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Title: A Study of Vulnerability in Health Research

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Declaration

This thesis represents my own original work, produced with supervisory assistance. All the relevant sources that I have used during the course of writing have been fully credited and acknowledged. This thesis has not been submitted for any other academic or examination purposes at this or any other university.

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Publications Arising From This Study

Dhai A. The research ethics evolution: From Nuremberg to Helsinki. *SAMJ* 2014;

104(3): 178-180.

Dhai A. The Evolution of Research Ethics in South Africa. *WMJ. (Awaiting publication).*

Dedication

In memory of my late parents Khatija and Mohammed Dhai whose nurturing, love and unstinting support from childhood to early adulthood laid the foundation for this PHD.

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Abstract

Vulnerability, an abstract concept in health research, has concrete effects both on those who are labelled vulnerable and those who are not. It has been used increasingly as an exclusion criterion in research but has been the least examined from an ethical perspective despite being linked in most research ethics guidelines and codes, both international and local, to questions of justice and informed consent. Neither has there been an agreed upon standard for identifying and responding to vulnerability. The guidelines, despite categorizing vulnerable research participants into groups and subpopulations, do not offer a robust and comprehensive definition of vulnerability.

The study aimed to analyse the notion of vulnerability in health research with a view to constructing an operational definition of the concept which would assist researchers and RECs to identify and understand vulnerabilities and strategize on maximizing protections for the participants without obstructing essential research.

Using normative, metaethical and historical methods of bioethical inquiry, this research has shown that the categorization of people into vulnerable groups is not justified as it could result in obstructing research, and paternalistically excluding participants from necessary research, or inadequately protecting participants enrolled in research. The study has resulted in an appropriate operational definition of vulnerability and a Vulnerability Assessment Scale being developed to assist Research Ethics Committees and researchers identify participants with vulnerabilities and develop focused safeguards for their protections. The concept of vulnerability in health research is no longer nebulous and vague and its definition is therefore no longer an unanswered question.

ACRONYMS

AMA: American Medical Association

ASSAf: Academy of Sciences of South Africa

BMA: British Medical Association

CIOMS : International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences

DoH : Declaration of Helsinki

CSIR : Council for Scientific and Industrial Research

ICH-GCP: ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6(R1)

IRB : Institutional Review Board

REC : Research Ethics Committee

MASA : Medical Association of South Africa

NHA : National Health Act

SA : South Africa

SAMA : South African Medical Association

SAMRC : South African Medical Research Council

SA Ethics Guidelines : Ethics in Health Research: Principles, Structures and Processes - the South African Department of Health Guidelines

SA GCP: Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa

SAIMR : South African Institute for Medical Research

UNESCO : United Nations Educational, Scientific and Cultural Organization

US: United States

WMA: World Medical Association

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Chapter 1: A STUDY OF VULNERABILITY IN HEALTH RESEARCH: BACKGROUND

1.1: INTRODUCTION

Vulnerability is used and referred to increasingly as a criterion in health research. It is, however, a concept that is perhaps the least examined from an ethical perspective in the context of research ethics. It is linked in most research ethics guidelines and codes, both international and local, to questions of justice in selection of participants, limitations of capacity to provide informed consent and unequal relationships between disadvantaged groups and researchers and sponsors. Because so many groups are now considered to be vulnerable in the context of clinical research, some commentators have expressed a concern that the concept has become too broad and hence lost its gravity and weighting[1]. In this chapter I briefly introduce the concept of vulnerability in health research and argue for the need to do this study. I conclude this chapter with an outline of the remainder of the thesis.

1.2 LITERATURE SURVEY

This section provides a brief overview of the issues associated with the notion of vulnerability in health research. These will be expanded upon in the chapters that follow.

1.2(A) Defining Vulnerability

It is generally accepted that one of the principal tasks of ethics in research is that of protecting participants from exploitation and other forms of harm[2]. According to the South African Concise Oxford Dictionary[3] the term "vulnerable" originated from the Latin term *"vulnerare"*, which means *"to wound"*. The meaning of vulnerable as offered in the dictionary is *"exposed to being attacked or harmed, either physically or emotionally"*. If one is to extrapolate from the dictionary definition of vulnerable, it would follow that ethics in

research is about protecting vulnerable people against harm and that all those who participate in research, if we take the definition above, are vulnerable.

Because research is a systematic set of activities to obtain certain answers to questions, the uncertainty principle is integral to research. Health research will involve uncertainty about the effects of interventions and outcomes on research participants. Hence, at all times there is the risk that participants involved in health research could be harmed. While the concept of vulnerability has developed broadly, vulnerability *per se* may narrow the focus of ethics in research, by diverting attention from important features of research like the institutional, social or economic environments where contexts in themselves can result in harms to participants[1].

1.2(B) Historical Perspective

Although the concept of vulnerability has not been adequately researched, it is not new. Vulnerability was referred to in 1978 in the Belmont Report[4], in the Declaration of Helsinki (DoH) in 2000[5] and the 2002 version of the International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences (CIOMS)[6]. The 2008 version of the DoH makes specific reference to vulnerability in two sections, articles 9 and 17[7], and the 2013[8] version in articles 19 and 20[b].

Exploitation of vulnerable groups and populations has transpired in health research for over a century[9]. For example, in 1897, Giuseppe Saranelli, an Italian researcher, injected several vulnerable subjects with the organism that he thought caused yellow fever with resultant morbidity and mortality, which is a scientific way of saying sickness and death. As news of

this spread around the world, scientists and researchers were harshly criticised for treating human beings as guinea pigs[10].

In the 1960s the works of Beecher from the United States (US) exposed much of the world to exploitation in research that was taking place in the scientific community. Beecher published an article highlighting 22 studies that were published in respectable journals and had been conducted unethically. Beecher's article showed that there were many ethical violations taking place in research, even among prominent researchers[11]. This was followed by widespread discussion in the US of wrongful research conducted there. These studies included the Willowbrook State School hepatitis study in children[12], the Brooklyn Jewish Chronic Disease Hospital cancer research in elderly debilitated and indigent patients[13], and the Tuskegee Syphilis study in poor African-American men[14]. The Nazi war atrocities involving harmful and dangerous research on prisoners are a further example[15]. Africa has not been spared either. Africa as a continent has large populations living in extremely poor conditions, which in itself is a form of vulnerability. Literacy is low or non-existent. Health care in these contexts is, in the main, minimal with the majority of Africans accepting authority without question[16]. It is therefore not surprising that as the demands for more stringency in research increased over the past 20-30 years as Western country researchers spread into the developing world to sites with medically naive populations, several incidents of unethical research involving vulnerable populations have been reported[17-26]. Hence, the need for reflection and examination of vulnerabilities in health research has been present for many decades.

1.2(C) Human Vulnerability

Being human, by implication, denotes vulnerability, with all humans beings exposed at some stage or other to the risk of suffering harm against their personal integrity, be it physical, emotional, psychological and / or spiritual[27]. Hence, human vulnerability is intrinsically connected to the essential notion of personal integrity and could be perceived as an inescapable dimension of human life and an integral component in the shaping of human relationships. Human vulnerability acknowledges that at some point, all human beings may lack the ability to protect themselves from harms which at times may even be inflicted by other human beings. While humankind as such is vulnerable, there are individuals, groups and situations for whom greater attention needs to be paid[27].

1.2(D) Approaches to Describing Vulnerability in Health Research

A number of different approaches to describing vulnerability in health research have been proposed. The United Nations Educational, Scientific and Cultural Organization (UNESCO) draft document on the subject[27] highlights two fundamental categories in respect to "special vulnerabilities" in the context of health research as being special disabilities, disease and limitations imposed by the stages of human life and social, political and environmental determinants. The document further states that vulnerability should be viewed with regard to its nature, cause and context, and possible remedies are suggested. Ballantyne and Rogers provide a conceptual definition that generates a theoretical framework for considering different sources of vulnerability[28]. They further elucidate that while vulnerability exists as a broad spectrum rather than a simple present / absent dichotomy, it is still possible to identify individuals / groups that are particularly vulnerable in research. They draw a distinction between two sources of vulnerability at a conceptual

level: extrinsic, as a result of external circumstances, e.g., social, and intrinsic, which is due to internal qualities of individuals themselves, e.g., medical illnesses, mental disabilities and extremes of age. Both these types raise complex ethical issues in the context of health research and while often appearing independently, may coexist and are sometimes interrelated[28]. Kipnis proposes a bioethical taxonomy when considering vulnerability in clinical research in which six types of vulnerability are distinguished by a positive response to a unique question.[29]. They are cognitive, juridic, deferential, medical, allocational and infrastructural. Other commentators include a seventh type, that of social vulnerability[27]. Robert Levine classifies vulnerability on the basis of risk of harms and the reasons why these participants are vulnerable[30]. While the National Health Act (NHA)[31] in South Africa (SA) refers to vulnerability when discussing research priorities for the country and local guideline documents[32,33] make mention of vulnerabilities in research, there is no guiding framework to assist the researcher and Research Ethics Committees (RECs) in recognising vulnerability, its nature, type and context with a view to offering recommendations on strategies for protection against exploitation. Moreover, the South African Department of Health Guidelines, "Ethics in Health Research, Principles, Structures and Processes"[32] (SA Ethics Guidelines) replaces "vulnerable" with "subpopulations requiring added protections in health research". However, several shortcomings of the subpopulation focus have been highlighted[29] and while there may seem to be something common to these disparate groups, it is not really apparent what that characteristic or set of characteristics is.

1.2(E) Vulnerability, Exploitation, Risk and Harm

That vulnerability is associated with a strong potential for exploitation must be highlighted. The fact that research participants require protection from exploitation underscores a highly

disturbing issue in this context: that the researcher, sponsor and others may see an opportunity to capitalize and take unfair advantage of the situation to the individual's or group's detriment[34]; hence the concept of exploitation. It is stated that this concept is also complex and at times ambiguous[34]. Resnik has proposed three basic elements, at least one of which is requisite for exploitation to be present: harm, disrespect and injustice[35]. In practice, however, these elements often overlap and interact. At an operational level, exploitation can result when, despite the risk of harm being recognised, the risky action is embarked upon with resultant harms. Weijer describes four categories of risk in research[36]. These are exacerbated where participants are vulnerable. The risk categories are physical, psychological, social and economic. While Weijer does not consider harm categories, because harms follow risks, harm categories should be in line with risk categories.

1.2(F) Protectionism

Protectionism is a well-entrenched principle in the ethics of research. Controversy does not lie in the existence of this principle but in its application, especially in light of several nuanced interpretations of the principle. In addition, alternative perspectives on protectionism have been offered[9]. Moreno distinguishes three versions of protectionism, weak, moderate and strong, framed in terms of how much discretion an investigator should be allowed when it comes to managing human participants in research. The critical issues in his analysis are the relationship among protections, the demands of science and the manner in which the conduct of researchers should be monitored and controlled.

1.2(G) Vulnerability, Personal Integrity, Human Dignity and Ethical Principles

The notion of vulnerability is closely linked with the notion of personal integrity. Where participants are vulnerable, there is potential for their autonomy to be infringed. This could impact negatively on their rights – not only to bodily and psychological integrity[37], but also to that of human dignity[38]. Human beings are moral agents and hence have rights to their own values and preferences. When vulnerable, one or more of the elements of informed consent[39] could be eroded, resulting in individuals participating in research as a consequence of coercion and / or lack of understanding. Kipnis[29] states that

> "... in the minds of many investigators the paradigmatic research subject remains more or less a mature, respectable, moderately well-educated, clear thinking, literate, self-supporting US citizen in good standing – that is, a man who could understand a 12-page consent form and act intelligently on the basis of its contents."

This description is a far cry from the typical research participant in Africa where levels of literacy are low and poverty rife. Yet, in collaborative international research, the consent forms presented to the Research Ethics Committees for review and approval are often those designed for the literate US citizen.

Beauchamp and Childress have proposed four clusters of principles which derive in the common morality as being central to biomedical ethics[40]. The four clusters comprise:

> (1) respect for autonomy (a norm where the decision-making capacity of autonomous persons are respected);
>
> (2) nonmaleficence (a norm requiring avoiding the causation of harm);

(3) beneficence (a norm that provides for benefits and for balancing benefits against risks and costs); and

(4) justice (a norm for distributing benefits, risks and costs fairly).

This cluster of principles is utilized extensively in the context of health research ethics discourse and is intricately interwoven in the notion of vulnerability in health research, similar to ethical theories like Deontology and Virtue Ethics as will be shown in the following chapter.

1.3 DEFINING HEALTH RESEARCH

There are two acceptable definitions of research in the context of health in SA, i.e., from the Department of Health's NHA[31] and from Academy of Sciences of South Africa[41] (ASSAf).

The NHA[31] in its definitions section states that:

"... health research includes any research which contributes to the knowledge of –

(a) the biological, clinical, psychological or social processes in human beings;

(b) improved methods for the provision of health services;

(c) human pathology;

(d) the causes of disease;

(e) the effects of the environment on the human body;

(f) the development or new application of pharmaceuticals, medicines or related substances; and

(g) the development of new applications of health technology."

Section 72(7) of the NHA describes clinical trials as:

> "... a systematic study, involving human subjects that aims to answer specific questions about the safety or efficacy of a medicine or method of treatment."

From the above broad characterization of health research and clinical trials, it is clear that in the South African context this definition is not restricted to projects in the health sciences disciplines only and would cover a range of studies from other disciplines, e.g., the Humanities where social science studies involving individuals with vulnerabilities are a conducted and would also require review by a Research Ethics Committee (REC).

In November 2009, the ASSAf in its consensus report on "Revitalising clinical research in South Africa. A study on clinical research and related training in South Africa"[41] defined clinical research as

> "... research primarily conducted with human participants (and on materials derived from them, such as tissues, specimens and cognitive phenomena) during which investigators examine the mechanisms, causation, detection, progression and reversal of human disease."

While the ASSAf definition also encompasses a wide variety of research from a range of disciplines, it is not as extensive as that in the NHA and it could be interpreted as excluding studies involving the social processes in humans. It is inevitable that the subject matter of this research is inclusive of social aspects as pertaining to health and hence the more appropriate definition to use in this study is that of the NHA. Hence, despite there being two recognised and acceptable definitions of health research in the country, all reference to health research in SA in this thesis will be specifically in the context of the definition in the NHA.

1.4 AIM OF STUDY

Although several documents exist that provide a baseline for research participant protections, vulnerable participants require ethical consideration that goes beyond the baseline. There is no agreed upon standard for identifying and responding to vulnerability, especially in the African context[29]. Moreover, the guidelines, despite categorizing vulnerable research participants into sets of subpopulations, do not offer a robust and comprehensive definition of vulnerability. In addition, as will be seen in some of the chapters that follow, various approaches to the issue of vulnerability including its definition are offered in the literature. However, again, none is robust or comprehensive. The aim of my study therefore, is to analyse the notion of vulnerability in health research with a view to constructing an operational definition of the concept which will assist researchers and RECs to identify and understand vulnerabilities and strategize on maximizing protections for the participants without stopping essential research.

1.5 OUTLINE OF THESIS

Prior to embarking on the analysis of the notion of vulnerability, an appreciation of the approach to ethics in the context of health research is essential and hence Chapter II focusses on the approaches to ethical enquiry. A discussion of moral status and its link to human dignity and vulnerability in the research context is also necessary for the analysis. The objective of chapter III therefore is to explore the concepts of moral status and human dignity and their relationship to vulnerability and how all three concepts are intricately linked in health research. This thesis also gains from historical inquiry as health research has been responsible for creating historically unprecedented ethical problems and has also added new dimensions and complexities to old problems[42]. In chapter IV abuses and

exploitation in research with resultant violations of human dignity and disrespect for moral status leading to protectionism will be described and discussed. Chapter V examines and analyses international guidelines and codes in terms of how they have handled specific vulnerabilities. Because of the rapid progress in systematic health research in the 20th century, and because of the offensive way in which it was misused by researcher-physicians from many countries[43], a historical approach will be utilised again in order to explore the treatment of specific vulnerabilities in these protective instruments through time. Using the same historical approach, Chapter VI deals with the national protective instruments approach to vulnerability in SA and because of the large number of health research projects undertaken in SA but funded by the US, US national protective instruments are also studied. Chapter VII reviews, analyses and critiques the literature on the subpopulation approach utilized by the guidelines and constructs a robust, comprehensive and practical definition of vulnerability, the application of which would assist REC members with identifying possible vulnerabilities and guiding researchers on appropriate safeguards for protection of participants within the research context. To this end, a Vulnerability Assessment Scale has also been developed in this chapter. Chapter VIII tests the definition and the Vulnerability Assessment Scale with the use of two South African Court Judgements where aggrieved vulnerable participants resorted to the Courts in anticipation of findings that would address the wrongs that they suffered. Chapter IX concludes this thesis by highlighting the merits of the definition and the Vulnerability Assessment Scale as developed in this thesis. They are of value not only during the review process, but they can also be utilized during the course of the research and even after the research is over to assist RECs guide researchers on optimizing protections for participants in research. Moreover, they can also be used as an adjudication tool should a dispute arise.

1.6 RESEARCH ETHICS COMMITTEE REVIEW

The research did not involve the participation of human research participants or the use of animals and a waiver of ethics review was applied for and approved. (See Annexure I for the waiver certificate.)

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Chapter 2: UNDERSTANDING ETHICS WITH SPECIFIC REFERENCE TO HEALTH RESEARCH

2.1 INTRODUCTION

Prior to embarking on an ethical analysis of the notion of vulnerability it is imperative that a brief explication of ethics be undertaken. Generally, ethics is considered to be the systematic study of norms and values in human conduct. Beauchamp and Childress[1] describe ethics as a generic term which covers a number of different approaches to understanding and examining the moral life. This chapter commences with a brief explanation of these approaches to ethical enquiry and then proceeds with a critical review of Beauchamp and Childress' account of ethics and its relationship to health research. Beauchamp and Childress are well known as leaders in the field of medical ethics since the seventies, and the principles they espouse are commonly drawn upon in the field of research ethics. A description of the three major ethical theories in the health research context (virtue ethics, consequentialism and deontology), their relationship to each other and their application in the research environment then follows.

2.2 APPROACHES TO ETHICAL INQUIRY

There are three basic types of inquiry in the field of ethics: normative ethics, metaethics and descriptive ethics[2]. In normative ethics, questions regarding which general moral norms for the guidance and evaluation of conduct should be used and the reason for their use are addressed. These norms are often referred to as principles in ethical theories and are usually starting points for developing norms of conduct appropriate for specific contexts[1], including health research involving vulnerable participants and populations. Some questions that normative ethical enquiry sets out to answer are: "What ought to be done?"; "What

ought not to be done?"; "What kinds of persons ought we strive to become?"[3]. In normative ethics, these questions are answered systematically and critically and the answers are justified[3]. In research ethics, normative ethics is concerned with arguments about such topics as the morality of enrolling children or mentally ill patients who are unable to consent into risky studies or whether research participants in international research ought to be enrolled in studies when there is uncertainty as to whether post study interventions will be affordable by the host country.

Metaethics sets out to investigate the meaning of moral terms, the logic and language of moral reasoning and elementary and essential questions of moral ontology, epistemology and justification[3].It has been stated that while metaethics is the most abstract type of ethical enquiry, it is vital to normative questions. In metaethics, the language, concepts and methods of reasoning in normative ethics are analysed. Prominent questions in metaethics focus on whether morality is objective or subjective, relative or nonrelative and rational or non-rational. In metaethics the meanings of terms like justification, responsibility, obligations and virtue are addressed[1]. Metaethics enquiry in health research would include questions like: " Ought the categorization of people into vulnerable groups be justified?", "Ought there be a moral obligation to compensate participants who have been injured as a result of their participation in the study?" and "Ought Research Ethics Committees have moral responsibilities to ensure special protections for research participants who are vulnerable?" Descriptive ethics involves the factual investigation of moral beliefs and conduct where scientific techniques are used to study how people reason and act[1]. There is no direct engagement with questions of what one ought to do or the proper use of ethical terms in descriptive ethics[3]. Empirical research using quantitative, qualitative or quali-quanti

methods of investigation, where the study of a question in ethics is undertaken, is an example of descriptive ethics. Research questions in this sphere include, "How do people think they ought to act in this particular situation of normative concern?"; "What facts are relevant to this normative ethical enquiry? " and "How do people actually behave in this particular circumstance of ethical concern?"[3]. Descriptive ethics enquiries in research ethics include questions such as: "How do researchers think they ought to act when participants are harmed in clinical trials?"; "Do people in poor contexts participate in research as a means to access healthcare?" "What do RECs understand by the term 'vulnerable'?" In summary, descriptive ethics is concerned with what factually or conceptually is the case and not with whether the case is ethically valuable or what the outcome of the case ethically ought to be. The subject matter of this thesis involves the use of both normative and metaethical inquiry. Descriptive methods are beyond the scope of this research and hence have not be undertaken. However, this thesis also gains from historical inquiry as health research has been responsible for creating historically unprecedented ethical problems and has also added new dimensions and complexities to old problems[4]. While historical approaches are not fundamental to ethics inquiry, when facts are not just simply presented but also used to provide an interpretation of what ought to or ought not to have been done in the past, historical inquiry augments ethics research[5].

