and to facilitate and encourage pediatric clinical research.<sup>6</sup> At the supranational level, three different regulations govern pediatric research conduct. First, the Council of Europe issued the European Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine in 1997 (further, the Oviedo Convention).<sup>7</sup> In 2005, this convention was supplemented with an additional protocol on biomedical research.<sup>8</sup> To date, the Oviedo Convention is binding for the 17 EU member states (and 12 countries outside the EU) that have signed and ratified it. The Convention specifically addresses the issue of pediatric research in Article 17 (Table 2).

Second, Directive 2001/20/EC (further, the Clinical Trials Directive) mainly aims at a harmonization of the provisions regarding good clinical practice and the facilitation of multicenter clinical trials across the borders of individual EU member states.<sup>9</sup> All EU member states were bound to implement this directive into national law, with the freedom to adopt stricter provisions than those set down in the text of the directive (as long as the standards of protection and time limits captured in the directive were not violated). By consequence, there exists considerable variety among the national laws that implement

the Clinical Trials Directive. Obviously, differences in domestic requirements between EU member states must be taken into account when conducting a trial in a specific EU member state. The Clinical Trials Directive specifically addresses the issue of involving minors in research in Article 4 (Table 3).

**Table 2:** Oviedo Convention - Article 17

**Article 17: Protection of persons not able to consent to research**

1. Research on a person without the capacity to consent as stipulated in Article 5 may be undertaken only if all the following conditions are met:
  - i. the conditions laid down in Article 16, sub-paragraphs i to iv, are fulfilled;
  - ii. the results of the research have the potential to produce real and direct benefit to his or her health;
  - iii. research of comparable effectiveness cannot be carried out on individuals capable of giving consent;
  - iv. the necessary authorization provided for under Article 6 has been given specifically and in writing; and
  - v. the person concerned does not object.
2. Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorized subject to the conditions laid down in paragraph 1, sub-paragraphs i, iii, iv and v above, and to the following additional conditions:
  - i. the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition;
  - ii. the research entails only minimal risk and minimal burden for the individual concerned.

**Table 3:** Clinical Trials Directive – Article 4

**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 minimize 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 pediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of pediatrics, has endorsed the protocol; and
- i. the interests of the patient always prevail over those of science and society.

Third, Regulation (EC) No. 1901/2006 (further, the Pediatric Regulation) requires that clinical trials in minors be planned and conducted for all new products entering the market.<sup>10</sup> In this respect, sponsors must make a pediatric investigation plan after phase 1 trials in adults have been completed (in certain cases, waivers are possible). In return for the efforts to plan and conduct trials in minors, the Pediatric Regulation offers considerable rewards in the form of a prolongation of market exclusivity. The Pediatric Regulation also arranged the establishment of a pediatric committee within the European Medicines Agency that is (among other tasks) primarily responsible for the scientific assessment and agreement of pediatric investigation plans and for the system of waivers and deferrals thereof. In contrast to the European Convention and the European Directive, the Pediatric Regulation is exclusively dedicated to clinical research in minors.

### **DIVERSITY AND INCONSISTENCY OF THE CURRENT REGULATION**

Unfortunately, the legal frameworks that govern pediatric clinical research in the EU contain contradictory provisions and lack internal consistency in several matters. With regard to non-beneficial research, for example, Article 17.2 of the Oviedo Convention stipulates that in the absence of a direct benefit to the individual research participant, a minor can be involved in research only if the study entails minimal risks and minimal burdens, while Article 4e of the Clinical Trials Directive simply requires 'some direct benefit' to the research subject or a related group of beneficiaries. This indicates that the Oviedo Convention endorses a more restrictive policy than the Clinical Trials Directive and implies that early stage drug development may be compromised in member states that have signed and ratified the Oviedo Convention. Also with regard to the right of a minor to veto participation in clinical research, contradictory provisions exist: Article 4c of the Clinical Trials Directive stipulates that the (principal) investigator must consider the explicit wish of a minor to refuse or discontinue participation (given that the minor is capable of assessing information and forming an opinion), whereas Article 17.1v of the Oviedo Convention states that minors cannot be involved in a study when they object to research participation. Thus, the Oviedo Convention grants minors a more extensive decision-making capacity than the Clinical Trials Directive does.

