

South African National Health Act (No. 61 of 2003) vs. Emmanuel framework for ethical research (2004): implications for children research

by

Dimpho Ralefala

Student No: 211560787

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Supervisors:

Prof Mariana Kruger & Dr Nicola Barsdorf

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DECLARATION

I declare that the thesis titled “*South African National Health Act (No. 61 of 2003) vs. Emmanuel framework for ethical research (2004): implications for children research*”, which I hereby submit for the degree of Master of Social Sciences at the University of KwaZulu-Natal, Pietermaritzburg, is my own work and has not been submitted for a previous degree at any other tertiary institution.



Signature: _____

Date: 20 June 2017

Full name: Dimpho Ralefala

Supervisor



Signature: _____

Date: 20 June 2017

Full name: Professor Mariana Kruger

Co-Supervisor



Signature: _____

Date: 20 June 2017

Full name: Dr Nicola Barsdorf

DEDICATION

This work is dedicated to my wonderful husband, Mr Letlhogonolo Ralefala, and my beautiful children, Yolanda and Ethan. To God be the glory!

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
CIOMS	Council for International Organisations of Medical Sciences
HIV	Human Immune Deficiency Virus
HSSREC	Humanities and Social Sciences Research Ethics Committee
RECs	Research Ethics Committees
SA	South Africa
SA NHA	South African National Health Act
SPSS	Statistical Package for Social Sciences
UKZN	University of KwaZulu-Natal
WHO	World Health Organization
WMA	World Medical Association

ABSTRACT

The South African government promulgated the National Health Act (NHA) (Act No. 61 of 2003) in 2004, where Section 71 (promulgated in March 2012) regulates research involving human participants, including minors. This study evaluated potential implications of compliance of paediatric research with the NHA, as well as with the framework for ethical research proposed by Emanuel et al. (2004), through the review of 55 published journal articles involving children as research participants, published by researchers from the Department of Paediatrics and Child Health at Stellenbosch University from 1 March 2012 – 31 March 2013, after the promulgation of Section 71. The majority (89%) of the studies could be defined as non-therapeutic research, with no prospect of direct benefit for the individual child. Nearly all (90%) of the non-therapeutic studies involved minimal risk, while therapeutic studies, on the other hand, mostly involved more than minimal risk but presented the prospect of direct benefit to the individual participants in 66%. All therapeutic studies (100%) presented the potential for direct benefits to the research participants. While the majority (42/49; 86%) of non-therapeutic studies did not offer direct benefit to the participants, 4% of non-therapeutic studies did offer direct benefits to the child participants. Benefits could not be determined in 10% of non-therapeutic studies. Overall, the reported studies presented a favourable risk-benefit ratio. The majority reported ethics approval (73%), with therapeutic studies more likely to mention it than non-therapeutic studies. As the majority (65%) of studies were retrospective, waiver of consent for parent/guardian was obtained in 51% of the studies, while waiver of child assent was obtained in 76% of the studies reported.

This study established that the NHA places more stringent review standards for lower risk non-therapeutic research, but not for therapeutic research that is likely to involve more than minimal risk. Also, the NHA assumes that non-therapeutic studies present no direct benefits to child participants; however, this study found out that some non-therapeutic studies did present some direct benefits. The framework for ethical research proposed by Emmanuel et al. (2004) is proven a valuable framework in this study to determine if paediatric research is ethically acceptable. In situations where national regulations have been recently enacted, as in the case of the SA NHA (No. 61 of 2003) Section 71, it is very important to assess the implications to ensure that essential paediatric research can be conducted.

Keywords: Compliance, children, research, South African National Health Act, therapeutic research, non-therapeutic research.

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DEFINITION OF TERMS

The operational terms for this study are defined below;

- a) **Best interest** - the best interest of the minor is defined as ensuring that “significant decisions affecting the minor’s life should aim to promote, amongst others, the minor’s physical, mental, moral, emotional and social welfare (South African Government, 2014).
- b) **Child**: The South African Constitution (S28) and the Children’s Act (No. 38 of 2005, S1) define a child as “a person under the age of 18 years” (s 28 Constitution; s 1 Children’s Act 38 of 2005, in Department of Health, 2015). This term is often used interchangeably with “minor”, which is also defined as a person under the age of 18 by Section 17 of the Children’s Act (No. 38 of 2005).
- c) **Compliance**: According to the Cambridge online dictionary (Cambridge University Press, 2016), compliance is defined as “the act of obeying an order, rule, or request”.
- d) **Human subject**: The United States Code of Federal Regulations (45 CFR 46) (US Department of Health and Human Services (USDHSS), 2005) also defines a human subject as “a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information” (US Department of Health and Human Services, 2005). This term is often used interchangeably with research participant.
- e) **Non-therapeutic research**: The South African Department of Health’s *Ethics in health research principles, processes and structures* (2015), defines non-therapeutic research as “research that includes interventions that do not hold out the prospect of direct health-related benefit for the participant but may produce results that contribute to generalisable knowledge” (Department of Health, 2015).
- f) **Research**: According to the United States Code of Federal Regulations for research involving human subjects (45 CFR 46), research means “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalisable knowledge” (US Department of Health and Human Services, 2005).
- g) **Research Ethics Committee**: An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the

investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. (Department of Health, 2006).

- h) **Therapeutic research:** According to the South African Department of Health's *Ethics in health research principles, processes and structures* (2015), therapeutic research means "research that includes interventions that may hold out the prospect of direct health-related benefit for the participant" (Department of Health, 2015).

CHAPTER 1

INTRODUCTION AND BACKGROUND

A number of international bodies and most countries have promulgated guidelines to govern the conduct of research in human participants (Worku, Davis, & Morrow, 2016). Independent review of research involving humans by research ethics committees (RECs) is required to protect the welfare and interests of research participants. This came as a result of some inhumane research involving human beings such as was reported at the Nazi war trials and was involved in the Tuskegee syphilis study (Emanuel, 2003). The Constitution of the Republic of South Africa (Section 12.2c), promulgated in 1996, was the first law that legalised the requirement for individual informed consent of research participants in South Africa (Republic of South Africa, 1996). As a result, the requirement for individual informed consent became the basis for all South African laws, policies, and ethical guidelines on research involving human participants (Strode, Slack, Grant, & Mushariwa, 2005c).

However, this consent requirement initiated debates regarding the involvement of children in research as some scholars interpreted the need for consent as first person consent, and children cannot necessarily provide first person informed consent, since they are not yet competent. First person consent also implies that parents or guardians cannot give consent on behalf of their children (Strode et al., 2005c). Other scholars argued that the Constitution should not be interpreted literally and that a value-based interpretation should be adopted. They therefore argued that this interpretation allows for a parent or guardian to give informed consent on behalf of their children (Strode et al., 2005c). This confusion was later addressed in the National Health Act (No. 61 of 2003), which requires both consent from parents or guardians and consent from children, who are capable of understanding to participate in research (Republic of South Africa, 2004). The Act uses the terms 'minor' and 'child' interchangeably (Strode, Grant, Slack, & Mushariwa, 2005b). It is assumed that if the child does not have capacity to understand research participation, then the parental or guardian consent alone will be sufficient.

The NHA categorises research with minors as either therapeutic or non-therapeutic and also outlines a number of conditions that should be fulfilled in approving child research. These include the assessment of the risks and benefits for non-therapeutic research and considering 'the best interests of the child' principle as guidance for therapeutic studies (Republic of South Africa, 2004). Nonetheless, this categorisation of research by the NHA has led to debates in academia with some scholars arguing that this categorisation is not useful to ensure ethical research involving children (Strode et al., 2005b).

This study therefore aimed to assess the implications of compliance of child research with the National Health Act (No 61 of 2003) Section 71, as well as how effective it is in promoting the best interests of children through research. In situations where national regulations have been recently enacted as in the case of the SA NHA (No. 61 of 2003) Section 71, it is very important to assess the potential implications to determine other regulations, as well as to identify areas for potential improvement. The study also investigated whether the benchmarks for ethical review proposed by Emanuel, Wendler, Killen, and Grady (2004) can be used as an ethical framework to review paediatric research. These benchmarks include collaborative partnership, social value, scientific validity, fair selection of study population, favourable risk-benefit ratio, independent review, informed consent, and respect for recruited participants and study communities.

CHAPTER 2

LITERATURE REVIEW

2.1 Importance of conducting research with children

Health research involving child participants is essential to develop appropriate interventions promoting children's welfare (Cleaton-Jones & Vorster, 2009). Research is very important for the advancement of knowledge concerning the diagnosis, treatment, and prevention of disease and illness in children (Binik & Weijer, 2014). However, conducting paediatric research has unique ethical issues that need careful consideration (Knox & Burkhart, 2007). These ethical issues include potential increased risk of harm due to children's physiological differences from adults, third party consent by their parents or caregivers, and respect for their autonomy to decide to participate in research through eliciting their assent, where possible (Sofaer & Strech, 2011).

Extra protection measures are therefore needed to ensure that child participation in research is indeed voluntary and that the interests and welfare of children participating in research are protected. Most guidelines (The Belmont Report, 1979; Council for International Organizations of Medical Sciences, 2002; World Medical Association, 2013) state that research with children should be conducted only when research cannot be conducted with adults and when the aim is to benefit children. Some scholars are concerned that trying to protect children by excluding them from research involvement would result in even less knowledge about children from which to develop health care interventions for them (Morrow & Richards, 1996 in Neill, 2005).

Historically, children have been excluded from research that could benefit them and are often described as 'therapeutic orphans' because of the inadequacy of clinical information that could be used to treat childhood conditions (Grady, 2005). The exclusion of children from clinical studies and other health research has resulted in many therapies being prescribed, based on evidence extrapolated from adult clinical trials, without the appropriate investigation for their paediatric safety and efficacy. Paediatricians are often compelled to prescribe medicines that have not been tested for use in children, which may cause serious problems as the appropriate formulations and potential side effects in these populations are not known (Grady, 2005). A study conducted in five centres in Europe found that almost 50% of all medicines prescribed for children were either prescribed off label or used as unregistered medicines due to inadequate clinical studies involving children (Sofaer & Strech, 2011).

As Burns (2003) has indicated, extrapolating results from studies carried out on adults and generalising these findings to children may not be safe. This is because the biological responses to disease and, therefore, appropriate prevention and treatment strategies, change in fundamental ways throughout childhood with the changing physiology of growth. Understanding the relationship between childhood development and disease can only be gained by performing research on children at various stages of their development. The absence of adequate studies in the paediatric population hinders progress in the care of children and, for example, HIV/AIDS preventive research is of increasing importance, including the development of childhood vaccines against HIV (Burns, 2003; Strode, Grant, Slack, & Mushariwa, 2005a). According to UNAIDS, more than a quarter of the world's 40 million persons who are HIV-infected are between the ages of 15 and 24, and 700 000 of the new infections that arose in 2003 were recorded in children under 15 years of age (Jaspan et al., 2005). Adolescent participation in HIV vaccine trials is therefore paramount in order to determine the safety profile, appropriate dosing schedules, and the degree of immunogenicity in this age group, especially as these may differ because of physiological or hormonal differences between adults and younger adolescents (Alonsa, et al, 2005 in Slack, Strode, Fleischer, Gray, & Ranchod, 2007). Excluding children in an attempt to protect them from involvement in research would result in even less knowledge about possible interventions that may benefit them (Morrow & Richards, 1996 in Neill, 2005).

2.2 The history of child research

Children have been included in research ranging from clinical trials to observational studies, as well as basic science research, aimed at understanding normal paediatric anatomy and physiology (Lederer, 2003). The history of research involving children demonstrates past exploitation, largely due to their vulnerability and inability to protect themselves against violation of their rights and exposure to undue risk (Smith & Davis, 2017). Often such research involved children who were either from poor families, institutionalised, mentally ill, or physically disabled (Burns, 2003). A number of studies were conducted on children who were conveniently available to the researcher, as was the case when Edward Jenner first tested the smallpox vaccine in his own children (Burns, 2003).

At the end of the eighteenth century, Jenner observed that exposure to cowpox seemed to offer immunity against smallpox; hence, he conducted the first experimental vaccination of a human on his one-year-old son; he later experimented with eight-year old James Phipps by giving him the vaccine and then challenged him with a smallpox inoculation (Lederer & Grodin, 1994 in Diekema, 2006a). Jenner concluded that the vaccine was effective when the

children did not contract smallpox (Lederer, 2003). Likewise, in 1885, Louis Pasteur tested his newly developed rabies vaccine on Joseph Meister, a 10-year-old French child. Previously, Pasteur had conducted animal experiments that suggested the efficacy of the vaccine, but he had not administered the vaccine to any adult human patients prior to this experiment on a child (Lederer, 2003).

While this early research on children might have contributed to the advancement of medicine, certain studies were either not effective or were very dangerous (Lederer, 2003). Some of the most controversial studies involving children included a series of non-therapeutic studies conducted in the USA between 1944 and 1974. Mentally incapacitated children, institutionalised at the Fernald School in Waltham, Massachusetts, were fed radioactive iron and calcium in their cereal. Although parental permission was obtained, there was no full disclosure of all the facts. The information in the parental consent forms only indicated that the children would be receiving a diet rich in calcium and iron and did not mention that the 'special diet' included radioactive isotopes, nor did it mention any risks. The wording in the parental informed consent implied that this 'special diet' would benefit the children, when in fact it would not (Advisory Committee on Human Radiation Experiments, 1996; Moreno, 2001 in Diekema, 2006b). The Final Report of the Advisory Committee on Human Radiation Experiments established that in some non-therapeutic tracer studies involving children, it was found that children who were exposed to radioisotopes had an increased risk of developing cancer. (Advisory Committee on Human Radiation Experiments, 1996 in Diekema, 2006b). Another controversial study involving children was the Willowbrook Study, which studied the natural evolution of hepatitis and tested the effects of gamma globulin in preventing or slowing down the disease. Children participating in this study were deliberately infected with the hepatitis virus while early participants were fed with extracts of stools from infected individuals and later injected with a more purified virus preparation (Burns, 2003).

