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SCIENTIFIC CONTRIBUTION

Regulating trust in pediatric clinical trials

Wim Pinxten · Herman Nys · Kris Dierickx

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Abstract The participation of minors in clinical trials is essential to provide safe and effective medical care to children. Because few drugs have been tested in children, pediatricians are forced to prescribe medications off-label with uncertain efficacy and safety. In this article, we analyze how the enrollment of minors in clinical trials is negotiated within relationships of mutual trust between clinicians, minors, and their parents. After a brief description of the problems associated with involving minors in clinical research, we consider how existing "relationships of trust" can be used as a place where the concerns of research subjects can be more fully discussed and addressed. Building on the tacit recognition of trust found in The European Clinical Trials Directive we make policy recommendations that allow for clearer, more ethically informed guidelines for enrolling minors in clinical research.

Keywords Trust · Clinical trials · Minors · Informed consent · Medical law · Medical ethics

Introduction: issues in involving minors in clinical research

In the course of the twentieth century, it became increasingly clear that results from laboratory research, animal experimentation and research in adults could not offer proper data to develop safe and effective drugs for use in pediatric practice. Because adults and children differ significantly in pharmacodynamics (the way a drug affects the body) and pharmacokinetics (the way the body responds to the drug), results obtained in adults cannot easily be transposed to minors. A mere recalculation of drug dosages used in adults based on a child's weight or skin surface is not reliable (Gill 2004; Salazar 2003). As a consequence there are no viable alternatives to using minors in clinical trials.

In the aftermath of the Nazi experiments and a series of research scandals in the US (Beecher 1966) and the UK (Pappworth 1967) minors were excluded from clinical trials. This was thought to be an efficient way to protect minors, but this strategy was eventually judged untenable. Denying minors access to clinical studies makes children 'therapeutic orphans' (Shirkey 1968) and results in a high rate of off-label prescriptions (the prescribing of drugs not tested in children and not labeled for pediatric use).[1] As Ross (2006) notes, in the absence of tested drugs *every* treatment becomes an experiment.

The involvement of minors in clinical studies, however, is a precarious enterprise. There at least three reasons for this.

(1) The limited (and varied) level of maturity of children generates a plethora of ethical and legal issues.
(2) The small number of pediatric patients makes research on the diseases of children commercially less interesting (and hence less likely) than research on adult diseases (Salazar 2003; Shirkey 1999).[2]

W. Pinxten (✉) · H. Nys · K. Dierickx
Centre for Biomedical Ethics and Law, KU Leuven, Kapucijnenvoer 35, 3000 Leuven, Belgium
e-mail: wim.pinxten@med.kuleuven.be

[1] It is estimated that between 7 and 60% of prescriptions in pediatric hospital wards are off-label (Pandoflini and Bonati 2005).

[2] To correct the commercial disinterest in pediatric drug development, incentives stimulating the pharmaceutical industry to conduct pediatric trials were adopted in US and EU legislation (Rodriguez et al. 2003; FDA Modernization Act of 1997; EC Regulation 1901/2006).

(3) Clinical trials in children are practically difficult. The limited pool of children eligible *and* willing to participate in a clinical trial makes it difficult for physicians to recruit a sufficient number of research subjects (Hoppu 1999).

Negotiating the involvement of minors in clinical trials

Obtaining authorization to enroll minors in clinical research

In order to enroll minors in clinical research, researchers must gain the approval of a research ethics committee (REC) and obtain valid permission—including consent from parents and, when possible, assent from their child—to participate in a study.

Authorization to conduct research RECs weigh three issues in evaluating research proposals that involve children: necessity, safety, and consent. Research with minors will be approved only if: (1) there is no other way to gain the needed information, (2) the risk of harm is in proportion to the expected benefits and procedures exist for reporting harm and for stopping a clinical trial if the safety of subjects is threatened, and (3) parental consent that respects the child's presumed interests is granted and children are informed and involved—to the extent possible—in the decision.

Permission to enroll individual minors In the European normative framework, the paradigmatic research subject is a competent adult. This fact, together with age standards and other criteria for legally valid consent, make gaining valid consent from minors problematic. Given the legal impossibility of obtaining consent from minors, other methods to protect children involved in research have been developed. Most common is the use of parental consent, where the parent (or parents) of a minor make decisions about the child's clinical trial participation. This strategy, while practical, is not completely satisfactory. Simply ignoring minors in decisions about participation in research overlooks their decisional capacity and threatens to erode the ethical standards used for research with adults.

