ENROLMENT OF CHILDREN IN CLINICAL TRIALS: BOTSWANA PERSPECTIVE

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South African Research Ethics Training Initiative

(SARETI)

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Declaration

I declare that the thesis titled "Enrolment of children in clinical trials: Botswana perspective", which I hereby submit for the degree of Master of Social Sciences at the University of KwaZulu-Natal, Pietermaritzburg, is my own work and has not been submitted for a previous degree at any other tertiary institution.

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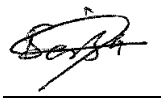
Signature: 

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Abstract

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Paediatric clinical trials are crucial to ensure safety and efficacy of medicines in children. This study explored parents' perceptions in Gaborone, Botswana, regarding children's participation in clinical trials. One hundred participants completed a self-administered questionnaire. The results showed that 93% of the participants had a good knowledge of clinical trials; 74% thought that children would benefit from clinical trial participation; 63% would not enrol their children in clinical trials; 55% suggested that children should only be enrolled once they have reached the age of 18 years; and 71% reported that only children with an active disease should be enrolled. A large proportion (82%) reported that children's participation should be voluntary, while joint parental consent was supported by 93% of responders. Regarding children's assent 91% deemed respect for children's assent essential, although 52% thought that children's assent should not override the parental decision. There was a statistically significant correlation between finding clinical trials in general important and children's participation in clinical trials ($p=0.008$, Fisher's Exact Test), as well as the need for individual consent $p<0.0001$, Chi-Square). There was also a statistically significantly association between respondents, who would allow their children's participation in clinical trials and who would encourage their family members and friends' participation in clinical trials ($p=0.0001$, Chi-Square). An overwhelming 94% advocated for special regulations in Botswana to govern paediatric clinical trials. Almost all participants (99%) explicitly expressed the opinion that there should be global regulations for paediatric clinical trials.

KEY WORDS

Children, Clinical Trial, Informed Consent, Proxy Consent

List of Acronyms

AIDS	Acquired Immune Deficiency Syndrome
BPCA	Best Pharmaceuticals for Children Act
CIOMS	Council for International Organization of Medical Sciences.
DoH	Declaration of Helsinki
EFGCP	European Forum for Good Clinical Practice
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IPTpd	Intermittent Prevention Therapy post-discharge
IRB	Institutional Review Board
NIH	National Institutes of Health
NTR	Non Therapeutic Research
OHRP	Office of Human Research Protections
PREA	Pediatric Research Equity Act
REC	Research Ethics Committee (often also referred to as IRB)
UK	United Kingdom
US	United States of America

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Chapter 1

Introduction

1.1 Orientation and Motivation for the study

According to Cato and Peterson (2002) approximately 80% of prescription medicines approved by the United States of America (USA), Food and Drug Administration (FDA), and marketed in the United States are not approved for use in children. This is due to the evolving physiology of children, which complicates drug development for children (Klaus, 2008). Children should benefit from new drug developments (Maxine, 1993) and clinical trials in children are essential to establish the safety and efficacy of medicines and vaccines (World Health Organization (WHO) Guideline, 2007).

Several international research ethics guidelines, for example the Declaration of Helsinki, provide guidance to ensure the protection of vulnerable participants, such as children, in research (Declaration of Helsinki (DoH), 2008). Leornard and Glantz (1996) suggested that this very important research should proceed only when the welfare of the participants is scrupulously protected. The key question in this investigation is whether the Botswana population will enrol their children in clinical trials.

Chapter 2

Literature Review

2.1 The need for clinical trials on children

Drugs can only be labelled for use in children if there is evidence of safety and efficacy in this population, which necessitates clinical trials involving children as participants (Kauffman, 1994). More than 90% of drugs prescribed in neonatal intensive care units are not licensed for neonates, while up to 30% of drugs prescribed by general practitioners have not been tested in children (Sutcliffe, 2003) – i.e. are prescribed "off-label". Conroy et al. (2000) defined off-label use as the practice of prescribing pharmaceuticals for an unapproved indication or in an unapproved age group, unapproved dose or unapproved form of administration. Gupta and Sachdev (2003) reported that off-label use might result in toxicity including mortality and serious unexpected adverse reactions, while inappropriate dose may cause ineffectiveness.

Due to the evolving nature of the physiology of the child from birth to adulthood, it is not possible to extrapolate safety and efficacy data from adult studies to children (Cvetkovich-Muntañol, 2011). Children have a greater water compartment, smaller airways, less protective muscle around their organs, a higher metabolic rate, lower blood pressure, and a less mature immune system than adults (Cvetkovich-Muntañol, 2011). Differences between children and adults that affect medical care also extend beyond the physical, and include communication barriers and emotional development (Cvetkovich-Muntañol, 2011).

Off-label or unlicensed drug use has focused the attention on the need for clinical trials involving children as participants to address safety and efficacy issues (Smyth, 2001). In the United States (US), the federal government and the National Institutes of Health (NIH) require the inclusion of

children in a broad range of research, while the Food and Drug Administration (FDA) offers 6 months additional marketing exclusivity to pharmaceutical firms that submit data pertaining to the use of tested agents in paediatric populations (NIH, 1998). The NIH has indicated that 70% of the medicines given to children have only been tested in adults.

According to Bhatti and Sanders (2011) the US leads the rest of the world by their early recognition of the need for legislation to ensure that medicines are developed for, and tested in, the paediatric population. The Food and Drug Administration Modernization Act (FDAMA) was promulgated in 1997, with paediatric exclusivity provisions to stimulate clinical trials in the paediatric population. This Act was followed by the Best Pharmaceuticals for Children Act (BPCA) in 2002, as well as the Paediatric Research Equity Act (PREA) in 2003, which according to Bhatt and Sanders (2011) all aimed to ensure that these necessary paediatric clinical trials were conducted to provide adequate information for product labelling in the paediatric population.

Following the US initiatives, the European Forum for Good Clinical Practice (EFGCP) called for legislation in Europe to promote research with children (EFGCP, 2004). In 2004, the Health Minister of the United Kingdom (UK) announced an initiative to encourage the development of medications for children, as the British government intended to spend 100 million pounds on new research involving medicines for children (Wendler, 2006).

Despite the vast disease burden affecting children in the developing world, there is still a paucity of research being done that directly relates to the health needs of children (World Health Organization (WHO), 2004). This disease burden among children in developing countries

challenges the international community, as well as national and local communities, to find an appropriate balance between the need for paediatric clinical trials, and the need to meet safety and other ethical requirements in evaluating, for example, vaccines in children (WHO, 2004). Well-planned and controlled clinical trials within the paediatric population are essential to ensure access to effective medicines for children (Boots et al., 2007).

2.2 Children as Special Research Population

Grodin and Glantz (1994) regard children as a particular vulnerable population due to the tension between protecting children from harm and exploitation, versus increasing knowledge regarding better medicines and interventions for children. In the 1970s, the National Commission for the protection of human subjects of biomedical and behavioral research issued the Belmont Report regarding the protection of human subjects in research (Belmont Report, 1979). The Commission offered additional guidelines and motivated for children to be classified an especially vulnerable population because they cannot consent for themselves and suggested that research should be done first on animals, whereafter, if possible and appropriate, on adult humans (US National Commission for the Protection of Human Subjects, 1977).

The child's ability to assent or consent is linked to their understanding and their maturity level. Burke et al. (2007) added that their maturity level necessitates additional protection, since informed consent obtained is proxy consent by the parents and assent by the child if age appropriate assent can be elicited, usually only from 7 years and older. Assent is defined as an 'agreement' by an individual not competent to give legally valid informed consent (e.g. a child or a cognitively impaired person), to agree to research participation or an intervention, and is a necessary requirement for the respect of the evolving autonomy of the child (Agulanna, 2010).

Children are in the process of developing cognitive competency, and have limited social power, which may limit their understanding of the research process, and renders them particularly vulnerable in research (Fombad, 2005). According to Green et al. (2003), imparting sufficient, comprehensible information to distressed parents and ill children may be difficult and therefore pose a barrier to their capacity for decision making.

2.3 International Guidelines on Research with Children

Section B, paragraph 15 of the Declaration of Helsinki (DoH) requires that if a research subject is physically or mentally incapable of giving consent or is a legally incompetent minor, the informed consent must be sought from the legally authorised representative in accordance with applicable law (DoH, 2008). The DoH further stresses that the above-mentioned groups should not be included in research unless the research is necessary to promote the health of the population represented and it cannot instead be performed on legally competent persons (DoH, 2008). Similar guidance provided in the Belmont Report mandates research participants with severely limited comprehension, inclusive of infants and young (Belmont Report, 1979). An investigator is required to ensure that the intended research cannot be conducted effectively on adults before including children as research participants (Council for International Organization of Medical Sciences (CIOMS), 2002).

Institutional Review Boards (IRBs) reviewing research involving children as participants, are required to consider the risks of harm or discomfort inherent in the proposed research and the anticipated benefits to the child participants or society in general (Office for Human Research Protections (OHRP), 2005). Based upon this assessment of risks and anticipated benefits to child

participants or others, the IRB must classify research into risk categories; the OHRP defined four risk categories in subpart D for child research participants (OHRP, 2005).

The United States and Europe require inclusion of children in a broad spectrum of research, especially drug trials where children can benefit directly from research, as mentioned above. The United States further requires the exclusion of children from research if: (i) the knowledge being sought in the envisaged research is already available for children or will be obtained from another ongoing study; (ii) the research topic being studied is not relevant to children; (iii) there is insufficient data available in adults to judge potential risk in children; and (iv) there are laws/regulations barring the inclusion of children in the research, and children can be excluded from research based on issues of study designs which preclude direct applicability of hypotheses and/or intervention for both children and adults, including different cognitive, developmental or disease stages or different age-related metabolic processes. e.g. longitudinal studies (OHRP, 2005).

