Research with children: Compliance with Section 71, South African National Health Act 61 of 2003

Irene Honam Tsey
Student Number: 214580934

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Supervisors: Prof Mariana Kruger, Dr Nicola Barsdorf
South African Research Ethics Training Initiative
(SARETI)

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Declaration

I do hereby declare that the thesis titled "Research with children: compliance with Section 71, South African *National Health Act 61 of 2003*" is my own work, which I hereby submit for the degree of Master of Social Sciences at the University of KwaZulu-Natal, Pietermaritzburg. This is my own work and has not been submitted for a previous degree at any other tertiary institution.

Signature:  Date: 1 March 2017

Full name: Irene Honam Tsey

Supervisor

Signature: _____ Date: 1 March 2017

Full name: Professor Mariana Kruger

Co-Supervisor

Signature: _____ Date: 1 March 2017

Full name: Dr Nicola Barsdorf

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Abstract

Health research with children is important to ensure access to potential benefits. However, these studies must comply with national legal and regulatory requirements, which should not impede essential paediatric research. This study evaluated the potential compliance with section 71 of the current South African National Health Act No. 61 of 2003 (NHA) by essential research with children prior to promulgation of section 71. The study aimed to compare therapeutic and non-therapeutic research with children according to: research type, risk-type and risk-level, the presence of direct benefit, and the involvement of more vulnerable children. The study also aimed to investigate the extent to which paediatric research was compliant with Section 71 of the SA NHA, as well as with the eight benchmarks of ethical research proposed by Emanuel et al (2004).

Sixty-eight child research publications published between 1st January 2013 and 1st January 2015 from a single academic paediatric department were systematically analysed. Concepts that are very key and relevant to the South African National Health Act and the Emanuel et al. (2004) benchmarks were defined and analysed. The majority of the studies were non-therapeutic research (85%, n=58) and 15% (n=10) were therapeutic research according to the definitions of section 71 of the South African NHA. The vast majority of therapeutic studies (90%) involved *more than minimal risk*, while the majority (54%) of the non-therapeutic studies involved only *minimal risk*. There was direct benefit to child participants in 29% of the studies: 90 % of the therapeutic studies offered direct benefit; surprisingly also 21% of the non-therapeutic studies offered direct benefit. Findings from the study revealed that both therapeutic and non-therapeutic studies involved some degree of risk: 80% of the therapeutic studies posed physical risk and 1% social risk; only 40% of the non-therapeutic studies posed physical risk, 3% social risk and 2% psychological or economic risk.

All studies had appropriate motivation for the inclusion of children in research and could not be done with adults. The majority (77%) reported seeking parental/guardian consent, while 18% reported child assent and 79% reported ethics approval. All the studies protected confidentiality and privacy of child participants and were in the best interest of children. One of the studies allowed independent consent by child participants who were mothers. The proposed Emanuel ethics benchmarks were found to be useful in appropriate ethics review of

paediatric research. In the current Section 71 framework, more review attention (even by delegated RECs) is paid to non-therapeutic research. The findings of this study, however, highlight that the current Section 71 requirements for child research review may not be adequately protecting children from risk, since we ought to apply more stringent attention to risk-benefit assessment as the more risky therapeutic studies are currently enjoying a less stringent standard under the NHA. In conclusion, emphasis ought to be placed on risk-benefit assessment rather than the South African NHA section 71's therapeutic and non-therapeutic definitions of research involving children, because this distinction is problematic and may not serve the best interest of children.

Dedication

This work is dedicated to God Almighty who made my graduate programme a success. It is also dedicated to my family who have been of great support towards my pursuit of this programme.

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List of abbreviations

NHA: National Health Act

CIOMS: Council for International Organization of Medical Sciences.

DoH: Declaration of Helsinki

SAGCP: South African Good Clinical Practice

FDA: Food and Drug Administration

ICH: International Conference on Harmonisation

IRB: Institutional Review Board

NIH: National Institutes of Health

OHRP: Office of Human Research Protections

REC: Research Ethics Committee, also referred to as Institutional Review Board (IRB)

WHO: World Health Organization

Chapter 1: Introduction and background

There is an ethical imperative to conduct research with children (persons younger than 18), as per the definition in the South African Constitution (*South African National Health Act*, 2003), towards understanding the pathogenesis of their diseases as well as test the safety and efficacy of treatments for them (Nienaber, 2013). Although it is challenging to conduct research with children in low-income settings, such research is urgently needed as they form a considerable percentage of the total population in developing countries (Cheah & Parker, 2014). Children should, however, be protected and the studies must comply well justified norms as well as existing regulatory and legal requirements governing research with children. It is therefore of great importance for all stakeholders to be proactive to ensure the effectiveness of ethical guidelines, laws and ethical codes with respect to protecting the welfare and rights of research participants who are children, while at the same time promoting responsible beneficial research involving children.

This study aimed to investigate the extent of compliance of paediatric research with the current National Health Act (NHA) Section 71 and the eight benchmarks of ethical research proposed by Emanuel et al (2004) as well as their promoting beneficial research for children. This study analysed published paediatric research conducted at a single academic paediatric department of Stellenbosch University between the 1st March 2012 to 31st March 2013 in relation to their compliance with the South African *National Health Act No. 61 of 2003* (2004) before Section 71 was promulgated. The studies were also analysed according to the ethical framework proposed by Emanuel and colleagues (Emanuel, Wendler, Killen & Grady, 2004) for ethical research in developing countries.

Chapter 2: Literature Review

2.1 Research involving children is essential

Historically, the exclusion of children from clinical studies and other health research has resulted in many therapies prescribed, based on evidence extrapolated from adult clinical trials, without the appropriate investigation for their paediatric safety and efficacy (Brierley & Larcher, 2010; Caldwell, Murphy, Butow & Craig, 2004; Kanthimathinathan & Scholefield, 2014; Modi, Clark, Wolfe, Costello & Budge, 2013; Roberts, Rodriguez, Murphy & Crescenzi, 2003; Truog, 2008). Since children differ from adults in both physiological and cognitive processes, it may not always be feasible or appropriate to extrapolate adult study findings to them (Baren & Fish, 2005; Knox & Burkhart, 2007; Kopelman, 2000). In addition, extrapolated findings from adult studies may have inadequate relevance and cause harm to children due to their differences from adults noted above and therefore paediatric research should be undertaken to ensure access to safe and effective padiatric therapies (Cheah & Parker, 2014; Modi et al., 2014). (Brierley & Larcher, 2009; Luce et al., 2004; Modi et al., 2014; Truog, 2008; UK Medical Research Council (MRC), 2004; Weijer, 2004; World Medical Association (WMA), 2013). Nevertheless, clinical and sociological research with the population of children remains severely inadequate in low- and middle-income countries, including in South Africa (Morris, 2012). Limited research relevant to children implies that children are denied the potential benefits of research relevant to their specific needs and in the long term, the best interests of children as a group are not served, and children are exposed to avoidable risks (Modi et al., 2013; Truog, 2008). Furthermore, the assumption that vulnerable children (children who are disabled or mentally handicapped) should be provided with extra protection has resulted in a disinclination to include them in research that may benefit them (Wolfe, 2012).

2.2 Children are vulnerable

Children are vulnerable based on a number of factors including but not limited to the following: (i) they commonly lack the capacity to make mature decisions; (ii) they are subject to the authority of others; (iii) they (and their parents) may be deferential in ways that can mask underlying dissent; (iv) their rights and interests may be socially undervalued; (v) they may have acute medical conditions requiring immediate decisions not consistent with informed

consent; (vi) they may have serious medical conditions that cannot be effectively treated; and (vii) they (and their parents) may lack important socially distributed goods (Kipnis, 2003).

Protection of vulnerable research participants, especially children, is essential in research (Cavet & Sloper, 2005). Participants are vulnerable when they have limited or no capacity to protect their individual interests (CIOMS, 2016). In the context of research, the vulnerable are those who are more likely to be harmed and exploited (Lange, Rogers & Dodds, 2013). Such participants can be prone to both deliberate and unintended harm (Schwenzer, 2008). As noted above, children are particularly vulnerable since they have limited autonomy when their parents/legal guardians are providing the informed consent which is a requirement for their child's involvement in research (Strode, Slack & Essack, 2010a). Voluntary informed consent by parents may also be problematic, for example, in the context of schools as parents may feel that their refusal to consent to their child's involvement might damage the school services offered to their children if the research team includes school staff (Flewitt, 2005).

According to Morrow and Richards (1996), older persons tend to have the opinion that children are weak, a claim also enforced by the law, which views children as a powerless group with no responsibility. The vulnerability of children is also categorised in two ways, firstly, their vulnerability is owing to the fact that they are physically weak, with relatively little knowledge and experience. Secondly, they are structurally vulnerable due to their "lack of political and economic power and civil rights" (Lansdown, 1994, p. 35). Also, children are vulnerable because they do not always have the ability to express their needs and guard their interests (McIntosh et al., 2000), making them dependent on adults for their security and upkeep (Brierley & Larcher, 2011; Knox & Burkhart, 2007). Children in some settings such as those living in low- and middle income countries may be more vulnerable due to poor socio-economic circumstances and are more prone to die young (Sharp & Millum, 2015).

Children may also be particularly vulnerable in the context of research in emergency situations. This is because, during emergencies, parents may find themselves in a position of severe stress, with compromised decision-making ability due to extreme stress of the emergency, the time-critical nature of the intervention, or their own condition, such as a mother after delivery under general anaesthesia (Modi et al., 2014). As a result, if research participation is only possible with parental consent, this may prevent the participation of many new-borns and children in

emergency research (Roberts et al., 2013). Parents themselves may also be vulnerable (Shilling & Young, 2009) and not necessarily take decisions that are safe for their children (Flewitt, 2005).

The vulnerability of children makes it a complex process to promote their best interests as a group through research, while at the same time protecting their rights and welfare as individual research participants (Kopelman, 2000). However, while it may be complex, it remains essential to involve children in research towards addressing their unique health needs and promoting their best interests (Baren & Fish, 2005; Knox & Burkhart, 2007) while at the same time ensuring their protection (Cheah & Parker, 2014).

2.3 Current ethics guidelines and regulations for research with children

Guidelines vary in their protection of children, with some restricting children's participation in selected research whereas others deny their participation completely (Kopelman, 2014). More recently, there has been a move away from more restrictive ethics guidelines, which exclude children as participants in research, towards those that allow them to participate when there is an acceptable balance between risks and benefits.