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. This can be accomplished by means of 'assent'—the affirmative agreement of a minor to participate in research (45 CFR 46 subpart D). Specification of the need for assent is a step toward more informed participation of children in research but it does not clearly define the role and position of minors in the decision to participate in research. As Olechnowicz et al. (2002) observed, assent can be implemented in different ways: clinicians can opt for a "patient-centered" (clinicians begin by seeking the agreement of the child), a "parent-centered" (clinicians begin by seeking the permission of the parents), or a "joint patient-parent approach in decision making" (clinicians invite children and their parents to decide upon participation).

Three basic concerns when enrolling children as research subjects

Decisions to involve a minor in a clinical trial are complex. Gaining permission to enroll a child in a study is *not* a linear process where subjects provide their consent (or assent) at a distinguishable moment in time, i.e. when a document is signed (André et al. 2005; Snethen et al. 2006). Decisions to enroll a minor in a clinical trial are "stretched out" and require the cooperation of the multiple parties. Communication and information are essential in this procedure (Hoppu 1999; Salazar 2003). From the patient's perspective, three concerns are central.

Opportunities First, the child and parents must be convinced that it is worthwhile to enroll in a clinical trial. The opportunities presented by research participation are diverse and may not provide benefit to the participant. Participation in research that contributes to the health and well-being of other minors, or future patients, or to the progress of science in general, may be judged worthwhile even when direct benefit to the participant is unlikely. Lacking some form of opportunity for the participant—be it direct or altruistic—the necessity of research is difficult to justify.

Feasibility Second, the child and his or her parents must assess the feasibility of research participation. Research participation involves a considerable burden for both minors (e.g. taking drugs, blood sampling, hospitalization, follow up, physical inconveniences) and their parents (e.g. travel for study participation and follow up, drug administration, log keeping, reporting adverse events). The decision to assume these burdens must be shared by parents and their child.

Decisional freedom Third, the involvement of minors in decisions to participate in clinical trails rests upon the decisional strategy used by the family. Parents have considerable autonomy in the way they involve their children in decision making processes. Snethen et al. (2006) identify four ways minors may be involved in decisions about study participation: exclusionary decision-making (no involvement of the child), informative decision-making (the child is informed but has no decisional power), collaborative decision-making (the child is at the center of the decision-making process, but decisional power and responsibilities remain, for the most part, with the parents), and delegated decision-making (the decision is delegated to

the child). The decisional strategy used varies by family type and culture.

Difficulties in addressing patient concerns in research participation

Clarity of information and decisional autonomy are essential to making good decisions about the involvement of minors in clinical trials. Unfortunately, the many contingencies and dependencies involved in research with minors make it difficult to ensure good information and unconstrained choice.

Contingencies The setting of pediatric clinical research is rife with contingencies. The benefits and risks of participation in a clinical trial are difficult to determine resulting in ambiguous information and uncertain prognoses. Further, the provision of information is not an unbiased process. Physicians (or other clinicians) who invite minors and their parents to consider research participation provide *reasons* to enroll in a study, and in some cases these reasons are not health related. Simon observed that most of the altruistic discourse in enrollment discussion is provided by physicians and not by patients or parents (Simon et al. 2006). Conflicts of interest on the part of researchers also hinder the provision of clear and reliable information. Physicians may have a personal agenda in enrolling minors in clinical trials, such as enriching their personal career, obtaining research funding, or pleasing colleagues. Bias and conflicts of interests can also influence parental decisions, especially when financial incentives are involved. Recognizing this problem, laws prohibit excessive compensation for inconvenience and hardship.

Dependency In making the decision to participate in a clinical trial, the autonomous judgment of both minors and their parents can be impaired by relationships of dependency. In most cases minors and their parents are highly dependent on medical staff to provide and interpret the data relevant to their decision. The considerable asymmetry in information and interpretative skills between researchers and research subjects forces minors and parents to rely upon medically qualified staff to clarify the relevant data (Hazen et al. 2007).

Similarly, minors must depend on their parents to obtain authentic involvement in decisions. The decision to enroll a minor in a clinical study and the degree of the child's involvement in the decision making process are largely left to the parents. Although the active involvement of minors in the decision is highly valued in ethics and law, the actual decision about enrollment of a minor in a clinical study occurs in the privacy of the family. Parents are trusted to make decisions on behalf of their children and to balance the interests of the minor to be enrolled and those of other family members (Ross 1998). Interventions in the privacy of the family are very rare. On occasion (depending on domestic legislation), the autonomy of parents may be limited by the obligation to respect the express dissent of a minor.

The contingencies and the unavoidable dependency associated with the research setting increase the vulnerability of both minors and their parents, forcing them to rely on others to obtain the information they need to make rational and responsible decisions.

Handling patient concerns in relationships of trust

In absence of trust, research participation is unlikely (Mainous et al. 2006).

