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Ethical principles and legal requirements for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials

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Abstract The involvement of minors in clinical research is inevitable to catch up with the lack of drugs labeled for pediatric use. To encourage the responsible conduct of pediatric clinical trials in the EU, an extensive legal framework has been developed over the past decade in which the practical, ethical, legal, social, and commercial issues in pediatric research are addressed. In this article, the European legal framework surrounding pediatric clinical trials is analyzed from the perspective of the major ethical concerns in pediatric research. The four principles of biomedical ethics will be used as a conceptual framework (1) to map the ethical issues addressed in the European legal framework, (2) to study how these issues are commonly handled in competent adults, (3) to detect workability problems of these paradigmatic approaches in the specific setting of pediatric research, and (4) to illustrate the strong urge to differentiate, specify, or adjust these paradigmatic approaches to guarantee their successful operation in pediatric research. In addition, a concise comparative analysis of the European regulation will be made. To conclude our analysis, we integrate our findings in the existing ethical discussions on issues specific to pediatric clinical research.

Keywords Pediatric research · Directive 2001/20/EC · Bioethics · Health law · Minors

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Introduction

The safety and efficacy of a large number of the drugs used in pediatric practice has not been demonstrated for the specific use in children [26]. Because children are not simply small adults, results of clinical trials in adults cannot often be reliably extrapolated to minors [27]. Therefore, there is an urgent need to perform clinical trials on children.

At present, it is widely recognized that it is not possible to provide children with a variety of safe and efficacious drugs comparable to those available to adults without involving minors in clinical trials. To catch up with the lack of licensed drugs that are labeled for pediatric use, regulatory efforts have focused on facilitating, encouraging, and rewarding the conduct of clinical research in minors. Nonetheless, the development of safe and efficacious drugs for use in children remains a precarious enterprise [11]. Several constraints work against the marketing of drugs tested in children and labeled for pediatric use, among which practical difficulties (e.g., recruitment issues, cf. [2, 18]), strict ethical and legal requirements (e.g., restrictive policy concerning nonbeneficial research, cf. infra), and economic issues (e.g., the limited potential for return on investment in pediatric trials, cf. [23]). In the EU, this predicament is addressed in an extensive legal framework that has been developed over the past decade.

In this article, the European legal framework surrounding pediatric trials is analyzed from the perspective of the major ethical concerns in pediatric research. First, the content and implementation of the European legal framework will be presented and clarified using the four principles of biomedical ethics [5]. The well-known principles of justice, nonmaleficence, beneficence, and autonomy will be used as a starting point (1) to map the ethical issues addressed in the European legal framework,

(2) to study how these issues are commonly handled in competent adults, (3) to detect workability problems of these paradigmatic approaches in the specific setting of pediatric research, and (4) to illustrate the strong urge to differentiate, specify, or adjust these paradigmatic approaches to guarantee their successful operation in pediatric research. Second, a concise comparative analysis of the European regulation will be made. To conclude our analysis, we will integrate our findings with the existing ethical discussions on issues specific to pediatric clinical research.

The European legal framework

The urgent need to conduct clinical research in minors has called for legislative action. In Europe, various regulations have been promulgated by diverse legislative bodies over the past decade, aiming at the facilitation and promotion of pediatric research and the harmonization of standards of good clinical practice.

In this article, three criteria are used to determine the scope of relevant legislation. First, the scope is limited to legislation issued at the European level (i.e., the European Union or Council of Europe). Domestic legislation of individual countries is thus not taken into account. Second, the scope is limited to legal provisions that are related to ethical concerns in the conduct of pediatric clinical trials. By consequence, regulation focusing on administrative or technical issues such as the production of investigational medicinal products or the labeling of drugs falls outside the scope of this article. Third, only provisions specifically addressing the involvement of minors in clinical trials fall within the scope of this article. General provisions regulating the involvement of competent adults in research are not discussed exhaustively, although these provisions may also apply to the involvement of minors in clinical trials. In accordance to these criteria, the European Convention on Human Rights and Biomedicine, the European Clinical Trial Directive, and the Pediatric Regulation fall within the scope of this article.

