

**THE PARTICIPATION OF CHILDREN IN HIV/AIDS CLINICALS TRIALS:
ETHICAL AND LEGAL CONSIDERATIONS**

by

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DECLARATION AND COPYRIGHT

Student number: **4286-664-2**

I, the undersigned, **S. Ntumba Mujinga**, hereby declare that **THE PARTICIPATION OF CHILDREN IN HIV/AIDS CLINICALS TRIALS: ETHICAL AND LEGAL CONSIDERATIONS** is my own original work and that it has not been presented at any other University for a similar or any other degree award, and that all the sources that have been used or quoted from have been acknowledged by means of complete references.

Signature (Mrs. S. Ntumba Mujinga)

Date

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DEDICATION

To Viana Balimaka Remy, with all my love, and to the children we will have together, I dedicate this dissertation.

SUMMARY

This dissertation examines the legal position relating to the participation of children in research, especially in HIV preventive clinical research in South Africa. HIV/AIDS presents a real threat to humanity and particularly to the welfare of children. The participation of children in this type of trials is therefore vital. Children, as vulnerable participants, must also be protected from harm resulting from research. The study also considers the nature of HIV preventive clinical research, pointing to the inconsistencies in the legislation governing children's participation in HIV preventive vaccine trials. The dissertation concludes that the question of the participation of children in HIV preventive clinical research poses many challenges, as the position in the South African law and relevant ethical guidelines are inconsistent and contradictory. The study recommends in the final instance that the relevant statutory provisions and ethical guidelines be harmonised in order to clear up the inconsistencies.

KEY TERMS

HIV/AIDS; medical research; ethical guidelines; HIV preventive clinical trials; vaccine; informed consent; children.

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AIDS has changed Africa, and the world, forever. AIDS is not just another disease. It is the worst pandemic humanity has ever faced, and it is at the heart of the future development and identity of Africa. Across Africa there is a spirit of determination to at last attack the epidemic with full force. The planning phase is over. The time of small-scale pilot project is over. Full-scale engagement has begun.¹

¹ Piot P, Executive Director: Joint United Nations Programme on HIV/ AIDS (UNAIDS). Address at the 12th International Conference on AIDS and STDs in Africa (Dec. 9. 2001). Available at: <http://www.unaids.org/whatsnew/speeches/eng/piot091201ougadougou.html> (accessed 27 February 2008). See also Haber E “The United Nations’ response to HIV/AIDS” (2002) 18 *Law School Journal of Human Rights* 467-474

CHAPTER 1

INTRODUCTION

Outline

- 1 Problem statement**
- 2 Hypotheses**
- 3 Research methodology and limitations of the study**
- 4 Concepts defined**
 - 4.1 HIV and AIDS**
 - 4.2 Children**
 - 4.3 Informed consent**
 - 4.4 Clinical trials**

1 PROBLEM STATEMENT

With more than 16 000 new people infected daily throughout the world, HIV/AIDS is clearly a disease of global significance, and is a major priority for the world community.² Today, approximately 40 million adults and children are living with HIV/AIDS, and more than 28 million of those infected live in Sub-Saharan Africa.³ In terms of absolute numbers, South Africa has the highest population of people living with HIV/AIDS for a single country.⁴ In South Africa, children are the most vulnerable group, and are at great risk of HIV infection. HIV/AIDS is considered to be one of the greatest threats to the realisation of children's rights in South Africa, because more than 40% of the population of approximately 45 million is under the age of eighteen, and they have an estimated HIV

² Keymantri M "HIV vaccine trial I: South Africa – an ethical assessment" (2002) 27(2) *Journal of Medicine and Philosophy* 197-215 at 197.

³ UNAIDS *Regional HIV/AIDS Statistics and Features* (2001). See figures listed by UNAIDS at <http://www.unaids.org/worldaidsday/2001> (accessed on 27 February 2008).

⁴ Ngweni C "Aids in Africa: Access to health care as a human right" (2000) 15 *South African Public Law* 1-25 at 2.

infection rate of between 5 per cent and 15 per cent.⁵ This means that more than two million South African children under the age of eighteen could currently be infected with HIV.⁶ Thousands of babies are infected peri-natally. It is estimated that without antiretroviral treatment, about 30 per cent of babies born to infected mothers will themselves be infected. For example, of the total number of babies born in 2002, more than 90 000 of them were HIV positive.⁷ Although the Department of Health's 2007 National HIV and Syphilis Antenatal Survey⁸ indicates a general decline in HIV prevalence from 2006-2007, the HIV prevalence estimate in older age groups (eg 30 – 34 and 35 – 39 years) is a concern as it remains at similar levels with a tendency towards an increase.⁹

The combination of these factors shows one how alarming the situation is, and provides support for the claim that, for the common good of society, babies and young children should be the target population for HIV preventative vaccines. It is submitted that their enrolment in clinical trials would be a necessity in order to gather scientific data on the effect of HIV vaccines on preventing infections or diseases relevant to them. An effective preventative HIV vaccine could be a powerful tool in the struggle against the expanding HIV pandemic. The World Health Organization (WHO) takes the view that the participation of children is indispensable for research into diseases of childhood and conditions to which children are particularly susceptible.¹⁰ Research with children is also essential in order to determine the correct dose of medicines already used for adults. Simply adjusting for size is rarely adequate, as children differ from adults in terms of the

⁵ Van Wyk C "HIV preventive vaccine research on children: Is it possible in terms of South African law and research guidelines?" 2005 (68) *THRHR* 35-50 at 35. See also Brookes *et al* "National household HIV prevalence and risk survey of South African children" at www.sahara.org/children_study.htm, cited by Slack C & Kruger M "The South African Medical Research Council's Guidelines on Ethics for Medical research—implications for HIV-preventive vaccine trials with children" (2005) 95(4) *South African Medical Journal* 269-271.

⁶ Van Wyk 35.

⁷ Van Wyk C "HIV/AIDS policy in South African schools" (chapter 9) in Harris N & Meredith P (eds) *Children, education and health: international perspectives on law and policy* (Hampshire: Ashgate 2005) 183-189 at 184.

⁸ Department of Health *National HIV and Syphilis antenatal sero-prevalence survey in South Africa 2007*, available at www.doh.gov.za (accessed 20 January 2009).

⁹ *National HIV and Syphilis Survey* at 17-20.

¹⁰ Smith T *Ethics in medical research: A handbook of good practice* (1998, Cambridge: Cambridge University Press) at 175.

rate at which they metabolise and eliminate some medicines.¹¹ Young infants may eliminate medicines more slowly due to the immaturity of their liver and kidneys, while older infants and children eliminate some medicines more quickly. Therefore, in order to assess the safety and correct doses of medicines to be used in children, clinical trials have to be conducted, but only after trials have shown a good safety profile in adults.

However, although it has been established that vaccine trials may ultimately benefit children all over the world, especially in Africa where children are at a great risk of HIV/AIDS infection, their participation in this kind of research must be carried out in line with ethical standards. Vaccine development programmes should explore the legal, ethical and health considerations relevant to their participation in vaccine research. Because of their vulnerable situation, the potential exists that participants in HIV vaccine efficacy trials in South Africa may be exploited.¹² The risks and benefits of children's participation in such trials must be carefully considered.

Section 12(2)(c) of the Constitution¹³ provides that everyone has the right to physical and psychological integrity, which includes the right not to be subjected to medical or scientific experiments without their informed consent. The informed consent of people participating in research is essential. Where such consent cannot be obtained due to the incapacity of the participant (in the case of children), proxy consent of a parent or guardian is recommended.¹⁴ Informed consent is regarded as one of the primary ways of ensuring that research participants are protected against exploitation.¹⁵

The position regarding the informed consent of children who are participating in research seems to be unclear. This situation is due to the contradictory and inconsistent nature of

¹¹ Smith 175. See also Kauffman R E "Drug trials in children: ethical, legal, and practical issues" (1994) 34(4) 296-299.

¹² Nienaber A G *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* (LLD-thesis Pretoria: University of Pretoria 2007) 360.

¹³ of the Republic of South Africa, 1996.

¹⁴ See Van Wyk "HIV preventative vaccine research on children: Is it possible in terms of South African law and research guidelines?" at 49.

¹⁵ See Nienaber at 360.

South African law and relevant ethical guidelines. Guidelines 18.7.2.1 and 18.7.3¹⁶ of the Medical Research Council's Guidelines on Ethics for Medical Research (HIV Preventive Vaccine Research)¹⁷ contrast sharply with the conditions laid down by the National Health Act¹⁸ in section 71¹⁹ and by the Children's Act²⁰ in sections 129(2) to 129 (3).²¹ For example, the National Health Act makes no distinction between children above and below the age of 14, and requires, in the case of non-therapeutic research on children, the consent of the Minister of Health. On the other hand, guideline 18.7.3 of the Medical Research Council's Guidelines²² requires, for non-therapeutic research, the proxy consent of parents and the agreement of the child for participation.

With regard to the nature of HIV vaccine research and the level of risks relating to this type of research, the research question is as follows:

Is the enrolment of healthy children in HIV vaccine trials permitted in the light of the South African Constitution, current legislation and relevant guidelines?

The nature of these trials must be also considered. There is presently no agreement on

¹⁶ These guidelines provide that if a research ethics committee classifies an entire HIV vaccine trial as "therapeutic research", the independent consent for participation can be given by a child from the age of 14 years and older. For children under this age, parental consent, as well as assent from the child according to his or her evolving capabilities, is required. For non-therapeutic research, parents must provide proxy consent for participation, and the child must assent to this, provided that the risks are no more likely and no greater than the risks normally encountered in the normal medical or psychological examination of children.

¹⁷ See MRC *Guidelines on Ethics for Medical Research*, Book 5: *HIV Preventive Vaccine Research* (4th edition, 2002).

¹⁸ Act 61 of 2003.

¹⁹ Section 71 distinguishes between therapeutic and non-therapeutic research, laying down a different set of rules in each case for a minor's participation in research. In the case of therapeutic research, the consent of the parent or guardian of the minor is required and, if the minor is capable of understanding, the consent of the minor is also required (see s 71(2) (c)–(d)). In the case of non-therapeutic research, the Act requires the consent of the Minister of Health, as well as the consent of the parent or guardian of the child, and if he/she is capable of understanding, the consent of the minor (see section 71(3) (a) (ii)–(iv)).

²⁰ Act 38 of 2005 in which the age of consent to medical treatment is 12 years and older, with sufficient maturity and mental capacity to understand the benefits, risks, social and other implications of the treatment (s 129(2)). For a child under the age of 12 years, but who is of sufficient maturity, the consent of a parent, guardian or caregiver is required.

