Medical Research on Human Subjects in South Africa:

A Critical Assessment of the Work of Research Ethics Committees.

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Declaration

I the undersigned hereby declare that the work contained in this dissertation is my own original work and has not been previously in its entirety or in part been submitted at any university for a degree.

Signature Date

Opsomming

Navorsing op menslike subjekte gee aanleiding tot ‘n konflik tussen mediese vooruitgang as ‘n voordeel vir die samelewing en die beskerming van deelnemers as iets waarby die individu direkte belang het.

Voor 1960 het die diskresionêre gesag vir die beskerming van deelnemers by die individuele navorsers berus. ‘n Golf van navorsingsvergrype, van Tuskegee in 1932 tot die Beecher onthulling in 1966, het egter veranderinge in die rigting van ‘n stelsel van beginsel-gebaseerde regulasie gestimuleer. Navorsingsetiekkomitees (NEKs) en Institusionele Beoordelings- en toesigrade (IBRs) is gevolglik belas met die verantwoordelikheid om toe te sien dat mense wat deelneem, sover moontlik beskerm word. Sedert 1966 is hierdie stelsel van navorsingshersiening en -toesig internasionaal tot stand gebring – ook, aanvanklik, by een instansie in Suid-Afrika.

In 1997 het plasebo-beheerde HIV-vertikale oordrag-proewe in ‘n aantal ontwikkelende lande, insluitend Suid-Afrika, tot ongekende kontroversie op die terrein van navorsingsetiek aanleiding gee, internasionaal en nasionaal. In 2000 het die bedrog met borskankerproewe, uitgevoer deur dr Bezwoda by Baragwanath Hospitaal, internasionale aandag op navorsing in Suid-Afrika gevestig. Hierdie gebeure het egter die effektiwiteit van die stelsel van etiese toesig in Suid-Afrika en elders in die wêreld bevraagteken. Die mees kommerwekkende onlangse insident was die dood van navorsingsvrywilligers by sentra van uitmuntendheid in die Verenigde State. Daar is beweer dat as daar tekortkominge in die navorsingsetiektoesigsisteem in ontwikkelende lande is, daar ‘n groter moontlikheid bestaan dat dit ook (en moontlik meer) in ontwikkelende lande voorkom. Ongeveer dieselfde tyd is die Interim Nasionale Gesondheidsnavorsings-etiekkomitee (INGNEK) [*Interim National Health*

Research Ethics Committee (INHREC)] in Suid-Afrika gestig om die etiekoorsigstelsel in Suid-Afrika te ondersoek en te reguleer.

Met dit in gedagte is die huidige studie onderneem om die verskillende strukturele-, prosedurele- en substantiewe etiese uitdagings wat regverdigbare en etiese oorsig van en toesig oor navorsing in Suid-Afrika in die gesig staar, vas te stel. Daar is van ‘n kombinasie van konseptuele, filosofiese refleksie en empiriese navorsing in hierdie proefskrif gebruik gemaak. Die empiriese werk maak gebruik van sowel kwantitatiewe as kwalitatiewe navorsingsmetodes. Die kwantitatiewe opname bestudeer die samestelling van NEKs wat toesig hou oor kliniese proewe in Suid-Afrika, met die klem op komiteesamestelling, -struktuur en die toesigproses. Die kwalitatiewe navorsing is gedoen met behulp van van semi-gestruktureerde onderhoude van tien NEK-voorsitters in Suid-Afrika om die komplekse substantiewe aspekte, soos onder andere ingeligte toestemming, standaard van versorging en deelnemervergoeding, te ondersoek.

Terwyl die etiek-toesigstelsel in Suid-Afriks op ‘n redelike vlak funksioneer, is daar ‘n groot verskil tussen verskillende NEKs. NEKs is geografies verspreid en funksioneer dikwels in isolasie sonder ‘n geleentheid om te kommunikeer en idees te deel. Ten opsigte van die institusionele NEKs bestaan daar ‘n duidelike kontras tussen histories benadeelde instansies en histories bevoordeelde instansies. NEK-lidmaatskap word, tien jaar na demokrasie, steeds gedomineer deur blanke mans. Gemeenskapsverteenwoordiging is onvoldoende. Die meerderheid NEKs word gedomineer deur wetenskaplikes en klinici. Die toesig- en hersieningsprosesse in die verskillende komitees verskil grootliks, met vertragings wat wissel van 10 dae to 10 weke. Prosedurele- en burokratiese vereistes het ‘n impak op die vermoëns van NEK-lede om by debatte oor belangrike substantiewe etiese aangeleenthede betrokke te raak, soos byvoorbeeld die standaard van versorging, ingeligte toestemming en deelnemervergoeding. Opleiding en opvoedkundige behoeftes verskil wyd oor die land.

Ernstige aandag moet geskenk word aan die wyse waarop NEKs in Suid-Afrika saamgestel is. Herstrukturering van NEKs met ‘n visie op verbeterde verteenwoordiging in terme van ras, geslag en geloof is ‘n prioriteitsvereiste. Gemeenskapsverteenwoordiging en lidmaatskap van nie-wetenskaplikes moet verder ondersoek word. NEKs in Suid-Afrika moet die vraag of hulle sowel wetenskaplike- as etiektoesig moet uitvoer, of sl slégs etiektoesig, opnuut ondersoek. Die nasiensproses vereis ‘n paradigmaskuif, vanaf ‘n klem op rapportering van gebeurtenisse, na monitering van ingeligte toestemmingsvorms sowel as na ‘n kultureel toepaslike ingeligte toestemmingsproses. ’n Paradigmaskuif is noodsaaklik ten einde die fokus te verskuif vanaf ingeligte toestemming na ‘n meer omvattende toesig- en nasiensraamwerk. Beleid rakende standaard van versorging en deelnemervergoeding moet verduidelik en geartikuleer word.

Alhoewel die rol van NEKs in die beskerming van menslike deelnemers aan navorsing bevraagteken word, is dit duidelik dat NEKs in die meerderheid van gevalle wel ‘n belangrike rol vervul. Hul funksie kan natuurlik uitgebrei word. Dit sal gefasiliteer word deur opleidingsprogramme en ‘n elektroniese nuusbrief. Verantwoordelikheid vir die beskerming van mense wat deelneem aan navorsing berus egter nie uitsluitlik by NEKs nie. ‘n Kollektiewe verantwoordelikheid, gedeel deur navorsers, instellings, navorsingsetiekkomitees, borge en deelnemers is ‘n integrale vereiste vir hierdie beskerming sowel as vir die verwerwing van nuwe, geldige en relevante wetenskaplike kennis.

Summary

Human participant research raises a conflict between medical progress as a societal good and the protection of participants as an individual good.

Prior to 1960 the discretionary authority for the protection of participants resided in the hands of individual investigators. However, a wave of research atrocities from Tuskegee in 1932 to the Beecher expose in 1966 stimulated a change to a principle based system of regulation. Research Ethics Committees (RECs) and Institutional Review Boards (IRBs) were henceforth charged with the responsibility of human participant protection. Since 1966, this system of research review was established internationally and at one institution in South Africa.

In 1997, placebo-controlled HIV vertical transmission trials in a number of developing countries including South Africa raised unprecedented controversy in research ethics internationally and nationally. In 2000, the fraudulent breast cancer trials conducted by Dr Bezwoda at Baragwanath Hospital drew international attention to research ethics in South Africa. However, the events that called into question the efficiency of the system of ethical review most poignantly were the recent deaths of volunteers in research at centres of excellence in the United States. It was charged that if there were deficiencies in the research ethics review system in developed countries, these were more likely to be present in developing countries. Around the same time the Interim National Health Research Ethics Committee (INHREC) was established in South Africa to explore and regulate the ethical review system in South Africa.

Cognisant of these issues, the current study was undertaken to establish the various structural, procedural and substantive ethical challenges facing justifiable and ethical review of research in South Africa. A combination of conceptual

philosophical reflection and empirical research was employed in this dissertation. The empirical work employed both quantitative and qualitative research methodology. The quantitative survey explored the composition of RECs reviewing clinical trials research in South Africa with an emphasis on committee composition and structure as well as the review process. The qualitative research was conducted using semi-structured interviews of ten REC Chairpersons in South Africa to explore complex substantive issues like informed consent, standards of care and participant remuneration, inter alia.

While the review system in South Africa is functioning at a reasonable level, there is wide variation from one REC to the next. RECs are geographically distant and function in isolation without opportunity to communicate and share ideas. Amongst institutional RECs, there is a stark contrast between historically disadvantaged institutions and historically advantaged institutions. REC membership, ten years into democracy remains white male dominated. Community representation is inadequate. Most RECs are dominated by scientists and clinicians. The review process is widely variable with delays in review ranging from ten days to ten weeks. Procedural and bureaucratic demands impact on the ability of REC members to engage in debate on important substantive ethics issues like standards of care, informed consent and participant remuneration. Research ethics training and educational needs vary widely across the country.

Serious attention must be paid to the way in which RECs are constituted in South Africa. Restructuring of RECs with a view to improving representation in terms of race, gender and religion must be prioritized. There is a need for community representation and non-scientific membership to be explored. RECs in South Africa need to revisit the question of whether they should be conducting both scientific and ethics review or ethics review alone. The review process requires a paradigm shift in emphasis from adverse event reporting to monitoring, from informed consent forms to a culturally relevant informed consent process. A

paradigm shift is indicated to shift the focus from informed consent to a more comprehensive review framework. Policies regarding standards of care and participant remuneration must be clarified and articulated.

Although the role of RECs in human participant protection has been questioned, it is clear that in the vast majority of cases, they are fulfilling an important role. Their function could certainly be enhanced. This is being facilitated by training programs and an electronic newsletter. However, responsibility for human participant protection does not reside in the domain of the REC alone. A collective responsibility shared by researchers, institutions, research ethics committees, sponsors and participants is integral to human participant protection and the generation of new, valid and relevant scientific knowledge.

Acknowledgements

This dissertation represents the culmination of a long journey that began in 1997 when my interest in research ethics was first stoked by the international debate on HIV research being conducted in South Africa. This interest escalated when I received a scholarship from Harvard University in 1999 to attend my first course in International Health Research Ethics. My association with Dr Richard Cash has continued and my interest in research ethics has grown. His excellent program at the School of Public Health continues to flourish and I have had the opportunity to attend it again both in 2003 as a result of support from Professor Nulda Beyers and at Richard's invitation in 2004.

The idea for this dissertation was conceived in 2001 when as a Fogarty Fellow at Columbia University, New York City, I was exposed to the work of Professor Ron Bayer. I am grateful for his insights and guidance in the initial stages of my work.

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ACRONYMS

CIOMS	Council for International Organizations of Medical Sciences
DHHS	U.S. Department of Health and Human Services
DOH	Declaration of Helsinki
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
INHREC	Interim National Health Research Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
MCC	Medicines Control Council
MRC	Medical Research Council
NBAC	National Bioethics Advisory Council
NIH	National Institute of Health
OHRP	Office for Human Research Protection
PI	Principle Investigator
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SAE	Serious Adverse Event
SAGCP	South African Good Clinical Practice

Contents

General introduction and problem statement

1. Introduction

In spite of the enormous advances that medical science has made for the benefit of humankind, particularly over the last century[1], scientific research on human participants sometimes creates a conflict between the generation of new scientific knowledge and the protection of study participants. Research Ethics Committees (RECs) are charged with the responsibility of protecting potential and enrolled study participants. Recent deaths of study participants at centres of excellence in the United States have called into question the ability of RECs in the developed world to offer adequate protection to human participants in research. By extrapolation, the competence of RECs in developing countries has been called into question.

The problem I wish to address in this dissertation concerns the challenges facing RECs in the protection of human research participants, with special emphasis on the situation in a developing country such as South Africa. As a developing nation, we experience specific problems relating to informed consent from educationally disadvantaged study participants or participants of diverse cultural and linguistic origins. The debate on the standard of care constantly questions the use of placebos in clinical trials. Remuneration of economically challenged trial participants impacts on the voluntary nature of participation. The ethical conduct of HIV vaccine trials poses a special challenge to RECs in South Africa. There are a number of ethical issues that pertain to continuing review such as adverse event reporting and monitoring of approved research. These problems remain largely unresolved.

[1] As is the case with all science, medical science can also, and indeed often has been, an instrument of social progress. I shall deal with some of these instances of undeniable progress at the beginning of chapter 2. Most of the dissertation will, however, be occupied with the instances where things can, and indeed have gone wrong in the practice of scientific medical research.

Certain problems that are experienced in South Africa are also experienced in other parts of the world, such as the dual function enshrined in ethics committees to review the science and the ethics of research protocols (Redshaw, 1996: 76-82). The question remains whether there is adequate expertise on local RECs in the event of dual review.

The main focus of this dissertation therefore has to do with the complex of problems that face effective and morally justifiable ethical review of medical research in South Africa.

2. Historical Background

Science has both a descriptive component and an experimental component. The descriptive component is the result of passive research based largely on observation and description of the course of events in disease. This has been invaluable in the generation of knowledge. However, observation alone, in the absence of controlled experimentation is inadequate. Hippocrates (460 - 370 BC) has been credited for initiating the descriptive science of medicine (Ivy, 1948: 1). He was aware that physicians in his time practiced medicine on a case-by-case basis and hence the knowledge and practice of medicine could not be generalised. When Hippocrates described experience in medicine as "uncertain", many physicians were aware that a treatment that would be successful in one patient might not work on another patient. In desperation, physicians often tried remedies that were previously untested, sometimes with unexpected success. The Hippocratic maxim "benefit and do no harm" helped physicians to maintain a "constant intent to cure".

> *For most of medical history, the experimental (which in Latin means "putting to the test of experience") was folded into the therapeutic; patients were experimental subjects only as their doctors worked to heal them.*
>
> (Jonsen, 1998: 125)

The evolution of deliberate experimentation represented an escape from the limitations of observational research. Galen (131-201 AD) was credited with the initiation of the experimental science of medicine including the use of animals (Garrison, 1929). After his death, throughout the Dark Ages and for most of the Middle Ages the experimental method was not used in medicine (Bull, 1959: 221). As a result of dissection of the human cadaver (which had previously been forbidden) and via animal experimentation, Vesalius (1514-1564 AD) revealed inaccuracies in Galen's conception of the circulation of blood (Beecher, 1959: 462). In 1628, Harvey's discovery of the circulation resulted from controlled observation on animals and man (Ivy, 1948: 2).

It was only in the 18th century that experimentation impacted significantly on medical knowledge with Edward Jenner's work on the smallpox vaccine. Even then, his son was his first research subject. Louis Pasteur, during his experimentation on rabies, agonized over inoculating the first human subject and did so only when it was required in a life-saving situation demonstrating the use of extreme discretion in the conduct of experimentation (Rothman, 2003: 22). In the 19th century, Claude Bernard made an important contribution both to physiological research and the ethics of research when he wrote in 1865:

> *The principle of medical and surgical morality consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science.*
>
> (Rothman, 2003: 23)

His principles remained within the Hippocratic tradition of keeping experiments therapeutic in intent (Jonsen, 1998: 127). His work has been documented as the "most significant formulation of research ethics in the nineteenth century" (Rothman, 2003: 23).

Prior to the Second World War, research was "almost always therapeutic in intent" (Rothman, 2003: 30). Experimentation in the context of the doctor-

patient relationship was conducted in a manner that was consistent with patient and community expectations and the ethics of human investigation did not require much attention. Research that transcended the boundaries of the doctor-patient relationship was an intimate small-scale exercise where a few physicians conducted experiments on themselves, their families and neighbours. Physicians conducted these experiments at their own discretion at a time when the integrity of individual doctors was held in high regard by patients, communities and colleagues.

The Second World War heralded a distinct change in the conduct of human experimentation. The research endeavour was transformed from a small-scale cottage industry to a national program in the United States. At that stage, research had lost its purely therapeutic nature and experiments were designed to benefit others – especially soldiers on the battlefield. The interests of science and society took precedence over the individual interests of research subjects. The utilitarian justification for war was, by many, extrapolated to research, and participant protection was subjugated to the urgency of progress in medical research. During the Second World War researchers achieved enormous victories over smallpox, typhoid, tetanus, yellow fever and other infectious diseases. This coincided with the discovery of the sulpha drugs in 1935 and penicillin in 1945. Wartime notions of "drafts" and "forced military duty" impacted on the mindsets of researchers who were very active at that time. Many drew parallels between soldiers who had been conscripted and subjects who had been enrolled in research projects. In 1942 Hitler went so far as to say:

> *As a matter of principle, if it is in the interest of the state, human experiments are to be permitted."* It was unacceptable for *"someone in a concentration camp to be totally untouched by war, while German soldiers had to suffer the unbearable*.
>
> (Quoted in Rothman, 2003: 61)

Henceforth, medical experimentation on vulnerable groups continued without sanction and many violations of participant rights ensued.

Prior to the Second World War, research was primarily therapeutic in nature and consequently, treatment and research were intertwined. However, when therapeutic research became organised and groups of individuals were deliberately submitted to experimentation and when non-therapeutic experimentation became an important part of the research endeavour, the roles of investigator and physician ought to have become distinct. Instead, the lines between therapy and research remained blurred.

A central concept in the debate surrounding research ethics is the important distinction that must be drawn between the doctor-patient relationship and the investigator-participant relationship. Traditionally, the doctor-patient relationship is based on concern for individual patients and the patient is seen as an end in him- or herself. In therapeutic research, the study participant may stand to benefit to a certain degree while he or she does not benefit at all in non-therapeutic research or in placebo controlled therapeutic trials where the participant might be randomized to the control arm of the study. Under such conditions, the benefit to science and society is bound to be significant enough to render the research participant a means to an end.

As a result of this precarious relationship between participant and investigator, the research participant requires special protection of his/her rights. In South Africa, as in most developing countries, care and research are often integrated, placing research subjects in a very vulnerable position. Our legacy of apartheid further increases the asymmetrical nature of the investigator participant relationship resulting in greater risk of exploitation of disempowered research participants.

During and subsequent to the Second World War, many problems have arisen either because the distinction between doctor-patient and researcher-participant has not been recognized or because special protection has not been afforded to participants resulting in the violation of their rights. The utilitarian justification for the Second World War as an endeavour of national interest and societal good was extrapolated to research. In many ways, the war against nation states was transformed into a war against disease.

The research atrocities of the Nazi concentration camps were brought into focus at the Nuremberg Trial of 1946 and the Nuremberg Code was the first attempt to protect the rights of research participants. In spite of this, research violations continued – Tuskegee, Thalidomide, Willowbrook…

Violations of the rights of research participants exposed the "stark conflict of interest between clinical investigators and human subjects, between researchers' ambitions and patients' well-being" (Rothman, 2003: 10). This resulted in a shift from individual researcher discretion and integrity to collective decision-making. A system of peer review and international regulations and guidelines substituted self-regulation by individual researchers. Trust in the discretion of individual researchers was replaced by trust in Research Ethics Committees (RECs) and Institutional Review Boards (IRBs).

The Declaration of Helsinki in 1964, made the first reference to the review of research by an ethics committee. In 1966, the Surgeon-General in the United States called for each application to conduct research funded by the Public Health service to be reviewed by an Ethics Committee. Similarly, in 1966 Canada and the United Kingdom also recommended committee review of research proposals. The first REC in South Africa was established in 1966 at the University of the Witwatersrand. New Zealand introduced a requirement for committee review in 1972 and Australia followed in 1973. Some of the Scandinavian countries followed suit in the 70s and 80s (McNeill, 1998: 372-73).

Ethical review of health research conducted on human participants by RECs has become an institutional requirement in most countries today. Even though the practice has its origin in Western countries, it has been adopted globally. Apart from the Declaration of Helsinki, a number of other guidelines were developed to address the ethics of research in general and in developing countries in particular. The guideline of the Council for International Organisations of Medical Science (CIOMS) drawn up by the

World Health Organisation (WHO) in 1993 pays specific attention to health research ethics in a developing country.

While these international guidelines had been accepted unquestioningly for many years, HIV research in 1997 called into question placebo-controlled studies and standards of care in developing country based research. Doctors Lurie, Wolfe and Angell initiated a heated debate in the *New England Journal of Medicine* in 1997 when they questioned the lack of clinical equipoise in HIV vertical transmission trials being conducted in developing countries around the world. This debate reached a climax when Dr Angell drew an analogy between these trials and the infamous Tuskegee syphilis study. Charges of ethical imperialism were hurled at her by developed- and developing-world investigators. The impact of this crisis in international research ethics was poignant in many respects. One consequence of this controversy was the widespread review of both the Declaration of Helsinki and the CIOMS guideline from 2000 to 2004. Many of these revisions remain controversial and unresolved. The reliance on guidelines and regulations in ethical review was intensified and reinforced in developed and developing countries alike. This type of ethical review has attracted criticism as it is argued that an obsession with procedural correctness is detracting from a substantive approach to ethical reasoning by REC members. Further criticism of the debate is the far-reaching consequences the debates and guideline revisions have had on other types of research. This begs the question of whether the HIV vertical transmission trial debate, now employed as a case study for the discussion of research ethics in general, is an appropriate case study for widespread generalizations.

In spite of the heightened international awareness of research participant protection and revised regulations and guidelines precipitated by the HIV pandemic and HIV research, the deaths of research participants in developed countries in 1996, 2000 and 2001, has resulted in a second wave of interest in the risk-benefit ratio of research as well as adequacy of review by research ethics committees. These recent controversies in research ethics in the USA (Steinbrook, 2002: 716-20) and in South Africa (Weiss, 2000: 2771-77) raised

by research disasters at first world centres of excellence therefore make it necessary to revisit the concept of ethical review by RECs in developed countries but especially in developing countries. This is a very large concern given the fact that dual review of research is mandated in multinational research yet 44% of developing country researchers surveyed reported that their studies are not reviewed by a local REC (Hyder, 2004: 68).

3. The South African Situation

South Africa is a popular research site for conducting clinical trials. The clinical trial industry increased by 40% between 1997 and 1998 (Christley, 1998: 56-59). The pharmaceutical industry budget for clinical trial research for 2000 was R826 million (Joffe, 2002). Some of the reasons quoted for conducting research in Africa rather than in developed countries include lower costs, lower risk of litigation and less stringent ethical review (Wilmshurst, 1997: 840).

The system of ethical review in South Africa dates back to 1966 when the first REC was established at the University of the Witwatersrand. Since then, a number of other RECs affiliated to major tertiary institutions were formed. Today there are approximately 22 local RECs in South Africa, two of which are private institutions. In keeping with the apartheid policies historically entrenched in South Africa, many of these RECs have been dominated by white male South African scientists or clinicians. The South African Good Clinical Practice (SAGCP) guideline specifies composition of RECs in terms of race and gender. The empirical research component of this dissertation examines the composition of RECs at the time of the survey (2003-2004) to assess whether, ten years into democracy, RECs are now representative of population demographics in South Africa. Another important feature of the composition of an REC relates to community or lay representation on the committee. This has recently been increased from one lay member to two lay members per committee, and should preferably include people from the community being researched. This is an area that will be explored in the survey conducted on RECs in SA.

While the practice of ethical review by health research ethics committees is firmly entrenched in South Africa, the quality and consistency of ethical review in South Africa is largely unknown. To date there have been no published studies on the work of RECs in South Africa. The need for such data was highlighted in 2000 when Werner Bezwoda from the University of the Witwatersrand raised national and international attention to research ethics in South Africa. Bezwoda had presented a paper at the annual meeting of the American Society of Clinical Oncologists in 1999 on the treatment of high-grade breast cancer with high dose chemotherapy. A team from the United States visited his research site in South Africa to verify his results only to find marked discrepancies between the data presented and existing data (Weiss, 2000: 999-1003). This was the most widely publicized case of research fraud in South Africa and the role of the REC was questioned. However, the investigation revealed that the protocol had not been submitted to the REC at the University of the Witwatersrand – the oldest and most established REC in South Africa.

The quality and extent of ethical review in South Africa is also a source of concern for the newly constituted National Interim Health Research Ethics Committee (NIHREC) in South Africa – the body created by the Department of Health to regulate and co-ordinate all ethical review activities in South Africa.

South Africa is a captive site for multinational collaborative research. The CIOMS guideline specifies dual review of research protocols for multinational research (CIOMS, 1993). Concerns have been raised that RECs in developing countries may not promote high standards of research participant protection as a result of a lack of financial and adequately trained human resources (Hyder, 2004: 68). In the absence of acceptable practices of ethical review, foreign collaborators are hesitant to become involved in research in South Africa, with the consequence that their considerable contributions in terms of expertise and resources may be withheld. The challenge in this regard is to better understand the level of research review capacity in South Africa and to define the “gap” that needs to be bridged to satisfy optimal

accreditation criteria to be developed by the National Interim Health Research Ethics Committee.

4. The Complex of Substantive Ethics Review Challenges in South Africa

RECs in South Africa experience specific substantive ethical problems relating to the review of clinical trials: informed consent, the use of placebos, remuneration of trial participants, post trial benefit to study participants, the use of international guidelines and the review of HIV vaccine trials. There are also problems pertaining to continuing review of approved research such as adverse event reporting and monitoring of research. These problems continue to generate concern yet escape resolution. I shall briefly discuss the main issues that are of concern in this dissertation.

Informed consent is a major challenge in South Africa where the majority of research participants are educationally disadvantaged. Autonomous decision-making requires both freedom from controlling influences and freedom from limitations such as inadequate understanding (Beauchamp, 2001: 58). In the research setting, lack of understanding of scientific concepts and complicated clinical trials impair autonomous decision-making. In collaborative research, federal regulations and donor agency rules require detailed and elaborate consent documents. Are these appropriate in terms of what research participants would see as important protections of their rights? Are consent documents serving to indemnify sponsors and investigators rather than protect study participants? In addition, our multicultural, multi-linguistic society requires a unique approach to the informed consent process. In traditional African societies, the Nguni philosophy of Ubuntu defines personhood very differently from the Western notion of autonomy (Mkhize, 2004: 46). This has important implications for family and community consent as distinct from individual consent. Many cultural beliefs also impact on obtaining written informed consent as opposed to verbal consent.

Remuneration of trial participants is particularly challenging amongst poor communities in South Africa where a fine line exists between what is regarded as adequate recompense for trial participation as compared with what is regarded as coercive. The Medicines Control Council (MCC), a regulatory agency in SA, has since 2003 unilaterally decided to stipulate a payment of R150 ($24) per visit to research participants as opposed to R50 ($8) a visit previously accepted by all RECs. South African RECs currently face the challenge of reaching consensus on how much research participants should be remunerated for participation in research and who has a mandate to determine adequate non-coercive recompense.

Issues related to the *standards of care in a developing country* are largely unresolved. While the debate around this concept originated in the context of international collaborative research where different standards of medical care exist between host and sponsor nations, it is now debated in country specific research where different standards of care exist in different regions. In such a setting, as in South Africa, different standards of care might also exist between the public health sector and private health care institutions. It is uncertain whether we should adopt a universal standard of care as opposed to a local standard of care or what is described as a *de facto* standard as compared with a *de jure* standard, each of which could be local or global. (London, 2000: 379-97). Terminology relating to a standard of care for the control group ranges from “best current” to “ best proven” to “best available” to “highest attainable and sustainable” and these definitions need to be clarified. Several proposals have been created in an attempt to resolve the ambiguity and these will be critically appraised.

Given the inequities in health care between developed and developing nations*, what should happen when the trial is over*? Do wealthy sponsoring nations have an obligation to trial participants or even developing world communities when the research is over? Should this be negotiated by investigators with sponsors on behalf of study participants when the project is submitted for ethical review? What should accrue to participants and local communities when the research study has ended – experimental drugs only or

a contribution to infrastructure in the form of clinics and local health care providers? This remains a contentious issue and is currently being debated by the World Medical Association and local RECs.

A number of *international guidelines* impact on the review of research in South Africa. Much of the regulation of research has originated in developed countries. Current international regulations and guidelines have been described as paternalistic and imperialistic. International guidelines based on universal principles are allegedly not always applicable in many developing countries where cultural, political and socio-economic contextual differences do not merge with Western concepts of personhood and autonomy. To what extent are these international guidelines being used by South African RECs? There are also a host of local research ethics guidelines in South Africa – the Medical Research Council (MRC) Guidelines which comprise 5 different books and the South African Good Clinical Practice Guideline. It is unclear which guidelines are being used by RECs and what the problems are in implementing such guidelines.

Undoubtedly, the greatest challenge for RECs in South Africa will rest with the *review of HIV vaccine trials*. While significant problems have already been encountered with phase one trial submissions, greater problems are anticipated with phase three trials. The contentious issue of enrolling children and adolescents in HIV vaccine trials is an example of the many issues that RECs will grapple with over the next decade. Other issues relate to informed consent, assessment of the risk-benefit ratio of participation, treatment of HIV positive participants who are screened out during recruitment or during the conduct of the trial. This is another example of how science informs ethical deliberation as the completed phase three HIV vaccine trials to date clarify some of the vexing ethical issues inherent in the trials.

South African RECs conduct both *scientific and ethical review of research*. Is justice being done in this dual review system or is it time to consider other options? Does adequate and appropriate scientific expertise exist on local

RECs? If not, how can that be remedied, given the kinds of constraints that exist in South Africa?

Having taken all of the above issues into consideration in the initial review of research protocols, RECs have an ongoing responsibility in the form of *continuing review*. This involves monitoring the research to ensure that the study is being conducted in accordance with the protocol. It also requires a continuous safety assessment of any serious or unexpected side-effects of the experimental treatment. Such side-effects are also referred to as serious adverse events. Monitoring and safety reporting remain two highly problematic areas of continuing review both internationally and locally.

5. Methodological Issues

This dissertation is based on both empirical and conceptual research. While it is a concern that empirical ethics research could detract medical ethics from its "true intellectual base in philosophy", it is important to acknowledge that "philosophical argument often depends on empirical issues" (Hope, 1999: 219). This is borne out by the examples of the HIV vertical transmission trials and HIV vaccine trials presented in this dissertation. The contribution that the empirical method can make to medical ethics will be presented in a manner that is complementary to the conceptual philosophical method. Hence, methodologically, I am proceeding on the basis of both my empirical findings and independent philosophical-ethical reflection in response to most of the findings.

6. Empirical Research Component

The empirical research component of this dissertation, includes both a questionnaire-based survey of RECs as well as the outcome of semi-structured interviews with REC chairpersons in South Africa conducted during 2003/2004. Hence both quantitative and qualitative research methodologies have been incorporated.

The empirical research conducted for the purposes of this dissertation focuses on the ethical dilemmas faced in the review of clinical trial research. Hence, the RECs included in the sampling process were those RECs that reviewed a significant proportion of clinical trial protocols. Smaller RECs that review predominantly academic research were excluded.

In the quantitative section, emphasis is placed on the structural and functional components of RECs in South Africa reflecting both their constitution and the review process. The REC has been described as "a creature of a liberal, Western and pluralistic society". It is also constituted in terms of the "highly bureaucratized institutional structures of modernity". Such systems emphasize "procedural solutions to social controversy". As a result RECs may be "process orientated to the extreme" (Moreno, 1998: 476). It has been charged that reliance on procedural aspects of review enshrined in guidelines and regulations that have their origin in the developed world may be insufficient to guarantee ethical standards of research in the developing world (London, 2002: 1080). The quantitative survey assesses this and looks at the impact of REC constitution on function. It also assesses the impact of bureaucratic procedures on substantive ethics issues in human participant research examined in the qualitative research component of the study. These substantive issues were explored during semi-structured interviews with chairpersons or vice chairs of the major RECs in South Africa. A semi-structured interview guide was employed to conduct the interviews to elicit information on substantive ethical issues in clinical trial research in South Africa. A number of important themes emerged from these interviews and are discussed in detail in Chapter Seven.

The empirical research component presented in this dissertation aims to identify the extent and nature of structural, functional and substantive ethical problems inherent in the ethical review system in South Africa with a view to formulating solutions to some of the major challenges being faced. It is intended that the solutions proposed will assist to improve the quality of ethical review in South Africa. It is also intended that reflection on the substantive ethical issues that are problematic will empower South African

researchers to negotiate multinational collaborative research contracts from a position of strength with the ultimate objective of securing the protection of South African participants who volunteer for research projects.

7. Structure of the Dissertation

Chapter One examines the ethical issues that underpin the use of human subjects in medical experimentation. The peculiarity of experimentation is discussed in respect of the conflict generated by the unavoidable use of humans as guinea pigs in the name of science and society. In order to resolve this conflict, different theories are invoked as justification. These range from justification based on a sacrificial theme to a social contract theory. Of central importance is the concept of genuine informed consent. Here a hierarchy exists in terms of the most suitable subjects who are best equipped to provide valid consent. Undoubtedly, scientists and researchers themselves lie at the top of this hierarchy. Hence this chapter reflects on the tradition of self-experimentation by researchers as a point of departure. However, self-experimentation in itself cannot sustain the research endeavour, hence the justification for the use of healthy volunteers and patients must also be provided.

As the research endeavour evolved further and further away from self-experimentation to the use of groups of volunteers outside the scientific community, the potential for exploitation has increased exponentially. *Chapter Two* highlights the historical accounts of exploitation of the rights of human research participants from 1932 to 1966. The Tuskegee Syphilis Study conducted in Alabama between 1932 and 1972 is discussed and some of the research experiments conducted in the Nazi Concentration Camps at Dachau are recounted. The Thalidomide disaster that resulted in phocomelia in newborn infants is discussed. The Beecher expose is also explored using the Willowbrook Experiment as a case study.

As a result of the exploitation detailed in Chapter Two, the international regulations and guidelines that resulted are outlined and critically appraised in

Chapter Three. This includes the Nuremberg Code of 1946 as a result of the Nuremberg Trial, the 1964 version of the Declaration of Helsinki from the World Medical Association, The Belmont Report in 1979 after the Thalidomide disaster and the Tuskegee exposure. The World Health Organisation's guideline for developing world research – CIOMS 1993 will be discussed. Finally, the International Conference on Harmonisation Guideline (ICH-GCP) of 1997 will be briefly introduced.

Chapter Four gives an account of the evolution of the HIV research debates that emerged in 1997. The scientific and ethical arguments surrounding these debates are presented. The response from South Africa is documented and the results of the South African arm of this very controversial study are presented. This represents a very interesting illustration of how science informs ethical deliberation. However, before such results were available to inform the debate, an attempt was made to revise major international documents – The Declaration of Helsinki 2000 and Council for the Organization of Medical Sciences (CIOMS) 2002. The context and content of these revisions are also discussed in Chapter Four.

Chapter Five describes and critically evaluates research disasters in developed countries since 1996. It begins with a description of the events surrounding the death of Nicole Wan, a University of Rochester student. The issues involving the death of Jesse Gelsinger in a gene therapy study at the University of Pennsylvania in 2000 are examined. This chapter also dissects the intricacies of the Ellen Roche case that occurred at Johns Hopkins in 2001. Investigation into these problems has exposed the inadequacy of ethical review in some of the most developed institutions globally. The case studies have also exposed a serious lapse in investigator responsibility. This sets the stage for the concern that hence exists in respect of RECs in developing countries using South Africa as a prototype, bearing in mind the perception that South Africa is one of the more developed developing countries globally.

C*hapter Six* introduces the main part of the dissertation. In this, as well as in the next chapter, the empirical study on the nature and work of RECs in South Africa is reported and discussed. Chapter Six deals with the *quantitative* part of the study, and Chapter Seven with the *qualitative* study. Chapter Six presents the results of a questionnaire-based survey conducted on major RECs in SA during 2003/2004. A status report on the composition and functioning of some of the major RECs in South Africa is contained in this chapter. Composition is reflected in terms of gender, race, professional and non-affiliated expertise. The ethics review system is described. Procedural issues related to workload and the review process are surveyed. Training and development of REC members is explored. Commentary on the relevant issues is included.

Chapter Seven contains a critical discussion of the complex of substantive issues in research ethics that RECs are currently grappling with, and that were alluded to earlier in this introduction – see paragraph 4, pp. 10-13. These issues are informed consent, standards of care, use of placebos in research, post-trial care of participants, participant remuneration, and the ethics of HIV vaccine trials. These themes have emerged from an analysis of semi-structured interviews with REC Chairpersons and reflect the ethical deliberation taking place on RECs in South Africa. The comments of the various chairpersons have been collated on each theme and are presented, followed by a commentary to contextualise each theme on a national and global level.

An important outcome that must be achieved in South Africa relates to reaching an adequate consensus on a host of research ethics concepts to achieve national standardisation and a high level of consistency in ethical review. In addition, initiatives are necessary to improve research participant protection in this era of high risk and novel research. The major problems identified in the empirical research conducted will be summarised and recommendations will be made in *Chapter Eight* to address some of the major issues being faced in research ethics in South Africa. Recommendations will of necessity relate to improvements in REC structure and function such as

REC composition and the structure of the REC system in South Africa. They will also extend to improvement of substantive research ethics issues in South Africa. These recommendations will explore ways in which the informed consent process can be enhanced. The implementation of some of these recommendations will also be described.

However, even if the review system in South Africa is functioning at an optimal level, this in itself is insufficient to avert research disasters of the magnitude that have recently occurred. The findings of this study, examination of recent research disasters at centres of excellence, in particular, the Bezwoda case in South Africa, and a review of international literature indicate that participant protection cannot be ensured even by a highly efficient REC. This situation arises when individual researchers are inadequately trained, evade the system of ethical review or conduct scientific fraud after receiving ethics committee approval. Hence, scientific integrity is examined in *Chapter Nine* using Professor Bezwoda as a South African case study.

In *Chapter Ten*, the final chapter, my conclusions will be briefly presented and discussed.

8. Contribution to the ethics review system in South Africa

Based on empirical data and conceptual analysis, proposals are made in this dissertation to restructure both RECs and the ethics review system in South Africa – see, in particular, chapter eight. It is also proposed that local RECs reviewing clinical trials form a national association. An electronic communication network to link all RECs in South Africa is described. While many initiatives are underway in South Africa to improve capacity of REC members, clinical investigators must receive rigorous training simultaneously. A principle based ethics review system combined with an ethic of responsibility on the part of investigators is presented as an important requirement to improve participant protection in research. The development of an enhanced Good Clinical Practice training program for investigators and REC members is briefly discussed as an important solution. Finally, patient

advocacy within research is neglected both on RECs in the form of community representation and in research settings. Participants in research are important but neglected role-players in the research endeavour. Education programs to empower research participants and actively engage them in the informed consent process are suggested as an innovative idea for South Africa.

At an international level, the relationship between research and health care is explored. Redefining this relationship will impact significantly on a number of substantive ethics review issues in South Africa.

Chapter 1

Human Experimentation – The Early Days...

The ethics of experimentation with human participants revolves around a critical moral point where science and ethics intersect. There is no doubt that the goals of medical progress conflict with the inviolability of the human person. Research ethics committees aim to offer protection to human participants in the course of research. However, what moral goods are they aiming to protect? Most RECs are aiming to protect human health and safety while simultaneously trying to promote medical progress, making the assumption that informed consent will allow for both goals to be achieved satisfactorily. Jonas in 1969 raised the question of whether informed consent, in itself, is enough and Emanuel echoes this sentiment today in the 21st century when he argues that informed consent in and of itself is insufficient to justify human experimentation (Emanuel, 2000: 2701).

Experimentation, although originally sanctioned by natural science, did not raise moral problems as long as inanimate objects were involved. However, as soon as animate sentient beings were used as experimental subjects, questions of conscience arose. Medical experimentation using human beings who possess both sentience and rationality is morally problematic (Macklin, 1975: 435-37). Human experimentation especially in medical research raises questions of human dignity:

> *What is wrong with making a person an experimental subject is not so much that we make him thereby a means, which happens in social contexts of all kinds, as that we make him a thing, a passive thing merely to be acted on and passive not even for real action, but for token action whose token object he is. His being is reduced to that of a mere token or sample.*
>
> (Jonas, 1969: 107)

The entire process of human experimentation invokes the Kantian concept of the use of people not only as a means to an end but as ends in themselves. The research setting has the potential to regard human participants as useful instruments to achieving the goals of the investigator and hence it is important to take cognisance of the Kantian formulation:

> *One must act to treat every person as an end and never as a means only*
>
> (Quoted in Beauchamp, 2001: 350)

Kant essentially would approve of the research endeavour as long as a participant was treated as an end in him or herself as well as a means to an end. Whether this can be achieved in non-therapeutic research or in placebo controlled therapeutic research is unclear.

From Hippocratic times, medical practice was not clearly distinguished from experimentation (Jonsen, 1998: 125-165). Unlike the doctor-patient relationship, where the human patient is an end in him/herself, the investigator-participant relationship renders the study participant a means to an end. The objectification of the human subject in the context of medical research creates a conflict between individual interests and societal interests and renders it necessary to justify the possible infringement on human dignity.

Such justification may be based on a sacrificial theme or a social contract theme where health is viewed as a public good. Jonas, in his ground breaking article on the ethics of human experimentation in 1969, refers to the commonly used conceptual framework of individual good versus societal good. He argues that the basic good of an individual is a known and accepted entity. However, the concept of societal good is less clear. If research is an established societal good, society may have a moral right to the resultant common good in which case consent of individuals would not be necessary.

Human subjects could then be conscripted for research in the same way soldiers are conscripted for military duty.

The sacrificial theme as justification for participation in research has been invoked on the basis of its historical compulsory role in early communal life. War invokes a strong use of this justification where soldiers are conscripted by law without consent. During times of war, a sacrificial justification was employed for research as it was employed for conscription of soldiers. World War Two created an intensification of the research endeavour. In 1941, President Roosevelt's Committee on Medical Research (CMR) urged institutions and investigators to produce "rapid improvement in military medicine". Approximately 600 protocols costing $25 million were "sponsored and supervised by the CMR". Much of the research, especially infectious disease research was conducted in prisons, mental hospitals and military camps. The prisoners involved in malaria research at Michigan's Joliet prison were praised for their "contribution to the war effort". According to David Rothman,

> *the nation was at war and a sense of urgency pervaded the laboratories…. the rules of the battlefield seemed to apply to the laboratory*.
>
> (Rothman, 2003: 85)

While Jonas does not wish to draw a parallel between early human sacrifice and experimentation, he concedes that

> *something sacrificial is involved in the selective abrogation of personal inviolability and the justified exposure to gratuitous risk of health and life, justified by a presumed greater good.*
>
> (Jonas, 1969: 111)

Jonas, however, dismisses the possibility of conscription of research subjects. He argues that conscription of soldiers must be distinguished from the research endeavour because conscription for war is in the setting of a real

national emergency while the research endeavour is an artificial situation – “token action” - not born out of dire need and where benefit to society is uncertain. He describes experimentation as “fictitious”. In war “we conscript them according to law” (Jonas, 1969: 109-10). As such, society may have only a moral claim and not a moral right to the common good. In this event consent would be absolutely necessary.