'Therapeutic research' and 'non-therapeutic research' are terms sometimes used to differentiate types of research (McRae, 2005). The South African National Health Act states that therapeutic research involves research that holds out the prospect of direct health-related benefit for the child participant. On the other hand, non-therapeutic research involves studies that do not hold out the prospect of direct health-related benefit for the child participant, but the research aims to generate generalisable knowledge about the condition under study, and there is usually potential benefit to the class of child participants in future (Kopelman, 2000). The relationship between therapeutic and non-therapeutic research involving children is an issue debated upon as an ethical issue in the literature as well as in guidelines (Hull, 2000). The Declaration of Helsinki (World Medical Association, 2013) has moved away from the specific use of the terms 'therapeutic' and 'non-therapeutic' research to differentiate between acceptable and unacceptable research, by rather using risk-benefit assessment as guidance, making it comparatively less restrictive (Emanuel, 2003). Previous versions recommended that persons who lack the capacity to volunteer or give informed consent (for example, children) may only

be enrolled in therapeutic research (World Medical Association, 2008), while the current version (World Medical Association, 2013) specifies that research with the vulnerable is justified when it is intended to promote the health of the group represented by a potential research participant.

United States (U.S.) regulations mandate that children should be included in research unless their exclusion is justified by good scientific or ethical reasons (DHHS, 2009). The U.S. Common Rule Title 45 (Public Welfare) Code of Federal Regulations, Part 46 (45 CFR 46) Subsection D makes no distinction between research being 'therapeutic' or 'non-therapeutic' but rather uses a benefit-risk assessment (DHHS, 2009). The guideline categorises research involving children into four risk levels: (a) Research not involving greater than minimal risk; (b) Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects; (c) 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; 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. All applicable conditions under Subsection D of 45 CFR 46 are to be satisfied for all kinds of research involving children in order to merit an approval from a United States REC or Institutional Review Board (IRB). The guidelines balance the anticipated risks and benefits and look at the prospect of research benefits, who gets these benefits, and if the benefits are reasonable with regard to the associated risks. In terms of benefits, consideration is given to both direct benefits to research participants as well as benefits to the general population, especially the population of children and their well-being (DHHS, 2009).

The IRB has the sole mandate to review and approve research in the first three categories. The fourth category requires review and approval by the U.S. Food and Drug Administration (FDA) and/or the U.S. Department of Health and Human Services (DHHS) after consultation with experts in the field (DHHS, 2009). This category of research is considered for approval if it provides a justifiable reason to add to more knowledge in understanding and avoidance of severe health related problems that could affect the wellbeing of children (DHHS, 2009). This consideration, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either that the research in fact satisfies the conditions of all the other

categories, as applicable, or the following: (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) the research will be conducted in accordance with sound ethical principles; and (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians (DHHS, 2009).

If research has the prospect of direct benefit to the individual child participants, the risk considered acceptable could be greater than minimal, but should be justified by the anticipated benefit. For research involving no prospect of direct benefit to individual child participants, but likely to yield generalisable knowledge about the child's disorder or condition, the risk considered acceptable is a minor increase over minimal risk. The guidance is not specific as to how far from, or close to, minimal risk it should be for the fourth category of research, thus the fourth category is silent on the acceptable level of risk. All categories require the assent of the child as well as consent of their parent(s). Furthermore, the guideline makes provision for a waiver of parental consent when the IRB determines such consent is not a reasonable requirement for a particular study.

It is clearly imperative that children are protected from undue research risks. The U.S. federal regulations mandate IRBs to approve non-therapeutic research posing a minor increase over minimal risk when it involves children who have the disease or medical condition that the research addresses. However, the same type of research involving healthy children can only be conducted after approval from the Secretary of the Department of Health and Human Services. The ethical basis for the distinction between research involving healthy children and research involving children with a disease or medical condition has received limited attention. However, this distinction is considered ethically sound (Morris, 2012) and points to an alternate, and ethically more helpful, regulatory distinction in research involving children than the therapeutic/non-therapeutic research distinction. For example, the risk of radiation to a minor who has no medical need for it and the risk of the same radiation to a child who is used to such an experience due to a condition should not be overlooked. As a result, risk should be objectively assessed taking into consideration the context in relation to a child's experience of the condition (Modi et al., 2014).

While not as specific as the 45 CFR 46, but in line with the 45 CFR 46 (Subpart D), the CIOMS (2016) guidelines on children do not make a distinction between therapeutic and non-

therapeutic research. CIOMS (2016) recommends that research with children should be conducted to obtain knowledge relevant to the health of children, with the consent of parents/guardians as well as the assent of the child. The guidelines also give RECs the mandate to approve studies involving older children without necessarily obtaining parental consent, if the research topic is deemed sensitive (CIOMS, 2016). The CIOMS guideline also allows research on healthy children where it involves risks that do not exceed those associated with routine medical or psychological examinations i.e. minimal risk research (CIOMS, 2016). Emanuel argues that a slight increase over minimal risk should also be considered acceptable (Emanuel, 2003).

2.4 The South African National Health Act on research with children

The South African *National Health Act 61 of 2003* (2004) (NHA) Section 71 aims to protect research participants, including children (Strode, Grant, Slack & Mushariwa, 2005). Section 71 of the NHA which addresses requirements for research involving children came into effect in 2012 (Motsoaledi, 2014). This section specifies that if the proposed child research is for therapeutic purposes, the research may be conducted under the following conditions: if it is in the best interests of the child; with the consent of the parent or guardian of the child; and, if the child is capable of understanding, with the assent of the child (*South African National Health Act*, 2003). If the proposed child research is for non-therapeutic purposes, the same consent requirements apply. In addition however, after promulgation, the National Health Act (NHA) Section 71 required the consent of the minister for non-therapeutic research with child participants, irrespective of the level of risk (Strode et al., 2010a). The act required that even minimal-risk non-therapeutic research be reviewed by the minister; for example additional testing on routinely collected blood samples (Strode et al., 2010a) . Non-therapeutic research however provides generalisable information that may result in the improvement of the health of children in future. In this regard, the potential benefit of this non-therapeutic research stated above may supersede the associated risk of the research process (Strode et al., 2010a).

The requirement of ministerial review for all non-therapeutic research increased bureaucracy and the implication was that a large volume of non-therapeutic research protocols need the minister's approval (Strode et al., 2007). This study for example, would have been defined as non-therapeutics, requiring the approval of the minister as it does not hold direct benefits for

the child participant. In view of this many researchers would have been discouraged from conducting essential non-therapeutic research involving children (Strode et al., 2007). In addition, this publicised act did not include procedures on how ministerial consent was to be acquired (Morrow, Andrew & Kling, 2015). Following public objections in October 2014, ministerial consent was officially delegated to RECs registered with the National Health Research Ethics Council (Motsoaledi, 2014). The procedure for review of these non-therapeutic studies with children still however remains more onerous than that for review of therapeutic studies and RECs are required to review non-therapeutic research with children according to a stricter standard, regardless of the risk level.

Despite the evolution of both national and international regulations and guidelines to move away from this distinction between therapeutic and non-therapeutic research, the South African *National Health Act 61 of 2003*, section 71 emphasises this distinction. It is however, at times difficult to make the distinction between therapeutic and non-therapeutic studies (Nienaber, 2013). For example, therapeutic studies may have associated non-therapeutic interventions such as drawing blood for the purpose of research (Nienaber, 2013). The therapeutic and non-therapeutic distinction is also problematic for a number of other reasons. First, the focus on this distinction between therapeutic and non-therapeutic research may be misleading, arbitrary, or create false expectations (Kopelman, 1995; Nienaber, 2013). There is also sometimes the misconception that therapeutic research always offers solutions (Woods, Hagger & McCormack, 2014). In many instances, it is perceived that therapeutic research is associated with benefits whereas non-therapeutic research is not (Woods et al., 2014). This is not always true because, given clinical equipoise, therapeutic research may not guarantee effective treatment for participants (Woods et al., 2014). Although therapeutic research may have therapeutic intention, it is still however research, and as such has the intention of adding to knowledge, just as for non-therapeutic research (Woods et al., 2014).

Moreover, when participants understand therapeutic research to pose potential benefit such as cure for a disease (for example, in a patient suffering from a life-threatening disease), it may lead them to enrol in a study due to therapeutic misconception (Shilling & Young, 2009). Therapeutic misconception refers to instances where therapeutic research is confused with treatment (Nicholson, 1986). In the hope of receiving a cure or treatment for their children suffering from a life-threatening disease, parents may ignore potential excessive risks due to

false expectations as a result of the blurring between treatment and research associated with some prospect of therapeutic value (Shilling & Young, 2009). An example of therapeutic misconception is the belief of the parents that a child participant will derive direct benefit from a study intervention (Appelbaum, 2002; Durand-Zaleski et al., 2008; Kanthimathinathan & Scholefield, 2014; Luce et al., 2004; Mason, 1997; Molyneux et al., 2013; A. D. Morris, Zaritsky & LeFever, 2000; Oduro et al., 2008; Truog, 1999; Woolfall et al., 2013).

It is important to note that children may benefit indirectly from participating in research not related to medical intervention. Some scholars are of the view that the focus should not only be on the physical health of people which for the purpose of this study is children but also other aspects of their wellbeing (Barsdorf & Millum, 2017). Broström and Johansson (2014) argue that non-therapeutic research is necessary to improve medical care for children in general. Children also generally benefit when involved in research. These benefits can be more important than minor risks associated with research (Wendler, 2012). It is worthwhile involving children in some non-therapeutic research (Williams, 2012), while recognising that there are some associated limitations to using moral benefits as the main basis for justifying non-therapeutic research with children (Wendler, 2010). The decision about approval of all research studies should be steered by assessing carefully foreseeable risks in comparison with potential benefits to the individual and the group affected by the illness (Modi et al., 2014).

Current ethical guidelines governing research with children generally assert that procedures or components of the study that do not hold out the prospect of direct benefit should pose no more than minimal risk, or a minor increase over minimal risk. Procedures or components of the study that hold out the prospect of direct benefit must be reasonable in relation to the potential risks (Department of Health, 2006). Adolescent HIV vaccine trials for example could conceivably fit the requirements above. Many procedures in HIV vaccine trials will likely be classed as holding out the *prospect of direct benefit* with the potential direct benefit being in general, prevention of HIV infection. Other associated benefits could be (for example, physical examinations; medical history-taking; sexually transmitted infection (STI) testing; HIV testing; pregnancy testing; contraceptive provision; and circumcision assessments). These specific components would therefore not be held to minimal risk/minor increase over minimal risk, but would be held to a sound risk–benefit ratio and rigorous minimization of foreseeable risks. Some other trial procedures may hold out *no prospect of direct benefit* (for example, blood

draws for laboratory testing), and these procedures would need to approximate minimal risk/minor increase over minimal risk and be justified by the knowledge gained (Slack, 2011, p. 21).

Strode et al. (2010b) identify other areas with inconsistencies in Section 71 of the *National Health Act 61 of 2003*. These are in terms of the capacity of children to consent, who may not have the capacity, and the boundaries regarding the independence of children or their proxies to consent. Strode et al. (2010b) reported inconsistencies that would make stakeholders' interactions with children problematic in an effort to comply with legislation. The NHA is also not in harmony with other existing legislation. The Constitution of South Africa, as well as the South African Children's Act define a child as someone under 18 years of age. They therefore need the assistance of parents or legal guardians for consent (*South African Children's Act*, 2005; Strode et al., 2010a). However, Subsection 38 of the South African Children's Act states that children from 12 years of age can consent independently to medical treatment and other key health interventions, if they demonstrate 'sufficient maturity' (*South African Children's Act*, 2005). For example, they can consent to HIV testing from age 12, when it is in their best interests, and below the age of 12 years if they demonstrate 'sufficient maturity' (*South African Children's Act*, 2005). In addition, they can access contraceptives from the age of 12 and girls can consent to a termination of pregnancy at any age (*Choice of Termination of Pregnancy Act, 1996*; *South African Children's Act*, 2005).

