

Are Children Always Vulnerable Research Participants?*

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Abstract

International guidelines stipulate that in order for children to participate in research, consent must be obtained from their parents or guardians. This is because researchers and ethics committee members have historically viewed children as vulnerable subjects. We, the authors of this article, think that in terms of decision-making for participation in medical research, children are not always vulnerable. Vulnerability is context- and study-specific. In this article, we argue that the blanket categorisation of children as vulnerable research subjects is ethically problematic. Significant numbers of mature minors, particularly in low-income settings, are currently being ruled out of research participation because their parents are unavailable or refuse to provide consent, despite the possibility that they might wish to do so and that such research has the potential to be of real benefit. Consequently, older children are under-represented in all types of clinical research. We here have illustrated our arguments using two case studies. In cases where research is important; meets international scientific and

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ethical standards and has been approved by relevant ethics committees; where the research team is trained to take consent; and where the information is presented in a way that is accessible to children, then children should sometimes be allowed to consent for themselves, rather than always being dependent on an adult. If children are able to provide valid consent to medical research in their own right, they should be allowed to do so, regardless of their age. The requirements for valid consent that we propose are competence, voluntariness, maturity, independence and contextual appropriateness.

Keywords: vulnerable subjects, children, research participants, competence, voluntariness, maturity, independence, contextual appropriateness

Introduction

Researchers and ethics committee members have historically viewed children as vulnerable subjects. This is evident in national and international guidelines in which vulnerable persons are defined as those who are relatively (or absolutely) incapable of protecting their own interests.

Although definitions vary, a good illustration of this is the 2002 Council for International Organizations of Medical Sciences' (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, which defines vulnerability as "a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group" and provides that "special provision must be made for the protection of the rights and welfare of vulnerable persons" (CIOMS 2002). Having set out this definition, the guidelines include research with children as one of its paradigmatic examples of research with vulnerable groups. The commentary on the CIOMS Guideline 13 states that "Classes of individuals conventionally considered vulnerable are those with limited capacity or freedom to consent or to decline to consent. They are the subject of specific guidelines in this document (Guidelines 14, 15) and include children, and persons who because of mental or behavioural disorders are incapable of giving informed consent". They then go on to set out the special requirements for the ethical conduct of such research.

What is Vulnerability?

In practice, as well as in theory, the meaning, nature and scope of the concept of "vulnerability" is contested and hard to pin down. Empirical research has

shown that there are many challenges faced in understanding and using this key concept in practice (Loue and Bebe, 2013). Critics of the concept include Kipnis (2001), who has argued persuasively that if it is to be used at all vulnerability is best understood as inherent in *situations* rather than in people. For example, a pregnant woman may be vulnerable in the context of some proposed interventions but not vulnerable in others. Kipnis argues further that vulnerability is best understood as dynamic, that is, vulnerability and the need for and adequacy of special protections may fluctuate or develop over time, suggesting the importance of periodic review and ongoing reflection in practice.

According to Kipnis, notwithstanding the importance of situations, seven characteristics often evident in children have the potential to make some contexts more likely to be ones in which vulnerability is possible: (i) they commonly lack the capacity to make mature decisions; (ii) they are subject to the authority of others; (iii) they (and their parents) may be deferential in ways that can mask underlying dissent; (iv) their rights and interests may be socially undervalued; (v) they may have acute medical conditions requiring immediate decisions not consistent with informed consent; (vi) they may have serious medical conditions that cannot be effectively treated; and (vii) they (and their parents) may lack important socially distributed goods.

Lack of Capacity to Make Mature Decisions as a Key “Vulnerability”

Our focus in this article is on only one of these seven vulnerabilities, the first of Kipnis’ factors arising in research with children—the claim that they commonly lack capacity to make mature decisions. The other six vulnerabilities are also important, and raise questions about the scope of their applicability to children and young people, but for the purposes of focus these are beyond the scope of the present article, which discusses capacity and maturity as an illustration of the potential morally significant implications of the application of the broad judgement of “vulnerability” to children and young people.

