A critical review of health research ethical guidelines regarding caregiver consent for HIV research involving minors in South Africa: Ethical and legal issues

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Background. Over the past decades there have been tremendous efforts to improve the ethical conduct of research involving humans throughout the world. As a one-size-fits-all philosophy can no longer work, most countries have developed specific legal and ethical guidelines for research, tailored to their own context. We reviewed South African (SA) ethical guidelines and Health Research Acts as they pertain to the role of caregivers in consent practices for minors' participation in HIV/AIDS-related research.
Methods. An argument-driven review was conducted on two SA Acts and Guidelines respectively: the SA National Health Act of 2003; the Children's Act No. 38 of 2005 and the Department of Health Ethics in Health Research Guidelines 2nd edition of 2015 and the Good Clinical Practice Guidelines of 2006, with a particular focus on minors as research participants. We also examined the relevant ethical and legal guidance using an exemplar of paediatric HIV testing within research conducted in SA.
Results. Available ethical guidelines for caregivers' consent in research involving minors are still not comprehensive or aligned with SA regulations governing research with minors. The recent revision and development of the National Health Research Ethics Guidelines (2015), regarding the role of caregivers in consent practice for minors' participation in health research, may be a positive move in clarifying the proper role for caregivers when enrolling minors in research.
Conclusion. Caregivers are deemed to have a role to play in research involving minors. Therefore, the inconsistencies in existing ethical guidelines and governing regulations regarding the role of caregivers in paediatric HIV research, need to be addressed following the recent ethical paradigm change.

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Health research and medical treatment are different in terms of their objectives, procedures, justifications, risk-benefits analysis and ethical responsibilities.[1] The goal of research is the discovery of new knowledge, largely through research with human participants.[1] Health research has undeniably produced substantial social and economic benefits through the development of innovative medical treatments, equipment and refined methods for improving and saving millions of lives worldwide.[1,2] Without the involvement of research participants these advancements in healthcare would not have been achieved. In principle it is essential that the effectiveness and safety of medicinal products be tested scientifically before their widespread use.[3] Testing of medicinal products in the population in question, without compromising their well-being, is vitally important to minimise research-related risks and/or clinical hazards as well as adverse reactions. Yet studies have shown that many of the medicines used in children might not have been tested for use in their specific age group, due to the widely-held perception that children should be protected from the potential harms of participation in medical research at all costs.[4,5] In South Africa (SA) 'children' refers to a person under the age of 18 years (section 28 of the Constitution; section 17 of the Children's Act 38 of 2005).[6] The National Health Act No. 61 of 2003,[7] section 71, interchangeably uses the terms 'minor' and 'child' in the section on research with human subjects.

Research involving children is complex. Firstly, their physical, cognitive and emotional development has not reached maturity and because their development is dynamic and changes throughout childhood, they may not be able to make mature decisions for themselves,[8,9] including providing informed consent for research participation. Secondly, young children are dependent on others for their well-being, but these individuals may not always be the best judges of what will promote the child's best interests.[9,10] In this regard, child-headed families, which are common in developing countries, raise many conflicts and concerns. Thirdly, children are not small adults; they are physiologically and anatomically distinct.[9] It is therefore, generally, not appropriate to directly apply results of medical products tested in adults to the paediatric population, as the products may have different risk and efficacy profiles in children.[8,11-13]

Given their insufficient decision-making ability and their dependency upon adults for their care, children's participation in research requires

the informed consent or permission of their parents or guardians. In addition to parental/guardian consent, children of sufficient age and cognitive development are required to provide assent (preferably in writing) for their research participation.[8] In this context, a parent refers to a biological or adoptive parent who has the authority and duty to act on behalf of his/her child; and a legal guardian is someone with the legal authority and corresponding duty to care for the child and act in the child's best interests.[6,14] However, there are many cases where children are cared for by someone other than their parent or legal guardian. A caregiver is any person other than a parent or guardian, who factually cares for a child,[15] and may include any of the following:

- a foster parent
- a person who cares for the child with the implied or express consent of a parent or guardian of the child
- a person who cares for the child while the child is in temporary safe care
- the person who heads a child and youth care centre where a child has been placed
- the person at the head of a shelter
- a child and youth care worker who cares for a child who is without appropriate family care in the community
- and a child heading a child-headed household.[6]

SA still has a high burden of HIV infection among children.[16] This is one of the priority areas for health research in the country, necessitating research involving children/minors.[17] Studies suggest research on HIV testing and counselling is the most important starting point for developing HIV-related effective treatment, care, support and prevention.[18] In turn, researchers have ethical responsibilities and obligations to research participants throughout the process of research, including testing medical interventions.[2,4] However, one cannot assume that all research will be conducted in an ethically appropriate manner without special and additional legal and ethical guidelines to ensure protection of vulnerable research participants, including children.[19] These special protections were developed in response to historical examples of studies where research investigators worldwide considered their study outcomes to be more important than protecting individual participants in research.

