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REVIEW ARTICLE

Informed Consent in Pediatric Research

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Abstract Pediatric drug research is gradually becoming more and more accepted as the norm for assessing whether a drug is safe and efficacious for infants and children. The process of informed consent and assent for these trials presents a major challenge. The aim of this review is to map historical, ethical and legal aspects relevant to the challenges of informed consent in the setting of pediatric drug research. The impact of age, level of maturity and life circumstances on the process of obtaining informed consent as well as the relations between consent and assent are discussed. There appears to be a lack of regulatory clarity in the area of pediatric clinical trials; while numerous statements have been made regarding children's rights to autonomy and their ability to care for themselves and for younger ones, the ever changing status of adolescence is still difficult to translate to informed consent. This may delay scientific and clinical advancement for children who are at the very junction of being independent and not needing parental permission. Obtaining consent and assent for pediatric clinical trials is a delicate matter, as both parent and child need to agree to participate. The appropriate transfer of information to guardians and the children, especially concerning potential risks and benefits, is at the heart of informed consent, as it serves to protect both patient and physician. As many adults lack health literacy, one must ensure that guardians receive relevant information at a level and in forms they can understand regarding the trials their children are asked to participate in.

Key Points

The appropriate transfer of information to guardians and the children, especially concerning potential risks and benefits, is at the heart of informed consent, as it serves to protect both patient and physician.

There is compelling evidence that most children younger than 9 years of age lack the capacity to consent for participation in clinical trials.

In some jurisdictions, institutional review boards approve the participation in drug research of healthy volunteering children during early adolescence.

1 Introduction

Unethical medical experiments that were conducted on human subjects for most of the 20th century reveal a disturbing pattern. While well intended and allegedly beneficent to humanity, these studies exemplify abuse of power by medical professionals to its worst degree as unsuspecting subjects were used for research purposes by the same physicians they trusted. This abuse of power was especially evident in two infamous studies: the Tuskegee syphilis study (1932–1972) where African American patients of low socioeconomic background were not

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offered effective antibiotics for their syphilis infection in order to follow the natural course of their illness [1], and the US government-funded studies of human exposure to radiation (1944–1974) conducted across the US [2], where the most vulnerable groups of society were deemed expendable for research purposes [1, 2].

Extreme racial discrimination of humans, combined with scientific aspirations, led Nazi physicians to commit the most horrid of atrocities in human subject studies (1939–1945). Prisoners served as study subjects simply because it was their only way to avoid being murdered. When passing judgment and sentencing the Nazi criminals, the Nuremberg military tribunal formed a code of conduct aiming to prevent the happening of such calamities in the future [3]. The Nuremberg code [3] stated that voluntary informed consent has to be obtained from all research subjects. This excluded minors, mentally handicapped and unconscious individuals who cannot legally consent. If the Nuremberg code were to be executed literally, no research in children could ever be ethically performed. Acknowledging this weakness, the Helsinki Declaration of 1964 permitted consent by the legally authorized representative of any potential research subject who is deemed incapable of giving informed consent [4]. This is presently the accepted norm by governments and medical associations worldwide. Informed consent is indeed a necessary prerequisite, but not a sufficient condition for an ethical study to take place. However, discussion on the child's ability to represent the population expected to benefit from the outcomes of the study is beyond the scope of this review.

Current definitions of childhood, adulthood and legal ages of consent vary by geography, culture and legislative history. Some countries define anyone younger than 19 years as a child, while in many others the 16th birthday marks the beginning of adulthood. At any age, consent obtained from minors is complex, given their vulnerability to exploitation and their maturity to grasp all relevant consequences of participating in the research. Societal and legal norms regarding adolescents in need of clinical intervention have been presented both in North America and in Europe [5, 6] and will be discussed below. However, having the right to influence their own treatment course is different from consenting to participation in a clinical trial, where both the potential benefits and risks are still unclear and therefore being investigated.

2 Measuring Children's Capacity to Consent to Research

The issues surrounding children's ability to understand health data affecting their health has been addressed by several studies.

Lee et al. [7] investigated how youths comprehend an assent form in the setting of a Hepatitis B vaccine trial. One hundred and twenty three adolescents 12–17 years of age (average age was 15 years) read a consent form and completed a comprehension test. The percentage of subjects who demonstrated absolute comprehension (100 % correct answers) was 56 %. This may imply that had they been asked to make a decision, almost half would have based their decision on information they did not fully understand [7].