In addition to these contradictory provisions, the European legal framework contains numerous contingencies that require extensive interpretation. It is not clear, for example, what must be understood to be 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 Trials Directive refers to minor research participants as 'patients' and links benefits to the 'group of patients'. The fact that many terms are not

clearly defined is likely to negatively affect the implementation of the European legal framework and creates the need for accurate guidance and support.

At the level of domestic regulation, requirements for the inclusion of minors in clinical research (e.g., age criteria) vary from country to country, which obviously has profound implications for the conduct of multinational trials.<sup>11</sup> The differences in interpretation and assessment of the acceptability of risks among European member states have important consequences. For example, trial protocols can be rejected in one member state because the risks or burdens exceed the applicable minimal risk and minimal burden thresholds, but still take place in other European member states, where these thresholds are not adopted into national law. Obviously, this may be very frustrating for researchers and minor patients and their parents who are committed to the trial. It also might concentrate certain types of non-beneficial research in a selected number of EU member states, while successful trials will result in drug licenses that cover all EU member states. This generates important justice-related issues. The premise that risks and burdens call for a proportionate counterpart, by preference in the form of a direct benefit to the research subject, challenges the involvement of minors in phase 1 research or the use of healthy controls in pediatric clinical trials. There is considerable controversy over the fact that some risks and burdens would not need any compensation and that mere altruism can have a place in clinical research.

## **ETHICAL ISSUES IN PEDIATRIC CLINICAL RESEARCH**

The extensive body of legal regulation that has been developed over the past 15 years has not reduced the need for sound ethical reflection. In this chapter, we will discuss two major ethical concerns in pediatric clinical research: the acceptability of research risks and the informed consent process.

### **ACCEPTABILITY OF RESEARCH RISKS**

Clinical trials entail risks and burdens. Minors are a vulnerable population, and one should be vigilant to expose vulnerable subjects to risks and burdens. Therefore, procedures have been made to review the acceptability of risks and burdens in pediatric clinical trials, in which research ethics committees play a prominent role. The main rationale behind the assessment of research risks is that such risks call for compensation. This rationale is made operational in the principle of proportionality, according to which risks can be justified by a proportionate counterpart, for example in the form of a direct benefit to the research subject. Against this background, therapeutic research (research that is likely to generate a direct benefit for the subject involved) is often distinguished

from non-therapeutic research (research that is not likely to generate a direct benefit for the subject involved). While proportionality can be regarded as a general principle, exceptions are possible. Very small risks and burdens (often defined as 'minimal risks' and 'minimal burdens') for example can be deemed acceptable without a proportionate compensation in the form of a direct benefit to the research subject.

In practice, deciding upon risks is a precarious enterprise. First, it is hard to measure benefit, risk, and burden and to assess their proportionality in a reliable way. Although risks may be determined using objective criteria or other systems for risk evaluation,<sup>12</sup> such criteria do not account for the subjective personal experience of risks, burdens, and benefits of research subjects, which may be closely related to their condition, disease, and personal experience.

Second, also the review of risks and burdens by ethics committees is not a mechanical or fully objective procedure. Indeed, the deliberation of one and the same protocol by different ethics committees may have significantly different outcomes. Several factors, such as differences in the composition of ethics committees (which varies from country to country) or differences in the methods and procedures (e.g., for assessing risks), may nourish diversity in outcome. For example, in many European countries, non-beneficial research is subjected to a stringent minimal-risk- and minimal-burden threshold, while in others, no explicit distinction between therapeutic and non-therapeutic research is made by law, and proportionality between risks and benefits is not linked to specific risk thresholds.

## **INFORMED CONSENT FOR PEDIATRIC CLINICAL RESEARCH**

The doctrine of informed consent has been widely used to serve two functions. Legally, informed consent settles the relationship between the researchers and the subjects participating in the research. Ethically, informed consent serves as an operational implementation of the principle of respect for persons. As such, informed consent is to protect research subjects from deception, coercion, and abuse.