²¹ See Nienaber *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* at 383.

²² *HIV Preventive Vaccine Research* (Book 5).

whether HIV preventative vaccine trials should be classified as therapeutic or non-therapeutic research. According to guideline 9.8 of the MRC's Guidelines (see Book 5 of the revised guidelines) HIV preventive vaccine is considered as research of a non-therapeutic nature. This point of view is also shared by Van Wyk, who states that "part from the unacceptable level of risks, preventive vaccine research is by its very nature interventional research, which in terms of the MRC guidelines, should never be allowed on children."²³ Those who view these trials as therapeutic argue that participants in such trials need to be at high risk of HIV infection, in order to ensure the degree of effectiveness of the vaccine.²⁴ They are at increased risk of infection because of their lifestyle or because of social, cultural and economic circumstances.²⁵ For this reason, they will benefit from the purpose of the research, namely an effective, preventative HIV vaccine and such research should therefore be considered to be "therapeutic".²⁶

2 HYPOTHESES

- 2.1 A less restrictive interpretation of section 12(2)(c) of the Constitution would allow children to give their own informed consent to all medical research.²⁷ Informed consent is a well-established requirement for the ethical conduct of research.²⁸ At an international and local level, ethical guidelines on informed consent provide guidelines for the protection of participants in HIV vaccine trials in South Africa.
- 2.2 Given the threat of the HIV/AIDS epidemic to children, it is deemed critical by scientists that children and neonates are enrolled in clinical trials in order to generate safety, immunogenicity and efficacy data relevant to them.²⁹ Because of

²³ Van Wyk "HIV preventative vaccine research on children: Is it possible in terms of South African law and research guidelines?" 48.

²⁴ See Nienaber *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* at 489. Nienaber 489. See also Van Niekerk A "Moral and social complexities of AIDS in Africa" in: Van Niekerk A and Kopelman L M (eds) *Ethics & AIDS in Africa: The challenge to our thinking* (2005, California: Left Coast Press) 53ff.

²⁶ Nienaber 489. See also Ladimer I "Biological research for the community: Legal and ethical perspectives" (1977) 55 *Bulletin of the World Health Organisation* 111-115.

²⁷ Van Wyk 38

²⁸ Nienaber 393.

²⁹ Van Wyk 36.

the stigma attached to HIV infection and the victimisation of people who are (or are perceived to be) HIV positive, the rights of participants in the various trials must be held sacrosanct, as must those of the community in which HIV vaccine trials are conducted.³⁰ Risk should be balanced with the potential benefit that may accrue from HIV vaccine trial participation.³¹ Preventative HIV vaccine trial participation has the potential to benefit the individual participant and the community in a number of ways,³² notably:

- 2.2.1 Increased feeling of self-worth because the trial participant is helping others;
- 2.2.2 Increased access to and better quality health care;
- 2.2.3 Counseling on risk-taking behaviours;³³
- 2.2.4 Increased community awareness of scientific and epidemiological aspects of HIV;
- 2.2.5 An efficacious HIV preventative vaccine. This benefit suggests why preventative HIV vaccine trials are going ahead and attracting participants, despite the precarious nature of the knowledge so far gained about the possible risks and side-effects of these trials.³⁴
- 2.2.6 Guaranteed access to antiretroviral treatment if and when required; and
- 2.2.7 The knowledge that the child is contributing to the advancement of science and the attempt to halt the progression of widespread disease.³⁵

3 RESEARCH METHODOLOGY AND LIMITATIONS OF THE STUDY

This study - a dissertation of limited scope - involves a literature review of relevant text

³⁰ Nienaber at 5.

³¹ Nienaber at 338.

³² Nienaber 338.

³³ In this regard, see also Francis D P *et al* "Candidate HIV/AIDS vaccines: Lessons learned from the World's first phase III efficacy trials"(editorial review) (2003) 17 *The Lancet* 153.

³⁴ Nienaber 340.

³⁵ Stobie M, Strode A & Slack C "The dilemma of enrolling children in HIV vaccine research in South Africa: What is in the child's best interest"? In: Van Niekerk A & Kopelman L (eds) *Ethics and Aids in Africa* (2005) 190-207 at 191.

books, journal articles and case law. The study provides a critical analysis of the relevant South African literature and case law relating to children's participation in HIV preventative vaccine trials. A review of the literature has revealed that not much has up to date been written on the legal aspects relating to children's participation in HIV vaccine trials.³⁶ Although it has been established that the number of South African children being infected by HIV is high, as is extremely important for these children to participate in preventative HIV vaccine clinical trials, most international HIV vaccine trials conducted so far have focused on adults, a few on neonates, and none on adolescents.³⁷ As it has not yet been proven that the immune response of adolescents and adults is similar, adult data on vaccine trials cannot necessarily be extrapolated to adolescents.³⁸ The ethical-legal complexities regarding the participation of children in HIV vaccine trials merit the evaluation of the level of research-related risk, and the informed consent of the participant.

A number of articles published recently and to which this study will refer deal with adolescent preventative HIV vaccine trials in South Africa, highlighting the increasing incidence of HIV infection in this particular age group. Others investigate the implications of the new National Health Act, the Constitution and local and international ethical guidelines regarding children's vaccine trial participation and the notions of risk and informed consent. Similarly, this mini-dissertation will focus on the legal and ethical questions of South African children's participation in preventative HIV vaccine trials.

The narrow scope of this study does not, unfortunately, permit an analysis of all the relevant fundamental rights of children that are implicated in this study, such as the right to freedom and security of the person (section 12), the right to privacy (section 14), human dignity (section 10), right to access to health care services (section 27(1)(a), as well as relevant rights relating to children specifically under section 28 of the South African Constitution. The discussion will be limited to those issues related to section 12

³⁶ Legal publications dealing with this topic specifically are limited to those contributions by Nienaber and Van Wyk (referred to extensively in this study).

³⁷ Van Wyk 36.

³⁸ Van Wyk 36.

of the Constitution, as discussed in chapter three below.

Chapter two of this study will examine relevant clinical and ethical considerations relating to HIV vaccine efficacy clinical trials, as well as determine whether this kind of research falls into the category of therapeutic or non-therapeutic research. Relevant international and domestic guidelines relating to research involving human subjects will also be explored in this chapter.

Chapter three will examine specific legislative provisions relating to children's participation in research, the issue of informed consent, and relevant case law.

Chapter four will present a summary and recommendations following from the problems and *lacunae* identified in the first three chapters.

4 CONCEPTS DEFINED

It is necessary at the outset of the study to explain the central concepts of this study in more detail. These concepts are HIV and AIDS, the reference to “children” in this study, the concept of informed consent, and finally, the term “clinical trials”.

4.1 HIV AND AIDS

AIDS is the acronym for the Acquired Immune Deficiency Syndrome. This disease is called acquired because it is not a disease that is inherited. It is caused by a retrovirus, HIV (Human Immunodeficiency Virus) that enters the body from outside. Immunity is the body's natural ability to defend itself against infection and disease. A deficiency is a shortcoming - the weakening of the immune system, so that it can no longer defend itself against opportunistic infections.³⁹ A syndrome is a medical term for a collection of specific signs and symptoms that occur together and that are characteristic of a particular

³⁹ Van Dyk *A HIV/Aids care and counselling: A multidisciplinary approach* (3th ed) (2005, Pearson Education) at 3.

condition.⁴⁰ Although the term “disease” is used when one talks about Aids, it is in reality not a specific illness. It is a collection of many different conditions that manifest themselves in the body (or specific parts of the body), because HIV has so weakened the body’s immune system that it can no longer fight the disease-causing agents that are constantly attacking it.⁴¹

HIV can be found in the following body fluids with a sufficient concentration to be able to be transmitted: blood, semen, vaginal and cervical discharges and breast milk. It is transmitted in the following ways:⁴²

- Unprotected sexual intercourse;
- Receipt of or exposure to the blood, blood products semen, tissues or organs of a person with HIV, syringes and/or needles for intravenous drugs, or by injecting infected blood;
- From a mother to her fetus before birth, or to her baby during birth, or after birth by breastfeeding.

4.2 CHILDREN

The Children’s Act⁴³ states in section 17 that legal majority is attained at the age of eighteen. Thus, a child or minor is henceforth a person below eighteen years of age. References in this study to a child or children hence refer to a person below the age of eighteen years.

⁴⁰ Van Dyk 3.

⁴¹ Van Dyk at 4.

⁴² South African Law Reform Commission *Fifth Interim Report on aspects relating to AIDS: The need for a statutory offence aimed at harmful HIV-related behaviour* (2001) 25-66.

⁴³ 38 of 2005.

4.3 INFORMED CONSENT

Consent is a ground for justification which excludes the unlawfulness of an action that would otherwise amount to a delict.⁴⁴ The person suffering harm waives his or her right, to the extent that he or she permits another person to violate his or her interests.⁴⁵ The person thus committing the act cannot be held liable for any damage caused. The principle that such a person is not culpable when the injured person has consented to the injury or risk to injury, is embodied in the maxim *volenti non fit iniuria* (i.e. a willing person is not wronged), which forms part of South African law.⁴⁶

Informed consent in the context of vaccine trials means that the research participants should know that they are taking part in a research project. The nature and purpose of and all relevant information about the research must be provided to them. Thus, they will be able to assess the risks and benefits of participating in this kind of research. Time for reflection should also be given to them, and they should be told that they can withdraw at any time without penalty.⁴⁷ Sections 129(2) and 129(3) of the Children's Act specifically require the capacity of the child (of twelve years and older) to understand the relevant benefits and risks involved in a medical intervention or research. However, even if mature, some children may not be able to understand the importance to participate in certain types of research or trials, or the relevant risks which can result from these.

⁴⁴ Art 71(1)(b) of the National Health Act which provides that "notwithstanding anything to the contrary in any other law, research or experimentation on a living person may only be conducted with the written consent of the person after he or she had been informed of the objects of the research or experimentation and any possible positive or negative consequences on his or her health". See also, the revised 2002 MRC Guidelines on ethics for medical research: General principles (Book 1) paragraph 5 on informed consent in the research environment; and Slack C *et al* "Enrolling adolescents in HIV vaccine trials: Reflections on legal complexities from South Africa" (2007) 8 *BMC Medical Ethics* at 5.

⁴⁵ Van Wyk 38.

⁴⁶ Van Wyk 38. See also in general, Deutsch E "The function of the ethical committees" (1988) *Acta Juridica* 187-196; and Annas, G *Informed consent to human experimentation: The subject's dilemma* (1977, Cambridge: Mass Ballinger).

⁴⁷ Van Wyk C "The participation of minors in preventative HIV research trials in South Africa: Legal and human rights considerations" (2003) 22 *International Journal of Medicine and Law* 589-598 at 590.