Currently, the legal age for consenting independently to research is 18 years of age (Strode et al., 2010a). Research evaluating contraceptive usage among 17 year olds will be problematic, for example as these adolescents cannot consent independently and need their parents' consent, while they may not want to divulge information regarding their sexual practices to their parents. Confidentiality is the key issue in such research, which is likely to limit such research if parents/legal guardians are to be involved in the consent process. According to Collogan and Fleischman (2005), the child's assent or consent must be supported by parental consent, but this needs careful consideration in sensitive study areas such as sexual health, contraception, and adolescent sexual behaviour, with the onus on the part of researchers to ensure confidentiality. Some parents may not even understand the research (Broström & Johansson, 2014; Courser, Shamblen, Lavrakas, Collins & Ditterline, 2009) or know their children well enough to make decisions in their best interests while one of the key issues for proxy consent

is adequate understanding (Bull & Lindegger, 2011; Iserson & Lindsey, 1995; Nelson et al., 2011; Wertheimer, 2012). Furthermore, in some instances such as emergencies, valid parental or proxy consent may be impossible (Tindana et al., 2012), or even cause more harm than good (Eltorki, Uleryk & Freedman, 2013; Gefenas, 2007). For example a parent with a child that has been involved in a serious accident leading to injury may not be in the right frame of mind to give reasonable consent even though that may not be their intention (Caldwell et al.,2003). A study of consent options for a paediatric critical care research revealed that some parents were likely not to accurately read documents related to a study that is given to them as a result of being stunned by the mere size of documents (Morris et al.,2006).

Another example which highlights the difficulties inherent in the current legislation is that of HIV-prevention research. Enrolling adolescents into HIV vaccine trials with regard to Section 71 of the *National Health Act 61 of 2003* (2004) becomes complex (Slack, Strode, Fleischer, Gray & Ranchod, 2007). Still, the lingering questions is: Would adolescents enjoy confidentiality when it comes to issues concerning HIV status, sexually transmitted infections, pregnancy results and sexual risk information, if their parents/legal guardians have to consent for them? Children's privacy rights have not been dealt with directly in the act although outside of the research context, this is recognised at age 12 (*South African Children's Act*, 2005). This demonstrates that, regardless of the evolution in understanding, young children and the recognition given them in many other contexts, their abilities may be underestimated in the area of research (Heath, Charles, Crow & Wiles, 2007). It would also be worthwhile to consider the inconvenience of having to involve parents/legal guardians in assisting even older children and adolescents when they can consent on their own, and the availability of such parents/legal guardians for such activities (Slack et al., 2007).

2.5 Other South African ethics guidelines on research with children

Other South African ethical guidelines such as the *Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (SA GCP)* (Department of Health, 2006) take a different approach to child research. This guideline recommends the assessment of studies with children be based on the risk-benefit ratio, as well as the social benefit of such studies (Department of Health, 2006). This document states that research with children is acceptable for studies with no direct benefit to participants when they present no greater than

minimal risk. When a study presents more than minimal risk, but holds out the prospect of direct benefit for participants, the risks must be justified by the anticipated benefit. Consideration is also given to research that presents more than minimal risk but does not hold out the prospect of direct benefit to participants. In this regard, when the study has a high probability of yielding generalisable knowledge, the risk should be only a minor increase over minimal risk. With regard to informed consent, these SA GCP guidelines require parental consent and child assent for clinical trials (Department of Health, 2006). For other forms of health research, the norms require consent from a parent and, for older adolescents in low risk research, the minor's independent consent. The guidelines also make provision for consent by custodians of children in some circumstances (Department of Health, 2006). In addition, the South African Department of Health research ethics guidelines (Department of Health, 2015a; *South African Research Ethics Guidelines,* 2004), in its 2nd edition states that in some situations children and especially older adolescents may consent independently to research as long as:
(i) the research poses no more than minimal risk to them; (ii) there is an ethical justification through engagement with communities and other involved parties for which children should independently consent; (iii) the REC has approved that parental consent should be waived (Department of Health, 2015b).

In contrast with this guideline, the NHA accepts only parental/legal guardian consent for all health research (*South African National Health Act 2003*). This implies that children without parents or legal guardians would be excluded from participating in research that could be of great benefit to them (Nienaber, 2013). Many children in South Africa however live with family members who are neither their parents nor legal guardians. Statistics indicate that the number of children without legal guardians is as high as children who have lost their parents, and may be living under the care of an adult who has not legally adopted them (Zuch, Mason-Jones, Mathews & Henley, 2012). According to the South African Human Rights Commission/UNICEF (2011), only 32% of South African children live with both of their biological parents and 19% have lost one or both parents. Additionally, UNICEF estimated that there are 3.7 million orphans in South Africa (UNICEF, 2003) and according to a study by the South African Institute of Race Relations, 98,000 children lived in child-minded households as of 2008 (Holborn & Eddy, 2011).

Furthermore, there are variations in the rates of child development and maturity. As such, some children, though below the age of majority, can give informed consent on their own (Wendler, 2012). Eight-year-old children or younger have been considered in some circumstances capable of making independent decisions in medico-legal issues (Fundudis, 2003; Modi et al., 2014) and in research from the age of five years (Danby & Farrell, 2005). In addition, in some low-income settings, children may be in a better position, and more cognisant of and exposed to technology, than their parents. These children can also read and write, understand health-related issues pertaining to them better than their parents because they have had the opportunity to go to school, and are more connected to the wider world, which gives them easy access to information through the web and other sources. As a result, it is not unusual for children in settings such as these to be more educated than their parents and to be in good stead to make relevant decisions pertaining to them (Cheah & Parker, 2014). Although children are treated as a single homogeneous group, who need the consent of their parents, there are diverse categories of children with a combination of capabilities: some children may have the legal capability to consent to health-care decisions, some are capable of independent decision-making in all aspects affecting their lives and some also may be able to contribute meaningfully to discussions and the process of decision-making (Sénécal et al., 2016). This indicates that the decision about whether children are able to provide consent should be critically considered based on various variables including determination of maturity of the child. In view of the NHA's limitations and the additional restrictions on non-therapeutic research, a host of essential but low-risk studies, classified as non-therapeutic by the SA NHA, are likely not to be conducted due to unnecessary delays (Strode, Slack, Wassenaar & Singh, 2007).

Morrow et al. (2015) argue that certain guidelines and legislation may restrict potentially essential research that may in fact serve the best interests of the child participants and children in general. The requirement of only parental consent as a protection measure for involving children in research as stated by the SA NHA may therefore not be adequate. The risk and a risk-benefit assessment is essential; and should be part of guidelines (Morrow et al., 2015). Therefore, involvement of children in health research should be dependent on the cautious evaluation of the level of risk in comparison to the potential benefit, as well as the parameters for such risk (Glass & Binik, 2008), rather than limiting children's involvement based on the mere "therapeutic" or "non-therapeutic" nature of the research. Moreover, the term 'direct benefit' must be well-defined to include being a health benefit that is received by the individual

research participants enrolled in the clinical trial, and to include the findings from the intervention that is being studied but not from any other interventions that are clinical, irrespective of their being included in the research procedures (Nelson, 2010).

It is suggested that a context-specific approach should be adopted to assess the ethics of research with children, including taking into consideration both how to promote the best interests of children as a group (through research), and promoting the best interests of individual child research participants (Kopelman, 2000). This would avoid unnecessarily limiting certain studies with children, irrespective of what the social benefit might be. Nevertheless, important variables, such as the levels of risk, should be central in evaluating proposed studies with children (Morrow et al., 2015). Additionally risks associated with a disease, treatments and clinically required procedures must, however, be clearly distinguished from the risk of the study (Modi et al., 2014).

Kopelman argues that there is an urgent need to seek a satisfactory solution to the problem of discrepant guidance and regulations by identifying the best ways to regulate research with children rather than just considering the type of permissible research involving children, as a particular study may not hold out the prospect of direct benefit for the individual child participant, but may promote the welfare of children as a group (Kopelman, 2000). Evidently, it is crucial to ensure alignment between the South African National Health Act and other South African legislation and research guidelines, to guide and promote beneficial research promoting children's welfare (Morrow et al., 2015). One identified ethics review approach to assist with ethics review of paediatric research is the proposed benchmarks by Emanuel et al. (2004), for the ethical review of research in developing countries, which have been adopted as key norms and standards in the second edition of the South African Department of Health ethics in health research guidelines published in 2015 (Department of Health, 2015b).

2.6 Eight benchmarks for the ethical review of research in developing countries.

Emanuel et al. (2004) proposed eight benchmarks for the ethical review of research in developing countries. The first is *collaborative partnership* with all relevant stakeholders in research. Under this benchmark researchers and sponsors (including all other stakeholders) have meaningful roles to play. This is to minimise the possibility of exploitation of various concerned parties, in this regard, children. Also, by involving the relevant partners through

collaborative partnership helps them to determine the importance of a health problem especially in the context of research; whether it is appropriate and helpful for a study population, and if it meets their needs as children, in the context of this study. Furthermore, the collaboration must ensure that all partners share responsibilities in the conducting, planning and oversight of research as well as the integration of the research into the health care system. This benchmark calls for respect for communities and their way of life, as well as social practices pertaining to children, to be incorporated into a study design and implemented, in an attempt to offset risk.

The second benchmark is *social value*. It is imperative under this benchmark, with reference to research with children, to assess the importance or value of the research to the group of children. To be ethical, the research must be socially valuable. This calls for clearly outlined values such as: identifying the beneficiaries of the research, the potential value of the research to the beneficiaries with regard to a social need (in what ways the research will be of benefit to children as a group), mechanisms to boost the social value of the research, and upholding existing available health care services. According to Barsdorf and Millum (2017), to ensure that a study has social value, the population targeted for a particular study – in the context of this study: children – must stand to benefit from the results of the study. Adhering to this benchmark will ensure that potential participants are not exposed to inconvenience or risk of harm without possible benefit i.e. knowledge will be generated to improve the health and welfare of children.

The third benchmark is *scientific validity*. Even a valuable question can be poorly researched, resulting in unreliable or invalid data. Research must be well designed and conducted (e.g. clear aims, rigorous design, adequate sample, sound data analysis). Poorly designed research that is not scientifically sound is unethical because it wastes limited research resources and exposes participants to risks and inconvenience for no purpose if the research yields inaccurate conclusions or misleading answers. The study design must also be practical and acceptable within a given social, political and cultural setting and enable generalisability of the findings to the group – in this case, children.