In Africa, many countries have an established ethical infrastructure, which caters for paediatric research; the South African regulations place extra requirements in paediatric research by classifying research as either therapeutic or non-therapeutic. Therapeutic studies are defined as those that seek generalizable knowledge but intend to provide medically beneficial and acceptable therapy for the individual, while non-therapeutic studies are defined as those that seek generalizable knowledge but do not intend to provide therapy to benefit the individual directly (Kopelman, 2000). Section 71 of the South African Health Act no 61 of 2003, describes the conditions under which children may be included as research participants. The conditions outlined for non-therapeutic research (NTR) includes an obligation to obtain consent from the

Minister of Health, who has to determine if NTR involving minors meets scientific, ethical and public policy justifications (South African Health Act).

Although the South African Health Act clarifies a number of issues, it also creates new problems by requiring ministerial consent for all NTR involving minors regardless of risk level (Strode, 2007). According to Strode et al. prior uncertainties with non-therapeutic child research have largely been clarified by section 71(3), making the purpose of this additional procedural requirement unclear, hence an assumption that the South African parliament wished to provide additional protection for minors in high-risk research without direct benefits, as is provided for in other jurisdictions, e.g. in the US Code of Federal Regulations.

The Ugandan research guidelines require the establishment of adequate provisions for the solicitation of children's assent in order to enrol children in research that does not offer a prospect of direct benefit (UNCST, 1998). The Kenyan guidelines for the ethical conduct of biomedical research involving human subjects, advocates respect for children's dissent unless there's no other medical alternative from which the child could benefit (Kenya NSCT, 2004).

Sammons et al. (2007) and Dalla-Vorgia et al (2001) researched US, European and British guidelines, which all require parental or legal representative consent for a child's participation in research and there is great emphasis on seeking a child's assent and respecting their dissent.

2.4 Botswana Context

Currently in Botswana, research with children poses many challenges due to lack of established ethical-legal infrastructure, despite the existence of numerous international research guidelines. There is a significant distinction in the statutory definition of a child in Botswana; the Botswana Mental Disorders Act defines a child as anyone below the age of 16, while section 49 of the

Interpretation Act of the Constitution, notes the age of majority as 21. The Penal Code of Botswana (1964) sets the age of consent to sexual activity as the age of 16, whereas the Children's Act (Botswana Children's Act, 2009) regards anyone below the age of 18 as a child. Although the Penal Code fixes the age of consent to sexual activity at 16, Section 67(1)(b) of the Constitution permits sexual activity to any citizen of Botswana who has attained the age of 18 (Fombad, 2005 (a). In Botswana, children below the age of 7 are termed 'infants' and are regarded as lacking the capacity and ability to give consent under any circumstances (Fombad, 2005). For minors, those over 7 years of age, but still under the age of majority, the need for parental or legal guardian consent depends on 'the age and maturity of the child and his ability to understand the whole procedure' (Fombad, 2005 (b). To address the above conflicting definitions, a clear definition of a child is required, as well as an established effective ethical-legal infrastructure, which will promote enrolment of children in clinical trials. At the same time there is lack of regulatory framework for clinical trial research with children in Botswana.

Botswana, as a sub-Saharan African country, has major infections as part of their disease burden, which includes a high prevalence of Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) (UNICEF Botswana Statistics, 2009). Nearly a quarter (23.9%) of the population aged 15–49 is infected, as well as an estimated 150 000 children aged between 0–14 (UNICEF Botswana Statistics, 2009). With a population of approximately 1.8 million people these numbers are devastating. The latter has lead to rapidly increasing number of clinical trials, including HIV vaccine trials, being conducted in the country, hence the need to conduct well-regulated trials on children as they too are beneficiaries of future biomedical vaccines.

The purpose of this research is to determine whether parents will allow their children to participate in clinical trials. The results of the study may yield important knowledge, to guide ethicists, researchers, policy-makers and relevant stakeholders in developing specific paediatric research guidelines in Botswana.

Chapter 3

Aim and Methodology

3.1 Aims of the Study

The aim of the study is to explore the perceptions of parents in Botswana, regarding the enrolment of their children as research participants in clinical trials.

3.2 Research Question

What are the perceptions of parents in Botswana regarding enrolment of children in clinical trials?

3.3 Research Methodology

This is a questionnaire-based survey. Participation was voluntarily and all participants were literate. According to Babbie and Mouton (2001) data analysis in the quantitative paradigm entails that the analyst breaks data down into constituent parts to obtain answers to research questions. This further needs interpretation of the analysed data to elicit meaning and answers to research questions.

3.4 Sampling Design and Participant Selection

For the purpose of this study the necessary characteristics for inclusion in the study were; being a parent older than 18 years with children younger than 18 years of age.

The participants were selected using convenience sampling and were recruited in Gaborone at the Princess Marina Hospital at the under-5 children's clinic, when they brought their children for their monthly check-up. Study aim and procedures were thoroughly explained to potential

participants and they were informed that participation was completely voluntary, and that their decision not to participate, would in no way affect the services they receive at the clinic.

Participants provided written informed consent and the informed consent form and questionnaires were available in the two official languages in Botswana (Setswana and English; see appendices 2, 3, 4, 5, 6). This ensured that the participants fully understood the requirements of the study so that they could fully express themselves without any language barriers. In light of voluntary participation, participants were made aware of their right to withdraw from the study at any time, if they so wished.

3.5 Statistics

SPSS was used to analyse the data, the Chi square and Fisher tests were used to measure the correlations. Cronbach's alpha test was used to measure internal consistency, to determine how closely related a set of items is as a group. Six items were used to measure cronbach - alpha. (1. Have you ever-participated in clinical trials before? 2. Importance of clinical trials; 3.Should children participate in clinical trials? 4. Parents who would allow their children to enrol in clinical trials, 5.Should a child's decision (assent) override the parent's decision or vice versa?; And 6. As a parent do you feel that there should be guidelines or regulations in place that protects children in health research?

3.6 Ethical Considerations

Both the Botswana National Health Research Ethics Committee (appendix 7) and the University of KwaZulu-Natal Humanities and Social Sciences Research Ethics Committee approved the

study (appendix 8). All participants provided written informed consent for participation as discussed in section 3.4.

Participants were assured of anonymity during and after completion of the study; no identifiable data such as names, identity card numbers or any other information that could be linked to the participant, was requested. There was no direct benefit for participation but may have future benefit by sensitising the parents to the need for paediatric clinical trials. There were no risks associated with participation in the study.

Chapter 4

Empirical Findings

4.1 Demographic Data

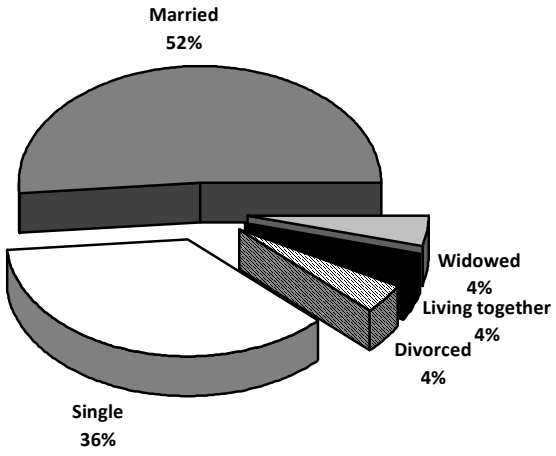
4.1.1 Age

The participants' mean age was 36 years with a range of 24 to 82 years. The majority (72%) were between 20 to 40 years, while 26% were between 40 to 60 years and 2% were between 60 and 85 years. The male to female ratio was 1:1.5.

4.1.2 Marital Status

(n=100)

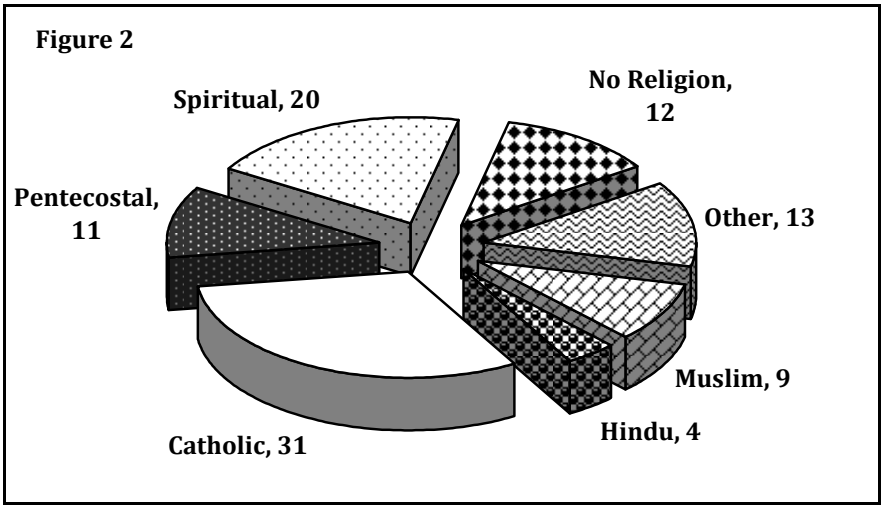
Figure 1



Half (51%) of the participants were married, while 36% were single parents and 12% were either widowed, divorced or living together (Figure 1).

4.1.3 Religion

(n=100)



The majority (42%) were Christian (31% Catholics and 11% Pentecostal), while 20% reported a belief in spiritual healing. Another 12% reported no adherence to any religion, 9% and 4% indicated being Muslim and Hindu respectively, while 13% indicated affiliation to other religions (Figure 2).

4.1.4 Educational Level

The majority (61%) of the parents completed tertiary education, while 28% completed secondary school. Another 8% partially completed secondary school, and 2% completed primary school, and only 1 participant never attended school.

4.1.5 Employment Status

More than half (67%) of the participants were employed, 28% were unemployed, 3% were self-employed and 2% responded by indicating "other" as employment status. Income per month ranged from more than P4000 per month (56%), to P2000–P4000 per month (16%), while the lowest income was less than P1000 per month (1%) and nearly a third (27%) had no income at all (P7.2 = 1 US$).