The Problem

With regard to the vulnerabilities of children as research participants generated by worries about capacity and maturity, the CIOMS commentary on their guidelines states that:

The investigator must obtain the permission of a parent or guardian in accordance with local laws or established procedures. It may be assumed

that children over the age of 12 or 13 years are usually capable of understanding what is necessary to give adequately informed consent, but their consent (assent) should normally be complemented by the permission of a parent or guardian, even when local law does not require such permission. Even when the law requires parental permission, however, the assent of the child must be obtained. (Commentary on Guideline 14)

This commentary could be approached from a number of angles. Our concern here is with the implications of the paragraph above for children over the age of 12 or 13 years whom the guidelines suggest are, “usually capable of understanding what is necessary to give adequately informed consent” and yet are also specified as unable to participate in research without the permission of a parent or guardian. It is our view that this definition of children as vulnerable research subjects in the guidelines has the potential to cause practical and ethical problems in practice and to fail to take sufficiently seriously the autonomy of significant numbers of young people.

Case Studies

In what follows, we present two contrasting cases of situations in which the assumption of vulnerability and the associated requirements for parental consent cause practical ethical problems. The clinical studies are real but the “cases” are fictional though realistic and grounded in our experience of conducting and supporting research in low-income settings. Both of these cases studies are situated in the context of real research programmes currently being conducted by the Mahidol Oxford Tropical Medicine Research Unit, which was established in 1979 as a collaboration between Mahidol University in Thailand and the University of Oxford in the United Kingdom to conduct research on tropical diseases. The main office and laboratories are located within the Faculty of Tropical Medicine in Bangkok, Thailand but research is carried out in many different locations both in Southeast Asia and more widely in Africa and South Asia. At any one time, the Unit has around 60 to 70 active clinical studies on malaria and other neglected diseases such as melioidosis and unexplained fever, of which many do not exclude children (SEAQUAMAT 2005; Ashley et al. 2014). In addition, we have conducted a number of large paediatric clinical trials; for example, we recruited more than 5,000 children with severe malaria in a pan African study (Dondorp et al. 2010), and our study in the Democratic Republic of Congo recruited more than 600 children with uncomplicated malaria (Onyamboko et al. 2014).

It is important to note that both the clinical studies below have been approved by the relevant scientific and ethics committees, and that the inclusion of paediatric patients in these studies has been judged by them to be justified. In both studies, consent is (or will be) obtained by experienced teams who have the skills to explain the information clearly, to assist the decision-making, and to respect the potential participants' decisions without putting undue pressure on them.

Case One: The Typhus Study

This is a prospective observational minimal-risk study to be conducted in a hospital in Chiang Rai, northern Thailand (clinicaltrials.gov identifier: NCT02398162). The study will recruit adult and paediatric patients aged 7 years and above with the objective of understanding the immune response of scrub typhus which may help in the development of a vaccine against scrub typhus. Scrub typhus is a prevalent infectious disease spread by mites. Patients will be treated in accordance with routine clinical care. The study only involves research-specific venous blood sampling at weeks 0, 2, 12 and 52 with volumes that are considered safe (in accordance with the guidelines of the Seattle Children's Hospital) and requires two additional visits to the clinic. There are no other research procedures. Participants (or parents of child participants) will be reimbursed according to average local wages for their time lost and transport to attend extra visits to the clinic. In accordance with local ethics committee guidelines, prior to participation in the study, consent must be sought from parents/guardians of all children aged < 18 years. In addition, children aged 7 to < 13 years must sign an assent form, and those aged 13 to < 18 years a consent form. A child aged 13 to < 18 years who wants to take part in the study is not allowed to do so if his parent/guardian does not consent. It is interesting to note that although the age of majority is 20 years in Thailand, most ethics committees allow individuals aged 18 years and above to consent for themselves.

Lek is a 15-year-old Thai girl who works in a farm not too far from the hospital where the study is conducted. She appears to understand the study and its requirements, and she has told her doctor that she would like to participate. Her doctor told her that in order to participate, one of her parents would have to provide consent but her parents live in another village, about two hours away on foot. This means that Lek cannot be enrolled in the study.