Section 12(2)(c) of the Constitution⁴⁸ provides that everyone has the right to physical and psychological integrity, which includes the right not to be subjected to medical or scientific experiments without their informed consent. The informed consent of people participating in research is essential. Where such consent cannot be obtained due to the incapacity of the participant (in the case of children), the proxy consent of a parent or guardian is recommended.⁴⁹ Informed consent is regarded as one of the primary ways of ensuring that research participants are protected against exploitation.⁵⁰

The position regarding the informed consent of children who are participating in research appears to be unclear. This issue will be discussed in detail in chapter three below.

4.4 CLINICAL TRIALS

The terms “clinical research” and “clinical trials” are referred to in this study.

4.4.1 Clinical research

This term refers to research “involving human subjects that is designed either to enhance the professional capabilities of individual physicians or to contribute to the fund of knowledge in those sciences that are traditionally considered basic”.⁵¹ Clinical research is thus research carried out on humans, and, by definition, therefore excludes research carried out on human blood or tissue samples and research on animals.⁵² It is also carried out on healthy individuals in order to expand scientific knowledge. The benefit of clinical research is for the individuals who are taking part in the research, or society as a whole.

⁴⁸ Of the Republic of South Africa, 1996.

⁴⁹ Van Wyk 49.

⁵⁰ Nienaber 360.

⁵¹ Levine R J *Ethics and the regulation of clinical research* (2th ed) (1981, Baltimore: Urban & Schwarzenberg), cited by Nienaber at 64.

⁵² Levine, cited in Nienaber 64..

4.4.2 Clinical trials

Clinical trials can be defined as trials conducted to test drug safety and efficacy in humans. They provide the first opportunity to introduce an experimental substance to human beings.⁵³ The internationally accepted standard for vaccine research involving human subjects typically requires that human trials be done in three phases:⁵⁴

- Phase I studies usually involve only a few human subjects, all of whom are healthy. In HIV vaccine studies, subjects in phase I trials will probably also show no known risk factors or behaviour.
- Phase II trials continue to study safety, but the additional foci of this phase are also dosage and immunogenicity, e.g. proper dosage levels and effectiveness in stimulating some kind of immune response. If a vaccine candidate shows promise in phase II trials as well, it may then go on to be tested in phase III.
- Phase III trials, sometimes called efficacy trials, are intended for a more complete assessment of safety and effectiveness in the prevention of disease, involving a larger number of volunteers in a multicentre adequately controlled study.

The next chapter will briefly explore the nature of HIV preventive vaccine trials with the purpose of answering the question whether such trials are considered to be therapeutic or non-therapeutic in terms of national and international guidelines.

⁵³ Mariner W K “The ethical conduct of clinical trials of HIV vaccines” 1990 *Evaluation Review*: 538-562 reprinted in *AIDS: Society, ethics and law* (Schueklenk U (ed)) (2001, Aldershot: Ashgate) 318-343.

⁵⁴ Kerns TA *Ethical issues in HIV vaccines trials* (1997, Seattle: North Seattle Community College) at 72.

CHAPTER 2
CLINICAL AND ETHICAL CONSIDERATIONS RELATING TO CLINICAL
TRIALS

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 - 4.3.2 Good practice guidelines
- 5 Conclusion**

1 INTRODUCTION

Medical experimentation, which has been recorded as far back as the time of Hippocrates, demands the striking of a delicate balance between the need to advance medical science and the equally important need to protect the inherent dignity and integrity of the individual.⁵⁵ Clinical research refers to research involving human subjects, and which is designed either to enhance the professional capabilities of individual physicians or to contribute to the fund of knowledge in those sciences that are traditionally considered to be basic.⁵⁶ From this definition it is clear that the individual research participant might not benefit directly from the research that is being conducted - research may be undertaken in order to contribute to the “fund of knowledge.”⁵⁷ It is also important to note that clinical research is sometimes carried out with healthy individuals who are exposed to risk solely to expand scientific knowledge.⁵⁸

This chapter will address the relevant ethical considerations relating to HIV vaccine efficacy clinical trials and determine whether this kind of research falls into the category of therapeutic or non-therapeutic research. Because of their particular nature, HIV vaccine efficacy trials offer some benefits and pose specific risks for participants. Relevant international and domestic guidelines relating to research involving human subjects will also be explored in this chapter.

2 CLINICAL TRIALS

2.1 INTRODUCTION

⁵⁵ Burchell J “Experimentation on Human subjects: Protecting dignity and advancing medical science” 1988 *Acta Juridica* 216-233 at 216.

⁵⁶ Nienaber AG *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* (LLD-thesis Pretoria: University of Pretoria 2007) 64. See also in general, Rick N G *Drugs from discovery to approval* (2004, New Jersey: John Wiley & Sons).

⁵⁷ Nienaber 64.

⁵⁸ Nienaber 65.

As argued in the previous chapter, the only hope of arresting the alarming spread of HIV is the development of an effective vaccine. Vaccine development involves steps such as basic research, pre-clinical evaluation and production, and clinical trials with human subjects. It is recognised that without research involving human subjects, major medical breakthroughs would never have been achieved. Historically, clinical research has led to the development of drugs, such as antibiotics and antiviral drugs, as well as procedures such as heart and lung transplants. Thus, neglecting this kind of research will have disastrous effects.

2.2 TYPES OF CLINICAL TRIALS

Two kinds of clinical trials can be identified, namely clinical drug trials and clinical vaccine trials. The difference between these two types of clinical trials bears on the composition and size of sample and to whom it will benefit.⁵⁹ In the context of this study, the focus will be on the vaccine efficacy trials which fall within the ambit of the present topic.

2.2.1 Clinical drug trials

Clinical drug trials are designed to test drug safety and efficacy in human subjects. Subjects recruited for participation in clinical drug trials, at least at the stage of establishing and confirming efficacy, almost always have the disease the drug is designed to treat.⁶⁰ Despite the concerns of some that illness makes them vulnerable to undue influences, subjects are nevertheless patients in need of treatment, and although the effectiveness of the drug is uncertain, it is perhaps one of the very few options which could benefit them directly.⁶¹ Finding an effective therapy has potential immediate benefit for an individual with the given disease, and potential future benefits for the

⁵⁹ Grady C *The search for an AIDS vaccine: Ethical issues in the development and testing of a preventive HIV vaccine* (1995, Bloomington: Indiana University Press) 65.

⁶⁰ Grady 65.

⁶¹ Grady 65.

group of individuals who have the disease, and for society at large, because of the advancement of useful knowledge.⁶²

2.2.2 Clinical vaccine trials

Clinical vaccine trials are designed to test vaccine safety and effectiveness in human subjects. Subjects recruited for participation in this kind of trial are healthy volunteers who are at risk of the disease which the vaccine is designed to prevent.⁶³ It is also possible that they will never be exposed to, or infected with, the putative agent, or that it could only occur many years later.⁶⁴ Subjects in vaccine research accept some risk and uncertainty for the possibility of a potential future benefit which they may never need. The community or the society is the primary beneficiary from this research by reducing risk and disease, and for the advancement of usable knowledge.

2.3 PREVENTIVE HIV VACCINE EFFICACY TRIALS

The benefits of funding an effective preventive vaccine for HIV are enormous, both for the individual and for society. The successfully vaccinated individual will be protected against future infection and non-vaccinated members of society will be protected, as the ‘pool’ of infection will have been decreased.⁶⁵

To assess the efficacy and safety of the vaccine, it must be important to conform to the procedure established. The internationally accepted standard for vaccine research involving human subjects requires that human clinical trials have to follow three phases. These phases are important to be respected because of the registration and the license for general public use of the vaccine.

⁶² Ibid.

⁶³ Grady 65.

⁶⁴ Ibid.

⁶⁵ Nienaber 65. See also Schoub B “Vaccination as an intervention against viral diseases: Will this work for HIV? (1992) 20 *CME* 561, at 184; Delves P J and Riot I M “The immune system”(2000) 343 *The New England Journal of Medicine* 37, at 42.

2.4 PHASES IN CLINICAL TRIALS

2.4.1 Phase I: Clinical pharmacology

This phase assesses the safety (or toxicity) of the vaccine, and the immune system's response to it.⁶⁶ At this stage, the trial has to determine that the test vaccine does not produce side effects in human participants. This phase lasts about eighteen months to two years,⁶⁷ and the number of trial participants is smaller,⁶⁸ compared with the other phases. In addition, as efficacy is not at issue here, trial participants do not need to be at a high risk of HIV infection.⁶⁹

2.4.2 Phase II: Clinical investigation

This phase is generally intended to study potency and immunogenicity,⁷⁰ and to determine appropriate doses and routes of administration, with the possibility of collecting data on potential effectiveness.⁷¹ Trials are conducted with larger numbers⁷² of closely monitored participants, some of whom should be at high risk of HIV infection.⁷³ The duration of this phase is about twenty-four months.⁷⁴

2.4.3 Phase III: Clinical trial

This trial assesses efficacy (whether the vaccine will prevent HIV infection or slow down or prevent disease progression).⁷⁵ A large number of trial volunteers⁷⁶ are used during

⁶⁶ Van Dyk A *HIV/AIDS care and counselling: A multidisciplinary approach* (3th ed) (2005, Pearson Education) 21.

⁶⁷ Van Dyk 21.

⁶⁸ Mostly less than a hundred, usually twenty to fifty participants.

⁶⁹ Nienaber 73.

⁷⁰ Such as immune system's responses against HIV.

⁷¹ Mariner K W "The ethical conduct of clinical trials of HIV vaccines" 1990 *Evaluation Review* 538-562 reprinted in *AIDS: Society, ethics and law* (Schueklenk U (ed)) (2001) 318-343 at 322.

⁷² Usually hundreds of participants.

⁷³ Nienaber 73.

⁷⁴ Karim SS "Conducting HIV vaccine trials in South Africa" (2002) 20 *CME* 588 at 589.

⁷⁵ Van Dyk 21.

this stage, and these volunteers should be at a high risk of HIV infection. The duration of this phase is usually three to four years or more.⁷⁷

Because of their particular nature, HIV vaccine efficacy trials offer some benefits and pose specific risks for participants. Some of these are mentioned below, paving the way for the subsequent a detailed examination of the benefits and risks of participation (see chapter 3 below).