2.3 MORALITY

As the principles in ethical theory stem from common morality, it is also essential that the notion of common morality be explored. Where norms of right and wrong in human conduct are agreed upon so extensively that they grow into a stable social compact, the resulting collective shared understanding is considered common morality[1]. Common

morality as a concept can therefore be viewed as a social institution with core tenets shared by all; i.e., common morality is not merely a morality in contrast to other moralities. Common morality is normative for everyone. All persons are rightfully judged by its standards[6]. Beauchamp and Childress refer to these core tenets as universal norms[1]. It is these universal norms that comprise the substantive matter of common morality and they can be applied to all persons everywhere. It may be understood in terms of broad ethical principles or as comprising basic rules of obligation[6] and includes standards for conduct and moral character traits like integrity and compassion. The common morality also supports human rights. All human conduct is judged by these norms or standards[1, 7].

Even if morality has core tenets that are shared by all, there are ideologies and beliefs related to morality that are not core and hence not universally shared. These non-core ideologies are referred to as particular moralities because they contain moral norms that are not shared by all cultures, groups and individuals. However, these norms should not violate the norms in the common morality[1]. Professional morality with standards of conduct that are accepted and supported by those in the profession, e.g., standards for the ethical conduct of health research, is an example of particular morality.

2.4 PRINCIPLES

Beauchamp and Childress have proposed four principles which stem from the common morality as being central to biomedical ethics[8]. The four principles are:

(1) respect for autonomy (a norm where the decision-making capacity of autonomous persons are respected);

(2) nonmaleficence (a norm requiring avoiding the causation of harm);

(3) beneficence (a norm that provides for benefits and for balancing benefits against risks and costs); and

(4) justice (a norm for distributing benefits, risks and costs fairly).

These four principles are utilized extensively in the context of health research ethics discourse and are also intricately interwoven in the notion of vulnerability in health research. All principles have equal moral worth and no one principle can claim moral priority over other principles[7].

2.4(A) Autonomy

The origins of autonomy derive from Greek, with *autos* and *nomos* denoting "self" and "rule" respectively. While originally referring to self-rule or self-governance of independent Greek city states, autonomy has, through time, been extended to individuals[9]. Two conditions are fundamentally indispensable for autonomy[9]:

(a) Liberty – independence from controlling influences; and
(b) Agency - capacity for intentional action.

The principle of respect for autonomy acknowledges the right of autonomous agents to hold views, make choices and take actions based on their values and beliefs. Respect includes that, where necessary, the individual will be assisted in developing the ability to competently make autonomous choices. Both negative and positive obligations are included in this principle. The negative obligation is broad and entails that for actions to be truly autonomous, they should not be constrained by controlling influences of others[9]. A negative obligation in health research would be to avoid coercion during recruitment of research participants in order to ensure that voluntariness to participate is not interfered with. The

positive obligation entails that autonomous decision making is facilitated by treating the individual with respect when disclosing information and assisting the individual with actions that promote autonomous decision making. The positive obligation gives recognition to the fact that there may be a need for the involvement of others in order to bring to fruition the principle of respect for autonomy[9]. In the context of health research, it is this positive obligation that makes it necessary not only to disclose all essential information but in addition to ensure understanding of the information and the implications for the participant once enrolled. Furthermore, voluntariness of decision making must be probed for and ensured. Community involvement coupled with innovative methods of information sharing prior to and during enrolment of participants in health research are examples of positive obligations. Assisting participants in achieving their ends and building up their capacities as agents go a long way in avoiding treating research participants exclusively as a means to researchers' ends.

Persons who lack decision making capacity are vulnerable and may lack competence. Needless to say, decisions on competence require standards for its determination[9]. There are several competing standards of competence and incompetence in the literature. Beauchamp and Childress favour the use of standards for incompetence over standards for competence because of the general presumption that in the absence of a determination of incompetence and incapacity, an adult should be considered competent and should be treated as such. There are a number of "inabilities" currently required under competing standards in the literature which are presented in the following schema by Beauchamp and Childress as[9]:

"1. Inability to express or communicate a choice.

2. Inability to understand one's situation and its consequences.

3. Inability to understand relevant information.

4. Inability to give a reason.

5. Inability to give a rational reason (although some supporting reasons may be given).

6. Inability to give risk/benefit-related reasons (although some rational supporting reasons may be given).

7. Inability to reach a reasonable decision (as judged, for example, by a reasonable person standard)."

Three types of abilities arise out of these standards[9]:

(a) The basic ability to formulate a preference (standard 1)

(b) The ability to understand information and appreciate a situation (standards 2 and 3)

(c) The ability to reason through a life decision that would be of consequence to the individual (standards 4, 5, 6, 7).

Diminished autonomy will arise where there are controlling influences by others, e.g., lecturers doing research on their students, or where individuals are incapable of deliberating, e.g., those with mental illnesses, or acting in accordance with their own wishes, ideas or plans, e.g. the dependent elderly participant.

As liberty is a necessary precondition for autonomy and because autonomy is accorded significant moral value, moral justification is required should there be any infringement upon, limitation or usurpation of liberty. Mappes and DeGrazia advance six general reasons

which are most frequently considered when limitations of liberty are at issue. These are sometimes called "liberty-limiting" principles [6].

Justifiable reasons for restricting liberty are[6]:

1. To prevent that person from harming others (harm principle).
2. To prevent that person from offending others (offense principle).
3. To prevent that person from harming him or herself (paternalism).
4. To benefit that person (paternalism).
5. To prevent that person from acting immorally (legal moralism).
6. To benefit others (social welfare principle).

In the context of health research, researchers have used reason 3 to justify excluding people who are vulnerable from health research. Reason 4 has been used to justify including people in research who, because of language barriers or difficulties with understanding, do not comprehend adequately what their participation will entail but the researcher is of the opinion that it would be in the best interests of the individuals to participate. These reasons for exclusion or inclusion into research cannot be justified if researchers have not assisted participants with acquiring agency.

It is important that researchers and RECs understand the meaning of paternalism so this type of unjustifiable conduct can be safeguarded against in research. There are several definitions of or explanations for paternalism in the literature. Mappes and DeGrazia state that perhaps the most widely cited definition of paternalism is that by Gerald Dworkin[10] who defines it as "… the interference with a person's liberty of action justified by reasons referring exclusively to the welfare, good, happiness, needs, interests, or values of the

person being coerced."[10.] However, coercion seems to be necessary for paternalistic acts but patients and research participants are often subjected to paternalistic acts that do not necessarily involve coercion in the practitioner-patient or researcher-participant relationship. This definition is, hence, rightfully criticised by Mappes and DeGrazia who offer the following more workable definition: "Paternalism is the interference with, limitation of, or usurpation of individual autonomy justified by reasons referring exclusively to the welfare or needs of the person whose autonomy is being interfered with, limited or usurped." Autonomy is considered by degree in this definition[6]. Beneficence is also discussed here, and nonmaleficence, while not mentioned explicitly, is implicitly inferred.

Beauchamp and Childress advance a simpler definition which includes the principles of autonomy, beneficence and nonmaleficence. They explain paternalism to be:

> "… the intentional overriding of one person's known preferences or actions by another person, where the person who overrides justifies the action by the goal of benefiting or avoiding harm to the person whose will is overridden."[11]

In the context of health research, Research Ethics Committees make paternalistic decisions as to the inclusion or exclusion of groups of potential research participants on the basis of vulnerability without taking into consideration their preferences. In my opinion, the definition by Mappes and DeGrazia, while not explicitly including nonmaleficence, would be the more appropriate one to use in the health research context.

While cognisant of the negative obligations of the principle of autonomy, it must be remembered that competing moral considerations could override respect for autonomy. Hence this principle, similar to the other three principles, has only prima facie standing[8,9].

2.4(B) Nonmaleficence

An obligation not to intentionally inflict harm is asserted by the principle of nonmaleficence. It is closely associated with the maxim, *Primum non nocere,* which translates to "Above all [or first] do no harm." While this maxim is frequently referred to by healthcare practitioners, its origins are unclear.[12]

The principle of nonmaleficence very concisely captures the universal consideration that there is an overriding duty of anyone who undertakes to care for a patient or enrol a participant in research not to harm the patient or participant. It must be stated that this duty is not an ultimatum to achieve the impossible. However, practitioners and researchers need to live up to reasonable standards of performance in their professional and/or scientific conduct and are expected to be cautious, competent and compassionate[13]. Nonmaleficence is often explained using the terms harm and injury. Injury refers to harm on the one hand and injustice, violation or wrong on the other[12]. However, when put simply, the principle of nonmaleficence requires that needless risk of harm is avoided and when risk is an inevitable aspect of the professional or scientific activity, e.g., in health research, risk should be minimized as far as is reasonably possible. Failing to act with due care violates the principle of nonmalefecence, even if no harm results, while acting with due care does not violate this principle, even in the face of resultant harm[13].

Although several authors combine nonmaleficence and beneficence, nonmaleficence obligations are generally more rigorous than beneficence obligations. In certain instances nonmaleficence obligations could take priority and override beneficence obligations despite the latter resulting in highest net utility as regards outcomes[12]. A harmful action could impede, defeat or ruin a party's interests. Beauchamp and Childress in their writings, while

affirming their recognition of mental harms and other setbacks to interests, focus, in the main, on significant bodily harms. However they do go on to state that in the context of medical research, the economically disadvantaged, very sick and vulnerable bear a disproportionate burden of the risks of harms due to their ready availability, and they express deep moral concern on the unjustified overutilization of these groups. They also acknowledge that harms could extend beyond individuals to affect whole groups[12]. While there is general agreement that internal controls to protect participants through a system of research ethics are necessary, they caution against overprotection as this too results in harms to society because of delays in the progress of much needed research.

2.4(C) Beneficence

Stemming from the common morality, this principle places an obligation on us to contribute to the positive welfare of persons. A practitioner-patient or researcher-participant relationship imposes on the practitioner or researcher the duty of promoting the patient's or participant's welfare. The duty of beneficence is inherent in the role of the professional. In this context, simply avoiding harmful acts is insufficient. Positive steps are called for in order to assist others. The principle refers to "... a statement of moral obligations to act for the benefit of others"[11]. Beneficence, in terms of the common morality, does not place obligations of extreme sacrifice and altruism[11] and while in principle beneficence has no limits, in practice it must.

In the milieu of research ethics, the principles of nonmaleficence and beneficence are usually considered together and translate to the risk/benefit ratio in the study where risk refers to a possible occurrence of harm in the course of the research process. It is expected that the overall probable benefits of the research (to participants, but more so to society)

will outweigh the possible risks to individual participants. Hence, the risk/benefit asymmetry: probable risks of harms to participants during research and possible benefits to others in the future.

2.4(D) Justice

The two primary notions of justice are that equals should be treated equally and that the distribution of burdens and benefits should be fair[14'15]. The former is expressed in the formal principle of justice which is interpreted as "Treat like cases alike (and different cases differently)"[16]. This formal principle of justice is sometimes referred to as the principle of formal equality[14]. It is "formal" because no specific respects in which equals ought to be treated equally are recognised. In addition, no criteria are made available for determining whether individuals are actually equal and all it does is state that persons equal in whichever respects considered appropriate need to be treated equally[14]. While this formal principle is undisputed, and the fact that equals ought to be treated equally is not debatable, it lacks content and substance and is frequently difficult to apply in specific contexts[14,17]. Applying this formal principle in the context of international health research is an example of difficulties that its use entails: it is widely accepted (and emanates from the formal principle of justice) that if it is not ethical to conduct a particular health research study in countries in the developed world, it would be equally unethical to conduct the study in countries in the developing world. However, upon interpretation of this statement, and when the differences in contexts including the differences in benefits and risks are considered, it is unlikely that this statement could strictly apply[17]. The confusion, doubts and problems created by the formal principle of justice, albeit important, are addressed by the use of material principles of justice[14].

One of the material principles of justice is distributive justice, which is defined as "fair, equitable, and appropriate distribution of benefits and burdens determined by norms that structure the terms of social cooperation."[14] Distributive justice as fair access to participation in research and access to proven beneficial interventions resulting from the research has since the nineties gained prominence as a result of the needs of patients with HIV/AIDS to gain expanded access to experimental therapies both within and outside the clinical trial and to continue accessing therapies once the trial had been completed[14]. Imposing undue burdens and denying expected benefits are violations of the standard notion of distributive justice. In health research, distributive justice requires a fair distribution of burdens and benefits of the research itself[17] . Because criteria for fairness may differ in different contexts, arriving at a precise general definition of what constitutes fair distribution is not easy. For this reason, equity, a core concept in fair distribution, is drawn upon. It is in terms of equity that no one group should receive disproportionate benefits or bear disproportionate burdens[17].

Exploiting the vulnerabilities of participants is one of the ways in which justice as fairness is violated in research because those with greater power or resources take unfair advantage of those with less power or fewer resources[17]. Macklin positions this into a subcategory of distributive justice because the nature of the wrong in this situation is that of inequitable treatment. She further states that it is less likely that populations in developed countries will be exploited as compared to those living in developing countries. This then results in an inequitable selection of research participants across international boundaries. Ruth Macklin correctly stresses that while justice always relates to fairness in some way, it is not limited to fair distribution[17] in the context of health research, and as a response to several forces

and influences which are dealt with in subsequent chapters, fair inclusion or exclusion of participants has also started being emphasised as a significant aspect of justice[15]. In addition, competing values of justice in this context have also emerged, and include the social need for research, benefit to participants and protecting them from harm and exploitation[16].

Other notions of justice that are pertinent to the health research context are procedural and compensatory justice[17]. Procedural justice is an important expression of fairness. The process in which decisions are made and the manner in which actions are carried out must also be fair. The Research Ethics Committee, a duly constituted body whose task is that of protecting the rights and welfare of human participants in research, involves itself in a process of procedural justice when it prospectively reviews research protocols[17].

When research participants are injured as a result of their participation in a study they need to be compensated and treated for any injuries incurred. Participants must also be compensated for their time, inconvenience or any other costs they may incur as a result of their involvement in the research. It is not fair to expect participants to bear the costs incurred as a result of study participation. In addition, they deserve recompense for any harm they have suffered. This conception of justice is known as compensatory justice[17].

Justice, therefore, broadly speaking, can be interpreted as fair, equitable and appropriate treatment in terms of what is due or owed to persons[14]. Moreover, the other principles, autonomy, beneficence and nonmaleficence also contribute to safeguarding just and fair treatment. In the context of health research justice includes[18]:

" 1. equitably distributing the burdens and benefits of research across the general population;

2. treating like situations in the same way;

3. offering equal opportunity for all qualified persons to participate in research;

4. treating all research volunteers with the respect due them as collaborators in the pursuit of scientific knowledge;

5. providing appropriate oversight of studies involving human subjects, including follow-up care and compensation for research-related injuries;

6. protecting the general population from misinformation or from exposure to unnecessary risks;

7. not invading the bodily integrity or privacy of research subjects without obtaining their informed consent; and

8. preventing, ameliorating, or curing disease without transgressing the dignity of individuals."

It is clear that a unified principle of justice that captures the various conceptions and uses of justice in the health research context is not easily arrived at. In addition, it is also clear that depending on context and situation, justice as fairness must include the other three principles as presented by Beauchamp and Childress to be effective in its application.

2.4(E) Wrapping up the Principles

As seen from the brief discussion of principles all four principles can be drawn upon to assist in a comprehensive ethical analysis in health research and, in particular, research involving vulnerable participants or populations. These principles are not without their limitations, and while no one principle is superior to the others and there is no hierarchy of principles, one or other principle can be overridden in order to give way to the most compelling principle in certain situations.

In addition to principlism, there are several moral theories that can be drawn upon for reflective study in bioethics. An understanding of the major theories is also necessary for the ethical exploration of the notion of vulnerability. A brief examination of these theories follows in the ensuing section of this chapter.

2.5 ETHICAL THEORIES

The role of theory is somewhat complex, but it can be perceived as providing a unifying perspective that creates or connects multiple phenomena and in this way generates knowledge[19]. Theories also assist with direction and recommendations on the case in point and in the particular milieu. Concepts are provided for distinguishing differing characteristics of some phenomena and for responding to queries about relationships between different types of phenomena. Points of view are created to facilitate recognising perspectives that may otherwise be ignored, neglected or even undervalued. Simply stated, in the context of ethics, theories synthesise moral rules, thereby generalising diverse moral experiences. Reason-giving guidance, commonly known as justification for actions to be undertaken, is provided[19]. This reason-giving guidance is often relied upon when trying to

ensure that particular conduct is moral, e.g., ethical guidelines for the inclusion of vulnerable participants in health research. An appreciation of ethical theories translates to an appreciation of the many diverse endeavours towards comprehending the complexities and hence the richness of the world of human life[19].

Time has witnessed the emergence of many competing ethical theories. None of these qualifies as the most satisfactory and comprehensive for facilitating ethical reasoning for all situations, including those involving vulnerability in the context of health research. Each theory is enriched with particular strengths and prejudiced by particular weaknesses. Moreover, while debatable, it has been stated that no theory has been established to be superior or inferior to other theories. And neither has it been found that theories derive from each other[19-21]. While several ethical theories exist, it is sufficient for the purpose of this thesis to examine the three theories that are currently most influential in advancing reasoning in the context of science and scientific research, i.e., Virtue Theory, Consequentialism and Deontology[19]. There is no particular ranking or preference of these theories and the order of discussion is based on the historical order of their emergence.

2.5(A) Virtue Ethics

In Aristotle's *Nicomachean Ethics,* written about 325 B.C ., attention is drawn to the development and nurturing of virtuous traits of character as a primary function of morality[19]. Aristotle made a distinction between two types of virtues, intellectual and moral. Intellectual virtue refers to excellence in thinking with reasoning constituting the activity itself. Moral virtue equates to excellence in activities carrying out the instruction of reason[19]. Aristotle responds to the question "What is the good of man?" with "... an activity of the soul in conformity with virtue."[22] Accordingly, an understanding of ethics requires an

understanding of what makes someone a virtuous person. Aristotle gave much weighting in his discussions of ethics to particular virtues including courage, self-control, generosity and truthfulness. In addition, reason was viewed as the source of practical wisdom by the Greeks, and hence, for them the virtuous life could not be detached from the life of reason. Prior to Aristotle, ancient thinkers like Socrates and Plato also focussed on virtues when discussing ethics and approached ethical analysis by examining the character traits that would create a good person. The aim of life was to fare well and flourish and this could only be accomplished if humans developed virtuous character traits, capacities, skills or excellences in their conduct or behaviour[22].

Virtue ethics has been widely criticised. Some claim that it does not take into consideration that different cultures could be at variance in opinions on what constitutes virtue and, correspondingly, vice[19]. Some virtues may foster the performance of unethical actions[20]; e.g., loyalty and solidarity amongst researchers in the research enterprise could discourage reporting of breaches in scientific integrity. While virtue ethics is more likely to work where an environment of virtue and trust exists, it is unlikely that it can be applied in situations where such an environment has not been established[20]. Moreover, it emphasises character but provides no insight on correct courses of action as it is silent on action guidance[19]. In addition, because its focus is on individual agents, it is not appropriately placed to evaluate morality at a collective level – i.e., institutions, policy making and the like[19].

Although virtue ethics theory has been widely criticised, it does have several advantages of note. Without doubt, it provides a natural and appealing account of moral motivation[20-22]. Furthermore, impartiality features as the dominant theme in modern moral philosophy as will be seen in the discussions that follow. However, the importance of impartiality in the

moral life is thrown into doubt especially in the context of relationships with family and loved ones. Hence, some virtues like love and friendship are partial while others, like beneficence towards people in general may be impartial[22]. In the context of health research and vulnerability, virtue theory is well suited in assisting researchers navigate care giving and information sharing. A caring, compassionate researcher in this milieu is unquestionably critical to the researcher-participant liaison. In addition, normative appeals to human nature and virtues of researchers are often drawn upon as compelling reasons when questioning the prudence of pursuing certain types of research[20]. Hence, although virtue ethics theory is unable to provide a complete set of resources for normative evaluation of health research involving vulnerable populations, it nevertheless does provide some very useful ones.