As a result of increasing public awareness of unethical research such as the Willowbrook study, and other adult studies such as the Nazi concentration camp research and the Tuskegee syphilis study, regulations and guidelines for research with human participants were formulated to protect human participants, including children, in research (Diekema, 2006a).

2.3 Ethical issues in child research

Children are categorised as a vulnerable population in a number of international guidelines and require extra protection when being included in health research (The Belmont Report, 1979; Council for International Organizations of Medical Sciences, 2002; World Medical

Association, 2013). This is because children are not legally competent to necessarily comprehend research information and be able to participate in informed and rational decision-making (The Belmont Report, 1979). The vulnerability arises in part from the fact that they cannot adequately consider the risks and benefits of participating in research for themselves, and thus cannot provide informed consent (Ramsay, 1970). As a result, parents' permission/consent is often required, together with the child's assent (for those who are able), before a child can be involved in research. This is meant to protect children from being exploited in research.

2.3.1 Informed consent

Most guidelines require that parental informed consent be sought for any research that involves children (The Belmont Report, 1979; Council for International Organizations of Medical Sciences, 2002; World Medical Association, 2013). Some countries require informed consent from both parents, which may complicate things even further, especially in instances where the parents are separated. When meeting with parents, the researcher is obligated to present the study with clarity (Ferguson, 2002). The informed consent process is one of education, and participants, or in this case, parents, need to understand what they are being asked to consent to. Parents need to voluntarily decide whether they will allow their children to participate as research participants, based on a clear understanding and personal assessment of the potential benefits and risks for their child (Pickler & Martin, 2010). The South African National Health Act (No. 61 of 2003) limits the ability to provide proxy consent to parents and legal guardians. Strode, Richter, Wallace, Toohey, and Technau (2014), argue that this requirement is problematic and would affect a significant number of children who are orphaned due to AIDS. Children who do not have parents or legal guardians will not be able to participate in health research; hence they argue that caregivers should also be allowed to provide proxy consent.

2.3.2 Assent

Assent, in this context, is a child's affirmative agreement to participate in research. Mere failure to object should not be construed as assent (Knudson, 2002). According to Knox and Burkhart (2007), assent from the child should only be obtained after seeking permission from the child's parent or guardian, and this should be done before the child is enrolled in the study. In obtaining assent from the child, the child should be provided with information about the study procedures and their potential impact on the child, including discomforts and inconveniences that the child might experience. In addition, the child should be provided with information about the general purpose of the research in which they are being asked to participate (Knox & Burkhart, 2007). All of the explanations should be provided in the

language that the child understands, and they should be made as simple as possible so that the child is able to comprehend them. In addition, a child's assent should be obtained in a less stressful or intimidating environment. Children should be made as comfortable as possible so that they can feel free to voice their opinion.

Most international guidelines and national regulations for research require that assent should be obtained from children whenever they are involved in research. The SA NHA, however refers to this agreement by a child to participate in research as consent (Republic of South Africa, 2004).

However, there is little guidance on how this requirement should be implemented (Wendler, 2006). As a result, there are some debates in the literature regarding the age at which assent should be sought from a child, and at what age a minor should be able to give informed consent. For instance, Wendler (2006) argues that most children are able to comprehend a research study at the age of 14; hence, this age should be used as the threshold for assent unless instruments have been developed to measure the assent capacity of each child. On the other hand, Broome, Richards, and Hall (2001) set this age at six years, while the American Academy of Paediatrics indicates that children are usually able to understand research participation when they have attained an intellectual age of seven years and above, hence should be given an opportunity to participate in research decisions (Burns, 2003). In addition, children have evolving capacity for autonomous decision making. For instance, a longitudinal study may enrol children between 15 and 21 years; hence, some of these children may gain the ability to consent during the study when they turn 18 and, at that stage, their informed consent will need to be obtained.

There is no universally accepted age definition of adolescence or of the age of majority and ability to give consent for research participation. However the Convention on the Rights of the Child defines a 'child' as every human being below the age of eighteen years unless under the law applicable to the child, majority is attained earlier (United Nations Human Rights, 1989). This definition is limited to nations that have ratified it, including South Africa.

Typically, in more developed countries, the legal age of consent (and beginning of adulthood) is 18–21 years of age, and those younger than that require parental consent for most medical care and participation in research. However, in countries such as the US, adolescents over 14 years of age can give legal consent for certain kinds of health care, such as for reproductive and mental health, and this ability to give consent for medical care is often used as a precedence for their ability to give informed consent for participation in

certain types of research (Ensign, 2003). The South African National Health Act (No. 61 of 2003) does not permit children to consent independently to any form of health research. However, the Children's Act allows children to consent independently for a range of health-related interventions before adulthood, such as HIV testing at 12 years, and male circumcision at 16 years (Strode & Slack, 2011). Scholars argue that this restriction in the NHA will limit health research on certain issues including research on adolescent sexuality or illegal behaviours among others. This could have implications on the provision of evidence-based interventions targeted at addressing these issues (Strode et al., 2014).

2.3.3 Dissent

Whenever a child objects to or physically resists a procedure, the investigator should stop for a while and try to reassure the child or make a minor modification to try to reduce the child's distress. However, if the child's dissent is sustained, then the child should be removed from the study, especially if the child does not stand to benefit directly from that particular study. A child's dissent may only be overridden if the study intervention has been shown to be more effective than the intervention available in the community. However, sometimes to avoid the concern that the child is being forced to undergo a certain procedure for the good of society, and where the study medicine that seems to be more effective than what is available in the clinical setting, arrangements could be made to supply this to the child outside of the research context (Wendler, 2006). Wendler (2006) argues that expressions of dissent can indicate that a child is in pain or experiencing distress. Therefore, not respecting children's dissent exposes children to research that is causing them pain or distress. However, he also notes that some verbal or behavioural objection may not really reflect actual distress, while others may reflect only temporary distress. Therefore, instead of requiring that dissenting children should be automatically removed from the study, research ethics committees and researchers could adopt a policy of 'stop, assess and address' (Wendler, 2006).

2.3.4 Undue influence and coercion

Because children are under the authority of others like parents and teachers, this makes them susceptible to coercion and undue influence. As children subject to parental decision-making, they tend to expect adults' power over them and they are not used to being treated as equals by adults (Punch, 2002). As a result, children may feel under pressure to agree to participate in research. This may be especially true in instances where they know that the parent/guardian has already agreed to their participation. It is possible that parents may put their children under pressure to participate in a research study because of their perception of the relationship that they have with the physician or because of an incentive being offered in the study. Focusing on informed consent as the only form of protection for children, without

any other measures of protection such as benefit-risk assessment, may expose children to risky research (Strode et al., 2005b).

Payment to paediatric research participants becomes particularly problematic because of the child's vulnerability and dependence on adults as the primary decision makers. For researchers to ensure that parental permission for their child's participation is completely voluntary, they must keep in mind that poor families are particularly vulnerable to the pressure of monetary rewards for research participation. Offering large financial incentives may create unnecessary coercion by the parents for their children to participate in research (Meaux & Bell, 2001, and Thomas, 2005, as cited in (Knox & Burkhart, 2007).

2.3.5 Assessing the risk-benefit ratio

Most international guidelines stipulate that in order to judge whether research is approvable or not, research ethics committees should assess the risks and benefits of research and decide whether the research is approvable for children. This is a critical part of ethics review required to protect children from excessive risks while allowing appropriate research to take place (Shah, Whittle, Wilfond, Gensler, & Wendler, 2004). 'Minimal risk' is usually used as the threshold for the level of risk that children could be exposed to (Knox & Burkhart, 2007). According to Binik and Weijer (2014), minimal risk is a central concept in the ethical analysis of research with children. It is defined as the risks 'ordinarily encountered in daily life'. Although US federal regulations provide seemingly straightforward definitions of minimal risk research, making this decisions can prove complex, especially about whether the risk should be judged relative to a healthy person or the condition under study (Sugarman & Califf, 2014). There are major debates about when risks are reasonable in their relationship to potential benefits, and critique is often that RECs are not consistent in risk assessment (Shah et al., 2004). Risk-benefit assessment should also be contextualised, taking into consideration the sociocultural, economic, and political context in which the research is undertaken (Kruger, Ndebele, & Horn, 2014).

2.4 International guidelines for child research

The Nuremberg Code was promulgated in 1947 as the first international guideline for research involving human participants; this was a reaction to the post-war trials of doctors who were involved in the Nazi war experiments. The Nuremberg Code was the first research guideline to require individual consent for research participation, although it did not address specifically the participation of children in research. This was largely interpreted to mean that children could not participate in research as they could not give informed consent, and children were excluded from research for that reason (Burns, 2003).

This limitation was later addressed in the Declaration of Helsinki in 1964 which introduced the practice of obtaining consent from a legally authorised representative for participants incapable of giving informed consent, either because they were too young to understand research concepts or because they were mentally incapacitated (World Medical Association, 2013). The Declaration of Helsinki indicated, however, that assent should be sought from the concerned participants if they were able to (World Medical Association, 2013). This meant that children could participate in research. The Declaration of Helsinki provided additional guidance for extra protection for vulnerable populations, including children. This included that research should not be conducted with vulnerable persons who are unable to consent, unless the research is intended to directly benefit the individual research participants or improve the health of the groups that they represent. In addition, the research should involve no more than minimal risk or burden, and should be conducted with full informed consent (World Medical Association, 2013).

Despite the development of international guidelines such as the Declaration of Helsinki, a number of controversial research studies took place in the United States (Dainesi & Goldbaum, 2012). As a result, in 1977, the US National Congress assigned the National Commission for Protection of Human Subjects of Biomedical and Behavioural Research to report on the unique ethical issues involved in using children as research participants. The National Commission then identified three ethical principles: respect for persons, beneficence, and justice, as the basic principles for research involving human participants (Dainesi & Goldbaum, 2012). These principles form the core of what is now commonly known as the Belmont Report.

Similar to previous guidelines, the Belmont Report emphasised informed consent. Relevant to child research, this principle of respect for persons suggests that some persons, like children, have diminished autonomy and may not be capable of self-determination. Child research participants should therefore be accorded special protection. The principle of beneficence entails treating people ethically, not only protecting them from harm but also by performing acts that will help in securing and promoting their well-being. As a result, research involving children can be justified by the desire to explore ways that will help in treating childhood diseases and promoting child health, even if the participants themselves will not benefit directly from that research (The Belmont Report, 1979). The principle of justice requires that benefits and burdens of research should be distributed fairly. While child participants should only be recruited into minimal risk studies with already demonstrated safety in adults, it would equally be unjust to unnecessarily exclude children from research as that would unnecessarily exclude them from any direct and/or indirect benefits of

research (Royal College of Pediatrics and Child Health (RCPCH) Ethics Advisory Committee, 2000 in Neill, 2005)

In 2002, the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) promulgated guidelines for international research involving human participants. The CIOMS guidelines categorise children as a vulnerable population with a need for extra protection whenever they are involved in research. Guideline 14 of the CIOMS guidelines is specifically devoted to research involving children and stipulates requirements that need to be met before the commencement of child research. These include that the research addresses needs of children and cannot be carried out with adults, and that permission is sought from each child's parent or legally authorised representative, in addition to assent by each child (Council for International Organizations of Medical Sciences, 2002). Although the CIOMS guidelines indicate that a child's refusal to participate or continue in the research will be respected, it indicates that exceptions may be made for children deemed to be too young to understand the research procedure or where the child has a fatal condition and the research offers possible therapeutic benefit that is not available elsewhere. It also indicates that consent or permission from parents may be waived in certain situations, for example, where the research involves child abuse or adolescent sexual issues and the involvement of parents may expose the children to some risk or intimidation (Council for International Organizations of Medical Sciences, 2002). The above guidelines are now used in most countries as a template for national regulations and policies for research involving human participants, children included.

2.5 Regulation of child research in high-income countries

The United States Code of Federal Regulations on research involving human subjects, 45 CFR 46, has a section dedicated to research with children (Sub-part D). The regulations stipulate the types of research that are allowable with children and categorise child research according to the level of risk likely to be posed to children. The regulations also take into consideration whether the research is likely to offer any direct or indirect benefits to child participants. The four risk categories for child research include: a) research not involving more than minimal risk; b) research involving a minor increase over minimal risk, but with the prospect of direct benefit to the individual child participants; c) research involving more than minimal risk, with no prospect of direct benefit to individual child participants, but likely to yield generalisable knowledge about the childhood disorder or condition; and d) research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a

serious problem affecting the health or welfare of children (US Department of Health and Human Services, 2005).

The first three categories of research require approval by an Institutional Review Board (IRB) or Research Ethics Committee (REC), assent from children where applicable, and informed consent from parents or a legally authorised representative. The last category of research requires approval from the Secretary of the Department of Health and Human Services, who would have to consult with a panel of experts from relevant disciplines and the general public, and conclude that the research has the potential to yield results that could be used in understanding, preventing, or mitigating a serious health or welfare problem affecting children (US Department of Health and Human Services, 2005). The US Food and Drug Administration (FDA) regulations (21 CFR 50) further stipulate that in determining whether children are capable of providing assent, the IRB must take into account the age, maturity, and the psychological state of the child involved (Diekema, 2006a). This consideration should be made for any protocol that involves the participation of children in clinical investigations. The assent of the children may be waived under certain circumstances as deemed appropriate by the IRB; these include: (1) studies enrolling children who have limited capacity and who cannot reasonably be consulted, or (2) studies that have a potential direct benefit that is important to the health or well-being of the children, and is available only in the context of the research (Diekema, 2006a).