4.2: Table 1: Responses Regarding Clinical Trial Participation

Question	Options	Percentage	Total
Number of children	1	52%	100%
	2	29%	
	3	17%	
	4	2%	
Have you ever heard about clinical trials?	Yes	93%	100%
	No	7%	
How did you hear about clinical trials?	Health Facilities	12%	100%
	Radio	0	
	Television	88%	
	Friends and relatives	0	
Have you ever participated in clinical trials?	Yes	7%	100%
	No	93%	
Do you think clinical trials are important?	Yes	71%	100%
	No	27%	
	Not answered	2%	
Would you encourage your family/friends/relatives to participate in clinical trials?	Yes	60%	100%
	No	40%	
Should individuals make decisions on their own to participate in clinical trials?	Yes	61%	100%
	No	39%	
Motivation for encouraging independent decision making.	Respect for human rights	28%	100%
	Accountability for participation consequences	16%	
	Individuals should have attained the age of majority	5%	
	Individual consent is extremely important	37%	
	No motivation	14%	

Fifty-two percent of the study population had only one child, while 48% had more than one child. The mean was 1.7 children per family (range 2–4 children/family) (Table 1). An overwhelming 93% of participants knew about clinical trials, with only 7% indicating no knowledge of clinical trials (Table 1). Very few (7%) had participated in clinical trials, all of which were HIV/AIDS related studies, while 93% had never participated (Table 1). The majority heard about clinical trials through the media, specifically television (88%), whereas 12% heard about clinical trials from health facilities (inclusive of the 7% who participated in HIV/AIDS clinical trials).

The majority (71%) thought that clinical trials are important, 27% did not find clinical trials important, and 2% abstained from answering this question (Table1). The reasons for finding clinical trials important included the importance to develop curative and effective medicines (40%), to generate new knowledge and safety data (14%) and to find a cure for HIV/AIDS (2%). A small proportion of the participants (6%) raised their concern about the participants' health post trial as they thought clinical trials were dangerous, while 5% suggested that the conduct of clinical trials should involve animals instead of human beings. A minority (13%) did not answer this question.

Regarding the participation in clinical trials by family and friends, 60% reported that they would encourage participation, which was statistically significantly associated with respondents who would enrol their children in clinical trials (Table1; p=0.0001, Chi-Square). The majority (61%) stated that individuals should make independent decisions regarding participation in clinical trials (Table 1). The reasons quoted for the need for independent decision-making included

respect for human rights (28%) and accountability for consequences (16%). Some participants suggested that individuals should only make independent decisions if they have attained the age of majority (5%). For 37% of participants, parental consent was extremely important when minors are enrolled, whilst 14% did not give any motivation for their response (Table 1).

4.3: Table 2: Responses Regarding Enrolment of Children

Question	Option	Percentage	Total
Should children be enrolled in clinical trials?	Yes	37%	100%
	No	63%	
Motivation for inclusion or exclusion of children in clinical trials	Immaturity and inability to independent decision-making	32%	100%
	Fear of exposure to harm	9%	
	Alternative ways for testing medicines other on children	5%	
	Children can be exploited and abused in research	4%	
	Children are a gift from God	3%	
	Children should first attain the age of majority	3%	
	No reason provided	44%	
At what age should children be enrolled in clinical trials?	Birth – 5 Years	13%	100%
	Over 5 years	3%	
	Over 10 years	12%	
	18 years	55%	
	21 years	12%	
	None at all	5%	
Do you think clinical trials are beneficial to children?	Yes	74%	100%
	No	25%	
	Not answered	1%	
Why are clinical trials beneficial to children	Children will have access to treatment during clinical trials	40%	100%
	Access to vaccines	19%	
	Age specific treatment will be defined for children	3%	
	Clinical Trials are risky	10%	
	Respect for children's rights	5%	
	No motivation	23%	
When should children be enrolled in clinical trials?	If the disease affects children only	46%	100%
	If there is no alternative to testing the medicines	45%	
	Every time there is a clinical trial	4%	
	If the disease affects both children and adults	5%	

More than half of the participants (63%) did not support inclusion of children in clinical trials, versus 37% who did (Table 2). Nearly half of the respondents (44%) did not provide any reason for refusal to allow children to be included in clinical trials. Another third (32%) reported children's immaturity and inability to independent decision-making, while a minority reported the following as reasons: potential exposure to harm (9%); alternative ways of testing medicines than on children (5%); children are innocent and precious gifts from God (4%); and exploitation and abuse (3%). A minority (3%) suggested that children should have attained the age of majority to participate in clinical trials.

Eighteen years was deemed the rightful age to enrol children in clinical trials (55%), while the age of 10 years was considered by 12% of participants. Further suggestions were the ages of 2 years (12%), age 5 and above (3%) and any age from birth (13%). Five participants reported that children should never be enrolled in clinical trials (Table 2).

Almost three quarters (74%) of participants felt that children would benefit from clinical trials, while 25% did not believe that clinical trials were beneficial to children. One participant did not answer the question (Table 2). The proportion of respondents that thought children should participate in clinical trials, also found clinical trials in general important, as well as supporting individual consent for research participation, which was statistically significant (respectively $p=0.008$, Fisher's Exact Test; $p<0.0001$, Chi-Square). They would also allow their children to participate in clinical trials, which was also a statistically significant association ($p<0.001$, Chi-Square).

Reasons for finding clinical trials beneficial to children included the treatment that children would receive (40%), protection against diseases in vaccination clinical trials (19%) and the determination age specific dose (3%). Ten percent of participants found the risks in clinical trials, including the risk of death, to be problematic. Five percent of participants suggested that children's rights should be respected; hence children should not be enrolled against their will. 23% did not sight any motivation.

Regarding the type of clinical trials, 46% of participants responded that children should be included if the disease affects only them; while 45% thought that children should only be enrolled if there are no other alternatives to testing the medicines. A minority (5%) supported enrolment if the disease being tested affects both children and adults and another 4% responded that they would enrol their children every time there is a clinical trial (Table 2).

4.4 Table 3: Responses Regarding Consent Issues

Questions	Options	Percentage	Total
Which children should be enrolled in clinical trials?	Only sick children	71%	100%
	Only Healthy children	11%	
	Both sick and healthy children	12%	
	None	6%	
Do you think that children have the capacity to make a decision to participate in clinical trials?	Yes	12%	100%
	No	88%	
Would you ever consider to give permission to your child for participation in clinical trials	Yes	36	100%
	No	64	
Who should give permission for children to take part in clinical trials?	Both parents	93%	100%
	Mother	1%	
	Father	2%	
	None	4%	
What should happen when a child does not want to participate in clinical trials?	Leave the child alone	91%	100%
	Force the child	7%	
	Persuade the child	1%	
	Not answered	1%	
Should children's participation in clinical trials be voluntary?	Yes	82%	100%
	No	18%	
Should a child's assent override the parental consent?	No	52%	100%
	Yes	47%	
	In our culture, a child can't say no	1	
Is there a need for special Regulations in Botswana for enrollment of children in clinical trials?	Yes	94%	100%
	No	4%	
	Not answered	2%	
Is there a need for global regulations to govern paediatric clinical trials?	Yes	99%	100%
	No	0	
	Not answered	1%	

A majority of participants (88%) expressed that children do not have the capacity to consent to clinical trials, while 12% thought that children have the capacity to consent. The participants who found paediatric clinical trials important, also reported that children have the capacity to consent to clinical trial participation (p=0.0092; Fisher's Exact Test). With regard to parental consent: 93% reported that both parents should provide consent; 4% felt that no one should give consent or allow children to be enrolled in clinical trials; 2% thought fathers should, while 1% felt that a mother should be the parent to provide consent. When asked what should happen if a child refuses participation (dissent) in a clinical trial, 91% felt that a child's dissent should be respected; 7% would attempt to persuade the child to participate, while a minority (1%) felt that children should be forced. One participant did not respond to this question (Table 3).

Majority of parents (64%) will not give permission to their children to participate in clinical trials, while 36% would. 82% of parents supported children's voluntary participation in clinical trials while 18% disagreed (Table 3). More than half of responders (52%) were of the opinion that a child's assent should not override parental decision, while 47% articulated that a child's assent is more important than parental decision. One participant cited that culturally a child couldn't object to its parent's decisions (Table 3).

A large proportion (94%) of participants reported the need for special regulations in Botswana for the inclusion of children in clinical trials; 4% did not see the need, while 2% did not respond (Table 3). Reasons given were: special regulations will protect children from potential harm and exploitation (68%), special regulations will govern researchers (6%), and guard against any illegal practices (2%). For 5% of participants, special regulations will inform and educate the

public whereas 4% reported that special regulations would ensure respect for the rights of children. There was no motivation given by 15% of participants.

Almost all participants (99%) explicitly expressed the opinion that there should be global regulations for paediatric clinical trials, while only 1 participant did not answer the question (Table 3).

4.5 Suggestions

Participants reported the following: children should be enrolled as a last resort in clinical trials (15%) and clinical trials should yield direct benefit (31%). Parents were urged to help children to make decisions and not force them to do anything (4%). The need to have guidelines and regulations, which clearly specify the inclusion and exclusion criteria of children in clinical trials, was emphasised (2%). One participant was against medical experimentation on children and another one called for the government to ensure adequate protection of children's lives. Nearly half (46%) did not have any additional comments.

4.6 Summary

The study findings revealed the following for the 100 participants:

- 94% advocated for special regulations in Botswana to govern paediatric clinical trials;
- 93% of participants said that they had background knowledge of clinical trials;
- 93% suggested joint parental consent, and 52% were of the opinion that a child's assent should not override the parental decision;
- 91% felt that a child's dissent should be respected;
- 82% advocated for children's voluntary participation;
- 74% regarded paediatric clinical trials as important and beneficial

- 71% noted that only children with an active disease should be enrolled;
- 64% will not enrol their children in clinical trials;
- 55% suggested the enrolment age to be 18 years.
- There was a statistically significant association between support for family and friends' participation in clinical trials and enrolment of children in clinical trials (Table1; p=0.0001, Chi-Square).
- There was also a statistically significant association between respondents that will enrol children in clinical trials, and those that find clinical trials in general important, as well as supporting individual consent for research participation, which was statistically significant (respectively p=0.008, Fisher's Exact Test; p<0.0001, Chi-Square). They would also allow their children to participate in clinical trials, which was also a statistically significant association (p<0.001, Chi-Square).