The fourth benchmark is *fair selection of participants*. This entails adhering to the ethical principle of justice and provides for a just selection of participants so as to minimise risk and

protect vulnerable populations. First and foremost, participants should be selected according to the scientific goals of the study to ensure valid science, with relevant motivation as to why the study is being conducted with children. Furthermore fair selection of study participants ensures that risks are minimised, for example in choosing between which populations is eligible for a study. The least vulnerable population should be chosen which implies that research with children should take place (or should be conducted) , only if that same research objective cannot be obtained when conducted with adults. It is necessary, according to this principle, to select participants based only on sound scientific reasons and not because of their vulnerability. In other words, research carried out with children should be appropriate to their unique health needs.

The fifth benchmark is achieving a *favourable risk-benefit ratio* of a study. The potential benefits of the research must outweigh the potential risks and should be measured along with the social value of the study. In view of this, it is essential to ensure that the risks to child participants are outweighed by the benefits. However, where the risks are high, this may be justified by the social value of the study in the context in which the study participants live. The justification should be based on the value of the study with regard to benefits to be accrued by the child participant through the study intervention. This is also necessary in order to achieve the study objective. Another justification for research risk to child participants is benefit to be derived from knowledge to be gained by the study, for example, pertaining to the best interests of children. In general the underlying question is whether the study is worthwhile with regard to the expected level of risk to the child participants.

The possibility of ascertaining the true risk-benefit ratio only at completion of a study, makes risk-benefit assessment complex (Weijer, 2000). However, for the past ten years, assessment has been based largely on ‘component analysis’, developed by Weijer (Weijer, 2000; Weijer & Miller, 2004) or the ‘net risks test’. Both techniques emphasise the assessment of risk-benefit of specific study processes instead of undertaking a universal risk-benefit outline of the whole study. The techniques can equally be applied to other categories of health research, although they were developed mainly for clinical trials. The component analysis model is based on the principle that most clinical research involves both therapeutic and non-therapeutic components, interventions and processes. Therefore, risk assessment should be based on different ethical deliberations. The fundamental concept, however, is the prerequisite for ‘clinical equipoise’

which occurs when specialists are genuinely not sure what the ideal treatment should be for a particular health issue or condition (Weijer & Miller, 2004). Study interventions must meet the requirement for clinical equipoise and competent clinical care. There should be enough existing evidence to back the expectation of potential benefit (Kruger, Ndebele & Horn, 2014), for example, for children, evidence from study results from adult studies in the same vein. Experts and community members may be consulted for assistance to determine if risks involved are reasonable for the scientific design and the local context (Emanuel et al., 2004). Weijer and Miller (2004) propose that the REC must decide if a study signifies 'minimal risk' or 'minor increase over minimal risk' when vulnerable populations like children are involved. Minimal risk is the risk that is ordinarily encountered in daily life within a stable society (Emanuel et al., 2004). However, this assessment can be challenged due to varying interpretations. Nevertheless, the main concern in assessment is whether "the sum and balance of risks is acceptable in relation to the anticipated benefits that are likely to be obtained from the study" (Emanuel et al., 2004, p. 135).

The 'net risks test' developed by Weijer and Miller is another approach to the analysis of risks (Westra & Beaufort, 2011). This approach holds that the process of deciding whether research aspects are therapeutic or non-therapeutic is sometimes not clear and may not be necessary. Westra and Beaufort (2011) have proposed the following to guide a risk-benefit assessment: (1) to identify all study interventions and procedures and conduct a risk-benefit or burden assessment of each one to ascertain whether it is favourable or unfavourable; (2) to identify for each study intervention or procedure an alternative traditional care standard to ascertain the outcome if participants were to be treated as for each usual standard of care to assess the ratio of risk or burden to benefit; (3) compare to ascertain if the risk-benefit ratio associated with each procedure or intervention is the same as that which is associated with giving the standard of care. If the outcomes are the same, it implies there are 'no net risks' involved. However, if the risk-benefit profile of the study intervention is assessed as being more unfavourable than the usual standard of care would be, then there is 'net risk' involved. If the 'net risks' of the research intervention are not excessive or are considered justified by the new knowledge that is likely to be added by conducting the study, then the study can be approved, regardless of the 'net risk' of the usual standard of care being lower than that of the proposed research. However, imperative in the assessment of 'net risks' is cumulative risk which for example; while drawing blood once or twice may be seen as insignificant risk, serially drawing blood over several weeks

or months may create a significant burden (Kruger et al., 2014). Also of great importance in assessment is for reviewers to be aware that ancillary care cannot be classified as a benefit in risk-benefit assessment (Kruger et al., 2014).

The sixth benchmark is *independent review* of research. This is a requirement to ensure accountability and transparency. It also accords participants the needed protection from exploitation. However, the review must be done by a competent body mandated by law. This should be done by a competent REC in addition to any other regulatory body deemed appropriate. In South Africa the requirement is for an REC registered with the National Health Research Ethics Council (NHREC) to review and approve the research.

The seventh benchmark is *informed consent* and in the case of research with children, *parental informed consent and* the accompanying *informed assent of the minor*. This is an ongoing process which should be obtained through appropriate and feasible procedures. The process must take into consideration the social and cultural context of the study. Necessary considerations must be given to social practices of communities. For example, in most local social contexts, requiring that proxy consent be given only by parents/legal guardians will be insensitive as custodians could also play such a role when necessary. This is imperative because, in most local contexts, a 'guardian' is not necessarily the legal guardian but could be anyone who takes care of the child. Collaborative partnership should be also observed in order for the disclosure of information to be done in a sensitive way and within the cultural conventions in the local context. The understanding of this benchmark is also in line with social value and scientific validity of a study.

The final benchmark is *ongoing respect for recruited participants and study communities*. Privacy and confidentiality must be maintained and participants must be given the necessary information where appropriate. The privacy of participants must be ensured where necessary, especially when it comes to adolescents and very sensitive subject areas. This benchmark also calls for clearly outlined measures to be put in place to disseminate the results of the study in a manner appropriate for their understanding as participants and/or groups or their representatives. The outcome of the study must also be used for the benefit of the participants and the group under study, in this case, children. This is necessary to ensure that study results are disseminated and all relevant information shared.

An evaluation of whether a particular study is considered ethical is dependent on whether all eight of these benchmarks have been met. Using only one ethical benchmark in the evaluation process is inadequate. However, greater weight can be given to some benchmarks over others. The framework, although considered by some as complex, should work within general ethical values. The framework adds value and supplements international guidelines such as the Nuremberg Code, the Belmont report and the Declaration of Helsinki (Emanuel et al., 2004).

2.7 Conclusion

In South Africa and other low- and middle-income countries, paediatric studies are necessary in order to enhance care and safeguard the justifiable distribution of scarce but essential resources for the care of children. The care of children should, however, be based on excellent study evidence in order to safeguard and provide effective treatment for children. Relevant studies have nevertheless been restricted in these low- and middle-income countries (such as South Africa) due to excessively restrictive local guidelines which hinder essential research, all in the zeal to protect vulnerable groups such as children from harm (Morrow et al., 2015). The purpose of the present research was to comment on the compliance of child research with the South African NHA Section 71, and the feasibility in its current form in promoting the best interests of children. The results of this study may add to existing evidence to guide policy-makers, ethicists, researchers, and other relevant stakeholders in developing practical and context-specific research guidelines for reviewing child research in South Africa.

Chapter 3: Rationale of the study

3.1 Introduction

The purpose of this research is to investigate the potential impact of section 71 of the South African NHA 61 of 2003, on child research, in promoting the best interests of children and to examine a possible ethics review approach that can assist RECs to review research that may be in the best interests of children. It is also hoped that findings from this study will provide a basis to stimulate more debates around other approaches to reviewing child studies and add to advocacy efforts for South African law reform to address for example the problematic definitions of research.

3.2 Research Question

What potential impact may the current South African *National Health Act 61 of 2003* (2004) Section 71 have on essential health research for children?

3.3 Objectives

1. To compare "therapeutic" and "non-therapeutic" research with children according to: 1) research type e.g. clinical trial, descriptive study etc.; 2) risk-type and risk-level; 3) the presence of direct benefit; and 4) the involvement of more vulnerable children)
2. 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) prior to promulgation of Section 71 might be compliant with the current South African *National Health Act 61 of 2003* (2004) Section 71.
3. 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 in developing countries (Emanuel et al., 2004).
4. To assess whether section 71 promotes the best interests of children.

Chapter 4: Research methodology

4.1 Research design

The study is a retrospective descriptive review of published research involving children.

4.2 Sampling design

For the purpose of this study, all publications of studies involving children conducted in the Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University and published between 1st January 2013 and 1st January 2015 were included. These studies were conducted prior to promulgation of the *National Health Act 61 of 2003* Section 71 in March 2012..

4.3 Data collection and analysis

Key concepts relevant to the South African *National Health Act* and the Emanuel et al. (2004) benchmarks were defined and from these publications analysed as key variables, using a predetermined list. Information was extracted concerning, but not limited to, the type of study, study design, therapeutic or non-therapeutic research, age range of study participants, type of study risk to children, justification for conducting the study, study motivation, consent, assent, provision of ancillary care, REC approval, whether studies were multinational, whether studies involved local investigators, whether local investigators received training, direct benefits of study to child participants, confidentiality and privacy of child participants, supplementary community and familial consent procedures, and translation into local language (see Appendix 2).

Data collected was coded and entered into Excel, using the key variables described above (Appendix 2) and subsequently exported to SSPS Version 2.4. Data collected was checked for completeness and consistency, as well as invalid entries by both the principal investigator and primary supervisor. Open-ended questions were entered as string variables. Descriptive statistics (frequencies and proportions) were calculated. Data was plotted in graphs, charts and frequency tables to provide an overview and better understanding of the composite dataset. In its aggregated form, the data were then described with regard to impact of the *National Health*

Act 61 of 2003 on paediatric health research and compliance of these studies with the Emanuel et al. (2004) framework for ethical research.

4.4 Ethical considerations

This study presented minimal risk since it was a retrospective review of publications already in the public domain. Ethics approval was not needed, but as the study was to contribute towards a Masters dissertation, the protocol was submitted to University of KwaZulu-Natal (UKZN) REC for ethics review and approval (see Appendix 3). All relevant information was extracted from the publications in an anonymised format, with no names of investigators or titles of studies included. It is however possible that the identity of some research proposals might be exposed and this may cause problems for both the researcher and the REC if the information shows that the researcher did not comply to some of the requirements of the ACT, and to the REC because then the REC would have approved a research proposal that did not comply with the requirements of the ACT.

4.5 Validity, reliability and generalisability

The goal in all retrospective descriptive reviews is to minimise bias in the review process and enhance reliability and validity of review conclusions (Cohen, Manion & Morrison, 2013). Threats to validity and reliability cannot be completely removed in research; therefore, it is best to minimise them. In order to achieve this, the researcher implemented a number of strategies to self-correct the data during collection and analysis. The review of documents was guided by a predetermined list with key variables and done by more than one person. This was further supported by creating graphs and charts in Excel, and frequency tables and cross-tabulations in SPSS and Stata 11.1. The researcher ensured that documentation was of maximum quality. The aim of this research was to generate a basic understanding based on descriptive statistics rather than testing validity or reliability of hypotheses inferred from previous studies; therefore, the findings cannot be generalised to the wider population of all child studies in the country (Shaw, 1999).