3 THERAPEUTIC AND NON-THERAPEUTIC RESEARCH

3.1 INTRODUCTION

Two types of research involving human subjects can be identified. The one is carried out for the benefit of the patient/subject, and is called therapeutic research. Therapeutic research is undertaken in a controlled manner, often as a randomized, clinical trial.⁷⁸ Non-therapeutic research, on the other hand, is performed in order to acquire knowledge which, during the course of the experiment at least, is of no benefit to the subject.⁷⁹

3.2 CLASSIFICATION

The classification of clinical research into “therapeutic” or “non-therapeutic” has important implications, not only for consent issues, but also for the evaluation of risk and benefit, as different kinds of research involve different levels of risk.⁸⁰ It is therefore relevant to ascertain in which category of research HIV vaccine efficacy trials belong. The discussion that follows will turn to the relevant ethical guidelines and scholarly opinion on the classification of HIV preventive vaccine trials as “therapeutic” or “non-therapeutic” research. Although it is often difficult to distinguish between these two

⁷⁶ Trial volunteers may include up to thousands of participants.

⁷⁷ Van Dyk at 22.

⁷⁸ Oosthuizen G C, Shapiro H A & Strauss S A (eds) *Attitudes to clinical experimentation in South Africa* (1985, Cape Town: Hodder and Stoughton) at 35.

⁷⁹ Oosthuizen 35.

⁸⁰ Nienaber 486.

categories of research, it can be argued that therapeutic research involves direct benefit to the individual research participant and the latter cannot be exposed to a greater than minimal risk.⁸¹ In the case of non-therapeutic research that aims to benefit other people than the research participant and which aims to generate knowledge, the participant may be subjected to no more than minimal risk.⁸²

3.2.1 Medical Research Council: Guidelines

The MRC was created by the section 2 of the South African Medical Research Council Act,⁸³ with the objective to improve the nation's health and quality of life through promoting and conducting relevant and responsive health research.⁸⁴ The Ethical Guidelines of the Medical Research Council states that the benefits likely to accrue to the participant should outweigh the risk of harm. Normally, research involving patients should not involve risk that is greater than minimal.⁸⁵ In non-therapeutic research the healthy volunteer may be subjected to no more than minimal risk as a result of participation.⁸⁶

Although the difference between therapeutic and non-therapeutic research in the context of risk analysis and an individual's decision as to whether or not to participate in the research is generally acknowledged, the difference in practice is, however, seldom clear-cut.⁸⁷ This distinction between therapeutic and non-therapeutic research is often made in South African ethical discourse, as well as in legislation.⁸⁸ The question arising is into which category preventive HIV vaccine efficacy trials would fall - are such trials to be

⁸¹ Guideline 9.12.4.4 of the MRC's *Guidelines on Ethics for Medical Research: General principles* (Book 1).

⁸² Ibid.

⁸³ Act 19 of 1969, which is the predecessor of the present Act (Act 58 of 1991).

⁸⁴ For an overview of the Medical Research Council and its operations, see in general www.mrc.ac.za/ (accessed 18 January 2009).

⁸⁵ MRC *Guidelines on Ethics for Medical Research: General principles* (Book 1), guideline 9.12.4.4.1.

⁸⁶ Guideline 9.12.4.4.2 of Book I.

⁸⁷ Guideline 9.12.4.5.1.

⁸⁸ See, for example, sections 71(2) and 71(3) of Act 61 of 2003, which also distinguishes between therapeutic and non-therapeutic research.

regarded as therapeutic or non-therapeutic? This issue, considered next, has led to much uncertainty among South African scholars.

3.2.2 Scholarly views

One prominent South African legal scholar⁸⁹ states that because of the unacceptable level of risks, preventive vaccine research is by its very nature interventional research, and should never been allowed on children. Some scholars have cogently argued that instead of attempting to classify whole protocols as “therapeutic” or “non-therapeutic”, one should ascertain whether or not particular research interventions intend to confer direct health-related benefits.⁹⁰ According to Levine, this classification has several unfortunate (and unintended) consequences.⁹¹

For the purpose of this study the question is whether it is possible to argue that HIV vaccine efficacy trials are “therapeutic” research and hence justify a greater risk of harm to the individual. As seen above, preventive HIV vaccine efficacy trial participants need to be at risk of HIV infection in order to ensure that the effectiveness or not of the vaccine may be statistically proven. They should be at great risk of HIV infection because of their lifestyle or because of their social, cultural and economic circumstances.⁹² Some scholars argue that for this reason they benefit from the object of research funding an effective HIV vaccine, and that such research should therefore be considered to be “therapeutic”.⁹³ Even if participants at high risk of HIV infection do not personally benefit, the class of subjects to which they belong – be it injection drug users (IDU), men who have sex with men (MSM), or the particular community in which they live - may potentially benefit from the research, as they will be given counseling on high

⁸⁹ Van Wyk 49.

⁹⁰ Stobie M, Strode A & Slack C “The dilemma of enrolling children in HIV vaccine research in South Africa: What is in the child’s best interests?” In: *Ethics and AIDS in Africa* (Van Niekerk A & Kopelman L M (eds)) (2005) 190-207 at 197.

⁹¹ Levine R J *Ethics and regulation of clinical research* (1981, Baltimore: Urban & Schwarzenberg) 7.

Nienaber 489. See also Van Niekerk “Moral and social complexities of AIDS in Africa” in: Van Niekerk and Kopelman (eds) *Ethics & AIDS in Africa: The challenge to our thinking* (2005) 53ff.

⁹³ Ibid.

risk behaviors (a “therapeutic” intervention), and thus (it is hoped) reducing their chance of infection.⁹⁴ On the whole, it will be difficult to fit HIV-preventive clinical trials into the category of either “therapeutic” or “non-therapeutic” research.⁹⁵

Moreover, some types of preventive HIV-related research (such as research to find a microbicide against HIV-infection) may arguably be considered “therapeutic” research, whereas other types of HIV-related clinical research (such as preventive HIV-vaccine research) may be considered “non-therapeutic”.⁹⁶

3.3 CHILDREN AND HIV PREVENTIVE VACCINE TRIALS

Stobie, Strode and Slack⁹⁷ point out that in a context of frequently inadequate primary health care, the benefits of participating in HIV vaccine trials should not be underestimated, and that these are arguably in the “best interests” of the child trial participant. In addition, they assert that whole protocols should not be evaluated as being “therapeutic” or non-therapeutic. The most important thing to assess is whether the participation of children in a specific kind of research is in their best interests or not.

The next section will examine the relevant international and domestic guidelines on research involving human beings.

4 ETHICAL GUIDELINES AND DOCUMENTS

4.1 INTRODUCTION

Research involving human beings as subjects has produced substantial social benefits, and has made an enormous contribution to human development. However, research involving human subjects can lead to possible abuse of the participants. There is hence a

⁹⁴ Nienaber 489.

⁹⁵ Nienaber A “The statutory regulation of children’s participation in HIV-related clinical research: More questions than answers” 2008 (71) *THRHR* 671-674 at 675.

⁹⁶ Nienaber “The statutory regulation of children’s participation” 675.

⁹⁷ Stobie, Strode & Slack at 197.

need for ethical principles to guide scientific investigations in order to prevent any kind of abuse. In South Africa, clinical trials with human subjects to establish the efficacy or safety (or both) of new drugs (such as vaccines) is governed by legislation⁹⁸ as well as by international and national principles and guidelines for medical and research ethics.

International documents, such as the Nuremberg Code; the Council for International Organizations of Medical Sciences (CIOMS); the International Ethical Guidelines for Biomedical Research involving Human Subjects; the Belmont Report and the Declaration of Helsinki, are next scrutinized, as well as domestic documents such as the Medical Research Council's Guidelines on Ethics for Medical Research (2002).

4.2 INTERNATIONAL CODES OF ETHICS

4.2.1 Nuremberg Code

The Nuremberg Code, written in 1946 as the final part of the judgment in the Nuremberg Trials,⁹⁹ proposed minimal ethical conditions for medical studies on human subjects, and these are now reflected in the policies of all countries and the laws of many of these jurisdictions.¹⁰⁰

This code is a consequence of the cruel and inhuman nature of the experiments conducted during the Second World War in Nazi Germany. The Nuremberg Code contains ten principles. Article two of the Code provides that human experimentation should be conducted ethically, and cannot be obtained by any other means, and it forbids research that is random and unnecessary. The degree of risk should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

⁹⁸ Eg, the Medicines and Related Substances Control Act 101 of 1965, National Health Act 61 of 2003 and Promotion of Access to Information Act 2 of 2000.

⁹⁹ The Nuremberg Trials included the trials of doctors responsible for some of the inhuman experiments conducted at the orders of the Nationalist Socialist German Government during World War II.

¹⁰⁰ Dickens M "Research ethics and HIV/AIDS" (1997) 16 *Med Law* 187-197 at 188.

4.2.2 Declaration of Helsinki

The Declaration of Helsinki, which was adopted in 1964 by the World Medical Association's 18th Assembly as a further measure to the Nuremberg Code to protect society against abuse, consists of three sections.¹⁰¹ Section 1 covers basic principles; section 2 deals with medical research combined with clinical care (clinical research); and section 3 examines non-therapeutic biomedical research involving human subjects (non-clinical biomedical research). Unlike the Nuremberg Code, the Declaration of Helsinki distinguishes clinical (therapeutic) from non-clinical (non-therapeutic) research.

According to the section 3(1), medical research carried out on a human being must ensure that the individual participating must be protected against any kind of harm. Sections 3(3) and 3(4) state that the research should be discontinued by the investigator or the investigating team if in his/her or their judgment it may, if continued, be harmful to individual. The interests of science and society should never take precedence over the well-being of the research subject.

4.2.3 Belmont Report

In 1979, the American National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published the Belmont Report on Ethical Principles and Guidelines for the Protection of Human Subjects of Research (Belmont Report).¹⁰² Three fundamental ethical principles were described as being particularly relevant to the ethics of research involving human subjects: respect for persons; beneficence; and justice.¹⁰³

¹⁰¹ The Declaration has been revised several times, most recently in October 2000 and "Clarifications" have also been added to the 2000 revision, accepted in October 2002. See in this regard, Nienaber at 99.

¹⁰² See: [http://ohrps.osophs.dhhs.gov/human subjects/guidance/Belmont.htm](http://ohrps.osophs.dhhs.gov/human%20subjects/guidance/Belmont.htm) (accessed 20 November 2008).

¹⁰³ Nienaber *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* at 101.