While I agree that conscription of research participants is not justifiable by a research endeavour that produces uncertain benefit to society, I would argue that the basis for the Jonas argument is flawed in the following respects. Firstly, he raises a contentious point regarding the motivation for war. Just as the research endeavour may not be born out of dire need, so too may the situation of war not necessarily be born out of national emergency but rather a host of other political agendas. This view is expressed by Jimmy Carter ex-president of the United States regarding the war against Iraq. He describes the following principles of a “just war”:

1. The war can be waged only as a last resort, with all non-violent options exhausted.
2. The war’s weapons must discriminate between combatants and non-combatants.
3. Its violence must be proportional to the injury suffered.
4. The attackers must have legitimate authority sanctioned by the society they profess to represent
5. The peace it establishes must be a clear improvement over what exists.

He argues that the war against Iraq in the absence of international support violates these principles and hence does not justify the war (Carter, 2003). I would support this view.

It is understandable that in 1969 when Jonas wrote this article, the justification for wars waged at the time may have been valid, but this does not hold true today.

The second point that undermines the basis for the Jonas argument that one cannot draw parallels between the motivation for war and the motivation for research is the national emergency he ascribes to a war and the "fictitious" situation he ascribes to research. There are many examples today of research being motivated by national and international emergencies – the HIV pandemic and the Severe Adult Respiratory Syndrome (SARS) outbreak represent two important examples– yet even under these circumstances, one cannot conduct research without consent.

The Jonas argument rests on differentiating war and research to prove that conscription cannot be justified in research. However, a fair comment to make in the 21st century is that neither war nor research can justify conscription. He also assumes that most research is conducted in an artificial setting under non-emergency situations. It is however evident that circumstances exist for urgent research based in the reality of global health care needs.

Hence his argument can be reformulated as follows:

If research is a social good and society has a moral right to research, consent would be unnecessary. Participants for research could then be conscripted as soldiers are in wartime. However, war is not always based on national emergency, when it is claimed to be so, this may be questionable. Similarly, research is not always based on national urgency but even when it is, the situation is not so urgent as to require conscription. Hence neither war nor research justifies conscription. Therefore consent for research is always necessary.

On the other hand, a social contract theory would infringe on the rights of individuals for their own benefit and the benefit of society. The purely sacrificial nature of the participation is thus eliminated. Benefit is mutual and general and one cannot be expected to die for a cause. Jonas sees the research endeavour as lying somewhere between a purely sacrificial ritual

where society benefits at the peril of individuals and a social contract fulfillment where there is mutual benefit of individuals and society.

While medical research can be viewed as emergency research when extraordinary measures must be taken to save humanity, most of medical research is conducted in non-emergency situations to improve the health of society. It is an expectation of society that there is active and constant improvement in all domains of life. This is an expansive goal that definitely lacks urgency but it is certainly worth sacrifices in the name of progress. Progress is by choice an acknowledged interest of society. Science is a necessary instrument of progress and research is a necessary instrument of science. In medical science, experimentation on human subjects is a necessary instrument of research. Therefore, Jonas concludes that human experimentation has come to be a societal interest. However, he argues that such progress is melioristic. Future society receives the improvements we create as an act of grace, not as a right. Jonas illustrates this with an example: It is a right of future society to inherit a planet that is not plundered but it is not their right to inherit a cure for arthritis. This sentiment is echoed by Henry Beecher, in his world renowned article on "Ethics and Clinical Research" when he quotes Pope Pius XII:

> *…science is not the highest value to which all other orders of values….should be subordinated.*
>
> (Beecher, 1966: 1354)

As a result of the gratuitous nature of research, the way in which self-sacrifice for research is elicited is important. Freedom and voluntariness are the first conditions to be observed. The surrender of one's body to medical experimentation does not fall within a social contract. It can be argued that it does – as a form of repayment for experimentation in the past and medical progress that occurred in the past. However, in that case, Jonas argues, humans would be indebted to past martyrs, not society. As such society would have no right to call in the debt. Furthermore, gratitude is not an enforceable social obligation and does not imply emulations of the deed.

Provided the submission to medical experimentation in the past was a voluntary deed, it can be done again – based on free will.

Moral law, on the other hand, asks more of an individual than social contract. According to the Golden Rule, an individual is required to give as she or he wishes to be given to under like circumstances, but not in order that he or she be given to and not in expectation of a return.

In the positive formulation of the Golden Rule – do unto others as you would wish them to do unto you – the prescriptive force is gradually lost. We may expect someone to come to the assistance of his/her neighbour but we may not expect that person to give his/her life for the neighbour. If the person did give his or her life that would be morally praiseworthy but if he omitted to do this, it would not be morally blameworthy. Giving his life is a matter between him and God.

Jonas argues that moral value exceeds moral law; self-sacrifice is an ultimate commitment and must be respected. As such, who should be approached to make this level of commitment to participate in research? Who should be used as a guinea-pig in human experimentation? A patient already involved in the care of a doctor was the natural point of departure in early days of experimentation. However, the dependent nature of such a relationship would make voluntary consent problematic. In 1886, Dr Withington advocated a Bill of Rights to protect patients from the injustices that could arise in the pursuit of science (Withington, 1886: 15-19). In the early days of experimentation, a "roughly defined ethic" accompanied the use of patients for experimentation (Jonsen, 1998: 130). New treatments could be used on patients only if such treatments were to benefit patients. However, new treatments that had no relationship to the patient's illness could not be used on patients. Instead, the new interventions, especially if they were dangerous, had to be tested on volunteers with free and voluntary consent. In addition, the "researcher was to make himself the first volunteer" (Jonsen, 1998: 130).

The philosophical question of the worth of human life must be examined. Whose life should be sacrificed in the interests of science? Is the life of the investigator more crucial to future scientific endeavours and hence too valuable to be sacrificed? Early experimentation indicated that human life that was experimented on in unethical ways frequently involved prisoners and mentally ill patients. This was an indication that these members of society were accorded a lower status and were regarded as dispensable – a social utility standard of utility and expendability.

This is documented in the oldest world literatures that make reference to experimental work with man and animals. In ancient Persia the king would hand over condemned criminals for use in experimental purposes for science. Later, this practice was followed by the Ptolomies in Egypt (Beecher, 1969: 109).

This practice continued in modern times. Colonel R. P. Strong was a professor of tropical medicine at Harvard University. He is credited as the first investigator (in modern times) to use prisoners as experimental subjects. In 1904 he used prisoners who had been condemned to death in experiments on plague. Later, he used prisoners in the Phillipines to study Beriberi. These prisoners were given gifts of tobacco for their participation. In 1914, doctors Goldberger and Wheeler conducted experiments on Pellagra on white male convicts in the State of Mississippi who had apparently volunteered for the experiments (Ivy, 1948: 4). In many instances, participation in research was rewarded with a sentence reduction. This clearly indicates that participation in research under these circumstances was less than voluntary.

If informed consent is used as the basis for justifying the conduct of research then it follows that those who are experimented upon should be those who are most capable of providing consent. According to Jonas, the best educated with the greatest degree of choice – such as investigators themselves - should be at the top of the list. The person with the “strongest motivation”, the person with the “fullest understanding”, the “freest decision” is most capable of consenting. The scientist sits at the top of this hierarchy of people and is most

likely to provide free and fully informed consent that the research endeavour requires.

Dr Rosalyn Yalow, a scientist from the Bronx in New York, won the Nobel Prize in 1977 for development of a laboratory test known as the radio immune assay (RIA). This technique is used to measure very small amounts of substances in the body. Her discovery required an enormous amount of experimentation.

Like Jonas, her thoughts on informed consent are reflected in her statement:

> *In our laboratory, we always used ourselves because we are the only ones who can give truly informed consent.*
>
> (Altman, 1985: 314)

The most valuable and scarcest members, the least expendable members of society would have to be the first for risk and sacrifice provided that the research objective is worthy enough (Jonas, 1969: 120). The most vulnerable members of society - the mentally challenged, children, prisoners and vulnerable communities - would then fall to the bottom of the list of possible research subjects and would require the highest degree of protection.

Claude Bernard emphasized the importance of self-experimentation:

> *Morals do not forbid making experiments on one's neighbour or on one's self….Christian morals forbid only one thing, doing ill to one's neighbour.*
>
> (Quoted in Altman, 1985: 16)

Santorio Santorio is the earliest recorded self-experimenter. He lived in Italy from 1561 to 1636. He is recognised as the first physician to use a thermometer to measure body temperature. He also described a concept known as "insensible perspiration" used widely by physicians in the

prescription of intravenous fluids. Over a thirty year period he conducted a number of experiments on himself to document the response of his own body to various physiological and pathological conditions.

More than 200 years later, Max von Pettenkofer swallowed a pure culture of the cholera bacillus when he was 74 years old. Due to previous exposure to Cholera, he had developed immunity and did not become seriously ill despite the large dose of bacteria he had ingested.

When he recovered, he had the following to say:

> *I would have died in the service of science like a soldier on the field of honour. Health and life are, as I have so often said, very great earthly goods but not the highest for man. Man, if he will rise above the animals, must sacrifice both life and health for the higher ideals*.
>
> (Altman, 1985: 25)

In 1767, John Hunter inoculated himself with pus from a lesion containing gonorrheal pus and later developed both gonorrhea and syphilis. He concluded, erroneously, that gonorrhea and syphilis were manifestations of the same disease (Beecher, 1969: 110).

In 1789, Edward Jenner found himself in the midst of a swinepox outbreak in Gloucestershire and decided to immunise his ten month old son and two of his neighbour's servants. He inoculated his son with pus from a lesion on the baby's nurse who had herself contracted the swinepox infection. Eight days later the baby became ill and developed a skin rash. Several months later, Edward deliberately infected his son and the nurse with smallpox five times to test the efficacy of the immunisation. Neither the baby nor the nurse developed any symptoms of smallpox. Two years later, Jenner challenged his son with smallpox again. This time he had a severe reaction as a result of contamination of the inoculation material but he recovered. A year later, Jenner inoculated him with smallpox again and he survived. However, in the years following those inoculations, he was often unwell and displayed signs of

mild mental retardation. At the age of 21 he died of tuberculosis. Jenner was devastated but considered the swinepox experiment to be successful (Kerns, 2004).

Reed's Yellow fever experiments in the 1880s illustrated both the concepts of self-experimentation and the emergence of the healthy volunteer. Yellow Fever was a disease associated with high morbidity and mortality. During the Spanish American War thousands of soldiers had died as a result of the disease. The Panama Canal Project in the 1880s was halted as a result of the disease. The hypothesis was that the disease was mosquito borne. Dr Reed and three colleagues doctors Carroll, Lazear and Agramonte went to Cuba to verify the mosquito hypothesis. Their plan was to allow mosquitoes that had fed on patients with Yellow Fever to bite humans. They were the first subjects. Carroll and Lazear initiated the experiment and both became ill. Carroll recovered but Lazear died. Dr Reed decided to omit further self-experimentation and to recruit volunteers. Twenty five volunteers became ill but none of them died. The experiment identified the source and mode of infection in Yellow Fever and made an enormous contribution to medical science.

In the 1940s Dr Andrew Ivy stated that there should be no prior reason to suspect that death or disabling injury might result from an experiment. He referred to the Yellow Fever experiments where experimenters served as research subjects "along with non-scientific personnel" (Jonsen, 1998: 135).

Self-experimentation is generally viewed with scepticism. However, there are a number of arguments that could be used to justify self-experimentation (Davis, 2003: 179-182).

The "Good Faith" argument was raised by Henry Beecher in his suggestion that the willingness of an investigator to be a subject in his/her own trial is a good test of how reasonable he/she thinks it is to enroll others (Beecher, 1969: 110). However, the investigator's vested interest in the research may result in him/her underestimating the risks and overestimating the value of the

research. The investigator's health profile may also differ significantly from that of the subjects.

The "Golden Rule" argument classically refers to doing unto others as one would have done unto oneself. In research

> *one ought not to inflict risks on others in the cause of science that one is not willing to inflict on oneself.*
>
> (Davis, 2003: 177)

Similarly Kant's Categorical Imperative states that

> *I ought never to act except in such a way that I can also will that my maxim should become a universal law.*
>
> (quoted in Paton, 1964)

According to Davis, this argument "does not support a duty to experiment on oneself but rather a duty not to experiment on others if one would not be willing to experiment upon oneself." Dr Kenneth Mellanby, a British researcher, invokes this argument to support his decision to participate in any experiment at least once before asking a volunteer to follow suit (Altman, 1985: 309).

The "Risk Argument" refers to experiments where the risk seems too high to enroll lay subjects or has not been pre-determined. Self-experimentation might then prove the experiment to be less risky than originally feared with the resultant enrolment of lay subjects.

Unlike the above three arguments which attempt to justify self-experimentation, the "Investigator's Autonomy" argument emphasizes the investigator's right to self-experimentation. Based on the principle of autonomy an investigator has a moral right to self-experiment.

Hans Jonas has stated that

> *no scientist can be prevented from making himself a martyr for his science.*
>
> (Jonas, 1969: 110)

Respect for autonomy forbids the interference with sufficiently informed and competent people whose actions affect only themselves. Hence autonomy may be limited by the principle of harm to other people (Mill, 1986). The investigators autonomy argument holds true as long as no risk is posed to third parties.

The most common reasons doctors give for self-experimentation is that it allows them to "share the risk with a patient or volunteer and that it provides confidence to prospective subjects" (Altman, 1985: 303). In addition, there are other reasons cited such as reliability, dependability, convenience, curiosity, tradition and an ethical code reflecting the Golden Rule as applied to medical research (Altman, 1985: 304). Researchers believe they will be more reliable in adhering to protocol blueprints and more dependable in observations and data recording than non-scientific lay volunteers.

On the other hand, self-experimentation alone may not be practical for the following reasons:

1. The requirement for large numbers in experimentation would render self-experimentation by itself inadequate and scientifically invalid.
2. Double blinding is not possible.
3. The use of a control group is required in most clinical trials.
4. Investigators may be biased towards a new intervention
5. Investigators may minimise their risk calculations in their enthusiasm to proceed with the research.
6. Investigators may not meet one or more of the inclusion criteria to participate in the research like age or gender or disease being researched.

In many ways self-experimentation was used as a substitute for the ethics committee's sanction of research in an era when ethics committees had not been established. With the establishment of RECs and sanction for research on large groups of volunteers, the practice of self-experimentation faded into obscurity.

However, with the advent of HIV vaccine research in the 20th century, the notion of self-experimentation has been revisited. In 1986 Dr Daniel Zagury of the Pierre-et-Marie Curie University in Paris was the first person to test a candidate HIV vaccine on himself. The vaccine contained a protein from the outer coat of the HI virus called gp160 which was inserted into a live vaccine (cowpox) virus. After injecting himself with the vaccine, he tested his blood weekly for 9 weeks and detected antibodies to gp160. The purpose of this self-experiment was to test the vaccine's ability to produce an immune reaction in humans and to determine its safety. It was not intended to test efficacy of the vaccine (Altman, 1985: 26-27).

Since March 1998, a large number of doctors, health care professionals and healthcare advocates had volunteered for vaccine trials – currently in progress (IAPAC 2003). As recently as 2000 a group of clinicians volunteered to participate in trials of a live attenuated vaccine (Pinching, 2000: 44-46).

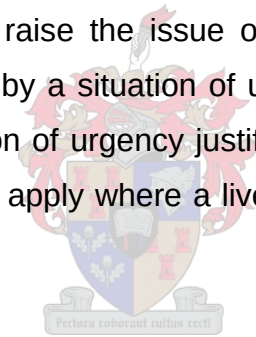
However, a survey conducted in the Western Cape, South Africa in 2001 amongst a group of doctors to assess their willingness to participate in a hypothetical phase 1 trial yielded interesting results. While 20% of the sample of 289 doctors initially agreed to self-participation, this figure dropped to 10% after trial related risks were contemplated (Moodley, 2002: 904-06).

While only 10% of the doctors were themselves willing to participate, 32% of doctors were happy to recruit lay people to participate – indicating a clear abrogation of the "Golden Rule" – do unto others as you would have done unto yourself.

Furthermore, commentators on self-experimentation emphasize the fact that willingness to perform the experiment in itself is insufficient. The critical issue lies in whether the researcher actually participates in the experiment. One can only assume that with low levels of willingness to participate in hypothetical HIV vaccine trials, actual participation in real time trials will be even lower. According to Sir George Pickering, Regius Professor of Medicine at Oxford in England, there is one golden rule to guide the researcher regarding the justifiability of the experiment:

> *Is he prepared to submit himself to the procedure? If he is, and if the experiment is actually carried out on him, then it is probably justifiable. If he is not, then the experiment should not be done*.
>
> (Altman, 1985: 313)

The HIV vaccine trials also raise the issue of the conceptual challenge to medical ethics that is posed by a situation of urgency as exists with the HIV pandemic. Does this situation of urgency justify self-experimentation? Does the "Risk argument" of Davis apply where a live attenuated strain of the virus is to be tested?



Despite the ethical justification for self-experimentation, even Jonas acknowledged that using the scientific community and the most highly educated non-scientific members of society exclusively would represent an ideal situation that would not be statistically or scientifically sustainable. Hence at some point it becomes absolutely critical to make a pragmatic shift from self-experimentation to experimentation on patients and healthy volunteers. This, however, would have to be done with the greatest caution, respect and freedom of enrolment and participation.

In the next chapter it will become evident how research atrocities were committed when the sanctity of participation in human research was not acknowledged and when participation was conducted without fully informed and voluntary consent.

Chapter 2

Research Ethics – A Historical Perspective

2.1. Introduction

Even though Jonas refers to medical progress as melioristic and gratuitous, it is important to acknowledge the enormous advances generated by the research endeavour in medical diagnosis and treatment. The global eradication of smallpox as a result of experimentation described in chapter one bears testimony to this. A range of other advances in all spheres of medical science impacted on patient care and quality of life as a result of experimentation. While the initial emphasis was placed on the eradication of infectious diseases, an objective greatly enhanced by the discovery of Penicillin and other antibiotics, this was later expanded to chronic diseases as well. There is no doubt that enormous benefits accrued to society as a direct result of the research endeavour. It is therefore not surprising that as the tradition of self-experimentation gave way to deliberate experimentation on groups of human subjects, the utilitarian justification for research was invoked. Unfortunately, in many instances this was equated with the utilitarian justification for war. The spirit of wartime urgency was extrapolated to research. During and after the Second World War pressure was brought to bear on researchers to provide cures for infectious diseases to protect troops and civilians alike. Between 1932 and 1966 there was an enormous expansion in research activity globally, but most notably in the United States. Individual good was subjugated to the common good without hesitation. In many instances, the rights of the individual were subjugated to the benefits of science and society. Human subjects were enrolled into research projects often without their consent and under a therapeutic misconception based on an unflinching trust of the medical profession.

The story begins in 1932…

2.2 The Tuskegee Syphilis Study

On 26 July 1972 the New York Times carried a shocking story:

> *For 40 years, the United States Public Health Service has conducted a study in which human beings with Syphilis, who were induced to serve as guinea pigs, have gone without treatment for their disease……the study was conducted to determine from autopsies what the disease does to the human body.*

The Tuskegee Syphilis Study began in 1932 and ended in 1972. Although initially planned for one year, it continued for 40 years. The population of Macon County, Alabama had one of the highest rates of Syphilis in the country.

600 Poor African-American men from Macon County were recruited into a project that set out to establish the natural history of Syphilis. 400 of these men had Syphilis and 200 were used as controls. Both patients and controls were told that they had "bad blood" and should have regular medical examinations including lumbar punctures.

These men had been promised free transportation to and from hospital, free hot lunch, free medical care for any disease other than Syphilis and free burial after autopsies had been performed. However, they were not aware that they were subjects in a research study!

When the study began, there was no definitive treatment for Syphilis. Heavy metals (arsenical and mercurials) were being used but were of doubtful efficacy. However, when Penicillin was discovered in 1945 and was found to be effective against Syphilis, this treatment was deliberately withheld from the men on this study as the researchers wanted to see what the natural history of untreated Syphilis would be. Even though it was known that Penicillin would

be useful in the early stages of the disease and most subjects were already in the late stages of the disease, the treatment was not offered to any of the volunteers (Altman, 1985: 18).

The Tuskegee Syphilis Study was not a secret. It was well known in the Public Health Service and had been published in medical journals. An employee of the Public Health Service, Peter Buxtun accidentally heard about it in 1966 and attempted to expose it. Even though he wrote a letter to the Centres for Disease Control (CDC) and got the study reviewed, a decision was taken to continue with the study. It was only in 1972, when he leaked the story to the media that steps were taken to investigate and terminate the study.

On 24 August 1972 the Tuskegee Syphilis Study Ad Hoc Panel comprising nine citizens was appointed to establish, inter alia, whether the study was ethical, whether and how it should be terminated. The report published in 1973 found the study to be unethical at its inception and during the continuation. It ordered the study to be terminated and the surviving victims to be compensated.

When the story was eventually exposed in 1972, 74 of the untreated subjects were still living (Jonsen, 1998: 146-48). However, by this time, 100 men had died of Syphilis, 40 of their wives had become infected and 19 babies were born with Congenital Syphilis.

The expose highlighted both racial discrimination and abuse of the poor and powerless as well as unethical research and clinical practices.

As a direct result of the Tuskegee study, the National Research Act was passed in 1974 in the United States and the Belmont Report was published in 1979. In 1997 President Clinton issued a formal apology to the study participants and their families on behalf of the United States government.

2.3. Experimentation during the Second World War

2.3.1 The Nazi Experiments

The Nazi experiments actually preceded the Second World War.

In 1933, in keeping with an emphasis on Eugenics, the “Law for the Prevention of Genetically Diseased Descendants” was in existence and sterilization was enforced. Within four years, 300 000 patients had been sterilized. As can be expected, sterilization research thrived.

In 1939, at the beginning of the war, the T4 Euthanasia Program was initiated in which adults and children who were deemed futile or terminal were killed and their organs were harvested.

Dr Klaus Karl Schilling, an eminent malaria expert, infected more than one thousand prisoners at Dachau with malaria. More than 400 died, many from complications of treatment with experimental malaria drugs, often given in excessively large doses (Altman, 1985: 16).

Other Dachau Concentration Camp experiments conducted with a military objective included:

1. The prolonged submersion of people in subfreezing water to test the limits of bodily endurance. Humans were held in tanks of ice water for up to three hours to test methods of resuscitation for pilots who had been chilled or frozen after falling into the sea (McNeill, 1998).
2. Locking prisoners in airtight chambers and then rapidly changing the pressures to duplicate atmospheric conditions that an aviator might encounter in falling long distances without a parachute or oxygen.
3. Infecting individuals with infectious disease like cholera, diphtheria and smallpox and then testing experimental and mostly useless vaccines on them.

4. Injecting phenol or gasoline into the veins of prisoners, who died within sixty seconds.
5. Testing to establish how long humans could survive without water and after eating huge amounts of salt (Altman, 1985: 17).
6. Exposing subjects to irradiation followed by castration of subjects to study the effects of X-Rays on the genitals. (Rothman, 2003: 61).

The Mengele Twin Studies also became notorious at this time. Josef Mengele was interested in the genetic study of twins. He collected twin children from the camps, measured their physical features, performed cross-transfusions, transplanted genitals and other organs and created artificial Siamese twins. He also used his twin collection for comparative studies, infecting one child and then killing both for autopsy (Jonsen, 1998 : 135).

At the end of the Second World War, the Nuremberg Trial was held and 22 doctors were found guilty of research atrocities. In 1947 the Nuremberg Code was developed. This code is based on ten principles – the most striking of which are the importance of research being based on good science and the concept of voluntary consent. The code is discussed in more detail in Chapter Three.

2.3.2 The Japanese Experiments

Coinciding with the Nazi experiments, Japanese doctors and bioscientists were conducting equally horrific experiments on Russian, Chinese, American, British and Australian prisoners. Japanese General Shiro Ishii was in charge of the Japanese Army Unit 731 that he had set up in 1935 in remote, high security headquarters in a village in Japanese occupied Manchuria. The experiments included freezing, ballistics and live vivisection. General Ishii's aim was to make a biological weapon that could win the war for Japan. These experiments were, however, kept secret for many years after the war as a result of an agreement between the United States government and the Japanese government. Japanese experimenters were granted immunity from prosecution in exchange for information about biological warfare (Williams,

1989). This reflects the pivotal role of politics in the development of codes of ethics for the conduct of research on human subjects (McNeill, 1998: 371).

2.4. The Thalidomide Disaster (1962)

In the 1950s Thalidomide was approved as a sedative in Europe. The drug was widely used on pregnant women for sedation, morning sickness and to prevent abortion or premature delivery. However, it had not been approved in the US by the Food and Drug Administration (FDA). Dr Frances O. Kelsey of the FDA had succeeded in keeping the drug, "Kevedon" manufactured by Merrel Pharmaceuticals, off the American market. She was sceptical about the scientific data. She declared that "Merrel had compiled an interesting collection of meaningless pseudoscientific jargon apparently intended to impress chemically unsophisticated readers." Dr Kelsey later noticed an article in the British Medical Journal indicating that some users of the drug had developed peripheral neuropathy.

By this time (1960) the pharmaceutical company (Merrel) had started a pre-marketing campaign "in the guise of a clinical investigation program" and enlisted about 1200 "influential physicians" to prescribe the drug (Jonsen, 1998: 140). The drug was given to 20 000 American women, 3750 of whom were of child-bearing age and 624 of whom were pregnant (Rothman, 2003: 64). Many patients were not aware that they had been taking an experimental drug, nor had they given their consent. During this time, Dr Helen Taussig of Johns Hopkins School of Medicine decided to investigate the European and British "epidemic of infant monsterism" where infants were being born with missing limbs and found that the condition was associated with the use of Kevedon. The drug had severe terratogenic side-effects termed phocomelia.

Merrel Pharmaceuticals informed doctors of the dangers of the drug and withdrew their New Drug Application from the FDA on 8 March 1962.

This story broke on 15 July 1962 in the Washington Post (Jonsen, 1998: 140-41).

As a result of this experience with Thalidomide, the government's control over the approval of new drugs strengthened. Pharmaceutical companies submitting applications for registration of drugs had to provide "substantial evidence of efficacy" in addition to safety. For the first time full and free consent from all participants in drug trials was required in the United States. However, this meant that investigators had to inform participants that the new drug was being used "for investigational purposes" and consent would be obtained from participants or their representatives except where investigators "deem it not feasible or, in their professional judgement, contrary to the best interest of such human beings". This was a far cry from later versions of informed consent (Jonsen, 1998: 141).

2.5. The Beecher Expose (1966)

Dr Henry Beecher, an anaesthetist at Harvard University, played a crucial role in exposing numerous instances of how researchers abused their discretion in the decades that followed the Second World War. As a researcher himself he had been sensitised to the slippery slope one enters in the context of research. He was however, committed to good science and was concerned that unethical research would undermine the validity of good scientific research (Rothman, 72-73). In 1966, he published 22 examples of unethical research out of a collection of 50 studies that he had read in leading journals at the time (Beecher, 1966: 1354-60). In these experiments, participants had been exposed to excessive risks, the need for consent had been ignored, in some cases poor, mentally handicapped individuals had been used as subjects and therapies of known efficacy had been withheld (Jonsen, 1998: 144).

The Willowbrook case study is an example of one of the studies he exposed:

2.5.1 The Willowbrook Story

Willowbrook State School was one of New York's largest institutions for mentally retarded children on Staten Island. In 1949, Hepatitis was first

detected amongst the children. In 1954 Dr Krugman and Dr Giles started to study the natural history of Infectious Hepatitis, an endemic disease amongst institutionalised children. The doctors wanted to infect new admissions to the institution with hepatitis and observe the progress of the mild flu-like illness that would result. Their reasoning was that all children admitted to the institution would eventually contract the disease, they would be admitted to an isolation unit where they would be protected from other infectious diseases, they were likely to have a sub-clinical infection followed by immunity and only children whose parents gave informed consent would be included. While their initial aim was to determine the period of infectivity of infectious hepatitis, their eventual aim was to develop a hepatitis vaccine and this was accomplished.

Commentary on Willowbrook and the Beecher Expose

As a result of the good outcome, this study generated a healthy debate. However, it was criticised for a number of reasons. The major question revolved around the benefit that would accrue to these children. If the natural environment would have resulted in them contracting the infection and developing immunity anyway, the experiment was non-therapeutic –and would benefit other children, not the participants.

Furthermore, according to Henry Beecher

> *An experiment is ethical or not at its inception; it does not become ethical post hoc, - ends do not justify the means.*
>
> (Beecher, 1966: 1360)

While critics of this study like Paul Ramsey rejected the concept of proxy consent in non-therapeutic research, his arguments would have severely prohibited paediatric research. The South African Medical Research Council guidelines on paediatric research are moderate in nature and permit reasonable research on children provided there is not more than minimal risk, provided that such research cannot be conducted on adults and provided that children will benefit from the research. On the other hand, American

guidelines require an explanation for why children are not included in research. This will be discussed further in Chapter Seven.

The Willowbrook study was also criticized for its potential to cause harm. At the outset, it was anticipated that the children would develop a mild influenza like illness however, in some cases progression to fatal liver destruction could occur and the development of cirrhosis later in life was possible (Beecher –as quoted in Beauchamp 2001). This would mean that the experiment would have exposed the children to more than minimal risk.

The next criticism related to the fact that there were alternative ways to control Hepatitis in the institution and the use of gamma-globulin inoculations had reduced the incidence of infectious hepatitis by 80 to 85%. It was charged that the paediatrician's duty was to improve the situation not to take advantage of it.

Finally, the nature of consent obtained was questioned. The concept of "group consent" was criticised as Krugman had taken consent from groups of parents instead of individual parents. The notion of voluntariness of the consent was also questioned when the doors of the institution were closed in 1964. However, children could be admitted to the research unit if parents were prepared for their children to be included in the project (Beauchamp, 2001: 428-30).

The Beecher expose called into question the motivation for a wide range of questionable behaviour by researchers. A number of explanations for such behaviour could be advanced, the most prominent of which was the pressure placed on researchers in the post-war years by institutions and government agencies alike. Most of the researchers in Beecher's protocols were "heirs to this wartime tradition". They were the "products of medical training in the immediate post-war period, trained to think in utilitarian terms and ready to achieve the greatest good for the greatest number" (Rothman, 2003: 79).

The Beecher expose drew attention to large numbers of patients having been placed at risk in the context of the research endeavour in the United States in the post-war period. However, in 1967 Pappworth published his book entitled "Human Guinea Pigs" in London in which he described many more cases of unethical research (Pappworth, 1967). He had collected more than 500 papers in England based on unethical experimentation (Beecher, 1966: 1355).

Commentary on Chapter 2:

The cases discussed in this chapter serve to illustrate the nature of some of the ethical violations that occurred both during and after the Second World War. These cases range from intentional blatant disregard for human participant protection such as Tuskegee and the Nazi experiments to commercial greed as in the Thalidomide case to overzealous but well intentioned researchers as in Willowbrook. Nevertheless, ethical violations in research in the post-war period were widespread. Beecher's expose was poignant in identifying these violations and in stimulating efforts to regulate research and promote participant protection. These efforts are described in Chapter Three.

Chapter 3

International Codes and Declarations for Research Ethics

3.1. Introduction

In the aftermath of the research atrocities outlined in Chapter Two and as a direct result of the various events, a number of international guidelines were sequentially developed in an attempt to regulate the conduct of research. The important documents in which these guidelines were enshrined were the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, the Council for International Organisations of Medical Sciences Guideline drafted by the World Health Organisation and the International Conference on Harmonisation (ICH-GCP) Guideline. As the early attempts at regulation were developed in direct response to very specific events in research, the early documents contained deficiencies that required serial improvements over time to meet the changing demands of a rapidly expanding research industry. As such, these documents may be viewed as a progressive series of guidelines with each one attempting to supercede its precursors (R. J. Levine, 1996: 235). They may also be viewed as "evolving yardsticks" and as such be "continually subject to critical appraisal and revision" (Richards, 2002: 796).

This chapter outlines the evolution of some of the major guidelines from 1947 to 1993.

3.2. The Doctors' Trial At Nuremberg

Of the major trials conducted at Nuremburg to try a host of war criminals the most significant from the perspective of research ethics was the Doctors' Trial conducted on 19 August 1947. The charges against the defendants in this

trial were brought in the name of the United States of America hence this event is documented as the case of the United States v. Brandt –so named after Karl Brandt, Hitler's personal physician - who represented the defendants. The case was conducted under the auspices of the United States military.

After a seven month long trial twenty doctors and three medical administrators were charged with "murders, tortures and other atrocities committed in the name of medical science" as outlined in Chapter Two. They were tried by a court of American judges who relied on the testimony of two American physicians and researchers – Andrew Ivy and Leo Alexander. Of the twenty-three defendants, sixteen were found guilty and seven, including Brandt were hanged for various crimes against humanity (McNeill, 1998: 370). Nine of the defendants were sentenced to long prison terms.

3.3. The Nuremberg Code

The Nuremberg Code represents the first attempt to provide guidelines for the conduct of research. It described the Nazi experiments as being contrary to

> *the principles of the law of nations as they result from the usages established among civilised peoples, from the laws of humanity, and from the dictates of public conscience.*
>
> (The Nuremberg Code, 1947)

According to Levine, this statement reflects the claim to universality made by the Nuremberg Code.

In essence, the following ten principles are enshrined in the Code:

1. Voluntary Informed Consent was emphasized and documented for the first time as a prerequisite for research. It also restricted the provision of consent to those who had legal capacity to do so:

This means that the person involved should have legal capacity to give consent.

(The Nuremberg Code)

2. The experiment had been for the good of society, unlike the many experiments conducted in the concentration camps based on the whims or political motivations of medical doctors.
3. The experiment was to be based upon prior animal studies. Many Nazi experiments were conducted for the first time on human subjects.
4. Physical and mental suffering and injury to participants had to be avoided, a concept clearly overlooked when research subjects were exposed to torture in the course of horrendous experiments.
5. There had to be no expectation that death or disabling injury would occur from the experiment as opposed to the blatant expectation of death that existed in many of the Nazi experiments.
6. Risk had to be weighed against benefits, a calculation never computed by Nazi physicians during the war.
7. Subjects were to be protected against injury, disability or death unlike what actually happened during the Nazi experiments
8. Only scientifically qualified individuals could conduct human experimentation, perhaps an inadequate specification as all the Nazi researchers were scientifically qualified yet conducted inhumane research.
9. The subject was able to terminate his/her involvement in the research project if he or she chose to do so, an opportunity clearly not accorded to subjects in Nazi Camp research.
10. The investigator could terminate the experiment if injury, disability or death was likely to occur, clearly a thought that did not occur to Nazi researchers.

It is evident that the code was written in direct response to the Nazi concentration camp research and hence it has a narrow focus but was an excellent first step in the regulation of the research endeavour.

Furthermore, the Nuremberg Code has been criticized for being a document drawn up by jurists and not doctors. As such it did not cover all research activities that medical doctors needed to conduct on human subjects. No provision was made for research on those who lacked capacity to consent like children and the mentally ill (R. J. Levine, 1996: 236). This would have excluded psychiatric research.

It did not mention review of research by an ethics committee. Instead, the responsibility for the conduct of research rested with the investigator.

Even though the Nuremberg Code had been in existence since 1947, it did not receive the recognition it deserved from the Anglo-American world as it was regarded as something peculiar to Nazi Germany. International groups were reluctant to accept the code as it included an absolute requirement for consent prior to any experimentation on human subjects.

In 1954, the World Medical Association (WMA) adopted a Code for Research and Experimentation that allowed for proxy consent in experiments on patients who did not have the capacity to consent for themselves (McNeill, 1998: 371).

3.4. The Declaration of Helsinki – 1964

The Declaration of Helsinki is criticised as being a watered down or diluted version of the Nuremberg Code as it extended the conduct of research to the very young, the unconscious and those lacking legal capacity such as the mentally ill. The Nuremberg Code specified that research could be conducted only on those capable of giving voluntary informed consent.

This document also drew a distinction between therapeutic and non-therapeutic research that has been debated since its inception:

> *In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially*

diagnostic or therapeutic for a patient, and medical research the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

(WMA, 1996)

Therapeutic research is viewed as justifiable due to the benefit that accrues to patients, while non-therapeutic research has the well-being of society in mind (Schuklenk, 2000: 162-63).

The distinction has raised criticism by several commentators most notably, Robert Levine who illustrates the unreasonableness of the distinction by juxtaposing two articles in the 1964 version referring to this distinction:

Article II.6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

Article III.2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.

Levine uses the hypothetical example of a study designed to explore the role of neurotransmitters in depression. He argues that such research cannot be justified on the basis of its therapeutic benefit for the patient, as required by article II.6, hence it must be considered to be non-therapeutic. Therefore, according to article III.2, the subjects of the research must be either normal volunteers or patients who have diseases other than depression.

In the 1970s this distinction was rejected in the United States, and federal regulations were used in its place. According to federal regulations, research had to be judged according to a level of risk and expected benefit. An intervention that provides direct benefit to the patient can involve virtually any

degree of risk to individual subjects. An intervention that does not benefit individuals must be justified by its intended benefit to society. In the case of children and non-therapeutic research, if the procedure carries more than a minor increase over minimal risk this must be reviewed at a national level (Levine, 1999: 531-32). This distinction will be considered again in Chapter Seven in the context of HIV vaccine trials in South Africa.

The Declaration in 1964 included 22 principles. A number of these issues had already been covered in the Nuremberg Code. In addition, the guideline specified that the experimental protocol should be reviewed by an independent committee (IRB or Research Ethics Committee):

> *The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.*
>
> (Declaration of Helsinki 1964)

As such, the Declaration of Helsinki was the first guideline to make formal reference to the need for an REC.

An issue that will be discussed at length in the next chapter is the reference to treatment of a control group:

> *In any medical study, every patient – including those of a control group, if any- should be assured of the best proven diagnostic and therapeutic method.*
>
> (Declaration of Helsinki 1964)

This specification of “best proven” treatment for a control group evolved into the centrepiece of the debate on the HIV vertical transmission trials that will be addressed in Chapter Four.

The Declaration of Helsinki's claims of universality are grounded in its reference to the World Medical Association's Declaration of Geneva and the International Code of Medical Ethics. The declaration refers to its recommendations as "a guide to every physician in biomedical research involving human subjects" (R. J. Levine, 1996: 235-59).

This declaration was amended in 1975 to account for the expanded scope of biomedical research. This version was written from an observation point closer to active clinical science (Riis, 2000: 3045). Further revisions took place in 1983, 1989, 1996 and most recently in 2000. The most significant revision took place between 1997 and 1999 in response to the HIV vertical transmission trials and these changes are reflected in the controversial 2000 version. The final revision will be discussed in Chapter Four.

In spite of the Declaration of Helsinki being in existence since 1964, the Tuskegee study continued until it was exposed in the media in 1972. This disregard for the Declaration of Helsinki resulted in the promulgation of the National Research Act in the United States.

3.5. The Belmont Report (1979)

When the National Research Act was signed into law in 1974, the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research was created. One of the charges to the commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioural research involving human subjects and to develop guidelines that would ensure that research is conducted in accordance with these principles. The Belmont report was drafted in 1979. Unlike the previous codes and guidelines that specified rules, this document discussed broad principles that could be interpreted and applied in different research settings. The Belmont Report was drafted in response to the expose on the Tuskegee study and hence reflected on the historical research violations that had preceded the expose. It emphasized three major principles of theological and secular ethics (C. Levine, 1996: 106). This report used the distinction

between clinical practice and research as its point of departure and then explored three principles of importance in the conduct of research:

1. Respect for Persons.

   This principle outlines two moral requirements – the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

2. Beneficence.

   Beneficence requires that researchers working with human subjects should in the first instance avoid harm but where this is not possible, maximize benefits and minimize harm to subjects.

3. Justice

   Justice in research refers to the fair selection of those who must bear the burdens of research. It is also important that this group of subjects reaps the benefits of such research. Justice is relevant to the selection of subjects at two levels - at an individual level and at a social level.

At an individual level it was advised that:

> *researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favour or select only 'undesirable' persons for risky research*

At the social level:

> *distinctions [should] be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons*

The national commission recommended that classes of subjects be selected in an order of preference - adults before children – and that some classes of potential subjects like prisoners and the institutionalised mentally infirm be selected only under certain conditions and perhaps not at all.

Application of the three principles leads to the consideration of informed consent, assessment of risks and benefits and subject selection.

(The National Commission for the protection of human subjects of Biomedical and Behavioural Research, 1979).

3.6 Council for International Organisations of Medical Sciences (CIOMS) 1993 Guideline

CIOMS is an international non-governmental organisation founded under the auspices of the World Health Organisation (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949. CIOMS started its work in the ethics of biomedical research in the late1970s. It set out to prepare guidelines

> *to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their socio-economic circumstances, laws and regulations, and executive and administrative arrangements.*
>
> (CIOMS, 1993)

In 1982, the Council had developed “Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects.”

However, the HIV/AIDS pandemic raised new ethical issues that had not been considered in the 1982 version. Furthermore, rapid advances in medicine and biotechnology, multinational research and research on vulnerable populations

necessitated a revision of the 1982 version. In 1993, “International Ethical Guidelines for Biomedical Research Involving Human Subjects” was issued.

The guideline was drafted by a heterogeneous group of people in terms of race, gender, nationality and profession. This enhanced its global validity (R. J. Levine, 1996: 243).

The CIOMS guideline, on the whole, was a much more comprehensive document than either the Nuremberg Code or the Declaration of Helsinki.

It expanded the narrow focus of the Nuremberg Code and corrected some of the conceptual errors in the Declaration of Helsinki. In addition, considerable attention was paid to ethical issues peculiar to developing world research.

Guideline Eight specifies the following in the context of multinational research:

- *persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably well in developed communities;*
- *the research is responsive to the health needs and the priorities of the community in which it is to be carried out;*
- *every effort will be made to secure the ethical imperative that the consent of individual subjects be informed; and*
- *the proposals for the research have been reviewed and approved by an ethical review committee that has among its members or consultants persons who are thoroughly familiar with the customs and traditions of the community.*

(CIOMS, 1993)

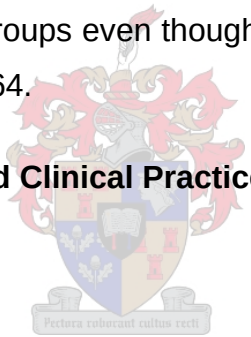
It expanded the concept of informed consent from individual informed consent to situations where a community leader may need to be involved in the process. Other methods to obtain informed consent could be incorporated based on the advice of the local REC.