SA is committed to adhering to international declarations and ethical guidelines in health research, including the Declaration of Helsinki,[3] the Singapore Research Declaration,[20] and Universal Human Rights Declarations.[21] This article critically reviewed two SA Acts and guidelines respectively (the Children's Act 38 of 2005;[6] the National Health Act of 2003;[7] Good Practice in the Conduct of Clinical Trials, 2006;[22] and Ethics in Health Research Principles, Structures and Procedures, 2015[15]) regarding caregivers' consent in research involving minors as research participants. The following research questions were reviewed:

- To what extent are the above ethical guidelines and Acts in harmony regarding the role of caregivers in consenting on behalf of a minor/child for research enrolment?
- Is it acceptable for caregivers to consent for a minor/child under their care to participate in paediatric HIV research, which may potentially benefit the minor participant and/or future children?
- How should we balance child participant protection and the potential benefits from research participation regarding the minor living with a caregiver?

Methods

We reviewed the Children's Act No. 38 of 2005,[6] the South African National Health Act of 2003;[7] as well as the Department of Health (DoH) *Ethics in Health Research Guidelines* 2nd ed., 2015[15] and the *Good Clinical Practice Guidelines*, 2006[22] to understand the conceptual use of caregivers and their role in consent practice for a minor to participate in health research. We did not review the SA regulations on research with human subjects. The conceptual use of caregivers and their role in consent practice for a minor to participate in health research was examined using one text example of paediatric HIV research that has been conducted in SA.[23]

Results

Critical review of existing guidelines

Regulatory Acts such as the National Health Act and the Children's Act set the context for existing ethical guidelines for research with children. Researchers and Research Ethics Committees (RECs) should make themselves familiar with the Acts and ethical guidelines bearing on children to be able to:

- make ethical and moral decisions about minors' enrolment in research
- minimise risks while promoting the best interests of the child participants
- ensure public accountability for their actions and for the trustworthiness of their research reports.

Under this section the existing South African National Health Act of 2003;[7] Children's Act No. 38 of 2005[6] as well as the DoH *Ethics in Health Research Guidelines* 2nd ed., 2015;[15] and the *Good Clinical Practice Guidelines*, 2006[22] are reviewed.

National Department of Health, National Health Act, Section 71 of 2003

Section 71(2) and (3) of the South African National Health Act of 2003 provides a framework for conducting research with minors. According to the Act, in health research involving children, 'the informed consent of the parents or legal guardians of the child and the consent (Health Act 2003 section 71(2) c and d) of the minor (if the minor is capable of understanding) is required in order to involve minors in research.[7,24] According to this Act, only parents or legal guardians of a child are allowed to consent to the child's participation in research. Even if the child has 'capacity', the Act requires both parental and child consent. Section 71 of the National Health Act only became operational in March 2012, posing a problem for researchers who wish to enrol minors living with caregivers, given that caregivers have no explicit authority under the Act.

National Health Act of 2003, section 71 (2) and (3) specified:

(2) Where research or experiment is to be conducted on a minor for a therapeutic purpose, the research or experimentation may only be conducted With the consent of the parent or guardian of the parent;
If the minor is capable of understanding, with the consent of the minor.
(3) (a) Where research or experimentation is to be conducted on a minor for a non-therapeutic purpose, the research or experimentation must obtain consent from:
(a) Minister of Health;
(b) Parent or guardian of the minor; and
(c) Minor, if the minor is capable of understanding, the consent.