Chapter 5: Results

5.1 Description of the source data

The researcher received a list of 81 publications of research involving children from the Department of Paediatrics and Child Health conducted between 1 March 2012 and 1 March 2013. On initial review, (n=13, 16.5%) publications were excluded from analysis, since ten were literature reviews, one duplicate was found, and two were letters to the editor, leaving 68 publications for analysis. This section describes the nature of the research with children in these 68 publications. The first section offers a descriptive comparison of "therapeutic" versus "non-therapeutic" research by child age and vulnerability, research type, risk level, and type of risk. The second section describes compliance of these studies with National Health Act and the eight ethics benchmarks proposed by Emanuel et al (2004). (Appendix 2 summarizes the key variables measured in the study).

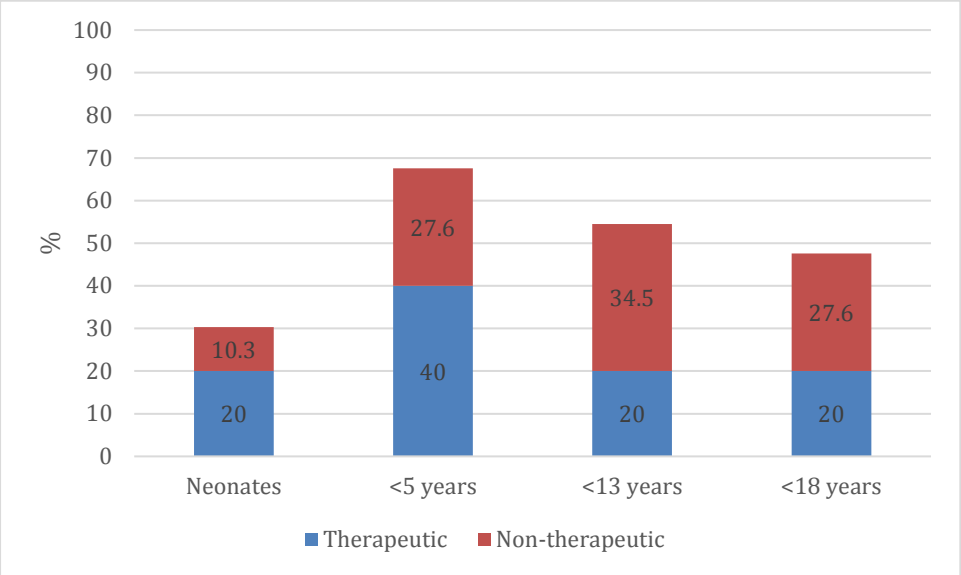
5.2 Descriptive comparison of "therapeutic" versus "non-therapeutic" research with children

The majority of studies (n=58, 85%), would, according to the SA NHA, be classified as non-therapeutic research with children, while only (n=10, 15%) were therapeutic research.

5.2.1 Age distribution of child participants

The ages of children recruited into these studies ranged from 0 to 18 years. Twenty-two studies (32%) included children younger than 13 years, twenty studies (29%) included children younger than 5 years, eighteen studies (26%) included children under 18 years and eight studies (12%) involved neonates. (See Figure 1). For all age categories there were more non-therapeutic studies than therapeutic studies, respectively (n=6, 10%) versus (n=2, 20%) for neonates; (n=16,27.6%) versus (n=4, 40%) for under 5-year old children; (n=20, 34.5) versus (n=2, 20%) for children under 13-years of age and similarly (n=16, 27.6%) versus (n=2, 20%) for children under 18 years of age.

Figure 1: Age distribution of child participants in therapeutic versus non-therapeutic studies



5.2.2 Inclusion of more vulnerable child participants

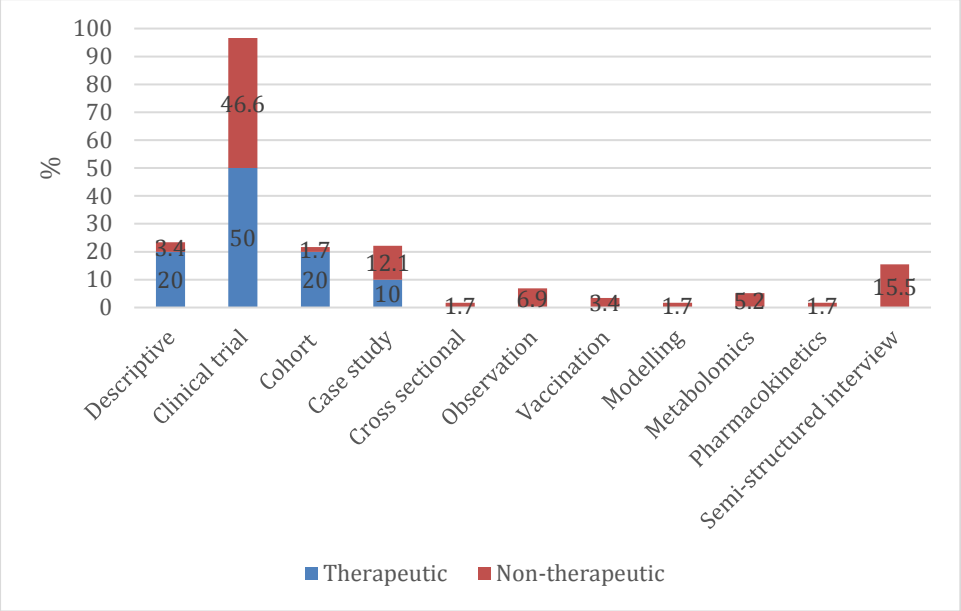
For all of the studies the study population was selected in ways to minimise risk and participants were fairly selected. Fifteen of the studies (22%) included more vulnerable children (children with disability or mentally handicapped) of which 3 were therapeutics studies and 12 were non-therapeutic studies.

5.2.3 Types of research with child participants

The majority of studies were descriptive studies (43%), followed by 13% pharamacokinetic studies, 10% observation studies, 9% clinical trials and various study designs including metabolomics, modelling, vaccination, cross sectional, cohort, and case studies (12%). Of the non-therapeutic studies, (n=27, 47%) were descriptive studies, while (n=7, 12%) were observational studies, and (n=9, 16%) were pharmacokinetic studies. Other designs for the non-therapeutic studies were modelling in 4 studies (7%), 1 prevention clinical trials (2%), 3 case studies (5%) and 2 cohort studies (3%). The remaining 3 non-therapeutic studies (5%) were respectively a semi structured interview, a vaccination study and a metabolomics study. The

study designs identified for therapeutic studies were 5 clinical trials (50%), 2 descriptive studies (20%), 2 cohort studies (20%) and 1 case study (10%).

Figure 2: Types of research with children for therapeutic versus non-therapeutic studies



5.2.4 Type and level of risk for child participants

Risk level: Almost half of the studies (n=32, 47%) involved *minimal risks*. Of these, were (n=1, 10%) for therapeutic studies and (n=31, 53%) for the non-therapeutic studies. (n=9, 90%) of the therapeutic studies and (n=27, 47%) of the non-therapeutic studies had the potential to be associated with *more than minimal risks.*

Risk type: Types of risks identified included physical risks in 31 studies (46%), social risk in 3 studies (4%), and psychological and economic risk respectively in 1 study each (1.5%). Eight of the ten therapeutic studies, (80%) posed potential physical risk with potential direct benefit to the child participants, while one of the therapeutic studies (10%) posed potential social risk. There were no psychological or economic risks identified for therapeutic studies. Of the non-therapeutic studies 23 (40%) posed potential physical risk, 2 (3%) posed potential social risk, 1 (2%) posed psychological risk and 1 (2%) posed economic risk (See Figure 4). In reviewing these publications, the risk-benefit assessment was deemed favourable in 100% of the studies,

although, as expected, the non-therapeutic studies mainly added generalizable knowledge to the class of child research participants.

Figure 3: Level of risk for therapeutic versus non-therapeutic research with children

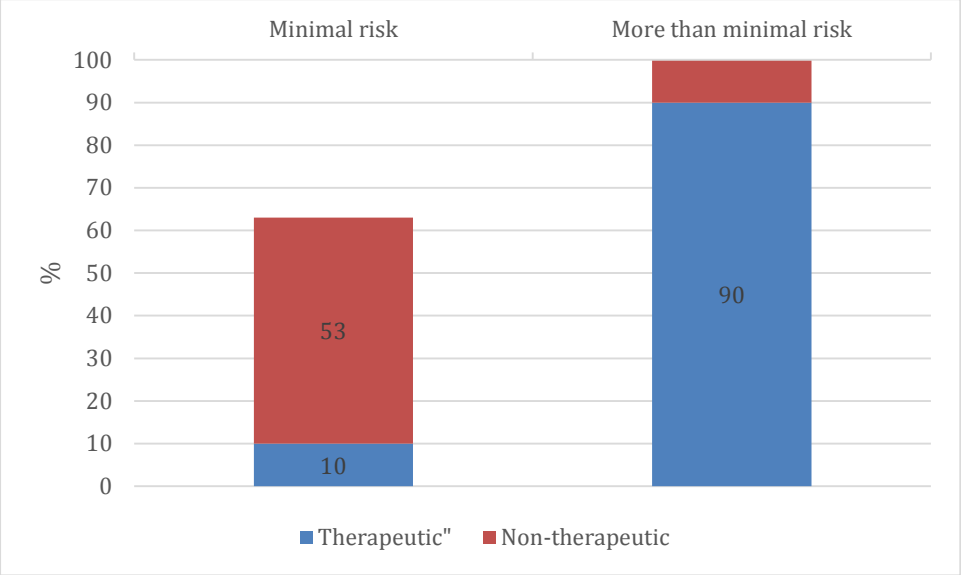
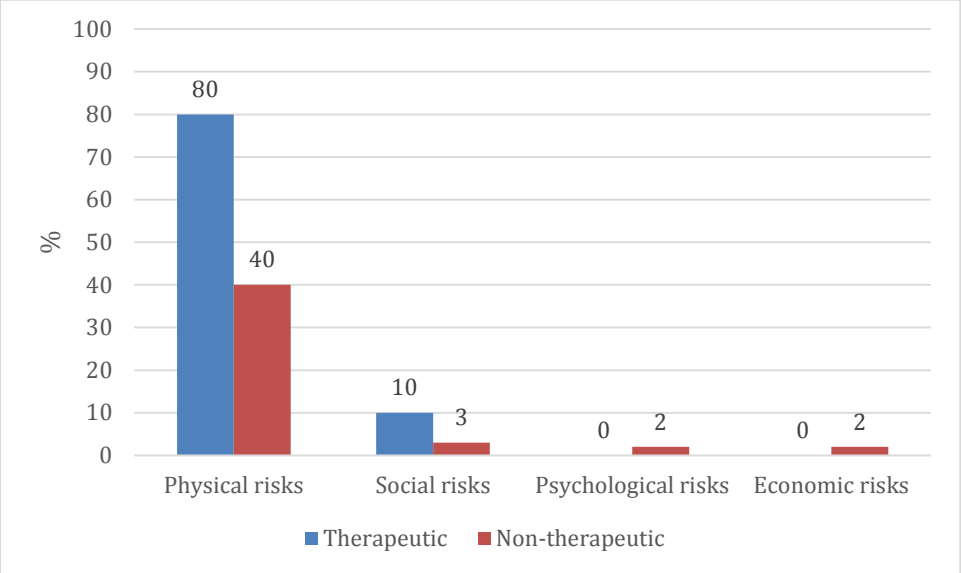


Figure 4: Type of risk for therapeutic versus non-therapeutic research with children



5.2.5 Direct versus indirect benefits for child participants

The majority (n=66, 97%) of the studies were in the best interest of children and only (n=2, 3%) studies were not applicable as these were descriptive studies of pathophysiology of conditions suffered by children. A little under a third (n=21, 31 %) of the studies had direct benefit. Ninety (90%) of the therapeutic studies posed potential direct benefit and 21% of the non-therapeutic studies had direct benefit. Less than (n=5, 7%) of all the studies reviewed mentioned provision of ancillary care for participants.