4.2.4 International Ethical Guidelines for Biomedical Research involving Human Participants

The Council of International Organizations of Medical Sciences (CIOMS), in conjunction with the World Medical Association (WMA), published its International Ethical Guidelines for Biomedical Research involving Human Subjects (CIOMS Guidelines) in 1982, and updated these guidelines in 1993 and 2002.¹⁰⁴ This document contained 21 guidelines, and issues discussed are, among others, validity of research,¹⁰⁵ benefits and risk of participation¹⁰⁶ and children and women as research participants.¹⁰⁷ According to guideline 5, which deals specially with the participation of children in research, the participation of children is indispensable for research into childhood and conditions to which children are particularly susceptible. The aims of the research should be relevant to the health of the children. The participation of children is conditioned by the obtaining of own informed consent of the children or proxy consent of the parents, guardian or care-giver. In the case of therapeutic research, risks are to be justified in relation to anticipated benefits to the child. In case of research not intended to benefit directly the child-subject, the risk following from such interventions should be minimal.

4.3 DOMESTIC CODES OF ETHICS

4.3.1 MRC GUIDELINES

The MRC Guidelines on Ethics for Medical Research which is issued by the Medical Research Council Act¹⁰⁸ has under its control all research carried out by or on the behalf of the MRC.¹⁰⁹ These guidelines are considered as one of the most important in the sphere of research in South Africa. The fourth edition of the MRC guidelines was recently published. The revised MRC Guidelines contain five books. Book five, entitled

¹⁰⁴ Nienaber 101.

¹⁰⁵ Guideline 1, CIOMS Guidelines.

¹⁰⁶ Guidelines 8-9, CIOMS Guidelines.

¹⁰⁷ Guidelines 14-16, CIOMS Guidelines.

¹⁰⁸ Medical Research Act 58 of 1991.

¹⁰⁹ Van Oosten F “The law and ethics of information and consent in medical research” (2000) 63 *THRHR* 5-31, at 7-8.

Guidelines on Ethics for Medical Research: HIV Vaccine Trials, is important in the context of this study, as it deals with the participation of children in HIV vaccine efficacy trials, which will be examined in detail in the next chapter.

4.3.2 Good Practice Guidelines

The Guidelines for Good Practice in the Conduct of Clinical Trials on Human Participants in South Africa (Good Practice Guidelines) was issued by the Department of Health (DOH).¹¹⁰ This document attempts to address several ethical issues relating to HIV/AIDS clinical and epidemiological research in South Africa.¹¹¹ Its preamble states that the guidelines are aimed at providing South Africa with “clearly articulated standards of good clinical practice in research that are also relevant to local realities and context.”¹¹² Although the field of activity of the Good Practice Guidelines is both academic and contact research in South Africa, it is important to keep in mind that they have no statutory power, unlike the MRC’s Guidelines, which were issued in accordance with a statute.¹¹³ These guidelines (Good Practice Guidelines) contain nine chapters, and guideline nine is important to this study, as it this guideline emphasises ethical considerations for HIV/AIDS clinical and epidemiological research.¹¹⁴ In terms of the introduction of guideline nine, the HIV/AIDS research guidelines emanated out of a series of consultations held by the Task Group on Ethical Guidelines for HIV research. Although this document addresses challenges posed by HIV/AIDS, it does not deal specifically with HIV vaccine trials, which will be addressed by later guidelines. Guideline nine recognises that clinical and epidemiological research involves complex

¹¹⁰ Issued in September 2000.

¹¹¹ Guideline 9.1 of the *Good Practice Guidelines* states : “This document attempts to address several ethical issues relating to HIV/AIDS clinical and epidemiological research in South Africa. There are also national and international vaccine initiatives in South Africa. This will stimulate the development of appropriate ethical considerations relating to vaccine research. With many ethical issues there are not always clear right or wrong answers. There are however several universally accepted ethical principles. These principles should be applied within the context of South Africa and this document is intended to facilitate a more uniform approach to common ethical issues relating to HIV/AIDS related research.

¹¹² See Preamble to the *Good Practice Guidelines*.

¹¹³ Nienaber *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* at 104.

¹¹⁴ See Guideline 9.

ethical challenges. These include issues such as access to clinical trials and informed consent. According to this guideline, good research and ethical standards should be applied in both vulnerable and non-vulnerable communities.

5 CONCLUSION

This chapter explored the nature and importance of clinical research. The issue whether it crucial for the good of humanity and especially for the person who is at high risk of HIV infection to conduct such trials, was also addressed.

Another question addressed in this chapter was the classification of HIV vaccine efficacy trials as “therapeutic” or “non-therapeutic research”. It was concluded that any attempt to classify this type of trial into one of these categories seems trivial, as the focus must remain on the benefit to society as a whole of finding an effective vaccine for HIV. This chapter also looked at the relevant international and local guidelines dealing with research involving human beings.

In the next chapter, the inclusion of children in preventive HIV vaccine trials in terms of South African legislation will be discussed. This chapter will also turn to the issue of informed consent against the background of relevant human rights issues.

CHAPTER 3

LEGAL FRAMEWORK RELATING TO CHILDREN'S PARTICIPATION IN RESEARCH

Outline

- 1 Introduction**
- 2 Legislation regulating the participation of children in research**
 - 2.1 Introduction
 - 2.2 Constitution of the Republic of South Africa
 - 2.3 Children's Act 38 of 2005
 - 2.4 Child Care Act 74 of 1983
 - 2.5 National Health Act 61 of 2003
 - 2.6 Choice on the Termination of Pregnancy Act 92 of 1996
- 3 Children's participation in research**
 - 3.1 Introduction
 - 3.2 Consent required for research
 - 3.3 Draft regulations
 - 3.4 Risks and benefits
- 4 Case law**
 - 4.1 Introduction
 - 4.2 *Castell v De Greef*
 - 4.3 *C v Minister of Correctional Services*
- 5 Conclusion**

1 INTRODUCTION

Given the number of people infected daily with HIV/AIDS throughout the world, and particularly in Sub-Saharan Africa, it is vital that something is done to stem the spread of this pandemic. HIV/AIDS is considered to be one of the greatest threats to the realisation of children's rights in South Africa, because more than 40 per cent of the population of 45 million is under the age of eighteen, and they have an estimated HIV infection rate of

between 5 and 15 per cent.¹¹⁵ South African children are the most vulnerable group, and are at high risk of HIV infection.¹¹⁶ Considering these factors, it is essential that children should be vaccinated against HIV infection before they become sexually active. Their enrolment in clinical trials is a necessity in order to gather scientific data on the effect of vaccines on preventing infections or diseases relevant to them.

However, it is not that simple. Although it has been established that vaccine trials may ultimately benefit children all over the world, especially in Africa, their participation in this kind of research must be carried out in line with ethical standards. The decision to take part in research is influenced by several factors, for example, informed consent, as well as risk and benefit analysis, in order to prevent any kind of exploitation of children due to their vulnerable situation.

In this chapter the relevant South African statutes regulating the participation of children in research will be examined, and inconsistencies between these highlighted. This chapter will also focus on case law relating to informed consent.

2 LEGISLATION REGULATING THE PARTICIPATION OF CHILDREN IN RESEARCH

2.1 INTRODUCTION

This section will consider various legislative provisions relevant to the participation of children in research. An overview of these sections will provide a theoretical framework for the discussion of children's participation in these trials in relation to issues such as informed consent, relevant fundamental human rights, as well as applicable case law.

¹¹⁵ Van Wyk "HIV preventative vaccine research on children: Is it possible in terms of South African law and research guidelines?" (2005) 68 *THRHR* 35-50, at 35.

¹¹⁶ Strode A *et al* "Ethical and legal challenges in enrolling adolescents in medical research in South Africa: Implication for HIV vaccine trials" (2005) 101 *South African Journal of Science* 224-228 at 224.

2.2 CONSTITUTION OF THE REPUBLIC OF SOUTH AFRICA¹¹⁷

Section 12(2)(c) of the Constitution states that “everyone has the right to bodily and psychological integrity, which includes the right not to be subjected to medical or scientific experiments without their informed consent”. This constitutional principle forms the over-arching framework for South African laws and guidelines on research with human volunteers.¹¹⁸ All laws, policies and ethical guidelines must be consistent with this provision.¹¹⁹ Van Wyk¹²⁰ argues that the term “medical or scientific experimentation” as used in section 12(2)(c) of the Constitution, probably means nothing other than medical research. If one opts for a strict interpretation of section 12(2)(c), it would mean that all medical research (therapeutic or non-therapeutic) involving people who are not able to give their informed consent is prohibited.¹²¹ A less restrictive interpretation of this constitutional provision would result in a better balance between the rights of legally incompetent people and society’s interest in medical progress.¹²²

There are also other constitutional rights applicable to the medical research involving children, including the rights to human dignity and to privacy.¹²³ The primary justification for privacy is respect for the individual, and the right to privacy and dignity are closely intertwined, as are the requirement of informed consent for medical treatment and the right to confidentiality.¹²⁴

Section 28(2) of the Constitution provides that “[a] child’s best interests are of paramount importance in every matter concerning the child”.

¹¹⁷ The Constitution of the Republic of South Africa, 1996.

¹¹⁸ Strode 225.

¹¹⁹ Strode 225.

¹²⁰ Van Wyk “The participation of minor in preventive HIV research trials in South Africa: Legal and human rights considerations” (2003) *International Journal of Medicine and law* 589-598, at 590.

¹²¹ Van Wyk 590.

¹²² Van Wyk 590.

¹²³ Section 10 states that everyone has “inherent dignity and the right to have their dignity respected and protected”, whereas section 14 states that “[e]veryone has the right to privacy, which includes the right not have – (a) their person or home searched; (b) their property searched; (c) their possessions seized; or (d) the privacy of their communications infringed.

¹²⁴ Van der Poel J “Omissions and doctor’s legal duty to warn identifiable sexual partners of HIV positive patients” (1998) *Responsa Meridiana* at 34.

2.3 CHILDREN'S ACT¹²⁵

The Child Care Act¹²⁶ 74 of 1983 has now finally been repealed, and has been replaced by the Children's Act 38 of 2005. Section 129(2) of this Act now determine that a child may consent to his or her own medical treatment or that of his or her child, if the first-mentioned child is over the age of twelve years, is of sufficient maturity and has the mental capacity to understand the benefits, risks, social and other implications of the treatment. Subsection (3) of the same provision states that a child may consent to the performance of a surgical operation on himself or herself or his or her child if the first-mentioned child is over the age of twelve years, is sufficiently mature and has the mental capacity to understand the benefits, risks, social and other implications of the surgical procedure, and if the child is duly assisted by his or her parent or guardian. Further, if the child is below the age of twelve years, or above but of insufficient maturity or unable to understand the benefits, risks and social implications of the treatment, the parent, guardian or caregiver may consent to the child's medical treatment.¹²⁷

It is important to note that although the Children's Act has replaced the Child Care Act, at the time of preparation of this study, not all the provisions of the Children's Act have come into operation. For the sake of completeness, the provisions regulation children's consent to medical operations and medical treatment before the enactment of the Children's Act should also be referred to.