Addressing the age of maturity of younger children to consent to research, two studies examined this issue directly and have identified a very similar cut-off.

Ondrusek et al. [8] empirically tested, through an interview, children's ability to consent for a study. Eighteen healthy children, aged 5–15 years, agreed to participate in a nutrition study aiming to measure extracellular fluid volume, after their parents consented. They were subjected to a variety of tests, including a venipuncture and being in a hood where exhaled air was collected. It was explained to the children that this was research and not clinical, and that they could withdraw their consent at any time. Despite age-appropriate information that was explained orally, as well as in a written form, none of the children under 9 years of age could describe the purpose of the study, or understood that it was not to do with their own health. Similarly, young children did not understand the planned procedures, potential harm, benefits and right to withdraw. Only two of eight children below the age of 10 years believed it was acceptable to withdraw from the study, whereas nine out of the ten older children were aware of this right. In fact, many of the younger children believed their parents would not be pleased if they had withdrawn. The study concluded that most children under 9 years of age cannot be expected to consent or assent to clinical research in a meaningful way [8].

Recently Hein et al. [9] proposed a standardized competence assessment instrument for children by modifying an existing tool, the MacArthur Competence Assessment Tool for Clinical Research. They tested this new tool for validity and reliability and correlated its assessment with children's age in an attempt to define cut-off for its use. Between 2012 and 2014 they tested the tool, which is based on a semi-structured interview, on 161 pediatric inpatients and outpatients ranging between 6 and 17 years of age (mean age 10.6 years). The scores on this new scale were compared with a 'gold standard' evaluation of these children by experts who considered, similar to the scale, four criteria: understanding, appreciation, reasoning and choice. Overall, the new tool had high levels of agreement with the experts' evaluations. Importantly, the new scale judged 37.9 % of the children incompetent to give consent. Not surprising, age predicted competence, and similar to

Ondrusek's study, in children younger than 9.6 years of age competence was unlikely at sensitivity of 90 % [9]. The authors suggested that in children aged 9.4–11.2 years, consent can be justified based on tested competence.

Putting these values in a larger societal context, it is interesting to consider minors' consent to sexual activity, where the law in many countries expects from this age group responsibility to protect their health by making informed choices; under 12 years is it illegal to provide such consent, while a youth of 12–13 years of age can consent to non-exploitative sexual activity with a peer of similar age (maximal age difference of 2 years is acceptable). Those of 14–15 years are allowed to give similar consent but for them the acceptable age difference with their partner is 5 years and teenagers of 16–17 years are allowed to have partners of any legal age, as long as it is considered a non-exploitative sexual activity. For the purpose of exploitative sexual activities (prostitution or pornography, for example) 18 years is the age of consent [10]. However, as much as the text is very clear with respect to the age of the potential partner, having a partner of appropriate age does not absolve the youth of the need to be educated in the issues of such activity. In contrast, no similar legislation exists regarding consent to clinical research.

3 Proxy Consent by Guardians

Proxy consent given by parents and other guardians is still the topic of extensive debate regarding the level of risks and medical procedures which a proxy can approve. The challenge faced in conducting research in children in general, and drug research in particular, is based on the clear understanding that adults are deciding on the best interests of younger people. At one extreme of this discussion there are ethicists who submit that one should not touch human beings unless they can consent to be touched. Ramsey [11], for example, claimed against any use in research of a non-consenting subject such as a child, even if no risk is involved. McCormick [12] disagreed and presumed that the child, if capable, would consent in many such instances and therefore proxy consent is valid. Moreover, being members of "a moral community", children, according to McCormick [12], are obligated to contribute to the advance of health and welfare of other members of the society, particularly other children. This view is countered by those who claim that unlike adults, children do not have social obligations.

A different view has been voiced by Ackerman [13], who submitted that children tend to follow "the course of action that is recommended… by the adults who are responsible for the child's well being". Hence, participation in research should not be different from many other activities guided by parents and guardians [13]. This argument loses much of its weight when dealing with adolescents who outgrow their tendency to obey their parents and might have developed their own views on consent and refusal [14].

Yet at the other extreme of this debate stands Gaylin, who submits that it should be the parental moral obligation to support their children's participation in research. According to him, the authorities should even educate the parent and child refusing participation on the topic of social responsibility [15].