5.3 Compliance with the NHA and the eight proposed Benchmarks

5.3.1 Compliance with Section 71 of the NHA

The studies reviewed against section 71 of the NHA which states guidelines for conducting child research had shown that all (n=68, 100%) were justified as being in the best interest of children. The majority (n=54, 79%) of studies mentioned they had obtained ethics approval from recognised research ethics committees (RECs), which was respectively (n=8, 80%) for therapeutic studies and (n=46, 79%) for nontherapeutic studies. More than three-quarters (n=52, 77%) of the articles mentioned seeking parental or guardian consent, while (n=12, 18%) of the articles also mentioned assent. Parental or guardian consent generally was mentioned for (n=9, 90%) of the therapeutic studies and (n=43, 74%) of the non-therapeutic studies. Assent was not applicable in (n=8, 80%) of the therapeutic studies and (n=29, 50%) of the non-therapeutics studies as the children were too young. Assent was not mentioned in (n=2, 20%) of the therapeutics studies and (n=17, 29%) of non-therapeutic studies, where it was appropriate.

5.3.2 Compliance with the 8 proposed Benchmarks

In reviewing the studies against the proposed 8 benchmarks the results had shown that just under a third (n=22, 32%) of the studies were multinational studies with (n=4, 40%) for therapeutic and (n=18, 31%) for non-therapeutic studies. The majority (n=46, 68%) were local institutional studies, and all studies (n=68, 100%) had local investigators on the research team. Research-related training for local stakeholders was mentioned for (n=2, 3%) of the publications. Study designs were appropriate for the research question for all (n=68, 100%) of

the studies and all the studies (n=68, 100%) had the appropriate motivation for including children as research participants. Participant selection was fair in all studies. None of the research objectives could be equally achieved if conducted involving adults as research participants. All the studies (n=68, 100%) were likely to yield significant results towards improving the scientific understanding of conditions, diseases or disorders relevant to children in the research and towards significant benefit to other children with similar conditions. All studies (n=68, 100%) justified the research as being in the best interests of children. The majority (n=54, 79%) of studies mentioned they had obtained ethics approval from recognised research ethics committees (RECs), which was respectively (n=8, 80%) for therapeutic studies and (n=46, 79%) for nontherapeutic studies. All of the articles (n=68, 100%) mentioned having measures put in place to protect the confidentiality and privacy of child participants. None of the articles mentioned consulting a community in establishing recruitment procedures and/or incentives. More than three-quarters (n=52, 77%) of the articles mentioned seeking consent, while (n=12, 18%) of the articles also mentioned assent. One longitudinal study involving HIV infected mother-child dyad mentioned that parental consent was waived for participants less than 18 years and informed consent obtained from mothers of children 16 years and older. In this same study, maternal caregivers who were not biological mothers were also included. The study required that for a child to be eligible to participate the child should have been in the care of the caregiver for at least six months. Another study on the other hand mentioned that some children were excluded from participating in the study because they were brought by adults who could not provide legal consent. Consent generally was mentioned for (n=9, 90%) of the therapeutic studies and (n=43, 74%) of the non-therapeutic studies. Assent was not applicable in (n=8, 80%) of the therapeutic studies and (n=29, 50%) of the non-therapeutics studies as the children were too young. Assent was not mentioned in 2 therapeutics studies and (n = 17, 29%) of non-therapeutic studies, where it was appropriate.

A third (n=22, 32%) of the studies mentioned that the consent forms were translated into the local language of the host community. More than half (n=41, 60%) of the studies needed supplementary community and familial consent procedures, although it was not possible to determine in analysis if these studies did actually did adhere to this requirement. There was a potential need for (n=9, 75%) and (n=32, 57%) of the therapeutic and non-therapeutic studies respectively for supplementary community and familial consent procedures.

5.4 Summary of the results

The study findings revealed the following for the 68 reviewed studies:

Therapeutic versus non-therapeutic research

- 85% of the studies were non-therapeutic and 15 % were therapeutic studies
- The vast majority of therapeutic studies (90%) involved *more than minimal risk*
- The majority of non-therapeutic studies (54%) involved *minimal risk*
- 29% of the studies reviewed had offered direct benefit to child participants
  - 90% of the therapeutic studies offered direct benefit
  - 21% of the non-therapeutic studies offered direct benefit
- 80% of the therapeutic studies posed physical risk and 1% social risk
  40% of the non-therapeutic studies posed physical risk, 3% social risk and 2% psychological or economic risk
- 22% of the studies involved more vulnerable children (including mentally or physical handicapped children)
  - 30% of these studies were therapeutic
  - 21% were non-therapeutic

Compliance with the NHA and 8 ethics benchmarks

- Motivation given for conducting the studies with children was appropriate for all the studies reviewed.
- All the studies reviewed were justified for including children.
- None of the studies could have been done with adults.
- 97% of all the studies were in the best interest of children.
- 79% of the studies mentioned receiving approval from recognised research ethics committees.77% of the studies mentioned seeking parental or guardian consent and 18% the child participant's assent
- 32% of the studies mentioned translating the consent forms into a local language
- All studies reviewed had local investigators as part of the research team
- All studies mentioned putting measures in place to protect confidentiality and privacy of child participants

Chapter 6: Discussion

6.1 Impact of the National Health Act 61 of 2003 section 71 on essential research with children

The majority of the child research reviewed in this study was non-therapeutic (82%) while only (18%) were therapeutic studies. This means that a very large proportion (82%) of these studies (n=58) would have needed ministerial consent according to Section 71 of the *National Health Act 63 of 2003* (2004) if they were conducted prior to the delegation of the ministerial duty to Research Ethics Committees (RECs) (Motsoaledi, 2014). Importantly, the results showed that the majority (53%) of non-therapeutic studies involved *minimal risk* whilst majority (90%) of the therapeutic studies involved more than minimal risk. However, even though the current section 71 of the NHA has delegated the ministerial duty for the review of non-therapeutic studies to RECs, it still does not outline any change in the level of stringent attention to be given to the review of non-therapeutic studies irrespective of their level of risk. The delegation of ministerial consent to RECs was however not spelled out in the ACT but in letters from the Minister to various RECs (Motsoaledi, 2014). By however assuming that all therapeutic studies are safe and offer direct benefit irrespective of their level of risk implies that the NHA is not protecting the best interest of children. Moreover from our current study, most of the non-therapeutic studies were associated with potentially minimal risk and therefore worth mentioning that prior to the delegation of ministerial consent to RECs, researchers would have been discouraged from conducting these essential, low risk studies with children due to anticipated unnecessary delays of having to stay in a queue for the minister to approve these studies as argued by Strode et al., (2007).

Emphasis must be placed on these South African NHA section 71's therapeutic and non-therapeutic definitions of research involving children because this distinction is problematic and may not serve the best interest of children. Unlike many other regulations governing research with children, the South African *National Health Act 61 of 2003* section 71 still uses the terms therapeutic and non-therapeutic as the criteria to determine allowable research with children (*South African National Health Act 61 of 2003*). Comparatively the United States regulations, for which paediatric research is deemed essential tries in its regulations to make it mandatory for children to be involved in research unless their exclusion is justified by good

scientific or ethical reasons (DHHS, 2009). The regulations do not define research as therapeutic or non-therapeutic, but use a risk-benefit model in assessment to determine appropriate research for and involving children (DHHS, 2009). This involves balancing the anticipated risks and benefits by determining the prospect of research benefits, both directly to participants or as benefits to the general population of children (DHHS, 2009). The terminology of therapeutic and non-therapeutic research may be misrepresentative (Nienaber, 2013) as the definition of therapeutic research is always misconstrued to be associated with direct benefits whilst non-therapeutic research is not (Woods et al., 2014).

In analysing the publications from the current study based on the proposed eight ethical benchmarks of Emanuel et al (2004), important to that is that the publications are in compliance for the majority of these benchmarks, which indicate that the framework is suitable for ethics review of paediatric research in general. From our findings, 90% of the therapeutic research offered direct benefit to child research participants, which demonstrates that not all therapeutic research necessarily offers benefits (Woods et al., 2014). Our findings reinforce the notion that although therapeutic studies may have therapeutic intention, in the context of research they are also conducted to generate knowledge just like non-therapeutic research (Woods et al., 2014). Interestingly 21% of the non-therapeutic research reviewed in this study also offered direct benefit to child participants, however none of the previous literature reviewed had made mention that supported this finding. These findings support Nelson's (2010) view that there should be a move away from defining direct benefit only as the benefit that participants in a study receives but to also include findings from interventions in a study. Another important finding from this study was that 22% of studies reviewed involved *more vulnerable* children, namely children with disability (physical and/or mentally) which is quite high. Studies have however shown that vulnerable children need extra protection and this has led to a disinclination to include them in research (Wolfe, 2012). More interesting is the fact that our findings revealed that the 22% of studies involving more vulnerable children were all therapeutic studies. The involvement of vulnerable children in the therapeutic studies could however bring to fore the debate on the assumption that therapeutic research is associated with benefits (Woods et al., 2014). Could it be that these more vulnerable children were included in these studies because they or their parents/guardians misjudged that they would get a solution to their problem.

Our study finding also revealed that both therapeutic and non-therapeutic studies involved some degree of risk. This brings to fore the importance of considering the possible risk associated with a study in determining the appropriateness of the study for child participants.