Because the concerns of parents and children are very personal and strongly related to the medical history of the minor, they are difficult to address in impersonal relationships. Hence, it is not surprising that impersonal recruitment strategies are generally unsuccessful (Knox and Burkhart 2007). Concerns about clinical trial participation—be they the child's or the parents'—are best situated in personal relationships, such as established relationships of trust between physicians, minor patients, and their parents. The handling of these concerns within personal relationships does not, however, relieve minors and their parents from the challenging task of deciding *who* and *what* to trust.

Trustworthiness Trustworthiness refers to the truthful, competent, sincere, and honest character of the trustee (Sztompka 2007). When clinicians, minors, and their parents negotiate the participation of a minor in a clinical trial, the interests of the child must be reconciled with the opportunities and hardship involved. In this process, minors and their parents are bound to rely on clinicians to close the gap in expertise and knowledge. Because misconception, manipulation, deception, and coercion cannot be precluded in the provision of information, the trustworthiness of the clinician who invites the child to participate is of great importance. Trust is required for minors and their parents to rely on the future and contingent actions of researchers (Sztompka 2007). In addition to trust in the person of the researcher, a child and his or her parents must trust the aims and methods of the proposed research.

Just as trust cannot be ignored, there is no suitable substitute for trust. O'Neill (2004) argues that mere transparency, autonomy, or accountability—although each is of great value—cannot compensate for trust. Therefore, and even in the face of its possible abuse, we must find a way to promote and enhance trust.

Trust issues in the European clinical trials directive

Entrusting issues

Trust is, as we have shown, essential to address the major concerns of minors and their parents with regard to clinical trial participation. While "trust" is not an explicit part of the regulations governing the use of minors in research, by assigning tasks and responsibilities to various trustees, European legislation implicitly recognizes the importance of trust. More specifically, the Clinical Trials Directive of the European Commission and the European Parliament (2001/20/EC, further: the Directive) serves to organize and distribute trust among specific persons and institutional bodies.

The Directive is not explicit in this regard. Rather, the legislation simply formulates general principles and leaves the interpretation of these principles to those charged with implementation. The provision of information and the active involvement of minors in the decision making process, are, for example, left to the field of pediatric research practice, as is the determination of what counts as successful accomplishment of these tasks. Clinicians, minors, and their parents must determine what constitutes appropriate information or suitable involvement of minors in decision making. Other decisions, however, are explicitly removed from pediatric researchers and given to external bodies, such as the national legislator, the EMEA (European Medicines Agency), or Research Ethics Committees.

European concerns At the European level, the main concern is to promote the European Union as a competitive research environment. The interventions intended to make Europe an attractive destination for research include the simplification of REC-approval in multi-centre clinical trials, the introduction of strict time limits for the provision of REC approval, and the provision of harmonized REC-procedures by means of detailed guidance issued by EMEA.

The desire to be competitive, however, does not overrule the need to protect research subjects. In this respect, the Directive explicitly states that the interests of the research subject always prevail over those of science and society. The Directive specifies a wide range of subject protection measures, calling on several existing ethical and legal documents—including the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice, the Declaration of Helsinki, and the Convention on Human Rights and Biomedicine—to provide a general framework for these measures. However, the interpretation, implementation, and control of the issues related to research subject protection (both adults and children) are entrusted to the individual Member States and/or those in the field of research.

Public concerns Two major tasks in arranging responsible scientific progress—the assessment of the necessity of research and the safety of clinical trials—are given to the individual Member States and handled by a Research Ethics Committee and/or the competent authority. The Directive specifies that in the assessment of pediatric research, RECs must call on pediatric expertise or get other expert advice on the clinical, ethical, and psychosocial problems associated with the participation of children in research.

With regard to the necessity of a clinical trial, RECs must assess whether the clinical trial generates some direct benefit to the group of patients and whether research is essential and cannot be done using adults or other research methods. RECs also must assess the safety of the clinical trials and determine whether the expected risks are proportionate to the anticipated benefits, whether the staff conducting the research is qualified, whether written information for informed consent is of sufficient quality, whether the provisions for indemnity or compensation are satisfactory, and whether pain, fear, discomfort, and other risks are accurately minimized. RECs are also charged with creating a system to monitor serious adverse reactions.

Private concerns The Directive provides only general guidelines governing the opportunity to be in research, the decisional freedom of minor subjects and parents, and the feasibility of participation. This means that researchers, minors, and parents must negotiate concerns about these issues within the general framework set down in European law. There is wisdom in this lack of regulation. The fact that these "private concerns" are left to the field of pediatric research allows them to be addressed within the existing relationships of trust between researchers, minors, and their parents. Overregulation would move these concerns from the relationships of trust to an inflexible bureaucracy.