The FDA regulations also outline conditions where the IRB can waive the assent requirement even when the participants are capable of giving assent. These conditions include: (1) the research should involve no more than minimal risk to the child participants; (2) the waiver will not adversely affect the rights and welfare of the child participants; (3) research could not practicably be conducted without a waiver of assent; and (4) whenever appropriate, the participants will be provided with additional pertinent information after participation (Diekema, 2006a). In cases where parental permission is needed, the IRB may find that the permission of one parent is sufficient for certain studies to be conducted. Where clinical investigations involve more than minimal risk and no prospect of direct benefit to the individual child participant, but are likely to yield generalisable knowledge about the child's disorder or condition, then permission should be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. Permission by parents or guardians must be documented in accordance with, and to the extent required, by the regulations on consent. When the IRB determines that assent is required, it must also determine whether and how assent must be documented (Diekema, 2006a).

The Canadian policy for research involving human participants is very similar in content to the US's 45 CFR 46. It also categorises child research according to the level of risk for child participants and the prospect of benefits. The Canadian policy defines three risk categories; (1) research that involves minimal risk to children; (2) research involving more than minimal risk, with the prospect of direct benefit to the individual child participant; and (3) research involving more than minimal risk, with no prospect of benefit to the individual child participant (Health Canada's Research Ethics Board, 2009). Unlike the US and Canadian regulations, the European regulations for research involving human participants do not classify research into risk categories but require that research involving children should have some direct benefits to children as a group and that the study is aimed at addressing a condition being suffered by the child or of such a nature that it could only be conducted with children (The European Parliament and the Council of the European Union, 2001).

2.6 Regulation of child research in low- and middle-income countries

Efforts have been made in low- and middle-income countries (LMICs) to develop and implement ethics guidelines, policies, and legislation for research involving human participants. Most guidelines devote some attention to research with vulnerable groups, including children, to what constitutes a child, the type of research children may participate in, and the levels of consent and assent required.

The Nigerian National Health Act of 2014 (Section 7, Sub-section 2) stipulates that where research or experimentation is to be conducted on a minor for a therapeutic purpose, the research or experimentation may only be conducted with consideration of the following: (a) if it is in the best interests of the minor; (b) in such a manner and on such conditions as may be prescribed by the National Health Research Ethics Committee; and (c) with the informed written consent of the parent or guardian of the minor. Where research or experimentation is to be conducted on a minor for a non-therapeutic purpose, the research or experimentation may only be conducted: (a) in such manner and on such conditions as may be prescribed by the National Health Research Ethics Committee; and (b) with the informed written consent of the parent or guardian of the minor (Federal Republic of Nigeria, 2014)

In Uganda, the research guidelines require the establishment of adequate provisions for the solicitation of children's assent in order to enrol children in research that does not offer the prospect of direct benefit. Assent to participate in research must be obtained from all children eight years of age and older, and from all persons incapable of self-determination. A child's assent is obtained after parental/guardian consent. The child's assent or dissent takes precedence over the parent or guardian's consent. Assent from all other persons

incapable of self-determination is obtained after consent from their representatives (Mokgatla-Moipolai, 2012).

The Kenyan guidelines for the ethical conduct of biomedical research involving human participants advocate respect for children's dissent unless there is no other medical alternative from which the child could benefit (Wahome, 2014). The guidelines further stipulate that, before undertaking child research, the investigator must ensure that: (1) the research might not equally well be carried out with adults; (2) the purpose of the research is to obtain knowledge relevant to the health needs of children; (3) a parent or legal representative of each child has given permission; (4) the agreement (assent) of each child has been obtained to the extent of the child's capabilities; and (5) a child's refusal to participate or continue in the research will be respected (Wahome, 2014).

2.7 Regulation of child research in South Africa

In 2005, the South African government promulgated the National Health Act (Act No. 61 of 2003) (Cleaton-Jones & Wassenaar, 2010), which regulates research involving human participants, including children. According to the Republic of South Africa (2004), child research is categorised into two classes, therapeutic and non-therapeutic research. Therapeutic research is defined as "research that includes interventions that may hold out the prospect of direct health-related benefit for the participant", whilst non-therapeutic research is "research that includes interventions that will not hold out the prospect of direct health-related benefit for the participant but may produce results that contribute to generalisable knowledge" (Department of Health, 2015).

The NHA Section 71 (2) permits therapeutic research to be approved with consideration of the best interest of the minor, consent of the parent or guardian, consent of the minor if they are capable of understanding among others (Republic of South Africa, 2004).

With regards to non-therapeutic research, Section 71 (3) requires the consent of the Minister of Health in addition to the above-stated requirements but does not require best interest to be considered. According to the Act, the Minister may not give consent for non-therapeutic research with minors in circumstances where: (a) the objectives of the research or experimentation can also be achieved if the research is conducted on adults; (b) the research or experimentation is not likely to significantly improve scientific understanding of the minor's condition, disease, or disorder to such an extent that it will result in significant benefit to the minor or other minors; (c) the reasons for the consent to the research or experimentation by the parent or guardian and, if applicable, the minor are contrary to public

policy; (d) the research or experimentation poses a significant risk to the health of the minor; or (e) there is some risk to the health or well-being of the minor and the potential benefit of the research or experimentation do not significantly outweigh that risk (Republic of South Africa, 2004).

The South African Department of Health has developed guidelines that govern research conducted in the country. These include the *Guidelines for good practice in the conduct of clinical trials in human participants in South Africa* (SA GCP) (Department of Health, 2006) and the *Guidelines for Ethics in health research: Principles, structures and processes* (Department of Health, 2015). The Medical Research Council of South Africa (2001) has also issued a number of guidelines including *Guidelines on ethics for medical research: General principles*.

Both the SA GCP (Department of Health, 2006) and the National Health Act (Act No. 61 of 2003)(Republic of South Africa, 2004), use the term minor and child interchangeably. The SA GCP stipulates that minors should participate in research only where their participation is indispensable to the research. Where research that involves minors is proposed, a research ethics committee should determine whether the research might be equally informative if carried out with consenting adults. If so, the research ethics committee should require strong justification for the inclusion of minors. The research should also investigate a problem of relevance to minors.

The SA GCP guidelines further indicate that research involving minors should only be approved if: (1) the research interventions, including those in observational research, present the child participant with no more than minimal risk. Minimal risk is defined as the probability and magnitude of harm or discomfort ordinarily encountered in daily life or during the performance of routine medical or psychological examinations or tests – referred to as ‘negligible risk’ in some guidelines; or (2) the research interventions present more than minimal risk but hold out the prospect of direct benefit for the child participant. The risks must be justified by the anticipated benefit; or (3) the research interventions, including those in observational research, present more than minimal risk and do not hold out the prospect of direct benefit to the participant, but have a high probability of yielding generalisable knowledge relevant to children (i.e. the risk should be justified by the risk-knowledge ratio). The risk should represent a minor increase over minimal risk. The intervention or procedure should present experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or education

settings. In all cases, the protocol must provide sufficient information to justify clearly why minors should be included as participants (Department of Health, 2006).

In terms of consent requirements, the SA GCP requires that for research with minors, the following should be obtained: consent from a parent or legal guardian in all but exceptional circumstances (e.g. emergencies). A caregiver (e.g. custodian, person providing long-term day-to-day care for the child) can act on behalf of a minor; (b) assent from the minor where s/he is capable of understanding. A child's refusal to participate in research must be respected (i.e. such refusal settles the matter). The guidelines define assent as a minor's affirmative agreement to participate in research. They further indicate that mere failure to object should not be construed as assent. The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the minor's assent when, in the judgement of the research ethics committee, the minor is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented (Department of Health, 2006).

South Africa's ethics guidelines also include the Department of Health's *Ethics in health research: Principles, structures and processes* (Department of Health, 2015). These guidelines resonate with the SA GCP (Department of Health, 2006) and NHA ((Republic of South Africa, 2004; Department of Health, 2006) in that they also use the terms minor and child interchangeably and outline similar conditions for the participation of minors in research. However, these guidelines do not provide a definition of a minor but define a child as a person who has not yet reached puberty, and an adolescent as a person who has reached puberty. In addition, these guidelines provide more detail on the requirement for obtaining parental permission. They stipulate that the research ethics committee may find that the permission of one parent is sufficient where the research does not involve greater than minimal risk to the child, or involves greater than minimal risk but presents the likelihood of direct benefit to the child. Permission from both parents is necessary where the research involves greater than minimal risk, is of no direct benefit to the child, but is likely to produce generalisable knowledge. However, permission of one parent may be sufficient for this type of research where only one parent is available for reasons including the death, incompetence, or disappearance of the other, or where a court has placed the child in the sole custody of one parent. In the event of conflicting views between the parents, the child's best interests settle the matter. These guidelines also indicate that an unmarried mother who is herself a minor may not consent to the participation of her child in research investigations. Her guardians (usually her parents) are also the guardians of her child and must thus consent to the child's participation (Department of Health, 2015).

These guidelines additionally outline conditions for research involving adolescents who may consent unassisted in the following scenarios: (a) the research, including observational research, places the adolescent at no more than minimal risk, and the nature of the research is such that, in the opinion of the research ethics committee, the parents, legal guardians, and/or community at large are unlikely to object to the adolescent consenting him- or herself to participation in the investigation; (b) the opinion of the research ethics committee must be informed by information gathered from the community concerned and by contributions from the lay members of the committee; (c) in all cases, the protocol must provide sufficient information to justify clearly why adolescents should be included as participants; and (d) in all cases, the protocol must justify clearly why the adolescent participants should consent unassisted (Department of Health, 2015).

The SA NHA requires consent of the parent or guardian of the child as one of the conditions for approving child research. This makes it difficult to approve research conducted in emergency situations where obtaining consent from the parent or guardian might not be possible. However, provision for such research is made in the SA GCP guidelines (Department of Health, 2006), which indicate that consent from parent or legal guardian is required in all child research, except in exceptional circumstances like emergencies. The other challenge with the blanket requirement of parent or guardian consent (as stipulated in the SA NHA) involves research dealing with sensitive issues that affect children, for instance, issues like child abuse, or sexual issues, which might complicate children's participation in such research if parents are involved. Other issues come out when involving children who are considered emancipated (e.g. pregnant teenagers or mothers; street children), which makes the consent process more complicated as it is not always easy in such cases to decide who should make a decision about a minor's participation in research. Nonetheless, this issue is more nuanced in the Department of Health Guidelines: *Ethics in health research: Principles, structures and processes* (Department of Health, 2015), which allows the participation of adolescents without parent or guardian consent in certain research conditions. Therefore, this inconsistency between the NHA and other guidelines governing the conduct of children research needs to be corrected, as it is likely to impede child research.

The NHA seems to be inconsistent with existing and proposed legislation regarding consent, which as a result, makes the process of obtaining consent for the participation of children in some research (such as HIV prevention trials) very complex. According to the NHA (No. 61 of 2003), children under 18 will require consent from a parent or legal guardian to participate

in research, whereas the Children's Act states that at 12 years and older, children can consent independently for HIV tests; this suggests that some children below 18 years will have the capacity to consent independently to some procedures and interventions within these trials, for example, independently consenting for HIV tests (Strode, Slack, & Essack, 2010). As consent/assent is the main protection provided for children in the NHA, it is important to prepare ethics review committees for the assessment of research involving children. A good potential framework for such ethics review is provided by the ethical benchmarks proposed by Emanuel et al. (2004).

2.8 Conceptual framework: Eight benchmarks of ethical research

The Emanuel et al. (2004) framework was designed as a universal tool for use in developing countries (Tsoka-Gwegweni & Wassenaar, 2014). Emanuel et al. (2004) proposed eight benchmarks that should be considered to ensure ethical conduct of research in developing countries. These benchmarks include: (1) collaborative partnership, (2) social value, (3) scientific validity, (4) fair selection of study population, (5) favourable risk-benefit ratio, (6) independent review, (7) informed consent, and (8) respect for recruited participants and study communities.

2.8.1 Collaborative partnership

Emanuel et al. (2004) argue that international researchers and sponsors conducting research in developing countries should develop a collaborative partnership with researchers, policy makers, and the research host communities. A collaborative partnership should fulfil the following: (i) it should engage all the relevant stakeholders in the country where the research is being conducted; (ii) all parties should be equally involved in the whole research process, including identifying the research problem, the value of the research, how the research will be conducted, and dissemination and implementation of the research results; (iii) the collaborative partnership should be based on mutual respect. This involves recognising and respecting the interests of the host community, their values, culture, and social practices. This should be considered in the design and implementation of the study. (iv) Disparities related to the research project between researchers and sponsors from developed countries and host communities should also be minimised. This could be achieved by building capacity in the host country through contributing to the health sector, training researchers and health care staff, or assisting in the establishment of an ethics review system, as well as development and implementation of standard operating procedures so that host communities become full and equal partners in the research. (v) Benefits from the conduct of the study and/or research findings should be shared equally with the host community, and (vi) there should also be a fair distribution of all the rewards

coming from the research study. This involves drawing up agreements on how intellectual property rights, royalties, and other financial profits will be shared, as well as appropriately acknowledging all the authors and those who contributed to the research (Emanuel et al., 2004). This benchmark is important for child research, as a collaborative partnership will ensure that the conduct of the research is in line with the local context and build local capacity for paediatric research, as well as facilitate the sharing of research benefits to either the research participants or children as a group.