2.5(B) Consequentialism

While the focus of virtue ethics is on character traits, i.e., agents as a whole, the trajectory of consequentialist ethics is on the situation and conditions that result as a consequence of an agent's actions. Moral value as expressed by the rightness or wrongness of an action is judged by its outcomes. The decisive factor in determining whether an act is right is if and only if the act is reasonably expected to produce the greatest good or the least harm when compared to alternative choices of action[19,20,23]. Hence, what counts as good is also a criterion used when applying consequentialism.

Consequentialism stems back to 1781 when Jeremy Bentham formulated the principle of utility which holds that when values are balanced, positive values must always override any other values. Simply formulated, the utility principle requires the greatest good for the greatest number. It also requires that this determination be made from an impartial perspective where equal consideration is given to the legitimate interests of each affected

party[19,20,23]. According to Bentham, an action is approved and supported or not endorsed according to the tendency which it appears to have to enhance or diminish the happiness of the group whose interest is in question; hence the introduction of the concept of hedonism[19,20,23]. In 1861, John Stuart Mill reinforced hedonism in consequentialist utilitarian thinking by making happiness the ultimate goal when judging the rightness or wrongness of an action. Mill maintains that actions are right when they tend to promote happiness and wrong when they tend to produce the reverse of happiness. Happiness is described as pleasure or the absence of pain[23]. Although the principle of utility was formulated by Bentham in the 1700s, it was only in the nineteenth century that classical utilitarianism (also known as the strong version of consequentialism) was systemised by Bentham and Mill in an endeavour to construct a decision-making rule whose objective would be to guide social policies in a changing world that was being transformed by the advent of science, technology and the Industrial Revolution[19]. Classical utilitarianism is summed up in the following schema of three propositions[19,20,23]:

a. It is solely by virtue of their consequences that actions are to be judged as right or wrong;
b. The only thing that matters when assessing consequences is the amount of happiness or unhappiness that is created; and
c. Each person's happiness counts the same.

The importance of utilitarianism from the historical perspective is that it contributed to democratic development and reform. It has also become exceedingly influential because it is compatible with democratic decision-making in the public sphere. It forms the foundation of almost all contemporary economics and most public policy formulations. Benefits and

harms that could accrue from alternate regulatory proposals are commonly weighed by policy makers prior to adopting those judged to produce the greatest overall action[19].

While sharing basic agreements, Bentham and Mill demonstrate two significant differences in their viewpoints which gave rise to act and rule utilitarianism[19,20,23]. In Bentham's act utilitarianism, it is required that each individual action be evaluated such that all outcomes are subjected to a common metric. On the other hand, Mill, in his rule utilitarianism, instructs that rules for action and not actions per se be evaluated and these should be assessed by the qualitative difference in their outcomes. Qualitative differences are judged on the basis of experience and anyone who has experienced two different outcomes will be able to judge which one is better and express a preference.

Utilitarianism, while an attractive theory in ethics, has had its fair share of criticism as it too is not completely adequate for all areas of the moral life. Concerns have been raised on conceptual issues related to the greatest happiness of the greatest number. "Greatest" is not necessarily the same for happiness or number and it has been proposed that it should be interpreted as the greatest average happiness[19]. In the context of education in research, this could mean greatest average education and training for the maximum number of students. Not only would this impact negatively against exceptionally good students, but average training could result in gaps in scientific knowledge with possibly damaging results for the research enterprise and unacceptable and preventable harms to participants.

Where utilitarians are concerned with the maximization of individual preference, i.e., rule utilitarianism, problems would arise when in considered judgement, these preferences and subsequent actions could be morally unacceptable[19]. In the context of health research, this could be a problem when a researcher's satisfaction and hence the research objectives can

only be achieved by exploiting the vulnerability of participants. In terms of act utilitarianism, immoral actions like lying to participants or withholding materially significant information from them may not only be permissible but may be morally obligatory when lying or withholding information would result in an overall maximization of utility. When a conflict between scientific rigor and participant welfare arises, utilitarianism will justify superseding obligations to a small group of participants because of a greater obligation to produce reliable data which could potentially provide future benefits to members of society at large, or even to the participant's particular social group[24]. Hence, a value structure could be encouraged whereby higher moral priority is given to the potential benefits of science and society over and above concrete and measurable risks to research participants. Risk and benefit are conceptualised as tangible entities with universal value subject to rational analysis by those other than participants. Hence, the type of ethical orientation promoted by utilitarianism is more of an abstract risk/benefit calculus guiding moral action. This is detached from the particular preferences and values a participant might consider significant in the context of specific risks and benefits. Moreover, this has the potential to minimize the researcher's moral obligations to individual research participants[24].

In addition, utilitarianism has been criticised for not being adequately resourced to guard against unjust social distributions where the interests of the majority could override the rights of the minorities because value is distributed according to net aggregate satisfaction[20].

Despite the many criticisms of utilitarianism, its great strength is that it does play a significant role in formulating public and institutional policies. The latter includes policies regulating the ethical conduct of research. Requiring objective assessments of everyone's

interests and making impartial choices in order to maximise good outcomes for all affected parties are acceptable and valuable norms of public policy. Moreover, if the legitimate goal of utilitarianism as elucidated above is primarily to promote welfare, the theory could also be perceived to be beneficence based[20].

Peter Singer in the late twentieth century revived classical utilitarianism and promulgated the commitment to impartiality as recognising the need to go beyond one's own likes and dislikes and to adopt the stance of an impartial spectator or ideal observer[25]. This would mean that one's own needs, wants and desires cannot, simply because they are one's preferences, count more than the wants, needs and desires of anyone else. Such an approach in moral reasoning would clearly result in the best consequences, on balance, for all that are affected. This slant in moral reasoning makes utilitarianism a highly attractive ethical theory.

2.5(C) Deontology

At the time that utilitarianism was being formulated as a theory in the 1700's, Immanuel Kant's deontological approach was being propagated as an alternative approach to ethics. Deontology derives from Greek, with "deon" meaning duty and "logos" meaning reason. The concept of deontology is therefore one of reasoned duty[19]. This corresponds to a common understanding of ethics being that of critical reflection on inclinations or desires. Hence, action not only makes character traits evident and results in consequences, but action emerges from willed intentions. Because human beings have many needs and desires, reason must be utilised to determine which to pursue. This then becomes the will and is expressed in a command or imperative[19,20]. Moral principles manifest in moral duties which define right action. The goal of moral action is to uphold the action itself and not to

perfect the character traits of an agent or produce a good state of affairs. According to Kant, the moral worth of an individual's action depends exclusively on the moral acceptability of the general rule of conduct or "maxim" on which the person is acting, i.e., the rule provides a moral ground that justifies the action. Maxims must be consistent. They must be capable of being conceived and willed without contradiction[19,20,26].

Ethical knowledge, which informs the will, takes the form of commands or imperatives. Kant argues for a categorical imperative and for this the ethical assessment of intentions is based in reason alone. Because categorical imperatives are canons of the acceptability of moral rules, and since they derive from a principle that everyone must accept, they are binding on the rational will and are absolute[19,20,26]. Kant's two most important formulations of the categorical imperative are:

1. One must act only in accordance with that maxim which one can at the same time will to become a universal law; i.e., one must be able to endorse the universal acceptability of a plan or action[19,20,26]. This formulation can be used in the context of health research, where it would draw on truth-telling and other related imperatives.
2. One must act in such a way that every person is treated as an end and never as a means only. Treating others as mere means results in a maxim that cannot be universalised. The importance of dignity, rights and personal autonomy are underscored in this formulation[19,20,26]. In health research, participants must be treated with the moral dignity and respect to which everyone is entitled. When participants are involved in a process whereby they agree to be used in the search for the answer to a research question, they will not be used as a means to an end they do not endorse. Even where research promises cutting edge breakthroughs and

huge benefits for society, participants would be treated unethically if fundamental ethical constraints like obtaining their voluntary informed consent are violated[20]. Respecting autonomy in turn respects human dignity.

Similar to virtue ethics and utilitarianism, deontology is not without its weaknesses and does not provide a comprehensive theory of the moral life. Because Kant's moral requirements are construed as categorical imperatives, his theory is not adequately resourced to handle problems when there are conflicting obligations. In addition, his emphasis on rules is perceived as overemphasising law[26] with little regard being given to relationships. Kant does not accord moral worth to actions conceived as a result of sympathy, caring and compassion. Only actions performed from the motive of duty are morally worthy. Clearly, caring, compassion and sympathy as motives for actions deserve moral recognition.

2.5(D) Wrapping up the theories

Despite the brief and simplified overviews of virtue ethics, consequentialism and deontology, the common denominator to all three has surfaced quite clearly: all have distinctive strengths and distinctive weaknesses. Each theory is instructive. Each theory contributes to our thinking about the moral life. Different aspects of the moral experience are highlighted in the different theories. Despite the risk of these theories clashing at times with considered moral convictions, these three theories all display insights into our common moral heritage[20]. For moral experience to be comprehensive it will require the involvement of agents (virtue ethics), actions (deontology) and results (consequentialism) – hence, contributions from all three theories[19,20]. It should also be noted that through the past century, many theories have emerged, either as complementary to these three or as standalone theories. These include Feminism, the Ethics of Care, Communitarianism and

Casuistry. While each has made worthy contributions to the field of moral reasoning and ethical analysis, the combination of agents, actions and results coupled with the application of the four principles is, in my opinion, the most appropriate method of moral assessment in health research.

2.6 CONCLUSION

Emerging from the brief description of the principles and theories above it is clear that all theories and principles will prove to be valuable tools when confronted with ethical dilemmas in the context of health research, and in particular from the perspective of the notion of vulnerability. The chapters that follow draw from these principles and theories as applicable and appropriate. The next chapter looks at the relationship between moral status, human dignity and vulnerability and the importance of the former two in safeguarding against exploiting the vulnerable in research.

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Chapter 3: MORAL STATUS, HUMAN DIGNITY AND VULNERABILITY

3.1 INTRODUCTION

Research ethics mandates special protections for participants considered to be vulnerable because of the danger of exploitation by some researchers and the need to respect the intrinsic value and dignity of those who do not have the means and / or ability to protect themselves. These concerns over vulnerabilities have been intricately linked with issues of moral status and human dignity.

In the different notions of moral status, the common denominator conferring moral status is human dignity. Because human dignity is so frequently referred to when promulgating protections for the vulnerable, vulnerability and human dignity have developed into inseparable concepts. It is therefore prudent to examine these three concepts and their application in health research.

In this chapter, I start off with a discussion of moral status and link this to human dignity and vulnerability in the research context. I then proceed to discuss human dignity and how this concept has been incorporated into international and national instruments to protect people with vulnerabilities against being harmed, wronged and exploited, in particular in health research. My discussions on moral status and human dignity form the basis for the conceptual analysis of vulnerability which follows thereafter.

3.2 MORAL STATUS

Beauchamp and Childress[1] opine that moral status as a term has been brought into bioethics discourse from law and the notion of legal standing. They categorise moral status into weak and strong types. In its weak sense, it refers to a grade or rank of moral

importance, but in its strong sense, it means to have rights, or the functional equivalent of rights. Put simply, this entails that while moral status exists independently of the moral obligation of others, it is in fact the basis of these moral obligations.

Having moral status merits the obligation of protections required by the moral norms referred to in the previous chapter. This is because having moral status signifies the potential for being morally wronged. There are several approaches to moral status[1]. They will not be discussed in detail in this thesis as they are not core to the subject matter under study.

Just as the notions of human dignity and vulnerability are ill-defined, there are several different notions of what constitutes moral status. The problems here also hinge on questions as to which individuals and groups are or should be protected by moral norms and whether members of these groups deserve moral protections and have moral rights[1]. In this context too, some authors challenge the need for this notion and recommend that this concept be dropped from the literature completely[2,3]. However, based on lessons learnt from history, this could be dangerous and in my opinion not advisable. In the past some human beings, and even large groups of humans, were treated as incapable of morality and having either no moral status or low-level moral status[1]. This is exactly how people who did not belong to the White race group were treated prior to 1994 by the Apartheid government of South Africa. Even within the non-White groups moral status differed, with groups from Indian origin, while having very few and limited rights, being given a higher moral status with more rights as compared to native Africans who were given hardly any rights as they were seen to have very little, or weak moral status, if any. Whether an individual or group has a full or partial set of moral rights depends on whether they are seen

to have full or partial moral status in morally tarnished societies[1] like those that existed in South Africa during Apartheid and that currently still exist in the world today. In several societies and cultures today women and the mentally disabled are still treated as though they lack full moral status.

While issues of moral status have also been raised in situations where individuals are incompetent and their decision-making roles are taken over by surrogates, all moral protections and forms of respect are not lost in this context. In fact, most obligations towards them continue and some may even increase. It is only certain rights that are lost by recognising the surrogate as the decision-maker and hence, a lowering of moral status in this respect, as perceived by some, for the individual unable to make a decison[1]. In other words, incompetent individuals do not have the same moral authority in respect of decision-making that they had prior to the determination of incompetency[1]. Mental incompetence is one among many other criteria used when assessing moral status and in determining rights and obligations. Children do not have the same moral authority as adults and are at times treated as if they have diminished moral status. In both these groups, their diminished moral authority will result in them being vulnerable necessitating increased protections[1].

Whichever way moral status is viewed, to have moral status is to deserve some protections as required by moral norms and these protections are afforded to those that can be morally wronged[1]. In the main, this has been the approach for moral principles and categories to apply to human beings. There are several approaches in the context of moral status and some approaches categorically state that the only property conferring moral status is human dignity[1]. Other approaches state that properties such as sentience, rationality or moral agency are necessary for the acquisition of moral status[1]. The individual approaches

do not resolve the main issues in respect to moral status[1]. Beauchamp and Childress describe these approaches and group them into five theories which, when combined, all contribute to the understanding of moral status[1]. The approaches are based on human properties, cognitive properties, moral agency, sentience and relationships respectively. While all of them are able to demonstrate sufficient conditions for moral status, none of them identify necessary conditions for moral status. The theories described by Beauchamp and Childress are discussed below.

3.2(A) Theory Based on Human Properties[1]

Often called the traditional account of moral status, this theory holds that characteristic and distinguishing human properties, those of *Homo sapiens,* bestow moral status. In this theory, all humans, and only humans have full moral status. Moral value is discerned by particular human properties. The latter also defines which beings comprise the moral community. An essential and adequate condition of moral respect is that of being a living member of the species *Homo sapiens*. Accordingly, biological criteria and species membership are necessary components in this theory.

This theory appeals to many, especially those who believe the properties of humanity form a basis of moral status, because it unambiguously covers all human beings. No one is excluded based on certain properties, e.g., mental incompetence, being in a persistent vegetative state or belonging to a particular race group or gender. It is cemented into morality and is fundamental to the claim that all humans have human rights. However, this theory is also criticised because any set of human properties are sufficient for moral status. Hence, embryos and fetuses would unequivocally have moral status - a much contested domain in bioethics which will not be discussed in this thesis as this subject has been

debated for centuries and there are no new arguments forthcoming. Nevertheless, this theory does supply a sufficient condition for moral status although it fails to identify a necessary condition for moral status.

3.2(B) Theory Based on Cognitive Properties[1]

In this theory, a specific set of cognitive properties that refer to processes of awareness, e.g., perception, memory, understanding and thinking, are necessary for moral status. According to this theory, individuals have moral status as they are able to contemplate and reflect on their lives using their cognitive capacities. In addition, their beliefs influence their determinations. Incompetent humans are unable to use their cognitive capacities and beliefs in these ways. The autonomous human being in respect of the competent human adult is conceived in this theory. Cognitive properties necessary for moral status in this theory include:

1. Self-consciousness as existing over time;
2. Freedom to act;
3. Capacity to engage in purposeful actions;
4. Ability to provide reasons for actions;
5. Ability to appreciate reasons for actions;
6. Capacity for beliefs, desires and thoughts;
7. Capacity to communicate using language with other people;
8. Rationality and higher order volition.

It is clear from the set of conditions above that the ability to exercise self-determination leading to informed consent or informed refusal decisions would mean possessing moral

status and therefore being deserving of moral respect and respect for dignity. Those without this ability would not be deserving of moral respect and respect for their dignity as they would lack moral status.

The problem with this theory is that many humans will be excluded if all the above criteria have to be satisfied for moral status. Infants, people with mental disabilities, elderly who are senile and others would be excluded from having moral status. Weak, vulnerable and incapacitated individuals would not have moral status and hence would not be deserving of moral respect and protections. All these individuals could be treated as though they lacked human dignity and would not qualify for protections of their vulnerabilities. As will be seen in subsequent chapters, many examples of abuses and exploitation took place in health research where individuals and communities were treated by researchers as though they lacked moral status. So, while this theory supplies a sufficient condition for moral status, it does not identify a necessary one either.

3.2(C) Theory Based on Moral Agency[1]

In this theory, an individual will have moral status if the individual has the capacity to act as a moral agent. Two conditions of moral capacity criteria have to be satisfied for an individual to be a moral agent: the ability to make moral judgements about the rightness or wrongness of actions and possessing motives that can be judged morally.

This theory dates back to Kant who advanced one of the most influential theories of moral agency. Beauchamp and Childress state that while Kant focussed on moral worth, autonomy and dignity, some of his formulations suggest that he is proposing conditions of moral status. Kant links autonomy and dignity intricately in that one has dignity only if one is an

autonomous agent. The capacity for moral agency confers moral respect and dignity and this is not possessed by individuals that lack the capability to be moral agents. Beauchamp and Childress interpret this account as one of moral status and state that they find this theory appealing because being a moral agent is without dispute a sufficient condition for moral status. This is so because moral agents are typically carriers of moral status in that they know they can be condemned for motives and actions, blamed for being irresponsible and punished when their behaviour is immoral. The concern they express with this theory is that those who lack autonomy and agency like people with advanced dementia would lack moral status, hence moral respect and value and therefore their interests would not be protected. Accordingly, people with certain vulnerabilities, like research participants who lack capacity would not merit protections because they lack moral status. Again, this theory generates a sufficient condition but not a necessary one for moral status.

3.2(D) Theory Based on Sentience[1]

Here moral status is determined by properties that include a range of emotional and affective responses that are neither cognitive nor moral in nature. The single most important property here is sentience, which is consciousness in the form of feeling, especially the capacity to feel pain and pleasure and to suffer. Causing pain harms and therefore wrongs individuals. Actions that result in harm are morally forbidden unless there are sufficient moral reasons to justify them. It is these properties of experiencing pain and suffering that give some measure of moral status because two of the foremost objectives of morality are to minimise pain and suffering and to prevent or limit a lack of concern and aggression toward those who are experiencing pain and suffering. All those that experience pain and suffering have moral status and are therefore morally wronged when others cause

them pain and suffering. People with vulnerabilities are therefore protected by this theory. The problem with this theory is that it takes us to the centuries old debate on fetuses and moral status because fetuses develop sentience after several weeks of development. In addition, individuals with severe brain injury and an inability to feel pain would not have moral status and would therefore not be deserving of protection and could be exploited in health research. Therefore this theory can also be interpreted as providing a sufficient but not necessary condition for moral status.

3.2(E) Theory Based on Relationships[1]

In this theory, relationships between parties, in particular those that establish roles and obligations, justify moral status[1]. A researcher-participant relationship is established in the context of health research. This is a relationship based on scientific need (researcher) and provision of research data (participant). Once this relationship commences, the participant gains a right to a particular respect that others cannot have a claim to, i.e., those who are not research participants. The participant does not have this status independent of the established relationship and the researcher does not have the same obligations to those outside such a relationship. Important to this relationship are trust, caring and empathy, and these are all the more necessary when participants are vulnerable. This theory provides for the conditions under which particular relationships, especially those requiring social interactions and reciprocity, are more robust and influential as compared to relationships with those outside this context[1].

Beauchamp and Childress go on to explain in this theory that moral status will not necessarily be acquired through a decisive incident that can, independent of communal relationships, be determined at a particular time. Moral status is conferred to classes of

people, like research participants, because historically, the human moral community has weighed up the importance of the researcher-participant relationship, together with the worthiness of reciprocal moral protections, to participants in this class. The basic requirement is that of protecting and caring for those in the established relationship. Moreover, should they become vulnerable because of the relationship, the obligations of protections and care will need to increase[1]. While this theory is appealing in the context of health research, it too provides sufficient but not necessary conditions for moral status.

As can be seen by the above discussion on the theories of moral status, a unified and comprehensive account of moral status is lacking. In addition, various morally relevant features of situations that lay out moral reasons for acting or not acting in particular ways with regard to others are required in the form of moral judgements that none of the theories of moral status is able to address[1]. A compromise position is to draw the best elements from each theory and combine them to formulate an account of moral status that accommodates multiple criteria,[1] thereby taking into consideration the diversity of views on moral status.