Guideline 15 lists obligations of sponsoring and host countries in the context of multinational research. With regard to dual review:

> *An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and the ethical standards applied should be no less exacting than they would be in the case of research carried out in that country.*

This guideline specifies dual review of research by both the host and the sponsor country REC. This is why it so crucial that high standards of ethical review are upheld in a developing country like South Africa.

Of note in the 1993 version of CIOMS is the absence of discussion about standards of care or control groups even though this was clearly articulated in the Declaration of Helsinki 1964.



3.7. The Evolution of Good Clinical Practice

3.7.1 United States

In spite of the Nuremberg Code's existence since 1947, American researchers regarded it as a document for Nazi doctors and scientists only. The lesson of Nuremberg seemed to have "made little impression on the American world of medical research" (Jonsen, 1998: 137). In 1964, as a result of the Declaration of Helsinki, review of research procedures was emphasized. However, in the 1970s fraud in research was still continuing in the United States in spite of Helsinki. In the 1970s and early 1980s, the Food and Drug Administration (FDA) developed regulations on informed consent, Institutional Review Board (IRB) or Ethics Committee review and approval, and investigational new drugs.

Collectively, these regulations, along with various guidelines, became known as Good Clinical Practices or GCPs.

3.7.2 Japan and Europe

The first GCP guideline was issued in Japan in 1990 and in Europe in 1991. These guidelines were much less extensive and stringent than the FDA requirements. In Europe and Japan, however, these were just guidelines rather than law. And they were not widely accepted. The various GCPs were widely variable and often inconsistent. This inconsistency, together with the globalisation of many pharmaceutical companies, gave rise to the need for development of an international standard, and so the ICH process was born.

3.7.3. ICH GCP

Since 1991, the European Union, the United States and Japan had been collaborating in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.

In 1996, the ICH Harmonised Tripartite guideline for Good Clinical Practice was released. The guideline came into effect in the European Union, the US and Japan in 1997. The ICH GCP guidelines are based on the Declaration of. Helsinki (International Conference on Harmonisation, 1997). This guideline is widely used in South Africa and abroad in clinical trial research. It forms the basis of many Good Clinical Practice training programs locally and internationally.

3.8 Commentary

The development of international guidelines coincided with a principle based approach to ethical deliberation. The Belmont Report of 1979 is the most blatant product of such deliberation. The three principles enshrined in the Belmont Report also form the basis for guidelines that were developed thereafter. Adoption of a principle based system of regulation of the conduct of research overshadowed in many ways the virtue based system of self-regulation prior to the Second World War. Individual researcher autonomy gave way to regulation by international guidelines and research ethics

committees constituted in accordance with the Declaration of Helsinki in 1964 and the National Research Act in the United States in 1974. The move to a principle based approach also represented a move from a utilitarian justification for research to a deontological approach. Jonsen describes the critique leveled against "the utilitarian principle as a fundamental maxim of research ethics". The utilitarian maxim, "for the greater good of the greater number" was frequently invoked by researchers who believed that it sanctioned the use of subjects without consent. This interpretation of "utilitarianism" was criticised by Dr Leo Alexander in his article "Medical science under dictatorship." (Jonsen, 1998: 152-53). The guiding documents all subscribed to the philosophy developed by Jonas when he described the research endeavour as a gratuitous venture requiring complete freedom of volunteers. It is hence not surprising that virtually all the major documents invoke the principle of respect for autonomy.

Although a host of guidelines had been developed between 1947 and 1993 attention was not focused on the content of the guidelines until 1997 when the ethics of HIV vertical transmission trials were called into question. However, as early as 1988, ethics commentators in developed countries started to anticipate the ethical considerations of conducting research in developing countries:

> *The basic ethical principles that guide human investigation, as defined by the Helsinki Declaration and the Nuremberg Code, need to be interpreted and applied within different cultural settings, many of which were unfamiliar to the international bodies that originally formulated these principles.*
>
> (Barry, 1988: 1083)

Barry argued that the basic ethical principles might have different meanings in developing countries and undertook an examination of cross-cultural bioethics. Her major concern rested with the American notion of personhood where individual rights, self-determination and privacy are emphasized. Application of the principle of autonomy as it was enshrined in international

guidelines of Western origin was predicted to be contentious in cross-cultural research. She also alluded to the use of ethical standards that ought to be applied as stringently as they were in developed countries (Barry, 1988: 1083-85). A number of her concerns eventually unfolded as cross-cultural research projects were initiated in Africa. Chapter four details the impetus provided by HIV research for a closer examination of existing guidelines.

Chapter 4

Controversies revisited: The Ethics of Research in Developing Countries

4.1 Introduction

As the HIV/AIDS pandemic ravaged Africa and other developing countries in South America and South-East Asia in the 1980s, it became inevitable that the research focus would move to these sites. In particular, sub-Saharan Africa was home to large patient populations at risk for HIV infection who could be "identified and studied". The National Institutes of Health (NIH) had started offering funding for collaborative research projects in Africa. However, American and European investigators "often unfamiliar with the culture, customs, and economic pressures within these developing countries" were "designing large-scale studies". Recognizing the urgency of the HIV/AIDS pandemic, Barry urged that consideration be given to the "ethical implications and cultural obstacles involved in conducting research in developing nations" (Barry, 1988: 1083). Marcia Angell, in an editorial in the New England Journal of Medicine in 1988, in response to Barry's article argued for a core of basic human rights to be adhered to in research settings anywhere in the world, taking local considerations into account. This would mean that the "ethical requirements of performing clinical research in Third World societies may be more, rather than less, exacting" (Angell, 1988: 1083).

Chapter Four describes the sequence of events that followed these earlier deliberations when in 1997 the research projects that were anticipated in 1988 were actually under way.

4.2 ACTG 076 and the Vertical Transmission Trials

In 1994, the results of the first randomised placebo controlled study on pregnant women infected with HIV were published. It was established that treatment of these women with the antiretroviral drug Zidovudine during pregnancy and delivery reduced the transmission of the virus from mother to child by 67%. From this point onwards, Zidovudine became the best proven standard of treatment for all HIV infected pregnant women in the United States (Connor, 1994: 1173-80).

The drug regimen used in this landmark study is, however, very expensive and totally unaffordable to Third World countries. The next logical step was therefore to investigate the possibility of shorter and hence cheaper courses of treatment.

The World Health Organisation urgently called for research in developing countries to explore simpler and less expensive drug regimens. The United Nations AIDS program (UNAIDS) and other organisations united to set up 16 clinical trials in 12 developing countries around the world. Nine of these studies were conducted by the National Institutes of Health (NIH) and the Centres for Disease Control (CDC). One of these trials (conducted in Thailand) was designed as an equivalency study – three short course regimens were compared and the control group was given the ACTG 076 regimen. However, 15 of these 16 trials were randomized and placebo controlled. HIV infected pregnant women in the study group were given a short course of Zidovudine and the incidence of transmission of the virus to their babies was established. However, the HIV infected pregnant women in the control group were given a placebo. And, this is where the controversy began (Lurie, 1997: 853-56).

4.2.1 The Placebo Debate

In April 1997, Dr Peter Lurie and Dr Sidney Wolfe of the Health Research Group (an arm of the watchdog organisation, Public Citizen), sent a letter to

the secretary of the Department of Health and Human Services, Donna Shalala which stated the following:

> *Unless you act now, as many as 1002 newborn infants in Africa, Asia and the Caribbean will die from unnecessary HIV infections they will contract from their HIV-infected mothers in nine unethical research experiments funded by your department through either [NIH or CDC].*

In September 1997, Lurie and Wolfe repeated their charges in the New England Journal of Medicine. They drew attention to the two studies being conducted in the United States where patients in all study groups had unrestricted access to antiretroviral drugs unlike the 15 short course trials in developing countries where women in the control group were given a placebo (Lurie, 1997: 853-56).

The editorial in the same issue of the journal written by executive editor Dr Marcia Angell, supported the views of Lurie and Wolf. In addition, she drew a parallel between withholding treatment in the placebo group and withholding treatment for Syphilis in the infamous Tuskegee study. This set in motion an unprecedented debate on the vertical transmission trials and the ethics of collaborative multinational research (Angell, 1997: 847-49).

4.2.2 The Scientific Debate

The Research Question and Clinical Equipoise

Lurie and Wolfe argued that by conducting a placebo-controlled trial the researchers were, by implication, asking the wrong question:

> *Is the shorter regimen better than nothing?*

The presumed answer to this question was that anything would be better than nothing. It is an essential pre-requisite that when a randomised clinical trial compares two different treatments for a disease that there should be no good

reason for thinking that one is better than the other. Hence, investigators need to be in this state of clinical "equipoise" when embarking on a randomised clinical trial. If there is any evidence that one option might be better than the other, then

> *not only would the trial be scientifically redundant, but the investigators would be guilty of knowingly giving inferior treatment to some participants in the trial*
>
> (Angell, 1997: 847)

Hence, randomised clinical trials create the potential for conflict between the investigator's role as doctor and research scientist. During recruitment, a doctor must ask a patient to submit him or herself to random assignment to one of two different treatments, one of which may be a placebo. This request can only be ethically justified if the researcher is in a state of genuine uncertainty regarding which treatment is better. This is so because randomisation is inconsistent with doing one's best for the patient as a doctor (Miller, 2003: 3-9). This rule applies to placebo-controlled trials in that it is only ethical to compare a potential new treatment with a placebo when there is no known effective treatment.

In the opinion of Lurie and Wolfe, the question that should have been asked was:

> *Can we reduce the duration of prophylactic [zidovudine] treatment without increasing the risk of perinatal transmission of HIV, that is, without compromising the demonstrated efficacy of the standard ACTG 076 [zidovudine] regimen?*
>
> (Lurie, 1997: 855)

In response to this charge, Varmus and Satcher retorted that they were looking to answer a much more complex question than Lurie and Wolfe suggested. Their concern was not simply to establish whether a short course of treatment was better than nothing but also whether the short course was

safe and if so whether the demonstrated efficacy compared to placebo was large enough to make it affordable to the governments in question. This viewpoint was supported by a South African epidemiologist, Abdool Karim, who argued that the fundamental research question related to whether short courses of antiretrovirals could reduce vertical transmission sufficiently to warrant their wide-scale implementation in South Africa (Abdool Karim, 1998: 564-66). Varmus and Satcher argued further that

> *the most compelling reason to use a placebo-controlled study is that it provides definitive answers to questions about the safety and value of an intervention in the setting where the study is performed, and these answers are the point of the research.*
>
> (Varmus, 1997: 1003-05)

The investigators believed that two different populations were being studied and it was not possible to extrapolate findings from the United States to Africa. The ACTG 076 regimen in the United States required that women receive HIV testing and counseling early in pregnancy, comply with oral treatment for several weeks and intravenous antiretrovirals during labour and refrain from breast-feeding. In addition, babies would have to receive six weeks of oral antiretrovirals. South Africa, in common with other developing countries, has a high frequency of home deliveries especially in rural communities (Abdool Karim, 1998: 564-66). In developing country settings, women present late for antenatal care, have limited access to HIV testing and counseling and depend on breastfeeding to protect their babies from malnutrition and diarrhoeal diseases. The safety of Zidovudine in populations who have a high incidence of malnutrition and anaemia was unknown. The cost of the ACTG 076 regimen was approximately $800 per treatment, far in excess of the per capita health care expenditure of under $10 in most developing countries (Varmus, 1997: 1003-06). Charges were also made that the critics' commentary of the trials "reflects a lack of understanding of the realities of health care in developing countries" (Halsey, 1997: 965-66).

The Utility of Existing Data

There was disagreement on the use of observational or historical data to provide the same information that could be obtained from the placebo arm.

Advocates of placebo-controlled trials and the WHO argued that "historical controls" were not reliable sources of data due to the change in vertical transmission rates from one country to another. Abdool Karim agreed and substantiated his claims with data from South Africa that indicated differences in vertical transmission rates from 1991 to 1994. He added that the vertical transmission rate is influenced by a number of factors including caesarean section rates, maternal viral load and breast-feeding rates. As such, the use of historical controls would lead to spurious and hence unacceptable conclusions (Abdool Karim, 1998: 564-66).

Critics of the trials believed that the differences between the ACTG 076 trial participants and those in Sub-Saharan Africa were being exaggerated and that HIV vertical transmission rates were known in Africa and were in the region of 20 to 30% making the use of historical controls possible.

Equivalency Trial Issues

When effective treatment exists, a placebo may not be used and subjects in the control group must be given the best known treatment (Angell, 1997: 847). Such a study is termed an equivalency study and the results are scientifically valid.

If the ACTG 076 regimen were used as the control group in the controversial vertical transmission trials, it would be termed an equivalency trial. Such a trial would be useful if it were proven that short course treatment regimens were as good as or better than the ACTG 076 regimen. It is also necessary for the expected outcome of the control to be known. Abdool Karim argued that the effect of 076 in South Africa is not known and could not be extrapolated from other settings given the differences in breast-feeding rates,

sexually transmitted disease rates, caesarean section rates, levels of viral load and other variables.

Advocates of placebo controlled trials held that equivalency trials required a much larger sample size to show a difference between two active arms of the study and hence they would take longer to complete, and cost more. Furthermore, the larger numbers of participants would result in exposure of more people to the risk of research.

4.2.3 The Ethical Debate

The Guidelines

Critics of placebo-controlled trials argued that the trials violated principles enunciated in several major international ethics guidelines. The Declaration of Helsinki was exhaustively invoked.

In support of her objections to the placebo-controlled trials, Angell cited the following tenets of the DOH 1996:

> *In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.*

And

> *In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.*
>
> (WMA, 1996)

Guidelines 8 and 15 of the WHO document - CIOMS (1993) – were frequently invoked.

Here, researchers were required to ensure, inter alia,

> *that persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably well in developed communities and that research was responsive to the health needs and priorities of the community in which it is to be carried out.*

Guideline 15 stated that the proposed study should be submitted for ethical and scientific review, and the ethical standards applied "should be no less exacting that they would be" for research in the sponsoring country itself. (CIOMS, 1993)

Advocates of the placebo trials cited the principles of the Belmont Report. Emphasis was placed on the shift from the principle of beneficence to justice – equitable access to clinical trials (The National Commission for the protection of human subjects of Biomedical and Behavioural Research, 1979).

Guideline Eight of the CIOMs document relating to responsiveness to local needs in research conducted in developing nations was also cited.

Hence the guidelines were used as ammunition to defend the positions of both proponents and critics of the placebo controlled trials indicating the internal contradiction that exists in many international documents.

Standard of Care

After the efficacy of the 076 regimen had been established in the United States in 1994 that became the "gold standard" in the prevention of mother-to-child transmission of HIV. Hence, both critics and proponents of placebo-controlled trials were in agreement that placebo-controlled trials could not be conducted in the United States.

Critics of the trials argued for a universal standard of care irrespective of where in the world the research was being conducted.

Proponents argued that participants in the control group would have received exactly the same standard of care if they had not participated in the trials – the local standard of care which at that time was no treatment in the developing world.

According to Marcia Angell, the justifications for these trials are

> *reminiscent of those for the Tuskegee study: Women in the Third World would not receive anti-retroviral treatment anyway, so the investigators are simply observing what would happen to the subjects' infants if there were no study. And a placebo-controlled study is the fastest, most efficient way to obtain unambiguous information that will be of greatest value in the Third World.*
>
> (Angell, 1997: 847)

Ethical Imperialism

Ethical Universality refers to the belief that the ethical principles that guide the conduct of research are the same wherever in the world research is conducted.

Ethical Relativism refers to the belief that ethical principles that guide the conduct of research vary from one cultural setting to another. This concept is based on scepticism and tolerance. Scepticism refers to the belief that actions may be defined as right or wrong by specific people in specific cultural contexts at specific times. Hence behaviour is culturally relative. Ethical relativity contends that the "impossibility of objectively determining moral action obliges tolerance toward other cultures" (Christakis, 1996: 261-78).

Hence in transcultural research, the ethical requirements of both cultures involved will need to be met. This approach is problematic in that a third

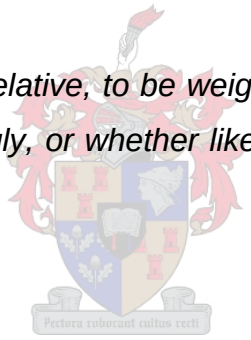
cultural system could regard the two systems involved as unethical and there is no provision made for conflict resolution.

Ethical pluralism on the other hand “acknowledges the key position of culture in shaping both the content and the form of ethical rules and it includes a mechanism of dispute resolution through mutual evaluation and negotiation” (Christakis, 1996: 261).

Critics of the placebo-controlled trials were accused of ethical imperialism – trying to impose their ethical standards on countries that had made their own judgements on the trials, based on their particular needs.

This debate predated the actual conduct of HIV vertical transmission trials. Marcia Angell, in 1988, raised the fundamental question of whether

> *ethical standards are relative, to be weighed against competing claims and modified accordingly, or whether like scientific standards, they are absolute*
>
> (Angell, 1988:1081)



She argued then, as she did in 1997, that fundamental principles of humane research should not be compromised. She maintained that

> *Subjects in any part of the world should be protected by an irreducible set of ethical standards, including the requirements that they not be subjected to unreasonable risks and that they be asked for informed consent to participate.*
>
> (Angell, 1988: 1083)

Local investigators, however, thought otherwise. Commentary from the Uganda Cancer Institute was as follows:

> *These are Ugandan studies conducted by Ugandan investigators on Ugandans.*

The studies in Uganda had been approved by local ethics committees.

Dr Nicolas Meda, an epidemiologist from Burkina Faso argued that health research in poor countries should be designed and conducted pragmatically, in keeping with local health needs and priorities. In 2002, he addressed a conference of European medical ethicists and made the following statement:

> *Dogmatic interpretation of universal ethical principles in medical research will paralyse research efforts to improve HIV/AIDS prevention and treatment in sub-Saharan Africa.*
>
> (Richards, 2002:325)

Marcia Angell argued that:

> *ethical imperialism obscured a more insidious danger to developing countries: ethical relativism, which opened the door to exploitation of he vulnerable peoples of the Third World.*

Critics of the trials dismissed the charge of ethical imperialism and drew attention to the conflict of interest many investigators were in due to the substantial amount of research money at stake. Marcia Angell argued that researchers who levied charges of ethical imperialism against her were not necessarily advocates of the poor in their countries.

Professor Hoosen Coovadia, one of the investigators involved in the Petra trials in South Africa, responded to her charge as follows:

> *In these debates it was implied that we are merely passive recipients of research plans devised in Europe or the USA. This is not so, and in many instances we actively seek assistance to pursue research ideas of importance to our people. Indeed, in South Africa the barren years of apartheid isolation have instilled in us a keen appreciation of international co-operation – the HIV projects are as much ours as they are the property of our international partners. We have demanding*

> *Ethics Committees in our Universities (the first was established at the University of Witwatersrand in 1966) and regularly updated guidelines on Ethics for Medical Research published by the Medical Research Council. Our research is therefore conducted in an environment where the protection of the individual and communities is safeguarded The assertions by Angell, Lurie and Wolfe accordingly challenge our sovereignty in making and implementing our own decisions.*
>
> (Coovadia, 1999: 194-195)

The debate on ethical relativism versus ethical universalism was highlighted by the attempt to apply international declarations in various developing world settings in the context of HIV vertical transmission trials.

Justice

Grodin and Annas based their objections to the trials on the principle of justice. They argued that poor participants should not bear the burdens of research that they were not going to benefit from. It was clear at the time the trials were conducted that the Ministry of Health in South Africa was not going to sanction the provision of short course antiretroviral treatment to pregnant women even if the trials did prove the treatment to be efficacious. His argument was underscored in Minister Zuma's decision in 1998 not to provide the four week course of treatment to pregnant women (Knox, 1998). In retrospect, that was probably a good decision. After all, the four-week treatment regimen did not prove to be efficacious. However, the basic tenet of the argument remains valid – a protocol should contain a plan to implement results.

4.3 Vertical Transmission Trials in South Africa – The Results

Many of the arguments posed by both critics and advocates of the placebo-controlled vertical transmission trials were validated or rejected by the results of the trials in developing countries.

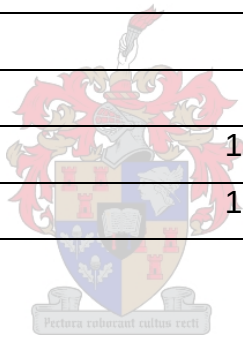
I will focus my discussion on the results of the Petra trials that were conducted in South Africa, Uganda and Tanzania between June 1996 and January 2000.

1457 HIV positive pregnant women were randomised to one of four groups: A, B, C or placebo. Groups A, B and C had different short course antiretroviral drug regimens.

To facilitate ease of understanding of results, the HIV transmission rates in the various groups are presented in Table 1 at month six and month 18:

Table 1: HIV Transmission at week 6 and month 18

TRIALS	HIV transmission Week 6	HIV transmission Month 18
PETRA A	5,7%	15%
PETRA B	8,9%	18%
PETRA C	14,2%	20%
PLACEBO	15,3%	22%



The results indicate that although regimens A and B were effective in reducing HIV transmission compared to placebo, this effect could not be sustained to 18 months. This can be attributed to the predominance of breast-feeding in these populations compared to the 076 regimen study population.

The investigators in this study have justified the use of placebo on the basis of a difference in study populations. They also indicate that if a placebo group had not been used or if the 076 regimen was used instead of placebo, two errors in interpretation would have occurred. The Petra C regimen would have been considered to be effective and the degree of effectiveness of all three groups would have been overestimated (PetraStudyTeam, 2002: 1178-86).

Similar results were established in the HIVNET 012 study in Uganda where breast-feeding impacted on HIV transmission rates at 20 months but to a lesser extent (Guay, 1999: 795-802).

Discussion

How do these results correlate with the criticism leveled against these trials in 1997?

The charge of lack of clinical equipoise cannot be substantiated. If there were no clinical equipoise, the short course treatment would have been more effective than placebo – this was only the case for six months after the study was initiated. Follow-up to 18 months however, revealed no statistically significant difference between treatment and placebo groups.

The reasons forwarded regarding the differences between the North American study population and the African study populations and uncertainty regarding how they would impact on the results were borne out in this study: breast feeding alone made an enormous difference to efficacy of short course regimens.

The criticism regarding the use of placebo was also unjustified: there are two good scientific and statistical reasons why an equivalence trial would not have been feasible as discussed above. It is most likely that an equivalence trial would have shown that 076 was better than short course treatment. How would that have helped the HIV epidemic in South Africa? (Coovadia, 1999: 194).

The principle of justice was not at issue – the department of health did not implement the short course treatment in 1998 – this has proved to be a good decision. The efficacy of the short course regimen compared to placebo was not large enough to make it affordable to the South African government. When Nevirapine was shown to be effective in the HIVNET 012 trials in

Uganda at a fraction of the cost of other short course regimens, treatment for pregnant women was made available in South Africa (Guay, 1999: 795-802).

The charge leveled against critics of the placebo trials was that they were ill informed regarding health care and research priorities in developing countries and this appeared to be the case as was reflected in the outcome of these studies.

Finally, it appears as if the charges of ethical imperialism leveled at Angell, Lurie and Wolfe by developing world researchers were justified and the results of the study serve to prove that.

4.4 Tuskegee Revisited

In the course of the debates surrounding the HIV vertical transmission trials, the justification presented for use of a placebo arm was the fact that the women on the placebo arm would have received no treatment (which was the standard of care in developing countries) in the absence of the clinical trial. Marcia Angell, in her critique of the use of a placebo arm in the trials, drew the following comparison to the Tuskegee Syphilis Study:

> *The justifications are reminiscent of those for the Tuskegee study: Women in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what would happen to the subjects' infants if there were no study.*

This comparison has been challenged by the investigators involved as well as by Fairchild and Bayer. Fairchild outlines the three features in the Tuskegee study that characterize the consistent research abuses that occurred.

> *First, the study involved deceptions regarding the very existence and nature of the inquiry into which individuals were lured. As such it deprived those seeking care of the right to choose whether or not to serve as research subjects. Second, it entailed an exploitation of social*

> *vulnerability to recruit and retain research subjects. Third, Tuskegee researchers made a wilful effort to deprive subjects of access to appropriate and available medical care as a way of furthering the study's goals.*
>
> (Fairchild, 1999: 919)

She objects to the analogy drawn in the context of the vertical transmission trials as "investigators clearly made efforts to inform the enrolled women that they would be part of a study to reduce maternal transmission" and that some would receive placebo.

The nature of consent obtained from study participants had however been challenged by researchers working in Thailand and South Africa.

In 1998, attention was drawn to the informed consent documents used in Thailand. Discrepancies were noted in the Thai and English versions of the documents. The Thai version described the placebo as a "comparison drug that does not contain zidovudine" while the English version described the placebo as an "inactive substance" which was "like a sugar pill". The Thai critics charged that the words "inactive substance", "placebo" and "sugar pill" did not appear in the Thai documents even though Thai words or concepts did exist for these words (Achrekar, 1998: 1331-32).

In South Africa, contention was also raised by the use of the word "chuff-chuff" drug which means "pretend drug" and "spaza" drug which alludes to "half the real thing" in colloquial terms. While "chuff-chuff" drug is acceptable, "spaza" drug is misleading (Prabhakaran, 1997).

Even though these controversies did exist regarding the content of informed consent documents used in the HIV trials, an informed consent process was followed in all the trials conducted in developing countries, some better than others. In no way did the HIV trials bear any resemblance to the Tuskegee study where there was an absence of the informed consent process altogether.

Fairchild goes on to contend that the social vulnerability of the women involved was not exploited. On this claim I will argue that these were vulnerable women. The United Nations UNAIDS definition of vulnerable communities includes communities with:

- Limited economic development
- Inadequate human rights protection and discrimination based on health status
- Inadequate understanding of scientific research
- Limited health care and treatment options
- Limited ability to provide individual informed consent

The black women enrolled in the trials in South Africa definitely shared a social and economic vulnerability with the African-American men in the Tuskegee study. To the extent that this study would not have been approved in the United States on American women, an exploitation of their vulnerability cannot be denied.

However, the placebo group served only as a comparison arm for the short course, potentially more affordable regimen being tested. Tuskegee was an observational study where all participants were deprived of affordable treatment. In the HIV trials women in the placebo group were deprived of treatment that was locally both unavailable and unaffordable. In this respect, an analogy with Tuskegee cannot be drawn.

Furthermore, Benatar argues that the analogy:

> *minimises the deception, maleficence, paternalism, lack of accountability, racism and gross exploitation demonstrated by the researchers in the Tuskegee study. The analogy serves to trivialize Tuskegee.*
>
> (Benatar, 1998: 221-222)

4.5 Declaration of Helsinki 2000 and CIOMS Revision 2002

Declaration of Helsinki 2000

As a result of the international concern evoked by the placebo debate, an attempt was made to amend the 1996 version of the Declaration of Helsinki.

A proposal was made to change the specification on treatment for control groups in the 1996 version from:

> *In any medical study, every patient – including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.*

to

> "*In any biomedical research protocol, every patient-subject, including those of a control group, if any, should be assured that he or she will not be denied access to the best proven diagnostic, prophylactic or therapeutic method that would otherwise be available to him or her….When the outcomes are neither death nor disability, placebo or other no-treatment controls may be justified on the basis of their efficiency.*

This revision was open for comment and a second debate ensued (Hutton, 2000: 185-206).

Those who objected to the change feared that the changes would weaken the principles of the declaration:

> *these revisions may inappropriately cause a shift to an efficiency-based standard for research involving human subjects and weaken the principles of the investigator's moral commitment to the research*

subject and the just allocation of the benefits and burdens of research, which have heretofore been the hallmarks of ethical research. The revisions will also logically lead to an explosion of research in developing countries that would be intended mainly to benefit developed countries – another affront to current notions of ethical research.

(Brennan, 1999: 527)

The change to "best available" could not be implemented in the face of the strong criticism leveled against the World Medical Association. Ultimately, the change to "best current" treatment for the control group was implemented in the 2000 version.

CIOMS 2002

While the 1993 version did not include a guideline on standard of care, the 2002 version added this consideration on in Guideline 11.

As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic or preventive intervention should receive an established effective intervention. In some circumstances, it may be ethically acceptable to use an alternative comparator, such as placebo or no treatment.

There is no elaboration on "established effective" intervention – is this established globally or locally in the developing country? This will be discussed further in Chapter Seven.

4.6 Commentary

While these major revisions were undertaken by the World Medical Association and the World Health Organisation in response to the placebo

debate, commentators started to question the basis for making such sweeping changes. It was charged that “tough cases make bad law”, so was it valid to generalize from the placebo trials? After all the HIV vertical transmission case study had unique features – these were trials on pregnant women where placebo use meant passively allowing transmission to infants. In many cases the risk calculations in using placebo were doubled by this situation alone. Using this case study as a precedent to make revisions in guidelines that affect all research would not be valid (Brennan, 1999: 530).

The validity of this comment has been borne out in the numerous footnotes that have been added to the Declaration of Helsinki since 2000 to avoid generalisation and ultimately to encourage case-by-case decisions on the use of placebo – this will be considered in more detail in Chapter Seven.

The revisions of both these international documents providing guidance in human participant protection evoked unprecedented attention in research ethics circles, amongst REC members and investigators alike. This occurred in developed and developing countries alike. Yet, in spite of the elaboration of the guidelines, human participant protection appeared to worsen in the United States.

Chapter 5

Continuing controversies in Developed Countries despite regulatory changes

5.1. Introduction

Since 1997 the vigorous debate around the HIV vertical transmission trials focussed unprecedented attention on the ethics of research in developing and developed countries alike. By 2000, the Declaration of Helsinki had undergone another revision and the CIOMS 1993 guideline was in the process of being revised as well.

Overshadowed by the HIV trial debate, the first major research catastrophe occurred in the United States in 1996. At the time, although the Nicole Wan case received considerable attention in the United States, this was not publicized as a major research ethics disaster internationally. Not until 2001 when Ellen Roche died and the international literature started to highlight the deaths of healthy volunteers in non-therapeutic research.

5.2 The Nicole Wan Case (Day, 1998: 449-51)

Nicole Wan was a healthy 19 year old student at the University of Rochester. She was involved in a trial early in 1996 investigating the function of lung cells. She underwent a bronchoscopy at the University of Rochester Medical Centre in New York. The local anaesthetic that facilitated this procedure was topical lignocaine. She required a considerably high dose of lignocaine to decrease the discomfort caused by the passage of the bronchoscope. After the procedure, she complained of chest discomfort but was nevertheless discharged one hour after the procedure. Later that day, she had an epileptic fit. On admission to the emergency unit, she was found to be in cardiac arrest

and died two days later. The proximate cause of death was a toxic lignocaine blood level.

This study had been on going for a number of years. The study protocol of 1981 had indicated a maximum dose of 300mg of Lignocaine.

The most recent study protocol did not specify an upper dose limit. There was no record of the dose of lignocaine administered. However, extrapolation of the dose was conducted from her blood lignocaine levels on admission and was estimated at 1200mg.

Investigation Findings

- This amendment had not been submitted to the REC as the researchers allegedly believed that deleting the upper limit did not have safety implications.
- The University's REC did not require formal approval of minor alterations that did not have safety implications.
- The REC had not performed an "in-depth" or "complete" re-review of the protocol over the protocol's 14 year lifespan.
- The consent form did not mention the possibility of death.
- A number of protocol violations were detected: The lignocaine solution used was a higher concentration than that specified in the protocol and 28 bronchial brushings were performed when the protocol specified "about ten".

Recommendations from New York State Department of Health (Day, 1998: 449-51).

1. RECs should pay attention to long running research programs with multiple protocols and amendments.
2. There should be more attention focussed on minimising risk to participants.

3. All amendments must be submitted to the REC.
4. Investigators should indicate how amendments will impact on risk.

5.3 The Jesse Gelsinger Case (Sibbald, 2001: 1612-14)

Jesse Gelsinger suffered from a partial deficiency of Ornithine Transcarbamylase (OTC) – a key enzyme in the urea cycle. This is a liver disorder in which the body cannot eliminate urea through the ammonia cycle. It affects one in 40 000 newborn children, most of whom become comatose within 72 hours of birth. They sustain severe brain damage and half die within a month of birth. The other half die by the age of five years. Gelsinger survived due to the partial deficiency coupled with a low protein diet and medication. On 13 September 1999 Gelsinger received an infusion of the OTC gene carried by an adenovirus vector – into his hepatic artery. The adenovirus usually causes mild colds. However, within hours of the injection of the virus vector Jesse experienced a severe immune system reaction to the vector and he died of multi-organ failure four days later.

When Jesse died, the FDA suspended the trial for the following reasons:

1. failure to train staff adequately
2. failure to develop basic operating procedures
3. inadequate informed consent.

As part of the informed consent process, Jesse was not informed that other patients had experienced serious adverse events or that three monkeys had died of a clotting disorder and severe liver inflammation after being injected (Sibbald, 2001: 1612-14).

Another major problem with this study was the failure to report adverse events to the Recombinant DNA Advisory Committee (RAC), the federal group that initially recommended approval of the study. During the hearing, investigators admitted that they had not followed adverse event reporting procedures. There was a failure to notify the FDA of serious but transient adverse events

in previous patients. Investigators also did not inform the RAC of changes to the study protocol – the change involved injecting the gene directly to the liver rather than intravenously. This was done in an attempt to prevent widespread vector distribution in the body. However, post-mortem findings indicated that the hepatic infusion had led to "significant vector [distribution] outside the liver" including high amounts in the spleen and bone marrow (Jenks, 2000: 98).

The reluctance of researchers to report adverse events and share other trial related information could be as a result of fear of loss of future patent rights in the event that a clinical trial produces a marketable product. In gene therapy trials in the United States, an adverse event can be considered to be proprietary information (Sibbald, 2001: 1612-14).

What was interesting about this case was the principal investigator – James Wilson. He is a world renowned expert in his field but also president and major shareholder of a private company – Genova inc. The company held patents for the procedure and provided funding for the research. The University of Pennsylvania and some of its board members owned stock in Genova. Of particular interest was the fact that Genova had granted research funds to Arthur Caplan, an international expert in the ethics of research in children – who had supported the project (Hoey, 2003: 10).

The outcome:

1. death of Jesse Gelsinger
2. his family filed a lawsuit against the university which they settled
3. Wilson resigned his post at the University
4. University of Pennsylvania issued strict guidelines that prohibit faculty or members of their family from having any material financial interest in a private company whose product they are evaluating. Harvard University followed suit as did a number of other institutions.

5.4 The Ellen Roche Case (Steinbrook, 2002: 716-20)

Ellen Roche was a 24-year old technician who worked at the Asthma and Allergy centre at Johns Hopkins University. She was recruited into a non-therapeutic research study as a healthy volunteer.

The study related to Asthma and the neural mechanisms in the lung that keep the airways open in normal people. The drug being used was a ganglionic blocker called Hexamethonium – a drug that would block the nerves and cause bronchoconstriction. The study was designed to provoke a mild asthma attack in order to elucidate the reflex that protects healthy people from developing attacks of asthma (Savulescu, 2002b: 3-4). In the 1950s and 60s, Hexamethonium was used to treat Hypertension but was withdrawn for human use by the Food and Drug Administration (FDA) in the 1970s.

The study started in April 2001. On 4 May 2001 Ellen was given the investigational drug, Hexamethonium, by inhalation. On 5 May, she developed a dry cough – became progressively worse and was hospitalized on 9 May with fever, hypoxemia and chest x-ray abnormalities. She got progressively more breathless and was transferred to the intensive care unit on 12 May. On 2 June 2001, Ellen Roche died as a result of progressive hypotension and multi-organ failure. On 19 July 2001 all research was halted at Johns Hopkins and an investigation was instituted.

RESULTS OF THE INVESTIGATION

(a) The study had a solid scientific basis and was well designed.

(b) The drug was scientifically sound

(c) The IRB/ REC was criticised:

It did not ask for more safety information on a drug that was not approved by the FDA and that was no longer in clinical use. Furthermore, the drug was being given via a non-standard route (inhalation)

(d) The investigator was criticized for not reporting the symptoms in the first subject promptly, not delaying the exposure of the next subject to Hexamethonium until the symptoms in the first subject had resolved, and not searching “more comprehensively” for previous reports where Hexamethonium had pulmonary toxicity.

(e) The Informed Consent document was insufficient. It did not list all the side effects of the drug, the risks of the drug were not clearly stated and the lack of the FDA’s approval was not mentioned. The word “medication” was used, not experimental drug.

Johns Hopkins University took full responsibility for the death of Ellen Roche and on 11 October 2001 announced a financial settlement with the Roche family.

5.5 Commentary

In non-therapeutic research involving healthy volunteers, the emphasis tends to shift from informed consent to prevention of harm. This is based on the assumption that participants in these trials are usually better educated than patient volunteers in phase three trials – often students or institutional employees volunteer. This in itself may serve as a point of contention regarding the voluntariness of participation. As an employee at Johns Hopkins, the potential for coercion or consent under duress exists. Ellen Roche’s name was obtained from a database of volunteers who had participated in previous studies. If, however, there was no coercion involved and her participation was based on altruism or was motivated by monetary reward, it is generally assumed that these volunteers are in a better position to understand the nature of the research and to make an informed decision regarding participation. The imperative then becomes protecting them from harm given the fact that very little benefit accrues to individual volunteers while science is seen as a major beneficiary.

In these cases, however, both informed consent and minimisation of harm were flawed. This meant the participants were not able to protect themselves

from making a risk-benefit analysis based on the information provided in the informed consent documentation and the investigator and REC had not taken adequate measures to minimize harm.

One of the 13 principles of good clinical practice specifies that adequate information regarding the investigational product is gathered by the investigator.

In the Ellen Roche case, there were two barriers to establishing all relevant investigational product information. In the first place, a study conducted using hexamethonium by inhalation in 1978 at the University of California, did not report the pulmonary toxicity as an adverse event as they regarded this to be unrelated to Hexamethonium. In fact, the investigator on the Ellen Roche case used that study as evidence that the drug was safe (Savulescu, 2002b: 3-4). This is indicative of the far-reaching consequences of publication bias, when researchers fail to publish all relevant results of research (Savulescu, 2002a: 1-2).

The second barrier to establishing accurate investigational product information resided with the investigator himself and his failing to conduct an adequate literature review. He relied on an internet search for investigational product information. There were journal articles dating back to the 1950s warning of lung damage as a result of inhaling hexamethonium According to the OHRP this information was “readily available via routine MEDLINE and Internet database searches, as well as recent textbooks on pathology of the lung” (Savulescu, 2002a: 1-2). A number of reports between 1953 and 1962 as well as a review article from 1972 were later found during the investigation. These articles had not been reviewed by the investigator. In reports published after 1980, five referred to pulmonary complications of Hexamethonium in the title (Savulescu, 2002a: 1-2).

While the ethics committee was criticised for not conducting a literature review themselves, I would like to argue that this is not a routine mandate of the REC. In routine practice, the investigator and the institutional department take

responsibility for reviewing the science of the study prior to submission to the REC. While most RECs review both the science and the ethics, there are usually inadequate trained personnel on an REC to repeat a literature review on every project submitted. This is a core responsibility of the investigator and perhaps this case has served to highlight the importance of this function. It is also perhaps a reason to reconsider the dual roles played by RECs in terms of reviewing both the science and the ethics of the protocol. This will be discussed further in Chapter Six.

The Ellen Roche and Nicole Wan case studies indicate that the traditional ways of protecting research participants – informed consent, voluntariness, risk-benefit analysis - have not been successful. While the above participants were able to provide informed and voluntary consent based on the information contained in the relevant documents, "aspects of each protocol", its "implementation and oversights were flawed" (Levine, 2004: 220).

As a result of these flaws two healthy young volunteers lost their lives. Given the melioristic role that Jonas has ascribed to the research endeavour, especially non-therapeutic research, such an outcome cannot be justified. However, these unfortunate events had a pivotal role to play in placing ethical review in the United States under intense scrutiny.

Donna Shalala, secretary of the Department of Health and Human Services, argued that "even one lapse is too many". According to her "the American people expect that clinical researchers will never compromise or neglect the safety of human subjects". The ultimate responsibility would rest with the institution (Shalala, 2000: 808).

What is evident in all three case studies is that investigational findings revealed that investigators had failed to conduct the studies in keeping with the principles of good clinical practice. On the whole the IRB reviews in the first two cases had minor flaws. It is only in the Ellen Roche case that the REC did not insist on FDA approval and that was their major failing.

Chapter 6

Research Ethics Committees in South Africa
A Status Report

6.1 Introduction

Between 1996 and 2001, the deaths of Nicole Wan, Jesse Gelsinger and Ellen Roche evoked considerable public concern. It was evident that there were widespread deficiencies in the review system. This resulted in a review of the structure and functions of RECs and IRBS in developed countries (Institute of Medicine, 2003). The adequacy of RECs in protecting research participants was called into question. Similarly, the question was being debated in developing countries, including South Africa, except with a graver degree of concern given the fact that RECs in developing countries have been historically under-resourced and over burdened.

The words of Dr Sidney Wolfe of the Public Citizen Heath Research Group echoed in both developed and developing world research ethics communities (Savulescu, 2002b):

> *if protections are flawed at esteemed places such as Hopkins, they are likely flawed elsewhere*..

It is with this concern in mind, that the empirical component of this dissertation was undertaken.

All research – both clinical trial and academic research - that is conducted in South Africa must be reviewed and approved by a local REC before the project commences. All drug related research must, in addition, be reviewed and approved by the regulatory agency – the Medicines Control Council (MCC). Research ethics approval is contingent on MCC approval where drug related research is concerned. The research ethics review system in South Africa consists of approximately 22 local RECs and an Interim National Health Research Ethics Committee (INHREC). Since 1994, when South Africa underwent a transformation from an "Apartheid" state to a democracy, an enormous amount of reform commenced in health regulation. The Health Act has been revised and the National Health Bill is in the process of becoming the new National Health Act. The INHREC has been established under the National Health Bill and reports directly to the Minister of Health. This national body has the overall responsibility to promote, ensure and monitor compliance by approved ethics committees in South Africa. At the time of this study, the INHREC was an interim body and had not as yet executed any of its mandates on local RECs.

In 1998, the Director-General of the Department of Health convened a working group to compile a national guideline for the conduct of clinical trials in South Africa. In 2000, Guidelines for Good Practice in the conduct of clinical trials in human participants in South Africa was published – referred to as SAGCP. The purpose of the guideline was to provide South African researchers, RECs, research sponsors and the general public with clearly articulated standards of good clinical practice in research that are contextualised to the local setting.