Case Two: The Vivax Study

This is a multicentre study of vivax malaria that aims to recruit adult and paediatric patients aged 6 months and above (clinicaltrials.gov identifier: NCT01814683). It is a randomised controlled trial of primaquine 1 mg/kg for 7 days, primaquine 0.5 mg/kg for 14 days and placebo in order to prevent the relapse of malaria. All patients will be treated with chloroquine for the acute phase of the disease. Primaquine is recommended by the World Health Organization and has been used in the treatment of malaria for many years, but for patients with G6PD deficiency (a common genetic blood disorder), it can cause haemolysis. The study excludes patients with G6PD deficiency. In patients who test normal on the G6PD test, there is a potential risk of haemolysis particularly in the primaquine 7-days group. As for follow-up visits, participants are required to visit the clinic to get their blood checked monthly for 12 months to determine whether or not they are ill. Outside of the study, patients would normally go back to the clinic only if they have any symptoms which signify that there is a relapse of the disease, which can be quite frequent. Participants (or parents of child participants) will be reimbursed according to local rates for the time lost and transport to attend extra visits to the clinic.

Thant is a Vietnamese 15-year-old girl who lives with her parents. She goes to school in the morning and helps her parents on a farm in the afternoon. She appears to understand the study and its requirements, and she has told her doctor that she would like to participate. Her doctor told her that in order to participate, one of her parents would have to provide consent. The study doctor asks Thant's father to sign a consent form but he refuses. In accordance with local ethics committee guidelines, prior to participation in the study, consent must be sought from parents/guardians of all children aged < 18 years. There is no requirement for assent or co-consent by adolescents in Vietnam. This means that Thant cannot be enrolled in the study.

Thinking about Consent and Vulnerability in Context

How should we think about these two cases and what are their implications for the scope of the role of the concept of "vulnerability" in research with children? First, it is important to note that there is much that is similar between Lek and Thant. Both understand the research and want to participate. Both are defined as "minors" by the relevant law (the age of majority is 20 years in Thailand and 18 years in Vietnam). Such cases present an important challenge

to the requirement in the guidelines that—because they are vulnerable—children should not participate in research without their parents' consent.

The requirements of the guidelines that consent be obtained from a parent or guardian are relatively unproblematic in cases where it is clear that children lack capacity, for example in the case of very young children. The situation is less straightforward, however, in older children such as Lek and Thant, where—as the CIOMS guidelines acknowledge—a significant proportion may have the capacity and maturity to provide valid consent but who are likely to be considered “minors” (Cheah and Parker 2014). This is an important ethical problem for at least three reasons: first, there are strong ethical reasons in favour of competent people making decisions about their own lives; second, in regions where the benefits will have the most impact, many children are currently being ruled out of research because their parents are unavailable, have little understanding of the research, or simply refuse consent (Cheah and Parker 2014). A third ethically significant reason why this is important relates to the importance of medical research on the diseases of childhood in low-income settings. Research is necessary if children in these settings are to benefit from new drugs and other interventions for diseases that are prevalent in these settings, e.g. malaria. In addition to its implications for their autonomy as individuals, exclusion of this group of children from important research relevant to their health needs or those of other children has the potential to have long-term negative consequences on the well-being of them as a group.

Valid Consent

Our purpose in this article is to argue that the blanket categorisation of children as vulnerable research subjects is ethically problematic. We believe this is true of all seven of Kipnis' criteria for vulnerability; but for the purposes of this article, we focus on the claim that because many children are vulnerable, all children should be barred from research participation unless they can obtain their parents' consent. We have chosen to use case studies to make our argument because situations such as those described above are relatively commonplace in low-income settings. They occur on a daily basis in most of our studies, for example, and this commonality is morally significant. In both cases, guidelines require that parents provide consent for the children before research participation is acceptable. In what follows, we will use the two cases and the differences between the two clinical studies to explore the factors relevant to the judgement of “vulnerability” in such situations. Taking the assessment of competence and maturity to provide valid consent as our focus, we shall argue that one or both

of Lek and Thant are not vulnerable relative to the decision at hand and should be allowed to consent to participate in the studies.

What are the requirements for valid consent? Generally speaking, in the case of adults, such consent is: (i) informed and understood; (ii) competent; and (iii) voluntary. In the case of children and young people, the requirement of “maturity” is often added. For the purposes of discussion, we are going to assume that both Lek and Thant have a good understanding of the nature and purpose of the research projects they are being invited to participate in. In what follows, we compare and contrast the two cases above in relation to the key requirements of competence, voluntariness and maturity. We then go on to explore two other potentially relevant concepts: those of independence and contextual appropriateness.