In its original design, the doctrine of informed consent has been grafted on the paradigmatic research subject of the competent adult. As such, valid decisions to participate in research must in principle be made voluntarily and by legally competent adults, after being duly informed on the nature, significance, implications, and risks and burdens of the research. For several reasons, this paradigm has serious workability problems when applied to the setting of pediatric clinical research. 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 (or have not been emancipated, e.g., by marriage).<sup>13</sup>

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, parents enjoy considerable discretion in the way they raise their children and all the decisions that this entails. Against this background, parents are almost always involved in decisions to enroll a minor in a clinical trial, even when the minor is mature enough to make decisions on his or her own.

The involvement of a competent adult acting as a surrogate/ proxy decision-maker is thus 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, if parental consent is to be held to the same ethical standard as informed consent provided by a competent adult, the child who is participating in research must somehow be involved in the decision-making process. Several decision-making strategies, including: 1) Dual consent (by the minor and the proxy decision-maker); 2) Consent by the proxy and assent (affirmative agreement of a minor to participate in research) by the minor; 3) Respect for the dissent of the child, therefore aim at encouraging shared decision-making and a fair differentiation of decision authority between the proxy decision-maker and the minor research subject.

## **VULNERABILITIES IN THE INFORMED CONSENT PROCESS**

Informed consent, proxy consent, assent, and dissent are simple in design. In practice, however, (proxy) informed consent, informed assent, and dissent are complex and precarious processes, in which all involved face important obstacles.

First, informed consent is delicate because understanding what it means to participate in research appears hard to realize in practice. For example, research shows that parents sometimes do not remember having consented to enroll their child in a clinical trial.<sup>14-16</sup> Also the understanding of information and recalling what one has consented to are difficult. In this respect, Chappuy and colleagues have described an apparent discrepancy between the evaluation of the adequacy of information by parents, and the actual understanding and recalling of this information by these parents.<sup>16</sup> Parents also tend to overestimate their understanding in comparison to an assessors' estimation of parental understanding.<sup>17</sup> In addition, specific elements, such as random allocation and potential risks, are difficult to understand for parents. The parental understanding of the concept of random assignment, for example, has been shown to be doubtful,<sup>18 19</sup> and in a study done by Ballard and colleagues, only 5% of the parents who understood the study understood the potential risks.<sup>14</sup> The poor understanding of information applies to the consent as well as to the assent process.<sup>20 21</sup>

Second, informed consent presupposes a distinction between research and therapy. In pediatrics, however, research does not necessarily start where therapy ends. This is particularly true for the setting of pediatric oncology, where nearly all patients are receiving their treatments in the context of a trial. But also in other settings, several factors may blur the theoretically rigid distinctions between therapy and research. For interventional studies, for example, it may not suffice for parents to be informed about the trial, the risks, and the benefits according to the specificities described in the study protocol. Rather, they may want to know why it would be worthwhile for their child to participate in this trial, taking the medical history and current treatment regimen into account. As such, trials may enter the therapeutic realm. In addition, minors and their parents often find it difficult to understand and keep in mind the difference between research and therapy, which may induce 'therapeutic misconception' in the informed consent process.<sup>22</sup> Therefore, when research is framed in a therapeutic context, it is of key importance that research is also distinguished from therapy. In this respect, it is particularly important to communicate for example what the patient can expect after the trial has been terminated.

Third, the considerable differentiation in expertise, tasks, and responsibilities among minors, their parents, and clinicians constitutes asymmetric relationships that complicate decisions on clinical trial participation.<sup>23</sup> This asymmetry creates a dependency of minors and their parents upon each other and upon clinicians to provide, explain, and frame information, which raises serious ethical concerns about conflicts of interests, uncritical loyalty towards physicians, and information bias.<sup>24-27</sup> Nonetheless, all of these issues can be addressed adequately and need not be a hurdle to the establishment of relationships of mutual trust between all individuals involved in the decision.<sup>28,29</sup>