2.4 CHILD CARE ACT

Section 39(4) of the now repealed Act provides that "a child above the age of fourteen years can independently consent to medical treatment, and that a person of eighteen years or older can independently consent to therapeutic medical research". In the case of children under fourteen, it is generally accepted that parents or guardians may give proxy consent in respect of medical treatment.

¹²⁵ Act 38 of 2005

¹²⁶ 74 of 1983.

¹²⁷ Section 129(4) of the Children's Act.

2.5 NATIONAL HEALTH ACT¹²⁸

The National Health Act came into operation on 2 May 2005.¹²⁹ This Act deals specifically with consent for minors' participation in research. In terms of section 71(1)(b) of this Act, "research or experimentation on a living person may only be conducted with the written consent of the person after he or she has been informed of the objects of the research or experimentation and any possible positive or negative consequences on his or her health". This provision is important with regard to the HIV vaccine trial, because the informed consent of the individual participant is required.

Informed consent implies that all information about the research and its known side-effects are provided to the participant. Section 71(2) requires consent from both the parent or guardian and the child, regardless of his or her age, for all research, including 'therapeutic' research. It states, in terms of the participation of children in research, that "[w]here research or experimentation is to be conducted on a minor for a therapeutic purpose, the research or experimentation may only be conducted - (a) if it is in the best interests of the minor; (b) in such a manner and on such conditions as may be prescribed; (c) with the consent of the parent or guardian of the child; and (d) if the minor is capable of understanding, with the consent of the minor". This section will be critically examined below as its provisions contain inconsistencies with existing and proposed legislation and ethical guidelines.

Section 71(3)(a), which deals with non-therapeutic research, states that "where research or experimentation is to be conducted on a minor for a non-therapeutic purpose, the research or experimentation may only be conducted - (i) in such a manner and on such conditions as may be prescribed; (ii) with the consent of the Minister; (iii) with the consent of the parent or guardian of the minor; and (iv) if the minor is capable of

¹²⁸

Act 61 of 2003

¹²⁹

See *Government Gazette* No 27503 of 19 April 2005.

understanding, the consent of the minor”. This subsection constitutes the protection of children against unscrupulous practices.¹³⁰ It will also be examined in more detail below.

The National Health Act reintroduces a distinction between therapeutic and non-therapeutic research,¹³¹ but does not define these terms. This classification is problematic as most research involves some interventions that are not intended to confer direct health-related benefits.¹³² It is understood that therapeutic research contains many non-therapeutic elements (that may have no benefit to an individual research participant), and, after all, in the case of the placebo trials, the therapeutic trial research participant may not benefit at all.¹³³ Similarly, therapeutic research has at best merely the *potential* to benefit to the individual research participant.¹³⁴ Therefore, considering these arguments, it would be difficult to make a distinction between “therapeutic” and “non-therapeutic” research. In the previous chapter, the question whether HIV preventive clinical trials should be classified as “therapeutic” or “non-therapeutic” was discussed, and it was concluded that it is indeed difficult to classify HIV preventive trials in either of the cited categories.¹³⁵ Consequently, deciding whether the Minister’s permission is required for minors’ participation in preventive HIV-related research is also problematical.¹³⁶

2.6 CHOICE ON TERMINATION OF PREGNANCY ACT¹³⁷

In terms of this Act, any female of any age¹³⁸ may have her pregnancy lawfully terminated upon request during the first twelve weeks of the gestation period of her

¹³⁰ Nienaber A G *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* (unpublished LLD-thesis Pretoria: University of Pretoria 2007) 467

¹³¹ See paragraph 3.2.2 of chapter 2: “therapeutic” research is defined as research aimed to benefit the individual research participant, whereas “non-therapeutic” research is defined as research aimed to benefit other people than the research participant.

¹³² Strode A *et al* “How well does South Africa’s National Health Act regulate research involving children?” (2005) 95(4) *South African Journal of Medicine* 265-268, 267

¹³³ Nienaber A “The statutory regulation of children’s participation in HIV-related clinical research: More questions than answers” (2008) 71 *THRHR* 671-677, at 674.

¹³⁴ Nienaber 674.

¹³⁵ See paragraph 3.3.2 of chapter 2

¹³⁶ Strode at 675.

¹³⁷ Act 92 of 1996.

¹³⁸ Section 1(xi) defines “woman” as any female person of any age.

pregnancy.¹³⁹ Where the pregnant woman is a minor, the medical professional concerned is only under an obligation to advise her to consult her parents, guardian, family or friends before the pregnancy is terminated.¹⁴⁰ Despite the fact that most of these first-trimester abortions do not involve any serious surgical interventions, it nevertheless creates an anomaly in the sense that a grave decision of this nature does not require any parental consult or guidance.¹⁴¹

Therefore, this provision is in conflict with the terms of section 71(2) of the National Health Act, which requires the consent of parent or guardian for research or experimentation involving children.

3 CHILDREN'S PARTICIPATION IN RESEARCH

3.1 INTRODUCTION

Research with children presents a powerful tension between two sometimes conflicting social goals: protecting children from harm and exploitation, while at the same time increasing our body of knowledge about children in order to develop beneficial medical, psychological and social interventions.¹⁴² Three basic principles which are relevant to research involving human subjects are: informed consent, risk/benefit assessment and the selection of research subjects.¹⁴³

In the context of this study, emphasis will be placed on informed consent and risk/benefit assessment.

There are, however, inconsistencies between current laws concerning the consent needed for a minor's participation in research. These inconsistencies are pointed out through a

¹³⁹ Section 2(1)(a).

¹⁴⁰ Slabbert MN "Parental access to minors' health records in the South African health care context: Concerns and recommendations" 2004 (2) *Potchefstroom Electronic Law Journal (PER)* 1-21, 7.
¹⁴¹ Slabbert 7.

¹⁴² Grodin M A & Glantz L H *Children as research subjects: Science, ethics and law* (1994, Oxford: Oxford University Press) preface.

¹⁴³ Belmont Report, paragraph C ("Applications"), report accessed at <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm#xethical> (visited 20 May 2009).

comparison of different provisions, ranging from the now repealed section 39(4) of the Child Care Act, sections 129(2) and 129(3) of the Children’s Act, as well as section 2(1)(a) of the Choice on Termination of Pregnancy Act,¹⁴⁴ as well as sections 71(2) and 71(3) of the National Health Act. These contradictions can also be observed in the MRC Guidelines and Good Practice Guidelines. The next section will look more closely at these inconsistencies.

3.2 CONSENT REQUIRED FOR MEDICAL RESEARCH

Consent is grounds for justification, and excludes the unlawfulness of an action that would otherwise amount to a delict.¹⁴⁵ Where such consent cannot be obtained due to the incapacity of the participant (in the case of children), proxy consent of the parent or guardian is recommended.¹⁴⁶ Van Oosten outlines the requisites for consent as follows:

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- Consent must be legally recognised, in other words, it must accord with the *boni mores* or public policy.¹⁴⁸
- The person who consents must have the legal capacity to consent, that is, the consenting person must be legally and factually capable of understanding information and deciding on a course of action.¹⁴⁹
- In order to be valid, consent needs to be appropriately informed.¹⁵⁰
- Consent must be free and voluntary/clear and
- unequivocal/comprehensive/revocable.¹⁵¹

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Contradiction with section 71(2) of the National Health Act, see paragraph 3.2.5.

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Van Wyk “HIV preventative vaccine research on children: Is it possible in terms of South African law and research guidelines?” 38.

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Van Wyk 41.

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Van Oosten F “The law and ethics of information and consent in medical research” 2000 (63) *THRHR* 5-31, at 14-30.

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Van Oosten 14.

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Nienaber *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* 422.

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Greene S & Hogan D “Researching children’s experiences: Approach and Methods” in: *Researching children’s experiences: Approach and methods* (2005, London: SAGE Publications) at 69.

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Van Oosten 29.

Informed consent is regarded as one of the primary ways of ensuring that research participants are protected against exploitation.¹⁵² The concept of informed consent was affirmed in the case of *Castell v De Greef*,¹⁵³ which will be discussed below. In this case, the court stated that a patient should be informed of all material risks inherent in the proposed treatment.

For the purpose of this study, researchers may be said to have extra responsibilities when the participants are children.¹⁵⁴ It is necessary to ensure that a child fully understands the implications of the research. The question arising, however, is whether children have the capacity to give consent to participate in HIV vaccine trial research. The position regarding the informed consent of children who are participating in research appears is far from clear as a result of conflicting provisions.

In the past, section 39(4) of the Child Care Act provided that children of fourteen years and older could independently consent to medical treatment (which included medical research),¹⁵⁵ and children of eighteen and older could independently consent to medical interventions. For children under the age of fourteen, the proxy consent of a parent or guardian was required in respect of medical research. Presently, in terms of the Children's Act, sections 129(2) and 129(3) have lowered the age to consent to medical treatment to twelve years by stating that children of twelve years and above should be entitled to independently consent to all medical interventions, provided that they have sufficient understanding. Proxy consent of a parent, guardian or caregiver is required in terms of section 129(4) of the Children's Act. The parent's, guardian's or caregiver's consent is also required if the child is under the age of twelve years, or if the child, despite being twelve years old or above, does not have the sufficient maturity or ability to understand the benefits, risks and social implications of the interventions.

¹⁵² Nienaber 360.

¹⁵³ 1994 (4) SA 408 (C).

¹⁵⁴ Lewis A & Lindsay G "Researching children's perspectives" in: *Researching children's perspectives* (2000, Buckingham: Open University Press) 12.

¹⁵⁵ Van Wyk "HIV preventative vaccine research on children: Is it possible in terms of South African law and research guidelines?" at 37.

The National Health Act, on the other hand, does not provide for a child a capacity to give independent consent to participate in research, as was the case with the Child Care Act¹⁵⁶ and is presently permitted in terms of the Children's Act.¹⁵⁷ Thus, children will be assisted by their parent or legal guardian if they wish to be involved in research. This may be seen as an impediment to their privacy, and minors will refuse to take part in research because seeking parental consent will necessitate a violation to their privacy.¹⁵⁸

Furthermore, section 71(2) of the National Health Act stipulates that the consent can only be given by the minor if he or she is capable of understanding, which differs from the approach taken by the Children's Act, which determines that the minor's wishes are important, and should be taken into consideration, even if he or she cannot understand.¹⁵⁹

The National Health Act, when referring to parental consent for medical interventions, in addition refers to "a" parent or guardian.¹⁶⁰ The consent of one parent or guardian may therefore be sufficient. The fact that only a "parent" or "guardian" may consent to the minor's participation in research, and not another person that has the care of the minor may pose problem in the case of children in children's homes or other places of safety, or where their parents cannot be reached.¹⁶¹ One consequence of this requirement is that it may result in the exclusion of children without parents or guardians from research which may be of direct benefit to them.¹⁶²

¹⁵⁶ See section 39(4) which allowed a child of fourteen years and older to independently consent to "medical research".