Chapter 5

Discussion

5.1 The Importance of Paediatric Clinical Trials

This study was the first to investigate parents' views regarding enrolment of children in clinical trials in Botswana. Kuiz and Gill (2003) stated that optimal medical care is reliant on evidence-based intervention and there is a significant deficit in our current knowledge of the quality and efficacy of many therapeutic measures in children. Cote et al. (2006) described children as "therapeutic orphans" because of the deficit of appropriate studies in their age group. The majority (71%) of parents in this study reported clinical trials to be important which is in accordance with the findings by Douglas et al. (2011), who explored factors influencing parental decisions to allow their children to participate in paediatric infectious diseases clinical trials. Douglas et al. found that parents believed that clinical trials are helpful (64%) and beneficial to children (70%).

Even though 64% of responders in this study did not support the idea of enrolling their own children in clinical trials, 36% of them expressed that they would enrol their children in clinical trials if the study offered some prospect of direct benefit to the child. Conray et al. (2000) found similar results in which they reported that 59% of parents felt that children should only participate if they receive direct benefit from research. Similar results were also found by Masiye et al. (2008) in a study, which explored why mothers chose to enrol their children in Intermittent Prevention Therapy post-discharge (IPTpd) Malaria Research in Malawi. In contrast, Langley et al. (1998) discovered that most parents enrol their children in clinical trials for altruistic reasons such as the desire to contribute to medical knowledge and desire to help others and that their consent was mainly affected by perceived risk where there is no direct benefit. Langley's study

focused on parents' perceptions in an existing trial, while this study testes parents' perceptions in an hypothetical trial.

A critical issue in paediatric clinical drug trials is defining at which point in drug development children should be enrolled and if healthy children can be enrolled. The International Conference on Harmonization (ICH) (2000) requires that the entire development programme of medicinal products for diseases affecting children exclusively or predominantly, be conducted in the paediatric population beginning with phase I or II. Seventy-one percent of parents in this study suggested that only children with an active disease should be enrolled in clinical studies; almost half (46%) of the responders suggested inclusion of children if the disease for which the drug is tested for, affects only children. These findings are consistent with an American survey of 2 100 parents at the C.S Mott Hospital regarding participation of children in research. Thirty-six percent of parents in that survey noted that they would allow their children to participate if they have the disease being studied (Davis, 2008). Metzger et al. (2008) found similar results, revealing that 91% of parents would consent to enrol their children if the study serves to solve a medical problem from which the child suffers**.** Wendler and Jenkins (2008) also found that 36% of parents would allow their children to be in a study if the child had the disease being studied.

5.2 Consent, Assent and Dissent

Most of the participants' responses mirrored those addressed in paediatric research guidelines, namely, that participation should be voluntary (82%) and that any child should be allowed to dissent or even withdraw, as indicated by 91% of the participants. Fifty-two percent of responders were of the opinion that a child's assent should not override the parental decision. Swartling et al. (2009) researched parental views regarding children's rights to decide about

participation in research. They reported that 41.6% of parents were against children being allowed decisional authority.

Studies exploring the perception of parents regarding children's dissent to participate in research are very scarce. In this study, 82% of parents suggested that children's participation in clinical trials should be voluntary and that children's dissent should be respected (91%).

The majority (55%) of responders suggested the age of 18 as the enrolment age in paediatric clinical trials, contrary to some studies, which have suggested ages between 7 and 14 as possible age group for assent (Ondrusek et al., 1998; Wendler, 2006; Wendler et al., 2003). The Federal Policy for the Protection of Human Subjects (1983) requires that children must be re-consented at the age of 18, using the adult informed consent mechanism in order to continue in the study. The contradictory statutory definition of a child within Botswana legislation and the limited studies exploring parental perceptions regarding the rightful age for consent, assent and dissent for enrolment of children in clinical trials, necessitates further research to explore parental opinions on the latter. It also necessitates studies to determine the ability of Botswana children to assent to clinical trial participation. Weithorn (1982), assessed the competency of children and adolecsents to make informed treatment decision, and found that overall, 14 year olds did not differ from adults and that 9 year olds apperaed less competent than adults with respect to their ability to reason about and understand the treatment information provide.

Ninety-three percent of parents in this study proposed that both parents should give consent for their children's research participation. Similarly Mason and Allmark (2000) revealed that 97% of parents in the Euricon study felt that they should give consent for participation of their children

in clinical research. John et al. (2008) investigated parental views concerning their child's ability to make a decision regarding research participation. In their findings, 75% of responders felt that a parent should make a decision about the study participation.

5.3 Regulation of Clinical Trials

Various countries have established and implemented paediatric specific guidelines and support the inclusion of children in research. In the United States the Office for Human Research Protections (OHRP) (www.hhs.gov/ohrp/policy/) coupled with the Federal Statutes has also joined forces with the FDA (www.fda.gov) to promote development of medicines in children. In Africa, several countries have taken the lead; the South African Good Clinical Practice Guidelines, second version, was implemented in 2006 (http://www.kznhealth.gov.za/research/guideline2.pdf, 2006). The Ugandan and Kenyan National Councils for Science and Technology (NCST) implemented guidelines regulating the conduct of human subject research in 1998 and 2004 respectively (Ugandan NCST, 1998; Kenyan NCST, 2004). The findings of this study by most parents (94%) advocate for specific regulations in Botswana governing the inclusion of children in clinical trials.

5.4 Limitations

The limitation in this study is that most parents were reasonably well educated, with 61% having graduated from tertiary institutions. Despite the high educational level the majority of parents (65%) expressed reluctance to enrol their children in clinical trials. Moseley et al. (2006) conducted a cross-sectional survey of parents' trust in their child's physician. They observed lower levels of trust in those who had tertiary education and private insurance. These findings suggest that well-educated parents from higher socio-economic strata are likely to be more

knowledgeable and may have higher expectations from their child's physician, resulting in lower levels of trust if their expectations are not met (Moseley et al., 2006). Based on the findings of this study, there is a possible relationship between parental education, trust and willingness to enrol one's child in clinical research. These factors are complex and multi-factorial, requiring further research. Another limitation was that the study reached out to only one hundred parents, hence their views may not necessary be reflecting the opinions of all parents in Botswana.

Cronbach-alpha was 0.598, which suggested low internal consistency in the data. It should be noted that Cronbach's alpha, which is closer to 1 reflects the higher internal consistency of the items. The low Cronbach's alpha could be suggestive of the fact that these individual variables cannot be lumped together as they do not measure the same concept.

5.5 Conclusion

The general findings of this study revealed the urgent need to have specific regulations for peadiatric trials in Botswana. Parents in Botswana preferred a joint consent for children's participation in research and were also of the opinion that a child's assent should not override the parental decision. Children's voluntary participation was advocated for as well as respect for children's dissent. Although most parents will not enrol their children in clinical trials, most of them would, if the proposed research yields prospective and direct benefit to the child.

Conducting clinical trials in children is a challenging enterprise at the best of times, and more so when the trial is to be conducted in different countries (Matsui et al. 2003). These challenges include the need for developmentally appropriate outcome measures for children of different ages, the complexities of parental involvement and family decision-making, and the adaptations required in research procedures and settings to accommodate children's physical, cognitive and emotional development (Reider, 2003). Understanding and complying with the special ethical

and regulatory protections in paediatric research constitutes an additional challenge. These various challenges underscore the need for those reviewing research protocols that include children to have adequate expertise in different areas of child health and research. The importance of ethical considerations in international clinical trials involving children cannot be overstated, and adherence to a high ethical standard is essential.

5.6 Recommendations

5.6.1 Recommendations from the literature

Based on the literature review, the researcher would like to make the following recommendations:

i. The fact that children have their own unique medical/health needs and problems, research involving this population should be advocated for to ensure that correct treatments and dosages are formulated for this population. This will prevent the current practice of extrapolating data from adult study results to children and off-label prescriptions.

ii. There is a need for global regulation of clinical trials with children, to avoid flagrant variations between countries. This will lead to harmonised guidelines, and strengthen the protection of all human participants in research regardless of their geographical location.

iii. There is a need for establishment of ethical infrastructures, especially in low-resourced countries where a vast amount of research takes place. This will strengthen the capacity to ethically review research resulting in adequate research oversight and protection of human participants in research.

5.6.2 Recommendations from empirical findings

i. Parents expressed their perceptions regarding their knowledge of clinical trials, in which clinical trials were equated with treatment. To prevent these misconceptions, the researcher recommends that public education regarding clinical trials should be

conducted in all areas where research is conducted in Botswana. Society should be made aware of research that is taking place in their respective communities.

ii. The researcher recommends that there should be national guidelines to regulate clinical trials in Botswana that are conducted on the paediatric population, as this will maximise protection of human participant research and the benefits of research. This will also make the work of research ethics committees easier in terms of reviewing paediatric studies.

iii. The researcher recommends that the definition of a child should be revised, documented and harmonised to avoid confusion. The age of assent should be clearly defined and specific research that is permissible with respect to age should be determined.

iv. Lastly, further research on issues surrounding child assent and children's capacity to make autonomous decision for research participation versus parental consent in developing countries is recommended.

5.6.3 Concluding statement

It is evident that paediatric clinical trials are critical and potentially beneficial. This study has explored parental perceptions regarding paediatric clinical trials and found that parents were protective of their children and only supported clinical trials with the potential for direct benefit. There is also an urgent need for the establishment of an ethical-legal infrastructure to promote, regulate and govern paediatric medical research in Botswana.

References

Agulanna, C. (2010). The requirement of informed consent in research ethics: Procedure for implementing a crucial ethical norm in African communal culture. *EuropeanjJournal of scientific research, 44*(2), 204-219.

Babbie, E., Mouton, J. (2001). *The practice of social research*. Cape Town: Oxford University Press.