Competence

In order to be judged capable of giving valid consent, Lek and Thant have to meet the relevant criteria for competence—often described as involving the ability to understand and retain relevant information, to weigh or judge the relative merits of the options, and to make and communicate a decision (UK Mental Capacity Act 2005). They need to be capable of understanding the relevant risks, benefits, commitments, study procedures and objectives of the study.

In the case of the Typhus study, which Lek is interested in being recruited into, the study is observational and involves no more than the risks of venipuncture, which is minimal. It would be helpful to know if Lek has had the experience of venipuncture and whether her experience was good or bad. There are no foreseeable long-term consequences or any foreseeable physical or emotional harm, but Lek needs to have the competence to appreciate that there are no individual benefits to herself even if there are potential benefits to future patients.

The risks involved in the Vivax study, in which Thant is interested in participating, are also minimal, though this is a drug study. This means that participants need to be capable of understanding that there is a risk of side effects caused by the drug primaquine, however small it may be. On the other hand, if patients are in the placebo arm, the “risk” is that there is likely to be one or more episodes of relapse of malaria. Like the Typhus study, the Vivax study involves additional venipunctures and the study team should determine if Thant is happy with them. As for benefits, patients can expect no relapses if they happen to be randomised to the primaquine arms. However, in the placebo arm, there are no anticipated individual benefits.

In addition to risks, for both studies Lek and Thant have to be capable of understanding the commitments of the study, the most important of which is that they have to attend follow-up visits.

Perhaps the most abstract of all, and hence most difficult to understand, is the objective of the each study. In the Typhus study, although the study is only observational, the objective of the study may be more difficult to explain compared to the Vivax study. Should Lek and Thant have the competence to understand the objective of their respective studies in addition to the risks, benefits and commitments of the study, then we think that they meet the competence criteria.

Voluntariness

An additional key requirement for valid consent is that such consent be voluntary. Even if they are competent, those recruiting Lek or Thant would need to be confident that have made their own free choice about whether or not to participate.

There are a number of ways in which consent might fail to be voluntary. In resource-poor settings, for example, the provision of healthcare in research projects can often act as an inducement. If participation in research were the only way for these children to gain access to clinical care, this could potentially mean that their decision to participate was not voluntary in the required sense. This consideration is the same for both adults and children. In children, we have to be aware of additional ways in which they might be coerced or less than ideally voluntary. They might consent because they “need approval” from adults or are afraid of those in authority such as doctors and researchers, believing that they are not “allowed” to refuse participation. Another consideration is that children may be more prone to inducement, e.g. cash for time off work and tokens of appreciations in kind. In both case studies, participants are reimbursed for their time and transport. Although the amount is small and reflects the daily wage, it may be viewed as quite substantial by young persons. Because of the number of study visits, the Vivax study has a total reimbursement that is much more than the Typhus study and consent takers should be aware of the implications.

Maturity

One counter-argument sometimes made against the claim that children can meet the relevant criteria for competence and voluntariness is that whilst they

might appear to be making a voluntary choice, they can often lack sufficient “maturity” or life experiences to make important decisions with long-term implications. We agree that maturity may be relevant to some decisions about research participation and that evidence of lack of maturity might on occasion mean that despite their competence in other respects, it would be inappropriate for a child to be allowed to consent in their own right.

Maturity, which is undeniably a challenge to assess (Koren et al. 1993), is a prerequisite for making decisions that are more significant in their consequences, involving perhaps substantial changes to a person’s life prospects or where the decision may have irreversible effects.

Both the Typhus and Vivax studies only involve assessments in an outpatient clinic with no foreseeable impact on future life or potential for irreversible side effects. The decisions do not appear to have any long-lasting consequences. Many adolescents like Lek and Thant are sufficiently mature to make these decisions.

On the other hand, if the interventions or procedures were more serious, for example involving a new drug with potentially serious side effects, then the threshold of maturity would appropriately be set higher.