European Convention on human rights and biomedicine

In 1997, the Council of Europe promulgated the European Convention (European Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine) [8]. In 2005, this 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 January 2005) [9]. To date, the European Convention is binding upon the 13 EU member states (and eight countries outside the EU) that signed and ratified it, and its additional protocol is binding upon the four EU member states (and one country outside the EU) that signed and ratified it.[1]

The European Convention specifically addresses the issue of pediatric research in article 17. Also, articles 6 and 16 are of some relevance, as they provide details on the protection of persons not able to consent (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 on the subject of pediatric research in article 17.

European clinical trial directive

The European 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) [13] 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. 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 European Directive were not violated (article 3,1). The European Directive specifically addresses the issue of involving minors in research in article 4.

In addition to the provisions of the European Directive, the scientific guidelines of the European Medicines Agency (EMEA) must be followed. In this respect, the guideline "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population" [12] was recently issued by EMEA to guide the implementation of the European Directive in pediatric research practice.

Pediatric Regulation

Even though the European Directive was a milestone in the facilitation of clinical trials, further legislative initiatives were needed to address the lack of interest in developing

[1] A list of countries that signed and/or ratified the convention can be consulted at http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=&DF=&CL=ENG.

drugs for the young. To correct the disinterest of the industry in developing and marketing drugs for children, the Pediatric Regulation (EU Regulation 1901/2006 of the European Parliament and of the Council of 12 December 2006 on Medicinal Products for Pediatric Use and Amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004) [14] requires that clinical trials in minors be 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.

Ethical principles and pediatric clinical research conduct

Various types of bioethical reflection can be used to identify, clarify, and discuss ethical issues in pediatric research. In this paper, a principle-based approach will be used as a conceptual framework to interconnect (1) the main ethical issues in involving human persons in research, (2) the common approaches of these issues in competent adults, (3) the workability problems these paradigmatic approaches have in the pediatric research setting, and (4) the regulatory answers to these workability problems.

Although principles are a well-validated tool for ethical reflection, their generality may render them somewhat difficult to apply directly to specific ethical issues. Therefore, in this article, the four principles of biomedical ethics—justice, nonmaleficence, beneficence, and autonomy [5]—will be tailored to the specific issues of involving minors in research by describing them in terms of four fields of social, scientific, and regulatory action. Obviously, overlap between these four fields of action will exist, as the four principles cannot be distinguished strictly from each other in content and scope.

Justice

The formal principle of justice can be set forth in several ways: to each person an equal share or a share according to (1) need, (2) effort, (3) contribution, (4) merit, and (5) free market exchanges [5].

Obviously, the unmet medical needs of minors are a major reason to encourage the development of safe and efficacious drugs for the young. Free market exchanges are also relevant to the development and provision of safe and efficacious drugs for children, as the pharmaceutical industry is a key player in this process. In contrast, effort, contribution, and merit are not commonly cited as motives to develop and distribute drugs for pediatric patients. Therefore, in this article, the principle of justice will be referred to as a "share according to need" and a "share according to free market exchanges."

Main issues in clinical research and paradigmatic approach in competent adults

To respond to existing therapeutic needs, safe and efficacious drugs must be developed and made available to patients who can benefit from them. The development, safety, efficacy, and availability of drugs all entail ethical issues.

The current paradigmatic approach leaves the development and distribution of drugs in large part to the market. Requirements for obtaining marketing authorization seek to guarantee that drugs are safe and efficacious. According to these requirements, the terms of use must be captured in the corresponding license that provides details of the patients, ages, indications, dosages, routes of administration, and contraindications associated with each drug [7].

Workability problems of the paradigmatic approach in competent adults in pediatric healthcare and implementation of the principle of justice

While requirements for obtaining marketing authorization are effective to assure the safety and efficacy of drugs that enters the market, these requirements fail to supply the population of minors with an equitable variety of drugs.

Due to the high complexity of testing drugs in children, the costs of testing a drug in minors may well exceed the potential return on investment and, therefore, render it economically unattractive to label drugs for pediatric use. As a result, there is a dearth lack of drugs for use in children, and in many instances, pediatricians have no therapeutic options apart from using drugs off-license or off-label [15]. The high rate of off-license and off-label drug prescriptions in pediatric practice is disturbing, as it entails experimental drug use outside of the controlled conditions of a clinical trial [28].

In the ongoing efforts to develop and provide drugs for the young, the principle of justice is made operational in the pediatric research setting as the provision of safe and efficacious treatments for minors.