Children's Act 38 of 2005

Section 10 of the Children's Act No. 38 of 2005[6] specifies the ability of children to consent independently to medical care (but not to research) based on the age, maturity and stage of development of a child. Every child has a right to take part in an appropriate way in matters that affect him or her, and views expressed by the child must be given due consideration.[6] According to the Children's Act, section 130, a subset of children may consent independently to HIV testing from the age of 12, when the child has reached sufficient maturity and has the mental capacity to understand the benefits, risks, social and other implications of the test outcomes. Children below the age of 12 may consent to HIV testing as part of medical care, if they demonstrate sufficient maturity to understand the associated benefits, risks and social implications.[6] The Children's Act describes caregiver responsibilities as including, but not limited to, caring for the child, and consenting on behalf of the child for medical treatment. The Children's Act is silent regarding research with child participants, although it does mention the best-interest principle. Section 7 of the Children's Act states that in all cases such as care, contact and protection of the child the guiding principle should be the best interests of the child.

According to section 130 (2) (a) of Children's Act No. 38 of 2005 consent for a HIV test on a child may be given by, among others:

(a) The child, if the child is-

(i) 12 years of age or older; or

(ii) "Under the age of 12 years if the child is mature enough to understand the consequences and social implications of test."

(b) The parent or caregiver, if the child is under the age of 12 years and is not of sufficient maturity to understand the benefits, risks and social implications of such a test.

Good Practice in the Conduct of Clinical Trials with Human Participants (GCP)

Section 2.3 of the SA 2006 guideline for Good Practice in the Conduct of Clinical Trials with Human Participants[22] highlights the need for special attention regarding certain research that involves minors, women, and prisoners, among others, to avoid or reduce abuse or harmful practices on research participants in the name of research.

In the guideline section 2.3.1.1 of consent requirements, it is stated that:

1. Consent from a parent or legal guardian should be obtained in all but exceptional circumstances (e.g. emergencies). *A caregiver (e.g. custodian, person providing long-term day-to-day care for the child) can act on behalf of a minor*.
2. Assent from the minor where she/he is capable of understanding.

The document recognises the need for protection of minors in research and a specific section is devoted to good clinical practice in the conduct of clinical trials enrolling minor research participants.[22] The role of caregivers is discussed in the document under two sections; however, these sections seem to contradict each other in their recommendations. The consent requirement section 2.3.1.1 of the GCP statement states that a caregiver (e.g. custodian, person providing long-term day-to-day care for the child) can act on behalf of a minor when minors are research participants. However, in the same document (section 2.3.12.2.1 on clinical and epidemiological research) it is stated that caregivers are not allowed to consent on behalf of a child for confidential HIV testing. There is therefore conflict if HIV testing is part of the research for which the child is enrolled. It is suggested that revisions to the GCP (2006)[22] should contain clearer statements in this regard.

In the guideline section 2.3.12.2.1 of consent requirements it is stated that:

In the case of children, informed consent must be obtained from a parent or lawful guardian as well as from the child if sufficiently mature. Consent for HIV testing should from part of the consent document for research that requires HIV testing of an individual.

Ethics in health research: Principles, structures and processes (2015)

The National DoH *Guidelines for ethics in health research: Principles, structure and process* (2015),[15] recently amended, provides an updated and strengthened guide to ensure that research in SA is conducted responsibly and ethically. The revised guidelines provide the opportunity for caregivers to act as parental proxies when consenting for child participation in research, if there are no parents or legal guardians. This suggests that the role of caregivers in consent practices for minors' participation in research has received renewed recognition. Section 3.2.2.3 of the revised 2015 guidelines,[15] in provisions addressing 'orphans without guardians', addresses the challenges posed in the informed consent process, with children who do not have parents. It provides a list of parental substitutes to consent to minor enrolment in certain health research. The following persons may provide consent, in descending order of priority:

The parental substitutes should be used in descending order, as listed.

i. The minor chooses whether to participate and thus expresses his/her will ***AFTER***

ii. The parent gives assistance with understanding (so the minor makes an informed choice)

iii. If no parent, then guardian: either court-appointed OR as indicated by the parent in a Will (s 27 Children's Act)

iv. If no guardian, then foster parent (per order of Children's Court) (Note that social workers should request that the authority to give permission should be included expressly in the court order authorising foster care)

v. If no foster parent (per iv. above), then caregiver (s 1 Children's Act: defined as '…any person other than a parent or guardian, who factually cares for a child and includes – a) a foster parent; b) a person who cares for the child with the implied or express consent of a parent or guardian of the child; c) a person who cares for the child whilst the child is in temporary safe care; d) the person at the head of a child and youth care centre where a child has been placed; e) the person at the head of a shelter; f) a child and youth care worker who cares for a child who is without appropriate family care in the community; and g) the child at the head of a child-headed household')

vi. If minor is caregiver in child-headed household and no supervisory adult (s 137 Children's Act), then trusted adult nominated by minor, including but not limited to social worker, community worker.