2.8.2 Social value

For clinical research to be considered ethical it needs to have social value through the creation of new knowledge that can be used to improve health. Otherwise, conducting research without social value will expose research participants to risks without any good reason and also waste resources (Emanuel, Wendler & Grady, 2000 in Emanuel et al., 2004). The research should have social value to children as a group. Emanuel et al. (2004) have outlined the following conditions to be met to ensure the social value of research: (i) all potential beneficiaries of the research study should be clearly identified; (ii) potential benefits of the research for each of the people who stand to benefit should be identified and described; (iii) strategies should be developed to increase the social value of the research. This involves dissemination of research findings to all the relevant stakeholders in suitable languages and formats; and (iv) the conduct of the research should not destabilise or weaken the existing system (Emanuel et al., 2004).

2.8.3 Scientific validity

All research should be scientifically valid and should generate reliable results that can be used to benefit the relevant populations; otherwise, research participants would be exposed to research risks for nothing (Emanuel, Wendler & Grady, 2000 in Emanuel et al., 2004). The research sample size should be sufficient to produce findings that are generalisable and the research methods should be objective. In the same manner, child research should be conducted in accordance with established scientific methods and procedures so as to generate findings that could be used to benefit children.

To meet the requirement of scientific validity the following is necessary: (i) research must be designed such that it addresses the health issues of the population being studied (Macklin, 2001 in Emanuel et al., 2004); (ii) the research study design should be such that it will achieve the objectives of the study without denying research participants healthcare services that they are entitled to or demanding services that are not reasonably available in the local healthcare system; and (iii) the research study should also be designed in such a way that it

can reasonably be conducted in the host country, taking into consideration the social, political, and cultural environment of the community where it is being conducted (Bloom, 1998 in Emanuel et al., 2004).

2.8.4 Fair subject selection

For fair subject selection, the following requirements should be met: (i) the study population should first and foremost be selected for scientific reasons, for instance, high prevalence, incidence, or transmission rate for an infectious disease. (ii) In selecting a study population, potential risks to the population should be taken into consideration and be minimised as far as possible. (iii) The selected host community should also be able to actively participate in planning and conducting the study and making sure that the research findings are implemented. (iv) The vulnerability of the selected study population should also be taken into consideration and measures be put in place to safeguard and protect the population; these may include ensuring confidentiality and freedom to refuse participation in the study (Emanuel et al., 2004). When conducting research with children, it is equally important to assess whether the selection of research participants is done in a fair manner, so as to ensure that no children are being selected only because of their vulnerability rather than for scientific reasons.

2.8.5 Favourable risk-benefit ratio

Clinical research should offer a favourable risk-benefit ratio to participants; in cases where the potential risks are greater than the benefits to the participants, then the risks may be justified by the social value of the study (Emanuel, Wendler & Grady, 2000 in Emanuel et al., 2004). The following are necessary: (i) in considering if a risk-benefit ratio is favourable, it is important to take into account the context of the participants; for instance, there may be differences in the underlying risks of a certain disease because of variations in incidence, medicine resistance, genetic susceptibility, and social or environmental factors. (ii) To assess a favourable risk-benefit ratio for the community, all the potential risks and benefits to the community should be identified and the community should be allowed to decide whether they accept the risks in relation to the benefits that will be obtained from the study (Weijer & Emanuel, 2000 in Emanuel et al., 2004). However, the community's decision should also be assessed and confirmed by people with research experience (Emanuel et al., 2004). Therefore, it is essential to assess the risk-benefit ratio of child research, so as to ensure that children do not end up being involved in research that exposes them to unreasonable risks with no or little benefit. A number of countries including the USA and Canada require a risk-benefit analysis to be conducted for child research, while the SA NHA only requires it for non-therapeutic research.

2.8.6 Independent review

All clinical research protocols, including those that are conducted on children, should be subjected to an independent ethical review. This would address issues of conflict of interest by researchers and would also ensure public accountability (Emanuel, Wendler & Grady, 2000 in Emanuel et al., 2004). Ethics review committees should be competent to conduct the reviews and should do so independently (Emanuel, Wendler & Grady, 2000 in Emanuel et al., 2004). Therefore, there is a need to empower ethics review committees by training them.

2.8.7 Informed consent

Emanuel et al. (2004), have suggested the following criteria for valid informed consent: (i) the local community should assist in coming up with recruitment procedures and provide guidance on the type of incentives that should be given participants, which should be in line with cultural, political, and social practices. (ii) Research information should be disclosed in such way that it is sensitive to the context of the host community. The local language should be used to disclose information and other culturally appropriate means of communication like idioms and analogies should be used so that potential participants can understand. (iii) In some cases, researchers may need to acquire permission at different levels, for instance from village elders or heads of households, before asking for the consent of the actual participants (Weijer & Emanuel, 2000 in Emanuel et al., 2004). (iv) When obtaining informed consent, researchers should employ consent processes that are acceptable in that particular community but should make sure that there is an independent witness to confirm that consent was indeed voluntary. (v) Researchers should also make sure that participants are aware of their right and freedom to refuse to participate or withdraw from the research (Karim et al, 1998 in Emanuel et al., 2004). Measures should be put in place to avoid coercion by family or community members (Emanuel et al., 2004). The SA NHA also requires that consent from a parent or guardian, as well as assent where possible, should be obtained before enrolling a child in a research study. This is very important to ensure voluntary participation of children in research.

2.7.8 Respect for recruited participants and study communities

Researchers continue to have an obligation to participants, former participants, and the local community throughout the conduct of the study. Thus, (i) the first and most important obligation include devising and implementing measures to ensure that participants' information is kept confidential. However, participants should be informed of the risk of breach of confidentiality despite researchers' best efforts. (ii) Participants should also be respected by being informed of their right to withdraw from participation (Karim et al, 1998 in Emanuel et al., 2004). (iii) Participants and the host community should be notified of any new

information that relates to the research, such as a new risk that has been discovered. (iv) Researchers should indicate the measures they would use to monitor the development of the disease, adverse events, and any untoward changes in health. They should also describe what processes would be followed in order to provide care in the above-indicated circumstances and what kind of compensation would be provided for research-related injuries. (v) Researchers have an obligation to ensure that participants are informed of the research findings at the end of the study including their implications for public health and healthcare policies. This therefore means that explicit strategies should be outlined indicating how participants and host communities will be informed of the research results (Weijer & Emanuel, 2000 in Emanuel et al., 2004). This is critical for child research too, as children and their parents/guardians also deserve to be respected while participating in research.

2.9 Applying the eight benchmarks to child research

The benchmarks provide a systematic framework which can be used to ethically design and assess research in developing countries. However, the application of this framework may be affected by differences in the health, social, and cultural aspects of a research setting, in terms of how the different benchmarks are weighted or prioritised (Daniels et al, 2000 in Emanuel et al., 2004). While these benchmarks were not designed specifically for child research, they are largely applicable as they are very comprehensive and cover the principles outlined in international guidelines like the Declaration of Helsinki, CIOMS, and others.

2.10 Conclusion

Conducting research with children is very challenging because of the special requirements that need to be fulfilled to ensure ethical conduct of research. The most common ethical issues that emerge in child research include the requirement to ensure that they are protected from harm, and respecting their autonomy to participate in research by making sure that the consent of their parents, as well as the child's assent where possible, has been obtained (Sofaer & Strech, 2011). A number of international bodies and countries have now promulgated guidelines and regulations to govern the conduct of research with children. However, some scholars have noted that overregulation of child research could result in even less knowledge generated about children that could slow down developments of care and new interventions for children (Morrow & Richards, 1996 in Neill, 2005). In situations where national regulations have been recently enacted like in the case of the SA NHA (No. 61 of 2003) Section 71, it is important to assess the implications to ensure that essential paediatric research can be conducted. Therefore, the aim of this study was to assess the

implications of compliance of child research with the National Health Act (No. 61 of 2003) Section 71, as well as how effective it is in promoting the best interests of children through research. The benchmarks for ethical review proposed by Emanuel et al. (2004) were used as a conceptual framework to guide this study.

CHAPTER 3

RATIONALE FOR THE STUDY

3.1 Problem statement

There may be limitations in the National Health Act (No. 61 of 2003) Section 71 that need to be addressed in ensuring the best interests of children when conducting child research. The NHA seems to be inconsistent with existing legislation such as the Children's Act (No. 38 of 2005) (Republic of South Africa, 2005) regarding consent (Strode et al. (2005b); Cleaton-Jones & Vorster, 2009). According to the National Health Act (No. 61 of 2003), children under 18 require consent from a parent or legal guardian to participate in research, whereas the Children's Act states that minors 12 years and older can consent independently for medical procedures and treatment, including HIV tests, indicating that these children might have the capacity to consent independently to these procedures and interventions within clinical trials (Strode et al., 2010).

The National Health Act (No. 61 of 2003) further categorises child research into 'therapeutic' and 'non-therapeutic' despite the fact that this categorisation of research has been contested (Strode et al., 2005b). There are also certain inconsistencies in the interpretation of the NHA. For example, (i) Section 71(2) requires that a child's 'best interests' be considered when reviewing therapeutic research, yet no such obligation is necessary for non-therapeutic research; and (ii) a risk standard is described for non-therapeutic research in Section 71(3)(a)(iv), but no risk standard is described for therapeutic research. This indicates that a more stringent review standard is placed on non-therapeutic research, which may not be in the best interests of children in terms of promoting non-therapeutic research that could ultimately benefit children as a group. In addition, compared to generally more risky therapeutic research, many forms of non-therapeutic research entail minimal to no risk. Therefore, this stricter review standard seems misplaced.

In addition, the National Health Act (No. 61 of 2003) also stipulates that research involving children may not be approved if it poses a significant risk to them, but no definition or measurement of significant risk is provided (Strode et al., 2005c). It also does not provide an objective risk standard for deciding when it will be necessary for parents or guardians to consent to research with an adolescent (Strode et al., 2005c).

Another limitation with the National Health Act is that Section 71(3)(b)(ii) implies that non-therapeutic research involves minors with an existing medical condition, making it difficult to

classify research with healthy minors that may not confer direct health-related benefit (such as phase 1 trials).

This study investigated compliance of paediatric research with the South African National Health Act (No. 61 of 2003) Section 71, as well as with the ethical benchmarks proposed for clinical research by Emanuel et al. (2004). The child research analysed here was conducted after the promulgation of this section of the Act. The rationale for conducting this study was to investigate the potential impact that the SA NHA may have on essential research involving children. It is hoped that the findings of this study will assist in recommendations to ensure that child research participants are adequately protected, and that child participants and children as a group benefit from research. In addition, the findings of this research will contribute to the literature on ethics review of paediatric research in South Africa as currently there is no empirical research that has been done on this area of research ethics regulation in South Africa.

3.2 Research aim

This study aims to assess the potential impact of the South African National Health Act (No. 61 of 2003) Section 71 on paediatric research through a descriptive analysis of paediatric research articles published by the staff of the Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, after the promulgation of Section 71. This study also aims to investigate whether the ethical benchmarks proposed by Emanuel et al. (2004) are an appropriate guide for design and ethics review of paediatric research.

3.3 Research question

What potential impact may the current South African National Health Act (No. 61 of 2003) Section 71 have on essential health research for children?

3.4 Specific research objectives

- a. To compare 'therapeutic' versus 'non-therapeutic' research with children according to: research type; risk type and risk level; benefits; and the involvement of particularly vulnerable children.
- b. To investigate the extent to which paediatric health research conducted at the Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences (FMHS), Stellenbosch University (SU), after the promulgation of Section 71 might be compliant with the current South African National Health Act (No. 61 of 2003) Section 71.

- c. To investigate the extent to which paediatric health research conducted at the Department of Paediatrics and Child Health, FMHS, SU, complies with the proposed ethics review framework of eight benchmarks for research (Emanuel et al., 2004).

3.4 Hypotheses

- 1) H_0 : The categorisation into therapeutic and non-therapeutic research is not useful to determine whether child research is ethically acceptable.
 H_1 : The categorisation into therapeutic and non-therapeutic research is useful to determine whether child research is ethically acceptable.
- 2) H_0 : The framework of benchmarks of ethical research of Emanuel et al. (2004) is not a valuable framework to use to determine if the proposed child research is ethically acceptable.
 H_1 : The framework of benchmarks of ethical research of Emanuel et al. (2004) is a valuable framework to use to determine if the proposed child research is ethically acceptable.

CHAPTER 4

RESEARCH METHODOLOGY

4.1 Study design

This was a descriptive study, which reviewed published paediatric journal articles of the Department of Paediatrics and Child Health at Stellenbosch University from 1 March 2012 till 31 March 2013. The study divided the publications into categories of therapeutic or non-therapeutic studies and included analysis of research type, risks and benefits, as well as the involvement of particularly vulnerable minors.

4.2 Data collection

A structured data collection sheet developed by the researcher was used to extract data from the publications (see Appendix B). The structured data collection sheet was divided into two sections namely: Section A (according to the South African National Health Act (NHA) (No. 61 of 2003) Section 71, and Section B (according to the benchmarks for ethical research by Emanuel et al., 2004). The data collected included the following variables:

Section A:

- age groups of children involved in research
- whether research published was therapeutic or non-therapeutic
- in the best interests of the minor
- the levels of risk involved in the studies
- types of benefits to the children
- motivation for the involvement of children as research participants
- obtaining of consent and assent

Section B:

- collaborative partnership
- social value
- scientific validity
- fair selection of study population
- favorable risk-benefit ratio
- independent review
- informed consent
- respect for recruited participants and study communities

All research articles involving children were coded, and a coding frame with the codes, names of researchers, and titles of the articles was created and stored separately from the data collection; this was not used for analysis. This ensured that the researcher analysed the data without any identifiable information.