Vulnerable persons and populations and their moral status evoke another moral resource, i.e., the human response of sympathy[4]. Moral sympathy is a trait identical with compassion. It usually involves empathy and in the context of health research would be included in the attributes of a virtuous researcher. While the capacity for sympathy does not necessarily imply generosity or favourable responses, it enables the researcher, albeit imperfectly, to enter the thoughts and feelings of the vulnerable participant[1]. People differ in their human responses and their capacity to evoke sympathy, with a greater degree of sympathy shown towards those close to them and less sympathy towards those remote from them.

Dissimilarity and distance from others may limit sympathy[1,4]. This situation of limited sympathy could arise in the context of health research where researchers and research ethics committee members are socially removed from the participant populations. Severely limited sympathy could help explain such phenomena as exploitation of vulnerable research participants.

While there are limits to the notion of moral status, Beauchamp and Childress affirm, and rightly so, that despite its limitations, the notion of moral status is of paramount moral importance as practices like slavery and abuses of human subjects in research succeeded historically in part because of defective criteria of moral status and inattention to basic rights and dignities, leading to exploitation of those with vulnerabilities. The recognition of moral status is important because it can generate interest in and support essential moral protections. It is therefore crucial to respect the moral status of participants with vulnerabilities in health research as this respect would serve to highlight that safeguarding them against exploitation would be a morally justifiable action. In addition, respecting their moral status would also give regard to protecting their dignity as human beings. Moral status, dignity and vulnerability are without doubt, intricately linked and as will be shown in subsequent chapters are necessary considerations in the context of health research.

3.3 HUMAN DIGNITY AS A CONCEPT AND ITS RELATIONSHIP TO MORAL STATUS AND VULNERABILITY

It has been claimed that human dignity, similar to vulnerability, is a ubiquitous concept found in the literature of many disciplines[5]. Its worth as a notion has been questioned and it has been criticised as at best a nebulous replacement for other, more precise notions and at worst, a “mere slogan” that acts as a smokescreen to cover up arguments and biases that

lack credibility[6-10]. Macklin claims that dignity is a "useless" concept in the panorama of bioethics and dignity means "no more than respect for persons or their autonomy"[7], i.e., the need to obtain voluntary informed consent, to protect confidentiality and to avoid discrimination and abusive practices. She states that it is not deserving of a space in bioethics. She argues that elimination of dignity from bioethics discourse would not make any difference to the content of bioethics[7].

Immanuel Kant attempted to place universal human dignity on a foundation based on rational thinking. One of his most important formulations of the categorical imperative was that one must act in such a way that every person is treated as an end and never as a means only. Treating others as mere means results in a maxim that cannot be universalised. The importance of dignity, rights and personal autonomy are underscored in this formulation[11-15].

For Kant, dignity meant the intrinsic worth that is inherent in being human[6]. All people possess dignity because of their rational autonomy and it is this human dignity that mandates equal respect for all persons and forbids the use of another merely as a means to one's own ends. Kant's clear celebration of autonomy and his embargo on the use of individuals as pieces of equipment have had a lasting impact in research ethics and more specifically in the context of protecting participants who are vulnerable. Research participants are not to be treated as a means to answer a hypothesis posed or as mere things, and every wrong done to them infringes their human dignity.

While this significant formulation of Kant's categorical imperative has the impact of evoking unembellished awe, at times of grandiose proportions, it is not without its drawbacks when viewed through the lens of rational, critical thinking. In situating human dignity within the

confines of rational autonomy, all other aspects of humanity and being human were dispensed with. Those without rational autonomy like children and the mentally ill, i.e., significant vulnerable groups in research ethics, did not qualify for the ownership of human dignity and hence equal respect. Therefore, because of his focus on rational autonomy, Kant's account of the moral life is very narrow and does not offer clear moral guidance on basic questions of human dignity. Moreover, dignity should not be downgraded to just Kantian autonomy as it is an intrinsic human value that is important as a matter of constructive morality in human relationships[16].

Forster contends that what makes humans tick and what makes them tick well, i.e., what makes them thrive, are all connected to human dignity[17]. Human dignity, to him, is the precondition for human thriving and flourishing. He further states that dignity is not necessarily connected to bodily integrity in that one can be physically compromised and still have dignity. Forster transports human dignity even further back to the time of Aristotle, Socrates and Plato and links the concept to virtue ethics. These philosophers conceived the aim of life as being to fare well and flourish and this could only be accomplished if humans developed virtuous character traits, capacities, skills or excellences in their conduct or behaviour[18]. A problem with this classical notion of dignity is that it lends itself to unwelcome distinctions between people and its focus is on individual agents and gives little consideration to the fact that thriving and flourishing are best achieved at a collective level. People, as social beings, do not do well by themselves. If dignity is a precondition for thriving and flourishing, then dignity is held in a joint account in a nexus of relationships[17].

Beyleveld and Brownsword sum up the situation quite aptly when they state[15]:

> "In sum, human dignity appears in various guises, sometimes as the source of human rights, at other times as itself a species of human right (particularly concerned with the conditions of self-respect); sometimes defining the subjects of human rights, at other times defining the objects to be protected; and, sometimes reinforcing, at other times limiting, rights of individual autonomy and self-determination."

Notwithstanding opponents of human dignity in bioethics dialogue, this phrase is an articulation of a fundamental value that is widely accepted. Reference to and reliance on human dignity is found in most of the leading international documents, including the following:

I. The Charter of the United Nations[19], Preamble:

> "We the people of the United Nations, ... reaffirm faith in fundamental human rights, in the dignity and worth of the human person, in the rights of men and women and of nations large and small ."

II. The Universal Declaration of Human Rights[20] Article 1:

> "All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood."

III. The International Covenant on Civil and Political Rights[21] Article 10:

> " ... all persons deprived of their liberty shall be treated with humanity and with respect of the inherent dignity of the human person."

IV. The International Covenant on Economic, Social and Cultural Rights[22] Article 13:

" ... education shall be directed to the full development of the human personality and the sense of its dignity."

V. The Universal Declaration on Bioethics and Human Rights[23] Article 3.1

"Human dignity, human rights and fundamental freedoms are to be fully respected."

VI. The Declaration of Helsinki[24] Paragraph 9:

"It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects."

VII. Council for International Organisations of Medical Sciences[25] Commentary on Guideline 2:

"A national or local ethical review committee responsible for reviewing and approving proposals for externally sponsored research should have among its members or consultants persons who are thoroughly familiar with the customs and traditions of the population or community concerned and sensitive to issues of human dignity."

VIII. The Universal Declaration on the Human Genome and Human Rights[25]. UNESCO (1997).

Reliance on human dignity in this Declaration is not only implicit, but it is also pervasive[15]. Respect for human dignity is stressed in the preamble several times and the first four Articles which comprise Part A of the Declaration are grouped under the heading of "Human Dignity and the Human Genome". Article 2 is most focussed on respecting human dignity and reads as follows:

> "(a) Everyone has a right to respect for their dignity and for their rights regardless of their genetic characteristics.
>
> (b) That dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity"

Following Part A, seven Articles explicitly refer to human dignity, three of which are specific to research:

Article 10:

> "No research or research applications concerning the human genome, in particular in the fields of biology, genetics and medicine, should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals or, where applicable, of groups of people."

Article 15:

> "States should take appropriate steps to provide the framework for the free exercise of research on the human genome with due regard for the principles set out in this Declaration, in order to safeguard respect for human rights, fundamental freedoms and human dignity and to protect public health."

Article 21:

> "States should take appropriate measures to encourage other forms of research, training and information dissemination conducive to raising the awareness of society and all of its members of their responsibilities regarding the fundamental issues

relating to the defence of human dignity which may be raised by research in biology, in genetics and in medicine, and its applications."

Moreover, several national laws, policy documents and guidelines also refer to human dignity. In SA, some pertinent legal instruments and guideline documents are:

I. The Bill of Rights of the Constitution of South Africa[27] Section 7 (1):

" ... affirms the democratic values of human dignity, equality and freedom."

II. The Bill of Rights of the Constitution of South Africa[27] Section 10:

" Everyone has inherent dignity and the right to have their dignity respected."

III. The Founding Provisions of the Constitution of South Africa[28] Section 1 starts off with:

" The Republic of South Africa is one, sovereign, democratic state founded on the following values:

(a) Human dignity, the achievement of equality and the advancement of human rights and freedoms."

IV. Ethics in Health Research: Principles, Structures and Processes,[29] the National Department of Health's Guidelines (SA Ethics Guidelines) for health research, besides pointing to issues involving dignity in its Preamble and Introduction, gives it full guiding principle status in Section 2.1, the Principle of Respect and Dignity:

"Respect for the dignity, safety and well-being of participants should be the primary concern in health research involving human participants."

V. The Health Professions Council of South Africa (HPCSA), the statutory regulator for the majority of health professionals in the country, in its General Ethical Guidelines for Health Researchers[30] refers to dignity in sections 6.1.1 and 6.2.1:

> "6.1 In order to always act in the best interests of research participants, health researchers should always:
>
> 6.1.1 Place the life, well-being, health, privacy and dignity of their research participants before all other interests."
>
> "6.2 In order to demonstrate respect for their research participants, health researchers should always:
>
> 6.2.1 Respect the privacy and dignity of research participants."

Table 1: PERTINENT INTERNATIONAL AND SOUTH AFRICAN INSTRUMENTS AFFIRMING DIGNITY

International	**South Africa**
• Charter of the United Nations, Preamble • Universal Declaration of Human Rights, Art 1 • International Covenant on Civil and Political Rights, Art 10 • International Covenant on Economic, Social and Cultural Rights, Art 13 • Universal Declaration on Bioethics and Human Rights, Art 3.1 • Declaration of Helsinki, Para 9 • Council for International	• Constitution of South Africa, Founding Provisions, Sec 1 • Constitution of South Africa, Bill of Rights, Sec 7 • Constitution of South Africa, Bill of Rights, Sec 10 • Ethics in Health Research: Principles, Structures and Processes, Sec 2.1 • General Ethical Guidelines for Health Researchers (HPCSA), Sec 6.1.1, 6.2.1

Organisations of Medical Sciences, Guideline 2 • Universal Declaration on the Human Genome and Human Rights, Preamble and several Arts.	

None of the documents mentioned above defines or explains human dignity. This state of affairs is similar to most research ethics policy and guideline documents (both international and country level) where vulnerability is mentioned and protections are pronounced; vulnerability is either, ill-defined, not defined or not explained. However, it is clear that the dignity of the human person as a basic ideal is universally acknowledged and that this acknowledgement is carried through within and between national boundaries. Moreover, jurists, philosophers and political leaders increasingly maintain that because human dignity is generally recognised as a basic ideal, independent support for this notion is unnecessary[31]. Schachter states that dignity has become so significant that it is widely invoked as a legal and moral ground for dissent against degrading and abusive treatment and that no other ideal seems so clearly accepted as a universal good[31]. Most certainly, invoking human dignity in these instruments establishes a universal baseline beneath which no treatment of human beings should ever drop. This baseline could well be of value in establishing boundaries for the protection of vulnerable participants in health research as will be seen in the Vulnerability Scale that has been developed in Chapter 7.

3.3(A) The Meaning of Human Dignity

Human dignity is not specifically defined in the international instruments and its meaning, content and foundations are not explicitly described. Hence its inherent meaning has been left to perception, instinct and intuition, all of which are essentially influenced by cultural

factors. When dignity is drawn into the equation in particular concrete situations, it is assumed that violating human dignity can be recognised even though the term is abstract and not defined[11], and to quote Schachter[31] "I know it when I see it even if I cannot tell you what it is."

However, operational difficulties do inevitably arise because of the lack of definition of human dignity in general terms in international and national policy and guideline instruments. These include problems with drawing specific implications for relevant conduct. The etymology of the word "dignity" draws from the Latin term "dignitas" which means worth[31]. One of the meanings of dignity in the South African Concise Oxford Dictionary [32] is "intrinsic worth" – a meaning that could well be used to define "dignity" in the instruments referred to above.

It follows, therefore, that respect for human dignity would translate to respect for the intrinsic worth of the individual, independent of the individual's capacity of rational autonomy. This in turn translates to how one (moral agent) would treat the other (individual with reciprocal moral status). In the arena of research ethics; the moral agent would equate to the researcher and the individual with reciprocal moral status, the participant.

Coercive acts in health research are incompatible with due respect for the dignity of participants. Being demeaned or humiliated as a result of participation in research clearly violates the dignity of participants. This now draws into the equation the psychological dimensions of human dignity. Notably, this type of lack of respect could destroy or reduce the self-respect that is so necessary to the intrinsic worth of being human. Respect for intrinsic worth recognises that a person is entitled to his or her own beliefs, attitudes, ideas

and feelings. Physical or psychological coercion is as striking an affront to human dignity as physical abuse or mental torture both within and outside the research context.[31]

The notion of human dignity involves a complex concept of the individual. While appreciating a distinct personal identity interwoven into individual autonomy and responsibility, it also gives recognition to the individual self as part of a larger collectivity that must also be considered in the meaning of the inherent dignity of the person.[31] Even as part of a larger collectivity, no one individual will have more human dignity than any other[14]. Metz rightfully affirms that having human dignity in a sense could mean possessing a superlative non-instrumental value that deserves respectful treatment. Human dignity is "good for its own sake and to a greater degree than anything else in the physical world and that grounds human rights[14]." Specific reactions are demanded by the value of human dignity because having human dignity means being owed respect of the type associated with human rights[33]. Basically, to recognise one's human rights is to uphold an important natural duty to treat someone in a certain positive way; e.g., dignity is the value that supports the judgement that there are strong moral grounds not to discriminate against or exploit research participants, especially those with vulnerabilities. Dignity refers to the inviolability of human life and in this way expresses the outstanding position of human beings in the universe. It also expresses the moral responsibility of individuals to each other and in this context Rendtorff offers an explanation for human dignity that links in well with moral status and can also be applied as a basis for protecting individuals with vulnerabilities. Rendtorff's explanation is as follows[16]:

1. It is an expression of the intrinsic value of the human being in a community or society;

2. It includes respect for the moral agency of the individual;
3. It signifies that every individual must be considered as being without a price and unable to be commercialised;
4. It also refers to the indeterminate position of human beings in the universe because they are able to create their own destiny;
5. Self-esteem, pride, shame, feelings of inferiority and degradation are essentially matters of human dignity expressed in relationships between individuals;
6. Dignity can establish restrictions on individuals in certain situations because of the necessity of human civilized behaviour.
7. Dignity relates to metaphysical experiences of individuals in existential limit by degrading treatment; and
8. In the context of human rights, human dignity indicates the intrinsic worth and fundamental equality of all human beings.

The above analysis makes a compelling argument that human beings are morally important because they have dignity. It is because we are human that we have dignity; i.e., dignity is characteristic of being human and it is the essential and inviolable core of being human and also of what gives one moral status. The analysis also makes a compelling argument that respect for human dignity and moral status are indispensable components of ethical standards for the treatment of participants in health research and that every human being, regardless of the degree to which he or she is autonomous, or vulnerable, has invincible worth. Human dignity and moral status are natural properties of research participants which must be recognised by researchers and research ethics committee members. Respecting

human dignity and moral status is core to protecting vulnerable research participants against exploitation and other forms of harms and wrongs.

Understanding vulnerability in the health research context is examined in the section that follows.

3.4 UNDERSTANDING THE NOTION OF VULNERABILITY

Over the past few decades, research ethics has witnessed a proliferation of discussion and debate on the steady manifestation of vulnerability in almost all aspects of its discourse, with concern for vulnerability occupying the centre-stage of bioethical enquiry. Despite it being linked in most research ethics guidelines and codes, both international and national, to questions of justice in selection of participants, limitations of capacity to provide informed consent and unequal relationships between disadvantaged groups and researchers and sponsors, it has been a very poorly examined concept from an ethical perspective in the context of research ethics. Similar to human dignity and moral status, these documents are either silent on the meaning of vulnerability or where attempts have been made to explain the concept, these have been very sketchy. Because so many are now considered vulnerable in the context of health research, concerns have been expressed that the concept has become too broad and hence lost its gravity[34-37].

Generally, bioethical literature links vulnerability to risk of harm, exploitation and limited capacity for autonomy. Exploitation is linked to violation of human dignity and disrespect of moral status. The problem with all this theorizing on vulnerability is that vulnerability as an ontological condition of humanity[38,39] has not been adequately examined as separate to context-specific and context-sensitive kinds and sources of vulnerability. The question that

therefore comes to the fore is how human vulnerability should be understood. At one end of the spectrum, we find that all human life is conditioned by vulnerability because of our "embodied, finite and socially contingent existence"[40] whereas at the other end of the spectrum, the term denotes more than the ordinary universal vulnerability of humanity. People vary in their exposure to risk and in their abilities and resources to counter such risks. It is to these people with greater exposure to risk and decreased resources to counter risks that greater duties of justice and specific moral obligations are required. Hence, many vulnerabilities move beyond the universal and are context dependent and warrant ethical responses because of their significance within particular settings[16].

Ordinary vulnerabilities as a result of our humanity are unavoidable and the more than ordinary vulnerabilities should be safeguarded against in the health research context. It is necessary to identify the different sources of vulnerability and the different ways in which they are manifest in order to correctly inform appropriate moral responses to these vulnerabilities. Meticulously enunciating the concept of vulnerability will, in addition, assist in responses not being too narrow or too broad. In the former case, the source of the vulnerability that merits a response may not have been recognised and in the latter, a person or a group may have been misidentified as being more than ordinarily vulnerable with resultant paternalistic protections[40].

Rogers, Mackenzie and Dodds state that the theorists who understand vulnerability as an ontological condition of our humanity associate the concept with its derivation from Latin, *vulnus* which means "wound", and with the capacity to suffer, innate to human embodiment[40]. Illness, propensity to disease, aging associated with impairment and disability, and death and dying are inescapable to our corporeal existence[40]. Ordinary

human vulnerability is also linked to the inherent sociality of human life in that embodied social beings are both dependant on the care and support of others and also vulnerable to their actions. Hence, the universal dimensions of vulnerability are emphasised and the concept is grounded in human embodiment, sociality and dependency[40]. It is therefore unambiguously clear that the human condition in itself implies vulnerability. All humans are permanently exposed to the risk of being wounded both physically and mentally. Vulnerability is an inescapable dimension of both the life of individuals and the shaping of human relationships. Human vulnerability entails that everyone, at some point or the other, lacks the ability or the means to protect themselves[41].

Michael Kottow[42], similar to the theorists above, states that vulnerability is a human condition from which we all suffer, and because of its universality, we all agree that equal protection is due to every member of society. However, when it comes to research on human beings, he states that participants are not vulnerable, but they are susceptible to harm, especially if the research is done in less developed countries. He alleges that research ethics has been slow to observe this notion of susceptibility and by mislabelling participants as vulnerable rather than susceptible, researchers and sponsors avoid seeing the deprivation these people suffer and hence neglect their ethical obligations to offer them remedial help. He defines susceptibility as:

> "... a determined state of destitution and therefore can only be reduced or neutralised by measures that are a) specifically designed against the destitution in question, and b) actively applied. The susceptible, like the sick, require targeted treatment to palliate their misery."

He goes on to illustrate that the distinction between vulnerability and susceptibility also symbolises the difference between being intact but fragile (vulnerable) and being injured and being predisposed to compound additional harm (susceptible). An awareness of this distinction, he states, should assist in giving additional pressure to the rejection of double standards in research. He advocates removing the term vulnerable as it is currently used from the research ethics literature completely. This revolutionary approach to vulnerability has not met with much support. It is my opinion that Kottow's recommendation has not been supported largely because he arrived at a conclusion without adequate and careful analysis of the notion of vulnerability. Moreover, his focus was on the disparities between developed and less developed countries and issues of distributive justice. He was silent on the other types of vulnerabilities commonly seen in health research. This is a very narrow and dangerous approach to the debate on vulnerabilities in health research. In addition, he gave very little regard to the reasons behind the escalation in emphasis of the term in research ethics, i.e., the scandals and tragedies that have bedevilled health research through time resulting in principled responses by moral agents with respect to the need to protect participants in research, the subject matter of the following chapter. Although Kottow's standpoint does very little in assisting with a way forward as regards the nebulous dimensions that vulnerability has assumed in research ethics, his view on the issue is mentioned here for the sake of completeness.