The way forward

At first glance, the European Clinical Trials Directive seems to provide a comprehensive and complete framework for protecting research subjects. The interests of the European Union are dealt with served at the European level, public interests are given to the domestic sphere of competent authorities and Research Ethics Committees, and private concerns of clinicians, minors, and their parents are left to pediatric research practice to be worked out within relationships of trust. There are, however, important gaps in the system.

The problems associated with the contingencies and dependencies found in clinical research with children are poorly addressed in the Directive.

Discussion: coping with the downside of trust

To some, the act of trusting can seem naïve, opening research subjects to the possibility of abuse. What can we do when trust fails? How can we deal with the deception, coercion, or harm associated with the contingencies and dependencies involved in research participation? In order to improve the process of recruiting, informing, and including minors in clinical trials we must acknowledge the downside of trust.

Informed consent, assent, and dissent

The doctrine of informed consent plays an important function in the pediatric setting by specifying liability and confirming (symbolically) enrollment in a clinical trial. On the other hand, informed consent in pediatric clinical trials fails to address several concerns of minors and their parents in the decisional process. This is especially true in decisions where parents have no choice, e.g. when the only medical interventions for their child's illness are experimental (Deatric et al. 2002). The problems of informed consent for pediatric research are not relieved by the use of assent. Because minors are not capable of settling liability issues, the only added value of assent is as a formal affirmation of willingness to participate in research. While this affirmation is important (it provides tangible evidence of the commitment of the minor), the signature on the assent document puts too much weight on the role of formal documentation.

Focus on the documentary evidence of consent and assent turns ethical standards into bureaucratic ones and distracts from important and ongoing relationships of trust. It is in these relationships where the true concerns of research participation are addressed. We believe that the best way to involve minors in decisions about research participation is to embed those decisions in an ongoing patient–physician relationship characterized by mutual trust. It is in these relationships that children and parents can freely express their concerns about the research and about the decisional capacity of the child subject.

Recruitment

Impersonal recruitment strategies, including recruitment by an independent person who does not know the details of a child's medical condition and history, do not work (Knox and Burkhart 2007). Not only do they yield few participants, they have little potential to address the concerns of minors and parents contemplating enrollment in a clinical study.

As with consent/assent, relationships of trust are a good locus to negotiate the inclusion of a minor in a clinical trial. There are, however, important caveats about this recruitment strategy: (1) even within relationships of trust there is the potential for bias and (2) not all physicians are able to address the concerns of minors and parents about clinical trial participation. Minors and parents must be empowered to identify and discuss their concerns, and physicians must be instructed in responding to the issues of pediatric research.

Empowering minors and their parents In our opinion, the best way to overcome the problems associated with using existing relationships of trust as the location of informed consent discussions is the appointment of an independent counselor. This counselor will inform minors and parents about their fundamental rights as research participants, help them to identify and discuss their concerns, and make them aware of the potential biases of the physicians who are recruiting them for a clinical study. The counselor must be able to explain the consent documents, and aspects of the clinical trial, and to answer questions that minors and parents may be reluctant to ask the physician. The counselor must have sufficient expertise to assess the information provided to minors and their parents and to examine whether the concerns of minors and their parents have been adequately addressed. The availability of an independent counselor—one who is capable of providing advice and judging whether minors and their parents were correctly invited and well informed—will strengthen the trustworthiness of research and help minors and their parents to decide where to place their trust (O'Neill 2004).

Creating expertise in physicians The delicate task of informing minors and their parents about why it would be good for a minor to participate in research requires: (1) knowing the child and his or her medical background well, (2) being aware of the child's ability to cope with the hardship of participation in a clinical trial, and (3) being familiar with decisional styles characteristic for a family. Physicians who know the family well are well positioned to do this. Dealing with the concerns of minors and their parents about participation in a clinical trial, however, requires more than knowledge of the medical and social situation of the child.

In order to promote the ethical inclusion of minors in clinical trials, physicians must enhance their communication and information skills. Although studies suggest that few physicians actively ask for such measures (André et al. 2005), we are convinced that such a measure is a necessary step for the implementation of a normative framework that addresses the true concerns minors and parents.

Laws, directives, and guidelines provide the framework for the protection of the subjects—both adults and children—of medical research. But these "paper rules" must be affirmed by the "real rules" that govern what occurs in research practice. With regard to pediatric clinical research,

the real rules of research—and real protections for minors—are found in relationships of trust between physician-researchers, children, and parents. These relationships have a high yet under-employed potential to address subjects' concerns about research participation. By creating know-how in physicians and empowering minors and their parents, relationships of trust can become the place where patient concerns are effectively discussed and addressed, where minors truly can be involved in decisions, and where ethical and legal standards are effectively implemented in pediatric research practice.

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