4.3 Sample size and selection

As stated above, the researcher reviewed the published articles on child research by staff at the Department of Paediatrics and Child Health at Stellenbosch University from 1 March 2012 – 31 March 2013, after the promulgation of Section 71 of the NHA. All the articles were in the public domain and made available to the researcher by one of her supervisors, who is the executive head of the abovementioned department. The time period was purposefully selected because this period falls into a year before the Act was promulgated; hence, reviewing articles from this period would not result in any negative consequences for the REC that approved the studies or authors of the articles if non-compliance was identified as compared to reviewing articles published after promulgation. The inclusion and exclusion criteria described below were used to select the research articles:

Inclusion criteria

- Child research published between 1 March 2012 and 31 March 2013
- Research involving persons below 18 years
- Both therapeutic and non-therapeutic studies

Exclusion criteria

- All research articles involving persons 18 years of age and above
- All research articles published before 1 March 2012 and after 31 March 2013
- Published articles not involving human subject research, for example, literature reviews, letters to the editor and case reports.

4.4 Data analysis and validation

The data collection sheet was validated by pilot testing with a review of a sample of five published paediatric research articles. According to Cohen, Manion, and Morrison (2013), quantitative data may be validated by employing careful sampling procedures, using suitable research tools, and applying appropriate statistical methods to the data. All the data collected were coded and entered into the Statistical Package for Social Sciences (SPSS) Version 24. The data were cleaned for any errors and checked for invalid entries. All data

entries into SPSS were verified with the original data sheets, and a normal curve was drawn for all questions to check for outliers. All outliers were rechecked for correctness.

Data analysis was conducted using SPSS and Microsoft Excel software packages. Data analysis involved categorising data into therapeutic or non-therapeutic studies, and analysis by research type, risks and benefits, as well as the involvement of particularly vulnerable minors. Descriptive statistics were generated including frequency tabulations, cross-tabulations, and data were summarised into graphs and charts, where appropriate.

4.5 Ethical considerations

This study was considered to present minimal risk. The data used in this study were published articles in the public domain. There was no contact with any human participants or access to private information; hence, there was no need to request permission from the authors of the published papers as these are already in the public domain. However, the Executive Head of the Department of Paediatrics and Child Health at Stellenbosch University is the supervisor of this dissertation and provided permission on behalf of the department. The critical and objective evaluation of published studies is considered an integral part of knowledge advancement and scientific discourse.

In order to ensure confidentiality and prevent any potential social and academic career harm, the specific research findings do not link to any individual authors and no names were collected or were used in the report. Each research article was given a unique identifier or code so as to de-identify the article. A link-log with file names and codes was developed and kept safely in a locked cabinet. A structured checklist developed by the researcher was then used to collect data from each research article, using only the unique study number and no identifiable data. Data files on the computer were locked and protected by passwords, while all the hard copies related to this study were stored in locked cabinets. Access to the checklists and record log were also restricted in order to maintain confidentiality. The University of KwaZulu-Natal (UKZN) Human and Social Sciences Research Ethics Committee reviewed and approved the study (see Appendix A).

CHAPTER 5

FINDINGS

5.1 Description of the source data

Of the 76 articles reviewed, a total of 55 were analysed, after excluding review articles (n=11), editorials (n=3), and clinical case reports (n=7), as these studies do not constitute human subject research.

5.2 Descriptive comparison of ‘therapeutic’ versus ‘non-therapeutic’ research with children

The majority (49; 89%) of the articles published were classified as non-therapeutic research, whereas only 6 (11%) published research articles were classified as therapeutic research, according to the definitions of the NHA Section 71. The majority (32; 58%) of published studies were retrospective, which included the majority of the non-therapeutic research articles (32/49; 65%), with only 35% (17/49) being prospective non-therapeutic research. All the therapeutic studies were prospective.

5.2.1 Age distribution of child participants

Therapeutic studies mostly involved children younger than 5 years (50%), followed by 6 – 11 years (25%), and 12 – 17 years (25%), with no neonates (0 – 28 days) (Figure 1). The majority of non-therapeutic studies (38%) also included children younger than 5 years of age, followed by 6 – 11 years (28%), 2 – 17 years age group (27%), and neonates (7%). Studies could include multiple age groups or categories.

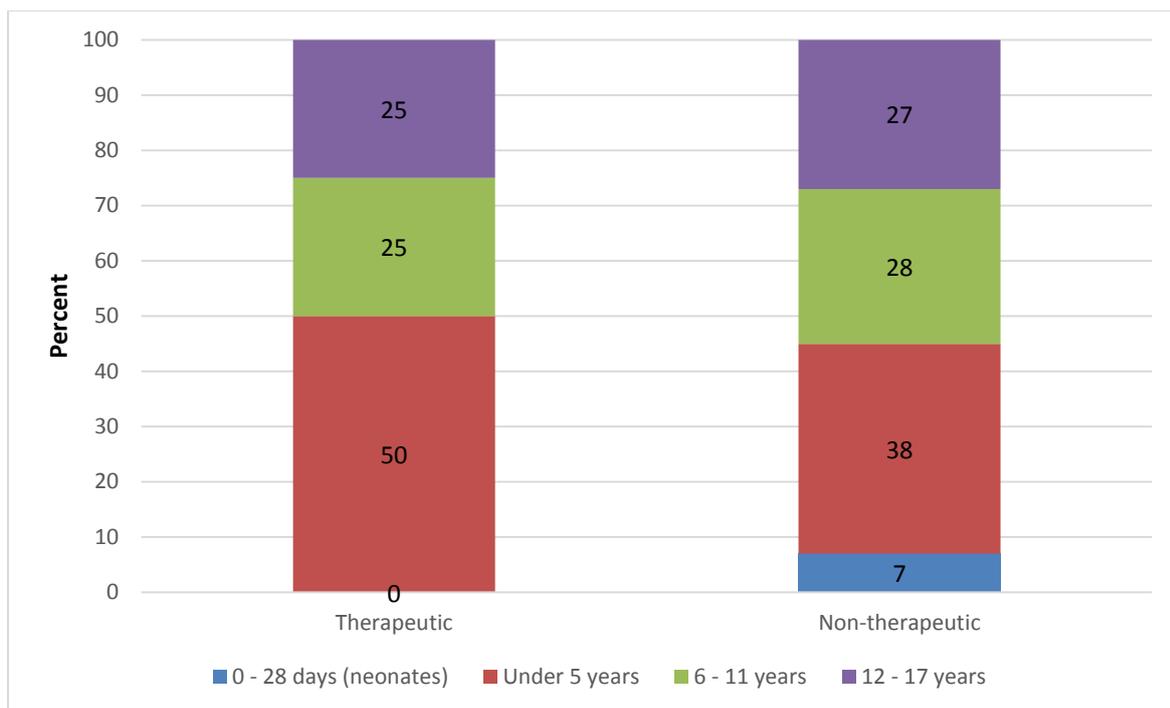


Figure 1: Age distribution of child participants in therapeutic versus non-therapeutic studies (some studies included multiple age groups/age categories)

5.2.2 Level and type of risk for child participants

Level of risk

The majority (45; 82%) of the studies involved minimal risk, while six (11%) studies involved more than minimal risk with no prospect of direct benefit to individual participants, but with generalisable information for the class of patients. Only four (7%) of the publications reported studies with research involving more than minimal risk, but with the prospect of direct benefit to the individual child participant. The majority (44/49; 90%) of non-therapeutic studies involved minimal risk, while only five (10%) of these studies involved more than minimal risk with no prospect of direct benefit to the individual child participant, but with potential generalisable knowledge for the class of patients. Most (4/6; 67%) of the therapeutic studies posed more than minimal risk, but with potential for direct benefit to the individual child participants (Figure 2).

Type of risk

All the studies (55; 100%) presented a favourable risk-benefit ratio. Therapeutic studies were more likely to present potential physical risks (6; 100%), with the addition of social risks in 50% (3/6). Non-therapeutic studies posed potential social risks in 71% (35/49), physical risks in 29% (14/49), emotional risks in 10% (5/49), while 10% (5/49) presented no foreseeable risks. Studies could have multiple types of risks (Figure 3).

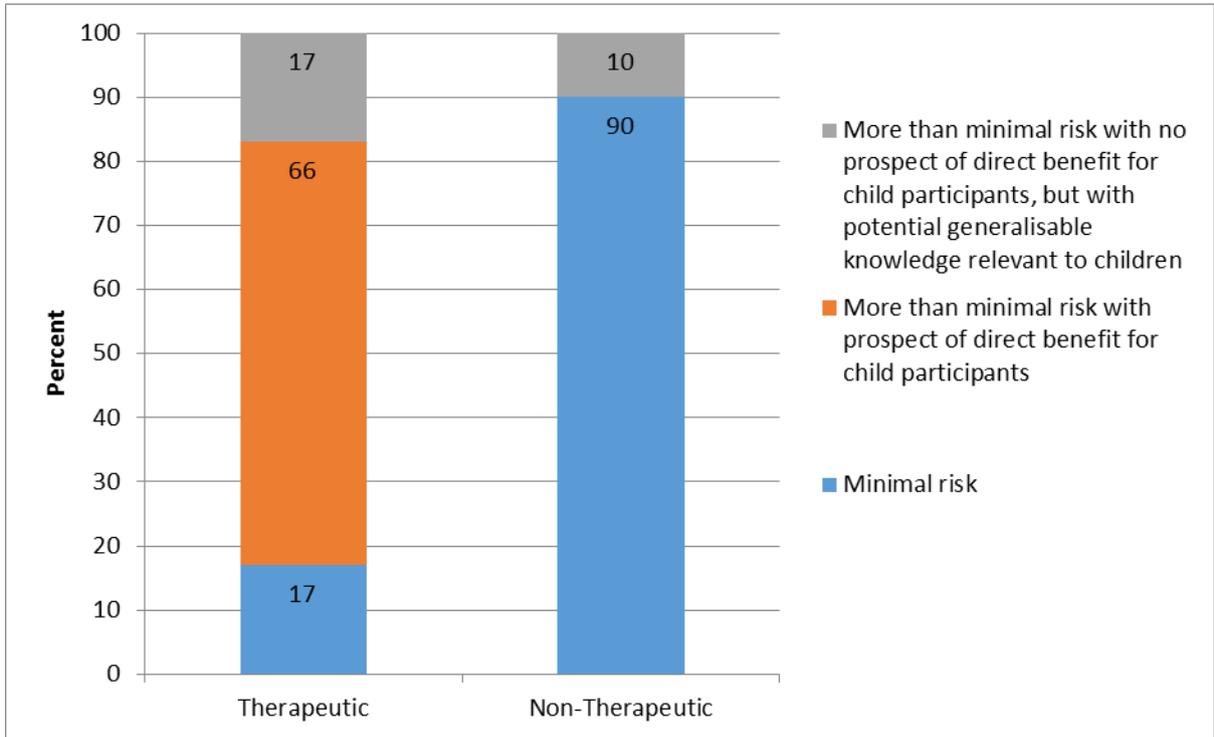


Figure 2: Level of risk for child participants

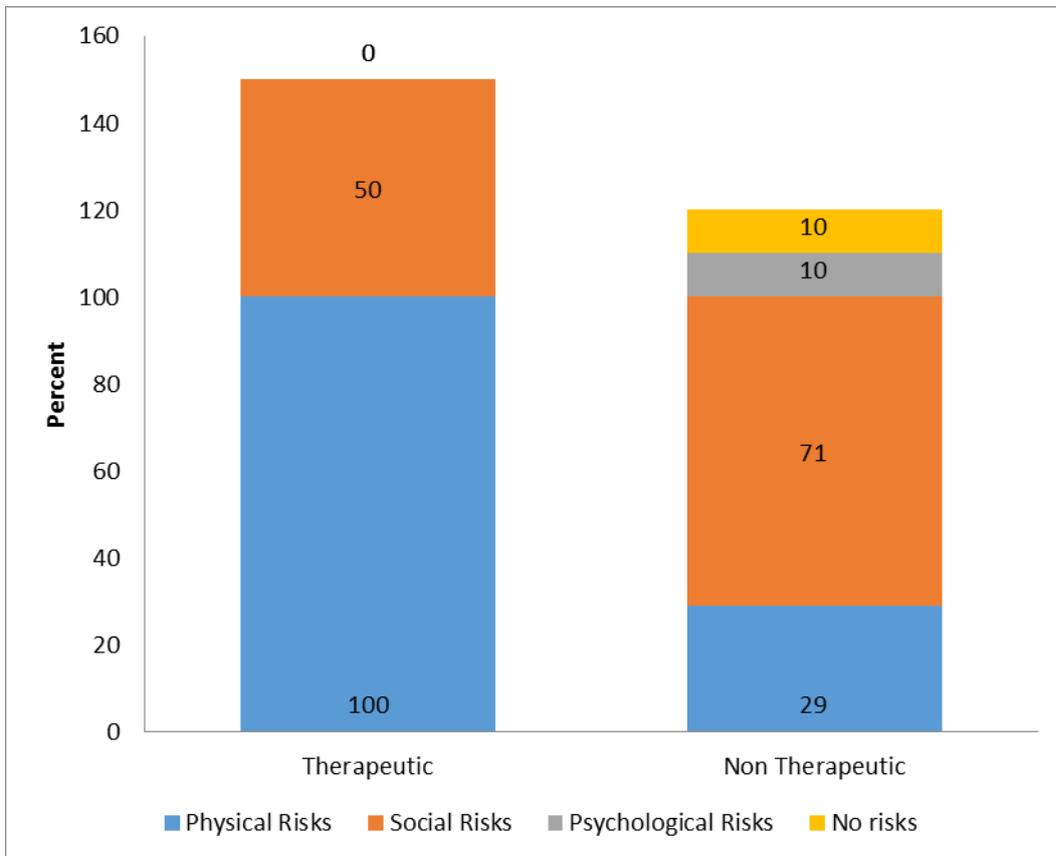


Figure 3: Type of risk for child participants (studies could include multiple types of risks).