Bhatti, S., Sanders, C. (2011). Paediatric Regulations US and EU. Retrieved on September 9, 2011, from www.samedanltd.com

Boots, I., Sukhai, R.N., Klein, R.H., Holl, R.A., Wit, J.M., Cohen, A.F., & Burggraaf, J. (2007). Stimulation programs for pediatric drug research. Do children really benefit? *European Journal of Pediatrics, 166*(8), 849-855.

Botswana 2009 Children's Act. (n.d). Retrieved on November 28, 2011, from http://www.aclr.info/images/stories/uploader/Publication_files/Acts/Botswana_Children_Act_08_of_2009.pdf.

Botswana Mental Health Disorder Act. (n.d). Retrieved on November 28, 2011, from http://www.laws.gov.bw/Volume%2013/Chapter%20%2063%2002%20Mental%20Disorders.pdf.

Botswana HIV/AIDS Statistics.(n.d). Retrieved September 9, 2010, from http://www.unicef.org/infobycountry/botswana_statistics.html.

Burke, T., Abramovitch, R., & Zlotkin, S. (2005). Children's understanding of the risks and benefits associated with research. *Journal of Medical Ethics, 31,* 715-720.

Carmen, M.G., & Joffe, S. (2005). Informed consent for medical treatment and research: a review. *The Oncologist, 10*(8), 636-641.

Cato, A., & Peterson, M.B. (2002). Dilemmas of clinical trials in pediatric populations. In *Clinical drug trials and tribulation*. Marcel Dekker Inc, New York. ISBN: 0-8247-0314-6.

Conroy, S., Choonara, I., Impicciatore, P., Mohn, A., Arnell, H., & Rane, A. (2000). Survey of unlicensed and off label drug use in paediatric wards in European countries. *British Medical Journal, 320*, 79–82.

Conroy, S., McIntyre, J., Choonara, I., & Stephenson, T. (2000). Drug trials in children: problems and the way forward. *British Journal of Clinical Pharmacology, 49*(2), 93–97.

Coté, C.J., Kauffman, R.E., Troendle, G.J., & Lambert, G.H. (1996). Is the therapeutic orphan about to be adopted? *Pediatrics, 98*(1), 118-123.

Council for International Organizations of Medical Sciences (CIOMS). (2002). International Ethical Guidelines for Biomedical Research Involving Human Subjects. Retrieved 17 July 2010, from www.cioms.ch/publications/layout_guide2002.pdf.

Cvetkovich-Muntañol, A. (2011). Paediatric clinical trials: one size doesn't fit all. *Foresight An INC Research Publication, 4*(2). Retrieved 31 October 2011, from www.incresearch.com/enews.

Dalla-Vorgia, P., Mason, S., Megone, C., Allmark, P., Bratlid, D., Gill, A., Morrogh, P., Plomer, A., & Reiter-Theil, S. (2001). Overview of European legislation on informed consent for neonatal research. *Archives of Disease in Childhood: Fetal Neonatal, 84*(1), F70–F73.

Douglas, S.J., Casey, M., Faust, S.N., Liossi, C. (2011). Exploration of the factors influencing parental decisions to allow their children to participate in clinical trials in paediatric infectious diseases. *Archives of Disease in Childhood*, *96*(1), A46-A47.

Davis, M.M. (2008). Are parents willing to allow children to participate in clinical research? *IRB Advisor, 8*(7), 73-76.

Ethical considerations arising from vaccine trials conducted in paediatric populations with high disease burden in developing countries. (n.d). Retrieved 9 September 2010, from www.who.int/vaccines-documents/.

Federal Policy for the Protection of Human Subjects. (n.d). Retrieved 11 September 2010, from http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html.

Fombad, C.M. (2005a). Protecting children's rights in social science research in Botswana: some ethical and legal dilemmas. *International Journal of Law, Policy and the Family, 19*(1), 102-120.

Fombad, C.M. (2005b). Children and informed consent to HIV/AIDS testing and treatment in Botswana. *University of Botswana Law Journal, 2,* 33.

Green, J.B., Duncan, R.E., & Barnes, G.L., & Oberklaid, F. (2003). Putting the 'informed' into 'consent': a matter of plain language. *Journal of Paediatric Child Health, 39*(9), 700–3.

Grodin, M.A., & Glantz, L.H. (1994). *Children as research subjects. Science, ethics and law*. Oxford University Press: New York. ISBN: 0-19-507103-4.

Gupta, P., & Sachdev, H.P. (2003). Safety of oral use of Nimesulide in children: systematic review of randomized controlled trials. *Indian Pediatrics, 40*, 518-531.

Hirtz, D.G., & Fitzsimmons, L.G. (2002) Regulatory and ethical issues in the conduct of clinical research involving children. *Current Opinion in Pediatrics, 14*(6), 669-675.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. (n.d). Retrieved 14 September 2010, from www.ich.org.

IRB Guidebook. (n.d). Retrieved 14 September 2010, from www.hhs.gov/ohrp/irb/irb_glossary.htm.

John, T., Hope, T., Savulescu, J., Stein, A., & Pollard, A.J. (2008). Children's consent and paediatric consent: is it appropriate for healthy children to be the decision-makers in clinical research. *Archives of Disease in Childhood, 93*(5), 379-383.

Kauffman, R.E. (1994). Drug trials in children: ethical, legal, and practical issues. *The Journal of Clinical Pharmacology, 34*(4), 296-299.

Klaus, R. (2008). Ethical, regulatory and scientific challenges in peadiatric drug development. *Pharmaceutical Medicine, 22*(4), 221-234(14).

Kopelman, L.M. (2000). Children as research subjects: a dilemma. *Journal of Medicine and Philosophy, 25*(6), 745-764.

Koren, G., Kearns, G.L., Reed, M., & Pons, G. (2003). Use of healthy children as volunteers in drug studies: the ethical debate. *Journal of Clinical Pharmacology and Therapeutics, 73*(3), 147–152.

Gill, D., & Kurz, R. (2003). Practical and ethical issues in pediatric clinical trials. *Applied Clinical Trials Online.* 41-44.

Langley, J.M., Halperin, S.A., Mills, E.L., & Eastwood, B. (1998). Parental willingness to enter a child in a controlled vaccine trial. *Clinical and Investigative Medicine, 21*(1), 12–16.

Leonard, H., & Glantz, J.D. (1996). Conducting research with children: legal and ethical issues. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*(10), 1283-1291.

Broome, M.E. (1999). Consent (assent) for research with pediatric patients. *Seminars in Oncology Nursing, 15*(2), 96–103.

Masiye, F., Kass, N., Hyder, A., Ndebele, P., & Mfutso-Bengu, J. (2008). Why mothers choose to enrol their children in malaria clinical studies and the involvement of relatives in decision making: evidence from Malawi. *Malawi Medical Journal, 20*(2), 50-56.

Maxine, E. (1993). The impact of HIV/AIDS on the family and other significant relationships. The African clan revisited. *AIDS care*, 5(1), 5-22.

Maayan-Metzger, A.M., Kedem-Friedrich, P.K., & Kuint, J. (2008). Motivations of mothers to enroll their newborn infants in general clinical research on well-infant care and development. *Journal of Pediatrics, 121*(3), e590-6.

Mason, S.A., & Allmark, P.J. (2000). Obtaining informed consent to neonatal randomised controlled trials: interviews with parents and clinicians in the Euricon study. *The Lancet, 356*(9247), 2045–2051.

Matsui, D., Kwan, C., Steer, E., & Rieder, M.J. (2003). The trials and tribulations of doing drug research in children. *Journal of the Canadian Medical Association, 169*(10), 1033-1034.

Moseley, K.L., & Clark, S.J., & Gebremariam, A. (2006). Parents' trust in child's physician: using an adapted trust in physician scale. *Ambulatory Pediatrics, 6*(1), 58–61.

National Council for Science and Technology. (2004). Guidelines for the ethical conduct of biomedical research involving human subjects in Kenya. Retrieved 20 April 2011, from https://webapps.sph.harvard.edu/live/gremap/files/ke_NCST_guidelines.pdf.

National Health Act, 2003. Government Gazette Republic of South Africa;

2000. Retrieved 10 October 2012, from http://www.saflii.org/za/legis/num_act/nha2003147.txt

The European Forum for Good Clinical Practice news. (n.d). Retrieved 18 September 2010, from http://www.efgcp.be/Downloads.

Guidelines on ethics for medical research. Book 1. (1993). The legal and moral justification for research, section 5.3.1.2.2. South African Medical Research Council. http://www.mrc.ac.za/ethics/ethicsbook1.pdf.

National Institutes of Health Policy and guidelines on the inclusion of children as participants in research involving human subjects. (n.d). Retrieved 16 September 2010, from www.grants1.nih.gov/grants/guide/notice-files/not98-024.html.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Belmont Report. (n.d). Retrieved 16 September 2010, from www.hsr.od.nih.gov/guidelines/Belmont.html.

National Council for Science and Technology. (2004). Guidelines for the ethical conduct of biomedical research involving human subjects in Kenya. Retrieved 2nd November 2012, from https://webapps.sph.harvard.edu/live/gremap/files/ke_NCST_guidelines.pdf

Ondrusek, N., Abramovitch, R., Pencharz, P., & Koren, G. (1998). Empirical examination of the ability of children to consent to clinical research. *Journal of Medical Ethics, 24*(3), 158–165.

Paediatric research should take centre stage. (2004). *Lancet, 364*(9436), 732.

Rieder, M.J. Conducting global paediatric clinical trials. *Pharma Focus Asia*. Retrieved 2 March 2012, from http://www.pharmafocusasia.com/knowledge_bank/articles/paediatric_clinicaltrials.htm.

Sammons, H.M., Malhotra, J., Choonara, I., Sitar, D.S., Matsui, D., & Rieder, M.J. (2007). British and Canadian views on the ethics of paediatric clinical trials. *European Journal of Clinical Pharmacology, 63*(5), 431–436.

Smyth, R.L. (2001). Research with children (editorial): Paediatric practice needs better evidence – gained in collaboration with parents and children. *British Medical Journal, 322*, 1377–1378.