Over the last decade, this debate has been widened with the issue of enrolling healthy children in non-therapeutic drug research that has also arisen. The scientific rationale is based on the need to know the pharmacokinetic properties of drugs in healthy children in order to be able to understand how specific disease states change these values. The ethical arguments highlighted above were contrasted against the empirical evidence that children entering their adolescent years can assume responsibility for participation. In fact, in several American pediatric centers, the institutional review boards (IRBs) approve such studies [16]. It is presently not clear whether this trend will survive ethical and legal challenges in other jurisdictions [17].

As documented below, common practice has taken the middle road between the two extremes expressed by Ramsey on the one hand and Gaylin on the other.

4 Essential Components of Informed Consent in Pediatric Research

4.1 Free Choice

Parents and children above a certain age specified below should be totally free to refuse to sign consent. This freedom may be endangered by one of several factors.

4.1.1 Coercion

While coercion may not be explicit, parents may feel forced to participate in a study conducted by a pediatrician caring for their child. They may fear that refusal will affect the quality of care their child receives. To allay such fears, the consent form should indicate that refusal to consent, as well as a later decision to withdraw the child from the study, will not affect the quality of care the youngster receives. It has been argued that such a statement may not be sufficient to deal with this source of implicit coercion. In many hospitals, protocols are introduced and consent is sought from the parents or guardians by health professionals not participating in direct patient care. Hansson and

Hakama [18] have taken this even further suggesting that the attending physician should hand over the role of giving information, delegating the consent process and all future communication regarding participation in the trial to an independent representative of the trial. However, this extreme approach may not be practical, as often the principal investigator is the expert in the field who can answer the questions of the family more effectively than other team members.

4.1.2 Inducement or Reward

Involvement in pediatric research may be time-consuming and financially costly to the family. Loss of work and other expenses involved in hospital visits (e.g., parking, food) may diminish motivation for participation, even among individuals who understand and recognize the importance and relevance of the study. Therefore, there is a consensus that families should be reimbursed for such expenses. Moreover, it is conceivable to compensate parents and adolescents for their time, as many teenagers are working and earning during their spare time. However, it is equally important to avoid disproportionally high reward which may distort the concept of free choice to consent and act as coercion [19, 20]. In Toronto, the research ethics board (REB) allows reimbursement for expenses, and for loss of time calculated using the minimum wage for the given year.

4.2 Complete and Understandable Information

The research plan of the particular study has to be clearly explained with all the details, including the drug and its known risks, and the risk and discomfort of the planned procedures (e.g., venipuncture). The parents, other guardians and indeed the child after a certain age, should be able to have, after reading such information, a clear view of what is the standard of care as compared with the proposed research. As often the research procedure overlaps with the clinical management of the child, they should be able to distinguish what is not routine. The details of the research procedure should be well described, with their attendant risks and potential benefits. If no benefits are expected, this should be clearly stated.

The ability of parents and children to understand written information is extremely variable. It is presently estimated that 14–22 % of American adults are functionally illiterate, and even carefully written information will be out of their reach [21]. The associated term 'health literacy' had been coined to describe a person's ability to understand health-related information provided in non-medical language. A recent study on health literacy in the emergency department of a single medical center in the US has documented that 25 % of the patients had marginal or inadequate health literacy [22]. In Toronto, the REB targets the information to comply with Plain Language regulations (a US government-wide group of volunteers working to improve communications from the federal government to the public; webpage: http://www.plainlanguage.gov/). In many North American institutions, the language is set at Grade 4 level. The information given to parents must include all other available procedures or courses of treatment for the particular condition under study that are not part of the proposed protocol.

To ensure clarity, all information should be written. In some institutions the consent documents are divided into an 'Information Sheet' that should be read carefully before signing the 'Consent Form'.

The issue of how much information should be given to parents and children has to be decided for each protocol by the REB. Sometimes too many details may dilute or mask the main issues that should concern the parents. In various countries the regulations deal differently with the question of how much information physicians have to give to research subjects. In Britain it is defined as the amount of information a reasonable member of the medical profession would give to a patient with the same set of circumstances. In other common law jurisdictions (Canada, New Zealand) and in the US, the adopted approach defines it as the amount of information that the reasonable patient would want to know [23]. There is a Canadian precedent to indicate that in research the physician is obligated to give exactly as detailed information as would be offered to a patient undergoing a similar non-research treatment, if not more. Walter Halushka took the University of Saskatchewan to court after suffering unexpected cardiac arrest during voluntary participation in a clinical study of a new drug. Failure to inform Mr. Halushka [24] that he was about to receive a novel and, as of then, previously untested anesthetic was harshly criticized by the judge. Addressing the same issue, the British Medical Association published online a 'Consent tool kit' (http://bma.org.uk/practical-support-at-work/ethics/consent-tool-kit) stating that "Doctors must take care to ensure that patients asked to consider taking part in research are given the fullest possible information presented in terms and a form that they can understand".