5.2.3 Benefits for child participants

All therapeutic studies (49; 100%) presented the potential for direct benefits to the research participants. While the majority (42/49; 86%) of non-therapeutic studies did not offer direct benefit to the participants, 4% of non-therapeutic articles did offer direct benefits to the child participants. Benefits could not be determined in 10% of non-therapeutic articles.

5.2.4 Inclusion of more vulnerable child participants

It was not possible to determine whether more vulnerable children were included in any of the therapeutic studies. Just under half of non-therapeutic studies did not include any more vulnerable children (23/49; 47%), while the inclusion of more vulnerable children could not be determined in 18 (37%) of non-therapeutic studies, as study inclusion and exclusion criteria were not clearly defined in the article. Only 16% of non-therapeutic studies reported the inclusion of more vulnerable children, namely either physically or mentally disabled children or neonates.

5.3 Compliance of paediatric research with the NHA

5.3.1 Best interests of the minor

The research was in the best interests of children for all (55; 100%) of these published articles. In addition, the research objectives could not have been equally achieved if the research was conducted with adults.

5.3.2 Informed consent from child's parents or legal guardian and consent of the child

All six therapeutic research articles (100%) reported parental informed consent.

Slightly over three quarters (37/49; 76%) of the research articles reporting on non-therapeutic studies did not mention parental informed consent, while only 24% (12/49) reported it. None of the studies reported caregiver consent. (Figure 4). The majority of the studies (28/37; 76%) where consent was not mentioned involved retrospective research with a reported waiver of consent and with custodian of the data consent.

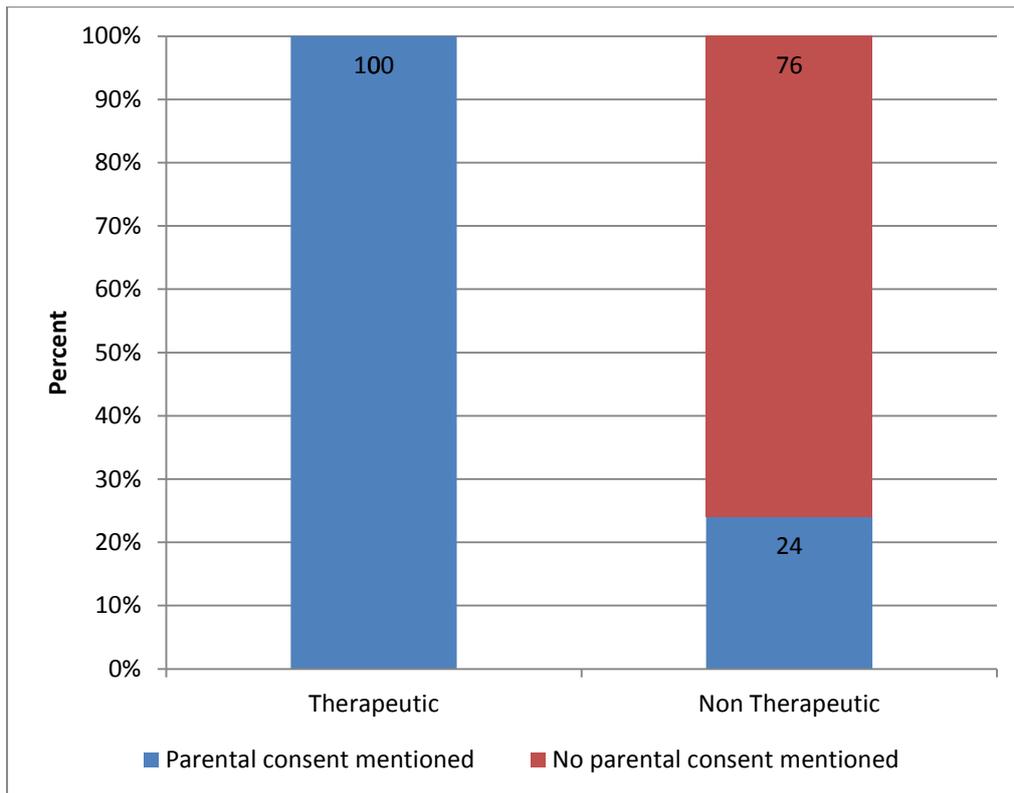


Figure 4: Informed consent from child’s parents or guardian

Child consent was not mentioned in 94% (46/49) of non-therapeutic studies and 67% (4/6) of therapeutic studies, as they were either retrospective studies (58%, 32/55) with a waiver of consent or involved children below the age of five years including neonates (4/6; 67%). However, a third of therapeutic studies 33% (2/6) mentioned that the child’s consent was obtained, while only 6% (3/49) of non-therapeutic studies mentioned children’s consent (Figure 5).

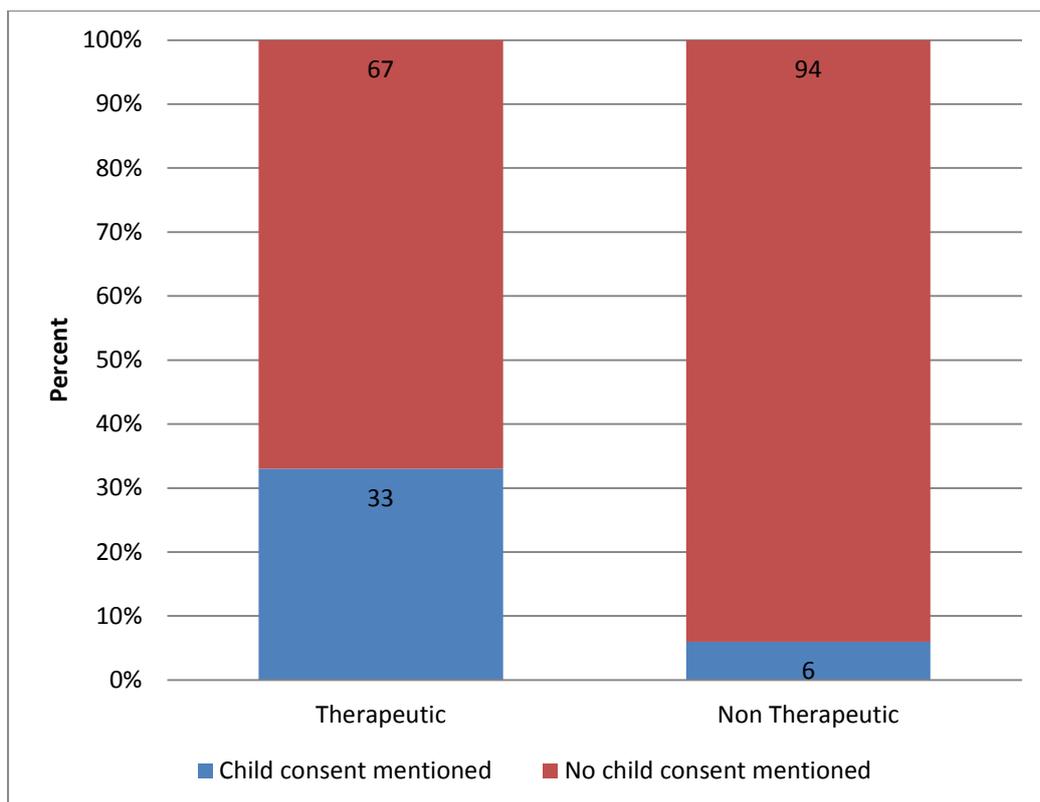


Figure 5: Consent from child participants

5.3.3 Approval by a REC

The majority of the articles (40; 73%) mentioned that approval was obtained from a REC, but this was not mentioned in the rest (27%). All therapeutic studies reported REC approval (6; 100%), compared to only 69% (34/49) reporting REC approval for non-therapeutic studies.

5.3.4 Motivation for involving children as research participants

Table 1 below summarises responses regarding the motivation for involving children as research participants. One third (2/6; 33%) of the articles reported therapeutic research, which compared treatment or treatment programmes regarding health care issues that concern children, while two other studies (33%) assessed the use of a medicine amongst neonates and infants. One of the six therapeutic studies (17%) assessed the effect of a medicine for a condition that affects only children, while one other study (17%) determined event-free survival in the treatment of endemic Burkitt lymphoma with cyclophosphamide and intrathecal methotrexate.

The majority (23%) of non-therapeutic articles described a certain condition that affects children, of which nine studies (19%) investigated a potentially better diagnostic or screening tool, while eight (16%) determined the prevalence of a condition that affects children. Five non-therapeutic articles reported pharmacokinetic studies. The other non-therapeutic studies

(6/49; 12%) examined the risk factors for a particular condition, 6% examined the outcome after a standard intervention for premature infants (surfactant and neonatal continuous positive airway pressure/NCPAP), 4% compared infection-related outcomes in an HIV-exposed uninfected population versus HIV-unexposed uninfected population, while another 4% assessed developmental outcome of children exposed to HIV. A few studies (2%) compared treatment or programmes on issues that concern children and 2% assessed vaccine immune responses in HIV-exposed but uninfected (HEU) and HIV-uninfected and -unexposed (HUU) infants. The remaining 2% described a nutritional programme used for the management of children with tuberculosis.

Table 1: Motivation for involving children as research participants

Motivation for involving children as research participants		Therapeutic or Non-therapeutic		Total
		Therapeutic	Non-therapeutic	
If yes, what is the motivation for involving children as research participants?	To determine prevalence of a condition that affects children	0 (0%)	8 (16%)	8 (14%)
	To assess the effect of a medicine for a condition that affects children	1 (17%)	0 (0%)	1 (2%)
	To compare treatment or programmes for issues that concern children	2 (33%)	1 (2%)	3 (5%)
	To compare infection-related outcomes in different populations	0 (0%)	2 (4%)	2 (4%)
	To establish a better diagnostic or screening tool	0 (0%)	9 (19%)	9 (16%)
	To examine the outcome of a certain condition or situation	0 (0%)	3 (6%)	3 (5%)
	To describe a certain condition that affect children	0 (0%)	11 (23%)	11 (20%)
	To determine risk factors for a particular condition	0 (0%)	6 (12%)	6 (11%)
	To assess vaccine immune responses in a comparative study	0 (0%)	1 (2%)	1 (2%)
	To improve the event-free survival	1 (17%)	0 (0%)	1 (2%)
	To assess the use of a medicine in a certain paediatric population	2 (33%)	5 (10%)	7 (13%)
	To assess developmental outcome of children exposed to a certain condition	0 (0%)	2 (4%)	2 (4%)
	To describe a programme used for the management of children's diseases	0 (0%)	1 (2%)	1 (2%)
	Total	6 (100%)	49 (100%)	55 (100%)

5.4 Compliance of paediatric research with the framework for ethical research proposed by Emanuel et al. (2004)

Using the ethical framework for research proposed by Emmanuel et al. (2004), this study revealed that a small majority (55%) of the articles involved multinational researchers. All the studies (100%) had a local principal investigator on the research team. All the studies posited potential benefit to children as a group and were found to be scientifically valid. Selection of study participants was found to be fair in 80% of the studies and could not be determined in 20% of the articles reviewed, due to the necessary information not being reported.

Only 15% (8/55) of the articles reviewed involved children who were thought to have been more vulnerable (disabled children, mentally handicapped children, neonates), while this could not be determined in the other articles. Nonetheless, all studies (100%) were thought to have provided a favourable risk-benefit ratio overall. The majority of the articles (73%) mentioned REC approval, while 27% of the articles did not mention REC approval. Articles reporting therapeutic studies were much more likely to mention approval of research by a research ethics committee (100%; n=6) compared to 69% (34/49) of non-therapeutic studies. About 31% (15/49) of articles reporting non-therapeutic studies did not mention that approval was obtained from an REC.

The acquisition of parent/guardian consent and assent are reported above (Figures 4 and 5). Translation of consent form into the local language of the host community was not reported in 96% of the articles, thus only 4% of the studies mentioned translated consent forms in the local language of the host community. It was found that supplementary community and familial consent procedures (e.g. proxy consent from a custodian) were reported in 49% of the studies, not needed in 45% of the studies, while could not be determined in 6% of the articles. The measures that were put in place to protect the confidentiality and privacy of research participants included anonymising records and samples (11%) and reporting research findings anonymously (100%).