According to this national guideline,

> *the main responsibility of ethics committees is to ensure the protection and respect of the rights, safety and wellbeing of participants involved in a trial and to provide public assurance of that protection by reviewing, approving and providing comment on clinical trial protocols, the suitability of investigator(s), facilities, methods and procedures used*

to obtain informed consent. In the execution of these responsibilities committees should be guided by relevant South African ethical guidelines, professional standards and codes of practice. The performance of ethics committees should be systematically audited in a structured way.

(Guidelines for Good Clinical Practice in the conduct of Trials in Human Participants in South Africa, 1999)

6.2 Methodology

The empirical component of the research employed a combination of quantitative and qualitative methods to address different components of the research question. All the quantitative data is presented in Chapter Six. Where relevant, portions of the qualitative data are also presented here. However, the bulk of the qualitative data is presented in Chapter Seven.

For both the quantitative and qualitative research, permission to administer the questionnaires and to conduct the interviews was sought telephonically from the Chairperson of each REC. All 12 REC chairpersons agreed to participate and appointments were secured at the various institutions in South Africa. Approval for the study was granted by the Research Committee, Faculty of Arts, University of Stellenbosch in 2002.

The quantitative component assumed the format of a descriptive survey of RECs in South Africa that was based on a structured questionnaire. This method ensured that each REC was exposed to the same questions so that their responses could be reliably compared (Bernard, 2002: 240). Development of the research tools (questionnaire and interview guide) was based on the following pre-existing information:

Firstly, the basic functions that are intrinsic to any research ethics review system were considered:

1. comprehensive review of protocols (including scientific, financial conflict of interest and ethical reviews)
2. ethically sound participant-investigator interactions
3. ongoing (and risk appropriate) safety monitoring, and
4. quality improvement and compliance activities.

(Institute of Medicine, 2003: 49)

Secondly, known deficiencies in the system including:

1. REC membership
2. education and training of REC members and investigators
3. lack of institutional commitment
4. inadequate initial and continuing review of protocols
5. informed consent
6. review of research on vulnerable populations

The questionnaire sought to gather information on membership, workload, efficiency, review procedures, infrastructure and resources. (see addendum for detailed questionnaire). It was administered to the administrative officer of each of 12 RECs in South Africa during 2003. This was completed with the assistance of the interviewer. This method of face-to-face completion of structured questionnaires enabled the form to be completed comprehensively (Bernard, 2002: 242-43). It also ensured a better response rate compared to self-administered questionnaires that are usually used in a postal survey. When the administrative officer was unable to respond to any of the questions these answers were obtained from the chairperson of the REC during the in-depth interview hence the use of exemplars from the interviews in the section on composition of RECs. This represents a combination of quantitative and qualitative methodology and can be viewed as a form of triangulation in combination with the use of documentation. Data was cross-checked from documentation containing standard operating procedures and membership lists.

This part of the research sought to answer the following question: How are RECs composed in terms of membership and briefly, how do they function?

6.3 Data Analysis

Data from the questionnaires was captured using Microsoft Excel spreadsheets and was analysed by an epidemiologist using the Statistical Analysis Systems (SAS) package. The descriptive information is tabulated – see tables 1, 2 and 3 in the addendum.

6.4 Sample

The RECs in South Africa were identified via the chair of the Interim National Health Research Ethics Committee (INHREC) who provided a list of 22 RECs. Of these three were private and 19 institutional. Nine of the 19 were attached to tertiary educational institutions: University of Cape Town (UCT), University of Stellenbosch (US), University of Pretoria (UP), Medical University of South Africa (MEDUNSA), University of Witwatersrand (Wits), University of Transkei (UNITRA), University of Kwa-Zulu Natal (UKZN), University of Orange Free State. The ninth REC is attached to the Medical Research Council (MRC) of South Africa.

The remaining 10 were smaller RECs attached to technicons – reviewing mainly academic research and not clinical trials. Many of these institutions were in a state of fluidity with plans for mergers with each other or other tertiary institutions. This is in keeping with policies for higher education in the Ministry of Education as part of a rationalisation process in tertiary educational institutions in South Africa. Hence they were excluded from the sample. Where RECs were attached to universities, only those in the Health Sciences Faculties were included in the sample as this is where the clinical trials are reviewed. RECs dealing with academic research in other faculties were excluded.

Hence nine institutional and three private RECs were included in the quantitative survey.

The data that follows has emerged from the quantitative survey. However, issues that emerged from the interviews that related to REC composition or function have been included in this chapter. In particular, dual review of the science and ethics of protocols and the role of the National Interim Health Research Ethics Council in relation to local RECs, will be discussed here.

6.5 Results of Ethics Committee Survey

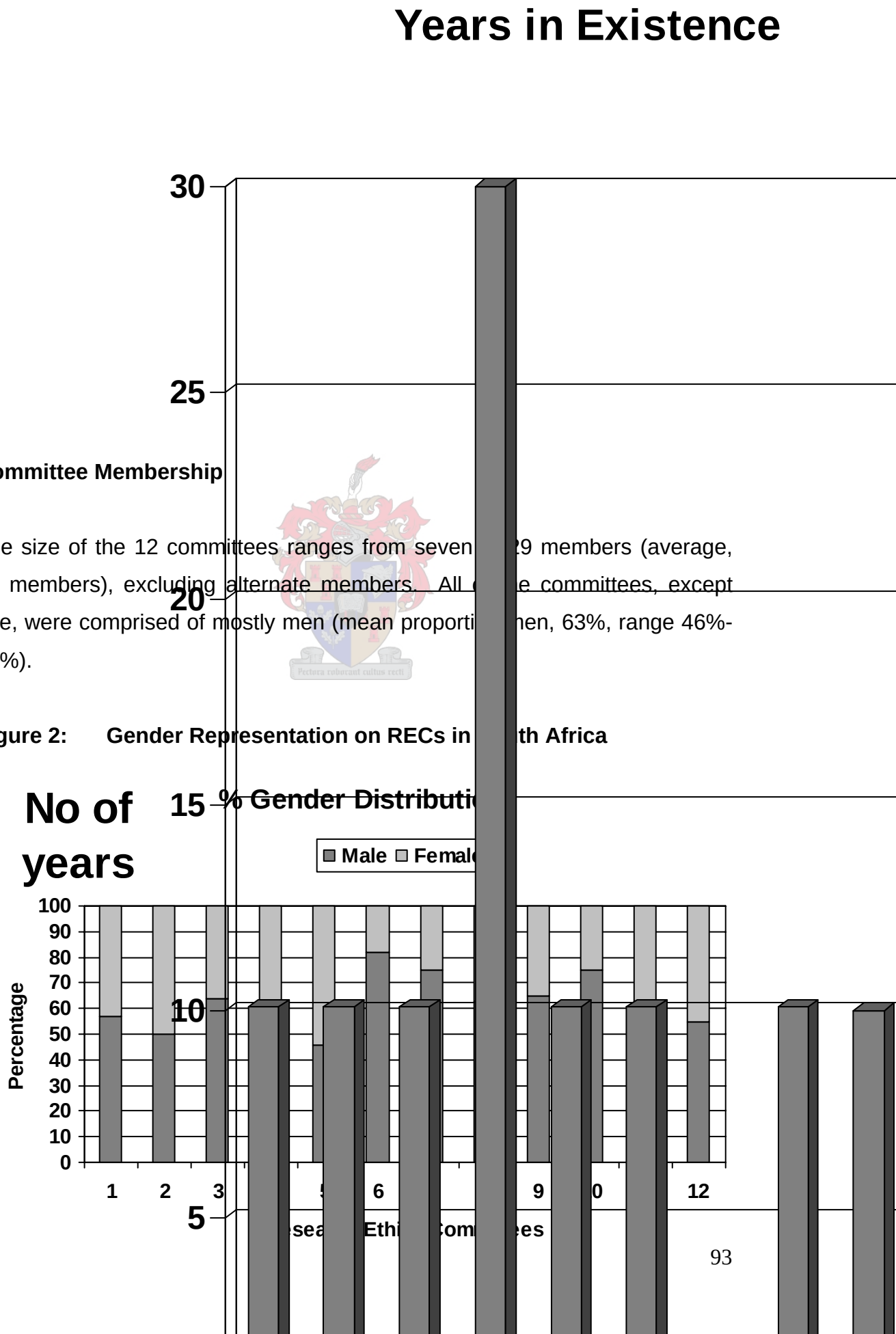
6.5.1 Composition

12 Ethics committees participated in the quantitative survey: nine institutional committees associated with University Faculties of Health Sciences, which review academic research (both clinical and epidemiological studies) and industry-sponsored trials, as well as three private committees (Pharmaethics, South African Medical Association (SAMA) and Anglogold) which review primarily industry-sponsored studies or money-related research as in the case of Anglogold. At the time of the quantitative survey, the Anglogold REC was operational. However, by the time of the interview, the REC had been dissolved and the Chairperson had resigned.

The data that follows reflects the structure and functioning of all 12 health sciences research ethics committees in the country.

Of the 12 committees, ten have been in operation for at least ten years, with the oldest established more than 30 years ago. The remaining two committees are less than a year old, both linked to historically disadvantaged academic institutions.

Figure 1: Duration of REC Existence in South Africa



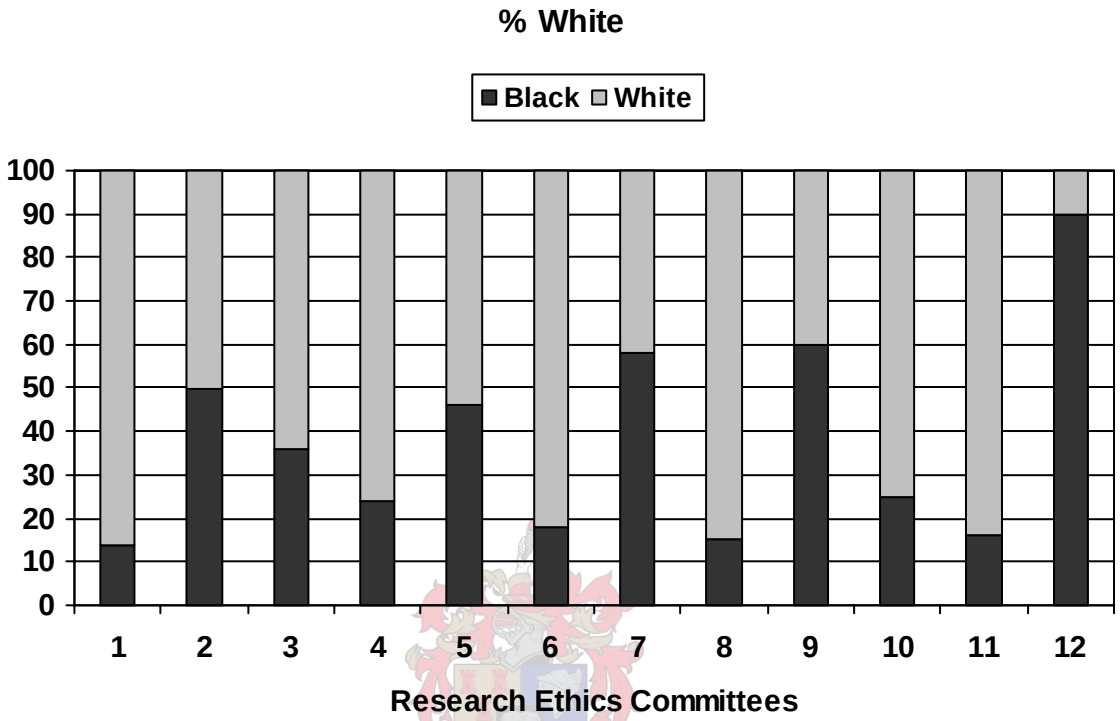
Committee Membership

The size of the 12 committees ranges from seven [illegible]29 members (average, 16 members), excluding alternate members. All [illegible]e committees, except one, were comprised of mostly men (mean proporti[illegible]nen, 63%, range 46%-82%).

Figure 2: Gender Representation on RECs in [illegible]th Africa

All but three committees were comprised of mostly white members (mean proportion white, 62%, range 10%-86%).

Figure 3: Racial Representation on RECs in South Africa



Most of the committees were comprised primarily of scientists, primarily clinicians, (56% of all committee members). At institutions, the RECs are larger, hence a variety of scientific disciplines are represented on the committee. The private RECs are much smaller than institutional RECs and have very limited scientific review capacity – one REC has only one scientific/clinical member.

Other backgrounds were more sparsely represented among committee members:

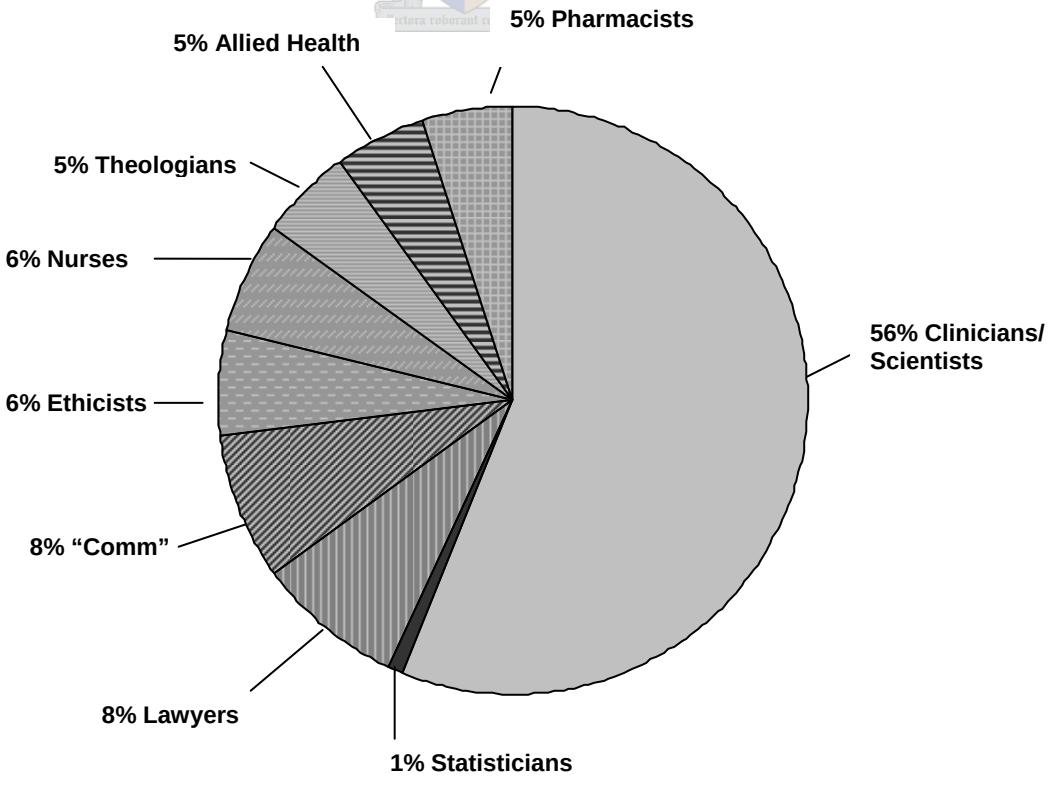
- Nurses (9 of 12 committees, 6% of all committee members)
- Lawyers (9 of 12 committees, 8% of all committee members)
- Ethicists (8 of 12 committees, 6% of all committee members)

- Theologians (all from Christian denominations; 9 of 12 committees, 5% of all committee members)
- Community representatives (10 of 12 committees, 8% of all committee members)
- Other allied health professionals (on 5 of 12 committees, 5% of all committee members)
- Pharmacists (on 5 of 12 committees, 5% of all committee members)

In addition, only a handful of committees included statisticians or epidemiologists (three individuals on three separate committees, representing one% of all committee members).

Of the ten committees reporting a community representative, the type of representatives included: priests, union members, educators (including a retired headmaster), local business people, students, a retired nurse, and an NGO member.

Figure 4: Professional Membership of RECs in South Africa



Of the 12 RECs, two committees reported that all their members were independent or not affiliated with the institution, while another two reported that none of their members were independent of the institution. The remaining eight committees reported that less than 50% of their members were independent or non-affiliated.

Five of the 12 committees reported that their term of membership was unlimited (indefinite); among the remaining seven committees, the duration of membership was between two and five years.

Only three of the 12 committees reported that they had procedures for the disqualification of members. This referred to the compulsory resignation of members who were involved in unethical research themselves or who performed inadequate review of protocols related to a conflict of interest.

Commentary on Composition

Racial diversity

According to Moreno, RECs may vary greatly in a number of different respects but

> *it is a given that they must represent various perspectives, including that of the institution's 'community', and that they should not be dominated by physicians. This is a reflection of the fact that the ethics committee idea is legitimized as an expression of certain themes of democratic liberalism, including especially the notion that moral controversies are best resolved through a process that takes into account multiple perspectives on the nature of the good life.*
>
> (Moreno, 1998: 477)

Four years after democracy was established in South Africa, the Department of Health set up a committee to establish guidelines for good clinical practice.

In 2000 “Guidelines for Good Clinical Practice in the conduct of clinical trials in human participants in South Africa” was published, hereafter referred to as the SAGCP 2000 guidelines. This guideline is currently undergoing revision. According to the Director-General of Health, this document is compulsory and where it differs from international guidelines, the local guideline is applicable.

Specific recommendations are outlined in section 8.2 regarding the composition of a South African Research Ethics Committee (REC). The REC must :

- Be representative of the communities they serve and reflect the demographic profile of the population of South Africa;
- Have a minimum membership of at least seven members; (nine members – revised guideline)
- Have a chairperson;
- Include members of both gender and not more than 70% of its members must be men or women;
- At least one lay person with no affiliations with the institution, not currently involved in medical, scientific or legal work and who are preferably from the community; (two lay persons in the revised guideline)
- At least one member with knowledge of and current experience in areas of research that are regularly considered by the ethics committee;
- At least one member with knowledge of, and current experience in the professional care, counselling or treatment of people (e.g. medical practitioner, psychologist, social worker, nurse); and
- At least one member who is legally trained.

These guidelines are similar to the ICH (International Conference of Harmonisation) Harmonised Tripartite guideline for Good Clinical Practice – referred to hereafter as ICH GCP except for minimum membership of five in the international guideline.

Where the SAGCP guideline differs from an international guideline, the South African requirement is to be followed provided it does not dilute an international guideline.

The survey of ethics committee membership in SA indicates that all committees exceed current minimum membership requirements in terms of numbers. However, composition in terms of gender and race does not meet SAGCP requirements. Most RECs in SA are white male dominant. Reasons given for this included the following:

> *The representation [on the committee] at the moment reflects what is happening at the university.*
>
> *Race is difficult [to represent on the committee] as people of all races are not available at the university.*
>
> *There is a question mark about representation because it has nothing to do with the activities of the committee, it is just to be more in line, now, with what is happening in the country… the ultimate is that the committee sticks to the guidelines, the national guidelines.*
>
> *I can't think we ever looked at race as an issue.*
>
> *We have tried… to really get our gender and race mixture right, and I think we have done that.*

It is a major concern that RECs in South Africa continue to fail to reflect gender and racial diversity in their membership. It is even more concerning that some REC chairs do not appreciate the need for gender or racial diversity in a multicultural country like South Africa. In most instances the lack of diversity on RECs is attributed to the university faculty community – most of whom are white males. The paucity of Black faculty members at most medical faculties in South Africa is one of the many consequences of South Africa's history of racial discrimination and the impact it had on the training of

Black medical students (Perez, 2004: 764). Blacks, in particular those classified as African under the apartheid system, were restricted entry into medical schools by a permit system in operation from 1959 to 1986 (Baldwin-Ragaven, 1999).

In 1967, the ratio of white doctors trained per million of the white population in South Africa was almost 100 times higher than the equivalent ratio for Blacks. In 1985, 83% of all doctors and 94% of all specialists were white (Kale, 1995: 1307). Post 1994, admission of Black students to formerly predominantly white institutions increased but the median percentage of African students studying medicine in 1999 remained approximately half the equivalent proportion for whites across South Africa's 8 medical schools (Lehman, 1999: 187-99). These eight medical schools are reflected in the survey undertaken for this dissertation.

The implications for the university faculty compositions are grave indeed. Ten years into democracy, insufficient redress has occurred to eliminate apartheid influences from major academic centres. In view of the research populations being mainly vulnerable populations of colour, the composition of RECs as predominant white male bodies could be perceived as reinforcing the asymmetrical power relationship that already exists between predominantly white researchers and predominantly black participants. As the body that represents protection of the rights of research participants the REC has to be perceived by the public and the participants to reflect justice and fairness.

The Code of Federal Regulations (45CFR46) in the United States refers to this concept when it outlines IRB membership in 46.107 (Department of Health and Human Services, 2001):

> *The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.*

Unfortunately in South Africa, a white male dominated body will be perceived to lack a sense of fairness or justice given our political history and will not be able to "promote respect for its advice and counsel". Hence, the SAGCP guideline, like the 45 CFR 46 guideline, specifies diversity of membership in terms of race and gender.

There are also other implications where diversity is concerned in terms of the informed consent process. It is essential that diversity exists on RECs so that culturally defined issues relating to research are acknowledged and incorporated. This refers to issues of written consent, spousal consent, community consent, inter alia. Diversity lends value to the ability of a REC to assess translations and this will be discussed later. Diversity itself needs to be present not only in the form of community members, of whom there are few in any case on South African RECs, but also in terms of scientific, clinical and non-scientific membership. Where community representatives are concerned, these are usually people of colour. Studies of non-scientific members have shown that up to 88% of such members have reported negative experiences with scientific members – these have included having their opinions disrespected, not being understood or not being taken seriously (Sengupta, 2003: 215). One can only imagine that these issues will be intensified when community representatives are diluted in a sea of white male scientific members especially in the South African context. There is no doubt that requirements for both gender and racial diversity on RECs transcend a mere political correctness and are specified to enhance the functioning of an REC at a more profound level.

Finally, in the formal letter sent to the IRB at Johns Hopkins University after the investigation into the death of Ellen Roche, the OHRP commented as follows as they suspended all federally funded research at the institution (Office for Human Subject Protection (OHRP), 2001):

> *OHRP is concerned that the current membership of the IRBs appears to lack the diversity, including consideration of race and cultural backgrounds and sensitivity to such issues as community attitudes, to*

promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, as required under HHS regulations at 45 CFR 46.107(a).

While it is sometimes the case that members of all racial groups are not available at some tertiary institutions, inadequate efforts are being made to recruit and retain such faculty members. Ten years into democracy in South Africa the ideology of apartheid is reflected in the REC membership at previously white universities.

Gender Representation

The disparity in gender representation is also problematic. Except for one institution, all Chairpersons of RECs in South Africa are male. Amongst REC members, the representation of women ranges from 18% to 54%. This parallels the gender disparities that exist in academia with very few women occupying senior faculty positions. Three RECs have male representation in excess of the 70% specified by the SAGCP guideline.

Professional Diversity

While most committees reflect professional diversity in membership, there is however, a dominant presence on most committees of scientists/clinicians. Amongst the 12 South African RECs surveyed, doctors, scientists and pharmacists together made up 61% of the membership. This exceeds international scientific/clinical membership trends. A survey of 89 IRBs in the United States in 2001 found that physicians, scientists and pharmacists together made up 46% of IRB membership.

While scientific/clinical membership is high on most RECs less than half of all RECs have a pharmacologist as a scientific/clinical member, yet all RECs in South Africa have a mandate to review both the science and the ethics of protocols. This represents a serious hiatus as almost all RECs included in the survey are involved in the review of clinical trials of investigational drugs. As

was demonstrated in the Ellen Roche case, drug toxicity was a key factor that resulted in her death. On this basis, it can be argued that a pharmacologist should form part of the core membership of any REC reviewing drug trials. This is not specified in the SAGCP guideline. On the one hand, in South Africa, it can be argued that the regulatory agency, the MCC, takes responsibility for assessing safety of the investigational product. On the other hand, as the REC and MCC conduct simultaneous review of protocols and the MCC verdict is not available at the time of ethics review, final ethics approval is usually deferred pending MCC approval. However, if the REC is mandated to conduct both scientific and ethics review, the scientific membership of the REC must include a pharmacologist. In the case of Ellen Roche, the regulatory agency, the FDA, was not able to fulfil the role of "safety net" as the investigator did not submit an application to the FDA for approval of the use of an investigational new drug. An important factor that eluded the REC at Johns Hopkins was the use of the drug via a new route and for a new indication. Prior approval of hexamethonium by the FDA was for hypertension in an oral formulation and by 1972, that approval had been withdrawn as a result of lack of efficacy of the drug.

Statistical review is becoming more and more challenging for RECs yet statisticians/epidemiologists comprise only one% of all RECs in the country.

The trend towards conducting more equivalence trials as opposed to placebo controlled trials has resulted in significant trial design changes. The advent of superiority and non-inferiority trials has highlighted the importance of sample size and adequate powering of studies. This was illustrated in the SAINT study conducted in Durban, Kwa-Zulu Natal to assess efficacy of two different regimens of treatment in preventing mother-to-child transmission of HIV (Moodley D, 2003: 725-735). The study was designed as a superiority study. However, it failed to show superiority and hence has been criticised for that design error (Colvin: 2002). Garattini argues that a trial should be designed to show the superiority of a new treatment over the best treatment available for the same therapeutic indication. Equivalence and non-inferiority trials reflect "a switch from the search for better drugs to the acceptance of drugs that are

similar to or not worse than those already on the market". He charges that it is conceptually difficult to establish the limits that define a drug as equivalent or not inferior. Furthermore equivalence or non-inferiority designs reflect economic considerations – smaller sample sizes are required compared to superiority trials (Garattini, 2003: 1199-200).

Furthermore, the conduct of underpowered trials is generally considered unethical except in very specific clearly defined cases (Halpern, 2002: 358-62). This includes small trials for rare disease in which the investigators document their plans for merging their results with those of other trials in a meta-analysis and early phase drug trials provided they are adequately powered for defined purposes that do not include randomised treatment comparisons. In both cases, informing participants that the study is going to be of limited benefit is seen as an ethical requirement. Given the complexity of trial design in recent years it is of great concern how an REC may function without a statistician or epidemiologist.

Ethicists are well represented on South African RECs. This survey found that 67% of RECs had at least one ethicist. The 2001 United States survey found that only 23% of the 89 IRBs surveyed had an ethicist (De Vries, 2002: 206).

Committee composition of private RECs is concerning. One REC has only one scientific/clinical member. This may be seriously inadequate for the wide range of medical disciplines in the private sector (usually specialists) who are submitting protocols.

Representation of Independent or Non-affiliated Members on RECS

Excluding the private RECs that are 100% independent, institutional RECs have independent or non-affiliated membership ranging from zero% to 19%. Most members of institutional RECs are affiliated to the institution. This parallels trends internationally – a survey of 89 IRBs in the United States conducted in 2001 revealed that 85% of IRBs have a majority of affiliated members. This was most marked on institutional IRBs where over 80% of

members are affiliated (De Vries, 2002: 206). Where the majority of members are affiliated to the institution, the potential for biased and inadequate review exists (McNeill, 1998: 377).

Members with no affiliation to the institution are important to lend objectivity to the review process and protect the REC from facing a conflict of interest in reviewing research that will benefit the institution. The two institutional RECs with no independent members are particularly problematic in this regard.

Lay and Community Representation

Lay representation is present in 80% of RECs but these are not always people from the community.

One REC commented as follows:

> *there is no lay [community] representation" on our committee. [The committee] is made up of professionals.*

Another REC chair commented:

> *Yes, we have a minister of religion and a nursing sister*.

Those RECs that had community representation on their committees stated that these members were actively involved in reviewing all protocols with special emphasis on the patient information leaflet. They considered whether these documents would be understood by participants and how the community would regard the research. The following comments were made:

> *Their dedication is not as good as one would want but they do lend a certain perspective that you cannot find from anyone else*

They provide: *impressions of how studies may influence the public…That's very important. In that way they are very good and they do lend a certain balance*.

Lay representation is sometime a problem as after two years these individuals have learnt the terminology and are not that lay anymore. However they play a valuable role in assessing the patient information leaflets.

The main thing that we would like them to do is represent the community, the other thing is to really give us feedback on how they think the research that's being conducted in a specific community will impact on that community…The other thing is the relevance of that research in a specific community…what we also expect from them is to see whether the translations that we do is really written in a language that's being spoken in this specific community.

With a representative ethics committee, many professional members of the committee are also members of the community.

The SAGCP guideline makes the following recommendation regarding lay membership.

At least one lay person with no affiliations with the institution, not currently involved in medical, scientific or legal work and who are preferably from the community

(Guidelines for Good Clinical Practice in the conduct of Trials in Human Participants in South Africa, 1999)

The South African Medical Research Council Ethical Guidelines for Research make the following recommendation regarding "lay" representation:

Committees should accommodate respected lay opinion in a manner that provides effective representation of the non-clinical community as

well as clinical interests. Lay opinion in the non- clinical community means opinions from a lawyer, social worker, religious leader, teacher or similar persons of standing able to contend with pressures from individuals within the broad health profession.

The guidelines also recommend

representation of disadvantaged communities, where research is to be carried out in these communities.

(South African Medical Research Council, 2002)

It is evident that while the SAGCP guideline regards lay representation as non-academic and representative of the community, the MRC guideline sees lay representation as non-scientific and seems to have an additional category of person as being the community representative. The justification for having non-scientific but other professional categories of people as lay representation is for there to be strength in the voice of the lay representatives. This sentiment is echoed by Sengupta and Lo when they refer to recruitment of "assertive" lay members who will not be easily intimidated by scientific members (Sengupta, 2003: 217). The suggestion from the National Bioethics Advisory Commission (NBAC) to increase non-scientific representation to 25% of the committee would also add strength to the voice of lay members on the committee.

A distinction needs to be drawn between lay representation and community representation. Lay representation on a research ethics committee usually refers to anyone who has no scientific or medical background. It could therefore include lawyers, ethicists, priests or theologians. In South Africa, these "lay" members are not always members of the community being researched. They have a higher level of education than lay community members and while they play an important role in lending a multidisciplinary approach to the review process, they are not ideally suited to assess the patient information leaflets from the perspective of a community member. Often they also do not speak an ethnic language.

Community representatives, on the other hand, would refer to non-professional, non-scientific members who belong to the community that is being researched.

Generally they would be conversant in the same language as the research participants and they would share a similar culture.

In most RECs in South Africa there is blurring of theses two different categories of representatives. Often the lay person is taken to be the lawyer or priest with much higher levels of education than the average of the community being researched. Often the priest is someone of the Christian faith with lack of representation of other religious sects in the community. Sometimes, the priest is also regarded as the "ethicist". In my opinion provision should be made for both categories of representatives – non-scientific and community representatives on every committee.

The roles defined for the lay/community member are two-fold:

Firstly, it is felt that they lend a unique "community" perspective to the review process. As representatives of the community, they provide insight into the relevance of a particular research project to the community. They also provide input regarding the impact that they think the research will have on their community.

The second role that these members fulfil relates to review of the patient information leaflet. Most committees, in the absence of using an objective measure of readability of patient information leaflets, rely on lay/community members to review this document. Experience abroad has shown that lay/community members help create clearer consent forms (Gillett, 2001: 1-6).

On 10 May 1999, when the IRB at Duke University Medical Centre was suspended by the Office for Protection of Research Risks (OPRR), the violations specified included

- Lack of a quorum at board meetings
- Casual waivers of experimental rules
- Insufficient public representation on the committee.
- A Duke official who assisted with bringing research grants into the university was also an IRB member – a role potentially in conflict with declining unacceptable research (Greenberg, 1999: 1773).

The role of community or "public members" on a committee is hence given significant weight.

There is a correlation between those committees that have a lay member who speaks an ethnic language and the attention that the committee pays to review of translated documents. The committees who focus mainly on English documents tend not to have lay representation from ethnic groups.

In addition to these two roles, Sengupta and Lo suggest expanding the roles of non-scientific/lay members via education and training to assess benefits and risks of a study protocol from a patient's perspective (Sengupta, 2003: 217). Such a role is confirmed by Gillett who has found that lay members encourage researchers to do a better job of explaining the risks and benefits to potential participants (Gillett, 2001: 1-6).

Given the roles that the various chairpersons have assigned to lay/community members of the committee, it seems more likely that a lay community representative should be seen as a unique person making a contribution to the committee separate from the non-scientific members who have their own unique contribution to make. It is also important that the dynamics of the committee are given attention. It is important for lay members to be respected by scientific members, for their opinions to be respected and for their contribution to be elicited on every protocol.

While the lack of scientific knowledge has been regarded as a disadvantage, it seems unfair to judge lay members in that regard. It is mainly for the fact that

they do not have a scientific background that their role is defined and their function on the committees is not to review the science, but rather to concentrate on participant protection issues. This in turn leads one to revisit the functions of the "ethics committee" – should the review of the science be split off from the ethics review? This will be discussed in greater detail later in this chapter.

6.5.2 Remuneration of Committee members

Half of the 12 committees did not provide any of their members with remuneration for participation. Of the remaining six, three provided remuneration only to independent members and/or community members, typically in the form of subsistence or travel costs. Two provided a per-meeting payment of approximately R600, while one provided members with R200 per protocol reviewed.

Commentary on remuneration

Remuneration of REC members is a long-standing, controversial issue that has not been addressed at most institutions in South Africa.

On the one hand, it has been argued that payment of REC members will compromise the objectivity of their reviews and create conflicts of interest. On this basis, it has become traditional both internationally and at most local RECs not to remunerate REC members. On the other hand, REC members are often full time faculty members with numerous academic and clinical responsibilities. The regular working day does not allow for protocol review, a process that is demanding more and more time and skill as protocols become more complex. As such most REC members are conducting protocol reviews in their private time for which they are not compensated. At the same time, REC members are not compensated in the form of "time off" from their academic or clinical responsibilities. Furthermore, they receive little recognition for their efforts. Wood et al warn that

lack of compensation or recognition communicates to IRB members a devaluation of their commitment to ethical research.

(Wood, 2002: 6)

It is hence not surprising that

Many IRB chairs are having difficulty securing and retaining IRB members.

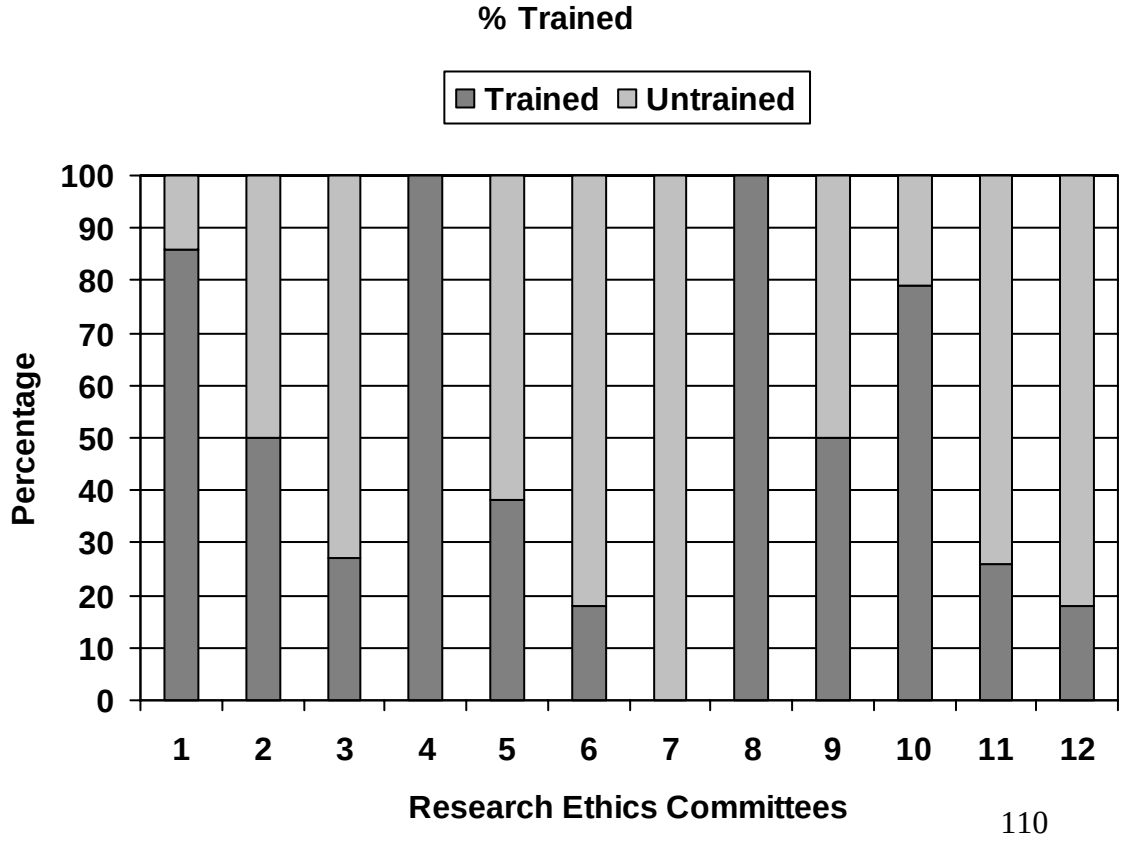
(Wood, 2002: 6)

The issue of REC member remuneration hence needs to be revisited and ways of remuneration should be devised that are not linked to outcome of protocol review or the number of protocols reviewed thus eliminating the traditional argument of conflict of interest.

6.5.3 Training and Development of members in research ethics

Survey Data

Figure 5: Research Ethics Training and Development of members



Interview Data

There is a wide differential between the different institutions in terms of training of REC members. While at two institutions all REC members have received training in research ethics, at other institutions none of the members are trained.

Most of the training has been attendance of Good Clinical Practice (GCP) workshops. Some RECs provide in-house training, time permitting, at meetings. Some RECs circulate articles on Research Ethics to members. While funding is an on-going problem at most institutions, many RECs indicated that funding for training is available as a result of fees charged for protocol review. Institutions with the lowest training levels are either not charging a fee for protocol review or are charging much less than the other RECs.

Most chairpersons are committed to providing training for their members.

Comments regarding training were as follows:

> *We could do better but we are not doing so*
>
> *We sponsor anything on ethics…workshops or congresses or GCP…there are opportunities and we sponsor those…they can apply for funds and usually it's not a problem*
>
> *For all members who have not received GCP training up to now, we plan to send at least two members a year for GCP training*
>
> *Two GCP courses are offered per year. We've strongly recommended that all members attend those GCP courses*

Commentary

While training varied widely from 0% on some RECs to 100% on others, on average 54% of REC members had received training in research ethics or GCP. Surprisingly, only 20% of members had research ethics training on 75% of the 89 IRBs in the United States survey in 2001 (De Vries, 2002).

Definite and urgent training needs exist at some institutions. However these institutions are conducting very little contract research and hence cannot build up funds like those RECS who charge a review fee.

The nature of the training is unclear. GCP training is offered at major centres in South Africa by a number of different organisations – some private, some institutional. However, there is no national system for accreditation of the various training courses. Most GCP courses are designed for study teams, contract research associates and experienced researchers. There are no GCP courses specifically aimed at REC members. However, a basic GCP course over two-three days is a good starting point for any REC member reviewing clinical trials. A diploma in research ethics is available at the University of Cape Town as part of the International Research Ethics Network for Southern Africa (IRENSA) program. A Masters course and modular short courses are available at the universities of Pretoria and Kwa-Zulu Natal in their combined program – the South African Research Ethics Training Initiative (SARETI). The diploma course enrols 8 South African REC members a year out of 184 members who sit on the major RECs. There are REC members who sit on purely academic RECs and smaller RECS who are not included in this survey. Hence there may well be more than 200 REC members in South Africa. While the modular courses in the SARETI program are suitable for REC members very few members have the time to spend on a masters course in research ethics.

Surprisingly, similar concerns regarding training exist in the United States.

Training requirements are enforced for NIH related research only. No curricular requirements are specified. Hence there is no assurance that important ethical issues are included in the training courses. The NIH has three computer –based courses:

1. an hour long course for researchers and key personnel in NIH Intramural Research Programs
2 a course for NIH IRB members
3. a course for anyone involved in human participants research (Wood, 2002: 7-8).

Hence training curricula and accreditation remain a pervasive problem nationally and internationally.

6.5.4 Ethics Review System

At present all RECs in South Africa, both institutional and private are local RECs. There are no regional or national RECs. An INHREC has been established but is as yet not a statutory body as explained in the introduction to this chapter.

a Committee Structure

Nine of the ten RECS surveyed assess both clinical trial and academic research. One REC has the review process divided into three separate committees – one to review clinical trials, one to review academic/human research and one to review animal research.

The private RECs review both the science and the ethics of clinical trials submitted by researchers in the private health sector. There is hence no pre-existing distinct scientific review. All REC functions rest with the full committee.

b Ethical Review – the science or the ethics or both?

All RECS in South Africa are reviewing both the science and the ethics of submitted research projects. Where the science is concerned, there appears to be "double review" especially at institutional ethics committees where each academic department has a Scientific Review Committee that screens the project from a scientific perspective before it is submitted for ethics approval. However, once the project reaches the ethics committee, both the science and the ethics are reviewed. The diligence with which this is done depends on the review mechanism employed by the committee. This can be illustrated as follows; some committees allocate each project to three reviewers – two of whom are members of the REC and one of whom is an external reviewer usually an expert in the field of the project. One of the REC reviewers concentrates on the science while the other looks at the ethics.

The use of an expert in addition to committee members ameliorates the discomfort felt by some clinical members who have to review protocols outside their field of expertise. It also contributes to a discussion on the standard of care for a particular study as the expert is more familiar with current standards. Some RECs are overwhelmed with the statistical design of studies that are submitted especially after the placebo debate that resulted in more equivalence studies being submitted.

Commentary

More sophisticated demands are being made of REC members in terms of the scientific review of protocols. This is better appreciated if one considers the elements of a scientific review:

What needs to be considered in a scientific review:

- Importance and novelty of the scientific question

- Strength of the scientific design and methodology feasibility of the research as designed
- Appropriateness of the statistical analysis plan
- Estimate of the probability of meeting the enrolment goals
- Need for, and structure of a Data and Safety Monitoring Board (DSMB)
- Assessment of the thoroughness of the evaluation of the relevant literature and previous studies, if available
- Strength of the qualifications of the investigator to carry out the protocol and the facilities available to him or her
- Appropriateness of the inclusion/exclusion criteria
- Dissemination plan(to enrolled participants and via publication)

Adapted from Responsible Research – Institute of Medicine, 2003.