Overcoming the issue of patients' and parents' inability to understand written explanation about studies, there is an increasing trend to present such data using different forms of multimedia [25, 26]. Similarly, group counselling, where parents can hear the information and interact with the researchers and other parents can increase their understanding. For example, this approach was used recently in a placebo-controlled trial of probiotic use for infantile colic [27].

An area of continuous debate is how to inform parents and guardians on rare but serious adverse effects of an experimental drug or procedure. There is considerable overlap between unnecessarily alarming families about a very rare event and not sufficiently informing them about significant problems.

4.3 Confidentiality

It is essential to keep all research documents confidential, and published results should not contain identifying details unless the family agreed to it (e.g., photograph of child's whole face). The goal of securing confidentiality has to be stated in the consent document. In protocols where the research may reveal information which may be legally sought by child protection authorities, the guardians/family should be informed that it may not be possible to secure confidentiality. Two recent review papers involved in adolescent health care emphasized the importance of confidentiality as a bridge to obtain the trust and cooperation of this population [28, 29]. It is of particular importance when issues such as sexual health remain taboo subjects between adolescents and their parents/caregivers, and the encounter with the health worker is the adolescent's only way to receive up-to-date information. The failure of the 'abstinence only until marriage' (AOUM) educational programs (an attempt to reduce the rate of teen pregnancies in the US) can serve as a stimulus to encourage youths to seek confidential counselling from health practitioners [30]. As participation in research is founded on these same principles of trust and cooperation, it is imperative to grant adolescents who are part of a clinical study the same degree of confidentiality.

4.4 Assent

It is now widely accepted that in addition to parental agreement to enroll their son or daughter into a study, the child should also express such agreement, referred to as 'assent'. Technically, the assent is a document that explains to the child in language s/he can understand the essence of what is planned in the research, as well as the fact that s/he can say 'no', or can change his/her mind midway through the research. The assent lacks the legal text appearing in the consent form, but REBs are presently expecting this document to be completed and signed. Assent should be obtained from children who understand the purpose, risks and benefits of the study. While for infants and young children the reasoning for a certain intervention has no meaning, beyond a certain age and level of independence, failure to disclose such reasoning may jeopardize the trust between the researcher and the child. This loss of trust may cause great difficulties in data gathering, setting follow-up appointments and may eventually lead to withdrawal. But how do we know that a child has reached the age of assent? The following discussion is dedicated to the efforts that have been made to capture this elusive parameter.

The American Academy of Pediatrics regards children with an intellectual level of 7 years of age or older capable of giving such affirmation. When the intellectual age cannot be approximated, the chronologic age of 7 is usually the cut-off point [31]. As shown above, new evidence suggests that the majority of children younger than 9 years of age lack the capacity necessary to meaningfully consent [8, 9]. These studies are in agreement with a study by Schwartz [32], where the perceptions of children with growth hormone deficiency were assessed. The investigator found that despite multiple discussions on the reason for their hospitalization, no children younger than 11 years were aware that they stayed in hospital for research purposes.

In contrast, Lewis et al. [33] approached elementary school children 6–8 years of age, described to them the details of a study of influenza vaccine and let them ask questions. The authors found that all the data needed to understand the risks, benefits and mechanics of the study were sought by children 7–9 years of age (but not by the 6-year-olds) through their questions. Subsequently, about half refused to participate, and only 15 % of the parents of those who did not refuse, signed consent [33].The authors interpreted the results as showing that children 7–9 years of age are capable of comprehending and refusing to participate in a research project [33]. It could be argued, however, that this study does not show individual responses; the report that children, as a group, elicited all needed information in questioning does not show the ability of each single child to do so, and therefore, does not reflect an age of maturity or capacity to understand even a simple research procedure.

A recent review published on this topic advocates for personalized assent in the range of 5–7 years of age, where for certain children under certain circumstances the age cut-off could be tailored so that their participation in the process of study recruitment would truly represent their intellectual ability [34]. In criticism of the attempt to establish a single age for assent the authors claimed that "The studies on children's capacity to understand information concerning research carried out to date have not given clear pointers regarding the age from which assent must absolutely be obtained in pediatric research" [32].