While vulnerability makes one susceptible to harm, vulnerability should not be replaced with susceptibility. In addition, vulnerability should be understood as essentially relational with one being vulnerable to certain types of threats to one's interests under the control of particular agents. In protecting the vulnerable, it is important to take into consideration that

because vulnerability is essentially relational, a person's vulnerability will give rise to special responsibilities on the part of those to whom she or he is vulnerable. Goodin in his book, "Protecting the Vulnerable", proposes the "principle of protecting the vulnerable." This translates to an obligation on the agent to act in such a manner as to prevent harms and protect the interests of those who are particularly vulnerable to the actions and choices of the agent[43]. Goodin's principle is grounded in the claim that vulnerability is the source of moral claim. In his view, most fundamental duties and responsibilities arise from relationships of dependency and interdependency that are not chosen and many relationships are less voluntary than often assumed. It is not the voluntariness or otherwise of the relationships that generate obligations but the individual's dependency, making her / him vulnerable to the agent's actions and choices. In his principle, vulnerabilities are firmly linked to correlative responsibilities, i.e., the more vulnerable the person, the greater the agent's responsibility to protect the individual's interests.

Goodin underscores the conceptual connections between vulnerability, harm and exploitation. This then allows for ease of identification of the potential for harm and exploitation in relationships entailing asymmetrical dependency, power, ability, resources, education or need. In his view, exploitation would mean taking unfair advantage of others. In relationships where the dynamics are such that inequalities of vulnerabilities or dependencies exist, opportunities arise for more powerful people to take advantage of more vulnerable people. Goodin's principle imposes an obligation on the more powerful party to be particularly vigilant against the misuse of their position of power, authority or privilege to take unfair advantage of the weaker ones and in addition, to protect those who are vulnerable to them. Furthermore, Goodin sees vulnerability as a matter of degree

dependent on the number of needs arising in the relationship and the amount of assistance that would be required to meet those needs.

Goodin's principle resonates harmoniously with the protections espoused in most research ethics guidelines and policy documents. However, it is lacking in that he gives minimal consideration to the obligations of fostering agency and autonomy and unwittingly opens the door to unwelcome paternalism.

Rogers, Mackenzie and Dodds [40] support relational theories[44-46] of autonomy in the context of vulnerability. Here, the case is made that autonomy is a socially constituted capacity. Extensive social scaffolding is required for its development, support and meaningful exercise. Its development can be impaired and its exercise impeded where relationships are exploitative or oppressive. Our inescapable dependency resulting in vulnerability to others provides the basis of this approach to autonomy. In the relational approach, agency and some degree of autonomy are important for a flourishing human life.

Goodin's principle of protections against harms, combined with relational approaches of providing the support necessary to promote autonomy of those that are more than ordinarily vulnerable, emerge as some of the substantial threads for the analysis of the tapestry of vulnerability in health research.

3.5 CONCLUSION

It is evident from the above that moral status, human dignity and vulnerability are closely linked. Vulnerability in the context of research ethics must be differentiated from the ordinary universal vulnerability of being human. Relationships are a necessary party to vulnerability. Careful analysis of the notion of vulnerability assists in avoiding viewing the

concept too narrowly or too broadly. Respecting the moral status and human dignity of research participants are important safeguards against exploitation of their vulnerabilities in the research context. Moreover, this ensures that because of their inherent worth they are protected from being treated as a means to an ends they may not endorse. In the following chapter, the results of violating the human dignity and not respecting the moral status of research participants will be illustrated as the reasons for such a robust focus on vulnerability in research ethics and its ensuing protectionist response.

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Chapter 4: DISASTER, DISGRACE AND DISHONOUR: THE ORIGIN OF PROTECTIONISM FOR THE VULNERABLE IN HEALTH RESEARCH

4.1 INTRODUCTION

Carol Levine has stated that research ethics was "born in scandal and reared in protectionism"[1]. Concerns about the conduct of researchers in healthcare date back to at least the end of the nineteenth century[2]. Because individuals and groups were being exploited and harmed, the concept of vulnerability emerged and steadily gained prominence[3,-5]. It is hence not surprising that, in parallel, concerns over the participation of vulnerable individuals and groups grew in prominence in national and international policy and guideline documents[5]. With this surfaced the all too familiar deontological and utilitarian tensions between scientific progress and societal interests on the one hand and individual rights and interests on the other, with the dilemma being identified as the goal of health research which is to improve human well-being. There is no question that health research sets out to acquire not only theoretical knowledge but also gains and benefits for many people and often society as a whole, and is therefore justified. The quandary, though, is how such an important shared purpose can be pursued with full protections of the rights and dignity of individuals[2], in particular those with vulnerabilities. Using a historic approach to inquiry, in this chapter I start off with a discussion on protectionism in health research and explore the scandals and tragedies in health research that led to the need for protectionism and the safeguarding of research participants especially those with vulnerabilities. This is followed with an examination of the Nuremberg Code and its significance and an introduction to protectionism in health research in SA. Unless specified, the term vulnerable in the remainder of this thesis is used to denote more than ordinary

universal vulnerability, i.e.; specific vulnerabilities that are determined by context and circumstances, including physical traits.

4.2 PROTECTIONISM IN HEALTH RESEARCH

According to Moreno[6], protectionism as a tenet in research ethics is the doctrine that human beings should be protected from the risks of participating in research. While protectionism per se should not be contentious, unless it is believed that scientific progress overrides the interests of human participants, controversy arises because of the lack of agreement on the interpretation and application of the doctrine in health research. Reliance on the moral virtues of the researcher could be perceived as an alternative to protectionism[6]. The problem with relying on this alternative is that it leaves the researcher with a high degree of control over participant management, a situation that existed as the norm before the middle of the last century and resulted in the many abuses and tragedies in health research. Even researchers with the very best intentions and abundant goodwill towards humanity can, through the zealous pursuit of their good goals be blinded into cutting corners. The classic 19th century novels Frankenstein[7] by Mary Shelley and Dr Jekyll and Mr Hyde[8] by Robert Louise Stvenson, illustrate this brilliantly.

Moreno goes on to demonstrate the historical emergence of three versions of protectionism, weak, moderate and strong. The type of protectionism is framed according to the amount of discretion researchers have over participants enrolled into studies[6]. Weak protectionism allows for reliance on researcher discretion with minimal constraints in the form of guidelines. Moderate protectionism establishes a framework of rules and policies within which the researcher practices discretion. Strong protectionism entails highly

constrained researcher discretion in the milieu of direct interventions by third parties, including active monitoring of research[6].

For a good understanding of the current system of protectionism, and its application to vulnerable individuals and groups, an understanding of the historical origins of protectionism is essential.

4.2(A) The Historical Origins Of Protectionism

4.2(A)I Tragedies in Health Research

The importance of health research must be acknowledged and moreover celebrated right at the outset. It is without doubt that studies in the healthcare context have improved well-being for almost all people globally. Even very early experiments with humans had positive outcomes. In the 1700's James Lind, a British surgeon, studied scurvy in sailors over a six year period aboard the HMS *Salisbury.* He used an interventional study design in which some sailors were provided a diet that included fresh fruits and vegetables and others, none (the control arm as in contemporary research methodologies), and in so doing was able to demonstrate that sailors in the control arm were more likely to develop scurvy as compared to those that received fresh fruits and vegetable[2,9]. Two and a half decades later, Edward Jenner tested the cowpox vaccine on his children and other children in the area where he resided. These children did not get smallpox, hence the origin of the smallpox vaccine[2,10]. Ironically, both these studies would today be regarded as morally highly problematic at best, and at worst, unethical.

While these successes of research were being celebrated, abuses and exploitation with resultant violations of human dignity and disrespect for moral status were starting to

surface in the field and by the 1890's, anti-vivisectionists were already calling for laws to protect children because of the increasing numbers of institutionalised children being subjected to vaccine experiments in Europe and the United States, and just after the turn of the century, the first attempt to test a polio vaccine was thwarted after the American Public Health Association condemned the program[6]. In 1897, Guiseppe Sanarelli, an Italian bacteriologist, injected five people with an organism that he had isolated to prove his postulation that it caused yellow fever. His action, which resulted in severe harm being suffered by the five, was widely criticised and remembered for some time thereafter[2]. By the end of the nineteenth century, research rules were imposed by the Prussian State[11,12], and the United States Congress contemplated the prohibition of medical experiments for particular groups, such as pregnant women, in the District of Columbia[6,13]. The Prussian Ministry of the Interior issued a regulation in 1891 that would not allow the treatment of tuberculosis with tuberculin against the patient's will, and although this was specific to the treatment and not research, it was amongst the first initiatives at clearly defining medical ethics regulations[12]. It also preceded research ethics regulation in Prussia, where in 1900, the Prussian Ministry of Religious, Educational and Medical Affairs issued a legal directive that "absolutely prohibited" non-therapeutic interventions on humans if the subject did not consent to this unequivocally. In addition, proper explanation of the adverse consequences of the intervention was necessary before the subject consented. This legal directive, a form of moderate protectionism, affirmed that voluntary informed consent as a requirement was fundamental to ethically sound experimentation[12].

4.2(A)II The Yellow Fever Board

In the wake of the Sanarelli scandal, Walter Reed was commissioned by the US surgeon general to identify the cause of yellow fever, a raging epidemic in Cuba at that time. Because of an atmosphere of huge disquiet as regards human experimentation, Reed adopted what could be described as Moreno's strong protectionist approach. He developed ethical guidelines to act as safeguards for the research which was to be overseen by the US Army's Yellow Fever Board. This Board could be described as the forerunner to what is today known as the Research Ethics Committee (REC) or Institutional Review Board (IRB). The guidelines included: self-experimentation by members on the Board; written contracts that clearly explained the risks involved in the experimentation for locals who were not members of the Board (the precursor to written informed consent forms); payment in gold for locals who volunteered; $100 compensation for those who became ill with yellow fever; enrolment to be restricted to adults more than 24 years of age; children to be excluded and all journal publications on the research to use the phrase "with his full consent"[2,14].

4.2(A)III Self-Research: The Impact of the Illusion of Medical "Martyrdom"

The safeguards utilized by the Yellow Fever Board, the contract process for obtaining explicit consent and the heroism of the Board members who participated as research subjects helped legitimise health research in the aftermath of emerging scandals[2]. It also led to medical researchers being "largely inoculated against regulation by the legendary status of self-experimentation by the Yellow Fever Board members"[6]. Dr Jesse Lezear, also as part of a self-research process, died after subjecting himself to mosquito bites. This helped to confirm the hypothesis of disease spread[2,6]. Reed's untimely death a few years later, as a result of an error by a colleague, was mistakenly believed to be because of his involvement

as a volunteer subject while on the Board. This added to the illusion that medical researchers were of such exceptionally moral character that they should be elevated to the status of "martyrs"[6]. Other exemplary cases of self-experimentation in the twentieth century include Werner Forssmann who, in 1930, practiced cardiac catheterisation on himself and won a Nobel Prize in Physiology or Medicine in 1956[15] for his work; and JBS Haldane who subjected himself to various gases in decompression chamber experiments in an attempt to find out how best the welfare of sailors in submarines could be protected[15]. However, it was the Reed Yellow Fever Board example that served as the primary reference point and a justification for self-regulation in medical research for many decades to follow. Despite the research tragedies of World War II and the Nuremberg Code of 1947[16], when medical researchers were being subjected to new levels of scrutiny in the 1960's, distinguished physician-scientist Walsh McDermott referred to the Reed example in order to stress the social worth and accompanying high moral standing of medical research[17].

4.3 THE EMERGENCE OF EXPLOITATION OF THE VULNERABLE

Notwithstanding the examples of Lind, Jenner and self-experimentation as cited above, examples of experimental research where people with vulnerabilities have been harmed have surfaced since medieval times. While not typical of experiments of that era, Frederick II is said to have experimented with neonates so he could obtain knowledge on the development of language in humans[12]. Avicenna, an Arabian physician and philosopher, tested interventions directly on people because he felt that testing these on animals would not have any relevance for its use on humans[12].

Briggle and Mitcham assert that, in the main, the first studies of experimentations on humans took place on slaves and the poor[15] and that this coincided with the development

of the new science of anthropology which Europeans used to study non-European peoples[15]. They state that, generally speaking, human experimentation was initially undertaken on those who were considered to be uncivilized and often less than human with diminished or no moral status. Even colonial and imperial rule was often justified by anthropological research which described the native peoples of Africa, the Americas and Asia as being of inferior intelligence and ability and hence in need of paternalistic rule by European powers or immigrants. Their anthropological findings were based on the category of race[15].

Amongst the greatest tragedies in human research experimentation, the heinous studies conducted during World War II by Nazi doctors on "racially inferior" Jews and other "deficient" groups[2,3,5,6,15] and by Japanese doctors on people, in the main Chinese, that they determined to be less than human[15,18,19] take centre stage as the most notorious.

4.3(A) Japan's Biological Warfare Program

An offensive and defensive biological warfare program was carried out by the Imperial Japanese Military between 1932 and 1945. The program, under the leadership of General Shiro Ishii, evolved in three stages and was responsible for some of the most notorious war crimes during World War II[18,19]. It started off as a laboratory at the Army Medical University in Tokyo in 1932, developed into a first research station in Beyinhe, China from 1932 to 1936 and subsequently advanced to a system of research centres in different Chinese cities from 1936 to 1945. The research centres included Unit 731 in Harbin, Unit 1644 in Nanjing, Unit 1855 in Beijing, Unit 100 in Mengjiatung and Unit 8604 in Guanzhou. The headquarters of the research centres and the biological warfare program was Unit 731 which functioned both as a university research department and a concentration camp[19].

Experiments were conducted using a variety of potential biological warfare agents so as to develop biological weapons. The agents included *Vibrio cholera, Shigella dysenteriae, Salmonella typhi, Salmonella paratyphi, Brucella melitensis, Yersinia pestis, Francisella tularensis, Corynebacterium diphtheria, Bacillus anthracis, Mycobacterium tuberculosis and Rickettsia prowazeki.* Controlled laboratory studies that investigated the lethality of the viruses or bacteria in biological warfare were conducted. The efficacy of weapons developed in this way was then tested through field studies in the different Chinese cities. Japanese scientists also conducted experiments whereby reactions of humans to cold, heat, electroshocks, x-rays, bloodletting, hunger and thirst were investigated. Victims were routinely killed for autopsy results of the research. The bodies were then incinerated in the crematory of Unit 731[19]. More than 3000 people worked at Unit 731 at the height of the research activity. Tens of thousands of men, women and children, 70% of whom were Chinese, died as a result of being subjected to experimentation conducted in these Units. Close to 30% of the subjects were Russian. Others included people from South East Asia and the Pacific Islands[18].

At the end of the war, as a result of the Khabarovsk War Criminal Trials, a small number of mainly low-ranking members from the Units received prison sentences, while at the Tokyo War Criminal Trials, these human experiments were only mentioned once by the prosecutor and the presiding judge decided not to pursue the charges because of a lack of evidence. Of note, both the prosecutor and judge were American[19]. Many scientists from Unit 731 went on to acquire prominent careers after the war in politics, academia, business and medicine. One of the reasons these scientists were not tried for war crimes similar to the trial of the Nazi scientists is probably because the information and experience gained from those

studies of biological warfare was of great value for the United States biological weapons development program and it is alleged that a deal to this effect was concluded between the United States and Japan in 1948[18]. The prosecution of the Japanese scientists could have interrupted the process of additional information of this nature being obtained and would have made public the information already obtained by the US, thereby destroying its military strategic value to the latter[19].

4.3(B) The Nazi War Atrocities

In the aftermath of World War II, the horrors of experimentations on concentration camp inmates were publicised during the Nuremberg Trials in Germany which lasted from December 1946 to August 1947.[3,5,6,15,20]. The trial specific to the medical atrocities is the case of the *United States of America* v *Karl Brandt et al* - also referred to as the Nuremberg Doctors' Trial[21]. Nazi doctors and bureaucrats were tried by the Allies for subjecting thousands of concentration camp prisoners to egregious experiments. 1,750 victims were identified in the indictment. This was an extremely small proportion of those killed or injured. There were 23 defendants, 20 doctors and 3 bureaucrats, and all of them were indicted with war crimes and crimes against humanity[20]. They were just a token assortment selected from the 350 candidates[2,6]. Telford Taylor, a United States brigadier general and chief counsel for the trial, described the studies that were performed in his opening statement before the Nuremberg Military Tribunal[2,22]. Emanuel, Crouch, Arras, Moreno, and Grady have summarised the experiments from the opening statement as follows[2]:

- *"High-altitude (low-pressure) experiments:* Prisoners were put into low pressure tanks to see how long they could survive with little oxygen. Many of those who did not die immediately were put under water until they died; autopsies followed.

- *Freezing experiments:* Prisoners were forced to remain outdoors without clothing in freezing weather for 9 to 14 hours, or were forced to remain in a bath of freezing water for three hours at a time. Rewarming of the bodies was then attempted, often without success.
- *Malaria experiments:* Prisoners were infected with malaria and then given a variety of supposedly anti-malarial drugs. Many died from these drugs.
- *Mustard gas experiments:* Prisoners were deliberately wounded and the wounds then infected with mustard gas, or they were forced to inhale mustard gas. Experimentation with various treatments followed.
- *Sulphanilamide experiments:* Wounds were inflicted on prisoners, and bacterial culture, gangrene-producing culture, wood shavings or glass shards were forced into the wounds, followed by treatment with sulphanilamide for wound infection. A control group consisted of prisoners who were subjected to the wounds and infections, but not given the sulphanilamide.
- *Typhus experiments:* Prisoners were injected with an antityphus vaccine and then infected with typhus. Prisoners in a control group were infected with typhus and received no treatment; others were infected with typhus simply to ensure that the typhus virus remained active within the prison camps.
- *Poison experiments*: Various poisons were fed to prisoners through their food. Most died immediately, and those who did not die were killed for purposes of autopsy.
- *Incendiary bomb experiments*: Prisoners were burnt with phosphorus material taken from English incendiary bombs so that doctors could examine the wounds.

- *Sterilization experiments*: Because sterilization by surgical means was considered too costly and time consuming, prisoners were subjected to chemical sterilization and x-ray sterilization experiments."

In addition to the above, anthropological studies in which hundreds of prisoners were killed so as to assemble a collection of skeletons were also conducted. They were killed because they were considered by the Nazi's to be prototypes of what they called the "repulsive but characteristic subhuman"[2]. The "Jewish Skeleton Collection" was one of the activities of the SS-Ahnenerbe (Ancestral Heritage) Society headed by Wolfgang Sievers. It was a collection of heads and bodies of murdered Jews compiled by August Hirt, anatomist at the Reich University of Strasbourg[20].

The aim of detailing the atrocities cited above is to underscore the robust and relentless exploitation and wrongs prevalent in medical studies at that time. The vulnerable were considered to be subhuman, of decreased intelligence, of no moral status and lacking human dignity. The Nuremberg Trial raised insightful issues on how and why doctors who were trained in the Hippocratic tradition were able to commit such egregious and heinous medical crimes. As medicine was supposed to be one of the "… world's most advanced scientific cultures …"[20] questions on whether these doctors actually understood that they were committing a crime were raised. The defendants' lawyers during the Nuremberg Doctors' Trial, using a utilitarian approach highlighted that the Allies had also engaged in medical experiments in servicing the war effort and hence there should be no grounds for the indictment[6, 20]. They also argued that the type of medical experimentation performed in the concentration camps (which included Auschwitz, Dachau, Sachsenhausen, Natzweiler Ravensbrük and Buchenwald)[20] during the war was commonplace even before the war. They

pointed out that there were no legal restrictions on such experiments[15]. As the prosecution's attempts at demonstrating that there were clear international rules governing medical experimentation wavered, the judges attempted to create their own set of rules, and two medical advisors to the judges, Drs Andrew Ivy and Leo Alexander, were tasked to do this[2,6,15]. They drafted a ten point memorandum entitled "Permissible Medical Experimentation"[15], which then became known as the Nuremberg Code[16], the aim of which was to obtain a way forward on one of human experimentation's most fundamental conflicts: that of balancing the need for advancing medical science for the benefit of society with the rights of individuals to "personal inviolability, autonomy and self-determination"[20]. While the judges at the trial were all American nationals, the trial was based on international law as outlined in the "London Agreement on the Punishment of the Major War Criminals of the European Axis" (London Charter) in 1945[20]. Although international law had previously not codified specific war crimes, the crimes specified in the London Charter included those contained in the Hague Regulation of Warfare (1907)[23], which Germany had signed[20]. Germany had also signed the Kellogg-Briand Pact of 1928[24] which condemned aggressive wars, and the Geneva Convention[25] in 1929 which specified in its rules on how prisoners of war should be protected[20]. Therefore both the judgement and the Code were *de jure* international in character. The Nuremberg Code (see Annexure II) is hence undoubtedly the first international medical ethics code[20].