Strode, A. Grant. C, Slack, C. Mushariwa M. (2005). How well does South Africa's National Health Act regulate research involving children? *South African Medical Journal*, 95, 265-268.

Sutcliffe, G.A., & Larcher, V. (2003). Testing new pharmaceutical products in children (editorial). *British Medical Journal, 326*, 64.

Swartling, U., Helgesson, G., Hansson, M.G., & Ludvigsson, J. (2009). Split views among parents regarding children's right to decide about participation in research: A questionnaire survey. *Journal of Medical Ethics*, *35*(7), 450-455.

Swartling, U., Helgesson, G., Hansson, M.G., & Ludvigsson, J. (2008). Parental authority. research interests and children's right to decide in medical research – An uneasy tension? *Clinical Ethics, 3*(2), 69-74.

Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2006). Retrieved 8 March 2012, from http://www.kznhealth.gov.za/research/guideline2.pdf.

Good participatory practice guidelines for biomedical HIV prevention trials. (2010). Retrieved 23 September 20120, from http://data.unaids.org/pub/Manual/2010/guidelines_biomedical_hiv_prevention_2010_en.pdf.

Uganda National Council of Science and Technology (UNCST). (2007). Guidelines for the conduct of health research involving human subjects in Uganda. Kampala. Retrieved 8 March 2012, from http://www.uncst.go.ug/dmdocuments/Guideline,%20Human%20Subjects%20Guidelines%20Marc.pdf.

U S Food and Drug Administration (FDA). Retrieved 17 July 2010, from www.fda.gov.

Weithor, L.A., & Campell S.B. (1982). The competency of children and adolescents to make informed tretment decision. Child Development, 53, 1589 – 1598.

Wendler, D.S. (2006). Assent in paediatric research: theoretical and practical considerations. *Journal of Medical Ethics, 32*(4), 229–234.

Wendler, D., & Jenkins, T. (2008). Children's and their parents' views on facing research risks for the benefit of others. *Archives of Pediatrics and Adolescent Medicine, 162*(1), 9-14.

Wendler, D., & Shah, S. (2003). A response to commentators on "Should children decide whether they are enrolled in non-beneficial research?" *American Journal of Bioethics, 3*(4), W37–W38.

Declaration of Helsinki. (n.d). Retrieved 23 September 2010, from www.wma.net.

Yeung, V. (2009). Clinical Trials in Children. In *Paediatric Drug Handling,* pp. 85-119. ISBN: 978-0-85369-686-5.

Appendix 1: Glossary of Important Terms

Informed Consent: Informed consent is defined as a voluntary agreement to participate in research which is based on full information and understanding of all implications (positive and negative) of participation

Assent: Assent is defined as an 'agreement' by an individual not competent to give legally valid informed consent (e.g. a child or a cognitively impaired person) to agree to participation or an intervention.

Medicines: Substances administered by mouth, applied to the body or introduced into the body for the purpose of treatment.

Clinical Trial: A clinical trial is a medical research study carried out on human beings in search of a better way to treat a particular disease.

APPENDIX 2

INFORMED CONSENT FORM

TITLE OF THE STUDY: ENROLMENT OF CHILDREN IN CLINICAL TRIALS: BOTSWANA PERSPECTIVE

INVESTIGATOR: BOITUMELO MOKGATLA-MOIPOLAI

You are invited to participate in a research project described below. The researcher will explain the project to you in detail, and feel free to ask any questions during the information session or thereafter.

Description of the study:
The aim of the study is to determine the perceptions of Batswana people about children participating in clinical trials. How Batswana feel about medicines being tested on children.

Details:

- The study targets parents of healthy children who are aged between 0-18 years.
- The purpose of the study is to find out, what parents in Botswana think about the idea of testing medicines on children. Do parents think that is important to test medicines on children, and why. What do parents think about giving consent for their children to participate in clinical trials? Should only one parent make the decision or should both parents be involved in decision making. What do parents think about with regards to enrolling healthy children in clinical trials? And when should children be enrolled in clinical trials?

Procedures:
If you decide to take part in this study:
You will be requested to fill in a questionnaire, and answer some specific questions. The questionnaire will take about 20-30 minutes of your time.

Details:

- The details of the study will be explained thoroughly to the participant, and any questions answered, to ensure that the participant has a good understanding of what is expected from them.
- Each participant will be given one questionnaire to fill, which will have a number on it, (participants do not have to write their names). They can be allowed to take it home to consult with their partners if they would like to.
- The research will be done in different districts of Botswana, with atleast 20 participants from each district.

Risks and Benefits.
Participants will not benefit anything from the study, but the information that will be collected will be used to educate and empower members of the public.
The participant will not be exposed to any danger.

Confidentiality:
None of the information will identify you by name, and you would not be requested to write your name on the questionnaire. The questionnaire will only have a number.

Voluntary participation and withdrawal:
Participation in research is voluntary. You have the right to refuse to be in this study. If you decide to be in the study and change your mind, you have the right to drop out at any time. You may skip questions if you do not want to answer them.

Questions, Rights and Complaints:
If you have any questions about this research project, please call the investigator: Boitumelo Mokgatla-Moipolai, at 71543980 or email at Boisa2002@yahoo.com. OR you can also contact the head of Human Research and Development Division at Ministry of Health: Mr Pilate Khulumani on 363 2018.

Consent statement

This statement certifies that I am 18 years of age or older and I have read the consent and all the questions have been answered. I understand that I may withdraw from the study at any time.
All of the answers that I provide will be kept private. I also know that I have the right to see the results of the study before they are published.
I will also have a copy of the informed consent.

_____
Signature of Participant

_____
Witness/Researcher

_____
Date

APPENDIX 3 **STUDY NO:**

MOKWALO WA TETLA

LEINA LA TSHEKATSHEKO: KAKARETSO YA BANA MO DIPATLISISONG KGOTSA DITEKELETSO TSA MELEMO MO BOTSWANA.

MMATLISISI: BOITUMELO MOKGATLA-MOIPOLAI

O kopiwa go tsenelela patlisiso ee latelang: Mmatlisisi o tla go tlhalosetsa sengwe le sengwe ka botlalo. O kopiwa gape go phuthologa go ka botsa dipotso nako e nngwe le nngwe.

KETAPELE:

Maikaelelo a patlisiso e, ke go sekaseka maikutlo a Batswana mabapi le go akarediwa ga bana mo dipatlisisong kgotsa ditekeletso tsa melemo.

Dintlha:

- Tshekatsheko e, e remeletse thatathata mo batsading ba ba nang le bana ba dingwaga tse di magareng ga 0 le 18.
- Maikaelelo a patlisiso e, ke go sekaseka maikutlo a Batswana mabapi le go akarediwa ga bana mo dipatlisisong kgotsa ditekeletso tsa melemo. A batsadi ba akanya gore go botlhokwa go akaretsa bana mo ditshekatshekong tsa melemo? Batsadi ba akanya jang ka go fa bana ba bone tetla go tsenelela ditshekatsheko tse? A motsadi a le mongwe o ka tsaya tshwetso ya gore ngwana o ka tsenelela dipatlisiso tse, kgotsa batsadi ka bobedi ba tshwanetse go fa tetla e? Batsadi ba akanya eng ka go akarediwa ga bana ba ba itekanetseng mo ditekeletsong tsa melemo. Bana ba ka akarediwa leng mo di- tshekatshekong kgotsa dipatlisiso tsa melemo?

TSAMAISO:

Fa o tsaya tshwetso ya go tsenelela patlisiso e, o tla kopiwa go tlatsa pampiri ya dipotso, e e ka go tsayang sebaka sa metsotso e le 20 go ya go e le 30.

Dintlha:

- Dintlha tsa tshekatsheko e, di tla tlhalosiwa ka botlalo, dipotso tse di ka nnang teng le tsone di tla arabiwa.
- Motsenelela tshekatsheko e mongwe le mongwe o tla fiwa pampiri ya dipotso, ee nang le nomore mo go yone. (Ga go tlhokafale gore ba kwale maina a bone mo go yone).Pampiri e e ka tseelwa ko lwapeng fa motsenelela tshekatsheko a na le keletso ya go botsisisa ba lelwapa la gagwe.
- Patlisiso e e tsile go dirwa mo dikgaolong tse di farologaneng mo Botswana. Go tla batliwa batsaya-karolo ba le masome a mabedi mo kgaolong nngwe le nngwe.

DIPHATSA:
Ga gona diphatsa dipe tse di ka tlhagelang batsaya-karolo mo patlisiso e. Thuto le megopolo e e tla tswang mo go yone, e tla dirisediwa go rutuntsha ba bangwe go akarediwa le gone go gakolola ba melao.

DITUELO:
Ga gona ditshenyegelo dipe tse di tla nnang teng mo go wena, fa o tsenelela tshekatsheko e. Gape ga o na go amogela madi ape fa o tsenelela patlisiso e.

TSHIRELETSO YA GAGO
Patlisiso e ga e na ka mokgwa ope fela, go dirisa leina la gago kgotsa sepe fela se se ka feleletsang se senola leina la gago kgotsa megopolo ya gago.

GO ITHAOPA
Go tsaya karolo mo patlisisong e, ke ka go ithaopa fela. O na le tshwanelo ya go gana go tsenelela patlisiso e, gape le gone go fetola mogopolo wa gago fa patlisiso e ntse e tsweletse. Fa o sa batle go araba potso nngwe, o letlelelwa go e tlola.

DIPOTSO, DITSHWANELO LE DINGONGOREGO
Fa o na le dipotso kgotsa dikakgelo mabapi le patlisiso e, o ka buisana le mmatlisisi, e bong Boitumelo Mokgatla-Moipolai, mo nomoreng ya mogala: 362 1778 (Office), kgotsa mogala wa 71543980, kgotsa
Email: boisa2002@yahoo.com. O ka ikgolaganya gape le moeteledipele wa lephata la ditshekatsheko (Human Research and Development Division) ko Ministry of Health: Rre Pilate Khulumani mo mogaleng wa 363 2018.