4.5 Consent by Minors

Weithorn and Campbell [35] examined the correlation between children's development and their competence to give informed decisions about medical treatment (but not

in a research context). They found that 14-year-olds demonstrated competence levels comparable to the adult study groups. The 9-year-old children were similar to adults in measures of competence, but they scored significantly lower on understanding and rationality. As these tests were done on white, middle class, healthy children with no cognitive impairment, the generalizability of these findings is not clear.

With respect to consent given by minors, the British Medical Association submits that "Current guidance emphasizes that even where the minor is competent to make this decision for him or herself; it would be inadvisable to proceed without the approval of someone with parental responsibility" (http://bma.org.uk/practical-support-at-work/ethics/consent-tool-kit). This means that in the same manner that the minor's consent is critical for enrollment when the parents / guardians are supportive of the study, it is clear that the minor cannot overrule the decision of the parent/guardian to decline participation.

As reflected above, a major component in children's ability to consent to research is their capacity to understand, appreciate, reason and freely choose [9]. While trying to protect children from excessive risk, there is evidence that the existing establishment is not congruent in the way it evaluates children's ability to consent. This is reflected in the following scenario: in many countries children are allowed to work as babysitters of younger children after taking a training course. For that end, The Canadian Red Cross is offering an 8-hour course for youth aged 11–15 years titled "Basic first aid and care giving skills". According to the syllabus, participants learn how to provide care to younger children in a variety of age groups (babies to school-age children), and how to prevent and respond to emergencies [36]. Canadian researchers compared the decisions babysitters are expected to take during a babysitting assignment versus those taken by prospective research subjects. The comparison revealed significant incongruency in the way the maturity of the same children would be evaluated as babysitters versus participating in research. For example, an 11-year-old babysitter is allowed to guard a toddler, bath him/her and even lie to a stranger knocking on the door that the "parents are busy now". These tasks assume high levels of understanding. In contrast, the same child is not allowed to volunteer in research. In other words, when adults need the child to allow them to spend an evening at a movie, the child is judged as sufficiently mature and responsible, whereas s/he is not allowed to decide to participate in research [37].

4.5.1 Consent by Emancipated Minors

Emancipated minors are adolescents whose unique life situation (marriage, parenthood, self-support or military membership) has rendered them with no legal bonds to an adult guardian, and are therefore judged able to give their consent for research. Typically these adolescents are managing their own financial affairs and not living with their parents.

4.5.2 Consent by Mature Minors

The term 'mature minor' is used for purposes of therapeutic decisions, and not for research. In the US, the mature minor may be capable to consent for medical treatment if the treatment has a direct benefit to the minor, if the minor is near majority (this may vary by the treatment required) and exhibits understanding of the procedures to be taken. A minor's ability to consent for medical care is especially important when seeking treatment for sexually transmitted infections (STIs), drug (including nicotine) abuse and pregnancy-related care such as contraception, prenatal care or termination of pregnancy. The 2013 survey by the US National District Attorneys Association (NDAA) provides an interesting description of the legislative trends among the various states concerning medical consent by minors: most states (46 of 50) allow minors to consent to contraceptives including 21 states where the prescription is not dependent upon any condition or circumstance (marriage, health issues, etc.). All states permit minors to consent to STI services; however, 11 states specifically require the minor to be of certain age (usually between 12 and 14) [38].

The question of waiving parental consent to research involving mature minors is much more complex, because, unlike the case of therapies, research interventions often do not offer direct benefit to the minor. While the situation in which a minor is receiving medical treatment without his or her parents being in the loop is quite conceivable, the question of allowing him/her to decide for themselves not to involve their parents in a research study is far from resolved, even if the protocol deals with adolescent health (e.g., treatment of STIs). The American Academy of Pediatrics submits that waiver of parental permission should be considered only if the risk is minimal, if the research addresses questions that can only be answered in this population, and that the treatment for the medical condition could be given to the minors based on their consent only [31]. For example, a new antibiotic treatment for gonorrhea in adolescents meets the above criteria [30].

5 Conclusions

In conclusion, the special issues and processes associated with consent are probably among the unique ethical characteristics of pediatric research. They often pose difficult

dilemmas for REBs, as well as for parents and children. The ever-growing changes in lifestyle of adolescents complicate and challenge societal judgment of the appropriate cut-off ages for affirmation, both at the consent and assent levels. When these are coupled with increasing understanding of children's maturation, it becomes apparent that regulatory, medical and public views on children's participation in the consent process will have to evolve continuously.

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