¹⁵⁷ In terms of sections 129(2) and 129(3) which allow the child to independently consent to medical treatment and surgical operation if the child is twelve years and older, provided that the child has sufficient understanding of the procedures or treatment.

¹⁵⁸ See Nienaber "The statutory regulation of children's participation in HIV-related clinical research: More questions than answers" at 674.

¹⁵⁹ Nienaber 674.

¹⁶⁰ In terms of section 71(2) of the National Health Act, therapeutic research may be conducted on minor only with the consent of the minor's parents or legal guardians, as well as the minor himself if capable of understanding.

¹⁶¹ Nienaber "The statutory regulation of children's participation in HIV-related clinical research: More questions than answers" at 673.

¹⁶² Nienaber 673. The child is not strictly a "user" as is defined in the National Health Act as a person "receiving treatment" in a health establishment, or "using" a health establishment (see definition of "user" in section 1 of the Act).

The National Health Act¹⁶³ requires also that in the case of research of a therapeutic nature to be conducted, that the “best interests” of the minor be taken into account. However, there is no guidance provided in the Act for establishing what the “best interests” of the minor are. This demands an assessment of whether or not subjecting a minor to a particular intervention is in their best interests, by weighing up various factors, such as the probability and magnitude of risks and benefits.¹⁶⁴

In the case of non-therapeutic research on minors, the consent of the Minister is required.¹⁶⁵ By making ministerial approval compulsory, however, where in the past it was left to individual ethics committees to decide whether a proposed research project is ethically justified or not, section 71(3) not only lengthens the approval process of such protocols, but also removes the discretionary powers of research ethics committees.¹⁶⁶ The consent of the Minister is required in addition to the consent of the parent or guardian of the minor. This requirement has a number of ambiguities, including which research falls into its scope and its place in the sequence of approvals.¹⁶⁷ Moreover, the Minister may not give consent to the minor’s participation in non-therapeutic research if – (i) the object of the research or experimentation can also be achieved if it is conducted on an adult;¹⁶⁸ (ii) the research poses a “significant risk” to the health of the minor;¹⁶⁹ or (iii) there is “some risk” to the health or wellbeing of the minor and the “potential benefit” of the research or experimentation does not significantly outweigh that risk.¹⁷⁰ Difficulties may arise as the Act does not define “significant risk”, nor is it a term used in South African ethical guidelines.¹⁷¹ Although the National Health Act attempts to create legal certainty regarding child participation in research, it fails to provide objective, clearly defined risk standards for determining when it is lawful for a parent or guardian to

¹⁶³ Section 71(2).

¹⁶⁴ See Strode at 226.

¹⁶⁵ Section 71(3) of the National Health Act.

¹⁶⁶ Nienaber “The statutory regulation of children’s participation in HIV-related clinical research: More questions than answers” at 674.

¹⁶⁷ Slack C, Strode A & Mamashela M “Research and the law: Ethical-legal challenges in adolescent HIV vaccine trials” (2007) *South African Journal of HIV Medicine* 12-13, at 13.

¹⁶⁸ Section 71(3)(b)(i).

¹⁶⁹ Section 71(3)(b)(iv).

¹⁷⁰ Section 71(3)(b)(v).

¹⁷¹ See Strode at 226.

consent to research with an adolescent.¹⁷² It is important to note that the description of “minor” in the National Health Act be read in conjunction with the Constitution and the Children’s Act, which set the age at 18 years.¹⁷³

Two ethical guidelines relevant to HIV vaccine research¹⁷⁴ also offer contradictory provisions regarding children’s consent to research. Section 9.6 of the Good Practice Guidelines, which deals with informed consent, neither mentions the age of independent consent to research, nor the person who may give consent. This approach differs from Guideline 12.7 of the MRC Guidelines,¹⁷⁵ which provides that legal requirements for capacity to consent must be met in order for children to participate in research. Furthermore, persons above the age of eighteen who are sound of mind may give consent to vaccine trial participation - if the person is below the age of eighteen, proxy consent from a parent or legal guardian is required. In certain circumstances, a person below eighteen years can consent independently. Guideline 18.7.1.1, along the same lines, provides that in South Africa, the involvement of a child (below the age of eighteen) in HIV vaccine research requires the proxy consent of a parent or legal guardian, as well as consent of the child, according to his or her level of maturity.

In order to highlight the inconsistencies between the different Acts and ethical guidelines discussed above, a table based on Nienaber’s example,¹⁷⁶ is presented below:

¹⁷² Strode 226.

¹⁷³ Section 17 of the Children’s Act.

¹⁷⁴ Guidelines for good practice in the conduct of clinical trials in human participants in South Africa, accessed at <http://homepage.vghtpe.gov.tw/~mre/goodexp/Fercap-Survey/SA-DoH-Good-Clinical-Research-Practice-Guideline.pdf> (visited 20 May 2009) and the revised 2002 MRC *Guidelines on ethics for medical research* (book 5:HIV preventive vaccine research), accessed at <http://www.sahealthinfo.org/ethics/book5.htm> (visited 20 May 2009).

¹⁷⁵ See Book 5.

¹⁷⁶ See Nienaber *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* at 469 and also, in general, Nienaber “The statutory regulation of children’s participation in HIV-related clinical research: More questions than answers”.

Sources of Law	Age of independent Consent	Who may give Consent
Child Care act 74 of 1983 (now repealed; replaced by the Children's Act 38 of 2005 below)	<p>"To medical treatment" - 14 years and above</p> <p>"To medical operation" - 18 years and above</p>	Parent or guardian of the child if under 14 years of age, and for an operation if the child is under 18 years of age.
Children's Act 38 of 2005	<p>To "medical treatment" - 12 years and above and of sufficient maturity and mental capacity.</p> <p>To "surgical operation" - 12 years and above, or if child is of insufficient maturity, with the assistance of a parent or guardian.</p>	Parent, guardian or care-giver
National Health Act 61 of 2003	<p>18 years of age</p> <p>For non-therapeutic research on minor (under the age of 18)</p>	<p>Parent or guardian</p> <p>Consent of the Minister</p>
Choice on Termination of Pregnancy Act 92 of 1996	Any age	N/A
MRC Guidelines	18 years and above and of sound mind. In certain circumstances, children below the age of 18 years can give his/her own consent. Consent of the child.	Proxy consent of a parent or legal guardian
Good Practice Guidelines	None mentioned	None mentioned

3.3 DRAFT HEALTH RESEARCH REGULATIONS

Relevant to this study are the “Regulations relating to research on human subjects” (draft health research regulations),¹⁷⁷ issued in terms of section 90 of the National Health Act.

Although its purpose is to supplement the requirements for the participation of minors in research in terms of 71(2)(3) of the National Health Act, clause 4 of the draft health research regulations neither elucidates, nor elaborates on the position set out in section 71 of the National Health Act.¹⁷⁸ It states that “[c]hildren can only participate in research in instances where the parent or legal guardian of the child gives consent for such a child to participate”. And, the “refusal to participate by a child should precede the consent of the parent/legal guardian”.¹⁷⁹ As seen above, section 71(2) of the National Health Act requires the consent of parent and legal guardian for therapeutic research and for non-therapeutic research, and section 71(3)(ii) requires the consent of the Minister. The question arising is whether the consent of the Minister in the case of non-therapeutic research is no longer necessary in terms of clause 4. Clause 4 also does not clarify the uncertainty in respect of who is permitted to consent in the case of children who are without parents or guardians and who are looked after by “care-givers”.¹⁸⁰ The addition of the word “legal” in the clause does not offer a solution because a “care-giver” is not a “legal” guardian in terms of South African law.¹⁸¹

The second part of the clause 4(c) is also problematical. The statement, “refusal to participate by a child should precede the consent of the parent/legal guardian” seems to suggest that the autonomous decision of a child is no longer relevant, as a child who refuses to participate in research may be forced by his or her parents or legal guardians to

¹⁷⁷ GG 29637, published 23 February 2007.

¹⁷⁸ See Nienaber *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* 470.

¹⁷⁹ Clause 4(c) of the draft health research regulations.

¹⁸⁰ Nienaber *Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa* 471.

¹⁸¹ Nienaber 471.

do so. This possibility is not only out of the step with current legislation,¹⁸² but is also likely to be considered *contra bonus mores*.¹⁸³

3.4 RISKS AND BENEFITS

Risk assessment is an activity in which everyone is daily involved - risks are a fact of life.¹⁸⁴ Participation in HIV preventive vaccine research may involve physiological,¹⁸⁵ psychological¹⁸⁶ and social¹⁸⁷ risks.¹⁸⁸

The term “risk” is material to consent in the sense that there is a risk attached to research undertaken with consent, depending on whether such research is therapeutic or non-therapeutic, or invasive (intrusive)¹⁸⁹ or non-invasive (non-intrusive).¹⁹⁰ In terms of so-called “risk/benefit analysis”, the risk to which the patient is exposed must be justifiable in relation to the value of the information sought, and “risk” refers to both the probability of harm resulting from an activity and to its magnitude.¹⁹¹ Beneficence, in short, requires that the possible benefits should be maximised and possible harms be minimised, not only for individual research participants, but also for society in general.¹⁹²

Inconsistency also exists between guidelines 7.1.3.2 of the revised MRC Guidelines¹⁹³ and section 71(3)(b) of the National Health Act concerning the risk standard in case of

¹⁸² See sections 29(2) and 29(3) of the Children’s Act 38 of 2005.

¹⁸³ Nienaber 470.

¹⁸⁴ Nicholson R H “Medicine research with children: Ethics, law and practice” (report on the ethics of clinical research investigations on children) (1986, Oxford: Oxford University Press) 1-225; at 76.

¹⁸⁵ The purpose of an HIV preventive vaccine is to induce an immunological response to counteract the HI virus if it enters the human body, or to prevent it from entering at all.

¹⁸⁶ Eg stress related to participation, lengthy trials involving intensely intimate matters and repeated HIV testing ; stigma and discrimination that may result if a volunteer’s participation becomes publicly know, anxiety related to exposure to culturally different scientific medical concepts, etc.

¹⁸⁷ Eg discrimination and stigma from the community.

¹⁸⁸ Guideline 9.2 of the MRC Guidelines, book V.

¹⁸⁹ Eg research which involves making observations without any direct interference with the subject (such as research involving the use of personal records).

Eg research which involves interference with the subject (psychological intrusion, including intrusion on privacy or physical invasion). See Van Oosten 11.