Nonmaleficence

The principle of nonmaleficence intimates that biomedical interventions should not intentionally inflict harm on the subjects of these interventions. This principle is often formulated as "first do no harm" (primum non nocere).

Main issues in clinical research and paradigmatic approach in competent adults

The numerous incidences of unethical research conduct that have occurred in the past century indicate that research can be unsafe, disrespectful of established ethical guidelines, and lacking in scientific quality [16].

Central to the current paradigmatic approach of unethical research is the review of research protocols by ethics committees. This procedure seeks to guard that research has added value, is safe and scientifically sound, and pays sufficient attention to ethical issues such as the provision of information and the protection of the research subjects.

Workability problems of the paradigmatic approach in competent adults in pediatric healthcare and implementation of the principle of nonmaleficence

In pediatric research, the desire to prevent unethical research can obstruct or prevent the development of drugs for pediatric use, as the act of balancing the protection of minors and the promotion of medical progress has proven to be complicated in the past several decades [29]. Therefore, pediatric expertise in ethics committees is essential in addressing the specific complexities of involving minors in clinical trials.

In the specific setting of pediatric research, the principle of nonmaleficence is made operational in the well-organized efforts to prevent unethical research, among which the review of research protocols by an ethics committee.

Beneficence

While the principle of nonmaleficence requires that biomedical interventions do not inflict harm on the persons undergoing these interventions, the principle of beneficence requires that biomedical interventions contribute to the welfare of these persons. This can be achieved in two ways. First, biomedical interventions can generate benefits in the research subjects themselves. Second, the drawbacks of biomedical interventions can be balanced with a newly generated benefit, either directly to the minor research subject or to another beneficiary.

Main issues in clinical research and paradigmatic approach in competent adults

The principle of beneficence is not easily applicable to research in humans. While a medical intervention that is not intended to cause a direct benefit to the individual concerned would be considered futile in the context of a treatment, the situation is clearly different in the context of research. Research does not necessarily aim at generating a direct benefit to the research subject. In the absence of a benefit, however, there is no counterbalance for the risks and/or burdens involved in research.

Paradigmatically, competent persons are considered to be capable of voluntarily accepting the risks and/or burdens involved in research. Therefore, the absence of a benefit need not be a hurdle to conducting valuable nonbeneficial research.

Workability problems of the paradigmatic approach in competent adults in pediatric healthcare and implementation of the principle of beneficence

Most minors are incapable of informed consent. As a consequence, a third party (the parents or another legal representative) has to decide upon the participation of a minor in a clinical trial. This proxy decision maker must serve the interests of the minor. When there is no benefit to counterbalance the risks and burdens involved in participating in the research, the interests of the minor in participation may be hard to demonstrate and the risks and burdens involved may be difficult to justify.

Given the strong emphasis on risks in research participation, the principle of beneficence is made operational in pediatric research in the efforts to counterbalance risks and burdens involved in research participation.

Autonomy

The principle of autonomy is closely related to the capacity for self-governance of competent human beings. This capacity enables individuals to make autonomous decisions that should be respected by others.

Main issues in clinical research and paradigmatic approach in competent adults

In clinical research, autonomous decision makers are often, paradoxically, highly dependent upon others, as they need information provided by experts to make rational and informed decisions [1]. However, the information provided can be biased, deceptive, or misunderstood (e.g., in case of therapeutic misconception, see [10, 24]. As a result, autonomous decision making may be compromised.

In competent adults, the ethical and legal doctrine of voluntary and informed consent is used as a paradigm for autonomous decision making. According to this doctrine, valid decisions to participate in research must be made voluntarily by competent persons (or their representatives) after being duly informed of the nature, significance, implications, and risks involved in the research. As a general rule, informed consent for research participation must be provided in writing. The doctrine of voluntary and informed consent is well-validated in ethics and law.

Workability problems of the paradigmatic approach in competent adults in pediatric healthcare and implementation of the principle of autonomy

In the pediatric setting, most research subjects are not capable of making autonomous decisions because they do not comply with the ethical and legal requirements to do so. The fact that most minors are incapable of giving a legally valid consent, however, does not preclude them from having certain decision-making skills, such as understanding what the decision is about, assessing information, and making rational decisions.