It is interesting to note that besides Germany being signatory to international instruments for protection of prisoners of war, by the end of the 19th century it started developing some of the most stringent and clearly defined medical ethics regulations[12] and in March 1931, the Reich Health Council (*Reichsgesundheitstrat*) issued the Regulations Concerning New

Therapy and Human Experimentation[26] (Annexure III). The far-reaching directives in these regulations were "… among the most comprehensive research rules by any standard at the time …"[12]. Some aspects which involved contentious issues like voluntary informed consent, therapeutic research, non-therapeutic research and benefits were much more structured and detailed as compared to the principles in the Nuremberg Code. It was stressed that the rights and dignity of subjects had to be protected at all times and on the issue of non-therapeutic research it underscored the prohibition of experimentation in all cases where consent had not been given. Unfortunately, despite the strong protectionism in the Guidelines, respect for moral status, upholding dignity and according special protections for subjects enrolled in research – fundamental values highlighted in the Reich Health Council's regulations - were ignored.

4.4 SIGNIFICANCE OF THE NUREMBERG CODE

Although this Code, consisting of ten characteristics for acceptable research involving humans, is one of the most widely known documents of ethics in research,[2] and is often cited as the most important document in the history of research ethics[27-30], it was not cited in any of the findings against the defendants and never became a formal part of law in Europe or North America. While it is clear that the courts believed protections were needed, it is unclear how much weighting they wished to give the Code in the operations of medical research[6]. Although they were urged by Drs. Ivy and Alexander to identify persons with mental disorders as in need of special protections, they declined to do so. In fact, the requirement that there must always be voluntary informed consent for all participants in any form of research undermined the relevance of their Code to research designed for vulnerable people with diminished or absent competence[6].

Nevertheless, the Nuremberg Code established fundamental human rights in medicine and research and placed the welfare of patients in the foreground of medical and research practice[20]. In addition, it would seem that the key contribution of the Code was to merge Hippocratic ethics and human rights into one code[27]. While moderately protectionist, its principles are strongly reflective of values emanating from deontology and virtue ethics. Principle 1, in linking the experiment with the voluntary consent of the experimental subject, has been of importance for the history of research ethics in that it reaches far beyond Nuremberg[20]. The status of voluntary consent had become a central element of health research since the late 19th century, albeit not respected as such. Because of the Code, and as part of the Nuremberg judgement, the principle of autonomy was for the first time assigned into international law[20]. International law is a combination of treaties and customs that regulate the conduct of states among themselves and draws from three main sources: customary international law, treaties and conventions and soft law (guidelines and non-binding judgements)[31].

Principles 2-8 and 10 of the Code require that physician-researchers protect the best interests of their subjects. Principle 8 specifically refers to their wellbeing, and principle 10 places an obligation on the researcher to terminate the experiment at any stage should there be reason to believe that continuing the experiment would in all probability result in injury, disability or death of the experimental subject. Principles 1 and 9 specifically refer to the protection and rights of the experimental subject and also proclaim that subjects can protect themselves as well. Principle 9 gives the subject as much authority as the physician-researcher to end participation before its conclusion[27]. As this principle was formulated as a right, it constituted another legal precedent[20].

The Nuremberg Code established in a distinctive and exceptional way a combination of Hippocratic medical ethics and human rights, the latter being part of international law. While Hippocratic medical ethics was an important pre-condition to protect the welfare and lives of patient-subjects, it was clearly insufficient in protecting human lives in the context of exploitation and abuses described above. Research subjects required specific rights that were part of international law if they were to be sufficiently protected from harm. Hence it can be stated that the Nuremberg Code is both a medical ethics code and a legal code[20]. Moreover, the influence of the Code on international documents (discussed in the previous chapter) is substantially significant and the Universal Declaration of Human Rights[32] which was adopted a year later in1948 makes claims closely associated with the Code[15]. The Preamble of the Declaration talks to the "disregard and contempt of human rights that have resulted in barbarous acts which have outraged the conscience of mankind." Article 5 states that "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment." and Article 27 states that "Everyone has the right freely ... to share in scientific advancement and its benefits." When read together, the Nuremberg Code and the Universal Declaration of Human Rights can be interpreted as establishing a basis for underpinning the principles of free and informed consent[15] and avoiding harms and exploitation in scientific experiments with human participants.

4.4(A) General Use of the Nuremberg Code

Despite the Nuremberg Code being given the status of an International Code for the ethical conduct of research at the end of the Nuremberg Trial, and despite it having substantial influence on international documents like the Universal Declaration of Human Rights, for many years after the introduction of these documents, researchers continued to function as

"business as usual" and did not seem to recognise that there were good reasons for concerns as regards protecting human participants in research[2,6,33]. The Nazi transgressions were attributed to the abnormalities associated with a totalitarian regime with unquestionable brutality. The notion was that researchers working in democratic states would not succumb to atrocities and exploitation of vulnerable participants enrolled in research. The Nuremberg Code was therefore viewed as not applicable to those in civilized democracies. It was a document necessary to restrain barbarians[2,33]. However, evidence emerged in the fifties that vulnerable individuals and populations were being exploited and harmed in research in democracies like the US, despite the safeguards in the Nuremberg Code[34]. Faden, Lederer and Moreno report that some researchers were starting to be genuinely and deeply concerned with problems surrounding experimentation with humans[33]. They also state that the organisers of the First International Congress of Neuropathology were so concerned that they invited Pope Pius XII to address them at their conference which was held in Rome in 1952. He was asked to speak on "The Moral Limits of Medical Methods of Research and Treatment" to a group of 427 medical researchers from all parts of the world. He highlighted to them the relatively recent lessons from the Nuremberg Trial and firmly endorsed the requirement that it was necessary to obtain informed consent from participants before enrolling them into trials. According to the Pope, the Nuremberg trials taught that "... man should not exist for the use of society; on the contrary, the community exists for the good of man."[33] These concerns about the power of medical researchers could have been the reason for the gradual disappearance from professional discussions of the term 'human experiment' and its replacement with the more reassuring term, 'research'[6]. Moreno reports that on the whole, the world of health research from the late forties to the mid-sixties was one in which a weak form of

protectionism existed, where responsibility for the participant was left to the discretion of the researcher steered by guidelines. Written informed consent, while well established in the clinical disciplines, e.g., surgery and radiology, was not common practice in health research[6].

Although some researchers were genuinely concerned, not all researchers were entirely comfortable with the constraints imposed on them by the Nuremberg Code. This is because the latter researchers placed, in the main, a utilitarian emphasis on the importance of scientific progress. In 1959, the Committee on the Re-evaluation of the Nuremberg Experimental Principles in the United States reported that while there was general agreement with the spirit of the principles, there was discomfort with a number of the "particulars"[33]. There were three broad categories of discomfort. Firstly, some felt that there were discrepancies between the practice of research involving patient-subjects and the "lofty, idealised" language of the Code. The other category was that of simple disagreements with some of the elements of the Code. The third category was an abhorrence of the very idea of a single, concrete set of standards to guide behaviour in the complex context of human experimentation[33]. It is therefore not surprising that in the United States a series of problems in research started emerging and in the sixties scandals seemed to break out everywhere[2,6,14].

Despite the discomfort in the US, the international medical community had no option but to reflect about its conduct in the aftermath of World War II and the Nuremberg Doctors' Trial. There were now great uncertainties regarding the role the medical profession had to play in a post-war society. This was of huge concern to national medical associations as well[34]. The reputation of the medical profession had been undermined, professionalism questioned and

the doctor-patient relationship damaged as a result of the Nazi medical experiments. Doctors all over the world were anxious that the profession as a whole could be affected negatively by the sweeping condemnation of the Nazi physicians. At potential risk also was funding for experimental research and the establishment of research institutes[34]. This apprehension resulted in increasing lobbying for the autonomy of physicians with a denouncing as totalitarian of any government scheme that advocated a greater degree of central or state planning of medical research by organisations like the Society for Freedom in Science[34]. Fears were expressed in the British Medical Journal that the individual conscience of the researcher could capitulate to the mass thinking of a totalitarian state[35] and the National Health Service in Britain was criticised as being too great an interference from the state in the arena of science and this in itself could lead to a Nazi or Soviet system of government[34]. The medical lobbyists were doing what the defendants at the Nuremberg Doctors' Trial had done – trying to shift the responsibility of the medical war crimes away from individual scientists onto an authoritarian state[34]. Therefore, it is not surprising that the revelations at the Trial were also a major factor leading to the foundation of the World Medical Association[21].

At the first meeting to discuss an international association of doctors and national medical societies held in London in 1946, there were 32 national medical organisations present. The objective of such an international association would be to promote international medical relations and the advancement of medicine and its social and cultural aspects. While Germany and Japan did not participate in the meeting, it is to be noted that American physicians declined to participate. The American Medical Association (AMA), however, requested two British doctors to act as observers on its behalf. The first meeting of the

newly formed WMA in 1947, which was held one month after judgements had been rendered in the Nuremberg Doctors' Trial, did have representatives from the AMA. The Declaration of Geneva[36] a statement on the physician's dedication to the medical profession was amongst the first acts of the WMA and was endorsed at the 1948 General Assembly. The importance of this Declaration is that when adopted, considerations of nationality, race, party politics, and social class would not interfere with the physician's responsibility for the patient's welfare. This applied to both situations of clinical care and research. Already in its very first Declaration, the WMA started the process of protectionism for those patients involved in research.

The Declaration of Helsinki (DoH) of 1964 was the first international set of guidelines for human experimentation and it "… reflected the longstanding interest of the World Medical Association (WMA) in issues of medical ethics and the enduring shadow of the Nazi medical war crimes."[21] The journey of the first DoH was long and turbulent. It involved more than a decade of active discussion and debate among the WMA members before the final document could be presented to the WMA's General Assembly for adoption in Helsinki in 1964[21]. Lederer states that the Declaration reflected philosophical differences, practical concerns, organizational politics and the financial structure of the WMA and despite it being a product of an international organisation, it *"… bore a sturdy American stamp."*[21]

Discussion on guidance from the WMA specific to human experimentation started in 1953 and right at the outset, the Chairman of the Ethics Committee of the WMA, Dr Paul Cibrie, a French physician-delegate to the WMA, advocated that the WMA's considerations of human experimentation be dissociated from the scientific crimes of Nazi medicine[21]. An additional problem was that there were differences over the practice of human experimentation in

different national settings and there was huge protest from the US that the requirement that healthy human subjects be fully informed about an experiment would seriously undermine research in that country. The Nuremberg Code was deliberated extensively by the WMA's Ethics Committee during this time. Some of the principles of the Code were rejected by some members as being too restrictive; e.g., there were utilitarian concerns that the requirement that all human experimentation be preceded by prior experimentation on animals would prevent important research. As modern medical science had evolved and essentially become very complex, the wisdom of laying down stringent rules to constrain investigators was questioned, in the main by the AMA.

The final version of the DoH which was also strongly influenced by the principles of deontology and virtue ethics, shared some features with the Nuremberg Code; i.e., animal and laboratory studies needed to precede human studies, investigators had to be scientifically qualified, subjects had a right to withdraw from research, the investigator had the responsibility to discontinue the trial where it was foreseen that the research subject could be injured and the subject had to consent to participate in the research or experimentation.

Differences between the Code and the DoH were that the DoH distinguished clinical research combined with patient care from non-therapeutic human experimentation and different consent requirements were introduced for these different types of research. The DoH specified written consent from a healthy subject but where the physician combined clinical research with professional care, there was no specification that consent had to be obtained in writing. The DoH also permitted experimentation on individuals who were

unable to exercise informed consent and children whose parents or legal guardians agreed to allow participation could now be included in research.

While the DoH was unanimously endorsed, not all WMA member associations were pleased with the outcome and there was open criticism about the American influence in the final document[21] . In addition, while the Americans had initially declined participation in the 1946 meeting, American financial support played a crucial role in the WMA's early years and this was critical to the survival of the fledgling organisation. Of note, the AMA required that the WMA maintain its headquarters at the New York Academy of Medicine in New York City. This ensured that the AMA played an important role in the daily life of the WMA and this lasted until 1974[21].

Despite the criticisms, and the difficult journey of the DoH, it has been hailed as one of the most successful efforts in rescuing medical research from the darkness of the tragedies resulting from the heinous atrocities in the name of medical research in Nazi Germany[21]. In addition, the 1964 version was explicitly protectionist:

> "In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out."

However, this protectionism was of "weak" category, as there was no requirement for a neutral third party like a REC to ensure safeguards. The latter was included in the version that followed in 1975.

4.4(B) Post Nuremberg – The Scandals Continue

Henry Knowles Beecher, a professor in research in anaesthesia, published a landmark article in the New England Journal of Medicine in 1966, entitled "Ethics and Clinical Research"[37]. Beecher detailed 22 cases of research conducted by leading researchers at leading research centres which he claimed violated the basic standards of ethical research. These studies had been published in highly acclaimed and reputable reviewed journals. He had submitted 50 cases in his original list but the number had to be reduced due to the space constraints of the journal[14].

The infamous 1963 Brooklyn Jewish Chronic Disease Hospital research is one of the studies he discusses. Here, three doctors, with the approval from the director of medicine at the hospital, injected "live cancer cells" into twenty-two chronically ill and debilitated patients. The patients were unaware that they were the subjects of research[38]. In another study, investigators withheld penicillin from soldiers with streptococcal throat infection, even though they were aware of the risk of death as a result of rheumatic fever[37]. In the Willowbrook study, also discussed by Beecher, children and adolescents with disabilities were deliberately exposed to hepatitis at a New York state facility with the aim of finding a preventative measure which was epidemic at that institution. Because of overcrowding, the hospital's wards were closed to admissions and parents whose children were on the waiting list were informed that their children could be admitted to the research ward immediately and then transferred to the facility[37].

While Beecher's aim was to draw attention to the abuses and not to vilify the researchers, he was not convinced that strict adherence to a code would be the solution. He concluded his paper by stating that the two most important components of an ethical approach in

research were informed consent and the "more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator."[37] Hence, Beecher, similar to many others, favoured weak protectionism, i.e., reliance primarily upon the virtue and discretion of the researcher. In an earlier paper in 1959[39] he expressed discomfort with the Nuremberg Code, and while supporting the importance of informed consent, he criticised the first clause of the Code as being too extreme and removed from the realities of the practicalities of research. He was also sceptical about the ability of any code in general to provide moral guidance to researchers. It is interesting to note that in 1961 when the US Army attached a new set of rules based on the Nuremberg Code to its standard research contract, Beecher, together with other members of the Harvard Medical School's Administrative Board, protested and managed to have the rules amended so that they read as guidelines[6,33]. His protest was not surprising considering he received funding from the army for his studies[33]. Several other distinguished scientist researchers, including McDermott[17], also openly expressed their lack of support for codes, rules and peer review processes. Louis Lasagna, also an eminent researcher, rhetorically and using a utilitarian argument, asked, "How many of medicine's greatest advances might have been delayed or prevented by the rigid application of some currently proposed principles to research at large?"[2] When a moratorium on prison research was proposed by the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research in 1977, Lasagna wrote in an editorial that the recommendations illustrated beautifully how good intentions to protect prisoners, because of tunnel vision, could lead otherwise intelligent people to destroy well conducted research that was meticulous about including informed consent[40]. Moreno[6] states that it is worth noting that both Beecher and Lasagna had good reason to reflect on the ethics of research in light of some of the work they did

together. Lasagne had been a research assistant in an Army-sponsored study that Beecher directed between 1952 and 1954 in which hallucinogens were administered to healthy subjects without obtaining informed consent. Schmidt and Frewer correctly sum up the situation when they state that while some in today's bioethics community would like to portray people like Henry Beecher as courageous whistle-blowers when constructing greatly biased historical narratives, they were actually largely opportunistic and their whistle-blowing were measured responses to a significant change in the political, social and cultural climate that challenged the power of medical science[34].

4.5 THE TRANSITION FROM WEAK TO MODERATE PROTECTIONISM IN THE UNITED STATES.

Just one year after Lasagna's defence of researchers, the Tuskegee Syphilis Study scandal erupted. The study was initiated in 1932 in Alabama in order to ascertain the natural course of syphilis, a condition that had reached epidemic proportions in African American males in the area[2,41]. The natural history of syphilis had already been demonstrated at the turn of the century by a study in Oslo and therefore there was no scientific rationale for the study. Over 400 mostly illiterate men were enrolled without informed consent or their partners being informed of the risk. When penicillin became available in the late 1940s, not only were the men not informed of this, but efforts were made to ensure they did not receive treatment or hear of it. By 1972, more than 100 had died because of advanced syphilitic lesions. The Tuskegee Syphilis Study was a manifestation of institutionalised racism in health care very similar to the situation in housing, employment and education at that time[2].

The impact of the turbulence in research ethics as evidenced by the Tuskegee Syphilis Study was the 1974 National Research Act which became law in the United States and led to the

establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research and the enactment of federal regulations governing research with humans[2]. The National Commission was responsible for the 1979 Belmont Report, ethical guidelines for the conduct of research. All this resulted in the transition from weak to moderate protectionism in research. The Tuskegee study also served to refute McDermott's and Lasagna's utilitarian justification of research.

Previously, another US funded set of studies had been conducted in Guatemala between 1946 and 1948 where in some projects people were deliberately infected with sexually transmitted diseases (STD) without their consent. Subjects included prisoners, soldiers from several parts of the army, patients in a state-run psychiatric hospital and commercial sex workers. They were exposed to syphilis, gonorrhoea, and chancroid. Serology experiments that did not involve intentional exposure to infection continued through to 1953 in these groups, children from state-run schools, an orphanage and several rural towns[42].

There were stark similarities between the Tuskegee Syphilis Study and the Gautemala STD research. They arose from the same laboratory of the Public Health Service, the Venereal Disease Research Laboratory (VDRL). Some of the same researchers were involved. The focus in part, was on the same disease. In both situations there were deliberate efforts to deceive experimental subjects and the wider community who may have objected. Some citizens in the US would have objected as is evident by an article in the New York Times in 1947 where the science editor described how small doses of penicillin if administered within a few days of intentional exposure of rabbits with syphilis prevented the disease from developing. The article stated that for definitive results on humans, people would have to be injected with syphilis first and this would be "ethically impossible" to do[42]. This article

must have been of particular interest to the researchers working on the rabbits as they were about to begin what was described as “ethically impossible”, with prisoners and psychiatric patients in Guatemala. The subjects in Guatemala however, were citizens of a different country and so the researchers went ahead with the studies somewhat secretly and deceitfully too[42]. It was only recently that these atrocities came to light and in November 2010, President Obama of the US requested the Presidential Commission for the Study of Bioethical Issues to oversee a thorough fact-finding investigation into the specifics of the study[42]. These and other examples of research atrocities involving researchers from the US are probably why there were so many objections to the Nuremberg Code and difficulties during the WMA’s journey to the DoH from American scientists and physicians.

The above section has described the history of disasters of ethics in research and protectionism from an international perspective up to the point of the Nuremberg Code. It continued in this vein post Nuremberg, but the focus changed to the failures in the United States and the development of its protections up to the Belmont Report and the Federal Regulations following the 1974 National Research Act. The reason for detailing the situation in the United States is that the principles[43] espoused in the Belmont Report have had great influence on several international ethics instruments that followed the Nuremberg Code , and the US is an influential sponsor for much international research, both Federal funded and pharmaceutical industry studies. Moreover, in the context of international research conducted in South Africa, a substantial source of funding for these studies is from the United States[44]. However, despite the fact that the protectionism movement in the United States was in response to scandals and tragedies in research, and there were lessons to be learnt for researchers there and elsewhere, reports of abuses and exploitation of vulnerable

populations in poorly resourced regions in the context of clinical research sponsored by the US continue to emerge[4,42,45,46].

4.6 PROTECTIONISM IN SOUTH AFRICA

The history of protectionism from a regulatory perspective in South Africa is quite scant and only emerged over the past two decades. This is understandable as prior to 1994 citizens in the country were oppressed and subjected to the repressive apartheid regime in which people who were not white were considered to be subhuman, lacking human dignity and of decreased or no moral status, similar to the European anthropological viewpoint described earlier in this chapter. However, the apartheid regime and philosophy was not successful in removing moral agency from the virtuous physician-researcher in the country and in the late sixties, after Beecher's seminal paper was published[37], steps were set in motion at the level of individual institutions where research was conducted to introduce protections for all, and in particular the vulnerable, that were involved in research. Peter Cleaton-Jones[47] states that the Beecher paper was considered such a milestone in research ethics that four months after its publication, at the suggestion of Professor John Hansen of the Department of Paediatrics at the then Baragwanath Hospital which was situated in a racially demarcated township, Soweto, the University of the Witwatersrand formed the Committee for Research on Human Subjects (Medical). Hence, this could be described as the birth of protectionism for the research participants in South Africa. The Committee was the first REC in the country and was probably one of the first in the world. The Committee underwent a name change in 2003 to the Human Research Ethics Committee (Medical)[47], is still functional today, and, in my opinion is one of the leading RECs in the country. From the mid seventies, other

institutions followed suit and currently there are over thirty RECs registered with the National Health Research Ethics Council in the country[48].