Table 2: Frequencies on data extracted using the Emanuel et al. (2004) eight benchmarks

Variable	n (%)
Collaborative partnership	
<i>Was it a multinational research?</i>	
Yes	30 (55%)
No	25 (45%)
<i>Were there any local principal or co-investigators on the research team?</i>	
Yes	55(100%)
Social value	
<i>Who were the beneficiaries of the research?</i>	
Children as a group	55 (100%)
Scientific validity	
<i>Was the scientific design appropriate?</i>	
Yes	55 (100%)
Fair selection of study population	
<i>Was participant selection fair?</i>	
Yes	44 (80%)
Not able to determine	11 (20%)
<i>Were there any more vulnerable children (disabled, mentally handicapped, etc.) involved in the study?</i>	
Yes	8 (15%)
Not able to determine	47 (85%)
Favourable risk-benefit ratio	
<i>Did the study provide a favourable risk-benefit ratio?</i>	
Yes	55 (100%)
Independent review	
<i>Approval by a Research Ethics Committee mentioned in the article</i>	
Yes	40 (73%)
No	15 (27%)
Informed consent	
<i>Was the consent form translated into the local language of the host community?</i>	
Yes	2 (4%)
Not reported	53 (96%)
<i>Was there any need for supplementary community and familial consent procedures (e.g. proxy consent from a custodian)?</i>	
Yes	27 (49%)
No	25 (45%)
Not able to determine	3 (6%)
Respect for recruited participants and study communities	
<i>Measures put in place to protect the confidentiality and privacy of research participants?</i>	
Records and samples were anonymised.	6 (11%)
Research findings were reported anonymously.	55 (100%)

5.5 Summary of findings

An analysis of all the articles published by academic staff members of the Department of Paediatrics and Child Health at Stellenbosch University from 1 March 2012 – 31 March 2013 using the South African National Health Act (NHA) (No. 61 of 2003) Section 71 revealed that the majority of the child studies involved non-therapeutic research (49/55; 89%), of which the majority (65%) were retrospective studies. All research was done in the best interests of the class/group of children and could not equally have been achieved if the research was conducted on an adult. Non-therapeutic studies were significantly likely to report research not involving greater than minimal risk (89%), and most of the risks presented included potential social risks (71%). Therapeutic studies, on the other hand, were likely to report research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (67%). Potential risks mostly presented by therapeutic studies included physical risks (100%). Overall, the articles reported research that presented a favourable risk-benefit ratio.

With regard to obtaining consent from the child's parent/guardian, it was observed that therapeutic studies were more likely to mention the acquisition of parent/guardian consent (100%), compared to non-therapeutic studies; however, it was established that this requirement was not applicable in most cases (57%), as these mostly involved retrospective studies with a waiver of consent. However, in terms of assent, it was found that obtaining a child's assent was most likely to be not applicable in both non-therapeutic (38/49; 78%) and therapeutic (4/6; 67%) studies, due to the child's age or as they were retrospective studies. Overall, most articles mentioned that approval from a REC was obtained (73%), with therapeutic studies more likely to mention it than non-therapeutic studies. In response to the impact of the NHA on paediatric research, it is clear that non-therapeutic research should require less stringent measures as they mostly involve minimal risk.

According to the eight benchmarks for ethical research proposed by Emanuel et al. (2004), most studies were multinational with a local principal investigator, and all were scientifically valid. All studies reported benefits for children as a group, while selection of study participants was fair for the majority (80%) and only 14% of articles reported involving more vulnerable children. Translation of consent form into the local language of the host community was not reported in almost all studies. Measures that were put in place to protect the confidentiality and privacy of research participants included anonymising records and samples (11%) and reporting research findings anonymously (100%). The ethical benchmarks for ethical research were therefore found suitable for ethics review of paediatric research.

CHAPTER 6

DISCUSSION

6.1 Introduction

This study investigated the potential impact of compliance of paediatric research with the South African National Health Act (No. 61 of 2003), as well as with the ethical benchmarks for clinical research as proposed by Emanuel et al. (2004).

6.2 Impact of the National Health Act (No. 61 of 2003) Section 71 on essential research with children

For all of the articles reported, the research objective could not equally have been achieved if the research was conducted with adults, which is consistent with the Republic of South Africa (2004). While this is not necessarily a general requirement of Section 71, it is however an ethical obligation. Section 71 only makes it a consideration that must be taken into account in assessing whether or not to grant ministerial consent for non-therapeutic research involving children.

As Burns (2003) has indicated, extrapolating results from studies carried out on adults and generalising their findings to children may not be safe as the biological responses to disease and appropriate prevention or treatment strategies change in fundamental ways throughout childhood. Understanding the relationship between childhood development and disease can only be gained by performing research involving children at various ages and stages of their development, which is also essential for the development of appropriate interventions or treatment strategies to promote child health (Cleaton-Jones & Vorster, 2009).

In the South African National Health Act (No. 61 of 2003), Section 71(2) necessitate that a child's 'best interests' be considered when approving therapeutic research, but is not a requirement for non-therapeutic research (Strode et al., 2005b). The best interest of the minor is defined as ensuring that "significant decisions affecting the minor's life should aim to promote, amongst others, the minor's physical, mental, moral, emotional and social welfare (South African Government, 2014). This study investigated 'best interests' for both therapeutic and non-therapeutic research and established that all research was conducted in the best interests of the class/group of children, although not necessarily in the best interests of the individual child participant. Although all therapeutic research benefited child participants directly as compared to non-therapeutic research, it was also more likely to present greater than minimal risk, but with a favourable risk-benefit ratio. Kopelman (2000)

indicated that balancing the best interests of children as a group in research and protecting the rights and welfare of individual research participants presents a difficult ethical and social problem. He argues that, until research is conducted, it is difficult to know if treatments will be safe or effective, while the testing may harm some participants. Department of Health (2015), *Guidelines on Ethics in Health Research: Principles, Processes and Structures* also indicate that the best interest principle is difficult to apply in the research context because research participation is unlikely to be in the best interest of a minor. These Guidelines state that good research design does not accommodate a best interest analysis easily.

Salter (2012) criticises the best interests standard as the ideal ethical and legal standard of decision making for children and argues that it should be rejected as it is often applied with too much inconsistency and confusion. According to Strode et al. (2005c), the principle of best interests of a child demands an assessment of whether submitting children to a particular intervention is in their best interests by weighing up various factors, such as the probability and magnitude of risks, as well as benefits. It requires risk to be determined on an individual basis rather than setting an objective standard independent of the particular class of children. Strode and colleagues argue that this individual application has been held to be both the strength and the weakness of the best interests principle (Strode et al., 2005c). There is therefore a need to establish the criteria that can be used to apply the 'best interests of the child' principle in a non-individualistic way, so that it is useful in the context of research. Otherwise, it might be difficult to conduct research that may not necessarily be in the best interests of the individual child, but for the group or class of children, for example therapeutic studies that involve the use of a placebo.

Unlike the South African National Health Act (No. 61 of 2003), the United States Code of Federal Regulations for research involving human subjects (45 Part 46) (US Department of Health and Human Services, 2005) does not require the best interests of the minor to be considered but rather that a risk-benefit analysis should be conducted (Republic of South Africa, 2004; US Department of Health and Human Services, 2005). This includes assessing whether risks to the child will be minimal or greater than minimal risk, and assessing whether there are prospects of direct benefits to the child. However, the US regulation does permit research that might not necessarily benefit the individual child but have substantial future benefits to children other than the subject, as long as the potential risk is a minor increase over minimal risk (US Department of Health and Human Services, 2005).

The NHA stipulates that research with children may not be approved if, amongst others, it poses a 'significant risk' to the health of a child, or 'some' risk that is not outweighed by

benefit. This only applies to non-therapeutic research and it is a requirement that applies to the granting of ministerial consent.

However, no definition is provided of 'significant risk', and this is not provided for in other South African guidelines (Strode et al., 2005a). As a result, this study used risk levels described in the Department of Health (2015), Guidelines on Ethics in Health Research: Principles, Processes which are also similar to the United States Code of Federal Regulations on research involving human subjects, 45 CFR 46 (Sub Part D), to evaluate the level of risk that children were exposed to while also taking into consideration the type of research in which they participated (US Department of Health and Human Services, 2005). A large majority of the studies (82%) involved risks not greater than minimal risk, including 90% of the non-therapeutic studies not involving greater than minimal risk.

Therapeutic studies, on the other hand, were likely to report research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants (66%). Potential risks presented by therapeutic studies mostly included physical risks (100%). Although the South African National Health Act Section 71(3)(a)(iv) describes a risk standard for non-therapeutic research, no risk standard is described for therapeutic research (Strode et al., 2005b). The findings of this study reveal that although a risk standard is considered for non-therapeutic studies, most of them are likely to involve a risk not greater than minimal risk, while on the other hand, therapeutic research is likely to involve a risk greater than minimal risk. This means that children participating in therapeutic studies are likely to be exposed to more risk compared to those who participate in non-therapeutic studies, although the therapeutic research usually presents the prospect of direct benefit to the individual participants. Therefore, this requirement should be amended to ensure that children are adequately protected. This will also ensure that the Act is consistent with the South African ethical guidelines which do not divide research into therapeutic and non-therapeutic but apply a uniform risk standard to all types of studies (Department of Health, 2015).

In the National Health (Act No. 61 of 2003), Section 71 stipulates that research involving children should be conducted with the consent of the parent or guardian of the child, and the consent of the minor if the minor is capable of understanding (Republic of South Africa, 2004). This study revealed that the child's consent and parent/guardian consent were not mentioned in the majority of the articles reporting non-therapeutic research, as the majority were retrospective studies (58%) with less than minimal risk. These retrospective studies involved review of patient records without any direct interaction with the minors, and a waiver

of consent for both the parent/guardian and the minors' consent were requested. The parental/guardian mandatory consent, stipulated in the NHA, may effectively prohibit retrospective paediatric research and this may ultimately harm the population it purports to benefit (Human Sciences Research Council, 2012). The South African Department of Health's *Ethics in health research: Principles, structures and processes* (Department of Health, 2015) recognises the special circumstances under which retrospective research is conducted, and provides that where data is collected from records, either retrospectively or prospectively, a research ethics committee may approve access to identified or potentially identifiable data without seeking the consent of those whom the data identifies. It is still very important for the NHA to be reconciled with these guidelines on the issue of consent for retrospective studies so as to ensure that children do not miss out on participating in important research because of the challenges with inconsistent regulations (Worku et al., 2016). In addition, the finding that no studies reported caregiver consent could mean that those children' whom did not have parents or guardians to consent on their behalf were excluded from research participation in order to be compliant with the Act. As a result, it is argued that caregiver consent should be recognised for certain types of research so that those who do not have parents or guardians are also provided with an opportunity to participate in research and derive any potential benefits that could come with such research participation.

The US code of federal regulations for research with human subjects (45 CFR 46.116) allows for waiver of informed consent (including for child research) in certain situations including research that involves no more than minimal risks and where the research could not practically be carried out without the waiver or alteration of informed consent; this includes retrospective studies (US Department of Health and Human Services, 2005). Scholars have previously pointed out the shortcomings in the existing ethical-legal framework in South Africa and have recommended revision of a number of issues within this framework (Worku et al., 2016). Worku et al. (2016) argue that the current requirement in the NHA for consent of either the parent or legal guardian of a child research participant may limit or exclude participation in research of minors living with their caregivers, as caregivers have no explicit authority under the Act. This requirement is not consistent with the Department of Health's *Ethics in health research: Principles, structures and processes* (2015), which allows for caregivers to act as parental proxies when consenting for child participation in research in situations where there are no parents or legal guardians (Department of Health, 2015). Strode et al. (2014), also argue that this exclusion of caregivers by the Act is not consistent with the Children's Act which recognises that

caregivers may consent to certain health interventions such as medical treatment and HIV testing on behalf of children. Therefore, this inconsistency needs to be addressed (Worku et al., 2016).

6.3 Compliance of studies with the with the proposed Emanuel et al. (2004) framework

In applying the ethical benchmarks of Emanuel et al. (2004) to the results of the study, all studies (100%) were authored by a local investigator as the principal investigator. Just over half of the studies (55%) also involved collaborators from outside South Africa. This is important for child research in that a collaborative partnership could ensure that the conduct of the research is in line with the local context, build local capacity for conducting child research, as well as facilitate the sharing of research benefits to the research participants or children as a group (Emanuel et al., 2004).

All the articles reviewed had a favourable risk-benefit ratio and were likely to benefit children as a group, which is consistent with the benchmarks for a favourable risk-benefit ratio proposed by the Emanuel et al. framework (Emanuel, Wendler & Grady, 2000 in Emanuel et al., 2004). The scientific design was appropriate in all the articles reviewed, again in line with the need for scientific validity proposed by Emanuel et al. (2004) (Emanuel, Wendler & Grady, 2000 in Emanuel et al., 2004).

Participant selection was fair in the majority of the articles (80%), and not able to be determined in 20% of the articles reviewed. The benchmarks for ethical research proposed by Emmanuel and his colleagues state that in terms of the requirements for fair subject selection, first and foremost is that the study population should be selected for scientific reasons. The vulnerability of the selected study population should also be taken into consideration, and measures be put in place to safeguard and protect the population; these include ensuring confidentiality and freedom to refuse participation in the study (Emanuel et al., 2004). This requirement concerning vulnerability was well adhered to in most articles that were reviewed, as only 15% of the articles reported research that involved children who were more vulnerable (disabled, mentally handicapped, neonates).

A significant majority (73%) of the articles mentioned that approval from a REC was obtained. This is a requirement for ethical research as outlined in the benchmarks proposed by Emmanuel and his colleagues, who indicated that independent ethical review is required for all clinical research protocols. This ensures accountability and also addresses issues of conflict of interest amongst researchers (Emanuel, Wendler & Grady, 2000 in Emanuel et al., 2004). This is also consistent with international guidelines (The Belmont Report, 1979;

Council for International Organizations of Medical Sciences, 2002; World Medical Association, 2013), as well as the South African National Health Act (No. 61 of 2003) Section 71 which requires approval from a REC for any research involving human participants.

Just under half (49%) of the articles reported research that needed to obtain community or familial consent. In some cases, researchers may need to acquire permission at different levels, for instance from village elders to heads of households, before asking for the consent of the actual participants (Weijer & Emanuel, 2000 in Emanuel et al., 2004). However, it should be noted that most of the studies reported were retrospective (58%); hence, community or familial consent were not necessary in these cases.

All articles reported research findings anonymously. This was a strategy to protect participants' confidentiality. According to Emanuel et al. (2004), researchers continue to have an obligation to all research participants including their local community throughout the conduct of the study. The first and most important obligation includes devising and implementing measures to ensure that participants' information is kept confidential. As the Council for International Organizations of Medical Sciences (2002) guidelines have indicated, one of the ways of protecting participants' confidentiality is anonymising data, so that participants cannot be identified in the study.