In decisions to enroll a minor in clinical a study, different participants negotiate their varying interests and concerns The role minors can and should play in these decisions may be hard to determine due to the constantly evolving capacities and maturity of minors. However, the principle of respect for minors implies that minors are appropriately involved in decisions about research participation. Therefore, in pediatric research, the principle of autonomy is made operational in pediatric research as respect for the minor by means of a fair distribution of power and responsibility in research participation decisions.

Ethical concerns addressed in the European legal framework

All four ethical concerns in pediatric research discussed above are addressed in various documents of the European legal framework. We will now explore how these ethical concerns are addressed in the content of the European legal framework.

The European Convention on human rights and biomedicine

The European Convention's provisions regarding the involvement of minors in clinical research are related to the ethical concerns of counterbalancing risks and burdens, preventing unethical research, and distributing decision-making power and responsibility fairly.

Counterbalancing risks and burdens

As a general rule, article 17,1ii of the European Convention provides that research on a person without the capacity to 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 the absence of a real and direct benefit, the risks and burdens are only deemed acceptable if two additional requirements are met. First, the research must aim at generating benefit to persons sharing the same age category, disease, disorder, or condition with the participating research subject (article 17,2i). Second, research may only entail minimal risk and minimal burden to the research subject involved (article 17,2i). In the additional protocol, the terms "minimal risk" and "minimal burden" are clarified. According to article 17 of the additional protocol, a research intervention only entails minimal risk if the results of that intervention generate, at the most, a very slight and temporary negative impact on the health of the person concerned and it entails only minimal burden if it is to be expected that the discomfort to the research participant will be, at the most, temporary and very slight. The explanatory report illustrates minimal risk as taking a single blood sample from a child (Explanatory Report, section 111).

The double requirement of generating a group benefit and limiting risks and burdens to no more than "minimal" puts strong boundaries on pediatric research. In accordance with the European Convention, several research interventions, such as clinical trials in early stages of drug development, are not permitted in children.

Preventing unethical research

The prevention of unethical research is also addressed in the European Convention. First, the convention states 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 (article 16,i) or by research involving individuals capable of informed consent (article 17,1iii). Second, article 17,1iv requires that authorization must be provided specifically and in writing.

Fair distribution of decisional power and responsibilities

The European Convention requires in article 17,1iv that the representative of the minor must grant his or her informed consent for the involvement of a minor in a clinical trial. Although the European Convention requires that the opinion of minors must be taken into consideration as an increasingly determining factor in relation to age and degree of maturity regarding therapeutic interventions (article 6,2), this provision does not occur in the provisions on research participation. However, the active participation of minors in decisions is not hereby precluded. On the contrary, the European Convention grants minors a veto right, as it is provided in article 17,1v, that research can only be carried out if the minor research subject does not object.

The European clinical trial directive

Like the European Convention, the European Directive delineates specific provisions regarding the involvement of minors in clinical research (article 4) and touches on the

ethical concerns of counterbalancing risks and burdens, preventing unethical research, and fairly distributing decision-making power and responsibility.

Counterbalancing risks and burdens

The European Directive provides for a counterbalance to the risks and burdens involved in pediatric research by requiring that the research generate a direct benefit. In article 4e, this direct benefit is defined broadly as "some direct benefit" that can be either an individual benefit (to the research subject) or a group benefit (to the group of patients). In the case of a group benefit, no additional requirements are applicable.

Along with the requirement that research generate a benefit, the European Directive also sets forth a preventive measure in article 4g, requiring that clinical trials 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 be constantly monitored, as stated in the same article, demonstrates the importance of this provision, as conformity with most requirements in the European Directive is only assessed at a single point in time.

Prevention of unethical research

The protection of minor research subjects is extensively addressed in the European Directive. Aiming at the harmonization of already existing guidelines on good clinical practice, the directive integrates the myriad principles captured in the historical codes of research ethics in which the protection of research subjects has consequently been a vast priority.

First, the well-known general principle that the interests of the patient always prevail over those of science and society is adopted in article 4i of the directive. This provision is notably subsumed in the specific provisions on clinical trials on minors.

Second, the European Directive states that minors should only be involved in research if there is a necessity to do so. Consequently, minors should not be involved in research when similar results can be obtained by research in competent adults or by other research methods, as provided in article 4e. In addition, this article requires that research be 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."

Third, article 4a of the European 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."