MOKWALO WA TETLA:
Mokwalo o o supa gore ke dingwga tse 18, le go feta, le gone gore ke badile le go tlhaloganyo gore patlisiso e, e ka ga eng, dipotso tsame tsotlhe di arabilwe ka mokgwa o o kgotsofatsang. Ke tlhaloganya gape gore ke tsenelela patlisiso e ka go ithaopa, le gore ke ka fetola mogopolo wame. Ke itse gape gore kena le tshwanelo ya go bona maduo a tekeletso e pele fa a ka phatlaladitsiwa.
Mokwalo le puisano tsotlhe di tla itsewe ke nna le mmatlisisi fela.
Ketla fiwa sesupo sa tumalano e.

_____
Motsaya Karolo

_____
Mosupi

_____
Letsatsi

APPENDIX 4

QUESTIONNAIRE

TITLE OF THE STUDY: Enrolment of children in clinical trials: Botswana perspective.

Principal Investigator: Boitumelo Mokgatla-Moipolai

Good day

I, Boitumelo Mokgatla-Moipolai, am a SARETI (South African Research Ethics Training Initiative) Masters student.

I want to invite you to participate in this research project. The aim is to find out what you think about children taking part in clinical trials.

Clinical trials are ways of testing new medicines and medical equipment to see if they are safe to use on people. We want to find out what you think about your child trying some of these new medicines or drugs. In other words, we want to find out if you will let your child try new medicines not used yet on other children.

Please complete the attached questionnaire, and feel free to ask any questions if you do not understand, or again, you can be allowed to take the questionnaire home, if you feel that you need more time, or your family's input. You do not have to give us your name or address, since we do not want to link your answers to you. This means we want to know what you think, but do not want to tell anybody else your opinion. I shall analyze the answers and prepare a report.

There is no right or wrong answers in this questionnaire. Therefore, it does not matter what you answer.
Please use a cross (**X**) against your answer.

1. Identification

1.1: Study Number: [ ]

1.2: District: 1. Southern 2. Central 3. North East 4. North West 5. Kweneng 6. Kgatleng 7. Kgalagadi 8. Ghanzi 9. South East

2.) Socio-demographic Data:

2.1: Age of respondent: [Years]

2.2: Sex of respondent:

1	Male
2	Female

2.3: Level of education:

1	No school
2	Primary school: standard 7
3	Secondary school: Form 2
4	Senior secondary school: form 5
5	Tertiary/University

2.4: Employment:

1	Employed
2	Self-employed:
3	Unemployed:

2.5: Income

1	Less done P1000
2	Between P2000-P4000
3	More than P4000
4	None

2.6: Relationship Status:

1	Single
2	Cohabiting
3	Married
4	Separated
5	Divorced
6	Widowed
7	Dating

2.7: Number of children that you have who are below 18 Years old:

2.8: Religious Affiliation

1	No religion
2	Catholic
3	Protestant
4	Spiritual
5	Moslem
6	Hindu
7	Other: Please specify

3.) CLINICAL TRIALS

3.1: Have you ever heard about clinical trials (ways of testing new medicines in a group of patients to determine whether medicines are working and if they are safe to use?

1	Yes
2	No

3**.2: How did you hear about clinical trials?**

1	Television
2	Radio
3	Friends and Family
4	Hospitals or health facilities
5	Educational facilities

3.3: Have you ever participated in clinical trials before?

1	Yes
2	No

3.4: If yes, what made you participate?

3.5: Do you think that clinical trials are important?

1	Yes
2	No
3	No answer

3.6: Please give reasons for your answer:

3.7: Will you encourage your relatives or friends to take part in clinical trials?

1	Yes
2	No

3.8: Should individuals make decisions on their own to participate in clinical trials?

1	Yes
2	No

3.9 Give reasons to your answer:

4.) Participation of Children in clinical trials:

4.1: Should children be enrolled in clinical trials?

1	Yes
2	No

4.2: Give reasons for your answer:

4.3: At what age do you think children should be enrolled in clinical trials?

4.4: Do you think that clinical trials can benefit children?

1	Yes
2	No
3	No answer

4.5: If yes, How? And if No, why do you think so?

4.6: When should children be considered as potential participants in clinical research?

1	Every time there is medicine to be tested
2	If the disease affects both children and adults
3	It the disease for which the medication will be used for, affects children only
4	If there is no other way of testing the medicine, besides on children
5	No answer

4.7: Would you ever consider giving permission to your child to take part in clinical trials?

1	Yes
2	No

4.8: Which children should be enrolled in clinical trials?

1	Only sick children
2	Only healthy children
3	Both Children
4	None

5.0: Issues of Informed Consent

5.1. a: Do you think children have the capacity to make a decision to participate in clinical research?

1	Yes
2	No

5.1. b: Who should give children permission to take part in clinical trials?

1	Mother
2	Father
3	Both Parents

4	Guardian
5	None

5.2: What should happen if a child does not want to take part in a clinical trial?

1	Leave the child alone
2	Force the child to participate if the clinical trial would benefit him/her
3	Persuade the child to participate
4	It is up to the child to decide
5	No answer

5.3: Do you think that children's participation in research should be voluntary?

1	Yes
2	No
3	In our culture a child cannot say no to an adult

5.4: Should a child's decision (assent) override the parent's decision or vice versa?

1	Yes
2	No
3	No answer

6.) Research Guidelines for Children in clinical research

6.1: Should there be specific special guidelines/rules for enrolling children in clinical trials?

1	Yes
2	No

6.2: Give reasons for your answer:

6.3: As a parent do you feel that there should be guidelines or regulations in place that protects children in health research?

1	Yes
2	No

6.4: Please state any other suggestions below.

Thank you for your participation and cooperation.

Appendix 5

POTSOLOTSO

LEINA LA PATLISISO: Go akerediwa ga bana mo ditekeletsong/ dipatlisiso tsa melemo

MMATLISISI: Boitumelo Mokgatla-Moipolai

Dumelang

Ke bidiwa Boitumelo Mokgatla-Moipolai, ke moithuti wa SARETI (South African Research Ethics Training Initiative)

Ke go laletsa go tsaya karolo mo patlisisong e. Maikaelelo ke go itsi ka maikutlo a gago mabapi le go akarediwa ga bana mo ditekeletsong tsa melomo.

Ditekeletso tsa melemo, ke nngwe ya ditsela tsa go batlisisa gore a melemo e babalesegile go ka dirisiwa mo bathong, le gone gore a e bereka sentle. Re batla go itse maikutlo a gago mabapi le go akaretsa ngwana wa gago mo ditekeletsong tsa melemo. Ka mantswe a mangwe re batla go itse gore ao ka letlelela ngwana wa gago go ka tsaya karolo mo ditekelotsong tsa melemo e e iseng e lekelediwe mo baneng gotlhelele.

Tsweetswee araba dipotso tse di mo pampering e, gape o phuthuloge go botsa dipotso fa go na le se o sa se tlhologanyeng, gape o ka tsaya pampitshana e go ya ka yone ko lapepeng, mme o kope ba lelwapa la gago go go thusa. Ga go tlhokafale go re o kwala leina la gago kgotsa ko o nnang teng. Se se raya gore re batla go itse fela ka dikakanyo le maikutlo a gago, ebile re go solofetsa gore ga re kake ra bolelela ope ka maikutlo a gago.
Ga go na karabo e e siameng le e e sa siamang. Ka jalo, phuthologa go kwala maikutlo a gago.

1. Ikitsiso

1.1: Nomore ya potsolotso: ☐

1.2: Kgaolo: _____

2.) Botshelo jwa motsaya-karolo:

2.1: Dingwaga tsa motlatsi: ☐

2.2: Bong jwa motlatsi

☐	Monna
☐	Mosadi

2.3: Thuto:

☐	Ga ke a tsena sekolo
☐	Ke tsene sekolo se se potlana go ema ka lekwalo lwa bosupa
☐	Ke tsene sekolo se se golwane, go ema ka Form 2
☐	Ke tsene sekolo se s egolwane go ema ka Form 5
☐	Ke tsene sekolo go ema ka Mmadikolo

2.4: Go Bereka:

☐	Ke a bereka

	Ke a ipereka:
	Ga ke bereke

2.5: Letseno

	Ko tlase ga P1000
	Go feta P1000
	Go feta P2000

2.6: Botsalano:

	Ga ke a nyalwa
	Ke nna le molekane
	Ke nyetswe
	Re kgaogane
	Re tlhalane
	Molekane o tlhokafetse

2.6: Palo ya bana ba ba ka fa tlase ga dingwaga tse 18:

2.7: Tsa tumelo

	Ga ke dumele mo go sepe
	Ke tsena Lontone
	Ke tsena kereke tsa pholoso
	Ke tseana kereke ya mowa
	Ke mo moslem
	Ke mo Hindu
	Tse dingwe: Tsweetswee tlhaolosa:

<u>3.) Ditekeletso tsa melemo</u>

3.1: Ao kile wa utlwalela ka ga dipatlisiso tsa melemo- tsela ya go batlisisa gore a melemo e bolokesegile go ka dirisiwa mo bathong le gone gore a e bereka sentle?

	Ee
	Nnya

3.2: O utlwaletse jang ka dipatlisiso tse?

	Sesupa ditshwantsho
	Seromamowa
	Ba lelwapa le masika
	Ditsala
	Dipatela le dikokelwana

	Dikolo le maphata a thuto

3.3: Ao kile wa tsenelela ditekeletso tse?

	Ee
	Nnya

3.4: Fa karabo e le ee ke eng se se dirileng gore o tsenelele ditekeletso tseo ?

3.5: O ne o tseneletse tshekatsheko kgotsa ditekeletso tsa eng?

3.6 : Ao ne wa feleletsa tshekatsheko eo ?

	Ee
	Nnya

3.7: Fa karabo e le ee kgotsa nnya, ka go reng?

3.8: Ao akanya gore ditekeletso tse di botlhoko?

	Nnya
	Ee

3.9: Ka tsweetswee fa mabaka a karabo ya gago:

3.10: Ao o ka rotluetsa masika a gago go tsenelela ditekeletso tsa melemo?