As is evident in the above guide for scientific review, emphasis is now being placed on assessing whether research is relevant, necessary and methodologically sound. This translates into a need for investigators to conduct a systematic review of the literature and justify why their project is being conducted. This approach in clinical medicine is referred to as Evidence Based Medicine (EBM). In the research setting this is referred to as research synthesis - which refers to the:

> *aggregation and integration of the results of related primary studies with the purpose of drawing conclusions from the totality of the relevant evidence.*
>
> (Savulescu, 1996: 1390)

This is important to ensure that research protocols are not answering questions that have already been addressed thereby subjecting participants to unnecessary risks and wasting scarce resources. Such information is also essential to judge the need for a placebo-controlled trial.

As a result, REC members need to have the ability to evaluate systematic reviews submitted to support an application to conduct research (Savulescu, 1996: 1391).

Additional skills are also required in terms of evaluating trial design, comparators and clinical or surrogate endpoints (Garattini, 2003: 1199). In the absence of a statistician or epidemiologist the duties of scientific REC members are becoming increasingly difficult.

The advantages of splitting the review into a scientific one and an ethical one are as follows:

1. The multidisciplinary team on the ethics committee would be better able to concentrate on the issues related to participant protection.
2. Lay and community members would feel more comfortable on the committee as most lay members cannot really participate in scientific review.
3. The review process from the ethics perspective will be accelerated.
4. A more thorough ethics review will ensue as will a more thorough scientific review.
5. Currently overworked ethics committees will not be unnecessarily burdened with protocols. Any project that does not meet scientific or statistical standards will not reach the ethics committee. Bad science is unethical and hence it is an ethical pre-requisite that such studies are screened out before excessive time and resources are spent on review of other components like the informed consent form etc.

What are the disadvantages of separating ethics and scientific review?

1. The process may be seen as prolonged requiring more human resources – however many RECs are top heavy in terms of scientific/clinical members and these excess members could be split off to conduct scientific review as a scientific subcommittee.
2. If not well co-ordinated, could increase review time overall.

3. There are conceptual objections to splitting scientific and ethics review.
4. Membership of an REC may be perceived to be “less prestigious”.

Current trends appear to be in favour of splitting scientific and ethics review thereby enhancing the individual review of each aspect (Institute of Medicine, 2003).

c. Interim National Health Research Ethics Committee (INHREC)

Interview data

- *Right now they are not making an impact. Perhaps with time it will serve as a watchdog for the different RECs…and see if standards are being maintained.*

- *I hope is that it will serve a facilitatory role to “get ethics committees together to formulate guidelines not rules”. Guidance with HIV studies in general and HIV Vaccine studies in particular would be welcome.*

- A “policing role” will not be welcome and “interference” with committee composition and functioning will not be acceptable.

- *That’s now the* “*big daddy*” *of all the ethics committees: the “watchdog” of ethics committees. I think that accreditation is important. Provision of training and support and working together as team would be a positive feature. If however, the role is “policing, it will not go off that well. If the plan is to dictate to everybody… people will resign from the ethics committees and they won’t be interested.*

- Some RECs felt there was not adequate involvement of RECS in the document from the Dept of Health (SAGCP). The document was

circulated too late with inadequate time for feedback and comments. They felt "*bulldozed into the process*".

- *All universities in South Africa are not represented here.*

- *INHREC will play an important role for accreditation. There are committees without standard operating procedures and membership lists or the full committee does not review the protocol.*

[The national committee will be good for this but] "they must just not want to interfere too much" – "on whether members should get paid or not and how much they're allowed to get paid and how much they're allowed to ask for a protocol, because it differs". It is not the "place of the INHREC to set limits because every committee functions on a different basis and we all don't have the same resources".

- The INHREC will "control all ethics committees". It will be a place where researchers and participants can complain. It will serve to "standardise ethics committees" and prevent "committee hopping". I "hope that it will police committees".

- *[INHREC is seen as] the Department of Health's attempt to monopolise ethics control, which in my view has failed. The Constitution very explicitly protects academic freedom, scientific research and universities.*

  [The problem could arise that] government department controlled ethics control would get into all sorts of arguments that are extraneous to the real ethics debate including politics.

- *Registration with the INHREC would be important. Our university is represented on the INHREC*.

Commentary

Those committees with representation on the INHREC are positive about its role – those that are excluded feel suspicious and are negative about the possibility of policing. The affiliation with the Department of Health is a source of serious concern.

Comments from the Chairperson of the INHREC:

> *The Ministry of Health and the Interim National Health Research Ethics Committee have been working for a couple of years on a set of guidelines for research ethics. It is hoped that these will be completed and published within the next few months. The Committee will also make available a document outlining the requirements for registration of Research Ethics Committees around the country when the National Health Bill becomes the National Health Act.*
>
> *As soon as the Act has been passed, I anticipate that the INHREC will no longer be functional and that a National Health Research Ethics Council will be appointed. The regulations on a National Health Research Ethics Council to be established in terms of Section 77 of the National Health Act will indicate how the Council will be constituted, how nomination of members will take place and the process whereby appointments will be made by the Minister of Health. The Regulations will also indicate the terms of reference of the Council*
>
> (Benatar, 2004: 2).

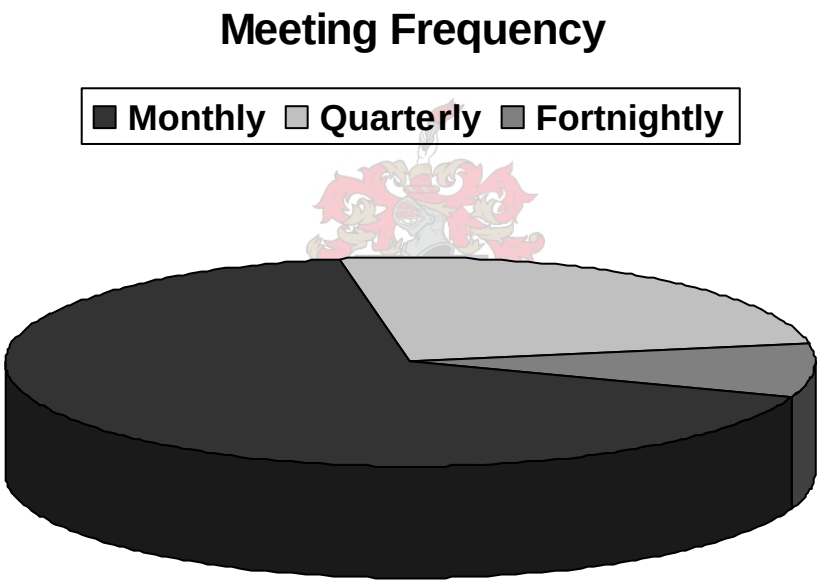
At present, the INHREC is an interim national body. It has not as yet impacted on local RECs in any way. The plan is, however, to develop a system of accreditation for all RECs in South Africa. Based on this system of accreditation, RECs will be classified as level one or level two RECs. Level one RECs will be allowed to review minimal or low risk studies only whereas level two RECs will be allowed to review moderate to high risk studies as well. How this determination of risk is to be made remains unclear. On the whole, a

national body in South Africa will be a positive addition to the ethics review system and provided it is fairly and appropriately constituted and efficient, it will assist greatly in achieving standardisation in research ethics review in the country.

6.5.5 REC workload and review procedures

Meeting frequency

Figure 6: REC Meeting Frequency



Three-quarters of the committees met either monthly or fortnightly, with the remaining three meeting only quarterly.

The mean number of members required for a quorum was seven, with wide variation (between 17% and 78% of the total membership) in the proportion of members required to form a quorum.

Protocol Review

Private RECs review both the science and the ethics of protocols. Institutional RECs usually have a scientific review before the protocol reaches the REC but review both the science and ethics again.

RECs circulated review documents to all their members. Eleven of the 12 reported that each protocol was discussed at a meeting of the committee. The remaining one committee divided itself into two sub-committees. Protocols were also divided between the two sub-committees. Only problematic protocols were discussed at a full meeting.

The number of reviewers per protocol varied from one to 13; the mean was five. One REC using three reviewers per protocol explained that while each member reviews one protocol in detail, he or she is expected to read only a summary of the other protocols submitted for the meeting. That summary is provided by the investigator.

Other RECs allocate each protocol to two reviewers – one reviews the science in detail and the other reviews the ethical issues.

Ten of the 12 reported requiring consensus to decide on a protocol, while the remaining two required voting.

Workload

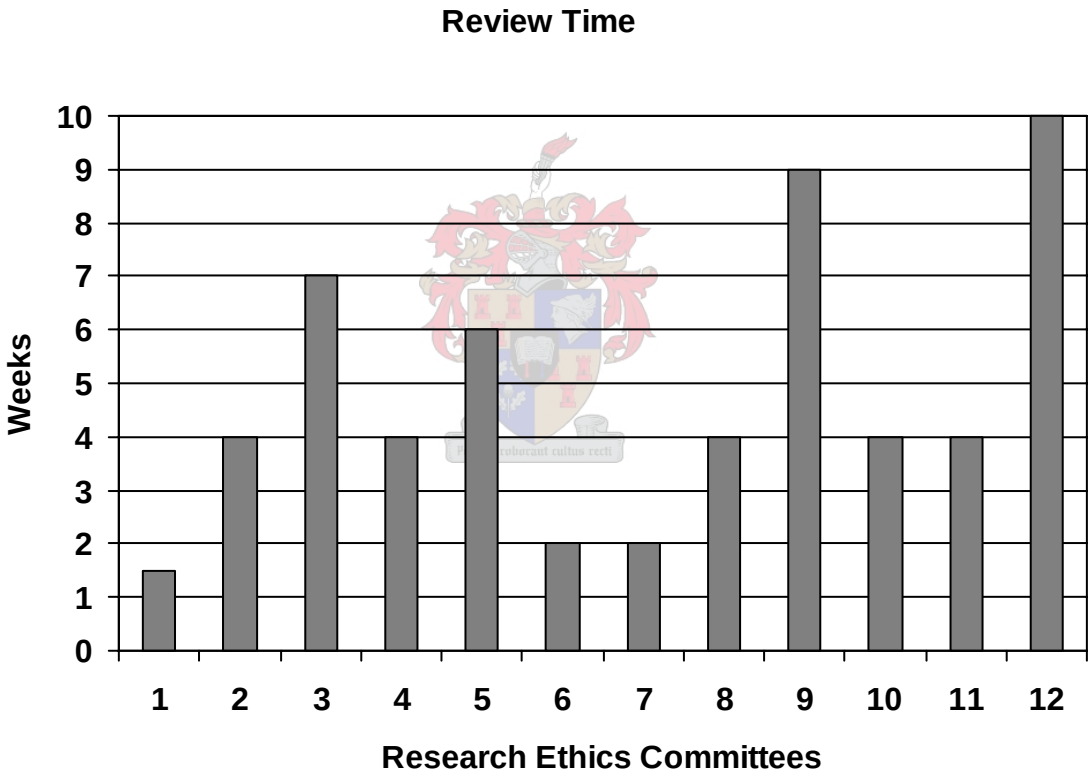
The average number of protocols reviewed per meeting varied from four to 30, with a mean of 12. This included both clinical trials and academic research for all RECs except one. The latter REC processes only clinical trials while academic research is processed by a separate REC altogether. This is the only institution in South Africa that has three different RECs, one for clinical trials, one for human research (academic) and one for animal research.

The mean estimated number of protocols reviewed during 2002 was 135, with a range from 30 to 360 (the total number of protocols reviewed during 2002 by the 12 committees was estimated at over 1600).

Six RECs had data for the number of protocols rejected during 2002. The rejection percentage for these six committees ranged from 0% to 10% with a mean of 4,52%.

Efficiency of protocol review time

Figure 7: Protocol Review Time



The average time from protocol submission to response was five weeks, with a range from ten days to ten weeks. The REC that meets fortnightly is able to process reviews within the shortest time possible. However, this is a private REC and has more fulltime members and members from the private sector who do not have the same workload as academic working at universities.

Review Charges

One-third of the committees (four of twelve) reported no charge for submissions, of the remaining eight which did charge investigators submitting a protocol, the average cost was approximately R2700 (range, R2000 to R5500).

Infrastructure and administrative staff

Nine of the 12 committees reported having an office dedicated to the committee's activities. One committee reported having no staff dedicated to the committee's operations. Of the remaining 11 committees, most (n=9) had at least one full-time staff member, with three committees reporting three full-time staff members.

Commentary on Workload and Review Procedures

It is evident that the various RECs around the country are functioning at completely different levels. There is wide variability in how the different RECs are resourced in terms of infrastructure and administrative staff.

Historically disadvantaged institutions have the following factors in common:

1. either no administrative staff or one part-time person
2. no dedicated offices at the time of the survey.
3. quarterly meetings
4. review the lowest number of protocols in the country
5. have the longest delay from date of submission of protocols to date of approval

Many tertiary level educational institutions are judged not only on the basis of their undergraduate and postgraduate teaching programs but also on their research output. There is hence the vicious cycle of fewer clinical trials being

conducted at institutions with a poor research record, perpetuating both institutional and investigator funding deficits.

The one private REC that meets fortnightly is able to review protocols in ten days. This is in keeping with the turnaround time at private IRBs in the United States. However, such a meeting frequency is only possible with fulltime members in the private sector.

While almost all RECs in South Africa review all protocols at a fully constituted meeting of the committee, it was a concern that one REC does not do this. This committee's review system bears a notable resemblance to the John's Hopkins IRB that reviewed the Hexamethonium study. The Office for Human Research Protections was "particularly concerned that that protocols had been extensively reviewed by subcommittees of the IRB but not by the full committee".

(Savulescu, 2002b: 3)

In keeping with international trends the number of protocols rejected by RECs in South Africa is very low. The mean of 3,8% compares with the 3% of rejected protocols in Spain (Dal-Re, 1999: 269). A similar situation has been described in France where 9% of protocols were rejected or where significant modifications were requested. This was interpreted as RECs being very kindly disposed to investigators even though the converse view is commonly held. The French study queried whether the low rate of rejections was related to the dominance of physicians and scientists on the committees. There was also the possibility that all protocols are not submitted to the ethics committee as this was not compulsory at the time (Isambert, 1989: 451).

On the whole, complaints levied against RECs remain a global phenomenon. Investigators, sponsors and REC members themselves regard the experience of ethical review as being extremely frustrating. The review system has been described as "time consuming, repetitive and inefficient" (Wood, 2002: 1). In South Africa, RECs that meet quarterly contribute to significant delays in the review process. A protocol review time of 10 weeks is long enough but does

not reflect the total time till final approval as most initial reviews require amendments by investigators prior to final approval. South African RECs share common problems in the review process with their counterparts globally, with the problems being accentuated at some historically disadvantaged institutions. These issues will be discussed further in chapter eight where the major challenges facing ethical review will be discussed and solutions proposed.

6.6 Commentary

A remarkable outcome of the quantitative survey is the wide range of variability amongst RECs in South Africa. This lack of consistency is reflected in a wide range of structural and procedural issues related to ethical review. It is also one of the major reasons for "ethics committee shopping" in South Africa. This phenomenon occurs when sponsors and/or investigators submit protocols to a number of different RECs simultaneously or in succession until a favourable outcome is achieved with one of the RECs who may be more lenient than the others. Such leniency in review may be related to a number of factors such as inadequate constitution of the REC, rapid review time, or inadequate training and education of REC members. It may also be related to differences in policy on substantive review issues such as approval of placebo-controlled studies but this will be discussed in detail in chapter seven.

At one level it is interesting to note the differences in RECs highlighted by the quantitative survey. At a more complex level it is important to acknowledge that variability in committee composition, variability in education of REC members and variability in review procedures impact significantly on the review process as a whole. The phenomenon of "REC shopping" results in a serious breach of research participant protection. It is thus imperative that consistency in REC structure and function is established – a role anticipated both by and for the new national body – the INHREC. However, until such time as this body is officially established other national initiatives must be implemented and these measures will be discussed in chapter eight.

The second significant finding in this survey relates to the crucial relationship between REC composition and the ethics review system. This pertains to both the scientific component and community advocacy on RECs. The rapidly expansive and intensive level of scientific review of research protocols that is becoming necessary underscores the importance of a new look at scientific review on all RECs. On the one hand, most RECs appear to have a stronger and more dominant scientific membership compared to non-scientific membership. However, the actual scientific expertise may be incomplete in terms of meeting all the requirements of scientific review in the 21st century. This refers specifically to the paucity of pharmacological and statistical representatives on RECs. While institutional RECs are stronger in terms of scientific review and have the potential to expand their expertise, private RECs and smaller RECs may be particularly vulnerable to deficiencies in the scientific review process. On the other hand, the conspicuous lack of community representation reflects the insignificance accorded to community and patient advocacy in the review process. These findings have important implications in terms of reconsidering the review system with a possible view to restructuring. This will be explored further in chapter eight.

While the quantitative survey has provided an indication of the status of the major RECs in South Africa in terms of structure and function, the qualitative component will delve into the substantive research ethics issues that South African REC chairpersons are deliberating currently. The results of the semi-structured interviews will be presented and discussed in chapter seven.

Chapter 7

Substantive Ethical Review Issues in South Africa

7.1 Introduction

Qualitative research methods involve the "systematic collection, organisation and interpretation of textual material derived from talk or observation" (Malterud, 2001: 483). The goal of qualitative research is the development of concepts that help to understand the social phenomena in natural rather than experimental settings, with an emphasis on meanings, experiences and views of all participants (Pope, 1995: 42-45).

Much of qualitative research is interview based. These interviews may be structured, semi-structured or in-depth. In structured interviews, a structured questionnaire containing fixed choice questions is administered by an interviewer who is trained to ask questions in a standardised manner. In depth interviews, on the other hand, are far less structured and may cover only one or two issues. Semi-structured interviews are conducted on the basis of "a loose structure with open-ended questions that define the area to be explored, at least initially, and from which the interviewer or interviewee may diverge in order to pursue an idea in more detail" (Britten, 1995: 251-52).

The semi-structured interview was chosen for this study because I anticipated interviewing the chairpersons of all major RECs in South Africa. These individuals are located throughout the country and have very busy schedules hence I was aware that I would have only one opportunity to conduct the interview. The chairpersons are also experienced clinicians or scientists in senior faculty positions who are accustomed to efficient use of their time.

Most indicated that they would have only one hour available for the interview. According to Bernard, a semi-structured interview should be employed when one is aware that one may have only one opportunity to conduct the interview (Bernard, 2002: 205).

Hence, the qualitative component of the empirical research took the format of semi-structured interviews. This part of the research sought to answer the following question: What is the nature and extent of substantive ethical problems being faced by RECS in South Africa?

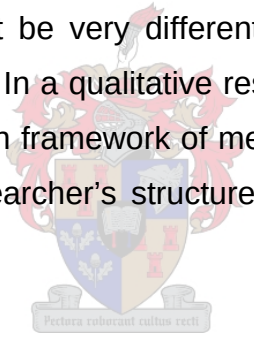
The interviews were conducted by the author during 2003 and 2004. All major institutions, both private and public, with RECs were contacted. Appointments were secured with the chairperson of each REC. Where the chairperson was unavailable, the interview was conducted with the vice-chair.

In qualitative research, sampling strategies are determined by the purpose of the research project (Britten, 1995: 253). Similarly, sample sizes are determined by factors such as depth and duration of interview and what is feasible for a single interviewer. The method of sampling used was purposive, that is, respondents were chosen deliberately. A total of nine interviews were conducted covering ten RECs. This was because one person interviewed was responsible for chairing both a university REC and a private REC. Two RECs from the quantitative research components were excluded: UNITRA and University of Western Cape due to the emphasis on academic research and not clinical trials at these institutions. The focus of this dissertation is largely directed towards the ethical issues currently being faced in the review of clinical trials in South Africa. Hence all RECs reviewing clinical trials located in faculties of Health Sciences were included. Committees reviewing academic research only were excluded. Where RECs were reviewing clinical trials and academic research, the interview focussed on clinical trial issues only. Within the ten RECs, the Chairperson was chosen for the semi-structured interview as he or she represented the longest serving member on the REC with the most intimate involvement with and exposure to the range of substantive ethical review challenges being faced at the moment.

This also represents the person who takes final responsibility for the functioning of the REC.

An interview guide was used to prompt discussion on a wide range of ethical challenges being faced by RECs in South Africa. The interview guide was prepared in advance based on the doctoral candidate's own experience as a member of an REC, as a clinical investigator and as a Trainer in Good Clinical Practice (GCP). It was also based on an extensive literature review of current controversial ethical review issues.

All interviews were conducted by the doctoral candidate to ensure uniformity in the conduct of the research. Interviews were conducted in accordance with the guide but flexibility was allowed to encourage rapport and spontaneity. The researcher remained open to the possibility that the concepts and variables that emerged might be very different from those that might have been predicted at the outset. In a qualitative research interview, the aim is to discover the interviewee's own framework of meanings and the research task is to avoid imposing the researcher's structures and assumptions as far as possible (Britten, 1995: 252).



It was very important that the interviewer appeared to be non-threatening and non-judgemental. Most RECs are sensitive about the nature of the work that they are doing as a result of frequent clashes with investigators and sponsors. The RECs that are less resourced than others also felt they were being compared or policed and this had to be avoided. One REC had to be assured of anonymity in the event of publication of results of this survey.

A unique challenge posed by a qualitative interview (as opposed to quantitative research) is the effect of an investigator on a study. A researcher's background and position will affect what is chosen as a subject for investigation, the angle of the investigation and the method deemed most adequate for this purpose. This is referred to as reflexivity. Reflexivity starts by identifying preconceptions brought into the project by the researcher. As an REC member, a clinical investigator and a GCP Trainer it was impossible

to enter into the study without preconceptions. Reflexivity was introduced into the analysis by an awareness of the preconceptions that I brought into the project by identifying and recording my frame of reference and theoretical framework before initiating analyses to look for data for competing conclusions (Malterud, 2001: 484).

The way in which the interviewer is perceived by interviewees is also important in terms of race, gender, class and social distance (Britten, 1995: 253). During the course of these interviews the effect of both race and gender of the interviewer were significant. This was obvious in the discussions around REC composition in terms of race and gender. Given the historical background of South Africa and the emphasis on transformation, including where composition of RECs is concerned, some chairpersons of REC that are predominantly white male dominated were uncomfortable in admitting this to an Indian female interviewer and in responding to questions regarding a plan to change this.

Each interview took approximately 40 to 60 minutes. Interviews were audio-taped and transcribed verbatim. Analysis of the texts was based in a grounded theory approach. This approach refers to a set of techniques for:

1. identifying categories and concepts that emerge from text, and
2. linking the concepts into substantive and formal theories.

This technique is widely used to analyse ethnographic interview data (Bernard, 2002: 462-76).

The procedure for analysis involves:

1. reading and re-reading the text to become familiar with the content
2. identification of the main issues emerging from the text
3. formulating themes on the basis of the emerging issues
4. reformulating themes to do justice to the text, while excluding prejudice and bias

5. developing a conceptual or theoretical framework to provide new meaning to and understanding of the theme

6. continuing with the process until the text is exhausted

(Meulenberg-Buskens, 1996)

Themes were identified, some of which were predetermined, and manually colour coded. These themes were then "decontextualised" – where part of the data was "lifted out and investigated more closely, together with other elements across the material" that deals with similar issues (Malterud, 2001: 486). Data was collated by the doctoral candidate. The collated data for each theme was organised into sub-themes where applicable. Where responses to a particular question or approaches to a specific problem varied widely, the range of responses is presented reflecting extreme positions at either end of the spectrum. The average position is also reflected. Innovative suggestions and new themes are indicated. For each theme, commentary is provided after the interview data is presented. The commentary reflects a critical appraisal of the data and contextualisation of the theme in terms of international debates. This represents recontextualisation where the data that was temporarily removed from its context for the purposes of analysis is returned to its place in terms of the bigger research question.

Emergent Themes and Ideas

Based on interview data a number of themes were extracted from the transcriptions. These pertained to both initial review and continuing review of research – two functions that must be fulfilled by a REC. Initial review refers to the review process that occurs from submission of a protocol to the committee until approval is granted. Continuing review occurs once the protocol has been implemented and spans the period from study initiation till study closure. Issues that arose in the initial review that were common to all the interviews were as follows:

1. Informed Consent
2. Placebo Use/Standard of Care
3. Declaration of Helsinki
4. Post Trial Treatment Provision
5. Participant Remuneration
6. Review of HIV Vaccine Trials

Issues relating to continuing review while the trial is in progress included

1. Adverse-event reporting
2. Monitoring

In addition to the predicted themes that arose, some new ideas were raised sporadically by some REC chairpersons and not others. These will be referred to as emergent ideas and included the following:

1. Ethics Review System Structure

The interviews exposed the candidate to different structures of the ethics review system compared to the structure existing at the candidates institution. These structures will be discussed later.

2. Private Sector Research

Most questions in the interview guide were framed in the context of institutional RECs. Interesting and unanticipated data emerged from some of the private RECS that were interviewed.

3. Audit of RECs

The concept of audit of RECs was raised by one of the interviewees as a result of his committee having underwent an audit process. This was specific to one REC and did not emerge in other interviews.

These emergent ideas will be discussed at the end of this chapter after the initial and continuing review themes have been discussed.

7.2 Themes related to Initial Review

7.2.1 Informed Consent

Interview Data

1. Concern was expressed regarding the length and complexity of patient information leaflets (PILs) by most REC Chairpersons. However a complete and thorough PIL is preferred by half RECs surveyed. Half of these RECs request a lay summary for the patient. There are requirements in terms of the information that must be contained in PILs. Most RECs have templates for PIL documents. Checklists are provided to investigators to ensure that all essential elements of informed consent are provided to participants. Assistance is available from REC members with drafting of the form if required.

> *We prefer a complete document. Much information is lost if documents are abbreviated. We do not request a summary of the document.*

> *We would like to see the full ethical consent form 7 to 14 pages. I think that is important both in terms of the learning process of the committee members, and in terms of what is done internationally. But, secondly, because of the very nature of our society, we'd like to see a much more simplified form encompassing the important aspects. So we always in fact ask for a simplified form in lay language.*

> *I think that especially for trials it is very important that the details must spell out everything you want to do.*

We request a lay summary.

The one thing that we're trying to do with the informed consent document is to keep it short, but it must have all the relevant information.

2. Translation requirements for PILs and informed consent forms differ on the various RECs. Of the ten ethics committees surveyed, four (40%) only review the English version of the PIL. They do not request translations, back translations or certified translations. These RECs maintain that translation is the sole responsibility of the investigator.

A further four RECs (40%) request translations and check the translations. This responsibility falls on the lay members who are able to read and correct the ethnic translations.

Two RECs (20%) request translations but do not check them. Translations must be done by a certified translator and a back translation must be submitted but these are not checked. These committees do not have members from ethnic groups and translations are, on the whole, the responsibility of the investigator. Hence 60% of RECs surveyed do not check translated versions of PILs at all.

Translations are problematic – Often the written language and verbal language differ. Rather give your research assistant training when they administer the document as to the essence of the document. English documents are verbally translated.

We have projects which were translated by people from language departments at universities and they [community representatives] just said to us: 'But our people will not understand this, this is not the language that's being spoken in this specific community'.

3. Apart form the content of PIL, the language used often results in PILs that are not user-friendly especially for educationally disadvantaged participants. There are frequent spelling and grammatical errors on the forms and the use of academic and technical language. Having a lay community member to assess PILs is regarded as being important. However, this REC does not have lay representation.

Except for one REC, no use is made of objective measures like the Flesch and Fry readability scores to assess readability of PILs. This REC uses these scores erratically.

Most RECs depend on reviewers to assess readability and had comments similar to the following:

> *As far as readability is concerned the members decide on that or, you know members will comment on whether they think this was too long or too difficult.*
>
> *We rely on reading it.*
>
> *I don't think there's an objective way that we use as such…the various members of the committee review the informed consent.*
>
> *The lay member reads I and we make sure it is user friendly.*
>
> *…it seems that it is difficult to get the forms to be user-friendly…sponsors are unhappy to change the forms.*

4. Interesting comments:

Emphasis on the process rather than the forms:

We certainly can improve our informed consent process but it is not going to come form improving our consent forms.

Linguistic expert as committee member

We have requested the board to appoint a linguistic specialist which they haven't done as yet so...people in the committee just check the translations.

Tests of comprehension as part of informed consent process:

A little test needs to be done and of they can answer ten questions they can sign informed consent.

Empirical research into the informed consent process by RECs:

I think there should be more studies on informed consent like they did in Natal. To see what patients actually understood.

I think the committee should conduct some research themselves on what happens in the informed consent process.

Independent Witness to the informed consent process

[A witness] must be present for each patient… irrespective of whether the patient can read or write and the witness must sign.

Commentary on these findings:

The most widely accepted source of evidence for the safety, tolerability and effectiveness of treatments is the randomised controlled trial (RCT). The main reason for this is a scientific one: properly conducted RCTs produce valid data that contributes to generalisable scientific knowledge. However, in the

process, the interests of participants may unavoidably be subjugated for the common good (Edwards, 1998: 1209).

Informed consent is fundamental to the ethics of randomized controlled trials and is a critical component of the research process. Defined as “an autonomous authorization by individuals of a medical intervention or of involvement in research” (Beauchamp, 2001: 78), the concept of informed consent is based on the principle of respect for autonomy. In general autonomy is defined as self-regulation or the capacity for self-determination.

We might ask why such respect is owed to persons? Kant argued that such respect acknowledges the unconditional worth of all persons, where each person possesses the capacity to determine his or her own moral destiny. Mill was more concerned with the “individuality” of autonomous agents. He argued that individuals should be allowed to develop according to their own convictions as long as the freedom of others was not impinged upon. He also believed that we are sometimes obligated to persuade others when they have false or ill-considered views (Beauchamp, 2001: 63-64). This may be viewed as a form of justified paternalism, especially in the medical setting when the “best interests” principle is invoked. In the research setting, this could be rather controversial, where persuasion of patients to participate in research must be strongly guarded against.

In the early history of research ethics informed consent was viewed primarily as a way to minimize the potential for harm. However, in the mid-1970s, the primary justification for informed consent was to promote autonomous choice (Beauchamp, 2001: 77). Hence, informed consent is enshrined in all major guidelines for the ethical conduct of biomedical research (International Conference on Harmonisation, 1997) and (WMA, 1996).

The main concern about consent is the way the process can fail, either because consent is not sought, or because participants may not adequately understand the issues involved. Given the central role of informed consent in the ethical conduct of clinical and epidemiological research, it is important to

understand the factors that may be associated with problems in the consent process.

The amount of information contained in informed consent documents and PILs is the subject of considerable debate on RECs throughout South Africa. International regulations specify the various elements that should be included in a PIL. CIOMS outlines 26 elements, ICH-GCP lists 20 and SAGCP lists 16. Given the litigious climate that most health care professionals currently work in and in view of the fact that this is extending to the research environment, current opinion is that these forms are intended to protect the researcher rather than the participant. Informed consent, however, is as much a legal requirement as a moral requirement.

The Code of Federal Regulations has summarized the essential elements of informed consent in what they refer to as the "Common Rule". It is essential that a study participant clearly understands that he/she is participating in a research study and that this is distinct from treatment. This is very important to establish at the outset to avoid therapeutic misconception (Lidz, 2002: 55-57). It is also important that all the risks and benefits of participating in the study are clear to the patient. Consensus has not been reached in South Africa regarding the extent to which risks should be specified – all possible risks or only material risks. CIOMS 2002 comments on information regarding risks as follows under guideline six:

> *In complex research projects it may be neither feasible nor desirable to inform prospective participants fully about every possible risk. They must however, be informed of all risks that a 'reasonable person' would consider material to making a decision about whether to participate….*

The Association of the British Pharmaceutical Industry (ABPI) favours the provision of all "pertinent" information. The participant should be aware of alternative treatments and how these may be accessed in the event of non-participation. It is essential that the participant is aware of the voluntary nature of the participation and the freedom to withdraw at any time without

usual treatment being compromised. In the event of research related injury, compensation should be clarified. Confidentiality must be ensured and waivers of confidentiality indicated in terms of sponsors, monitors and auditors who may need access to medical records in the course of the study. Finally adequate contact details of the investigator must be available to the participant should the need arise for questions, queries or other issues that may arise. The Department of Health and Human Services in the United States hence regards these elements as crucial to the informed consent process. Any further information is necessary when appropriate (Department of Health and Human Services, 2001).

The South African Department of Health, in their SAGCP guideline, adds a further eight elements. They would like the purpose of the study explained as well as the concept of random assignment. All trial procedures including invasive procedures must be outlined. The experimental nature of drugs and the study must be clarified.

Participant responsibilities must be mentioned including any expenses that will be incurred by participants in the course of the study. Remuneration for participation in the study must be stated. The sponsor's identity as well as any conflicts of interest the investigator may have will need to be disclosed.

The ICH-GCP guideline includes all of the above elements and adds on the following four elements: duration of participation must be conveyed to participants, the number of subjects enrolled in the study must be indicated, termination of participation must be outlined and the fact that participants will be supplied with new information that surfaces during the conduct of the trials (International Conference on Harmonisation, 1997).

The CIOMS 2002 guideline discusses a total of 26 elements, ten of which do not appear in any of the aforementioned guidelines. Four of these elements refer to post-trial issues. Participants need to be informed that information relating to the results of the trial will be made available to them when the study is over. It should also be specified when and what treatment will be available

when the study is over. This reinforces article 30 of the Declaration of Helsinki 2000 that is currently the subject of intense debate internationally and nationally. This will be discussed later in the chapter.

The fate of biological specimens taken during the course of the study must be delineated and additional consent sought for further use. Finally, the monetary gains that might accrue if a commercial product is developed as a result of the study should be discussed.

Other issues pertain to clarifying the dual role played by the investigator and the extent to which the investigator will provide medical treatment in the course of the study. The next two issues relate to participant rights - the right of access to medical records should be declared and the issue of whether the right to compensation will be legally guaranteed in the host country.

This is the only guideline that requires participants to be informed that a REC has approved the study. The final comment related to genetic testing and is usually contained in a separate consent form if genetic testing is to be done, so it will not be considered further in the context of a general consent form (CIOMS(Council for International Organisations of Medical Science), 2002).

What is very clear about the description of the elements contained in all the different guidelines is the manner in which the information provided to participants becomes progressively more comprehensive.

If one were to take the 20 elements in the ICH-GCP guideline and add the nine relevant elements from CIOMS (excluding the genetic testing element), one would have an exhaustive list of 29 elements! This could easily fill ten - twelve pages of a patient information leaflet. It would indemnify the investigator completely in terms of his/her responsibility to provide information relating to the trial. It is interesting that a number of RECs preferred such a comprehensive document.

In the current climate of research litigation such a position is tenable (Mello, 2003: 40-45). If we consider the three major cases where participants have died in the context of research form 1996 to 2001, all three cases had inadequate informed consent forms and in all three cases the deficiencies were related to information about risks. In the case of Nicole Wan, the consent form did not mention the "possibility of death" (Day, 1998: 450). After Jesse Gelsinger died, it emerged that adverse events detected in other human trials and in prior animal studies were not shared with him (Sibbald, 2001: 1612-14). In the Ellen Roche study the investigation revealed that the informed consent form was deficient in many respects. Hexamethonium was described as "a medication that has been used during surgery as a part of anaesthesia; this is capable of stopping some nerves in your airways from functioning for a short period" (Steinbrook, 2002: 1000). All the side-effects of hexamethonium were not listed. The section on risks stated that hexamethonium "may reduce your blood pressure and may make you feel dizzy especially when you stand up". Pulmonary toxicity was not mentioned. The experimental nature of the drug was not clarified, instead it was referred to as "medication" (Steinbrook, 2002: 717). The OHRP (the organisation that regulates institutions and other entities that conduct or oversee studies involving human subjects in the United States) criticized.

> *IRBs for approving informed consent documents that inadequately described the purpose of the research, the nature of the experimental design, and the risks- most notably death.*
>
> (Steinbrook, 2003: 629)

It is evident that RECs in South Africa, like RECs elsewhere are overly concerned with the documents involved and the indemnity it provides to both researchers and RECs alike rather than the process of obtaining informed consent. In fact only one interviewee discussed informed consent beyond the forms. Informed consent has evolved from being viewed as an "event" to being viewed as a "process". Even though the focus has shifted from the researcher's obligation to disclose information to the quality of the participant's understanding and consent, many RECs still focus on disclosure

(Beauchamp, 2001: 77). While this is a considerable improvement over previous informal procedures of obtaining consent, many critical issues relating to the process remain unresolved. For example, it is uncertain how much of the information provided is actually understood and used by participants in the decision-making process (Taub, 1986: 7). When one is dealing with educationally disadvantaged research communities, enhancing comprehension of trial related information becomes an ethical imperative.

Therefore, while some RECs prefer a comprehensive document they also attempt to accommodate the patient by insisting on a summary in lay terms for the patient. This is essential as, from the participant's perspective, a comprehensive form could be daunting and incomprehensible if one is dealing with an educationally disadvantaged participant. However, a summary in itself is insufficient.

In South Africa, translation of informed consent documents is extremely important as the majority of study participants have an indigenous language as their first language. Two factors impact negatively on the ability of a REC to process translated documents – lack of representation of ethnic groups and lack of lay, community membership.

Most of these documents are written in academic language by sponsors or Contract Research Organisations (CROs). Sometimes language departments of universities are used and the translated version is very academic. Hence the comments of one of the lay members on an ethics committee in South Africa:

> *Our people will not understand this. This is not the language that is being spoken in this specific community*.

Depending on certified translations is grossly inadequate. In SA, it is the duty of every REC to ensure that the English version is user friendly and that the translated version has been checked by a committee member. The suggestion of having a linguistic expert on the REC is hence a good one.

Shifting the responsibility for the translation to the investigator is an abrogation of the committee's duty to protect vulnerable study participants who eventually take home the written consent form to discuss with their families.

Most RECs review the English version of the patient information leaflet at a minimum. It is important that this version is reviewed thoroughly so that translated versions are user-friendly. Readability of patient information leaflets is a very important but very neglected concept. In order to enhance understanding of informed consent forms and patient information leaflets, it is essential that these documents are highly readable. Research in South Africa often uses very complex and detailed patient information leaflets written in academic language, sometimes imported from developed countries. This occurs in spite of the fact that a major concern with readability of informed consent forms exists in developed countries like the United States, where almost half of American adults read at or below the 8th grade level (Paashe-Orlow, 2003: 725). In South Africa we have the additional challenge of enrolling patients who are both educationally disadvantaged and unfamiliar with many complex research concepts. Hence, significantly more attention should be paid to patient information leaflets and the informed consent process in South Africa.

Most RECs depend on reviewers to assess the documents raising issues of subjectivity. This is a concern where RECs have mainly scientific members accustomed to reading academic journals and who fail to read the document from the patient's perspective. This highlights the need for an objective measure of readability. All except one REC was aware of and was using an objective method intermittently to assess readability of PILs.

Flesch and Fry readability scores to assess readability are well documented in the literature (Paashe-Orlow, 2003: 721-26) and (Grundner, 1978: 773-75).

The Flesch readability formula calculates the syllable count and the word count of the average sentence length in three one hundred word paragraphs in a PIL. These counts are then fed into a formula that produces a score. The

lower the score, the more difficult it is to read and understand the material. The Flesch-Kincaid system is widely available for computerised use as it is embedded in Microsoft Word (Paashe-Orlow, 2003: 725). The Fry scale provides a measure of the grade level reading ability required for understanding of the written material (Morrow, 1980: 56-58).

Given the tendency of RECs to prefer comprehensive consent forms and patient information leaflets, it is sometimes charged that RECs may inadvertently contribute to the complexity of the documents. A study to assess the readability of informed consent templates provided by RECs to investigators found that readability of the templates ranged from a 5th grade reading level to a 10th grade level (mode, 8th grade). The reading level generally aimed for is a 6th grade reading level though the authors of the study advise a reading level aimed at grade four to ensure promotion of the autonomy of most potential participants to engage in the research (Paashe-Orlow, 2003: 725). It is important for readability to be assessed and ensured in South Africa for comprehension to improve.

Apart from making informed consent documents more readable, tests of comprehension are an important component of the informed consent process. While this was suggested by one of the REC chairs interviewed, there is a growing body of literature exploring this topic (Taub, 1984: 17-21) and (Silva, 1988: 1-5). An empirical study conducted in Haiti found that only 20% of study participants receiving information as a single event from the physician-investigator passed an oral multiple choice test of comprehension while 80% of participants receiving the trial information over a seven - ten day period from a counsellor were able to pass the test. The second group received the information in small doses, verbally with the use of pictures and anatomical models (Fitzgerald, 2002: 1301-02).

A systematic review of all empirical studies conducted from 1966 to 2004 has been conducted by Flory and Emmanuel. Interventions used to convey trial related information in 42 trials were reviewed. Twelve studies used various forms of multimedia in place of or in addition to standard IC forms, 15 trials used enhanced IC forms, 5 studies evaluated the use of extended discussions

with participants, 5 trials used tests of understanding and feedback and 5 trials used miscellaneous methods in various combinations. Criteria used to judge these studies included whether they were randomized or not, whether they were simulated or conducted as part of a real trial, sample size and whether the study had been published. Overall, the use of multimedia did not improve understanding in 13 of the 15 trials. Where enhanced IC forms were used, in 9 out of 15 studies understanding had decreased while in 6 of the 15 studies understanding improved. Reducing the length of the form was found to be most beneficial. Extended discussion improved understanding in 3 out of 5 trials. The test/feedback method made a significant impact but was flawed methodologically. In the miscellaneous category, there were new methods such as a dry run of trial related procedures or a combination of methods but this did not impact significantly on results. Overall, it was advised that multimedia were best used to standardize information across trial arms. It was also felt that there might be benefit in illiterate populations but due to the expense of such methods they should be used if proven to be of benefit. The best method identified was the use of person-to-person contact in the context of extended discussions. On the whole, IC sub-studies did not negatively impact on enrollment in parent studies (Flory,2004). None of the studies included in the systematic review were conducted in South Africa or in other African countries. Hence it is imperative that such empirical research is conducted in Africa.

While comprehension of informed consent is critical the need for a culturally sensitive consent process cannot be sufficiently stressed in South Africa.
In South Africa, as in most parts of Africa, there are, a number of issues to consider: family or spousal consent is often required by participants in addition to their own consent, written consent may be problematic, explanation of scientific concepts may be difficult.

The Nuremberg Code, since 1947, has advised that consent be “voluntary”, “legally competent”, “informed” and “comprehending” (The Nuremberg Code, 1996). Since the late 1950s, however, the term “informed consent” has been

used (Levine, 1991: 207) – Law Med & Health Care. The Declaration of Helsinki makes reference to first person informed consent.