¹⁹¹ Van Oosten 11.

¹⁹² Van Wyk “Guidelines on medical research ethics, medical ‘experimentation’ and the Constitution” at 7.

¹⁹³ See Guideline 7.1.3.2 of Book 1 entitled “General principles”. Non-therapeutic research on healthy

non- therapeutic research. Indeed, the National Health Act's risk standard for “non-therapeutic” research is that of not “significant” whereas the reference to the risk standard in Guideline 12 of the Medical Research Council for “non-therapeutic” research refers to risk that is “negligible” — a risk so small it may be ignored.¹⁹⁴

4 RELEVANT CASE LAW

4.1 INTRODUCTION

Consent is grounds for justification which excludes the wrongfulness of an action. In the absence of informed consent, medical interventions are, as a result, unlawful or wrong. The broad concept of informed consent was affirmed in the cases of *Castell v De Greef*¹⁹⁵ and in *C v Minister of Correctional Services*.¹⁹⁶

4.2 *Castell v De Greef*

In this case the defendant, a plastic surgeon, was sued for damages by the plaintiff for alleged negligence in performing a surgical operation known as a subcutaneous mastectomy. The court concluded that the medical practitioner has failed to warn his patient of the “material risks”¹⁹⁷ and complications which might flow from a surgical operation or other medical treatment.

This case is relevant to the present study because, applied to the context of research with children; this means that a minor (if displaying sufficient maturity and ability to understand the risks and benefits of the procedure), as well as his parents or legal guardian, should be informed about the risks and benefits posed by the HIV preventive clinical

children (under the age of 18 years, according to the Constitution) should be approved only if the research places the child at no more than negligible risk) (see also Guideline 9.12.4.3).

¹⁹⁴ See Strode 267.

¹⁹⁵ 1994 (4) SA 409 (C).

¹⁹⁶ 1996 (4) SA 292 (T).

¹⁹⁷ A risk is material if in the particular circumstance: (a) the medical practitioner is or should reasonably be aware that the particular patient, if warned of the risk, would be likely to attach significance to it; or (b) a reasonable person in the patient's position, if warned of the risk, would be likely to attach significance to it.

research before giving their consent. The risks for participating in research lie for example in the serious social and psychological implications of a positive test result to which a reasonable person is likely to attach significance (in case of non-therapeutic preventive HIV-related research, the participants are HIV negative).¹⁹⁸

The legal consequences of a medical intervention performed without the patient's lawful consent are that the doctor or hospital may incur liability for breach of contract, civil or criminal assault (a violation of physical integrity), civil or criminal *iniuria* (a violation of dignity/privacy), or negligence, as the case may be, or that the doctor or hospital may be unable to recover a professional fee.¹⁹⁹

In *C v Minister of Correctional Services*, the concept of informed consent and pre-and post-test counselling in the context of HIV testing was examined in more detail.

4.3 *C v Minister of Correctional Services*

In this case, the main issue was the conducting of an HIV test on a prisoner without his informed consent, at the time when the Department of Correctional Services had adopted the principle that informed consent was a prerequisite for testing prisoners and had specified what norms were applicable. The Court awarded damages because of the failure of prison authorities to provide the prisoner with pre- and post-test counselling. It was stated that failure to provide the necessary counselling resulted directly in the deterioration of the prisoner's health.

¹⁹⁸ See Nienaber "The statutory regulation of children's participation in HIV-related clinical research: More questions than answers" at 675.

¹⁹⁹ Van Oosten F "Castell v De Greef and the doctrine of informed consent: Medical paternalism ousted in favour of patient autonomy" (1996) *De Jure* 164-179, at 166. On breach of contract, see *Behrmann v Klugman* 1998 (W) (unreported); on liability for assault, see *Stoffberg v Elliot* 1923 CPD 148 ff; *Layton & Layton v Wilcox & Higginson* 1944 SR 48 50; *Lampert v Hefer* 1955 2 SA 507 (A) 508E-F; *Esterhuizen v Administrator Transvaal* 1957 (3) SA 710 (T) at 718 ff; *S v Sikunyana* 1961 3 SA 226 (C) 232F-G; *Burger v Administrateur Kaap* 1990 (1) SA 483 at 489; *S v Kiti* 1994 SACR 14 (E) 18f-g; *S v Binta* 1993 2 SACR 553 (C) 561 j-562c; on liability for negligence, see *Lymbery v Jefferies* 1925 AD 236; *Prowse v Kaplan* 1933 EDL 257; *Allot v Paterson & Jackson* 1936 SR 221, 222-224; *Layton & Layton v Wilcox & Higginson* 50, *Dube v Administrator Transvaal* 1963 4 SA 260 (W) 269C-270 A; *Soumbasis v Administrator of the Orange Free State* 1989 (O) (unreported); on liability for civil *iniuria*, see *Stoffberg v Elliott* 152; and on the recovery of a professional fee, see *McCallum v Hallen* 1916 EDL 74.

This case is relevant because applied to the context of this study; it has demonstrated that the failure to obtain informed consent from a research participant may have a range of serious consequences. All research participants must be advised about the purpose of the research, the known side-effect of drugs and eventually any possible negative or positive health consequences.²⁰⁰ Time of reflection must be given to them for any approval or not to participate in the research.

5 CONCLUSION

This chapter has highlighted the requirements for children to take part in research, and places emphasis on the requirement of informed consent and the risks/benefits analysis. Given the fact that children are in a vulnerable situation and should be protected against any kind of exploitation, obtaining informed consent is very important in order to ensure their protection. This chapter also emphasises the inconsistencies that exist in South African legislation and ethical guidelines regarding the issue of informed consent in the context of HIV vaccine trials involving children. These inconsistencies make the issue of the participation of children in research unclear. In view of the urgent need of enrolling children in this kind of research, one hopes that these inconsistencies be addressed in order to harmonise all the conflicting provisions.

²⁰⁰ See Strode at 265.

CHAPTER 4

CONCLUSION AND RECOMMENDATIONS

Outline

- 1. Introduction**
- 2. Summary**
- 3. Conclusion**
- 4. Recommendations**

1 INTRODUCTION

The research question, as posed in the beginning of this study, was as following: Is the enrollment of healthy children in HIV vaccine trials allowed in terms of the South African Constitution, current legislation and relevant guidelines?

2 SUMMARY

This study has demonstrated that HIV/AIDS presents a real threat to humanity and particularly to the welfare of children. It is therefore essential to undertake research with children in order to gather scientific data on the effect of vaccines on preventing infection or disease relevant to them. There is also a need to protect children from harm resulting from research, and this also needs to be carefully considered.

The Joint United Nations Programme on HIV/AIDS notes that children should be recipients of future HIV preventive vaccines, and should be included in clinical trials in order to verify the safety, immunogenicity and efficacy of vaccines from their point of view.²⁰¹ Efforts should be made to design vaccine development programmes that address

²⁰¹ Guidance point 18 of the UNAIDS guidance document: “Ethical considerations in HIV preventive vaccine ” (2000), reprinted in 2004.

the particular ethical and legal considerations relevant to children, and to safeguard their rights and welfare during participation in research.²⁰²

Two key questions that had to be answered in the context of this study are firstly the question whether HIV clinical trials are “therapeutic” or “non-therapeutic” trials, and secondly, in view of the conflicting statutory provisions relevant to children’s participation in research, who should consent to children’s participation in this type of research.

With regard to the first issue, although it has led to differing opinion amongst South African scholars, this study supports the view of scholars who argue that it would be difficult to fit HIV-preventive clinical trials into either the category of “therapeutic” or “non-therapeutic” research.²⁰³ This view must be supported, because of the impossibility of distinguishing between “therapeutic” and “non-therapeutic” research.

In terms of the second issue, in the South African context, the ethical-legal framework governing research involving children contains provisions which are contradictory, especially relating to the person who should give informed consent. These inconsistencies make the position regarding the informed consent of children who are participating in research unclear, and consequently their enrolment in HIV clinical trials.

3 CONCLUSION

It is clear that the question of the participation of children in HIV clinical research in South Africa poses many challenges, as South African law and ethical guidelines are inconsistent. Children’s participation, especially on the African continent, in HIV preventive vaccine trials, is vital.

²⁰² Ibid.

²⁰³ Nienaber A “The statutory regulation of children’s participation in HIV-related clinical research: more question than answers” 2008 (71) *THRHR* 671-674, at 675.

The National Health Act,²⁰⁴ as was seen above, reintroduced a distinction between “therapeutic” and “non-therapeutic” research, but fails to define these terms. The provisions of this Act at these relate to children’s participation in clinical trials, are in conflict with relevant ethical guidelines. There is also not an objective and clear risk standard for what constitutes “therapeutic” and “non-therapeutic” research.²⁰⁵ Furthermore, the requirement in terms of the National Health Act regarding the approval of the Minister in cases of “non-therapeutic” research involving children, has a number of ambiguities, including the problem determining what type of research falls into this scope, as well as its place in the sequence of approvals.²⁰⁶

To sum up, the Draft Health Research Regulations,²⁰⁷ instead of bringing more clarity on the contradictory and inconsistent provisions of the National Health Act, have created more confusion.²⁰⁸ Therefore, although the enrolment of children in HIV-preventive clinical trials appears to be lawful in terms of the South African Constitution, current legislation and relevant guidelines, it needs to be accompanied by much clearer legislation and ethical guidelines to remove any of the inconsistencies pointed out in this study.

4 RECOMMENDATIONS

In the context of this study, the following recommendations are suggested:

- Revision of the ambiguous sections of the National Health Act in order to clear up the inconsistencies and contradictions created by its provisions, especially those relating to the question of the participation of children in research;

²⁰⁴ Act 61 of 2003, see section 71(2).

²⁰⁵ Strode A *et al* “Ethical and legal challenges in enrolling adolescents in medical research in South Africa: implication for HIV vaccine trials” 2005 (101) *South Africa Journal of Science*, 224-228.

²⁰⁶ Slack C, Strode A & Mamashela M “Research and the law: Ethical-legal challenges in adolescent HIV vaccine trials” (2007) *South African Journal of HIV Medicine* 12-13, at 13.

²⁰⁷ GG 29637, published 23 February 2007.

²⁰⁸ Nienaber 677.

- A revision of the Draft Health Research Regulations in order to harmonise the position relating to children's participation in research with the corresponding provisions of the National Health Act;
- A revision of the relevant ethical guidelines in order to ensure that these correspond to the legal position created by the above statutory provisions.
- Finally, considerable training is in addition required to ensure that the interests and welfare of children participants are guaranteed, as their participation is critical to HIV research and prevention and general health promotion.

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