In the beginning, guidelines for the protection of participants in research were lacking in the country. However, in 1978, Professor de V Lochner, then vice president of the South African Medical Research Council (SAMRC), visited the World Health Organisation in Geneva and upon his return, set to work on producing a set of guidelines for the SAMRC. In 1979, the first set of guidelines, entitled "Guidelines on Ethics for Medical Research", was produced by the SAMRC. These guidelines have undergone several revisions since[47].

The National Department of Health in 2000 produced Guidelines for Good Clinical Practice in Research[47]. This was updated in 2006[49]. Up to 2004, while some institutions had established REC oversight, in the main, protections in South Africa fell into Moreno's weak category. However, after the promulgation of the National Health Act[50] (No 61 of 2003), in 2004, protectionism transitioned to the strong category. Chapter 9 of the National Health Act focuses on health research and health research ethics, similar to the US National Research Act of 1974. As a result of the stipulations of Chapter 9, "Ethics in Health Research: Principles, Structures and Processes"[51] was launched in 2004. It is a response to the National Health Act and, while written as guidelines, has the authority of rules.

4.7 CONCLUSION

The Nuremberg Code was the first international document in research ethics. It was established as a response to the disasters and disgrace in medical research generated by the Nazi doctors. After many other abuses of vulnerable subjects in research in the United States, the Belmont Report was introduced and Federal Rules were established for

protecting those enrolled in studies. South Africa followed suit in establishing protections for participants of research from the late sixties. In South Africa, the protectionist approach was not as a response to scandals and tragedies inflicted on vulnerable participants by South African researchers but because of a sense of moral agency, moral responsibility and moral accountability of researchers in this country towards people they enrolled in research. South African researchers drew from Aristotelian and Hippocratic influences in their professional practice and embarked on the protectionist approach in an endeavour to guard against atrocities and human dignity violations similar to the ones that Beecher described, especially because sponsors and researchers from well-resourced countries, and in particular the US, had started finding less resourced areas highly attractive for the conduct of clinical research.

The following chapter will discuss and analyse the evolution of international guidelines and instruments from the perspective of protections of vulnerability in health research.

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Chapter 5: PROTECTING THE VULNERABLE – AN ANALYSIS OF INTERNATIONAL CODES AND GUIDELINES

5.1 INTRODUCTION

The previous chapter described abuses, tragedies and scandals in the context of medical research and the exploitation of individuals and groups with specific vulnerabilities, highlighting the chequered history of health research. The birth of protectionism was also discussed. In this chapter, international guidelines and codes will be examined and analysed for their treatment of specific vulnerabilities. Because systematic medical research progressed in leaps and bounds in the 20th century, and because of the offensive way in which it was misused by researcher-physicians from many countries[1], a historical approach will be utilised again in order to explore the treatment of specific vulnerabilities in protective instruments through time. The international guidelines utilised for examination are the World Medical Association's (WMA) Declarations of Helsinki (DoH), the International Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organisations of Medical Sciences (CIOMS) in collaboration with the World Health Organization, and the ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6(R1) (ICH-GCP). The WMA guidelines were chosen because they are the most widely used and highly acclaimed set of protections and have been incorporated in many national and international laws. In addition, they have had the greatest influence on South African guidelines and policies on ethics in research[2-5].

The Nuremberg Code (discussed in detail in the previous chapter), the DoH, and the Belmont Report[6] (to be discussed in the next chapter) are the key texts that have directed

the development of "Ethics in Health Research: Principles, Structures and Processes"[2], the South African Department of Health Guidelines (SA Ethics Guidelines) for the ethical conduct of health research. It is for this reason that other international documents like the UNESCO Universal Declaration on Bioethics[7] and Human Rights and the European Union Clinical Trials Directives[8], while extremely good, have not been selected for discussion, despite the latter together with the ICH-GCP[9] having had the most influence on medical research practices globally[1] . The European Council Directives have not had a major impact on South African instruments as most health research in South Africa is funded from sponsors in the US[10-12] who use the ICH-GCP as the guideline of choice for these research projects[13]. Moreover, the ICH-GCP and European Union Clinical Trials Directives claim to be based on a set of ethical principles for health research which have their origins in the DoH, possibly the very first version[1-14]. The CIOMS guidelines were written particularly to facilitate the application of the DoH in the developing world; they have been somewhat influential on the SA Ethics Guidelines and hence are pertinent for examination here. The ICH-GCP, which serves as an international ethical and scientific quality standard, has had a major influence on the Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa[3] (SA GCP). It will only be briefly discussed because, while it does make recommendations on vulnerable groups, it is highly technical in nature.

The Nuremberg Code remains a cogent articulation of the salient points of research ethics but because it was a response to a specific calamity in medical research, it exerted less influence than it should have in practice[15,16]. As seen in the previous chapter, it was drafted pursuant to a trial that stemmed from astonishingly bizarre circumstances and was viewed by opponents of external interference as a "reaction to extreme evil rather than as a guide

for clinical research with humans."[15]. It was not regarded as a requirement for decent and respectable doctors who did research. Moreover, the Code, which was the third section of the judges' decision at the Nuremberg trials, did not actually form the basis for the judgement delivered against the Nazi doctors at the end of the trial[15,16].

The opening of the Code, with its emphasis on the need for voluntary consent as absolutely essential, left little avenue for research involving those individuals who could not give consent for themselves. This meant that children, the mentally ill, those in emergency situations and others with compromised autonomy would not be able to be involved in research and classes of individuals could end up as therapeutic orphans. This is possibly one of the reasons for the World Medical Association initiating deliberations in 1953 towards establishing its own research ethics guidelines[15] and in 1954, adopting its "Resolution on Human Experimentation: Principles for those in Research and Experimentation"[17,18]. This document was revised over the next ten years and eventually adopted as the Declaration of Helsinki (DoH) in 1964[15,18]. Although the 1954 WMA Principles for those in Research and Experimentation and the 1964 DoH draw substantially from the Code[14,19], it is interesting to note that neither mentions the principles of the Code[1].

5.2 EXAMINATION AND ANALYSIS OF PERTINENT INTERNATIONAL GUIDELINES FOR RESEARCH PARTICIPANT PROTECTIONS WITH PARTICULAR FOCUS ON SPECIFIC VULNERABILITIES

5.2(A) Protecting the Vulnerable in Research - the Helsinki Evolution

The WMA was established in London in 1946 and held its first General Assembly in Paris in 1947. During this time deliberations and resolutions focussed on crimes committed in the

doctor-patient relationship since 1933 by certain members of the medical profession in Germany during World War II[18]. The Declaration of Geneva[20], an updated version of the Hippocratic Oath, and the International Code of Medical Ethics[21], adopted by the WMA in 1948 and 1949, respectively, were guidance documents for physicians specifically in the context of clinical care. These documents, however, have had a resounding influence on the DoH as evidenced by their use in the introduction of the DoH through all its revisions. Physician-researchers are bound by the words: "The health of my patient will be my first consideration"[20] (Declaration of Geneva) and "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest"[21] (International Code of Medical Ethics). The 1964 DoH[22] was the first formal declaration by the WMA for physicians doing research and served for the first time to distinguish biomedical researchers as a specific class of physicians[23].

Since its original formulation the DoH has undergone seven revisions and two clarifications. This is reflective of the fact that science and technology is progressing at a very rapid rate, since the nascent medical research of the 1950's, and the DoH has evolved to keep pace with these developments. Similar to the Nuremberg Code, all versions of the DoH provide protections for the universal vulnerability of all those participating in research. The Declaration of Helsinki has been referred to as the most widely accepted guidance document globally on medical research and has also been incorporated into many national and international legal instruments[14,15,18].

5.2(A)1 Declaration of Helsinki – 1964[22]

The major shift from the Nuremberg Code in the 1964 DoH was contained in its section

II.1[8]:

> "... If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient."

The sufficiency of a legal guardian's consent, i.e., the introduction of a role for a surrogate decision maker, was a pivotal departure from the Nuremberg Code which seemed to deny proxy consent a place in clinical research. Section II.1 of the 1964 DoH was an indication that the WMA recognised the ethical obligation to include those individuals with more than ordinary universal vulnerability in research and to expand on protections for them. This effort by the WMA also served as a safeguard against discriminating against those with added vulnerabilities from participating in a socially responsive exercise like research. In addition, the 1964 DoH introduced for the first time in research ethics documents a reference to vulnerable subgroups, i.e., those with inability to consent due to psychological, legal or physical incapacity.

5.2(A)II Declaration of Helsinki – 1975[24]

The first revision of the DoH was adopted in 1975. It was a significant revision and was twice as long as its predecessor. It placed greater emphasis on informed consent and introduced the concept of vulnerability as a result of dependency[9]:

> "I.10 When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or

> may consent under duress. In that case informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship."

Hence, not only did section I.10 create an additional subgroup – that of those subjects in dependent relationships - but it also made provisions to safeguard them against this dependency by introducing an added layer of protection in the consent.

With regard to incapacity, it made specific reference to "mental" incapacity and stipulated that in the situation of incapacity, surrogate consent would have to be obtained in accordance with national laws:

> "I.11 In cases of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with that of the national legislation."

By introducing the requirement for compliance with national legislation, section I.11 increased the protections to the subgroup lacking in capacity to consent and hence transitioned the DoH from being weakly protectionist to strong protectionism. Reference was made to socio-economic vulnerability in section II.3:

> "II.3 In any medical study, every patient – including those of the control group, if any – should be assured of the best proven diagnostic and therapeutic method."

> Giving assurance to those involved in the study that they would receive treatment following the study provided an undertaking that treatment would be continued even to those who could not as a rule afford treatment.

Other aspects of the Declaration that could be perceived as introducing added protections include section I.2 which established the requirement that the experimental protocol be "transmitted to a specially appointed independent committee for consideration, comment and guidance." While this added protection would apply to all participants and not just those with more than ordinary vulnerabilities, it was nevertheless an important addition to the Declaration.

Therefore the 1975 DoH strengthened the consent requirements, introduced the concept of socio-economic vulnerability, established the need for independent review and overall, augmented the protections and safeguards for participants in research.

5.2(A)III Declaration of Helsinki – 1983[25], 1989[25], 1996[27]

There were minor changes in the next three versions of the DoH (1983, 1989, 1996). The 1983[25] version strengthened protections for minors even further by stipulating that where a minor is in a position to consent, this consent must be obtained in addition to that of the legal guardian (section I.11). The 1989[26] version, in section I.2, established that the review committee should be independent of the investigator and sponsor and should be in conformity with the laws and regulations of the country in which the research experiment is performed. This introduced the concept of international research and provided for added protections for participants at distant sites with extant laws and regulations. However, this stipulation made no provision for those sites where laws and regulations for the protection

of participants in health research did not exist. This could be perceived as a weakness of this section. The 1996[27] version was a replication of the '89 version except for a minor wording change in I.4 and the introduction of the use of inert placebo where no proven diagnostic or therapeutic method existed (section II.3). There were no further additions as regards vulnerable groups.

5.2(A)IV Declaration of Helsinki – 2000[28]

The 2000[13] version of the DoH was arguably a significant advance over the previous ones. It has also been the most controversial version requiring further clarifications, in 2002[29] on the subject of placebos and 2004[30] on the subject of post-trial access to therapies. It is the first version to make direct reference to vulnerable populations and their rights to protections:

> "A.8 Medical research is subject to ethical standards that promote respect for all human beings and protect their health rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. 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, or for those who will not benefit personally from the research and for those whom the research is combined with care."

In just one section, six different vulnerable populations or groups were highlighted:

1. the economically disadvantaged,
2. the medically disadvantaged,
3. those lacking capacity to consent,
4. those subjected to consenting under duress,

5. those who would not benefit personally from research; and
6. patients (research combined with care).

The requirements for consent are strengthened even further in this version. Sections B.24 and B.26 state that where proxy consent is necessary because of a lack of capacity to consent, these groups should not be included in the research unless the study being undertaken is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent individuals; i.e., special justification will be necessary if research is undertaken in these vulnerable groups. It is interesting to note the 2000 DoH was silent on the need for special justification when enrolling into research the other vulnerable groups that it highlighted. This is possibly due to the inordinate obsession with autonomy and consent that seems to be the norm in clinical care and research.

Another section of the 2000 DoH that was expanded substantially was section B.13 on ethics review. While earlier versions had introduced the concept, it was for the very first time that the committee was called an ethics review committee. Although there were several stricter standards introduced for ethics review, the protections in this section were considerably weakened by the words “where appropriate” with regard to approval. In other words, it was necessary to submit the protocol for consideration, comment or guidance, but ethics approval was not an absolute requisite for the conduct of research. Therefore, the 2000 version of the DoH, in my opinion is not an example of strong protectionism.

5.2(A)V Declaration of Helsinki – 2008[31]

The 2008 version of the DoH[16] refers to vulnerability in several sections. It gives recognition to the fact that vulnerable populations could be denied access to research and specifies in A.5 that those populations who are underrepresented in research should be provided with appropriate access to research participation. Section 9 refers to some research populations as being particularly vulnerable and requiring special protections. “Particularly” is used to qualify vulnerable, hence drawing a distinction between universal vulnerability and specific vulnerabilities. These vulnerable populations are those without the ability to consent and those who may be subject to “coercion” or “undue influence”.

Section B.17 stipulates that medical research involving disadvantaged or vulnerable populations or communities is only justified if it is responsive to their health needs and priorities and there is a reasonable likelihood that they stand to benefit from the results of the research. This section introduces another vulnerable population, namely, the disadvantaged, but by the use of “or”, also brings in the notion that “disadvantaged” could be used interchangeably with “vulnerable”. By extrapolation, perhaps “disadvantaged” could replace the contentious term “vulnerable” with all its many complexities. However, disadvantaged lacks the gravitas of vulnerable and is perhaps too weak a term as compared to vulnerable. Section B.26 is similar to I.10 of the 1975 DoH and part of A.8 of the 2000 version where safeguards are stipulated against consent during duress. Section B.27 states that where potential research subjects are incompetent, they must not be included in research that has no likelihood of benefit for them unless the research is intended to promote the health of the population represented by the potential subject, the research cannot be performed with competent individuals and the research entails only minimal risk and minimal burdens. The minimal risk and burden stipulation could be perceived as being

protective to the point of being restrictive. With regard to ethics review and approval, it is interesting to note that the "where appropriate" with regard to approval has been omitted, hence strengthening and giving authority to the ethics approval process and thereby bringing back strong protectionism in the DoH .

The DoH had, through its evolution, up until 2008 established protections for particularly vulnerable populations and individuals with specific added vulnerabilities.

The DoH's particularly vulnerable populations included:

1. those in dependent relationships,
2. the economically disadvantaged,
3. the medically disadvantaged,
4. those lacking capacity to consent,
5. those subject to consenting under duress or coercion,
6. research combined with care (patients),
7. disadvantaged communities,and
8. those subject to undue influence.

5.2(A)VI The Declaration of Helsinki – 2013[32]

This latest version of the DoH was adopted in Fortaleza, Brazil in October 2013. Sections 19 and 20 of this version are specific to vulnerability and are entitled "Vulnerable Groups and Individuals" and addresses how they should be treated. During the revision process, there were suggestions that the different vulnerable populations be explicitly mentioned in the Declaration. There were too many different vulnerable populations suggested for inclusion and hence a selection would have had to be made. In addition, while certain populations

mentioned did have large numbers of vulnerable individuals, not all individuals in the proposed groups were necessarily vulnerable[33]. Hence, in an impressive move away from what has become the norm in international guidelines as regards vulnerable groups, groups have not been named explicitly in the current version which offers a general definition of vulnerability and briefly specifies the requirements for their participation in health research, as an alternative.

According to Section 19:

> "Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups should receive specifically considered protection."

This is the first version that has used "wrong" thereby giving emphasis to the moral significance associated with harms to vulnerable participants in health research. Wiesing and Ehni refer to "may have an increased likelihood of being wronged or of incurring additional harm" as the definition of vulnerability. They state that this definition has advantages in that it incorporates different reasons for individuals or groups to be considered vulnerable. Furthermore, the form of special protections they receive may vary depending on the type of vulnerability[33]. While this shortened definition is attractive, it is lacking in that it has left out an additional requirement for vulnerability: that of not being able to safeguard one's own interests. As will be seen in Chapter 7, just being at increased likelihood of being wronged or harmed does not necessarily make one vulnerable. Not being able to protect oneself in the context of being harmed or wronged is at the heart of what makes one vulnerable. The reasons offered for vulnerability in the 2013 DoH are research combined with medical care, i.e., patients (Section 14), dependence on others (Section 27),

consenting under duress (Section 27) and being incapable of giving informed consent (Section 28 and 30). Similar to the 2008 DoH, subjects who are incapable of providing informed consent can only be involved in research where risks and burdens are minimal. Again, the minimal risk and burden stipulation could be perceived as being protective to the point of being restrictive.

Section 20 states that:

> "Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from research."

While the three conditions laid out in this section strengthen the protection to participants with vulnerabilities and are introduced for the first time in this version of the DoH to apply generally to all vulnerable groups, similar provisions had already been established in the General Ethical Principles section of the CIOMS Guidelines (2002)[34] and the SA Ethics Guidelines[2] in 2004 in section 5.12. The 2000 and 2008 versions of the DoH do make reference to these provisions but only in the context of incapacity to consent.

Protection of vulnerabilities is bolstered even further with the principle in Section 15 stating that there must be appropriate compensation and treatment for subjects who are harmed as a result of participating in research. This is further enhanced in Section 22 which makes it necessary for information on provisions for treating and / or compensating subjects who are harmed as a consequence of participating in the research to be included in the protocol that is submitted to the Research Ethics Committee for review. This requirement for

compensation is of unquestionable assistance for RECs in their roles of safeguarding and protecting participants as this is an issue that RECs have had great problems with, within the context of international research sponsored by federal funds from the US[35]. SA GCP which makes compensation necessary in this regard has been flagrantly disregarded by these sponsors and researchers (including those from South Africa) and important research projects are delayed as RECs struggle with researchers and sponsors to get them to honour this obligation[35].

An additional requirement in this version is that Research Ethics Committees must be duly qualified. This means that the people safeguarding the interests of participants with vulnerabilities need to be competent to do so. This reads well with the SA Ethics Guidelines (section 4) which makes it necessary for institutions to ensure that their RECs are adequately resourced to ensure competent functioning and Section 72 (6)b of the National Health Act no 61 of 2003 which stipulates that the National Health Research Ethics Council must register and audit RECs. The DoH of 2013 is certainly an improvement over previous versions on the approach to and protections of participants with vulnerabilities. However, while it has not named any specific group in its section on "Vulnerable Groups and Individuals", it can be criticised for continuing to make reference to vulnerable groups. "People / Individuals with Vulnerabilities" would have perhaps been more appropriate.

Although there are claims that the 2013 version does not explicitly name any vulnerable groups[33], the following four groups are identified in the document:

1. research combined with medical care, i.e., patients (Section 14),
2. dependence on others (Section 27),
3. consenting under duress (Section 27), and

4. being incapable of giving informed consent (Sections 28 and 30).

There is no doubt that the DoH has changed substantially over time as regards participants with vulnerabilities with the latest version narrowing down the identifiable vulnerable groups to four. While the DoH has not named specific subtypes within these groups, the CIOMS Guidelines, on the other hand have used a combined approach of broad categories or groups and specific subtypes.