Fourth, according to article 4d of the European Directive, incentives or financial inducements to stimulate research participation, except for compensation, are prohibited.

Finally, article 4h of the European Directive requires that an ethics committee with pediatric expertise ("or after taking advice in clinical, ethical, and psychosocial problems in the field of pediatrics") endorse the research protocol. This ethics committee faces the challenging task of assessing whether the design of the research project sufficiently fulfills the ethical requirements captured in the European Directive.

Distributing decision-making power and responsibilities fairly

The European Directive serves the involvement of minors in decisions on research participation by stating in article 4b that minors must receive information "regarding the trial, the risks, and the benefits of the trial," in accordance with their capacity for understanding and provided by staff with experience with minors. In addition, article 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.

The guideline on the implementation of the European Directive issued by the EMEA (Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population) provides additional guidance in the fair distribution of power and responsibilities among decision makers. This guideline addresses a number of important issues in the involvement of minors in clinical trials. First, assent, a term that is not used in the European Directive, is recommended in the additional guidance 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 gray zone between legal capacity to consent and factual capacity is addressed. It is acknowledged that certain minors are mature enough to provide valid consent, even when they have not reached the legal age cutoff. In this respect, the guideline acknowledges that "emancipated minors" must give written consent to participation in research 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.

The pediatric regulation

The Pediatric Regulation solely addresses the issue of involving minors in clinical research and focuses on the issue of facilitating the development of safe and efficacious

care for minors of all ages. In article 2,1 of the regulation, minors are defined as the population between birth and 18 years of age.

The provision of safe and efficacious treatments to children

To encourage pediatric research aiming at the development of new drugs, the Pediatric Regulation requires that, for every request for marketing authorization, a Pediatric Investigation Plan (PIP) be negotiated early in the research (article 7). This PIP is to ensure that the data necessary to use a drug in all subsets of the pediatric population are gathered in the clinical research preceding the marketing authorization. However, waivers and deferrals to this general rule are possible under certain conditions. In addition, pediatric research is encouraged by means of strong incentives, as drugs tested in children obtain an extension of market exclusivity of 6 months (article 36). Also, for off-patent drugs, research in minors is rewarded by means of the "pediatric use marketing authorization."

To arrange the assessment of PIPs, waivers, and deferrals, article 3 of the Pediatric Regulation mandates the establishment of a Pediatric Committee, whose main tasks are the assessment of PIPs, waivers, and deferrals and the support and advice of the agency and commission.

Comparative analysis of the legal framework

The European legal framework surrounding pediatric clinical trials addresses various ethical issues. However, none of the individual documents that constitute the framework addresses the major issues in pediatric research in a systematic and exhaustive way. While the European Convention and the European Directive mainly focus on the counterbalancing of risks and burdens, the prevention of unethical research, and the fair distribution of powers and responsibilities in decision making of research participation, the Pediatric Regulation focuses almost exclusively on the development and provision of safe and efficacious drugs for minors.

Unfortunately, the European legal framework lacks internal consistency in certain matters. A comparative analysis of the three main documents of the European legal framework reveals contradictory provisions among the different documents, such as the provisions regarding nonbeneficial research and the veto power of minors in decisions of research participation. In the area of non-beneficial research, article 17,2 of the European Convention requires that, in the absence of a direct benefit to the individual research participant, a minor can be involved in research if the study only entails minimal risks and minimal burden, while article 4e of the European Directive simply 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. Consequently, early stage drug development may be compromised in member states that have signed and ratified the European Convention.

In relation to the power of a minor to veto participation in clinical research, contradictory provisions also exist. While article 4c of the European Directive states 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), article 17,1v of the European Convention states that minors cannot be involved in a study when they object to research participation. Thus, the European Convention theoretically grants minors more extensive decision-making power than the European 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 decision can be assessed, or why the European 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.

The interpretation and application of principles and requirements are largely left to those active in the field of pediatric research practice. Although it is true that efforts have been made to provide additional guidance in the interpretation and implementation of the legal framework, little practical support is offered to those responsible for implementing the law.

Discussion: ethical concerns in regulating clinical trials

Up to this point, we have integrated the (1) ethical issues in clinical research, (2) common approaches to these issues in competent adults, (3) workability problems of these paradigmatic approaches in the pediatric research setting, and (4) regulatory answers to these problems. Now, we will discuss the regulation of the ethical concerns in pediatric research and to relate our analysis of the European legal framework to specific discussions in bioethics.