Fourth, one should be vigilant that informed consent does not become mere 'documented consent'. For several reasons, the signature of a document by no means guarantees a duly informed, well-considered, rational decision. First, the fact that informed consent is granted by competent persons does not imply that competences are actually used to take a stance towards a study protocol. Rationality is not necessarily the golden standard of all important decisions we make in life, and other factors (particularly tacit elements like hope, trust, or dependency) may shape decisions to grant informed consent. Several studies indicate issues that work against rational decision-making, such as inadequacies in understanding the research,<sup>16-18 20 30</sup> and emotional distress.<sup>31</sup> Second, Pinxten suggested that consent discussions can be well-considered and rational decisions, but might be a priori decisions as well, representing and confirming a positive (or negative) stance towards research that parents already had before recruitment.<sup>32</sup> Third, time constraints and the urgency of the situation may influence the consent process, for

example in emergency settings, or when inclusion in the protocol must be completed shortly after the diagnosis of a serious disease.

## DISCUSSION AND CONCLUSION

Dealing with the ethical issues in pediatric clinical research is complex and delicate. Now that a growing body of ethical reflection and legal regulation aims to guide the ethical conduct of clinical trials in Europe for more than 10 years, it is important to reflect on how the available ethical and legal frameworks affect actual practice. For example, do the current ethical and legal frameworks adequately respond to the needs of the different stakeholders involved in the actual conduct of pediatric clinical research? And (how) are available guidelines implemented in practice? When addressing these questions, several considerations should be taken into account.

First, it must be emphasized that ethics, the law, and ethics committees do not establish ethical research conduct as such. Researchers and other health care professionals play a key role in the practical realization of ethical research conduct. The evolution of newer ways of data acquisition such as opportunistic sampling, dry blood spot technology, and the development of biobanks renders new challenges as well. Ethical requirements and legal regulations need to be interpreted and applied in practice, taking into account the heterogeneity of the pediatric population and the large diversity of research projects.

Second, one should be vigilant not to confuse the operational implementation of ethical principles, with the successful approach of ethical concerns as such. For example, obtaining signed informed consent does not automatically imply respect for persons.

Third, one should always keep in mind that it is all about the minor. In this respect, minors should not only get opportunities to participate in decisions concerning their health and/or participation in clinical research, they should also be given the freedom to take or leave these opportunities as they wish. For example, respect for minors may be fostered by maximizing their participation in the informed consent process (taking their understanding and maturity into account). Still, one should also consider the wish of a minor not to take part in the informed consent process, even if the minor concerned is sufficiently mature and capable of understanding what the trial is about. According to the current ethical and regulatory frameworks, however, this may not always be fully possible in practice, for example when assent or dual consent is explicitly required.

Finally, the challenge ahead is to foster ethical conduct in all involved. The mere existence of ethical reflection and legal regulation, by no means, implies a successful translation to practice. In addition, it would be unreasonable to expect from minors and their parents to just own the skills and know-how that are required to make well-considered decisions on participation in a clinical trial. However, at present, easily accessible support for minors and their parents in deciding on research participation is still largely lacking. The same holds for the challenging tasks that researchers or other medical practitioners face in pediatric clinical trials. Therefore, efforts should be made to employ the vast and unexplored potential of empowering all involved for the advancement of ethical conduct in pediatric clinical research.

## ADDENDUM

The article, on which this chapter is based, was published in 2013. At that time the new European Clinical Trials Regulation was being drafted. On April 2<sup>nd</sup> 2014 the European Parliament approved the new Clinical Trials Regulation (Regulation No. 536/2014).<sup>33</sup> As soon as it comes into force, expectedly in 2020, this regulation will repeal the Clinical Trials Directive (Directive 2001/20/EC)<sup>9</sup> discussed in this chapter. The goal of the new Regulation is to simplify and harmonize the scientific and ethical review of clinical trials in the EU. In contrast to the current directive, in which EU member states are bound to implement the requirements from the directive into their national laws, the upcoming regulation has direct binding legal force in all EU member states.