The majority (77%) of the publications analysed mentioned seeking parental or guardian's consent in conducting studies with children, and 18% of the articles mentioned seeking child assent. It is required by the *National Health Act 61 of 2003*, section 71 for both therapeutic and non-therapeutic studies to be carried out with the consent of the parent or guardian of the child and, if the child is capable of understanding, with the consent of the child (*South African National Health Act*, 2003). The National Health Act emphasizes that consent should be granted by a parent or guardian. Nevertheless, one of the publication analysed had mentioned that parental consent was waived for participants less than 18 years who were mothers themselves and informed consent obtained from mothers of children 16 years and older. The same publications reported that maternal caregivers who were not biological mothers to the children in the publication which was from a dyad study were also allowed to consent. Similarly, a systematic review study on clinical research with children without parental consent showed support for a waiver of parental consent in some studies involving children (Brierley & Larcher, 2010).

In contrast, the *National Health Act 61 of 2003*, section 71 accepts only parental/legal guardian consent for all health research. This NHA requirement seems to over-emphasise consent from parents or guardians, specifically, concerning children during research. The NHA also states that the legal age for consenting to research is 18 years (Danby & Farrell, 2005) however from this study that requirement for only 18 year olds to independently consent to research was not adhered to by some of the studies reviewed which further implies that the studies did not comply to that requirement by the section 71 of the NHA. However although the participants were not yet 18 years, they were mothers and probably in the best position to consent for themselves and their child. Contrary to the *National Health Act 61 of 2003* section 71, the Guidelines for good practice in the conduct of clinical trials (Department of Health, 2006) and the Department of Health Research guidelines (Department of Health, 2015a) prior to the current Act; and other international ethical guidelines as well as some critics, have stipulated that in some circumstances, a waiver of parental consent for children to give their independent consent is appropriate (CIOMS, 2002; Courser et al., 2009; DHHS, 2009; *South African GCP*

Guidelines for Clinical Trials with Human Participants, 2006). Moreover, in some situations the inconvenience of involving parents or legal guardians in the consent process during research with even older children should be taken into consideration (Slack et al., 2007). In addition, there are some situations where the research areas are very sensitive and require the onus of researchers to ensure confidentiality especially with adolescent children. This is however limited when caregivers have to be involved in all consent procedures (Slack et al., 2007).

One of the analysed publications reported that some children were excluded from participating in the study because the adult caregiver could not provide legal consent. Sadly these children may have been able to benefit from the study. Broström &Johansson (2014) as well as other scholars are of the view that sometimes the biological parents or the legal guardian may not be in the position to even know their children well enough to make decisions in their best interests (Broström & Johansson, 2014; Courser et al., 2009). By the section 71 of the NHA 61 of 2003 requiring only parental/legal guardian consent for all research involving children (*South African National Health Act, 2003*) is not in the best interest of children. Nienaber (2013) argues that such requirement implies that children without parents or legal guardians would be excluded from participating in research that could be of great benefit (either directly or indirectly) to them. Interestingly, many children in South Africa live with a caretaker or custodian and not with a parent or a legal guardian. Statistics also indicate that the numbers of children without legal guardians are high and children who have lost their parents may be living under the care of an adult who has not legally adopted them (Zuch et al., 2012). Moreover the seventh benchmark proposed by Emanuel et al. (2004) stipulates that the informed consent process must take into consideration the social and cultural context of the study. The guardian in most local contexts may not necessarily be the legal custodian but could be anyone who takes care of the child.

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

The reviewed publications were in compliance to a large extent with the proposed Emanuel et al. (2004) framework for ethical research in developing countries. Regarding the level of compliance of the studies with the Emanuel et al. (2004) framework, the results of our study showed that not all requirements by the eight benchmarks were met by the studies reviewed.

In contrast with Emanuel et al.'s (2004) stipulated requirement, for a study to be considered ethical, all the eight benchmarks should be met. This does not necessary imply that the studies were not ethical, but may be due to limited information published and the detail would have been in the full research protocol submitted to the REC, which was not available during the analysis. In other words, it might be that some of the studies were actually compliant with all the benchmarks but that was not apparent and there was no way of further investigating. According to Emanuel at al. (2004), it is inadequate to use one ethical benchmark in determining whether a study should be approved. However more emphasis could be placed on some benchmarks than others (Emanuel et al., 2004). In line with that it could be argued from our findings that some of the studies may have complied with the highly prioritised benchmarks. It could however not be determined which benchmarks fall under the category of "highly emphasised" as these were not defined by Emanuel et al. (2004). In general, it is recommended that a context-specific approach should be used in evaluating the ethics of research with children. This should however be inclusive of consideration of how to promote the best interests of children as a group (through research), and how to promote the best interests of individual child research participants (Kopelman, 2000).

The first benchmark proposed by Emanuel et al. (2004) states that, for a study to be accepted as ethically appropriate it must have collaborative partnership. Findings from our study showed that some studies were involved in collaborative partnership although the extent of collaboration could not be determined. According to the Emanuel et al. (2004), collaborative partnership is important to minimise the likelihood of exploitation of a research population, which for the purpose of this study are children. Compliance with this benchmark ensures that studies conducted with the child population align with their health needs and are of benefit to children as a group. Furthermore collaborative partnership helps to offset risk and vulnerability.

According to Sharp and Millum (2015), the population that hosted a study has to be a beneficiary of the results of the study. Similarly, the results of this current study had shown that all the studies reviewed had social value which is the second benchmark proposed by Emanuel et al. (2004). The benchmark stipulates that for a study to have social value is dependent on the resulting improvement of the health of children or adding to knowledge in terms of children in the context of this study. In contrast to the benchmark, which seeks to ensure social value, the South Africa NHA section 71 emphasises on whether a study offers

direct benefit or not. In the same vein other results from our study showed that all the studies reviewed were likely to add significant knowledge to child research and to a large extent the studies were in the best interest of children. Our study results further showed that very few (21%) of the studies had direct benefit for the participants meanwhile the beneficiaries of the studies conducted were mostly children. In line with this finding, the benchmark (social value) requires research with children to be assessed also based on their importance to children as group.

In order to ensure valid science the study design of a study should be able to achieve the objectives set for the study. According to Emanuel et al. (2004), a study must also be practical within a given and acceptable social, political and cultural context and must ensure the benefit of prospective beneficiaries. Similarly, all the studies reviewed in the present study had appropriate study designs and were justified for the involving children. Participants in the studies reviewed per our results were fairly selected and this included more vulnerable children. Similarly, the fourth benchmark proposed by Emanuel at al.(2004) is fair selection of study participants. By this benchmark it is required that participants for research be selected in such a way as to minimise risk whilst benefits are increased; and to protect the vulnerable. In lieu of the fact that all studies reviewed met this requirement implies that children as research participants were selected for the various studies in consideration for the fact that the studies objectives could only be achieved only when they (children) were involved. It is also important that participants are fairly selected as it cannot be undermined the need to avoid the use of findings from adults study for children. Studies have shown that children are different from adults in both their physiological and mental makeup (Modi et al., 2014) and as such it is not appropriate to use findings from studies done on adults in making decisions pertaining to the wellbeing of children. In line with this, additional findings from our study showed that none of the studies could have been conducted with adults to achieve the same study results needed for children. Also in support of fair subject selection is Kumra et al., (2014), who revealed in a study that it is important to conduct research with children and for children in order to ensure homogeneity for child research purposes.

Other findings from our study demonstrated that the research were mostly associated with potentially minimal risks for therapeutic studies with potentially more than minimal risks but also direct benefit, adhering to the proposed fifth benchmark by Emanuel et al. (2004) of a

favourable risk-benefit ratio. The benchmark however requires that in looking out for appropriate balance between risks and benefits, the social value of a study must be adequate to justify the potential risks and that is to say; is the study necessary for the participants and the general population? Interestingly the SA NHA does not go beyond the categorisation of a study as therapeutic or non-therapeutic in the assessment of studies as appropriate. It could be argued that the SA NHA perceives all therapeutic studies as always having favourable risk-benefit ratio.

According to Glass and Binik (2008) involving children in health related studies must depend on the careful assessment of the risk compared to the prospective benefit. Again the authors are of the view that allowing research with children should not be dependent on whether the study is therapeutic or non-therapeutic (Glass & Binik, 2008).

Majority of the studies reviewed in this current study mentioned receiving approval from Research Ethics Committees. This is in accordance with the sixth benchmark proposed by Emanuel et al. (2004), namely independent review of research. According to this benchmark, by demanding that RECs review and grant approval to proposed child studies before they are conducted ensures accountability and transparency. Moreover it also protects participants from exploitation (Emanuel et al., 2004). It is also worth mentioning by the minister delegating his duty as reviewer of non-therapeutic studies with children is a good step towards ensuring the best interest of children. This is because the REC had reviewed all health research proposals including research with children even before the promulgation of the South African NHA.

Our study revealed that informed consent was sought from parents/guardians and sometimes assent was sought from children. This is required by the seventh benchmark and in addition it is proposed by the third benchmark that sometimes it is necessary to consider a community and their way of life during the consent process. Regarding the present study, it was discovered that 60% of the studies reviewed needed some form of supplementary community and familial consent procedures. Belying this is the fact that none of the articles mentioned consulting a community in establishing recruitment procedures and incentives, and sometimes, the process of seeking consent and assent. Moreover consultation with community representatives may be a useful strategy in seeking informed consent or getting access the community members (UNAIDS-AVAC GPP, 2011). According to the benchmark, the consent process is an ongoing

process which should be obtained through appropriate and feasible procedures. Sénécal et al. (2016) are of the view that irrespective of the fact that children are viewed as one group who always need the consent of the parents, some children due to some circumstances may be able to consent independently in the context of research. The process of seeking consent must take into consideration the social and cultural context of the study (Emanuel et al.,2004). Similarly findings from the study showed that a study had mentioned that parental consent was waived for participants less than 18 years and informed consent obtained from mothers of children 16 years and older. This decision may have been necessitated by the research context.

The eighth and final benchmark by Emanuel at al. (2004), is respect for study participants and their communities. Some of the studies per our findings mentioned putting measures in place to ensure privacy and confidentiality which is in accordance with the requirements of the benchmark. According to the benchmark researchers are obliged to safeguard the wellbeing and interest of its study population and their community (Emanuel at al., 2004). Furthermore the benchmark also calls for clearly outlined measures to be put in place to disseminate the results of the study in a manner for their understanding, as participants and or groups or their representatives (Emanuel et al., 2004). In contrast our findings, none of the studies mentioned plans for dissemination of study results. However dissemination of results to stakeholders especially participating communities or their representatives is highly recommended by leading ethics guidelines (UNAIDS-AVAC GPP, 2011).

Chapter 7: Conclusions and Recommendations

7.1 Conclusions

The general findings of this study reveal the urgent need to ensure consistency in guidelines that govern the conduct of research with children; and in this case investigated the current South African *National Health Act 61 of 2003,* Section 71. It is clear from our findings that the majority of studies reviewed were non-therapeutic; and that the majority of these non-therapeutic studies were associated with minimal risk. In addition, and contrary to what is implied by the definition, some non-therapeutic studies offered direct benefit to child participants, whereas some therapeutic studies did not. Reflecting on the existing guidelines and regulations for child research, it is worth noting that in an attempt to protect children from potential harm, some guidelines have restricted certain studies that otherwise would have served the best interests of children (Kopelman, 2004). We propose that instead of defining paediatric research as therapeutic or non-therapeutic, such research should be assessed as ethical based on the risk-benefit or risk-knowledge ratio that can lead to generalisable knowledge (Kruger et al., 2014, pp. 63–70). Many essential studies have been ruled out without assessing their risk-benefit ratio and their social value (Morrow et al., 2015). It will be unfair to deny children the prospects of benefitting from studies relevant for their wellbeing.