In conclusion, all the studies/articles reviewed were compliant with the benchmarks proposed by Emanuel et al. (2004), and these were therefore useful in determining whether proposed paediatric research is ethically acceptable. This is a comprehensive framework as it covers most of the elements of ethical research outlined in international guidelines like the Declaration of Helsinki (Council for International Organizations of Medical Sciences, 2002; World Medical Association, 2013). This assertion is consistent with the argument by Tsoka-Gwegweni and Wassenaar (2014), who indicated that the Emanuel et al. (2004) framework was designed as a universal tool for use in many REC settings.

CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

7.1 Conclusions

It is important to assess compliance with and the implications of national regulations, especially in contexts where such regulations have been recently enacted as in the case of the SA NHA (No. 61 of 2003) Section 71. This assists in identifying the impact of such legislation and guidelines on essential research. It is clear from this study that defining paediatric research as therapeutic or non-therapeutic research according to the South African National Health Act (No. 61 of 2003) is not particularly useful in ensuring that children benefit from research, nor does it adequately protect them from harm. The emphasis on acquisition of parent or guardian consent could make it difficult to conduct retrospective studies and/or emergency research, which may not be possible without waiver of consent (Republic of South Africa, 2004). In addition, having a risk standard for non-therapeutic research, but not for therapeutic research, does not protect children, as this study established that therapeutic research was more likely to pose more than minimal risk. It will be in the interests of paediatric research if the NHA can be revised to include risk-benefit assessment, similarly to the United States Code of Federal Regulations on research involving human subjects, 45 CFR 46 (Sub Part D), to ensure adequate protection of children in health research. The benchmarks for ethical review proposed by (Emanuel et al. (2004)) were found to provide a useful framework for ethics review of paediatric research.

7.2 Recommendations

The promulgation of legislation that governs the conduct of research involving human participants, especially children, by the South African government is commendable. Efforts to improve the South African National Health Act (No 61 of 2003) Section 71 might include the following:

1. A risk-benefit analysis should be required for all research involving children. The findings of this study reveal that, although a risk standard is considered for non-therapeutic studies, most of these studies are likely to involve a risk not greater than minimal risk, while therapeutic research, on the other hand, is likely to involve a risk greater than minimal risk. This means that children participating in therapeutic studies are likely to be exposed to more risk compared to those who participate in non-therapeutic studies, although therapeutic research also usually presents the prospect of direct benefit to the individual participants. Therefore, this calls for a risk standard to be considered in all types of research, regardless of whether it is non-therapeutic or

therapeutic. Potential risks should be considered in relation to the potential benefits of conducting the study so as to determine if the study will be worthwhile to conduct.

2. The requirement to assess a child's 'best interests' when approving therapeutic research is not helpful in determining whether the research is ethically acceptable. Most research is done in the best interests of children as a group. Although it is usually advisable to assess whether the children will derive any direct benefits from the study, it is not really important to consider whether the study is in the best interests of the individual child in order to make an ethical decision on whether the study should be approved or not. Instead, the requirement could be rephrased to assess whether the research promotes the best interests of children as a group without violating the rights and interests of the individual child participants (World Medical Association, 2013).
3. The NHA should be aligned to other existing guidelines on the issue of consent such as the South African Department of Health's *Ethics in health research: Principles, structures and processes* (Department of Health, 2015), which allow for waiver of consent when conducting retrospective studies and caregiver consent in certain circumstances, as well as the South African GCP guidelines which allow for waiver of parent or guardian consent in exceptional circumstances (e.g. emergencies) (Department of Health, 2006).
4. The benchmarks for ethical review proposed by Emanuel et al. (2004) are comprehensive and cover most of the elements of ethical research outlined in international guidelines like the Declaration of Helsinki (World Medical Association, 2013) and the Council for International Organizations of Medical Sciences (2002). These benchmarks include collaborative partnership, social value, scientific validity, fair selection of study population, favourable risk-benefit ratio, independent review, informed consent, and respect for recruited participants and study communities. Further research assessing the proposals submitted for ethical clearance is recommended to establish the compliance with the SA NHA versus the eight benchmarks of ethical research proposed by Emanuel et al. (2004). It is believed that such study would generate more comprehensive results, as research proposals are usually more detailed compared to published articles.

CHAPTER 8

STUDY LIMITATIONS

The main limitation of this study is that some of the articles reviewed did not have all the detailed information relevant for answering some of the study questions. It was not possible to review the original research proposals as the local REC did not consent for the researcher to access these protocols. The purposive selection of the sample, as well as the limited sample size and scope, also limits the generalisability of the study findings to the rest of child research conducted in South Africa. However, the findings will contribute to informing policy-makers and other stakeholders on the feasibility of the National Health Act (No. 61 of 2003) Section 71 in its current form in promoting the best interests of children through research. The benchmarks for ethical research proposed by Emanuel et al. (2004) could be used to enhance the NHA so as to promote the best interests of children in research. More in-depth qualitative research reviewing research proposals submitted for ethical clearance could build on the conclusions made in this study, and perhaps gather additional information on the implications of the NHA for child research.

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APPENDIX A: Humanities and Social Sciences REC Approval



19 May 2015

Ms Dimpho Ralefala 211560787
School of Applied Human Sciences - Psychology
Pietermaritzburg Campus

Dear Ms Ralefala

Protocol reference number: HSS/0110/015M

Project title: Compliance of Paediatric Research with the South African National Health Act No. 61 Of 2003.

No Risk Approval

In response to your application dated 03 March 2015, the Humanities & Social Sciences Research Ethics Committee has considered the abovementioned application and the protocol have been granted **FULL APPROVAL**.

Any alteration/s to the approved research protocol i.e. Questionnaire/Interview Schedule, Informed Consent Form, Title of the Project, Location of the Study, Research Approach and Methods must be reviewed and approved through the amendment/modification prior to its implementation. In case you have further queries, please quote the above reference number.

Please note: Research data should be securely stored in the discipline/department for a period of 5 years.

The ethical clearance certificate is only valid for a period of 3 years from the date of issue. Thereafter Recertification must be applied for on an annual basis.

I take this opportunity of wishing you everything of the best with your study.

Yours faithfully

.....
Dr Shenuka Singh (Chair)

/px

cc Supervisor: Professor Mariana Kruger
cc Academic Leader Research: Professor D McDonald
cc School Administrator: Mr Sbonelo Duma

Humanities & Social Sciences Research Ethics Committee

Dr Shenuka Singh (Chair)

Westville Campus, Govan Mbeki Building

Postal Address: Private Bag X54001, Durban 4000

Telephone: +27 (0) 31 280 3587/8350/4557 Facsimile: +27 (0) 31 260 4809 Email: ximbap@ukzn.ac.za / snymnm@ukzn.ac.za / mohunp@ukzn.ac.za

Website: www.ukzn.ac.za


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APPENDIX B: Review checklist

SECTION A: SA NATIONAL HEALTH ACT NO 61 OF 2003

Unique Identifier:

<p>1. Specific ages:</p> <ol style="list-style-type: none">1. 0 – 28 days(Neonates)2. Under 1 year3. 1 – 5 years4. 6 – 11 years5. 12 – 17 years <p>2. Type of study:</p> <ol style="list-style-type: none">1. Prospective2. Retrospective3. Literature Review4. Case Report5. Editorial
<p>3. Was the research therapeutic or non-therapeutic? (tick box)</p> <ol style="list-style-type: none">1. Therapeutic2. Non-therapeutic
<p>4. If therapeutic, was it clinical or an intervention? (tick box)</p> <ol style="list-style-type: none">1. Clinical2. Intervention8. Not applicable <p>5. Was the research in the best interest of the minor? (tick box)</p> <ol style="list-style-type: none">1. Yes2. No
<p>6. If non-therapeutic, was it: (tick box)</p> <ol style="list-style-type: none">1. Social2. Educational3. Psychological4. Physiological5. Other (specify) _____7. Not applicable <p>7. Could the research objective be equally achieved if the research was conducted on an adult? (tick box)</p> <ol style="list-style-type: none">1. Yes2. No <p>8. Was the research or experimentation likely to yield significant results that will improve scientific understanding of the minor's condition, disease or disorder to such an extent that it will result in significant benefit to the minor or other minors? (tick box)</p> <ol style="list-style-type: none">1. Yes2. No

<p>9. Level of risk of the study: (tick box)</p> <ol style="list-style-type: none"> 1. Research not involving greater than minimal risk. 2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. 3. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalisable knowledge about the subjects disorder or condition. 4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. 												
<p>10. What were the potential risks to the children? (tick box)</p> <ol style="list-style-type: none"> 1. Physical risks 2. Social risks 3. Emotional/Psychological risks 4. Economic risks 5. Legal risks 6. No risks 7. Other (specify) _____ 												
<p>11. Did the research present a favourable risk-benefit ratio? (tick box)</p> <ol style="list-style-type: none"> 1. Yes 2. No 												
<p>12. Did the Principal Investigator (PI) provide sufficient motivation for the involvement of children as research participants? (tick box)</p> <ol style="list-style-type: none"> 1. Yes 2. No 												
<p>13. If yes, what is the motivation for involving children as research participants?</p> <ol style="list-style-type: none"> 1. To treat a child who presented with a rare condition. 2. To determine prevalence of a condition that affects children. 3. To find a cure or a solution for a condition that affects children. 4. To compare treatment or programmes to issues that concern children. 												
<p>14. Are consent and assent mentioned in the article? (tick box)</p> <table border="1" style="margin-left: 40px; border-collapse: collapse; width: 80%;"> <thead> <tr> <th style="width: 60%;"></th> <th style="width: 15%;">Yes</th> <th style="width: 15%;">No</th> <th style="width: 10%;">N/A</th> </tr> </thead> <tbody> <tr> <td>Consent for parent/guardian</td> <td>1.</td> <td>2.</td> <td>8.</td> </tr> <tr> <td>Assent for child</td> <td>1.</td> <td>2.</td> <td>8.</td> </tr> </tbody> </table>		Yes	No	N/A	Consent for parent/guardian	1.	2.	8.	Assent for child	1.	2.	8.
	Yes	No	N/A									
Consent for parent/guardian	1.	2.	8.									
Assent for child	1.	2.	8.									
<p>15. Is approval of research by a Research Ethics Committee mentioned in the article? (tick box)</p> <ol style="list-style-type: none"> 1. Yes 2. No 												

SECTION B: FRAMEWORK FOR ETHICAL RESEARCH PROPOSED BY EMANUEL et al. (2004)

A. Collaborative partnership (tick box)

1. Was it a multinational research study?
 1. Yes
 2. No

2. Were there any local principal or co-investigators on the research team?
 1. Yes
 2. No

3. Was any research-related training for the local stakeholders (e.g. research staff) conducted?
 1. Yes
 2. No
 9. Not able to determine

4. Were there any provisions for appropriate compensation for participants?
 1. Yes
 2. No
 9. Not able to determine

5. Were there provisions for fair benefit sharing?
 1. Yes
 2. No
 9. Not able to determine

B. Social value (tick box)

1. Who were the beneficiaries of the research?
 1. Research participants
 2. Children as a group
 3. Community

2. Were there any direct benefits to participants? (tick box)
 1. Yes
 2. No

3. If yes, what were the benefits of the research to the participants?

4. Was there any provision of ancillary care to the study participants? (tick box)
 1. Yes
 2. No
 9. Not able to determine

5. If yes, which kind of ancillary care was provided?
 1. Counselling
 2. Treatment to other conditions not being studied
 3. Palliative care

C. Scientific validity (tick box)

1. Was the scientific design appropriate?
 1. Yes
 2. No

D. Fair selection of study population (tick box)

1. What was the justification for including children in the study?
 1. To treat a child who presented with a rare condition.
 2. To determine prevalence of a condition that affects children.
 3. To find a cure or a solution for a condition that affects children.
 4. To compare treatment or programs to issues that concern children.
2. Was the population selected in such a way as to minimise the risks of the research?
 1. Yes
 2. No
 9. Not able to determine
3. Was participant selection fair?
 1. Yes
 2. No
 9. Not able to determine
4. Were there any more vulnerable children (disabled, mentally handicapped, etc.) involved in the study?
 1. Yes
 2. No
 9. Not able to determine
5. If yes, which measures were put in place to ensure their protection?
 8. Not applicable
 9. Not able to determine

E. Favourable risk-benefit ratio (tick box)

1. Did the study provide a favourable risk-benefit ratio?
 1. Yes
 2. No

F. Independent review (tick box)

1. Is approval of research by a Research Ethics Committee mentioned in the article?
 1. Yes
 2. No

G. Informed consent (tick box)

1. Was the community consulted in establishing recruitment procedures and incentives (refreshment, transport, etc.)?
 1. Yes

- 2. No
- 9. Not able to determine

- 2. If yes, who in the community was consulted?
 - 8. Not applicable
 - 9. Not able to determine

- 3. Was the consent form translated in the local language of the host community?
 - 1. Yes
 - 2. No
 - 8. Not applicable
 - 9. Not able to determine

- 4. Was there any need for supplementary community and familial consent procedures (e.g. proxy consent from a custodian)?
 - 1. Yes
 - 2. No
 - 8. Not applicable
 - 9. Not able to determine

- 5. If yes, how did the article outline how it will be achieved?

H. Respect for recruited participants and study communities (tick box)

- 1. What measures were put in place to protect the confidentiality and privacy?
 - 1. Data and samples were anonymised.
 - 2. Data was kept in locked cabinets and/or protected passwords.
 - 3. Access to data was restricted.
 - 4. Data collection done in a secure and private location.
 - 5. Research findings were reported anonymously.