Existing practice

Despite the existing discrepancies among legislative and ethical guideline documents, important and necessary research with children is being conducted throughout the country, for which caregivers have provided consent for the minors' research enrolment. Examples are: the Medical Research Council Population-level effectiveness of the World Health Organization; Prevention of mother-to-child-transmission

Option A study;[23] the Human Sciences Research Council National HIV survey;[24] and the KwaZulu-Natal study on the impact of infant feeding on HIV transmission and mortality at 18 months.[25] To address the existing gaps and lack of alignment in the legal and ethical issues related to paediatric HIV research with children, institutional guidelines or interim policy statements were developed to guide researchers and RECs in accordance with the existing DoH Research Ethics Guideline.[8] Although this was important to promote the inclusion of minors in relevant research, it could, however, create further inconsistencies among individual research institutional guidelines.

One case example is a national study conducted to measure rates of early mother-to-child transmission of HIV at 6 weeks postpartum as conducted by the SA MRC in 2010. In this study, among 10 357 study participants throughout SA, 378 respondents (3.6%) were caregivers who consented for minors.[23] Recognising the significant number of children living with caregivers, the survey methodology was designed to include all caregiver-infant pairs who presented at their local primary healthcare facility for the infant's 6-week immunisation (1st DTP dose) visit. In the study, the term 'caregiver' was defined as a person who feeds and looks after the child most of the week. This included any of the following: parents, legal guardians, family members, nannies or friends who routinely feed, bath, change nappies, or take the child for routine health services. Written, signed, informed consent for participation and for all procedures in the study was obtained from each eligible caregiver for the interview and dried blood sample sampling (separately).

Caregivers, other than parents and legal guardians, who brought the child to be tested and who participated in the study were not informed of the child's HIV test results,[23] with a view to protection of confidentiality and minimising potential associated harms to the child should a positive HIV status be disclosed. However, the potential benefits of caregiver information of HIV status were not fully considered, including the ability to provide optimal medical and nutritional care of the child.[26] According to the current DoH's Good Clinical Practice guidelines, section 2.3.12.2.1, 2006,[22] consent for children to participate in HIV-related health research must be obtained only from the parents or legal guardians, thus excluding consent from caregivers as employed in this study.[27]

However, this study did obtain ethical approval from the MRC and gatekeeper permission from each of the nine registered Provincial Health RECs, thus permitting the study to be conducted in their respective facilities. Ethical approval was also granted from the US Centers for Disease Control and Prevention, in Atlanta.[23] These processes suggest that while in practice the MRC REC follows a rigorous approach, it may deviate from existing Acts and guidelines in order to successfully engage caregivers to consent for participation of minors in HIV research.

Discussion

For researchers and RECs devoted to ethical practices in paediatric research, conflicting law and ethical guidance present challenges. This paper reviews some of these issues. According to Section 71 of the National Health Act of 2003,[7] caregivers may not consent to children's enrolment in health research. However, the Children's Act of 2005[6] allows caregivers to provide consent for HIV testing, for clinical purposes, on behalf of a child who lacks full capacity to understand the consequences and social implications of the test. The DoH's Good Practice in the Conduct of Clinical Trials with Human Participants (2006)[22] states that caregivers may provide consent to enrolment of children in clinical trials in exceptional circumstances (section 2.3.1.1) but may not provide consent for HIV testing (section 2.3.12.1). According to the National DoH *Guidelines for ethics in health research: Principles, structures and processes* (2015)[15] caregivers may provide consent for research enrolment of children in the absence of a parent, legal guardian or foster parent.

In HIV/AIDS-affected communities children may grow up with extended families. Studies indicate the important role that caregivers can play in paediatric research in the context of HIV in southern Africa, based on the increasing number of orphans living with caregivers and the associated socio-economic conditions.[28] There are also far-reaching implications for research on children. In essence, important health research with minors who do not have parents or legal guardians, may be limited. Studies warn that local regulations may impede important research by being overly restrictive, and that these regulations should be responsive to the emerging needs of the society.[29]