The development of safe and efficacious healthcare for minors

Throughout this article, it has been clarified that the lack of commercial interest in testing drugs in minors must be

corrected in order to guarantee the marketing of an equitable variety of drugs for pediatric use. Such a correction has been effected in the European legal framework, as the Pediatric Regulation offers an extension of market exclusivity as a reward for the conduct of pediatric clinical trials.

This incentive provided for in the Pediatric Regulation, however, is open to discussion on two counts. First, it is questionable whether the extension of market exclusivity is a reasonable and fair incentive. While the extension of market exclusivity seeks to compensate the high costs of pediatric trials, the actual profits generated as a result of this incentive are highly variable; in some cases, the extension of exclusivity not even compensates for the costs of conducting the trial, while in other cases, the conduct of pediatric trials is a lucrative enterprise.[2] This highly variable compensation for the costs of conducting pediatric trials challenges the fairness and effectiveness of this incentive. Second, an extension of market exclusivity may also work against the quality of research. As the extended exclusivity is granted regardless of the results of pediatric research (and the marketing of a drug for use in pediatrics), pediatric trials may be more economically oriented than healthcare oriented. Care must be taken to ensure that the incentives provided for in the Pediatric Regulation encourage the actual marketing of drugs for use in children and do not result in the pro forma conducting of pediatric trials, which are aimed at acquiring the reward than actually marketing drugs.

Counterbalancing risks and burdens

To prevent the interests of minors from being harmed in the process of proxy consent provided by the parents or another legal representative, the freedom to accept the risks and burdens of voluntarily participation in research is strongly restricted in pediatric research (cf. supra). The main restriction of this freedom is the fact that research in minors must aim at generating a benefit for the research participant or for a related group of beneficiaries. This strong emphasis on benefit engenders several ethical issues.

First, even though children have an understanding of the risks and benefits of research [6], it is hard to measure benefit, risk, and burdens in a reliable way or to assess their proportionality. Although risks may be determined using objective toxicity criteria, the benefits, risks, and burdens in research are not entirely objective standards. On the contrary, the experience and interpretation of risks, burdens, and benefits is highly personal and related to the condition, disease, and personal experience of the participant. Due to this subjective nature, it is not clear how risks, burdens, and benefits can be assessed in a reliable way and how the proportionality between risks and burdens can be determined. Second, the strong emphasis on benefit blurs the distinction between research and therapy. While the distinction between research and therapy was already flawed in pediatric practice due to the high rate of off-label treatments (which constitutes, to a certain extent, an experimental use of drugs), the strong emphasis on the necessity of a therapeutic benefit in pediatric research gives the impression that research is a kind of a pseudotherapy. This may result in a therapeutic misconception in the minds of minors and their parents.

Third, the requirement that research should generate a benefit imposes strong boundaries on altruistic behavior in minors. While it is commonly rejected that minors have a duty to participate in research, minors may be willing to participate in research for altruistic motives. However, the strong emphasis on benefit and the restrictions on non-beneficial research may constitute a hurdle to altruistic behavior in research participation. Therefore, one could reasonably ask whether pediatric research should not be opened up for altruistic behavior by (healthy) volunteers or patients not belonging to the group of expected beneficiaries [21]. Enabling minors to decide upon voluntary participation in nonbeneficial research themselves, however, remains ethically contested [3].

Fourth, incentives continue to be a sensitive issue [4, 19]. While it is generally recognized that no financial incentives other than compensation for the costs involved in research participation is ethically acceptable, it is not clear how difficulties in the recruitment of research subjects can be addressed without using incentives. In pediatric research, there is the additional complexity that a reasonable compensation of costs may appear to be a large amount of money to a minor.

The prevention of unethical research

The prevention of unethical research is arranged effectively. The numerous historical incidences of unethical research in human beings in general and minors in particular have called for response in court trials (e.g., the Nuremberg Trials), self-regulatory efforts of the medical community (e.g., the World Medical Association's Declaration of Helsinki), harmonized guidelines on good clinical practice (e.g., International Conference on Harmonization (ICH) E6, E11), and legal regulation (e.g., European Convention, European Directive).