It has been charged that individual informed consent is a western construct based on the Western notion of personhood. In particular, the American notion of personhood is "markedly rational, and also legalistic – prototypically expressed in the language of rights" (De Craemer, 1983: 19-34). This view is supported by Nhlanhla Mkize, a South African clinical psychologist based at the University of Kwa-Zulu Natal and contributing author of the book "Critical Psychology". According to him, unlike the Western concept of personhood that defines a person as rational, autonomous, individual, separate from others, the traditional African notion of personhood is relational, communitarian and extended. Reciprocity and interdependence are reflected in the Nguni notion of ubuntu. The family or community are regarded as the moral agent as a result of the family being the most important aspect of identity. A horizontal and vertical dimension of being is described where a person is connected to the living, the ancestors and those yet to be born. A deep respect for elders is cultivated and the authority of these elders is vested in a socio-moral responsibility to promote community and familial interests (Mkhize, 2004: 46). Christakis comments that an African might find it "difficult to see how the interests of the subject conflict with the interests of the society except, of course, if the society is not his own" (Christakis, 1988: 31-37). Shutte, a South African philosopher, echoes these sentiments in his work on Ubuntu. He concurs with both Christakis and Mkhize. In traditional Africa, the interest of the subject and of society are necessarily congruent. This is in keeping with the Nguni belief that "umuntu ngumuntu ngabantu" – a person is a person through persons. Each individual member of the community sees the community as themselves, as one with them in character and identity. There is no room for a separation between the individual and the community. People see themselves as "potential persons" who become fully human to the extent that they are included in relationships with others (Shutte, 1999).

Michele Barry, in 1988, in anticipation of the cultural issues that would influence HIV/AIDS research in Africa argued that the concept of personhood,

in some central African cultures, is defined by one's tribe village or social group.

> *Whereas in Western terms selfhood emphasizes the individual, in certain African societies it cannot be extricated from a dynamic system of social relationships, both of kinship and of community as defined by the village.*
>
> (Barry, 1988: 1083)

In such a setting, an investigator may need to approach community elders for their consent before attempting to obtain informed consent from individual persons. While her comments refer to central Africa, similar views are expressed in South Africa and elsewhere in Africa.

These alleged differences in conceptions of personhood have impacted on perceptions of how informed consent should be sought in Africa. This has ranged from perceptions that consent should be sought from family elders and community leaders instead of individuals, to obtaining individual consent in addition to family or community consent. Empirical work from Senegal illustrates the use of community consent instead of individual consent followed by the employment of individual consent two years later. In 1990, a study using a safer, acellular Pertussis (whooping cough) vaccine was initiated in a rural community in Senegal. Village chiefs were informed of the study and the project proceeded. In 1992, as a result of debate on issues of consent in the medical literature and on recommendation from the institutional review board, an information campaign was launched and verbal individual informed consent was sought. The introduction of an individual consenting procedure was evaluated later in the study to assess the feasibility and validity of seeking individual informed consent. In the pilot study 4 of the 55 mothers interviewed refused to participate in the study on the new vaccine, as they had opted to use the well known pertussis vaccine. These informed refusals were considered to be a sign of full understanding that the mothers had a choice in study participation (Preziosi 1997:370-373).

In 1999, a study conducted in the Gambia on a Haemophilus Influenzae type B vaccine also looked at differences in informed consent in urban as opposed to rural communities. Amongst the urban participants, 2% of the sample indicated that the village chief should be involved in informed consent decision-making and a further 2% indicated that a religious leader or imam should involved. In the rural community, 23% of the participants indicated that the village chief should be involved in the decision-making process while 15% indicated that the imam should be involved. None of the participants in either setting was prepared to accept that a community leader could make a decision on their behalf (Leach 1999: 139-148).

Ijsselmuiden argues that "there is no single African culture". Furthermore, extensive changes have occurred in traditional lifestyles as a result of urbanization, education and industrialization (Ijsselmuiden, 1988:831). As a result, communities that have undergone urbanisation would be in a position to provide individual informed consent. This is illustrated in the study by Leach et al.

In South Africa, the requirement for spousal and family consent differs as one moves from urban to rural communities. In many urban communities the human rights culture has become firmly entrenched and some individuals would be prepared to consent without consulting family members or community leaders. In rural communities, however, tribal leaders, family elders and spouses may need to be consulted as well.

It is hence important that investigators in South Africa are familiar with the preferences of the communities they research. Provision must be made for spousal and/or family consent in the informed consent process when requested. This would require adequate time being devoted to the process and adequate time being allowed for participants to consult with family members prior to participation. This may require a "mandatory waiting period" before consent forms can be signed. In Uganda, a 48 hour waiting period is granted for participants to discuss their participation in trials with family

members and return to the research site to authorize their participation (Loue, 1996: 49-50).

Culturally specific linguistic issues relating to informed consent have been discussed in Chapter Four in the context of vertical transmission trials and the terminology used to describe placebos both in South Africa and Thailand. This problem was also encountered in Uganda when participants were being prepared for HIV vaccine trials. Culturally and socially familiar analogies were employed to describe trial related concepts - “air supply” was used to describe placebo, “wrapping” was used to explain blinding and “lottery” was used to describe randomization (Mugerwa, 1999: 227). In a rural community in Senegal, investigators conducting a trial on a new pertussis (whooping cough) vaccine for children used an agricultural example to explain randomisation. Farmers in the area were familiar with the evaluation of fertilizers or seed varieties on randomized plots and this was used as an analogy (Preziosi, 1997: 370-71).

Requirement for written informed consent can be impractical in some developing communities where cultural issues relating to affixing a signature to a form result in verbal consent being preferred for research. In the Ugandan context, study participants might be afraid of the “potential consequences” of signing a document that “confirms their connection to foreigners” (Loue, 1996: 50). One would sign for a house, for example, but not for research. This has implications for what medical journals would regard as ethical. There are also implications for what ethic committees would regard as waivers of informed consent and how a witness can be used instead of a signed consent form.

The suggestion by one of the REC chairpersons to encourage empirical research into informed consent is a valid one. There is a paucity of empirical research into informed consent in developing countries and in South Africa in particular. In South Africa, only two studies have been published to date. The first study assessed informed consent in a population of women attending an antenatal clinic in Durban, Kwa-Zulu Natal. These women had been invited to

participate in a perinatal HIV transmission study. 88% of the women felt compelled to participate in the study. 28% of women perceived the research to be integral with service at the hospital. This study concluded that the consent was informed but not voluntary (Abdool Karim 1998: 637-40).

The second study was conducted in Bloemfontein. Here the objective was to assess whether informed consent for participation in a trial investigating the effect of vitamin A on vertical transmission of HIV was informed and voluntary. Despite the participants having eight years of schooling or more, they had "poor knowledge about the most basic details of the trial". However, the informed consent study was conducted more than a year since the study commenced and recall bias could have been a contributory factor. The authors concluded that subjects' participation could not be seen as informed. Regarding the voluntary nature of the consent, the same study found that although the respondents believed that their participation was voluntary they were clearly aware of the lack of alternative sources of care (Joubert, 2003: 582-84).

The third empirical study conducted in South Africa, currently unpublished but being peer-reviewed, examined the knowledge and perceptions of the informed consent process among individuals who had participated in influenza vaccine trials in two Cape Flats communities.

Four to 12 months after completion of the trials, participants were contacted to return to participate in the informed consent study that assessed understanding of trial procedures and the informed consent process. The questionnaires covered key issues including: the purpose of the study, awareness that the study was not part of routine treatment, the voluntary nature of participation and freedom to withdraw, randomization, placebos, as well as participant remuneration.

334 Participants, representing 93% of original clinical trial sample, completed the informed consent questionnaire. The mean age of respondents was 68 years, the median level of education was grade eight. Only 21% of the

sample understood that they were allocated randomly to the different treatment arms. Only 19% of the sample involved in the placebo-controlled study understood the concept of placebo as inactive medication. The study concluded that while a good general understanding of trial concepts was demonstrated, the concepts of randomization and placebos were poorly understood. This study also has the disadvantage of having been conducted long after the actual informed consent process was conducted. Informed consent in a developing community in South Africa may often be "less than informed" and innovative ways to improve understanding of the research process must be instituted (Moodley, 2004).

What all three studies have in common is evidence that the informed consent process in South Africa is far from satisfactory. Data such as this provides useful information to investigators and REC members alike to devote increased attention to the question of informed consent in South Africa. What is also evident is that the timing of such projects is important. While concerns exist regarding the timing of two of the three studies described some consolation can be derived from the study conducted on elderly patients in Sweden where it was found that 26% of study participants understood the randomisation process (Bjorn, 1999: 263-67). However, a test of comprehension should be instituted after the informed consent process but prior to enrolment.

It is clear that RECs will need to assess IC documents more carefully. It has even been charged that IC documents that are complex when submitted to the REC become even "longer and less readable" after REC review. In a study to assess the effects of the local review process on consent forms from two major clinical trials, the changes made to the forms by the local REC were analysed. Findings included a mean increase in reading level of 0.9 ($p<$ 0.001). A mean of 46,5 changes were made by the REC, most (85,2%) of which involved alterations to wording without affecting meaning. Errors were commonly introduced relating to protocol presentation or an informed consent element (Burman, 2003: 245).

Litigation in the context of research is increasing internationally. Recent deaths and lawsuits have attracted increased attention to this phenomenon. Large groups of patients enrolled could mean class actions against investigators, sponsors, institutions, REC members (Mello, 2003: 40-45). It is hence not surprising that RECs focus excessively on the comprehensive content of forms rather than how understandable they will be to participants. However, a recent complaint lodged against a research investigator in South Africa, coupled with a threat of litigation, indicates the need for RECs to pay more attention to comprehension of the informed consent process. A 66 year old gentleman, one of 12 participants in a trial of the drug "Caduet", a drug used to treat both hypertension and hyperlipidaemia, experienced worsening in his renal function a week after the drug was administered. He claimed that he "could not understand the contents of the form" and that he was not advised or educated about the drug. His 26 year old daughter, had the following to say about the consent process: *My father had no schooling history and not even I, a university graduate, could understand the jargon in that consent form.* The case is being investigated by the REC that approved the study (Sewchurran 2004).

It is clear that both the documents and the process related to informed consent can be considerably improved in South Africa. This will be discussed in further detail in Chapter Eight.

7.2.2 Placebos and Standard of Care

Interview data

The range of responses to placebo-controlled studies varied from extreme laxity to extreme caution with the majority of RECs exercising moderate caution within reason. These middle-of-the-road RECs appear to be handling the issue of placebo controlled trials on a case-by-case basis.

Except for the one committee that demonstrated a lack of awareness of the ethical and scientific issues related to the use of placebos in research, there is

an acute awareness of the risks to participants involved in placebo controlled trials. Most committees are extremely alert when a submission is received involving a placebo and will approve such a study only if no standard of care exists and if the study will not place participants at greater than minimal risk. However, one committee raised the concern that equivalence studies (as opposed to placebo controlled studies) requiring an extremely large sample size would expose more people to an experimental drug with its inherent and undetermined risks.

Most committees appear to employ very strict criteria when reviewing placebo-controlled studies. One committee is particularly diligent in assessing the risk benefit ratio, sample size and follow-up and requesting a motivation from investigators for the use of placebo. Another committee uses the placebo waivers provided by the Declaration of Helsinki as guidance.

> *If there is a placebo, that trial is scrutinised. The committee is very, very strict.*
>
> *We shudder…if it's a placebo control we shudder.*
>
> *For trials with active controls you need more patients. Theoretically, this increases the risk of exposure of patients.*
>
> *[for HIV studies] we'll never use a placebo, I mean if we receive a study with a placebo, I think there will be a lot of questions about that.*

In the context of controlled trials, establishing a standard of care is critical. While some committees have not reached consensus on this issue as yet, most Committees refer to the best available standard of care in the public health sector in South Africa as the benchmark. The standard is determined by expert reviewers in the various medical disciplines as well as by pharmacists in their capacity as committee members.

The control group must receive the best available standard in South Africa. Declaration of Helsinki asks for best proven.

[Standard of care] depends on the expert reviewer and it stretches across from the treatment of Asthma to the treatment of Leukaemia.

…in South Africa it is best available and affordable standard of care. This is clearly illustrated in HIV research.

…if you have an HIV trial, the patient must get the standard treatment, in other words if it's not available in the state sector, I mean you must make it available for your study.

Well, the best available treatment in South Africa, at least. I mean, if you're working in a private hospital – its run on first world sort of medicine, not exactly America or Europe- but the standard of care is really high, so it must be the best available treatment that's acceptable in the country.

Personally I'm just scared that the research in this country is going to be killed if you require too much from sponsors, and I think it is already happening.

Commentary

Doctors Lurie, Wolfe and Angell opened a Pandora's box of ethical dilemmas in 1997 when they critically appraised the placebo controlled HIV vertical transmission trials in developing countries around the world (Angell, 1997: 847-49). Since then the debate has been fuelled by researchers and ethicists from the developed and developing world. This has been described in detail in Chapter Four.

Enormous controversy was raised by the attempt to amend the guidance regarding treatment for control groups in the Declaration of Helsinki (DOH) in 2000. The attempt to change the standard of care from "best proven" to "best available" was thwarted by activists from developed and developing world countries alike. It is hence extremely interesting that even though the standard of care outlined in the DOH 2000 now refers to the "best current" treatment being provided to members of a control group, most ethics committees in South Africa subscribe to the "best available in South Africa" standard.

This is consistent with the findings of Kent et al in their systematic review of clinical trials conducted in Sub-Saharan Africa and published from January 1998 to November 2003. They wanted to establish whether these trials had employed the "best current" standard of care in their control groups. Trials included were in the fields of HIV, Tuberculosis and Malaria – as these illnesses represent a high burden of disease in Sub-Saharan Africa. Overall, only 16% of trials employed the "best current" standard of care. Their explanation of their findings was as follows:

> *investigators who design and conduct these studies, and ethics committees who review and approve them, consider trial design in the context of the local level of care rather than the international standard of care.*
>
> (Kent, 2004: 240)

It is evident that most RECs are hesitant to obstruct research in South Africa – there is an unspoken fear that pharmaceutical companies will take their research to other less stringent developing countries if South Africa insists on a standard of care that will render the conduct of research in the country very expensive. A similar argument is invoked by Wendler when he refers to the effect of a ban on research that is not conducted using the worldwide best treatment in the control group. He believes that insistence on use of the worldwide best standard would

> *block important research designed to improve health care for the world's poor.*
>
> (Wendler, 2004: 923)

The Declaration of Helsinki is prided as being a document that sets an international standard of care for participants all over the world. However, this declaration sets a standard of care that is extremely narrow.

Article 29 states that:

> *The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic diagnostic and therapeutic methods. This does not exclude the use of placebo or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.*
>
> (Declaration of Helsinki 2000)

Controversy abounds about whether "best current" refers to best current global standard or best current local standard? This is not clarified in the Declaration of Helsinki. The fulcrum of this conflict revolves around the "relevant reference point" – a global reference point versus a local reference point (London, 2000: 379-97).

More important however than the dispute over the relevant reference point is whether we consider the standard to be *de facto* or *de jure*, where *de facto* refers to a standard of care set by the actual medical practices of a community and the *de jure* standard refers to a standard set by the judgement of experts in the medical community according to the diagnostic and therapeutic practices that have proven to be most effective in a particular disease. This concept is supported by the current trend in medical practice referred to as evidence based medicine. This is important where the term "best proven" is used - as is the case in the Declaration of Helsinki 1996 and in the 2000 version where placebo may be permitted when no "proven" standard exists.

Here too a local *de jure* standard would involve expert opinion from the local community while a global *de jure* standard would refer to international expert opinion.

London's article is based on the Declaration of Helsinki 1996 that refers to the "best proven" standard of care. The attempt to change the 1996 version to "best available' did not materialise and so the 2000 version reads "best current".

Similarly, the Declaration does not specify whether it is best current locally or best current globally. Can there be a best current locally? – I think not. It seems most likely that best current would refer to the best international standard, especially since the Declaration of Helsinki is an international document. In fact, criticism that could be leveled against London's arguments includes a query of the existence of a local *de jure* standard. He himself maintains that even local experts in a local community would be aware of the best proven or best current standard of care even if it were unaffordable in the region. To me it is the toss up between adopting a local *de facto* standard of care – practiced due to financial constraints, not for lack of knowledge of the best standard - and a global *de jure* standard – established as the best proven treatment globally based on the principles of evidence based medicine. As such research must be conducted and designed based on the research question that exists in a particular country or region. If for financial reasons, a particular treatment is unaffordable, new cheaper treatment could justifiably be tested against placebo.

The placebo debate can only use this international guideline as a point of departure. In addition, further considerations need to be made. Hence, the WMA subsequently issued a clarification on this article that reads as follows:

> *A placebo controlled trial may be ethically acceptable, even if proven therapy is available for compelling and scientifically sound methodological reasons or where the method is being investigated for a*

minor condition and patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

(Declaration of Helsinki 2000)

Guideline 11 of CIOMS 2002 specifies choice of controls in clinical trials:

- *Placebo may be used:*
- *When there is no established effective intervention;*
- *When withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;*
- *When use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.*

The commentary on this guideline refers to temporary discomfort as a headache and to minor risk where the group that would receive placebo has only a slightly raised blood pressure or a modest increase in cholesterol.

The explanation provided for use of placebo when scientifically reliable results would not be achieved refers to the instance when an established effective intervention is not sufficient to provide a scientifically reliable comparison with the intervention being tested.

The various footnotes that have been added to these international guidelines imply that placebo controlled trials need to be considered on a case-by-case basis taking context into consideration. This is an example of the transition from a rule-based approach to ethical decision-making to a situational approach sensitive to cases based in reality rather than abstraction, to the consideration of context rather than the blind application of rules.

It is also evident that these guidelines are focusing their definition of a standard of care only on the drug that will be used. Benatar and Singer however allude to an expanded concept for standard of care. This includes equitable access to research, expenditure on total care and therapeutic drugs shown to be most effective in other locations. It extends to similar facilities, access to technology, general medical care, follow-up and on-going care. Finally, care includes research personnel of the same culture and language group as participants, who are equivalently qualified and trained as developed country sites to conduct research (Benatar, 2000: 824). This too reflects a postmodern influence on ethical deliberation, using a holistic approach to the conduct of research rather than a focused scientific, technical approach divorced from the bigger picture.

> *Excessive reliance has been placed on international declarations to define what is ethical, but declarations, like constitutions, need to be interpreted.*
>
> (Benatar, 2000: 824)

The standard of care debate remains incomplete because the standard of care has not been adequately defined. Furthermore the assumption has been made that the standard set by developed countries can be considered to be the norm (Benatar, 2000: 824). The debate over the vertical transmission trials in developing countries bears testimony to this.

This in turn draws attention to the enormous problems of global inequity where health care is concerned. There is a palpable gap in standards of health care between the developed north and the resource-depleted south (Benatar, 1998b: 295-300). At a local level, the discrepancy in the standard of care between private health care and state health in South Africa sets different standards for research conducted in the different health sectors.

The question is: should research participants in different parts of the world or even in different parts of the same country be subjected to different standards of care?

In South Africa, the best available and sustainable standard in the public health sector is used as the benchmark where research is conducted in public health care settings. The best available standard in the private sector would constitute an unfair inducement to participants who would normally have access to public sector health care. If however, research is being conducted in the private sector, the standard of care used in the control group would of necessity be the private health care standard of care as no patient with access to private health care would settle for treatment that is less than he or she would otherwise have access to.

Given the inequities in health care, innovative proposals have been compiled since the debate.

Dan Wikler of Harvard University, proposes the following: (Wikler, 2004).

> *All [control participants] should be offered care that is no worse than what they should have received had the study not been done.*

The rationale for his proposal is as follows: accepting placebo use in a trial because basic treatment is not affordable represents “taking advantage of another’s misfortune” and that is “exploitative” as would be the case if using the non-availability of treatment for HIV/AIDS in a developing country were the reason to justify a placebo arm in a trial.

In setting a standard of care for the control group he suggests using the World Health Report 2000 which provides a performance assessment of 191 Health systems. This would entail a comparison of the research site with all other countries with similar resources. The treatments provided by those countries could be ascertained and subjects could be assured of treatment provided by most of the highest ranking countries. This approach permits research on affordable therapies and does not deny people in developing countries care that they should receive. Wikler also highlights the disadvantages of such a proposal. It does not address the problem of international misdistribution of

wealth or high international drug prices. My concern would be related to the following factors:

1. Who calculates the drug regimen for this “developing country standard of care”?
2. Some developing countries are manufacturing their own generics – Brazil, Thailand and India are such examples. Would a pharmaceutical company testing a new drug be comfortable to pay for a generic manufactured in another country for use in the control group?
3. What happens to study participants after the trial – do they return to a state of “no treatment” if that is the local standard of care?
4. Placebo use in a clinical trial must be justified by a good scientific basis – as the HIV vertical transmission trials in developing countries including South Africa were.

Wendler et al argue that a standard of care that is “less than the worldwide best” should be acceptable provided the following conditions are met:

1. scientific necessity
2. relevance for the host community
3. sufficient host community benefit
4. subject and host community non-maleficence

(Wendler, 2004: 923)

Benatar suggest similar justification when he advocates using “the highest achievable standard of care” (Benatar, 2000: 825).

Use of the best current international standard of care would require a separation of considerations of treatment and research into two separate and distinct entities. By implication, research would have no relationship whatsoever to the local de facto standard of care. In that case the same standard of care would apply to research irrespective of where in the world the research is conducted. If the research question requires a placebo controlled study design, that study should be conducted anywhere in the world with

placebo. If a study required comparison to the “gold standard” in treatment for a particular disease, this would be provided by the sponsor to the control group at any site in the world. This would require the adoption of what Alex London describes as the global de jure standard of care. All research, even that conducted in developing countries, would then be generalisable to developed countries where the best standards of care are available. It is an idealistic model but one that is wide open to exploitation.

This will be discussed further in Chapter Eight.

7.2.3 Adherence to the Declaration of Helsinki (DOH)

Interview Data

There was a wide range of variability in the response of REC Chairpersons to this document.

At one extreme, it was evident that the Chairperson had not heard of the document and was completely unfamiliar with its contents.

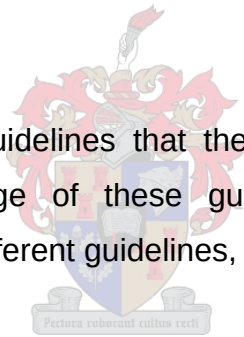
> *I would like to have some information on it because I can remember it vaguely, but it hasn’t been an issue that I have had to go over recently.*

On the other hand, a Chairperson was familiar with more than just the standard of care issue in article 29. He was aware of the waivers for placebo-controlled trials and he commented on post-trial treatment (article 30) as well.

Most RECs believed that the DOH might be too idealistic for SA as many REC’s are struggling to actually implement the standard of care part of the guideline. On the other hand while the DOH was regarded as an idealistic document it was regarded as a good document in view of the waiver for placebo trials depending on risk. The standard of care is “best current” but in SA it is best available and affordable standard of care. Post-trial treatment must be contracted in depending on type of patient, disease, exposure. This

REC required researchers to sign a separate form regarding the DOH and insisted on adherence to the declaration. Conversely an REC stated that sponsors do not take it seriously because most of them do not accept the 2000 version. Investigators don't know the declaration. He viewed this as a failing on the part of the REC for not insisting on investigator training. The REC had made GCP training for all investigators compulsory. Another REC had the following requirement regarding the DOH: In the informed consent form the investigator has to specify that she/he is following the 1996 version and not the 2000 version if a placebo-controlled trial is being conducted. Other RECs accepted the 2000 version only and not the 1996 version. The Medical Research Council (MRC) has adapted the DOH to South African conditions in the MRC booklet on research ethics. They do not insist that investigators abide by the DOH 2000 version. Instead they prefer investigators to indicate in their submissions to the MRC that they have read the MRC guidelines.

Most RECs list a host of guidelines that they refer to from time to time. However, in-depth knowledge of these guidelines is lacking. Where inconsistencies exist in the different guidelines, much confusion results.



It was interesting to note that a significant number of RECs were not aware of the contents of the local SAGCP guideline

Commentary

On the whole, most interviewees were not able to engage in an in-depth debate on the DOH. In spite of being aware of the standard of care debate and the reference in article 29 to the "best current" care for the control group, most RECs had decided on "best available" care rather than "best current". This supports the view of Lie et al in their claim that "the Declaration of Helsinki has lost its moral authority" with regard to the standard of care controversy (Lie et al, 2004: 190-93).

The comment from one REC that sponsors and investigators do not take the DOH seriously is echoed in Levine's claim that "many researchers routinely violate the requirements of the declaration". He goes on to add that "such routine violations and the attitudes associated with them tend to undermine the authority of the entire document" (Levine, 1999: 531).

Most RECs in South Africa have adopted a local standard of care for control groups in defiance of Helsinki 2000. Is this proof of ethical imperialism that has failed? Most Western documents are based on universal principles and concepts and do not take cultural and country specific issues into consideration.

Some RECs insist on the 2000 version of the declaration being quoted in the protocol and the patient information leaflet. The distinction drawn between the 1996 and 2000 versions of the declaration are only valid if all the differences between the two documents are acknowledged. While most RECs in South Africa insist on the 2000 version, they are not acutely aware of the full extent of the differences between the versions. The difference in article 29 relating to the standard of care relates only to a change from "best proven" to "best current" method for the control group. The full extent of the changes from 1996 to 2000 include the following:

Article One Medical research involving human subjects includes research on identifiable human material or identifiable data.

Article Eight Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Article Nine Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national, ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

Article 13 This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials.

Article 19 Medical researchers is only justified if these is a reasonable likelihood the populations in which the research is carried out stand to benefit from the results of the research.

Article 27 Negative as well as positive results should be published or otherwise (made) publicly available.

Article 29 The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic diagnostic & therapeutic methods. This does not exclude the use of placebo or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

Article 30 At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

Hence the REC that insists that adherence to the 1996 version is quoted only for placebo-controlled studies is incorrect in their interpretation of the new version and the change in version is irrelevant for placebo-controlled studies. If anything, the 2000 version with the waivers for placebo-controlled trial would be more relevant.

On the whole most RECs are adhering to a range of different local and international guidelines and most would prefer a single guideline. Of all the international guidelines, the CIOMS document is the most comprehensive and relevant. Regarding the range of local guidelines, rationalisation of guideline use in South Africa is a priority.

7.2.4 Participant Remuneration

Interview Data

All ethics committees are unanimous on the issue of avoidance of inducement to participate by paying research participants large sums of money. There is consensus on providing remuneration for travel and food for the day only based on the historical adoption of the reimbursement model in South Africa. This will be detailed below in the commentary.

There is however, lack of clarity on what the actual amount should be per visit. Traditionally, ethics committees in South Africa have allowed an amount of R50 ($8) per study visit. Some committees prefer that this amount not be reflected in the patient information leaflet as it will influence the decision to participate, especially where very poor vulnerable populations are being researched. One committee stipulates that the amount should be disclosed in the PIL. A recent recommendation by the Medicines Control Council (MCC) to investigators in South Africa requires that participants should receive R150 ($24) a visit for expenses incurred in participation in research and that this should be documented in the patient information leaflet read by the participant before deciding whether to participate in the research study. This has caused considerable uncertainty amongst researchers and ethics committees alike.

One committee maintains that an allowance for travel will differ depending on the distance being traveled and that the reimbursement for travel should be calculated on a case-by-case basis.

Commentary

There is controversy regarding the appropriate remuneration for research participants in South Africa. Most international and national guidelines on health research ethics vaguely warn against unfair inducement of individuals to participate in research but are otherwise silent on this issue. The most comprehensive guideline referring to participant remuneration is that of the Council for International Organisations of Medical Sciences (CIOMS). Guidelines Four (1993 version) and 11 (2002 revised draft) refer to 'inducement to participate'.

Guideline Four states, inter alia, that

> *subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research.*

Guideline 11 states, inter alia, that

> *subjects may be paid or otherwise rewarded for inconvenience and time spent.*

The guideline also details acceptable and unacceptable recompense, remuneration of guardians of incompetent participants and remuneration in the event of withdrawal from a study.

The notion of participant remuneration ranges from the promotion of research as a socially responsible activity, with no payment at all but rather recognition for the time and effort of participants (Russell, 2000: 126-30), to the view that a wage payment model should be used in which research subjects are paid an hourly wage based on that of unskilled workers (Andersen, 2002: 359-76). A number of different payment models are possible. Dickert describes three models: a market model, a wage-payment model and a reimbursement model.

The market model is grounded in traditional libertarian theory based on the principle of supply and demand. As such payment may be high for research that offers little benefit to participants yet involves risky or uncomfortable procedures. Payment may also be high when subjects need to be recruited very quickly or when few people are eligible for a particular study.

The wage-payment model is based on the notion that research participation is similar to other forms of unskilled labour. As such a fairly low, standardized hourly wage can be paid. This may be increased depending on risk or burdensome procedures. A completion bonus is permissible using this model.

According to the reimbursement model, payment is provided simply to cover the subject's expenses. This is based on the view that research participation should not require financial sacrifice on the part of participants. Usually this includes reimbursement for travel, meals and parking (Dickert, 1999: 198-203).

In South Africa the reimbursement model has been applied and consensus has been reached on this amongst all RECs as is reflected in the interview data. Our choice of this model can be justified as follows: South African research participants are often poor and can barely afford travel costs to a hospital or clinic for non-research purposes. Participation in research requires more frequent visits than routine treatment requires and participants will not be able to travel to the research site if they are not reimbursed for their travel expenses. Obviously these expenses vary depending on where the participant lives. Research visits also require that participants leave home very early and spend the day at the research site – hence they must be reimbursed for their meals for the day. In settings where the therapeutic misconception is a common phenomenon, the reimbursement also serves to distinguish research from treatment where no payment occurs.

The market model and the wage payment model would not work in South Africa. The market model would unfairly induce participation in research and the wage model, given our very high rates of unemployment, would also serve to lure desperate patients to the research site with negative sequelae.

Participants would underestimate the degree of risk involved in a study based on their need to earn a wage for the day. Logistic problems would be created at research sites with patients queuing and demanding an opportunity to be "hired" for research purposes.

The reimbursement model, on the whole, works well in South Africa. However, the amount of money that participants should receive for their participation is highly contentious. A balance has to be achieved between a rate of payment that is high enough not to exploit subjects and low enough that it does not create an irresistible inducement (Beauchamp, 2002: 547-64). The ethical concerns involved in participant remuneration have received attention in the international literature, yet surprisingly little research attention has been paid to this question in the South African context where research is frequently and unavoidably conducted on vulnerable populations. While many researchers have a strong opinion on the remuneration of study participants, there is little understanding of how participants themselves perceive remuneration for research.

A semi-structured cross-sectional study was conducted by the doctoral candidate and a colleague on 334 individuals from the Bishop Lavis and Elsies River communities in the Western Cape who had participated in two pharmaceutical industry-sponsored trials of an intranasal flu vaccine during 2001 and 2002 was conducted in 2003. For their participation in these trials, participants received R50 ($8) at each of three scheduled study visits and an additional R20 ($3) for unscheduled 'illness' visits over a 12-month follow-up period. For this study, individuals were interviewed in their home language (English or Afrikaans) by an independent researcher four - 12 months after completing the vaccine trial. All participants gave informed consent before being interviewed. The mean age of the 334 participants was 68 years (range 60 - 80 years) and the majority were female, with a mean educational level of Grade Eight. All the participants received R50 ($8) per study visit (R150 or $24 altogether), although several received up to R200 ($32) for additional interim visits. The majority of those interviewed (N = 281, 84%) felt that the compensation they received for participation in the trial was adequate,

although a minority (N = 36, 11%) recommended that the compensation per visit be increased to a median of R100 ($16) per visit (range R70 - R200 or $10 - $32 per visit). In open-ended questions regarding compensation, participants stated that they used the money received in a range of ways, primarily to purchase food for their families, to transport themselves or a family member to a clinic or hospital, or to meet cost-of-living expenses generally.

While drawn from a small sample within a particular community, these results indicate the complexity of a blanket compensation policy — as is being requested by the MCC —for participants in biomedical and epidemiological studies. In this setting, the standard of R50 ($8) per visit for three study visits spread over 12 months was deemed acceptable, yet it is likely that other communities may have substantially different standards — some greater, some lesser. And while there are sometimes concerns regarding the use of cash as compensation, these participants used their compensation to meet basic needs (Moodley, 2003: 677-78).

Generally, identifying the most appropriate level of compensation for participation in a particular study, as well as what form it should take, is an important and sometimes daunting task for researchers. The establishment of a single national guideline to be applied across all types of research throughout the country may be difficult. However, current literature suggests that research ethics committees should have written policies on participant remuneration and that these should be prorated and contextualised to the research population in question (Dickert, 2002: 368-73).

In general, health research ethics guidelines regard the issues of participant remuneration as residing fairly in the domain of the research ethics committee involved. In South Africa, however, the regulatory agency, namely the MCC, has decided to take this matter into its domain. Is it the mandate of the MCC to review the patient information leaflet and informed consent documents, especially where participant remuneration is concerned, or is this a role of the local ethics committee? Perhaps this is a matter that will be resolved by the

annual meeting of chairpersons of RECs or by the National Health Research Ethics Council.

While the importance of payment has been described as a potential way of unfairly inducing a patient to participate, less attention is paid to other aspects of trial participation that may influence both the recruitment and retention of study participants. Many of these other factors may have more import in developing countries than in developed world settings.

In South Africa, research in the public sector is often conducted at sites such as clinics and hospitals that conventionally offer treatment. It is therefore not unusual for research participants to be drawn from these centres where they regularly present for chronic care. To facilitate the research process, participants are given a card to allow them privileged access to the research clinic thereby avoiding the usual delays involved at a state health facility. This translates into a saving of many hours of waiting in queues to be admitted to the hospital and to gain access to hospital folders. This reduction in waiting time is seen as compensation for the inconvenience incurred in the clinical trial and is necessary to ensure that trial conduct is efficient. The availability of dedicated staff at the research clinic results in participants receiving personalised attention that they would otherwise not receive in a busy outpatient setting. Research often requires more intensive and more frequent medical examinations and hospital visits. In addition the need for telephonic contact in a research study may increase the perception on the part of the participant of personalised attention. During study visits sites may provide tea and refreshments to participants during their long wait for research related investigations and procedures. In some instances, the medication being provided as part of the trial may not be otherwise available at the state health facility and is perceived as an enormous benefit. Consider the HIV related trials held in South Africa prior to anti-retroviral provision by the government. Any medication that is received in the course of the trial also bypasses traditional waiting time at the dispensary that can usually be anything from one to two hours depending on the clinic or hospital. Sponsors sometimes provide small token gifts – sanctioned by the REC - during the course of the

trial. On the whole, there are many ways in which study participants in developed countries may perceive their involvement in research to be beneficial even though the trial itself is not designed for individual benefit.

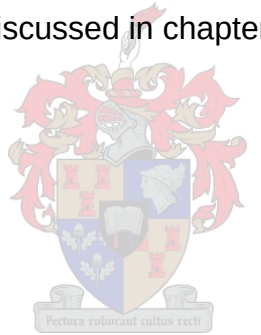
Having mentioned all the above factors, I have not even started with the issue of therapeutic misconception that is a dominant feature amongst trial participants who do not fully comprehend the research process.

Hence, it important that participant remuneration is seen in context of other trial related benefits and that the payment in itself is kept within reasonable limits.

At present some RECs have adopted the MCC specified amount, other RECs remain uncertain. This is matter that must be resolved in South Africa and options for resolution will be discussed in chapter eight.

7.2.5 Post-Trial Treatment

Interview Data



Policy regarding the provision of treatment to participants after the trial is largely undeveloped in South Africa.

While it is regarded as an important consideration in the research process by all ethics committees, the responses ranged from strict insistence that it is incorporated in the protocol to extreme uncertainty and discomfort with implementation.

Most committees require that provision is made for post-trial treatment provision, especially so if the treatment is unavailable in South Africa or if it is a new or novel treatment that has proven to be effective. Under these circumstances, if alternate treatment is available, one REC was comfortable that the investigator ensure that the patient knew how to access alternate treatment.

HIV research and Oncology trials have set a precedent regarding post-trial treatment. This has not extended to other types of research as yet. The duration of treatment after the trial has not been established. For HIV research it appears to be till treatment failure or death.

However, the fear exists that if insistence is placed on post trial treatment provision, South Africa will lose research projects to countries where this is not strictly enforced.

While ethics committee shopping occurs within South Africa, research site shopping occurs in the developing world as a whole especially when a specific country implements stringent rules.

Commentary

At the time of conducting the qualitative research interviews, post trial treatment had not been seriously deliberated on RECs in South Africa. It has, however, posed a significant problem with the emergence of HIV/AIDS. Prior to government antiretroviral rollout programs – that is- prior to 2003, clinical trials on anti retroviral treatment represented the only hope for many patients in terms of accessing care. RECs have been faced with the dilemma of approving trials where at the end of the study participants would receive no treatment or they would have to revert to less effective treatment. Some RECs have adopted policies such as “trial subjects must continue to receive the antiretroviral treatment after the trial ends until they cease to benefit or are enrolled into another trial” (Cleaton-Jones 1992: 887). Drug companies were not impressed with this decision. Their argument was that informed consent is provided by participants who then have no claim to treatment beyond the trial. Cleaton- Jones, however, contested this based on his view that South Africa has “large numbers of people insufficiently educated to understand the implications of what they are consenting to” (Cleaton-Jones 1992: 887).

In the last few months, post-trial treatment has become a global issue under considerable debate at the World Medical Association (WMA).

> *At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.*
>
> (Declaration of Helsinki 2000)

The focus on post-trial issues was stimulated by "parachute" or "safari" research that had been occurring in Africa without consideration for capacity development or sustainability of treatment tested during a clinical trial. The intention was to ensure that study participants' treatment and care would not be abruptly halted at the close of a study. It was also envisaged that participants who had borne the burdens of research would benefit from the research in some way.

The current controversy regarding article 30 of the Declaration of Helsinki 2000 revolves around the concept of the "best proven" method and whether a single study could provide conclusive proof of the best agent. There is also concern that pharmaceutical companies will not conduct research in developing countries if provision of treatment after the trial is a requirement. The World Medical Association (WMA) set up a working group to consider the controversy surrounding article 30 and developed the following proposal:

Proposed Changes to article 30– WMA meeting Sept 2003:

> *Before undertaking a study, the physician should make every effort to ensure that all patients entered into the study will have access to any available prophylactic, diagnostic or therapeutic method that the study proves to be the most effective and appropriate for such patients, once it has been approved by the appropriate authorities. When informing the patient about the study the physician will explain the treatment options after the study and how they relate to the patient's condition and will state explicitly if it is foreseeable or likely that the sponsors will*

> *not be able to provide effective and appropriate treatment to the patient after he or she leaves the study. Any arrangements for the continuation of treatment beyond the study, or the reasons for their absence, should be described in the study protocol that is submitted to the ethical review committee.*

This amendment was not accepted at that meeting. The Argentinean Medical Association objected to the amendment on the basis that it "strongly weakens the spirit of the declaration" (Sibbald 2003: 169). The Brazilian Medical Association was concerned that the change "might weaken the intent and provisions of paragraph 19 that states that:

> *Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results.*
>
> (Declaration of Helsinki 2000)

On the other hand, the amendment was accepted by the United States Department of Health and Human Services and multinational pharmaceutical companies (Canadian Medical Association Journal – Editorial 2003). The British, Croatian and Mexican medical associations also supported the change.

While opinion is divided on article 30, the WMA rules require at least 75% approval for documents dealing with ethics. As a result a WMA work group was constituted to explore this issue further. Their suggestions included the following:

1. to add a preamble explaining that the Declaration of Helsinki is a set of ethical guidelines, not laws or regulations;
2. to add a note of clarification that reaffirms the intention of paragraph 30 but avoids the possibility of misinterpretation;

3. to make no changes or additions to the Declaration.

The WMA work group, in their draft report, argue that article 30 should remain unchanged. Their official report back is expected in May 2004 (Frankish, 2003: 963). According to Dr Delon Human, secretary general of the WMA,

> *The aim of this paragraph is to guarantee that research participants are not worse off after a study than they are during the study. The WMA's primary consideration has always been that the best interests of patients be served, but also that no good ethical research should be restricted. At the same time, the WMA is adamant not to compromise the ethical principles that the medical profession stands for.*
>
> (www.wma.net/e/ethicsunit/pdf/wg-doh-jan2004.pdf)

Unlike the Declaration of Helsinki 2000, the CIOMS 2002 guideline, on the other hand, specifies benefit to the community. Guideline 10 deals with research in populations and communities with limited resources:

> *Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:*
>
> *any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.*

While Helsinki refers only to study participants as recipients of benefits CIOMS refers to the population or community.

The discrepancy inherent in these two documents creates confusion and makes it difficult for RECs to implement them. On the other hand, a synthesis of the two guidelines could assist in considering the concept of post-trial benefit in broader terms.

The concept of post-trial treatment is better operationalised if the concept of post-trial benefit is explored. What provisions can be made after a study is over?

1. Knowledge gained can be disseminated.
2. The study drug or intervention can be made available to participants.
3. The research clinic can be converted into a primary health care clinic for the community in the area.
4. Research staff may be employed for a period after the trial to provide primary health care services to the community.
5. Capacity development of research staff and community advisory board members can be instituted.
6. Equipment from the trial site may be donated to the institution or health care service.

It has been argued that investigators and sponsors have no responsibility to provide non-research related treatment to study participants or communities (Richardson 2004: 25-33). I would like to argue that investigators and sponsors have a moral obligation to provide treatment to study participants who develop co-morbidity during the course of the study if a country lacks infrastructure or medical supplies to treat such co-morbid illness. Participants also deserve to be treated for chronic illness that predated their enrollment in a trial. In practice it is extremely difficult to ignore co-existing disease even in the context of a clinical trial. If, however, one can rely on a robust referral system to provide such care to a study participant, that represents an ideal situation, often non-existent in developing countries. In essence I am advocating the use of research to address inequities in health care systems in multinational research where there is a wide gap between health care services between sponsor and host countries. Justification for such an approach could be invoked from a Rawlsian theory of justice where persons should receive an equal distribution of certain goods like health care services. Norman Daniels refers to “a positive societal obligation to eliminate or reduce barriers that prevent fair equality of opportunity, an obligation that extends to programs to correct or compensate for various disadvantages. It views

disease and disability as undeserved restrictions on persons' opportunities to realize basic goals" (Beauchamp 2001: 233-234). Hence article 30 of the Declaration of Helsinki, referring to post-trial treatment, can be expanded to include post-trial benefits to developing country health care infrastructure. Coupled to this, however, is engagement of governments to commit proportionally to health care infrastructure.