	Ee
	Nnya

3.11: Ao o ka rotluetsa ditsala tsa gago go tsenelela ditekeletso tsa melemo?

	Ee
	Nnya

3.12: A motho o tshwanetse go itseela tshwetso a le nosi go ka tsenelela ditekeletso tsa melemo?

	Ee
	Nnya

3.13: Fa mabaka a karabo ya gago:

4.) Go tsaya karolo ga bana mo ditekeletsong tsa melemo

4.1: A bana ba akarediwe mo ditekeletsong tsa melemo?

	Ee
	Nnya

4**.2: Fa mabaka a karabo ya gago**

4.3: Ngwana o tshwanetse go akarediwa mo ditekeletsong tsa melemo ba le dingwaga di le kae?

4.4: Ao akanya gore ditekeletso tsa melemo di ka tswela bana mosola?

	Ee
	Nnya

4.5: Fa karabo e le ee, ditekeletso tse di ka tswela bana mosola jang?

4.6: Bana ba akanyediwe leng jaaka batho ba ba ka tsayang karolo mo ditekeletsong tsa melemo?

	Nako le nako fa melemo e lekelediwa
	Fa bolwetse jwa molemo o o lekelediwang bo tsena bana le bagolo.
	Fa e le gore bolwetsi jo e leng gore molemo o o lekelediwang, bo tsena bana fela.
	Fa go sena tsela e nngwe ya go lekeletsa molemo, ntleng le go dirisa bana.

4.7: Ao akanya gore o ka a fa ngwana wa gago tetla go tsenelela ditekeletso tsa melemo?

	Ee
	Nnya

4.8: Ditekeletso tsa melemo di tshwanetse go dirwa mo baneng ba ba ntseng jsng??

	Ba ba itekanetseng
	Ba ba lwalang
	Bana botlhe

<u>5.0: Dikgang tsa tetla</u>

5.1: Ao akanya gore bana ba na le tlhaloganyo e e lekaneng go ka itseela tswetso ya go tsenelela ditekeletso tsa melemo?

	Ee
	Nnva

5.2: Fa karabo e le ee, bana ba akarediwe mo ditekeletsong tse ba le dingwaga di kae?

5.3: Ke mang o o tshwanetseng go fa bana tetla ya go tsenelela ditekeletso tsa melemo?

	Mmaagwe ngwana
	Rragwe ngwana
	Batsadi ka bobedi
	Motlhokomedi wa ngwana

5.4: A bana ba tshwanetse go tsenelela ditekeletso tsa melemo?

	Ee
	Nnya

5.5: Go diragaleng eng fa ngwana a sa batle go tsaya karolo mo ditekeletsong tsa melemo?

	A tlogelwe
	A patelediwe thatathata fa e le gore ditekeletso di tla mo tswela mososla
	A sokasokiwe gore a tsenelele ditekeletso
	A ngwana a itseele tshwetso
	Mo ngwaong ya rona, ngwana ga a nke a gana sepe fa mogolo a mokopa gore a se dire.

5.6: Ao akanya gore bana ba tshwanetse go ithaopela go tsenelela ditekeletso tsa melemo?

	Ee
	Nnya

<u>6.) Ditsamaiso tsa ditekeletso tsa melemo mo baneng</u>

6.1: A go tshwanetse go nna le melawana mengwe ee faphegileng ya go akaretsa bana mo ditekeletsong tsa melemo?

	Ee
	Nnya

6.2: Fa mabaka a karabo ee fa go dimo:

6.3: Jaaka motsadi, ao akanya gore go tshwanetse go nna le melawana mengwe e e sireletsang bana mo ditekeletsong tsa melemo?

	Ee
	Nnya

6.4: Tsweetswee, fa kgakololo kgotsa tshwaelo e nngwe le e nngwe, kgotsa sepe fela se o batlang go tlalaletsa ka sone fa tlase fa.

Ke lebogetse tirisano mmogo le go tsaya karolo ga gago.

Appendix 6

Participants Information Leaflet

TITLE OF THE STUDY: ENROLLING CHILDREN IN CLINICAL TRIALS: BOTSWANA PERSPECTIVE.

What are clinical Trials?

Clinical Trials are a way of testing new medicines to check if they work properly and also if they are safe to use on human beings (people). Since everyone can get sick and need medicines, it is important to have medicines tested for safety on human beings, and also to be shown that it works against the disease.

So far, many medicines have been tested on adults, and in most cases the information that has been obtained from the adult population, is usually taken and applied (extrapolated) to be used on children. But sometimes there are diseases that affect children alone, and to find the medicines that can cure or prevent such diseases, medicines then have to be tested on children too.

The aim of the study is to find out what parents in Botswana think about testing medicines on children. The study also wants to find out if parents think it is important to test medicines on children and why.

The purpose of this study is to find out what parents in Botswana think about the idea of testing medicines on children. Do parents think that is important to test medicines on children, and why? What do parents think about giving consent (permission) for their children to participate in clinical trials? Should only one parent make the decision or should both parents be involved in decision making? What do parents think about with regards to enrolling healthy children in clinical trials? And when should children be enrolled in clinical trials?

Appendix 7

Telephone: (267) 363200
FAX (267) 353100
TELEGRAMS: RABONGAKA
TELEX: 2818 CARE BD

MINISTRY OF HEALTH
PRIVATE BAG 0038
GABORONE

REPUBLIC OF BOTSWANA

REFERENCE NO: PPME 13/18/1 PS IV (68) 20 October 2009

Health Research and Development Division

Notification of IRB Review: New application

Mrs Boitumelo Mokgatla-Moipolai
P.O. Box 81010
Gaborone

Protocol Title:	**ENROLMENT OF CHILDREN IN CLINICAL TRIALS: BOTSWANA PERSPECTIVE**
HRU Protocol Number:	HRU 00560
Sponsor:	SARETI
HRU Review Date:	19 October, 2009
HRU Expiration Date:	18 October, 2010
HRU Review Type:	HRU reviewed
HRU Review Determination:	Approved
Risk Determination:	Minimal risk

Dear Mrs Mokgatla-Moipolai

Thank you for submitting a new Application for the above referenced Protocol.
This approval includes the following:

1.Application form
2.Proposal
3.Consent form
4. Data collection tool

This permit does not however give you authority to collect data from the selected sites without prior approval from the management. Consent from the identified individuals should be obtained at all times.

The research should be conducted as outlined in the approved proposal. Any changes to the approved proposal must be submitted to the Health Research and Development Division in the Ministry of Health for consideration and approval.

Furthermore, you are requested to submit at least one hardcopy and an electronic copy of the report to the Health Research, Ministry of Health within 3 months of completion of the study. Approval is for academic fulfillment only. Copies should also be submitted to all other relevant authorities.

If you have any questions please do not hesitate to contact Mr. P. Khulumani at pkhulumani@gov.bw, Tel +267-3914467 or Mary Kasule at mkasule@gov.bw or marykasule@gmail.com Tel: +267-3632466

Continuing Review
In order to continue work on this study (including data analysis) beyond the expiry date, submit a Continuing Review Form for Approval at least three (3) months prior to the protocol's expiration date. The Continuing Review Form can be obtained from the Health Research Division Office (HRDD), Office No. 9A 11 or Ministry of Health website: www.moh.gov.bw or can be requested via e-mail from Mr. Kgomotso Motlhanka, e-mail address: kgmmotlhanka@gov.bw As a courtesy, the HRDD will send you a reminder email about eight (8) weeks before the lapse date, but failure to receive it does not affect your responsibility to submit a timely Continuing Report form

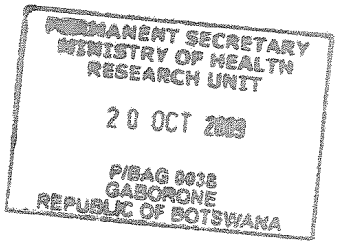
Amendments
During the approval period, if you propose any change to the protocol such as its funding source, recruiting materials, or consent documents, you must seek HRDC approval before implementing it. Please summarize the proposed change and the rationale for it in the amendment form available from the Health Research Division Office (HRDD), Office No. 9A 11 or Ministry of Health website: www.moh.gov.bw or can be requested via e- mail from Mr. Kgomotso Motlhanka, e-mail address: kmotlhanka@gov.bw . In addition submit three copies of an updated version of your original protocol application showing all proposed changes in bold or "track changes".

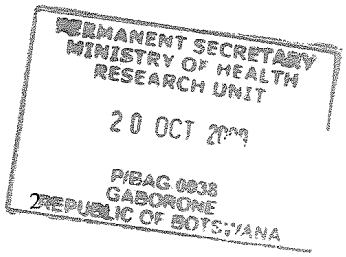
Reporting
Other events which must be reported promptly in writing to the HRDC include:
- Suspension or termination of the protocol by you or the grantor
- Unexpected problems involving risk to subjects or others
- Adverse events, including unanticipated or anticipated but severe physical harm to subjects.

Do not hesitate to contact us if you have any questions. Thank you for your cooperation and your commitment to the protection of human subjects in research.

Yours sincerely

P. Khulumani
For Permanent Secretary





Appendix 8

University of KwaZulu-Natal
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E-mail : naidoos4@ukzn.ac.za

18 May 2010

Mrs B Mokgatla-Moipolai
P O Box 81010
Gaborone
BOTSWANA

Dear Mrs Mokgatla-Moipolai

PROTOCOL: Enrolment of Children in Clinical Trials: Botswana Perspective
ETHICAL APPROVAL NUMBER: HSS/0248/2010 M: Faculty of Humanities, Development and Social Science

In response to your application dated 13 May 2010, Student Number: **208529733** the Humanities & Social Sciences Ethics Committee has considered the abovementioned application and the protocol has been given **FULL APPROVAL.**

PLEASE NOTE: Research data should be securely stored in the school/department for a period of 5 years.

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

Yours faithfully

Professor Steve Collings (Chair)
HUMANITIES & SOCIAL SCIENCES ETHICS COMMITTEE

SC/sn

cc: Prof. M Kruger
cc: Ms. B Jacobsen