[2] Similar to the Pediatric Regulation, US Legislation offers (already since 1997) a 6-month extension of marketing exclusivity as a reward for the conduct of pediatric clinical trials. A study of the economic return of the Pediatric Exclusivity Program in the US shows that the economic return of the 6-month exclusivity extension is highly variable with net return-to-cost ratios ranging from −0.84 (i.e., a loss of $11,088,214) to 73.63 (i.e., a profit of $507,899,374) (see Li et al. [23]).

The fair distribution of power and responsibilities in decision making on research participation

Central to research participation is the voluntary and informed consent granted by the research participant. In pediatric research, however, such consent most often cannot be obtained, as most minors are incapable of legally valid consent. The problems of implementation that the ethical and legal doctrine of voluntary and informed consent face in the setting of pediatric research are commonly addressed by diversifying the process of informed consent. This diversification may entail proxy consent given by the parents or another legal representative, assent or dissent by the child, and the provision of appropriate information to minors [22, 25].

While the diversification of consent successfully tailors the legal dimension of informed consent to the pediatric setting, it fails to address the ethical dimension of consent in a satisfactory way, as the ethical principle of respect for persons that underpins the doctrine of informed consent is eroded by such a diversification. Transferring the power to consent is transferred from the research subject to a third party distracts the attention from the central position of the minor in decisions on research participation, while there is no reason to compromise the principle of respect for persons in the pediatric setting [20]. Therefore, the active involvement of the minor in decisions to participate in research should not be an affirmation of a decision that was already made by the parents (as is the case in parental

Principle	Issue	Paradigmatic approach in competent adults	Workability problems in pediatrics	Regulatory answer to the workability problems	Implementation of the principle	Discussion
Justice	Newly developed drugs should be made available to all patient groups that can benefit from these drugs	Distribution via the free market	The high complexity and costs of conducting clinical trials in minors render it unattractive to market drugs for the young Market mechanisms	PIP must be negotiated for all newly marketed drugs	Provision of safe and efficacious treatments to minors	Are the provided incentives (extension of market exclusivity) fair and reasonable?
	The safety and efficacy of drugs must be proven in human beings prior to their commons use	Requirements for obtaining marketing authorization	and requirements for obtaining marketing authorization are ill-suited to arrange the provision of a large variety of drugs to children	Reward for the conduct of pediatric clinical trials by means of an extension of market exclusivity		Does the market incentive work against the quality of research?
Nonmaleficence	Research can be unsafe, disrespectful of established ethical guidelines, or lacking scientific quality	Review of the research protocol by an ethics committee	Specific pediatric expertise is necessary to assess protocols for pediatric studies	Pediatric expertise is required by law	Prevention of unethical research	The prevention of unethical research is arranged effectively
Beneficence	Research may not have the objective of contributing to the well-being of the individual research subject and entail burdens and risks	Most often, taking risks voluntarily is deemed ethically acceptable	Proxy decision makers have to serve the interests of the minor research subject. As a results, risks and burdens in nonbeneficial research are hard to justify	A strong emphasis on benefit in pediatric research regulation A restriction of nonbeneficial research	Counterbalancing the risks and burdens involved in research participation	Reliable assessment of risks and burdens? Distinction between research and therapy? Obstruction of altruistic behavior? Ethical acceptability of incentives?
Autonomy	Research participation should be a voluntary and informed decision	Ethical and legal doctrine of voluntary and informed consent	Most minors are factually and/or legally incapable of valid informed consent	Diversification of informed consent—parental consent—alternative involvement of the minor in the decision-making process (e.g., information, assent)	Fair distribution of powers and responsibilities in decision on research participation	Truly respectful attitude toward minors?

consent and assent of the child), but the starting point of decisions on research participation whenever possible (which may not be the case in small children).

Although the European legal framework recognizes that minors develop a growing capacity to understand and assess information and make informed decisions, the exact role that is attributed to minors in decisions on research participation often remains unclear. While the right of minors to be informed and to dissent is taken very seriously, there is no clarity concerning the active role that minors can and should play in the actual decision-making process apart from affirming or refusing participation. In addition, it is hard to determine the decision-making capacities of individual minors [17]. Therefore, practical support for the active involvement of minors in decisions on research participation could be of great help in making the principle of respect for persons operational in the setting of pediatric research.

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