Section 71 of the NHA of 2003 requires only parental/legal guardian consent for all research involving children, while many South African children are under the care of caregivers and not their parents or a legal guardian (Zuch et al., 2012). Section 71 is legislature implemented to protect research participants, including children (Strode et al., 2005). However, the unintended outcome of conforming to Section 71 may not be in the best interests of children as demonstrated by the findings of this study, where not all therapeutic research had direct benefits and where non-therapeutic research often did not pose any increase of risk more than minimal risk. Some commentators recommend a context-specific approach to assessing the ethics of research with children, including taking into consideration both how to promote the best interests of children as a group, and how to promote the best interests of individual child research participants (Kopelman, 2014).

Such restrictions of Section 71 of the NHA 2003 may negatively impact on paediatric research and create uncertainty in researchers and ethics committees during ethics review (Baines, 2011). The globalisation of paediatric research creates the need for an ethics review framework that is effective and applicable in different cultural contexts and this study provides evidence that the Emanuel et al. (2004) ethics framework is sufficient for such a purpose in the review of child research.

7.2 Recommendations from the literature

1. There is a need to harmonise Section 71 of the National Health Act with other existing child-related Acts to ensure the complete well-being of children. For example, the Act requires that children can only consent to be part of a research when they are 18 years of age. However, the *Children's Act 38 of 2005* states that children can consent independently to medical treatment, and other key health interventions, from 12 years of age, if they demonstrate 'sufficient maturity'. For example, they can consent to HIV testing from age 12, when it is in their best interests, and below the age of 12 if they demonstrate 'sufficient maturity'. They can access contraceptives from the age of 12 and girls can consent to a termination of pregnancy at any age (Strode et al., 2010). Therefore the legal age for consenting to research should be re-considered and be made flexible in some context to allow those below 18 years to independently consent to research.

2. There is a need to ensure convergence between the National Health Act and certain ethics guidelines. Other South African ethical guidelines take a different but practical approach to child research. These include the Department of Health's *Guidelines for good practice in the conduct of clinical trials* (2006) which recommends the assessment of studies with children based on the risk-benefit ratio as well as the social benefit of such studies and Department of Health's *research ethics guidelines* (2015b) which adopts a more nuanced approach to child research. The NHA should adopt the guidelines for good practice in the conduct of clinical trials (2006) and assess research involving children based on risk-benefit assessment and not on the mere fact of the study being therapeutic or non-therapeutic. Furthermore the emphasis on parental or guardian consent should be extended to consent by care givers who may not necessarily be legal guardians. One

of the studies reviewed, had mentioned excluding a child from participating in the study because of the non-existence of a parent/legal guardian for that child to consent for the child.

7.3 Recommendations from the empirical findings

1. The majority of the non-therapeutic studies reviewed were associated with potentially minimal risk studies whilst the majority of the therapeutic studies were associated with more than minimal risk. Moreover, some therapeutic studies offered no direct benefits to their participants. This implies that, too much emphasis should not be placed on studies labelled as non-therapeutic as this may be distracting and undermine other important variables such as risks and benefits in reviewing proposals.

2. The study also revealed the exclusion of children from research even when the studies could have benefitted because there were no parent/guardian to consent on their behalf. This requirement by the Section 71 of the NHA for only parental/legal guardian consent for all research involving children is not in the best interest of children as there are children being properly taken care of by persons not recognised by law as parent/guardian. This calls for an urgent amendment of that section of the act in order to ensure the best interests of all children, through their involvement in research. Future research could consider areas such as consultation with community/stakeholders representatives and results dissemination. Further studies could be considered surrounding indirect versus direct benefits in paediatric research as well as caregiver consent versus parental/guardian consent and their implications.

Chapter 8: Study limitations

The research aimed at generating a basic understanding and not testing validity or reliability of hypotheses inferred from previous studies. The study also only analysed sixty-eight journal articles; hence, the findings are not necessarily representative of paediatric research in South Africa and cannot be generalised to the wider population of all studies involving children in the country.

Information collected involved existing publications in the public domain with very limited information. Therefore relevant and detailed evidence may have been missed because the review excluded full reports of studies as well as their proposals. Future research should employ a more detailing qualitative method to expand upon the results of this study.

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Appendices

Appendix 1: Proposal Review Checklist

Section A: SA National Health Act No 61 Of 2003

Unique Identifier: _____

1. Age range of participants [1] 0-28 days (neonates) [2] Under 1 year [3] 1 – 5 years [4] 6 – 11 years [5] 12 – 17 years
2. Type of Research [0] Therapeutic [1] Non therapeutic
3. If therapeutic, was it clinical or an intervention? [1] Clinical [2] Intervention
4. If non-therapeutic, was it; (tick box) [1] Social [2] Educational [3] Psychological [4] Physiological [8] Not applicable
5. 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 children? (tick box) [1] Yes [0] No
6. Was the research in the best interests of the minor? (tick box) [1] Yes [0] No
7. Could the research objective be equally achieved if the research was conducted on an adult? [1] Yes [0] No
8. Level of risk of the study [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

9. What were the potential risks to the children?

[1] Physical risks

[2] Social risks

[3] Emotional/Psychological risks

[4] Economic risks

[5] Legal risks

10. Determine the risk-benefit ratio and if there was a net-risk involved using the table below

Research		**Standard care**	
Procedure	Risk/Burden-Benefit Assessment	Procedure	Risk/Burden-Benefit Assessment
Net overall risk/burden		Net risk/burden	

11. Did the research present a favourable risk-benefit ratio? (tick box)

[1] Yes

[0] No

12. Are consent and assent mentioned in the article? (tick box)

	Yes	No	N/A
Consent for parent/guardian	☐	☐	☐
Assent for child	☐	☐	☐
Was any potential child participant excluded from a	☐	☐	☐

	study due to lack of consent from legal guardian/parent?			
	Was parental consent waived for any of the studies?	☐	☐	☐

Section B: Framework for Ethical Research proposed by Emanuel et al. (2004)

A. Collaborative partnership?

1. Was it a multinational research?

   [1] Yes

   [0] No

2. Were there any local principal or co-investigators on the research team?

   [1] Yes

   [0] No

3. Was any research related training for the local stakeholders (e.g. research staff) conducted?

   [1] Yes

   [0] No

B. Social value

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?

   [1] Yes

   [0] 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?

   [1] Yes

   [0] No

   [8] Not able to determine

   If yes, which kind of ancillary care was provided?

C. Scientific validity

1. Was the scientific design appropriate?

   [1] Yes

   [0] No

D. Fair selection of study population

1. What was the justification for including children in the study?
2. Was the population selected in such a way as to minimise the risks of the research?
3. [1] Yes

   [0] No

   [5] Not able to determine
4. Was participant selection fair?

   [1] Yes

   [0] No

   [5] Not able to determine
5. Were there any more vulnerable children (disabled, mentally handicapped, etc.) involved in the study?

   [1] Yes

   [0] No

   [5] Not able to determine

   If yes, which measures were put in place to ensure their protection?

E. Favourable risk-benefit ratio

1. Did the study provide a favourable risk-benefit ratio?

   [1] Yes

   [0] No

F. Informed consent

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

   [1] Yes

   [0] No

   [5] Not able to determine
2. If yes, who in the community was consulted?
3. Was the consent form translated in the local language of the host community?

[1] Yes

[0] No

[5] 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

[0] No

[5] Not able to determine

If yes, how did the proposal outline how it will be achieved?

G. Independent Review

4. Was the study proposal reviewed by an independent Research Ethics Committee?

[1] Yes

[0] No

H. Respect for recruited participants and study communities

1. What measures were put in place to protect the confidentiality and privacy?
2. If the study was a clinical trial, would products of the study be made available to participants?

[1] Yes

[0] No

Appendix 2: Key variables used for data collection

	Key variable	Source of variable
1	Age range of child participants	
2	Is the research therapeutic or non-therapeutic? *Therapeutic research: Interventions that hold out the prospect of direct health-related benefit for the child participant.* *Non-therapeutic research: Interventions that do not hold out the prospect of direct health-related benefit for the child participant.*	South African NHA
3	Any 'more vulnerable' children in the study?	Emanuel et al. (2004)
4	Was study design appropriate?	Emanuel et al. (2004)
5	Type of study risk to participants?	Emanuel et al. (2004)
6	Was study motivation appropriate for children?	Emanuel benchmarks
7	Was consent mentioned in the study?	South African NHA/ Emanuel et al. (2004)
8	Was assent mentioned in the study?	South African NHA/ Emanuel et al. (2004)
9	Was the study approved by a REC?	Emanuel et al. (2004)
10	Protection of confidentiality and privacy mentioned?	Emanuel et al. (2004)
11	Was study in the best interests of children/patients?	South African NHA/ Emanuel et al. (2004)
12	Could research objective be achieved if study was done in adults?	Emanuel et al. (2004)
13	Was research likely to add significantly to knowledge?	Emanuel et al. (2004)
14	Was the study multinational?	Emanuel et al. (2004)
15	Any local investigators involved in the study?	Emanuel et al. (2004)
16	Any research-related training mentioned for local investigators?	Emanuel et al. (2004)
17	Is there justification for including children in the study?	Emanuel et al. (2004)
18	Who were the beneficiaries of the study? 1. Children 2. Children and adults	Emanuel et al. (2004)
19	Did study provide any direct benefits to participants?	South African NHA/ Emanuel et al. (2004)
20	Was any provision made for ancillary care to participants?	Emanuel et al. (2004)
21	Study population selected in ways to minimise risk?	Emanuel et al. (2004)
22	Fair participant selection?	Emanuel et al. (2004)
23	Was the community consulted in establishing incentives?	Emanuel et al. (2004)
24	Any need for supplementary community and familial consent procedures?	Emanuel et al. (2004)
25	Was consent form translated into local language of the host community?	Emanuel et al. (2004)

Appendix 3: University of KwaZulu-Natal research ethics clearance

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

02 April 2015

Ms Iren Honam Tsey 214580934
School of Applied Human Sciences
Pietermaritzburg Campus

Dear Ms Tsey

Protocol reference number: HSS/0109/015M
Project title: Child research compliance with Section 71, South African National Health Act 2003.

Expedited 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: Dr Nicola Barsdorf and Professor Mariana Kruger
cc Academic Leader Research: Professor D McCracken
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) 31 260 3587/8350/4557 **Facsimile:** +27 (0) 31 260 4609 **Email:** ximbap@ukzn.ac.za / snymanm@ukzn.ac.za / mohunp@ukzn.ac.za
Website: www.ukzn.ac.za