Scholars have previously pointed out the shortcomings in the existing ethical-legal framework in SA and have recommended revision of a number of issues within this framework. It has been suggested that the concept of a person with 'parental responsibilities and rights' should be used when necessary as a proxy for parental consent to research involving minors,[15,30] rather than focusing solely on biological parents and legal guardians. This change would promote valuable SA research with minors living with caregivers. Other authors have argued that existing guidelines should be amended so that children with sufficient decision-making capacity should be considered by RECs to consent independently, if the research is likely to afford minimal risk and there is no objection from communities.[14] Adolescent sexual and reproductive health research is particularly important in the SA context, owing to high teenage pregnancy, sexually transmitted disease and HIV rates in this population.[26,30] Previous authors have called for a re-examination of the informed consent language in section 71 of the National Health Act, No. 61, 2003 in order to better serve the interests of SA adolescents in sexual and reproductive health research.[14]

Community consultation is an important consideration in the process to address reform of the SA ethical-legal framework for child health research.[31] Given the principled nature of many of the concerns set out above, section 71 of the National Health Act of 2003[7] requires amendment as a matter of urgency. If research institutions are required to comply with the letter of these regulations, child research in SA will effectively grind to a halt, and this will ultimately harm the population it purports to benefit.[31]

Our study joins a body of literature[14,25,28-32] in advocating for greater inclusivity of caregivers in HIV research practices; to promote responsive research with children, while recognising that these child participants require extra protection. HIV testing is a complex issue with important implications and consequences to the child being tested. Clearly, information on the minors' HIV status has an impact on their lives. This raises important questions such as:

- What if the child is unaware of their HIV status?
- Should they know?
- Do they have a right to know?
- Should they be told by a researcher?
- How do researchers do this, without adding harm?

On the other hand, the ethical guidelines and legal frameworks in parts lack attention to these details; the documents appear to be inconsistent, ambiguous or silent on a number of critical aspects related to paediatric research with minors living with caregivers. As a result, there are inconsistences among SA research institutions in the conceptual use of the term 'caregivers'. The definition of who, as caregiver, would be considered an acceptable proxy; how to conceptualise a caregiver; and what information should be required from them or be provided to them in reducing research risks or harms needs clarity.

Taking into consideration the fact that many minors in SA do not have parents and very few have court-appointed guardians,[8] the revised 2015 Ethics in Health Research Guidelines[22] emphasise the right of a caregiver to consent on behalf of a child under their care. This paradigm shift in the revised document is seen as an ethically permissible change, responsive to societal need. Allowing caregivers to consent on behalf of minors could promote important research that might benefit minors as well as improve the caregivers' ability to provide effective care for their minor charges. We, therefore, support the stance that caregivers should be permitted to provide consent for child research participation. In instances where the potential child participant lives in a child-headed household, we argue that the head of household should not serve as a parent substitute, given his or her own status as a minor.

The inclusion of caregiver consent for child research participation would require that legislative and guideline documents (including the South African National Health Act of 2003, sections 71(2) a and (3)b;[7] Children's Act No.38 of 2005 section 130(2)(a);[6] and the Good Clinical Practice Guidelines 2006 section 2.3.1.1 and section 2.3.12.2.1[22]) be amended and aligned to better fit the circumstances of the country and to resolve controversies and inconsistencies regarding the use of caregivers' consent for inclusion of minors in research.

The ethical shift in SA regarding the role of the caregiver in providing consent for minors' participation in research is the result of a systematic and theoretical reflection on what is morally the right thing to do.[14,15,19,21] Having reached this point, there are still important issues which need attention. Firstly, the National Health Act of 2003 should follow the ethical paradigm change by amending the current stringent requirement that only parents or legal guardians may consent on behalf of children for all research participation. Similarly, the Children's Act of 2005 should be revised to include child health research considerations, including the role of the caregiver.[6] Lastly, the role of caregivers in consenting for child health research and clinical care needs to be clarified in an amendment of the current *Good Practice in the Conduct of Clinical Trials with Human Participants*.[22]

Recommendations

- Existing ethical guidelines appear inconsistent, ambiguous or silent regarding allowing adult caregivers to consent for the enrolment of children in necessary and responsible research, as well as consenting for HIV testing as part of clinical care or research. Adequate attention needs to be given to harmonise these discrepancies.
- By providing ethical frameworks, research with minors/children should move from the position of exclusion to one of cautious inclusion, in order to promote important and responsibly conducted research.
- Developing capacity of regulatory overseeing organisations such as RECs should be a priority to ensure careful ethical review of research protocols, in order to protect minors' welfare and prevent undue risk of harm, while promoting research with potential benefit for the health and welfare of children.

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