In research studies that do not have the potential to benefit the individual participant, the potential child participant needs to have the maturity to understand altruism. As the Typhus study offers no direct benefit to the individual participant, although the good deed might be small, the child would be participating out of sheer desire to help future patients. It has been shown that adolescents begin to understand and develop the ability to act from moral motivations at 11 to 12 years of age (Eisenberg 1991). This means that Lek is likely to appreciate what it means to be altruistic.

Independence

In addition to competence, voluntariness and maturity, we believe that another reasonable requirement for valid consent is independence. This could mean a research participant having his own accommodation and job, and the freedom to make decisions in daily life. This is also important for practical reasons where, for example, participants might need to make arrangements like travel to attend follow-up visits. This might suggest, for example, that because Lek is working and by contrast Thant is living as a child in a family, we might hypothesise that Lek is likely to meet the independence criterion, and Thant not. The key point is that the minor should be sufficiently autonomous in his daily life to have to make decisions of comparable complexity as the decision that he is asked to make about research participation. In respecting the principle

of autonomy, individuals who can shape their own lives should be allowed to decide whether to enrol in research in their own right.

Contextual Appropriateness

The way doctors relate to minors in research should be consistent with how they relate to them in clinical care. In many low-income settings, older children routinely seek medical care on their own, especially for less serious conditions. This is partly for practical reasons and partly cultural. Assuming that it is culturally appropriate to offer a child the option of standard care at the clinic without requiring his parents' consent, we should consider allowing him to consent for the research—if the decision is of comparable complexity to the decision he normally makes in daily life, and if he meets the other criteria for valid consent. This is being consistent. Contextual appropriateness also means that the decision-making reflects the culture of the society and family dynamics—within reason. If Thant normally gets her father's permission to do things, perhaps because she is a girl living in a relatively conservative society, then it is only consistent that she gets his permission to participate in the study. Understood more broadly, the requirement of contextual appropriateness suggests that children who are competently making decisions of comparable complexity, such as those being made by Lek, ought to be able to make decisions about research participation.

Clearly there are some children who are living independently against their will and making decisions for which they are unprepared. Asking them to decide to participate in research studies is adding insult to injury, imposing an additional burden upon them. Our proposal is not that all children living away from adult care are competent and mature. It is that when there is good evidence that this is the case, they ought to be able to make in their own right at least some decisions relating to participation.

Judgement, Accountability and the Law

In practice, for any given study and given site, the research team and ethics committees, in consultation with other relevant stakeholders such as community leaders or community advisory boards, will need to come to an informed view about the appropriate approach to consent in any particular project, and to put in place safeguards from abuse. In many cases, for pragmatic reasons, we recognise it may be appropriate for the chronological age be used as a proxy for vulnerability. Notwithstanding all of the above, we believe that in order to

prevent any abuse, there should be a lower age threshold for consent. This age limit is thought to be between 12 and 14 years for most experimental research, but may be lower depending of the nature of the research (Modi et al. 2014).

If the law requires, parents (or someone else like a child advocate, who is not necessarily a guardian) can co-consent or give “legal authorisation”—if they are available. We stress that authorisation is not the same as consent. Authorisation is a legal requirement whereas consent is an ethical requirement.

Conclusion

In this article, we have argued that in terms of decision-making for participation in medical research, children are not always vulnerable. Vulnerability is context- and study-specific. If they are deemed vulnerable when they are not, we are undermining their autonomy and taking their rights away.

We have illustrated this using two case studies. In cases where research is important—where it meets international scientific and ethical standards; it has been approved by relevant ethics committees; the research team is trained to take consent; and the information is presented in a way that is accessible to children—then children should sometimes be allowed to consent for themselves, rather than always being dependent on an adult.

If children are able to provide valid consent to medical research in their own right, they should be allowed to do so, regardless of their age. The requirements for valid consent that we propose are competence, voluntariness, maturity, independence and contextual appropriateness.

This, however, does not preclude parents taking part in decision-making or co-consenting. In fact, family decisions are encouraged wherever possible but the primary decision-maker should be the child himself, if he is deemed not vulnerable.

In our opinion, children are vulnerable in certain situations but are not in others. We believe that whether children are vulnerable or not is dependent upon the context—that includes the type and complexity of the decision they are asked to make, and the nature of the study they are asked to participate in.

We think that the more appropriate question we should ask is, “Can they provide valid consent?”

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