These issues must be discussed at the start of a study and negotiated between investigator, sponsor and ministries of health. Once agreement has been reached, post-trial benefit should be specified in the protocol or application form to the ethics committee. However, in calculating the risk-benefit ratio of a study, risks to participants must be balanced against benefits to participants during the trial. At no stage should risks to participants during the trial be balanced against benefits to participants or communities after the trial. Post-trial benefits will be discussed further in Chapter Eight where resolution is sought.

7.2.6 Review of HIV Vaccine Trials

Interview data

RECs varied in their response to how the review of HIV vaccine trials would be managed. At one end of the spectrum, an REC indicated that HIV vaccine trials would be reviewed like any other trial protocol. On the other hand, it was indicated that the ethical issues inherent in the vaccine trials are too intensive and extensive for one local REC to handle and should be decided at a national level within SA. Most RECs did not have a specific policy to deal with these trials except for the MRC committee who had been intimately involved with the development of a specific guideline on the Ethics of HIV Vaccine trials, one of the booklets in their series of five booklets outlining ethics in research. Two RECs were familiar with the guidelines on HIV Vaccine trials contained in the Department of Health's SA GCP - 2000 guideline. One committee intended to follow international guidelines.

Three RECs indicated the need to invite HIV experts and ethicists to update their RECs on HIV Vaccines prior to reviewing such protocols. At the time of conducting the interviews two RECs had received protocols for a phase one trial. These protocols had, however, presented the RECs with a challenge in terms of treatment of participants who would seroconvert during the trials. While two RECs had initially approved this phase one trial, both RECs subsequently withdrew approval after it was discovered that the sponsor did not intend to provide seroconverters with antiretroviral treatment (Altenroxel 2002). This set into motion intensive discussion around this point in SA around 2001-2002. It is therefore not surprising that six of the RECS interviewed were acutely aware of the consensus that had been reached on the obligatory provision of antiretrovirals to seroconverters. It was only after sponsors agreed to provide antiretroviral treatment to participants who seroconverted during the HIV vaccine trials that the two RECs involved granted approval for the conduct of phase I HIV vaccine trials in SA in 2003.

Two RECs indicated that they would like community preparedness programs in place at HIV vaccine trial sites and that willingness to participate in studies should be conducted on these communities. Protocols would need to include this information before RECs could review such protocols.

Commentary

HIV vaccine trials are fraught with ethical concerns both internationally and locally. Two phase one vaccine trials were approved and started in SA during 2003. These are safety trials on small groups of healthy volunteers. At present approximately 30 candidate vaccines are in phase one trials globally (Esparza, 2004). In the United States and Thailand, two large phase three efficacy trials have been conducted (Choopanya, 2004).

Debate culminated in the UNAIDS Document released in 2000 in which 18 guidance points dealing with the ethics of HIV Vaccine Trials were outlined (UNAIDS, 2000).

The fascinating way in which science and ethics are related has been borne out in the HIV vaccine trials. Prior to conducting the clinical trials, the ethical issues and concerns were overwhelming. Ethical deliberation helped to clarify some of the concerns. However, the actual conduct of phase one, two and three trials has helped to further clarify many perplexing concerns.

When deliberations on HIV vaccine trials first began in South Africa in 1998, a decision was taken to test only clade C vaccines in South Africa as this was the clade most prevalent in South African. It was argued that South African communities should bear the burdens of research for a vaccine that they could later benefit from. This was a very clear attempt to protect our communities from exploitation where sponsors from developed countries would test a vaccine here that would never be used on our communities in future. Here too, science helped to change this rule when it was discovered that cross-clade reactivity might occur and hence other vaccine clades might also benefit South African populations. At present we have both a clade C and a clade A vaccine in phase one trials in SA.

The ethical issue that has received considerable attention to date relates to the care of participants who seroconvert during the course of trials. The ethical dilemmas inherent in the provision of care to these participants centre around the moral responsibility of sponsors/investigators to provide care to such volunteers.

This moral responsibility is two-fold. Firstly the responsibility to patients who are screened out of the vaccine trial as a result of their being HIV positive and secondly, the responsibility of sponsors to participants who seroconvert during the trial.

According to guideline 21 of the CIOMS 2002 document,

External sponsors are ethically obliged to ensure the availability of:

- *health- care services that are essential to the safe conduct of the research ;*

Commentary on guideline 21 states

> *although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for diseases contracted in the course of the study. It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study.*

By extrapolation it would seem plausible to assume that the sponsor has no responsibility to those HIV positive volunteers identified during the screening process. However, the commentary continues to add that volunteers who "cannot be enrolled in a study because they do not meet health criteria" for admission to the investigation - as would be the case with HIV positive volunteers who are screened out of trials – "should, as appropriate, advise them to obtain, or refer them for, medical care". The commentary also indicates that sponsors and investigators should refer those "subjects or prospective subjects who are found to have diseases unrelated to the research". Hence it is imperative to ensure that a robust referral system is in place in the community before research commences.

Falling short of stating a moral obligation on sponsors to provide care for HIV positive volunteers, Guidance point 16 of the UNAIDS document indicates that

> *Sponsors need to ensure care and treatment for participants who become HIV-infected during the course of the trial.*

While there is no consensus on the standard of care that should be offered, a comprehensive care package is referred to and Guideline 16 suggests the

provision of the best proven standard of care as an ideal, but the provision of the highest attainable standard of care in the host country as a minimum.

In South Africa, research and care are integrally linked and often conducted at the same sites due to resource constraints. As such, it is impossible to conduct research without making provision for care, whether this is care for illnesses related to the research or unrelated morbidity.

The options to the sponsor in the provision of care range from a volunteer specific approach on the one hand to community wide provision of care on the other hand.

A volunteer specific approach could involve provision of care at trial sites independent of existing host country ARV programs. The standard of care provided could be that of the sponsor country or the host country.

Another volunteer specific option would be the provision of a higher standard of care funded by a trust fund financed by the sponsor but administered by the local government as suggested by Tucker in the South African setting (Tucker, 2003: 995). Such a scheme is both innovative and interesting. However, offering private medical care to participants who seroconvert will represent an inducement to participate. Such a scheme is individualistic and will benefit only trial participants who seroconvert. It will also be costly and hence limited to a period of a minimum of ten years as is outlined in the proposal.

However a more pragmatic and morally sound option would involve collaboration of the sponsor with local governments, working to strengthen existing infrastructure, in particular, existing ARV rollout programs. In this way, sponsor funding will assist to raise the standard of care to the highest attainable level in a developing country. Communities and not only volunteers will benefit. Inequity between trial volunteers and community members will be eliminated so it will not serve as an unfair inducement to participate. Such an approach will also make provision for the referral of HIV positive volunteers

who are screened out of the trial. The results of the first phase three trial conducted in Thailand indicated that 1570 participants had to be screened out of the trial due to their pre-existing HIV positive status. This represents a large number of patients who would have to be cared for, highlighting the importance of good health care infrastructure that must exist concurrently with the conduct of HIV vaccine trials. In fact, the HIV positive patients who are screened out represent a much larger challenge than those who seroconvert during the trials. The Thai study had 105 seroconverters in the vaccine arm and 106 seroconverters in the placebo arm a total of 211 out of 2500 participants who were enrolled in the study.

Given the current challenges being faced in South Africa with ARV rollout with only 16 out of a possible 66 sites being active, coupled with the need to train at least 14000 permanent health staff to sustain the program, financial assistance from research sponsors is indispensable. In exchange, trial participants, both those who are screened out and those who sero-convert during trials, could be assured of prioritized access to such programs. It is imperative that pragmatic solutions are found for the care of HIV positive vaccine trial participants in South Africa. It is the responsibility of the sponsor to assist to "ratchet the standard upward" rather than attempt to create "utopian" standards that are neither attainable nor sustainable (Benatar, 2000: 824-26). Sponsors argue that research initiatives cannot be used to reduce health care inequities. However, given the minimal options that exist to improve health care in developing countries, research remains the only currently viable option.

The above arguments pertain to the situation where HIV positivity is regarded as a primary end-point in an HIV vaccine trial and where those who sero-convert are regarded as falling outside the parameters of the study.

If, however, we look at the use of surrogate end points in a vaccine trial, retention of HIV positive trial participants will become an important consideration and the moral obligation of investigators to these study participants will change.

While much attention has been focussed on treatment of seroconverters in trials it is clear that this issue affects less than 10% of participants enrolled in clinical trials. On the other hand, informed consent procedures are going to affect all trial participants and attention needs to be focussed on this ethical issue in South Africa. Suggestions to improve the informed consent process in South Africa will be discussed in chapter eight.

The inclusion of children and adolescents in HIV vaccine trials is a current source of concern in South Africa. According to the current classification of research into therapeutic and non-therapeutic research in South Africa (MRC guideline) HIV prevention trials would fall squarely into the non-therapeutic category. As such, according to the National Health Bill, non-therapeutic research requires consent from parents/legal guardians, the children involved and the Minister of Health. Consent from children under the age of 18 years for research purposes is a new concept in South Africa. Traditionally, assent has been obtained from children under the age of 18 years for the purposes of research. Ministerial consent for such research could prove to be a logistical problem resulting in enormous time delays in initiating urgently needed research in South Africa. The delegation of this function to the National Health Research Ethics Council, when it becomes a statutory body, is a possible solution. Consensus is being reached that children and adolescents must be included in HIV vaccine research on the proviso that the vaccine has first been demonstrated to be safe in adults – one of the tenets outlined in the Belmont report in chapter three. In addition, it has been argued that if phase 1 and 2 trials can demonstrate no significant difference between adult and adolescent responses to the vaccine, it may be possible to obtain licensure for adolescent use without conducting phase 3 trials on adolescents (McClure 2004: 732). The view on research on children in the United States differs markedly from the protectionist view South Africa has adopted. The Revitalization Act of 1993 and policy established by the National Institutes of Health (NIH) and implemented since 1998 adopts the view that researchers need to justify reasons for not including children in research. In South Africa, the emphasis has been on justifying why children are included in research whenever this has been the case. Unlike the South African situation where

research on children is classified as therapeutic and non-therapeutic, the United States approach has focussed on risk (Miller 2003:102). The 45 Code of Federal Regulations part 46 developed by the Department of Health and Human Sevices (DHHS) outlines 3 major risk categories:

1. Research involving minimal risk
2. Research involving more than minimal risk with direct benefit to the children
3. Research involving more than minimal risk with no direct benefit to the children but research that will produce generalisable knowledge.

The need to include children and adolescents in HIV vaccine research in South Africa has resulted in many ethical issues being revisited – the emerging autonomy of the adolescent, beneficence - as such research will benefit children as a class and the principle of justice which requires that children are not excluded from research.

In a multicultural setting like South Africa, different concepts of autonomy of the child exist. At a meeting in Kwa-Zulu Natal in July 2004 hosted by the HIV AIDS Vaccine Ethics Group (HAVEG) to explore the issue of inclusion of children and adolescents in HIV vaccine research, an interesting view was expressed by Black community members regarding the autonomy of the child. In some communities, a person is regarded as a child as long as he or she is dependent on parental support and is still living at home. Under such circumstances, consent would have to be sought from parents before participating in research even if a person were over the age of 18 years. By extrapolation it would then be impossible for a child or adolescent younger than 18 years to participate in research without parental permission. There is a great deal of empirical research that is necessary in South Africa to inform the development of guidelines for conducting research on children and adolescents where HIV/AIDS is concerned.

7.3 Continuing Review: The Ethical Issues

The responsibility of the REC does not end with approval of a research protocol. Hence, the interviews also included questions on two important functions that the REC must fulfill once a trial is initiated. This includes adverse event reporting and monitoring. According to the ICH_GCP guideline, a Serious Adverse Event is defined as

> *Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.*
>
> (International Conference on Harmonisation, 1997)

Good clinical practice requires investigators and/or sponsors to report serious adverse events to sponsors and to RECs (International Conference on Harmonisation, 1997).

7.3.1 Adverse Event Reporting

Interview data

> *[Adverse event reporting] - That's a nightmare, I think for any and every ethics committee.*

This sums up the view of all RECs in South Africa. This is largely due to the huge number of adverse events that are reported both from the local site and from international sites. All adverse events are not related to the study drug and all are not serious.

In most RECs the role of reviewing adverse events has been assumed by the chairperson.

In four out of ten RECs surveyed, this function is delegated to a specific person/s:

Either the vice chair or specific REC member has this responsibility. Alternatively a subcommittee has been established comprising two REC members. In one instance a manager of the REC performs this duty.

In two out of the four cases this person/committee does not review protocols at all.
Four RECs have developed ways to cope with this enormous administrative burden:

Consensus exists regarding the importance of having a system in place to deal with this problem. Such a system can be manual or electronic.

These RECs have an electronic database to process adverse events. This works well provided the adverse event reports contain all the information required by the electronic system. The computer is able to flag the adverse events and generate a letter to the investigator when ten or more adverse events are detected on a study. However, the nature of the adverse event, its relevance and severity must be interpreted by a clinician. Hence one cannot rely solely on the electronic system to fulfil this function.

One of the four RECs also uses a colour coded sticker system to identify adverse events according to severity and relationship to study drug.

Two RECs have developed their own forms that facilitate the data capture of these adverse events.

How could the reporting of adverse events be improved?

Most RECs prefer to have only those adverse events that are related to the study drug reported to them.

We should demand of the sponsors that we only review adverse events that they think are related

It would also simplify the work of local RECS if adverse events from South African sites are reported separately from those occurring at international sites.

The idea of the NHREC assisting with multicentre studies was suggested. It was felt that it would be worthwhile to have a dedicated person attending to adverse events at a national level.

Consistent submission of adverse events by investigators would facilitate the work of RECs in this regard.

Some pharmaceutical companies complicate the work of REC's. The majority of RECS regard adverse event reporting to be the responsibility of investigators, not sponsors and prefer for investigators to follow simple rules to minimise the burden created by adverse event reporting.

Commentary

There is wide variation in how different RECs are coping with this very difficult yet important function of adverse event reporting. It is a vital way in which the health of research participants should be monitored and protected by an REC yet it is fraught with logistical problems at all levels. A very valid concern exists regarding the level of protection that is being afforded to study participants. It is argued that the current process fulfils the "bureaucratic requirement of data dissemination" but may not result in enhanced safety for participants in clinical trials" (Liauw, 2003: 426-428).

Most RECs, already overburdened with protocol review are looking for ways to simplify the adverse event reporting function. While the use of an electronic database is good, it cannot fully appreciate the significance of an adverse event. Those systems that react after only ten adverse events are reported

may appear to be efficient, yet in some clinical situations two adverse events of a particular nature, especially if related to the investigational drug, may be too many. This was clearly illustrated in the Ellen Roche case study where the first study participant developed a cough that was not reported to the REC and the second participant (Ellen Roche) also developed a cough but subsequently died. If dependence were being placed on a computer to monitor adverse events, nine people could easily have died before the 10th adverse event had been flagged by the computer!

A consistent complaint from all RECs surveyed was that safety reports from sponsors do not situate the adverse event in the wider context of the clinical trial. Hence it is difficult for the significance of the adverse event to be evaluated in context.

Data Safety and Monitoring boards (DSMB) represent a mechanism to monitor interim data in clinical trials to ensure safety of participants. The members of these boards are experts in the field of interest but are independent of the clinical trial itself (Slutsky, 2004:1143-1147). Liauw argues that data safety monitoring boards are in a better position to make judgements about safety, especially in relation to causality as they have access to more complete information. The major liability for adverse events in investigational clinical drug trials lies with the sponsor. As such, sponsors should take responsibility for establishing effective, independent data safety monitoring boards. RECs should insist that the data safety monitoring board process should be more transparent. Protocols should state whether or not an independent monitoring board is being established and the membership of the board as well as its terms of reference should be disclosed. The sponsor's internal operating procedure for handling adverse events should also be disclosed (Liauw, 2003: 426-428).

The current regulations and guidelines that define a serious adverse event includes any hospitalisation excluding those for elective procedures and scheduled operations or investigations, during the conduct of a trial. Often, sponsors and contract research organisations fail to bring this to the attention

of investigators at the start of a trial. If, on enrolment of a participant, all elective procedures requiring hospitalisation for the duration of the study are documented in the source documents, these do not meet the definition of a serious adverse event when they occur and hence do not have to be reported as such. This will considerably reduce the paper trail that already exists in adverse event reporting.

In South Africa, the INHREC will have to seriously consider the role it will play in national and international multi-centre trials. These studies entail a great deal of duplication of effort and reporting mechanisms. According to Califf et al, traditional RECs "within single institutions, acting alone, typically are not constructed to assess reliably the safety of participants across multicentre trials" (Califf, 2003). It is therefore not surprising that adverse event reporting and surveillance of multicentre trials is an area identified by local RECs in South Africa where the national committee can play an important role. This needs to be negotiated with the INHREC before it becomes a statutory body so that provision can be made for this in their mandate. In this regard, the latest guideline of the European Union that came into effect as of the 1 May 2004 can be invoked. The guideline referred to as 2001/20/EC is legally enforceable throughout the European Union. In the context of multinational collaborative research with Europe other countries will also have to abide by the regulation. The regulations relating to adverse event reporting are comprehensive. Of particular import, is the development of a single national electronic database to expedite the reporting of suspected unexpected serious adverse reactions (SUSAR). The efficiency of the system remains to be judged but it does represent a unique way of handling adverse event reporting at a national level (European Council and European Parliament-EU, 2004).

Ultimately, Good Clinical Practice training of all investigators will hopefully ensure standardised knowledge of adverse events and procedures for reporting to the REC that will contribute significantly to the role that the REC plays in participant protection. The final responsibility for the protection of study participants should lie with the investigator who is medically trained and

in the best position to recognise adverse events timeously. The REC can only play a secondary role in protection of participants once the trial is in progress.

7.3.2 Monitoring of Research

Interview data

Only one REC is actively involved with monitoring at a very low level – two-three site audits are conducted a year at random by REC members.

Two other RECs have had limited experience with monitoring – one attempted to do telephonic monitoring but were dissatisfied with the experience. Another REC had conducted one or two audits as a result of complaints.

For most RECs the monitoring function is limited to annual reports from investigators and adverse event monitoring.

Across the board, all RECs cite a lack of resources both financial and human to conduct a proper auditing function.

However, all RECs would like to conduct monitoring and have the following plans in mind:

1 Who should conduct the monitoring?

One suggestion was that a separate subcommittee of the REC consisting of two REC members should be responsible for random on-site monitoring. These members should not be involved in protocol review at all. Another suggestion was that a separate committee should be established to conduct monitoring. One committee suggested sharing the monitoring function with other RECs who are located geographically close together. One REC had appointed a full time committee member with a mandate to conduct monitoring but the process had not started at the time of the interview.

2 Which sites should be monitored?

Random monitoring was mentioned. Some high risk sites were identified such as sites conducting a high number of clinical trials, high risk research such as HIV vaccine trials, and oncology and respiratory studies. It was also thought that monitoring visits should be driven by complaints from participants and colleagues. Some RECs had received complaints while others felt that participants are not aware that complaints can be lodged with RECs and the awareness of this fact needs to be increased through efforts of RECs. One REC believed that academic research should also be monitored as these involved "less experienced researchers working with vulnerable populations".

3 What should the monitoring entail?

Site visits were cited as essential. Mention was made of speaking to study participants and of monitoring the informed consent process.

4 How could this be operationalised?

Although funding was a pervasive problem, one REC suggested building monitoring fees into review fees for clinical trials and building monitoring fees into academic fees for academic research.

Commentary

The extent and depth to which RECs conduct monitoring in South Africa is in keeping with international trends. A multinational survey of REC monitoring in 21 different countries revealed that only 11 countries were conducting monitoring and in most cases this involved only passive surveillance (quoted in Burgess, 2004:1).

While there is consensus in South Africa regarding the relevance of a monitoring function of an REC, internationally, this issue is met with more

ambivalence. On the one hand, proponents for monitoring regard this as an integral function and indeed, an obligation, of an REC. On the other hand, critics hold that monitoring represents a policing function that falls outside the domain of REC functions.

Robert Levine has argued vehemently against routine monitoring. His arguments are grounded in two main objections. Firstly, he charges that routine monitoring would erode the trust embedded in the relationship between RECs and investigators. His second objection pertains to the high cost-benefit analysis of monitoring. While the costs involved are high, monitoring does not "seem to catch many wrong doers anyhow". (Quoted in Weijer, 1995: 1974)

As a proponent of monitoring I wish to offer the following counter arguments.

Many programs of human participant protection have routinely traded on investigator integrity. RECs have very little knowledge of what actually happens to perfectly designed research protocols they approve. Often they trade on the following assumptions:

1 acceptance that researchers will do what they say they will do;
2. a willingness to believe that informed consent in practice will meet up to its moral rather than its legal obligations
3. confidence that conflicts of interest can be eliminated ;and
4. the desire to achieve participant protection will have a higher priority than the pursuit of knowledge.

(Adapted from Benatar, 1998: 221)

However, in many instances, this trust in investigator integrity has been eroded by investigators themselves. The Bezwoda case in South Africa (Weiss, 2000: 999-1003) and the Poisson case in Canada (Weijer, 1995: 1973) – both involving research fraud on patients with breast cancer – are living examples and will be discussed in more detail in Chapter Nine.

The comment from one of the REC chairs interviewed also supports the notion of monitoring as a result of lack of trust in investigator integrity:

> *The Bezwoda case…should have taught us a lesson about monitoring – we still do not monitor enough so we did not learn a lesson.*

While it may be argued that these represent isolated cases of breach of trust and hence cannot be used to establish a rule of universal monitoring, it is clear that in research on humans even a few cases of research fraud, especially in the magnitude of the Bezwoda and Poisson cases, is a few cases too many. These cases in and of themselves are sufficient to erode not only trust in RECs but also erosion of public trust. This in itself would destroy the research endeavour altogether. This is echoed in the words of Schwarz:

> *If integrity and credibility of the [research] process is called into question, our ability to produce new methods for the diagnosis and treatment of disease will be compromised. The ultimate penalty will be paid in decreased benefits to public health. It's that simple as well as that serious.*
>
> (Schwarz, 1991: 760)

This leads to the second counterargument to Levine's objections to monitoring. The cost benefit analysis of monitoring cannot simply be calculated in monetary terms. Agreeably the costs involved are high, however, the benefits accrued in preventing just one case of scientific fraud are enormous as is evidenced by both the Bezwoda and Poisson cases. It is true that it will not be possible to monitor all research projects, but a system of random monitoring will encourage researchers to comply with rather than to deviate from protocol specifications. Such a system will not obliterate research fraud altogether but will serve to deter investigators in the vast majority of cases from committing fraud.

Further support for the monitoring function of RECs is enshrined in some international guidelines relating to REC functions:

Article 19 of the 2000 version of the Declaration of Helsinki specifies:

> *The committee has the right to monitor ongoing trials*

The CIOMS 2002 guideline 2 refers to monitoring as follows:

> *The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.*

In spite of the controversy surrounding monitoring, a number of systems have been proposed to operationalise the monitoring function of RECs. These include continuing annual review, informed consent monitoring, monitoring for adherence to the protocol, and review to identify unapproved activities (Heath, 1979: 1-4). A fifth category includes monitoring of data integrity (Weijer, 1995: 1977-78).

Continuing annual review:

This is a minimum requirement for monitoring internationally and is by far the most that is being done in South Africa and elsewhere by most RECs. Most REcs require that a report is submitted to the committee annually indicating the number of participants enrolled, the progress of the study and any adverse drug reactions. If the adverse drug reactions are a source of concern, The REC may suggest that a data safety monitoring board be appointed to monitor the study further. Any new information that has been acquired by other studies should also be reported to the REC especially if such information disturbs the equipoise of the study. This might necessitate termination of the study.

Consent Monitoring:

Deficiencies in the informed consent process is a frequent finding when various regulatory bodies audit research. A survey conducted by the Office

for Human Research Protection (OHRP) on 175 institutions in the United States found that 25 % of the institutions had a deficiency in the informed consent process (personal communication - Melody Lin deputy director of OHRP, 2004).

Consent monitoring can range from a simple inspection of consent forms to observation of the process on site to testing participants' comprehension of the process. Faden et al reviewed consent documents for 214 research participants at the Johns Hopkins Oncology Centre over a three year period – March 1976 to March 1979). The entire process took a total of 160 hours to complete (Faden, 1980:9-10). The IRB at Harvard University, School of Public Health has been conducting informed consent monitoring on site since 2003. Monitoring is conducted by a specific person to whom the task has been delegated. He has travelled to Botswana and Nigeria to monitor the process. Some of his visits include sitting in on the interaction between investigator and participant with the permission of the participant (personal communication Jelal Hoosein).

Monitoring for adherence to protocol

This is a labour intensive process and is usually conducted by contract research organisations or sponsors to ensure adherence to Good Clinical Practice. Most RECs in South Africa are inadequately trained and under-resourced to conduct monitoring of this intensity.

Review to Identify Unapproved Research

This would have been the ideal way to detect the kind of research being conducted by Werner Bezwoda at the University of Witwatersrand. However, it is uncertain whether this is indeed a function of a REC. It is extremely difficult to determine which studies have not received REC approval. I believe that this type of monitoring clearly falls outside the mandate of a REC.

Monitoring of data integrity

This type of monitoring occurs when clinical trials are audited either in house by the sponsor or externally by a regulatory agency. When this occurs, a REC may request a report of the audit. However, in trials that are not audited, it remains an impossible task for a REC to conduct a full audit on a clinical trial – another function the REC is not mandated to conduct.

Monitoring of research that has been approved by a REC is regarded as an integral function of RECs. However, most RECs are unable to fulfil this function both nationally and internationally. It is hence important that each REC develops a plan for monitoring based on expertise and resources available to conduct such monitoring.

7.4 Emergent Ideas

The new ideas that emerged in the course of the interviews pertained to research in the private health sector and audit of RECs. They will be dealt with briefly as they represent largely unresearched areas that require further exploration in another study. Research conducted in the private health care sector of South Africa is submitted to one of two private RECs for approval. Many private practitioners are inadequately trained to conduct research and most private practitioners conduct research on their own patients with whom they have a pre-existing therapeutic relationship. This raises serious questions about voluntariness of participation by patients who are in a dependent relationship with their doctors. An important issues raised in the interviews was the problem of some doctors billing their patients' medical aid plans for research related investigations, drugs and consultations – a phenomenon referred to by one of the REC Chairs as "double-dipping". In the context of a clinical trial, all research related investigations, consultations and drugs are paid for by the sponsor. Hence these items cannot and should not be charged to a medical aid.

The concept of audit of RECs is unique in South Africa. Only one REC indicated that the REC had been audited by a private audit company. This audit had been financed by the institution. Eight other RECs had received a quality assurance visit by the Office for Human Research Protection (OHRP) in 2002 and were alerted to their short-comings. However, all documentation related to that process was confidential and hence could not be made available to the interviewer.

7.5 Commentary

The in-depth interviews facilitated a process of engagement with the critical challenges facing REC chairpersons in South Africa. There are widespread problems relating to both initial and continuing review both amongst institutional and private RECs. In addition, there are issues of significant concern where private sector research is concerned and this represents an opportunity for future in-depth empirical and conceptual research. Interesting links exist amongst the various themes identified in the course of the interviews. Undoubtedly, informed consent receives a disproportionate share of the review process. Standards of care and post-trial benefits share a common sub-theme – namely – both reflect the compromised position most RECs find themselves in when attempting to achieve a balance between protecting participants and promoting research. They must choose between the following options: securing a global standard of care as well as post trial benefits and risk losing research, or settling for local standards of care and sacrificing post trial benefits in order to attract and maintain a vibrant research industry in South Africa. The latter option would require that the universal standards aspired towards in the Declaration of Helsinki must, of necessity, be disregarded. Participant remuneration and post trial benefits are two concepts that can be viewed as being inversely proportional to each other. Increasing post-trial benefits could result in reducing in-trial participant remuneration thereby elimination the potential for undue incentives for participation. Enhancing post-trial benefits will contribute to an improved standard of care in developing countries. It will also raise the ethics of trial participation closer to those aspired towards in the Declaration of Helsinki and other international

documents. Ultimately all these issues will facilitate the ethical conduct of HIV vaccine trials in South Africa, a research priority for the third world. Chapter eight situates the various challenges that emerged from the empirical research in a conceptual framework and proposes solutions to each of the major challenges that have emerged. Recommendations for resolving the global challenges are also presented.

Chapter 8

Towards National Standardisation

8.1 Introduction

Internationally it has been charged that there is “an impending, if not actual, crisis” in the review of human participant research (Wood, 2002). In the context of the 4000 to 6000 IRBs in the United States, this is perhaps not an exaggeration.

In South Africa, many of the problems that exist in developed countries are present but on a much smaller scale. The empirical research conducted on the major RECS involved in clinical trial research in South Africa indicates the following:

1 wide variability across the country in the ability of RECS to conduct satisfactory ethical review.

2 a number of problem areas in research ethics review:

- 2.1 at a structural level,
- 2.2 in the course of the review process, both during initial review and continuing review or

2.3 in deliberation of substantive research ethics controversies.

These findings will now be considered in more detail:

8.2 Challenges in the Ethics Review System in South Africa

8.2.1 General

8.2.1.1 Variability in the Ethics Review System

The Bantu Education Act of 1953 placed control of education of Africans in apartheid South Africa in the hands of the Department of Native Affairs (Perez, 2004: 765). The Minister of the department, Dr H.F. Verwoerd, outlined his plans for the education of Africans as follows:

> *My department's policy is that education should stand with both feet in the reserves and have its roots in the spirit and being of the Bantu society…There is no place for him (the Bantu)in European community above the level of a certain form of labour.*
>
> (Roux, 1964:394-395)

As a result of The Bantu Education Act and a Bantu education policy that followed a system of inferior education for African people, the apartheid ideology was extended to higher education (Perez, 2004: 765). It is hence not surprising that RECs at Black universities have been in existence for only one year, are under resourced, lack infrastructure and training of members and review very little contract research.

The lack of standardization amongst the 12 RECs surveyed in terms of structure and the review process has its origins in the apartheid system in South Africa. While the effects of the system have been widely recognized at a socio-political and economic level, the effects in academia have been less clearly defined and documented, especially where tertiary educational institutions are concerned. This study, however, clearly demonstrates that the historically disadvantaged institutions have RECs that are in existence for one year while the historically advantaged institutional RECs have been established up to 30 years ago. What defines the institutions that sit at the extreme opposite ends of the spectrum is simply a differential in terms of

historical government support to tertiary institutions serving students of different racial groupings.

The large majority of institutions that have been in existence for ten years coincide with the change to a democratic government since 1994 and a greater awareness of participant protection and vulnerable communities.

Hence the quality of ethics review in South Africa is divided along racial lines. While the burdens faced by REC members are enormous under the best of circumstances, including developed world RECs, these burdens are intensified in historically disadvantaged institutions in South Africa in terms of experience, infrastructure, administrative support, training and capacity development.

The INHREC has a plan to divide RECs further in terms of level one and level two RECs. Level one RECS will be able to review high risk research while level one RECs will be able to review only low risk research. Given the current situation with RECs in South Africa it is most likely that historically disadvantaged RECs will only qualify for level one accreditation. In the absence of redress aimed at raising the level of functioning of RECs at historically disadvantaged institutions, the INHREC system of accreditation will serve to perpetuate the injustices of apartheid.

There are far-reaching consequences to the disparity in REC functioning. Level one RECs will only be able to review low risk research. Most RECs review the research that comes to their own institutions. From the data on workload at the various RECS, it is evident that historically disadvantaged RECs already have very little research activity at their institutions. This will be reduced even further by an accreditation system that discriminates against disadvantaged institutions. It is established that research is a major source of funding for institutions and investigators alike. Hence low levels of research activity at historically disadvantaged institutions will impact on the ability of those institutions to build research funds both at an institutional level and at individual investigator level.

8.2.1.2 Lack of Communication amongst RECs

RECs in South Africa function in isolation. There are no national policies in place to ensure uniformity in review requirements. RECs have not established a means of communication. Such a situation lends itself to the phenomenon of REC shopping which impairs human participant protection.

8.2.2 Specific Problems in the Review System

8.2.2.1 Structural

A. Composition

Most RECs except those at Black universities are white dominated. Hence these RECs fall short of the requirements of the SAGCP guideline for RECs to reflect the demographics of the country. Females are under represented at almost all RECs. Most RECs are top heavy where scientists and clinicians are concerned. There is poor representation of pharmacologists and statisticians.

Community representation is being confused with lay representation. Lay members on RECs in South Africa are non-scientific professionals like lawyers or theologians. All priests on REC represent the Christian faith. This is unacceptable in a multi-denominational society like South Africa. Except for the private RECS, very few members on institutional RECs are not affiliated to the institution. This leaves the REC in a serious position of conflict where research conducted at the institution is reviewed by the institutions own REC.

B. Committee & Review System Structure

Most RECs in South Africa review both academic and clinical trial research at a monthly meeting. This usually results in a large number of protocols per meeting, long meetings and an enormous workload for reviewers. This is intensified where all REC members are reviewing all the protocols for the

meeting. One institution has three RECs – one to review human (academic) research, one to review clinical trials and one to review animal research. Different faculty members sit on each of these committees. During the interviews, one of the larger RECs alluded to such a system of review as being preferable.

Scientific review is being conducted twice in most institutional RECs but only once at private RECs. This could represent duplication at the level of institutional RECs and inadequate scientific review by private RECs.

C. Administrative staff

Most RECs have at least one person responsible for the administrative workload of the committee. This is generally inadequate due to the enormous amount of administrative work in the REC.

D. Infrastructure

All RECs, except one, has a dedicated office for REC administrative work. This in itself is inadequate. Storage of documents requires further space and a good storage system.

E. Training and development of members

There is wide variability in training levels of REC members. Training ranges from 100% on some RECs to 0% on others. Funding appears to be problem at some institutions.

F. INHREC

There is ambiguity about the role that this national body will play in the South African system of ethical review. While there is a positive expectation in terms of education and training needs being met, there is a concern regarding the potential for a policing role. The system of accreditation has been questioned

and there is a concern that registration of level one and level two committees will perpetuate the apartheid structures that still exist within universities in South Africa. A wider role for the INHREC is anticipated by RECs in terms of its involvement in the review of multi-centre research and adverse event reporting. These roles are not anticipated by the INHREC for themselves.

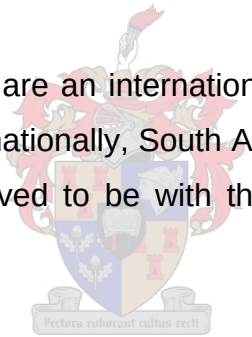
G. Remuneration of REC Members

There is wide disparity on the issues of payment of REC members. There is lack of national consensus in this regard.

8.2.2.2 Review Process

A. Delayed review

Delays in the review process are an international and national phenomenon. Compared to the delays internationally, South African RECs are actually more efficient than they are perceived to be with the range for review extending from ten days to ten weeks.



Factors contributing to the delays are as follows:

1. Double review of the science – most RECs are reviewing the science even though this has been done either by another committee or by a departmental review committee.
2. The requirement by some RECs for all REC members to review all protocols.
3. Infrequent meetings – those RECs meeting quarterly contribute more to the delay in the review process.
4. Inadequate administrative staff – the enormous amount of paper work has to be processed and this delays the process if there are only part-time administrative staff.

B. Informed consent forms

There is excessive focus on comprehensive content of informed consent documents. At the same time very little attention is paid to readability and layout of forms and translation of forms. There appears to be little concern with the impact of the forms on study participants with erratic policies regarding the provision of summaries for participants. Only three out of ten RECs require summaries for participants.

C. Adverse Event Reporting

The definition of serious adverse events results in many routine and unrelated hospitalizations of participants being reported. In the context of multi-centre studies adverse events at international sites are reported to local RECs. Inadequate information is provided rendering RECs incapable of contextualizing the adverse event. Adverse events that are both unrelated and related to the investigational product are reported. RECs receive reams of paperwork and have attempted to create databases to facilitate the process. However, there data bases serve only to flag adverse events after ten or more events occur at a site. A computer cannot assess the clinical significance of the event and hence unnecessary letter are generated by databases and sent to investigators. Data safety and monitoring boards and RECs do not liaise in any way. Ultimately, the reporting of serious adverse events in the way in which it is currently being done does not serve to promote the function of RECs to ensure the safety of study participants.

D. Monitoring

None of the RECs in South Africa is engaging in meaningful monitoring of the research that they approve. If it is being done at all, it is being conducted in an erratic manner or at such a low level that it fails to adequately serve the purpose of quality control. Most RECs are under resourced, both financially and in terms of personnel to execute this function. As a result, the most of

this function that is fulfilled is the review of annual reports on studies from investigators.

8.2.2.3 Substantive Review Issues

A. Standard of care

International guidelines that specify a universal standard of care for control groups in clinical trials have introduced conflict into the ethical review process in a developing country like South Africa. On the one hand, RECs would like study participants to receive the best standard of care possible. On the other hand, researchers and RECs in developing countries are in a compromised position with regard to sponsors in negotiating a universal standard of care. A policy for an international standard would cripple the research industry in South Africa. As a result, RECs are disregarding the Declaration of Helsinki, even though we are members of the World Medical Association. This has been borne out, both in a systematic review of the standard of care used in research in Sub-Saharan Africa (Kent, 2004), and from the interview data in this study. What has not occurred in South Africa is a clear expression of our decision – as considerable confusion exists amongst investigators, contract research organizations and sponsors regarding the standard of care policy in South Africa.

B. Post-trial treatment

Like the standard of care guideline, this is another guideline specified in the 2000 version of the Declaration of Helsinki that is not being implemented, again, for fear of stifling the research industry in the country. There is inconsistency in the recommendations of the Declaration of Helsinki and the CIOMS guideline. This relates to the obligation to provide treatment to study participants only (Helsinki) as compared to communities that study participants belong to (CIOMS). At an international level, this needs to be clarified. However, at a local level, RECs need to reach consensus on a

reasonable plan for the post-trial period. Firstly, the concept of post-trial benefit must be defined. This can be viewed as a study drug or intervention proven to be effective in a narrow sense or on a broader scale as a contribution to infrastructure development or capacity development in South Africa.

C. Remuneration

There is lack of clarity on the amount that should be paid to research participants in South Africa. It is also unclear whether the RECs or the MCC should make this decision. Inclusion of this information in informed consent documentation remains problematic.

D. Guidelines

The number of guidelines regulating research ethics is growing internationally and nationally. Guidelines like the Declaration of Helsinki are simply being disregarded when implementation is not possible. RECs make irrelevant specifications regarding which version of the declaration must be included in informed consent documentation and protocols, yet are themselves unclear of what the different versions espouse. Selective application of some articles of the guidelines is unacceptable. An obsessive dependence on guidelines in the ethical review process results in more attention being paid to a paper trail and beaurocracy rather than the business of research participant protection.
Developing countries make insufficient contributions to the development of international guidelines. Local guidelines are largely the result of “cutting and pasting” from international guidelines and do not reflect a country specific approach to the dilemmas being faced.

E. HIV Vaccine Trials

Most REC members have poor knowledge of the ethics and the science of HIV vaccine trials. Hence the dependence on ”experts” to assist in their decision making.

F. Informed Consent Process

Very little attention is paid to the informed consent process as such. This aspect of human participant protection is subjugated to an obsession with documents with an emphasis on providing indemnity to investigators and RECs, rather than participants.

None of the RECs in South Africa make reference to the process or have policies to highlight the process in any way. There is no requirement for tests of comprehension.

8.3 Resolution Options to Improve Research Review In South Africa

8.3.1 Eliminating Variability and Achieving Standardisation

Political and institutional redress are necessary to restore institutional inequity. South Africa has affirmative action programs and transformational policies in place since 1994 in an attempt to achieve equity. Ten years into democracy, it is quite apparent that this is a long term process that will be achieved with time. From the perspective of RECs in such institutions, however, the INHREC has a critical role to play in securing institutional commitment to support and improve the ethics review process.

Most RECs in South Africa function in isolation. It is important that a communication network is established amongst the various RECs in South Africa. As an interim measure, an electronic national newsletter has been established. This will be discussed in further detail later in this chapter as a recommendation. The INHREC will play the final role in introducing standardization by establishing criteria for all ethics committees in the country.

8.3.2 Changes to the Review System

8.3.2.1 Structural Changes Recommended

A. Composition

1. Active attempts must be made to establish diversity in terms of race and gender in REC membership.

2. Where professional diversity is concerned, scientific membership should include a pharmacist and a statistician/epidemiologist as far as is possible. The National Bioethics Advisory Commission (NBAC, 2001) in the United States recommended that non-scientists make up at least 25 % of an IRBs membership (National Bioethics Advisory Commission(NBAC), 2001).

The Institute of Medicine (IOM) report recommends that:

> *unaffiliated members, non-scientists and those who represent the local community and or the participants' perspective comprise at least 25% of the membership*
>
> (Institute of Medicine, 2003: 9)

This is however inadequate. Combining non-affiliated, non-scientific and community members is problematic as each of the three categories of membership is already under-represented. Furthermore, there is overlap between non-affiliated membership and the other two categories. This precludes adding them together. Non- affiliation must be viewed as a category that is distinct from professional categories of membership. Hence the NBAC proposal for each category (non-affiliated and non-scientific) to represent at least 25 % of REC membership is a good starting point for South Africa.

3. Community representation of the populations most frequently being researched in that region must be co-opted and trained. Religious membership, if any, needs to include more than one Christian priest.

4. Non-affiliated or independent members – The National Bioethics Advisory Commission (NBAC, 2001) has advised that at least 25% of IRB members are independent –that is – come from outside the institution. This is a good policy to implement in South Africa although we should aspire towards having at least 50% of REC members independent in the long term as the issues surrounding conflicts of interest escalate.

The SAGCP guideline is based on the ICH GCP guideline. However, ICH GCP does not deal with conflict of interest where the REC is concerned. This section has been added on to chapter eight of the SAGCP guideline on ethics committees. The SA GCP guideline specifies that RECs must have clearly formulated policies regarding conflicts of interest and that these must be made known to all members and to investigators. It also outlines the range of indirect and direct benefits that may place an REC member in a position of conflict.

It is essential that such a policy is included in the standard operating procedures (SOPs) of all RECS in South Africa.

As a result of the large proportion of scientific and clinical members on RECs in South Africa it is inevitable that some members play dual roles of investigators and REC members and submit their protocols to their institutional REC. It is standard practice that the member may not contribute to the discussion or vote on his/her protocol and this is adhered to on all RECs surveyed. However, the member often sits in on the discussion making it uncomfortable for colleagues to be completely honest and forthright about deficiencies that may exist in the submission. It would hence be important to implement the policy of having members leave the room for the entire duration of the discussion of their protocols.