Regarding pediatric clinical research, the new Regulation differs from the Directive in several respects. Some differences concern small details, while others are more substantial. For pediatric clinical research the main differences are related to the risk and burden thresholds in research without a potential direct benefit and the informed consent process.

Concerning the informed consent process for example, the regulation now states that a child who reaches the age of legal competence during a trial explicitly needs to consent before he can continue to participate (art 32:3 Clinical Trials Regulation). Another example, also relevant for pediatric clinical research, relates to new rules for informed consent in emergency situations. In contrast to the current regulation, article 35 of the Regulation now arranges conditions for the acceptability of deferred consent in emergency situations.

The main change concerning risk and burden thresholds in pediatric clinical research without a potential direct benefit can be found in article 32 of the new Regulation (table 4), which is the counterpart of article 4 in the Clinical Trials Directive. As previously discussed in this chapter, the current Clinical Trials Directive does not provide limits regarding the acceptable levels of risk and burden for pediatric research without a prospect of direct benefit; it doesn't even distinguish between pediatric research with or without a prospect of direct benefit (art 4 Clinical Trials Directive). By contrast, the new Regulation does make this distinction and sets limits to risk and burden in pediatric research without a prospect of direct benefit. It states that research with no direct benefit for the participating minor should have some benefit for the populations represented by the minor (group-relatedness) and may pose only minimal risk and burden to the minor in comparison with standard treatment of the minor's condition (art 32:1:g:ii Clinical Trials Regulation).

**Table 4:** Clinical Trials Regulation – Article 32

**Article 32: Clinical trials on minors**

1. A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:
  - a. the informed consent of their legally designated representative has been obtained;
  - b. the minors have received the information referred to in Article 29(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;
  - c. the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator;
  - d. no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;
  - e. the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
  - f. the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
  - g. there are scientific grounds for expecting that participation in the clinical trial will produce:
    - i. a direct benefit for the minor concerned outweighing the risks and burdens involved; or
    - ii. some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.
2. The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.
3. If during a clinical trial the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical trial.

Due to the directly binding nature of the upcoming regulation to all EU member states the Dutch Medical Research (Human Subjects) Act (WMO) had to be adapted and aligned

with the upcoming Regulation.<sup>34</sup> Before March 1<sup>st</sup> 2017, the WMO held more restrictive risk and burden thresholds for pediatric clinical research without a prospect of direct benefit (former art 4:1 WMO). Currently, the adapted WMO holds the same thresholds as the upcoming regulation (new art 3:1:d WMO). In practice, this means that there has been a shift in the Netherlands towards allowing non-therapeutic research with more risk and burden to be offered to children and their parents than before. The old Dutch standard imposed a limit of minimal risk and burden, but the new puts the threshold at minimal risk and burden compared to standard treatment. How this comparator is going to be used is inevitably a topic of discussion. What if the standard is very burdensome and risky, does that mean these children can be exposed to similar high risks and burden, for non-therapeutic research purposes?

In relation to the new Clinical Trials Regulation the European Commission expert group on clinical trials revised in 2017 the 'Ethical considerations for clinical trials on medicinal products conducted with minors'.<sup>35</sup> To draft this revision a working group lead by the Dutch Ministry of Health, Welfare and Sports was established.<sup>iii</sup> The main objective of this revision was to align the document with the upcoming Clinical Trials Regulation and with the latest scientific and ethical insights regarding research with children. The revised document is meant for all parties involved in research with children, including research professionals, RECs, other regulatory authorities and potential participants and their families. It gives guidance on various ethical aspects of pediatric clinical research from birth up to the age of legal competence to provide informed consent. This guidance addresses among others: the informed consent process, risk thresholds, and required expertise for trial assessment. For example, based on new empirical and ethical insights elaborate changes have been made pertaining to the involvement of children in the decision-making process. The document also discusses new insights into how to minimize risk and burden for children participating in research.

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iii I was a member of this working group. Insights from research presented in this thesis were implemented in the revision. They relate to taking into account motivations of parents and children not only in the recruitment and informed consent process but also during the design of the research, the importance of focusing on (logistical) burden and methods of minimizing that burden.

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