Historically disadvantaged institutions require increased institutional support in establishing dedicated REC offices and staffing. Capacity development is also required.

4. All RECs must ensure that all protocols except those that qualify for expedited review are conducted at a full meeting of the committee.

B. Review System Structure

The current structure of the review system in South Africa given the current membership that is skewed in a scientific direction, could be enhanced in one of two ways:

1. At all institutions, separate RECs could be established for clinical trials review and for academic research review. This model already exists at one institution and works well. Each REC would then have fewer proposals to review and meeting duration would be significantly reduced thereby increasing the efficiency and quality of the review process. Faculty members could then be spread across the two RECs with no member sitting on both committees. Each REC would conduct both scientific and ethics review.

2. Two RECs could be created divided according to medical speciality. Each would then review both academic research and clinical trials research in the specific disciplines. This would enhance the scientific review of protocols within specific disciplines as expertise would exist on the REC and experience would grow with each specific discipline. Members would also become familiar with clinical trial as well as academic research. Each REC would conduct scientific and ethics review (personal communication – Dr L. Horn, REC Manager)

Conceptually the issue of 'scientific' review and 'ethics' review lends a broader perspective to the review system structure in South Africa.

All institutional RECs already have a double system of scientific review. This might be a good idea given the scientific complexity of clinical trials. However, if RECs were to be restructured to include more non-scientific members and fewer scientific members, a formal scientific review committee distinct from the REC might be a good idea. This structure has been suggested by the Institute of Medicine in the United States. They suggest a three-pronged review process of the science, the ethics and conflict of interest. Scientific review could be conducted by a separate committee, a sub-committee or by using outside experts. This would ensure that proposals that have scientific deficiencies do not reach the REC. However, for those that do reach the REC, some consideration could still be given to the scientific merit of the study as ethical and scientific review are often interdependent. The saving in time for the REC would result from a summary of the scientific adequacy being presented to them (Institute of Medicine, 2003: 77).

A dedicated Conflict of interest review process is also suggested which would be a very good idea in South Africa given the fact that all institutional RECs are dominated by affiliated members.

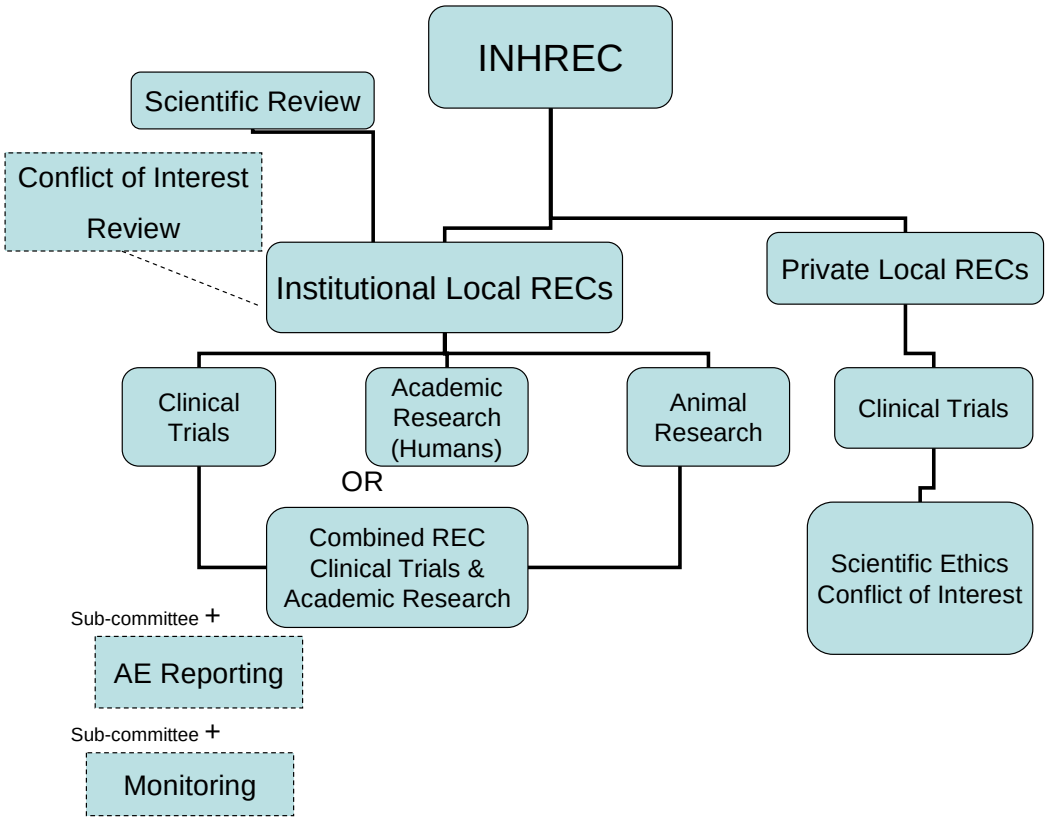
Further suggestions emerging from the empirical data include allocating distinct responsibility to sub-committees of the REC for adverse event reviews and monitoring.

Private RECs appear to be conducting all aspects of the review process together but could benefit from considerations of restructuring their systems to improve the review process. Given that some private RECs have a larger proportion of non-scientific than scientific members, they would benefit more from a distinct scientific review.

In South Africa, the INHREC would be the overarching body of both private and institutional RECs.

Figure 8 outlines a possible structure that the review system in South Africa could assume.

Figure 8: Ethics Review System Structure in South Africa



These models will be discussed in the REC network in South Africa till consensus is reached.

C. Administrative staff

All RECs require adequate administrative staff and achieving this requires institutional commitment. At a minimum, requirements are as follows:

1. an administrative manager
2. an administrative assistant
3. a secretary

4. a data capturer – if an electronic system is being used.

These staffing requirements must be met at all RECs in South Africa.

D. Infrastructure

All of the above staff members require office space. In addition, it is essential that adequate space is available for storage of files in keeping with FDA requirements such as fire proof, flood resistant storage systems with adequate temperature controls. It is the responsibility of all institutions to provide such infrastructure to ensure an efficient ethics review system.

E Training and Development

The Irensa training program sponsored by Fogarty International and located at the University of Cape Town offers a Diploma in Research Ethics. It is an excellent program and will in the long term contribute significantly to capacity development for ethics review in South Africa. However, it cannot meet the training needs of all members in the country. As a basic requirement all REC members reviewing clinical trials must attend a Good Clinical Practice (GCP) Training course. This in itself is insufficient, so on-going training programs must be attended. Some tertiary educational institutions in South Africa have established Bioethics units or departments. Each of these departments should have a mandate, and be provided with institutional support, to develop training programs tailored to meet the educational needs of REC members.

F. INHREC

This committee will become a statutory body in South Africa when the National Health Act is enforced later this year. It will play a crucial role in standardising the ethics review system in the country, in accreditation of RECs and in establishing curricula to meet the educational needs of REC members. However, it also has a crucial role to play in achieving equity

amongst institutions before implementing its accreditation criteria and prior to categorising RECs into level one and level two RECS.

G. Remuneration of REC members

A national policy must be established to ensure that all REC members are remunerated for their work. This is essential as most REC members conduct protocol reviews outside of their working hours. A fee should be established per meeting attended rather than per protocol reviewed. This fee can be extracted from the protocol review fee that is charged by most RECS.

8.3.2.2 Resolution Options for the Review Process

A. Delayed Review

The review process could be improved by:

- Separating the review of clinical trials and academic research
- Separating the scientific review from the ethics review.
- Increasing administrative staff
- Appointing a REC manager
- Employing an electronic data capture system
- Formulating clear policies to investigators so that complete applications are received in full and on time
- Allocating each protocol to two or three reviewers for detailed review and providing summaries to other members
- Allocating protocols to reviewers at least two-three weeks before the scheduled meeting
- Sending the committee's response to investigators electronically rather than via the postal system

B. Informed Consent Forms

If RECs want more comprehensive forms they need to be aware of the possibility of complicating the form. In addition readability should be improved rather than worsened. This can be attempted by objectively using a well established readability score. In addition, community representatives on the REC can double check the form for ease of understanding. There are also other issues that improve readability such as font size, use of bullets and spacing and emphasis of important issues. These need to be considered.

It is hence important that the most readable version of the patient information leaflet is translated, that the translation is checked by REC members familiar with the language and that a summary of the translated version is given to the participant.

C. Adverse Event Reporting

The definition of a serious adverse event must be revisited to include hospitalizations related to investigational products or trials procedures only.

The gross inefficiency in the system of adverse event reporting results in the concern for safety of human participants being lost in excessive paper trials. The monitoring of safety would be much better served by a data and safety monitoring board with biannual reports only to the REC. All multisite and international site adverse events should be submitted to a subcommittee of the NHREC where this function is fulfilled by dedicated staff. Here too, only related adverse events must be submitted.

D. Monitoring

All RECs must make provision for monitoring. Resources are better spent on monitoring than adverse event reporting systems. While it is not possible to monitor all research approved by the REC, a small percentage of trials can be monitored at random and high risk studies can be routinely monitored.

In view of recent deaths of research participants and the current climate of litigation in research, it is essential that all RECs, in developing and developed countries alike, employ a more vigilant system of review of “high risk” protocols.

Levine et al suggest a system of “special scrutiny” of high risk protocols using the following criteria:

1. Where research involves translating new scientific advances to studies in humans, especially when the intervention is novel, irreversible or both.
2 Where there is known or credible risk for significant harm
3 Where the protocol raises ethical questions about research design or implementation for which there is no consensus or there are conflicting or ambiguous guidelines.

8.3.2.3 Resolution Options to Improve Deliberation on Substantive Issues in the Review of Human Participant Research in South Africa

A. Standard of Care

Clear policy must be established regarding the standard of care in South Africa. Most RECs are adhering to the best available in South Africa. This can easily be justified as follows;

An international standard of care enshrined in the international guidelines on research ethics would only be possible to implement if research were clearly separated from treatment and regarded as a separate entity. As such international guidelines and principles would be applied to these research sites wherever in the world these existed. It would then also be necessary to implement article 30 of the Declaration of Helsinki – provision of the most effective medication identified by the study to the participants after the trial. This would mean that research, irrespective of where in the world it is conducted would be generalizable to developed world settings. This could

potentially lead to exploitation of developing world communities (where the drug would not be affordable for widespread use) for the benefit of developed countries.

Implementing a local standard of care as comparator would result in locally relevant research. Such research would provide answers to research questions relevant to developing world medicine such as the development of more cost-effective regimens.

By moving away from the concept of best available to highest attainable standard in the public health sector we are clarifying the issues further.

B. Post-Trial Treatment

The Declaration of Helsinki has to date focused on provision of effective treatment discovered during the conduct of the trial to participants after the trial. A broader conceptualization of the specification of the declaration could include provision of post-trial benefits rather than post-trial treatment. This could include infrastructure, capacity development, equipment or treatment, whichever is the most practical to achieve.

C. Remuneration

All benefits to participation in clinical trials must be considered. The payment of R50 per visit for regular trials is acceptable. Where great distances must be traveled to the trial site, payment should be calculated on a case-by-case basis. Payments for illness visits must be carefully considered as these can impact on the scientific validity of studies. Participant remuneration can be balanced against post-trial benefits. As post-trial benefits increase, participant remuneration can be reduced but not below a threshold level that is necessary to reimburse participants for all expenses incurred as a direct result of their participation in the trial.

D. Research Ethics Guidelines

There is a need for the research endeavour to be contextualised and for ethical decision-making to expand beyond didactic regulations and vague guidelines. It is highly desirable that a different approach using context, particularity and scepticism needs to be embraced incorporating an ethics of responsibility on the part of researchers and REC members alike.

Developing countries need to develop a voice to impact on international guidelines or develop local guidelines that override international guidelines with a Western paradigm. The developing world must be encouraged to contribute to ethical discourse with a focus on locally relevant and responsive questions, taking into account indigenous knowledge systems and cultural influences on the ethics of collaborative research. Different concepts of personhood need to be incorporated into the deliberation of ethical issues in developing communities but communities themselves must be given agency to participate in, contextualise and enhance the local review process. It is highly desirable that such initiatives are informed by empirical and conceptual research into the wide range of ethical issues in human research in South Africa.

South Africa needs to develop one guideline that is contextualized to our needs as a developing country and should be used by all RECs in the country. This will ensure uniformity of review. The current SA GCP guideline is currently being modified. This process must be thorough so that one comprehensive guideline exists.

Finally it must be appreciated that guidelines are important but require interpretation and should be viewed as aspirational documents rather than rules that are rigidly implemented in the absence of ethical reflection and argumentation

E. Review of HIV Vaccine Trials

It is imperative that all RECs in South Africa are exposed to a workshop that provides an update on both the science and the ethics of HIV vaccine research. This will empower all RECs to review protocols. It is important that the training reaches all RECs especially historically disadvantaged institutions as these institutions are located in areas of high HIV prevalence which are captive sites for phase three HIV vaccine trials.

In South Africa, the challenge of HIV vaccine trials has prompted “special scrutiny”.

The complexities involved in HIV vaccine research require a thorough and novel informed consent process which must be documented in the protocol. An appropriate test of comprehension should be conducted after the information giving but before authorization by participants. In addition, the informed consent process should be monitored by ethics committees who approve the protocol.

The recent experience of large phase three HIV vaccine trials in Thailand and the United States has highlighted the issue of placing large numbers of volunteers at risk of receiving an inefficient vaccine and precluding their participation in future trials of a more effective vaccine.

F. Informed Consent Process

Having fulfilled the legal requirements for the informed consent documents, it is essential that the ethical requirements of the informed consent process are fulfilled. These include more attention to the process rather than the forms. Investigators need to document the process that will be followed. It must be clarified when the detailed document will be made available to the participant to enable the participant to take the document home and read it at his or her leisure, allowing the involvement of family members in communities where family and spousal consent are culturally relevant. Sponsors should therefore

be encouraged to have the patient information leaflets available at the trial site at least two weeks before enrolment. Summaries should be given to participants initially followed by the comprehensive form. There should be documentation of other modalities that will be used to convey the trial information such as videos or flip-charts or models. A formal test of comprehension should be an essential part of the process and should occur prior to enrolment. Finally, empirical research in to the consent process needs to be encouraged in South Africa where a paucity of data exists.

8.4 Summary of Major Recommendations

8.4.1 National Association of Local RECs

It is strongly recommended that a National Association of RECs is constituted as a matter of urgency in South Africa. The mission of such an association should include the achievement of standardization of the ethics review process in South Africa to eliminate the wide range of variability that currently exists. The association should have its own standard operating procedures and should meet at least annually, preferably six monthly. One of its main functions should be aimed at achieving national consensus on the range of substantive research ethics issues relating to initial and continuing protocol review. It should also work towards achieving equity of all RECs in the country.

8.4.2 National Newsletter

Eliminating inconsistency in the review system in South Africa requires a national effort to form a communication network between geographically distant RECs. At most, local REC chairpersons will be able to meet annually. In the interim, a communication network is required to facilitate deliberation amongst the various REC members on a regular basis.

In this way, REC members can be encouraged to discuss and debate the challenges facing them. In an attempt to initiate this process, the chairperson

of the INHREC was approached to obtain support for the initiative. Thereafter, all chairpersons of the major RECs were contacted electronically and their support for the project was secured. In May 2004 the South African Research Ethics Committee (SAREC) Newsletter was launched. This is an electronic newsletter circulated on a quarterly basis to all REC members reviewing clinical trials in South Africa.

8.4.3 National Health Research Ethics Council (NHREC)

As soon as this body becomes a statutory entity in South Africa it will play a critical role in accreditation of local RECs. In addition it has an important role to play in promoting educational and training activities. Being directly associated with the Ministry of Health, it is also in a position to lobby for equity for all institutional RECs. In addition, there is a potential role in reviewing multicentre research and in safety monitoring.

8.4.4 National Research Ethics Guideline

South Africa desperately needs to commence a process of synthesis where the various guidelines are concerned. A single national guideline should be developed and implemented nationally.

8.4.5 Research Ethics Training and Development

There is an urgent need for widespread training of REC members, investigators and research participants. Curricula must be specified and training programs must be accredited. South Africa is fortunate to have two good programs fro research ethics training. However, investigator training, requires a great deal of attention. A wide range of GCP training courses are available in South Africa. None of these have been accredited and a lack of standardization of training requirements exists. Curricula reform and standardisation of training requirements must be specified.

8.4.6 Participant Advocacy

While RECs are charged with the responsibility of protecting research participants, it is being argued that agency of individuals, groups and communities needs to be recognized and strengthened. Expanding REC membership to include participants drawn from vulnerable communities is important and deserves serious attention in South Africa. The development of education programs in research for participants is also important.

8.4.7 Research Ethics Review System

RECs should decide on adopting one of two options for an effective review process:

i. If dual review of the science and the ethics of protocols is to continue, the scientific membership of RECs must be strengthened. This will require a pharmacologist and a statistician on every REC. Additionally a person skilled in literature review is essential

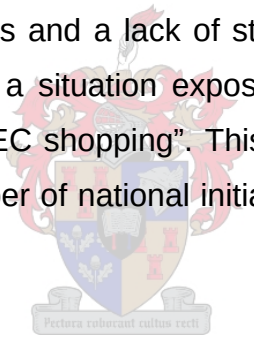
ii. If splitting the scientific and ethics review is to be considered, a distinct process must be set up for scientific and statistical review. Only protocols that have passed scientific review will be sent to the REC with a summary of the scientific review.

8.5 Commentary

This chapter reflects the major challenges facing the REC system in South Africa at the time of the survey. These challenges have been identified collectively from both the quantitative and qualitative research undertaken. The quantitative survey discussed in chapter six highlighted a number of inequities amongst RECs in South Africa at a national level. The qualitative interviews discussed in chapter seven illustrate the ethical challenges faced by RECs in South Africa as a result of global inequities in health care.

At a national level, the deficiencies outlined are extensive and have been addressed to different extents according to the magnitude of the problem. The main problems, however, relate to variability in structure and function of RECs. This variability is a function of the inequities in higher education which is a legacy of the apartheid system in South Africa. Institutional RECs at historically disadvantaged institutions are significantly under resourced compared to RECs at historically advantaged institutions. This impacts on training and capacity development of REC members and investigators. This, in turn, impacts on the amount of contract research that is conducted and reviewed at these institutions. Such inequities must be addressed at a political and institutional level with the implementation of redress procedures to alleviate the imbalances.

At a national level, another major deficiency relates to the lack of communication between RECs and a lack of standardization and consensus on a variety of issues. Such a situation exposes vulnerabilities in the REC system and lends itself to "REC shopping". This in turn compromises human participant protection. A number of national initiatives have been described to achieve standardization.



At an international level, inequity in health care services exists between developed and developing countries. This impacts on multinational research between well resourced sponsor countries and resource depleted host countries. The qualitative research component has reflected the complex of substantive challenges encountered in research ethics in South Africa largely as a result of health care inequities. This is indicative of the interdependence of health care and health research as complimentary public goods. Most international research ethics guidelines draw a distinction between health care and research. The only guideline that relates research and health care as a "morally praiseworthy" endeavour, is the CIOMS guideline and this has been discussed at length in the context of HIV vaccine research.

Responsibility of researchers with respect to health care provision ranges from no responsibility to partial responsibility. The National Institutes of Health is a perfect example of the former option. This institution provides funding for

research expenses only. Even compensation for trial related injury is not included. Treatment issues fall squarely outside the domain of the research project. On the other hand, some sponsors demonstrate partial treatment obligations. This includes some oncology and HIV related research where compassionate treatment is provided beyond the scope of the trial.
It is evident that the interdependent relationship between research and health care is being ignored. To do so creates ethical challenges to developing countries that remain perpetually unresolved. It is thus essential to revisit this concept in an international forum.

Ultimately, if the national and international challenges described are addressed and REC function is raised to an acceptable and efficient level in South Africa, will this guarantee human participant protection? The next chapter examines the role played by investigators in the review process and their contribution to participant protection.

Chapter 9

Participant Protection – Who's Responsibility?

9.1. Introduction

If the assumption is made that an efficient ethical review system can be established, is this adequate to afford human participants protection? The Bezwoda case study has shown us that even in the presence of robust ethical review, participant protection can be compromised by individual researchers who evade the system of ethical review or by researchers who deviate from protocols that have already been approved by RECs. What went wrong in the Bezwoda case? Did the REC fail to protect the participants or did the investigator do so?

9.2. The Bezwoda Case (Weiss, 2000: 999-1003)

Werner Bezwoda was professor of Haematology and Oncology at the University of Witwatersrand since 1992. In 1995 he announced that high-dose chemotherapy with bone-marrow transplantation increased survival in patients with metastatic breast cancer. In May 1999, he presented the results of a second trial on high dose therapy at the American Society of Oncology meeting. Again he concluded that women receiving high dose treatment had longer survival rates than women on normal dose therapy. Four other papers presented at that conference by other scientists failed to show a benefit.

A team approved by the United States (US) National Cancer Institute visited South Africa in 2000 to audit Bezwoda's results in preparation for the conduct of large-scale confirmatory trials in the United States (Farham, 2000: 553). Findings:

1. Bezwoda presented data on 154 patients at the conference – only 151 patients were listed in the enrolment register. Records for 58 patients were produced.
2. There were discrepancies in eligibility of patients including age, tumour category and number of axillary nodes involved. Only 20 of the 58 patients met eligibility criteria.
3. The presentation indicated that 36% of the study population were white women. Only 7% were actually white. The majority of patients were black women.
4. There were discrepancies in dosages of drugs used. Patients in the control group had not been given the treatment specified in the presentation.
5. Deaths in the high dose treatment group were under stated.

As a result of the above findings, the study was invalidated (Weiss, 2000: 999-1003).

On 31 January 2000, Peter Cleaton Jones – Chairperson of the REC at Wits, received a letter from Bezwoda in which he acknowledged scientific misconduct.

In a letter to the president of the American Society of Clinical Oncologists on 4 February 2000, Peter Cleaton-Jones indicated that:

> *…there have been serious ethical violations as well as misconduct and…the study is discredited and must not be used as a basis for further trials.*
>
> (Farham, 2000: 553)

Bezwoda claimed that he had not submitted his protocol to the REC at Wits as he regarded the study as being retrospective.

9.3. The Poisson Case Study (Weijer, 1995: 1973-1980)

Like Bezwoda, Dr Possion was also involved in a breast cancer study at St Luc Hospital, Montreal, Canada between 1977 and 1990. This was the largest and most prestigious breast cancer study in the world where two different modalities of therapy were being compared – radical mastectomy as opposed to lumpectomy. Due to the dilemma created in patients by the offer of radical mastectomy, recruitment was slow. His site, however, recruited 19% of all patients on the study. As a result, attention was drawn to his site. A number of violations were detected at his site. These included falsifying data, pressurising patients to participate, subjecting patients to unnecessary risk by placing them on cardiotoxic chemotherapy regimens even though he was aware of pre-existing cardiac disease in these patients. He had falsified data on 99 of the 1511 patients he had enrolled at his site. After results of this study were published in an international journal, all sites had to be re-audited and results re-published excluding his results. Fortunately, this did not impact on the overall results of the study.

Commentary on Bezwoda and Poisson

While these appear to be two isolated cases of research fraud, the extent of harm caused has far reaching consequences. Firstly there is the actual maleficence exhibited towards patients directly involved in the trial. In the second place, there is a level of maleficence towards potential patients who would have been recruited into larger trials to confirm Bezwoda's initial findings. In both the Poisson and Bezwoda cases, data presented was initially included in the body of knowledge used by other clinicians, surgeons and oncologists in the choosing a treatment modality for cancer patients based on evidence based medicine principles. Both studies had been published in international journals.

Furthermore, the erosion in public trust caused by these two events is immeasurable. One of the major reasons patients participate in research is based on the relationship of trust between doctor and patient. Commenting on this a gynaecologist based in Kenya had the following to say:

> *I would like to emphasize that most patients consent to nearly anything if asked by a trusted authority – in this case a medical person who is supposed to know what is best for the patient.*
>
> (Temmerman, 1992: 1102).

Researchers are under enormous pressure to conduct research and produce results. Often, their careers are linked to grants which depend on an ability to convince a sufficiently large number of participants to enroll in research projects. There is also a need to publish in order apply for promotion and apply for continued financial support. Research, as such, is conducted not only to produce generalizable knowledge but also to earn a salary and career advancement. It is therefore not surprising when researchers look for "short cuts to attractive answers" and this clouds the investigator's judgement about what is and is not appropriate What both these cases demonstrate is that in the absence of researcher integrity and trustworthiness, even well functioning RECs cannot protect participants. In the absence of RECs, the individual researcher and his or her integrity remains a crucial factor. (Altman, 1985:21).

It is claimed that "the primary virtue in health care is integrity" (Beauchamp, 2001: 35). Moral integrity entails living and acting in accordance with moral and ethical norms. The central element of this virtue is the consistent application of a set of values. Integrity demands a willingness to make sacrifices in order to defend these values. Integrity demands the acknowledgement that there are more important goals and values than the promotion of self interest (Gilligan 1997: 6-14). It is evident that both investigators had not established a certain moral threshold beyond which they were not willing to compromise their values and principles. Both cases demonstrate a serious lack of integrity.

Prior to 1966, each individual investigator bore responsibility for protecting the rights of human subjects participating in research (Taub, 1986: 7). The advent of RECs from 1966 onwards transferred a greater share of this responsibility from individual investigators to the committees. Responsibility shifted from a virtue based system of protection to a principle based system of REC protection. As early as 1969, Jonas described the researcher as "an interested party (with vested interests, indeed, not purely in the public good, but in the scientific enterprise as such, in "his" project, and even in his career)" and this makes him also "suspect". This precarious and conflicted position of the researcher "calls for particular controls by the research community and by public authority" (Jonas, 1969: 120). Such controls generally mitigate the problem but do not eliminate the problem completely.

Research fraud has highlighted the importance of a return to virtue ethics in addition to a principle based review system. Most guidelines have emphasized medical and scientific training of investigators. Very little mention has been made regarding researcher integrity:

> *The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.*
>
> (The Nuremberg Code, 1996)

The Declaration of Helsinki (2000)

> *Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent…*

(World Medical Association, 2000)

Council for International Organisations of Medical Sciences

> *The responsible investigator is appropriately qualified and experience, and commands facilities to ensure that all aspects of the work will be undertaken with due discretion and precaution to protect the safety of the subjects.*
>
> (CIOMS, 1993)

ICH GCP:

> *Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective tasks*
>
> (International Conference on Harmonisation Good Clinical Practice: Consolidated Guideline, 1997)

The earlier guidelines (Nuremberg and Helsinki) stress scientific qualifications of the investigator. CIOMS alludes to participant protection in addition. ICH-GCP specifies that the research team should be trained, not just the investigator and GCP encompasses both scientific training and the ethical issues inherent in participant protection.

In South Africa, the regulatory agency, The Medicines Control Council has declared GCP training compulsory for all clinical investigators.

Conventional GCP courses focus on rules and procedures. This is inadequate to foster a commitment to the conduct of ethical research. Attention must be focused on GCP curricula in South Africa to complement rule based teaching with a strong research ethics component including the importance of scientific integrity.

Commentators in current literature are highlighting the importance of investigator responsibility. Hence both an ethics of responsibility and virtue ethics needs to be revisited where investigators are concerned. A return to the practice of self-experimentation might also encourage a higher level of investigator responsibility and a deeper level of commitment to participant protection in the conduct of clinical trials.

> *It is not enough to ask society for unquestioning trust, nor can it be assumed that scientists are different from other human beings and totally incapable of error, deceit, misrepresentation or bias. The scientific community must be vigilant for this, since nothing less that the viability of the biomedical enterprise is at stake.*
>
> (Schwarz R.P.Quoted in Weijer et al, 1995: 1979)

Chapter 10

Conclusion

The recent crisis described in research ethics review systems in the United States have dominated the literature since 1996. This must be seen in the context of an extensive review system currently in existence in the United States, which has approximately 4000 to 6000 IRBs all operating at a local level.

While many similar concerns are shared in South Africa, the scope of the problem is distinctly different. At present we have approximately 20 RECs in total, some of whom are currently undergoing mergers as a result of institutional changes as part of a rationalization process in higher education in the country. In many respects, there is no sense of crisis where ethics review is concerned in South Africa. There are extensive deficiencies in the system, but they are more contained and can be addressed.

RECs in South Africa, in common with their equivalents globally, are overwhelmed with administrative duties, bureaucratic procedures and paperwork. This impacts negatively on their ability to engage in the substantive ethical issues underlying human participant research. It is hence imperative that all procedural functions that do not adequately contribute to participant protection are rationalized.

While some problems encountered in South Africa are similar to those challenging developed countries, there are problems that are unique to developing countries. This is related to the complex of reasons that motivate the conduct of research in a developing country as compared to a developed country. A host of questionable reasons are forwarded for conducting research in Africa:

> *Lower costs, lower risks of litigation, less stringent ethical review, the availability of populations prepared to co-operate with almost any study that appears curative in nature, anticipated under-reporting of side-effects because of low consumer awareness, the desire for personal advancement, and the desire to create new markets for pharmaceutical agent and other products*
>
> (quoted in Ijsselmuiden, 1992: 833)

While all multinational research is not underscored by such motivations, it remains an important priority to establish a robust ethical review system to ensure the protection of vulnerable communities.

In establishing a robust ethical review system, a number of national and international factors have been identified. At a national level, equity must be established amongst the various institutions. In addition, standardization must be achieved via a national association and a national communication network. Given the current REC membership in terms of professional representation and the growing demands in terms of scientific review, the ethics review system as a whole must be revisited. As the non-scientific and community representation increases, it will become necessary to consider adopting a distinct scientific review process that is not repeated at the level of the ethics committee. Distinct scientific review that precedes ethics committee review is being promoted as an important new trend in the review of research abroad. A similar measure in South Africa will represent a major paradigm shift for ethics review locally, and will be met with enormous resistance. In the long term, however, it may be a necessary and serious consideration for South Africa.

South Africa is home to millions of vulnerable communities – so termed for socio-economic reasons but also as a result of educational disadvantage.
As a result, RECs are overly but perhaps unavoidably concerned with informed consent at the peril of other important components of the review process like the relevance of the research, scientific validity and the risk-benefit ratio, inter alia. Informed consent documentation as well as the informed consent process must be considerably amended to accommodate

the special needs of participants in developing countries. At the same time, more emphasis must be placed on reviewing research projects submitted to RECs in the context of research priorities that exist in South Africa.

The interview data in this study clearly shows that RECs in South Africa are operating from a position of compromise in conducting their function of research participant protection. They have one of two options at present – maintain a position of compromise and retain the research industry in the country or set stricter criteria for sponsors and the pharmaceutical industry who wish to conduct research in South Africa and risk losing research projects. Given the global inequities in health care, research in a developing country must of necessity be viewed as a means to reducing such inequities. It has been established by the 10/90 report that only 10% of all available research funding is spent on 90% of the world's burden of disease – most of which exists in developing countries. The implication of this data means that a significant proportion of research that is conducted in South Africa and other developing countries is intended to benefit populations in developed countries. How then can the principle of justice be fulfilled – how do the populations who bear the burdens and risks of research benefit from such research? It can be argued that the concept of post-trial benefit presents a unique and valid opportunity to increase the benefits to populations being researched. Improvements in infrastructure secured in this way will contribute to improved health care for communities and for other research projects.

At an international level, a new conceptual framework must be created to incorporate research and health care in a complimentary and interdependent relationship. Such a paradigm shift would place obligations on sponsors and researchers to contribute to health care in developing countries in imaginative ways. Such contributions will not only elevate standards of primary health care in developing countries, they will also create robust referral systems for co-morbid and non-related illness arising in a wide spectrum of research conducted in developing countries. This will result in standards in health care and research progressively and consistently being raised. A paradigm shift of

this nature will be difficult to accomplish at a global level but remains a strong recommendation of this study.

Much has been written about the disparities in health care between the developed north and the developing south. One way of narrowing this gap involves inculcating a culture of global interdependence. This in itself is, however, insufficient as such a culture must evolve in tandem with institutional and governmental commitment to improving health care and research participant protection.

It is imperative that the ethics review system in South Africa is strengthened and empowered to negotiate with sponsors from a position of strength. Restructuring of REC membership composition to reflect the real diversity of South African society generally, but particularly in respect of representation of research participant communities themselves, must be addressed urgently.

While uncertainty has been raised regarding the effectiveness of RECs in protecting participants' rights as a result of recent research related deaths, this must be viewed in context. Ethics committee review, in spite of all its challenges and weaknesses, does protect subjects and promotes ethical research in the vast majority of cases. The occasional disasters are not wholly the fault of RECs but rather a combination of factors including investigator responsibility and culpability. This has been borne out in the interrogation of the deaths of Nicole Wan, Jesse Gelsinger and Ellen Roche. Protection of participants cannot be delegated to the REC alone. It is a combined effort of all members of the research team that results in such participant protection. Hence the training and educational efforts must include REC members, members of the research team and participants.

In 1969 Jonas referred to the "gratuitous" nature of the research endeavour that makes it imperative to grant the greatest respect, freedom and protection to human participants. Now, in the 21st century, we are being reminded that "Conducting research with human participants is a privilege granted by willing volunteers" (Institute of Medicine, 2003: 44). Al members of the research

team must be made acutely aware of this and protection of human participants must be built into every step of the research process.

There are widespread challenges to ethical review in South Africa but these challenges are not insurmountable. REC function in South Africa can certainly be enhanced. The recommendations outlined in this dissertation as well as the endeavours launched as a result of the empirical work in this dissertation are an attempt to do just that. The combined efforts of the various training programs in the country, the INHREC, the electronic communication system and the annual meeting of REC Chairs are positive and hopeful attempts at reconstruction and growth.

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ADDENDUM:

1. **Interview Guide**

2. **Questionnaire**

3. **Table 1 : Composition of Major RECS in SA (race & gender)**

4. **Table 2 : REC membership – vocation**

5. **Table 3 : Review Procedures of RECs in SA, 2003**

INTERVIEW GUIDE:

An outline of themes to be covered: The themes for the semi-structured interview to be held with the chairperson of each committee are as follows:

1. How long have you served on the REC?
   How long have you been chair/Vice-chair?

2. What has been your major challenge as chair of your ethics committee?

3. Are you satisfied with the constitution of your committee - gender/race/multidisciplinary nature/lay or community representation?
   Depending on the response - this can be elaborated with special focus on lay representation on RECs in SA.
   How do you deal with situations where a conflict of interest arises with one of your ethics committee members ?

4. Informed consent – what do you think about the length of documents? Are translations into ethnic languages appropriate? Is there expertise on the REC to evaluate ethnic translations? Do you have a system in place to objectively assess readability of informed consent forms? Do you request a summary of the informed consent form or an outline of the process of IC?
   Who should take informed consent – dependent relationship of investigator?
   Is there a template available for the Patient Information Leaflet?

5. Remuneration
   - food/transport
   - time off work
   - amount
   - gifts

6. Is there special emphasis placed on the justification of placebo controlled trials?
What is the policy of the REC?
Is the DOH reasonable/too idealistic in this regard?
Which version of DOH is used 1996 or 2000?
Do you think the DOH is applicable in SA?

When equivalence trials are planned, is there expertise on the committee e.g. a statistician to ensure that sample size is adequate?

7. Are there specific requirements for investigators to make provision for treatment for participants after the trial? Should this be an integral part of the protocol? Do you think that such provision of post trial treatment would make the risk-benefit ratio more acceptable to patients? Or will research participants be unduly favoured especially in SA where there is no treatment in the public sector for HIV/AIDS, for example?

8. Do you think that a 2 tier system of ethical review would be a good idea - scientific review by an expert panel of scientists, statisticians etc and ethical review of scientifically valid protocols by a multidisciplinary team of people including community representatives?

9. Would you like to audit research after studies have been approved by the REC? If no, what are the obstacles to the audit process?

10. What opportunities are there for training and development of REC members in ethical review of research? What would you like to see in this regard?

11. Do you specify GCP training for investigators?

12. Does your REC have a policy in place to handle submissions re HIV Vaccine Trials?

13. When dual review of protocols is required, do local committees feel pressurised to accept projects that have already been approved abroad or by developed countries?

14. How do you see the NHREC functioning in SA?

15. Adverse Event Reporting
    - Whose responsibility – sponsor (SAGCP) or investigator.
    - system of reporting

16. Which ethical guidelines do your ethics committee abide by and advocate – SAGCP, ICH-GCP, DOH, MRC, CIOMS ?

QUESTIONNAIRE:

A. DEMOGRAPHIC INFORMATION:

1.
INSTITUTION:_____

2. NAME OF COMMITTEE: _____
3. NAME OF CHAIRPERSON: _____
4. DATE OF ESTABLISHMENT: _____

B. COMPOSITION:

1. NUMBER OF MEMBERS: _____

2. GENDER:
   MALE_____FEMALE_____

3. RACIAL REPRESENTATION:

   BLACK_____WHITE_____

4. MEMBER PROFILES:

SCIENTIST:_____
CLINICIAN:_____
STATISTICIAN/EPIDEMIOLOGIST:_____
NURSING REP_____
PHARMACOLOGIST_____
LAWYER_____
ETHICIST_____
COMMUNITY REP_____
MEMBER INDEPENDENT OF INSTITUTION_____

5. HOW ARE MEMBERS APPOINTED?_
   consensus_____majority vote_____direct appointment_____

6. HOW LONG DO THEY SERVE ON THE COMMITTEE? _____

7. ARE THERE DISQUALIFICATION PROCEDURES?_____

8. WHAT IS THE RESIGNATION PROCEDURE? _____

9. ARE MEMBERS REMUNERATED? _____

D. OPERATING PROCEDURES:

1. MEETING FREQUENCY: _____

2. QUORUM: _____

3. DO ALL MEMBERS RECEIVE PROTOCOL DOCUMENTS?_____

4. ARE STANDARDISED APPLICATION FORMS USED?_____

5. IS EACH PROTOCOL DISCUSSED AT THE MEETING?_____

6. IS AGREEMENT REACHED BY CONSENSUS OR VOTING?_____

7. NUMBER OF PROTOCOLS REVIEWED PER MEETING: _____

   NEW PROTOCOLS _____

   AMENDMENTS _____

8. ANNUAL WORKLOAD – 2002:
   protocols received =
   number reviewed =
   number accepted =
   number accepted with suggestions for amendment =
   number rejected =

9. TIME DELAYS:
   -submission = _____ to approval = _____

10. CHARGE PER REVIEW OF PROTOCOL_____

D. INFRASTRUCTURE

1. ARE SPECIFIC OFFICES AVAILABLE FOR RECORD-KEEPING & MEETINGS? _____

2. IS SUPPORT STAFF EMPLOYED FOR ADMINISTRATION?_____

E. TRAINING & DEVELOPMENT

1. How many members have received training in research ethics?_____

2. Is funding available to train existing and new REC members?_____

Table 1. Description of Research Ethics Committees in South Africa, 2003

Committee number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Institutional (I) or Private (P)	P	P	P	I	I	I	I	I	I	I	I	I
Total number of members	7	8	11	29	13	11	12	27	20	16	19	11
Percent of male members	57	50	64	59	46	82	75	63	65	75	63	55
Percent of white members	86	50	64	76	54	82	42	85	40	75	84	10
Percent of members trained in research ethics	86	50	27	100	38	18	0	100	50	79	26	18
Number of independent members	7	1	6	3	13	1	0	2	2	3	2	0
Duration of committee membership (in years; U: unlimited duration)	(U)	(U)	3	(U)	5	3	3	3	2	2	(U)	(U)

Table 2. Professional composition of Research Ethics Committees in South Africa, 2003

Committee number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Total number of members	7	8	11	29	13	11	12	27	20	16	19	11
Composition of committee [N(%)]												
Clinician or scientist	1 (14)	3 (38)	4 (36)	18 (62)	7 (54)	6 (55)	10 (83)	19 (70)	14 (70)	12 (75)	11 (58)	6 (55)
Statistician or epidemiologist	1 (14)	0	0	0	1 (8)	0	0	0	0	0	1 (5)	0
Nurse	0	1 (13)	1 (9)	2 (7)	0	1 (9)	1 (8)	1 (4)	1 (5)	1 (6)	2 (11)	0
Allied Health professional	0	1 (13)	1 (9)	3 (10)	0	1 (9)	0	0	1 (5)	0	0	1 (9)
Pharmacist	2 (29)	1 (13)	0	0	0	0	0	2 (7)	0	1 (6)	2 (11)	0
Lawyer	2 (29)	1 (13)	0	1 (3)	2 (15)	1 (9)	0	1 (4)	1 (5)	0	1 (5)	1 (9)
Ethicist	0	0	2 (18)	3 (10)	1 (8)	0	1 (8)	1 (4)	1 (5)	1 (6)	0	1 (9)
Community representative	1 (14)	0	2 (18)	1 (3)	1 (8)	1 (9)	0	2 (7)	2 (10)	0	1 (5)	1 (9)
Theologian	0	1 (13)	1 (9)	1 (3)	1 (8)	1 (9)	0	1 (4)	0	1 (6)	1 (5)	1 (9)

Note that percentages may sum to slightly more or less than 100 due to rounding.

Table 3. Review procedures of Research Ethics Committees in South Africa, 2003

Committee number	1	2	3	4	5	6	7	8	9	10	11	12
Meeting frequency (1)	F	M	Q	M	Q	M	M	M	M	M	M	Q
Percentage of membership required for quorum	71	88	45	17	62	64	58	41	55	31	37	73
Average number of reviewers per protocol	7	2	11	2	13	2	3	3	10	1	2	11
Each protocol discussed at each meeting?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Estimated number of protocols reviewed per meeting	7.5	6.5	7	15	9	17.5	15	30	13	7	15	3.5
Number of protocols reviewed during 2002	140	70	30	80	31	241	100	357	181	61	300	30
Estimated delay from protocol submission to approval (weeks)	1.5	4	7	4	6	2	2	4	9	4	4	10
Charge for protocol review (Rand) (2)	5500	5000	0	4845	0	2000	0	4000	4500	4000	3000	0
Dedicated office space	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N
Support staff (3)	1.5	1	0	3	0.5	1	1	3	1	3	1.5	0.5

1. F: Fortnightly; M: Monthly; Q: Quarterly

2. The current exchange rate is approximately 1 South African Rand = 7.0 US Dollars

3. Staffing is estimated in full-time equivalents (FTE), where a full-time worker contributes one FTE and a part-time worker contributes 0.5 FTE

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