5.2(B) Protecting the Vulnerable in Research: International Guidelines for Biomedical Research Involving Human Subjects (CIOMS)[34]

The Council for International Organisations of Medical Sciences (CIOMS), an international non-governmental organization in official relations with the WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO), was established in 1949 and undertook work on ethics in relation to biomedical research with the WHO in the late 1970's. The aim of its guidelines was to establish the manner in which the principles of the DoH could be effectively applied, particularly in developing countries in light of their socioeconomic conditions, laws and regulations. The result of the CIOMS / WHO collaboration was the "Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects" in 1982[36]. These guidelines were endorsed in September 1981 by the 56th Session of the CIOMS Executive Committee, and in October 1981 by the 23rd Session of the WHO Advisory Committee on Medical Research before adoption in 1982[36]. The guidelines have undergone two further revisions (1993[37], and 2002[34]) and are currently under review again. CIOMS states that the reviews have been necessitated by rapid advances in science and technology, changing research practices such as increasing multinational and international research, studies involving vulnerable populations, and a

changing view in both rich and poor countries that human subjects' research is largely beneficial and not threatening, and there is the need to build in effective safeguards against exploitation [34]. According to CIOMS, applying universal ethical principles to research in a multicultural world where health care systems and standards of health care are considerably diverse is a fundamental challenge to international research ethics. A related issue is that of the human rights of research subjects in a range of sociocultural contexts. All these issues hinge around largely two principles, that of respect for autonomy and protection of dependent or vulnerable populations[34]. Just as the the DoH equated "vulnerable" with "disadvantaged", the CIOMS equates "vulnerable" with "dependent". However, it is unlikely that dependent could serve as a suitable substitute that would cover all types of vulnerabilities. The CIOMS has also published guidelines for researchers doing epidemiology research. This set of guidelines will not be discussed here.

5.2(B)I CIOMS 1982[36]

There are two parts to the first version of the CIOMS document. The first part is a report on a survey that was undertaken by CIOMS and WHO in 1976 to inform the guidelines and the second part is made up of the set of guidelines themselves, which uses as its foundation the principles of the 1975 DoH. The guidelines focussed on developing country issues and justified this stance by stating that while the principles laid down in the DoH were regarded as being universally valid, their modes of application varied in differing special circumstances. The aim of the guidelines was therefore not to duplicate or amend the DoH but to suggest how its principles could be applied in the special circumstances of the many developing countries. 45 national health administrations and 91 medical faculties in countries in which medical research was being undertaken on a limited scale and / or where

there were no explicit national criteria for protecting research subjects from involuntary abuse responded to the questionnaires that were sent out by CIOMS. A total of 60 developing countries replied to the questionnaires.

Aspects of the general survey will be discussed in detail as many issues highlighted then are still applicable in developing countries today. In terms of the survey, up until that time biomedical research had been undertaken predominantly in highly developed countries. The focus of the research was directed to diseases of "global relevance", on diseases affecting primarily the wealthy countries. However, there was growing acceptance of the need for increased collaboration with developing countries where communicable diseases, malnutrition, and unconstrained population growth were endemic, raising the likelihood that more applied biomedical research would have to be undertaken in those countries. There was recognition though that untoward pressure could crop up for research unrelated to local priority issues to be transferred to these countries. The survey report stated that costs of research and development could rise to inhibitory levels in developed countries and this could result in studies being undertaken in areas where they could be done the least expensively and with the least restriction. There was concern that this type of practice, once started, could rapidly gain in momentum. The concerns raised with regard to external sponsorship were as follows:

"... - the investigation may subserve external rather than local interests.

- foreign investigators and sponsors may not possess adequate insight into local mores, customs and legal systems.

- the absence of any long-term commitment to subjects involved in the research, and withdrawal of out-posted personnel on completion of their task, may result in local disillusionment.
- lack of accountability may deprive subjects of any form of compensation for incidental injury."

It is clear from the above that there was disquiet with regard to developing country subjects being exposed to exploitation and other forms of harms as a result of being involved in research sponsored by more wealthy countries, and while not specifically mentioned in the CIOMS (1982), the underlying issues here were context specific vulnerabilities. Of note, the concerns raised by the respondents to the questionnaires in 1982 remain very real concerns in developing countries even today.

In the guidelines section of the document, additional safeguards for those individuals and groups who required added protections were highlighted and discussed extensively in relation to informed consent. Guideline 6 asserted that informed consent in itself was an imperfect safeguard for the subject and for it to be effective as protection, it should always be complemented by independent ethical review of research proposals. In addition, many individuals, including children, adults who were mentally ill or defective, and those who were totally unfamiliar with modern medical concepts, were incapable of giving adequate consent. For these individuals, consent implied a passive and uncomprehending participation. Independent ethical review would be imperative if these individuals were to be adequately protected. It could be stated that the confidence of these guidelines in independent ethical review as an added layer of protections was somewhat naive as history has gone on to reveal that subjects in research have been harmed in the decades that

followed despite independent review[38]. With regard to children, it is interesting to note that the guidelines required the consent of a parent or other legal guardian and "willing cooperation" of the child to the extent that it was feasible. "Assent" was not mentioned. However, in the older child (no age mentioned) consent would be necessary together with the consent of parent or other legal guardian. The need for risk analysis was underscored in section 10 which pertained to pregnant and nursing women. However, the guidelines stated that there were no special problems with eliciting informed consent in this group. On the issue of mentally ill and mentally "defective" persons, the guidelines stated that the ethical considerations for this group were similar to those applying to children. While the agreement of the immediate family for their participation should be sought, the guidelines drew attention to the possibility that this permission could sometimes be of doubtful value as mentally "deranged" or "defective" patients were sometimes regarded by their families as an unwelcome burden. This is of particular importance and should perhaps be underscored in all relevant protections instruments.

Section 13 pertained to "Other Vulnerable Groups". Hence, it can be extrapolated that all the groups already mentioned in the guidelines were considered to be vulnerable as well. Section 13 stated that the quality of consent of potential subjects who were junior or subordinate members of a hierarchically structured group should be carefully considered as their willingness to volunteer could be unduly influenced by the expectation of "adventitious" benefits. Medical and nursing students, subordinate laboratory and hospital personnel, employees of the pharmaceutical industry and members of the armed forces were examples that fell into these groups. Sections 14 and 15 were specific to subjects in developing communities. It drew awareness to the likelihood that rural communities in this

situation may not have an understanding of the concepts, techniques and implications of experimental medicine and might therefore not be in a position to give adequate informed consent to the investigator. It was recommended that the decision as to whether or not the individual should participate should be elicited through the intermediary of a trusted community leader. The guidelines were silent on the possible negative impact the community leader could have on the voluntariness element of informed consent.

5.2(B)II CIOMS 1993[37]

Eleven years later, after a process of consultation and revision, the 1993 CIOMS guidelines were introduced entitled "International Guidelines for Biomedical Research Involving Human Subjects"[37]. This was similar to the DoH in that the first version was in 1964 and the second in 1975, eleven years later. This set of CIOMS guidelines comprised fifteen ethical standards for use internationally as a tool for the protections of human subjects involved in research, especially in the developing world. These tools established protections for general universal vulnerability and enhanced protections for specific additional vulnerabilities. Nine of these focussed on informed consent, ranging from individual consent to consent in specific contexts.

The subgroups stipulated for enhanced protections in the informed consent section are children, persons with mental or behavioural disorders, prisoners, and subjects in underdeveloped communities. With regard to children, guideline 5 stipulated that children must not be involved in research that might be equally carried out in adults and that the purpose of the research must be to obtain knowledge relevant to the health needs of children. Similarly, guideline 6 stated that persons with mental or behavioural disorders could not be enrolled in research if that research could have been carried out with those

persons in full possession of their mental faculties. Moreover, the purpose of the research had to be that of obtaining knowledge relevant to their particular health needs. In guideline 8, subjects in underdeveloped communities were contextualised in both developed and developing countries with the proviso that research could only be conducted in these communities if the research could not be reasonably well conducted in developed communities and that the research was responsive to the health needs and priorities of those underdeveloped communities. Hence special justification was required if research was to be conducted in these groups. However, with regard to research involving prisoners, there was no special justification requirement and guideline 7 stipulated only that prisoners who were seriously ill or at risk of serious illness were not to be arbitrarily denied access to investigational drugs, vaccines, or other agents that showed promise of therapeutic or preventative benefit.

Of note, immediately following individual consent, guideline 4 pronounced on inducement to participate and while it allowed for payment and medical services to subjects, these could be not be so large as to induce prospective participants to consent to participate in the research against their better judgement and hence serve as an undue inducement.

Guideline 10 on equitable distribution of burdens and benefits made specific reference to vulnerability and stipulated that special justification was necessary when vulnerable individuals were invited to participate in research, and if they were selected, the means of protecting their rights and welfare had to be particularly strictly applied.

Selection of pregnant or nursing (breastfeeding) women as research subjects was the focus of guideline 11 which stipulated that these women could only be subjects in research that involved no more than minimal risk to the fetus or nursing infant and the object of the

research was to obtain new knowledge about pregnancy or lactation. It also stipulated that, as a general rule, pregnant or nursing women should not be the subjects of just any clinical trials. Their involvement in trials should only be where the trials were designed to protect or advance these women, foetuses or nursing infants and where women who were not pregnant or nursing would not be suitable subjects.

Other relevant safeguards in this 1993 document included the requirement for ethics review and approval by an ethical review committee prior to the research being conducted (guideline 14), and in the case of international research, the protocol had to be submitted initially to the sponsor country's scientific and ethics review committees, and only after approval from those committees was the protocol to be submitted to the appropriate authorities in the host country for review and approval. The ethical and scientific review of the sponsor country had to be in line with the norms set by that country and were not allowed to be less exacting than they would be if the research were to be carried out in the sponsor country. Hence double standards for review were proscribed.

The 1993 CIOMS guidelines reveal an unfolding of two broad categories of vulnerability as a result of special contexts: vulnerabilities arising because of issues with informed consent and vulnerabilities as a result of subject selection as follows:

A. Special Context – Informed Consent Challenges:

1. Children,
2. Persons with mental or behavioural disorders,
3. Prisoners, and
4. Underdeveloped communities.

B. Special Context – Selection

1. The economically disadvantaged or dependent (fair subject selection),
2. Pregnant women,
3. Fetuses,
4. Nursing (breastfeeding) women,
5. Nursing infants.

5.2(B)III CIOMS 2002[34]

The subsequent revision of International Guidelines for Biomedical Research Involving Human Subjects resulted in the 2002 CIOMS Guidelines[34], a substantially improved set of standards. The Guiding Ethical Principles of the Guidelines utilises the principles of Respect for Persons, Beneficence and Justice as espoused by the Belmont Report[6]. Specific reference to vulnerability is made in the discussion of respect for persons and justice as follows:

> "Respect for persons incorporates at least two fundamental ethical considerations, namely:
>
> *a)* respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination; and
>
> *b)* protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse."

> "Justice refers to the ethical obligation to treat each person in accordance with what is morally right and proper, to give each person what is due to him or her. In ethics of

> research involving human subjects the principle refers primarily to distributive justice, which requires the equitable distribution of both the burdens and the benefits of participation in research. Differences in distribution of burdens and benefits are justifiable only if they are based on morally relevant distinctions between persons; one such distinction is vulnerability. 'Vulnerability' refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternate means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group. Accordingly special provision must be made for the protection of the rights and welfare of vulnerable persons."

In positioning vulnerable individuals in discussions of respect for persons and justice, CIOMS 2002 intricately aligns their protections with the need for enhanced safeguards during the process of informed consent, and / or selection as illustrated by the need to ensure fair and just treatment especially in the context of distributive justice, or both. Where the burdens and benefits are distributed such that particular groups with specific vulnerabilities (e.g. the underprivileged) are compelled to bear the risks of research for the benefit of the privileged, the principle of justice would be violated.

The principle of justice in the guidelines goes on further to lay down that sponsors and investigators should not take advantage of the relative inability of low resource countries or vulnerable populations to protect their own interests by avoiding their sponsor country's regulatory systems and conducting the research cheaply with weakened regulatory safeguards in order to develop products for their lucrative markets. This stipulation brings in

the notion of vulnerability in research as that of extending beyond individuals and populations to entire countries.

Distributive justice protections in the Guidelines also require that research projects in low resource countries or communities should improve their situation and leave them better off or at least no worse off. The research should be responsive to their health needs and products developed from the study should be made reasonably available to them. The study team should attempt to leave the population in a better position to obtain effective health care and protect its own health. The laudable intentions of justice in this aspect are watered down considerably by the words “reasonably available” which leaves post trial availability of treatments very much to the discretion of the sponsor and investigator.

In continuing its discussion on justice, the CIOMS principle extends its protections, from populations and countries to the needs of individual vulnerable subjects by stipulating that justice also requires that the research is responsive to the health conditions and needs of vulnerable subjects and that the least vulnerable should be selected to accomplish the purpose of the research. This gives recognition to the fact that the degree of vulnerability differs between individuals within vulnerable groups and hence the exposure to risk would also differ. CIOMS links justice to risk by pronouncing that risk from involvement in the research that does not hold out the prospect of direct health-related benefit to the subject must be justified by the anticipated benefit to the population that the research subject represents.

In Guideline 12 which is specific to the equitable distribution of burdens and benefits in the selection of groups of subjects in research, it is stated that there has been the perception, at times correct, that certain groups are overused as research subjects. Overuse has been

based on the ease of administrative availability of the populations in certain cases. This situation of overuse could arise at research sites and hospitals which are located where members of the lowest socio-economic groups reside, students in investigators' classes, residents of long-term care facilities, and subordinate members of hierarchical institutions. Because of their willingness to serve as subjects in return for relatively small stipends, indigent (impoverished) groups have also been overused as research subjects. In addition, prisoners, because of their regimented lives and conditions of economic deprivation, have been considered ideal subjects for phase 1 clinical trials. Overuse in research could extend beyond groups within a certain society, and to entire communities or societies as well.

By the emphasis given to vulnerability in the discussion of the principle of justice in research, CIOMS clearly gives significant credence to the fact that the notion of vulnerability in health research is complexly entangled with justice.

CIOMS 2002 has a full guidance point (Guideline 13) specific to vulnerability. This is followed by a comprehensive commentary. The guideline underscores the need for special justification and a strict application of rights and welfare protections when vulnerable individuals are invited to participate in research. The commentary commences with a definition of vulnerable persons as:

> "... those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests."

This definition is an expansion of the description of vulnerability in its section on guiding principles. However, it is clear from both descriptions that vulnerability, while context

specific, is caused by an inability to protect one's interests. The commentary then goes on to specify children and persons with mental or behavioural disorders as classes of individuals that are conventionally considered vulnerable because of a limited capacity to consent.

Other vulnerable groups detailed in this commentary are:

1. Junior or subordinate members of a hierarchical group: medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, who, because they work closely with investigators, tend to be called upon more often to serve as research subjects.
2. Elderly persons: are vulnerable only once they acquire vulnerability-defining features such as dementia, or when they are institutionalised.
3. Residents of nursing homes.
4. People receiving welfare benefits or social assistance,
5. The unemployed.
6. Patients in emergency rooms.
7. Ethnic and racial minority groups.
8. Homeless persons.
9. Nomads.
10. Refugees or displaced persons.
11. Prisoners.
12. Patients with incurable diseases.
13. Individuals who are politically powerless.
14. Members of communities unfamiliar with modern medical concepts.

15. Persons with serious, potentially disabling or life-threatening diseases (they are highly vulnerable).

It is interesting to note that women and pregnant women have been excluded from the list above. Guideline 16 gives recognition to the importance of not excluding women from research based on their potential to get pregnant. Guideline 17 on pregnant women as research subjects states that pregnant women should be presumed to be eligible for participation in research but with the proviso that special protections are necessary based on potential risks to the fetus. Fetal vulnerability is acknowledged in the commentary which states that where fetal abnormality is not recognised as an indication for abortion, and where there is a realistic basis for concern that fetal abnormality may occur as a consequence of the women's participation in the research, pregnant women should not be recruited in the study.

Analysis of the CIOMS guidelines reveals an emergence of both broad categories of vulnerabilities, similar to the DoH, and a highlighting of specific groups. The definitions of "vulnerability" in both documents, while having similar elements, differ considerably as well.

Table 2: DEFINITIONS OF VULNERABILITY: DOH (2013) AND CIOMS (2002)

DoH 2013	CIOMS 2002
• "Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm"	• "A substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternate means of obtaining medical care or other

	expensive necessities, or being a junior or subordinate member of a hierarchical group".
• "All vulnerable groups should receive specifically considered protection."	• "Accordingly special provision must be made for the protection of the rights and welfare of vulnerable persons."

5.2(C) Protecting The Vulnerable In Research: The ICH Harmonised Tripartite Guideline. Guideline For Good Clinical Practice (GCP) E6(R1)[9]

The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use developed its GCP Guidelines through a 4 step consultation process between 1995 and 1996 with the final version being approved in June 1996[9]. The set of guidelines for GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects and will be discussed only briefly because of its highly technical nature. The parties to this tripartite ICH GCP are the European Union (EU), Japan and the United States (US). The objective of the document is to provide a unified standard for these parties so the mutual acceptance of clinical trial data by the regulatory authorities of their jurisdictions is facilitated. When drawing up the guidelines, good clinical practices of the three parties and Australia, Canada, the Nordic countries and the WHO were taken into consideration. It is a comprehensive guide to the technical and operational aspects of scientific research. The guidance to researchers and sponsors spans the entire research process from the writing of the protocol and the investigator brochure to the final clinical study report. Details as regards REC membership and the review process are described. The process for monitoring and reporting of adverse events are also detailed.

"Vulnerable Subjects" are defined in section 1.61 of the Glossary as follows:

> "Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors and those incapable of giving consent."

Two broad categories of vulnerable groups emerge from this description: Groups with hierarchical structures and "other". Similar to CIOMS, ICH GCP has identified specific types of vulnerabilities to be included under these broad categories. A major criticism of the ICH GCP approach, though, is that "other" is too broad and ubiquitous a class, especially as the broad categories comprise only two types.

Section 3.1.1 of ICH GCP stipulates that an IRB / IEC should pay special attention to trials that may include vulnerable subjects when carrying out its mandate of safeguarding the rights, safety and well-being of all trial subjects.

Informed consent is discussed extensively in section 4.8 which starts off by requiring that when the investigator obtains informed consent, ethical principles that have their origin in

the DoH should be complied with. With regard to vulnerability, it is required that subjects should not be coerced or unduly influenced to participate or continue participating in a trial. A legally appointed representative is expected to consent on behalf of a subject who is incapable of giving informed consent. An impartial witness is to be present during the entire informed consent discussion where a subject or the legally appointed representative is unable to read. Specific mention is made of minors or patients with severe dementia. Added protections include not only a legally appointed representative but also the requirement that the subject be informed about the trial to the extent compatible with his or her understanding and, where capable, the subject should sign and personally date the informed consent. The process of obtaining consent is also highlighted in the emergency situation. Where prior consent is not possible, and the legally appointed representative is not available, the IRB/IEC should have to approve or give a favourable opinion with regard to enrolling the subject and deferred consent should be obtained. A clear category of vulnerability due to challenges with obtaining informed consent has now emerged.

Hence, the broad categories of vulnerability teased out of the ICH GCP Guidelines are:

1. groups with hierarchical structuring,
2. challenges with informed consent, and
3. other.

Table 3: CATEGORIES OF VULNERABILITY IN THE INTERNATIONAL GUIDELINES

2013 DoH	2002 CIOMS	1996 ICH-GCP
•Patients •Dependence on others •Consenting under duress •Incapable of giving informed consent	•Patients •Juniors /subordinates •Elderly persons •Limited capacity to consent •Residents of nursing homes •On welfare / social assistance •Unemployed •Patients in emergency rooms •Ethnic / minority groups •Homeless persons •Nomads •Refugees /displaced persons •Prisoners •Patients with incurable diseases •Politically powerless •Unfamiliar with modern medical concepts •Serious, potentially disabling or life-threatening diseases	•Groups with hierarchical structuring •Challenges with informed consent •Other

5.3 CONCLUSION

As has been shown above, the approach to vulnerability in the guidelines have been too broad and too narrow as evidenced by the numerous groups that are vulnerable. The questions that arise is where do individuals with vulnerabilities who do not belong to any of the groups fit in and what, if any special protections are accorded to them? Are they adequately protected by the guidelines? The 1964 DoH was the first international instrument to develop protections for subjects involved in research that went beyond universal vulnerabilities. The DoH demonstrated a need to expand on safeguards for vulnerable individuals and groups and while an extensive list of categories of vulnerability emerged from the different versions through time, the latest version seems to be heeding the call in the literature over the past few years to do away with group / population terminology towards a more reasoned approach to protecting participants with vulnerabilities. The approach in the CIOMS Guidelines is too wide-ranging and almost anyone who is involved in research will require protections for special vulnerabilities. This approach is therefore of not much assistance to Research Ethics Committee members when reviewing protocols where potential participants may have vulnerabilities. Unfortunately, as will be shown in the chapter that follows, the SA Ethics Guidelines approach to people with vulnerabilities is very similar to CIOMS. This chapter considered the approach to vulnerability from the perspective of three major international guidelines. The following chapter discusses the approach to vulnerability in guidelines from a national country-level perspective.

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Chapter 6: NATIONAL GUIDELINES AND REGULATIONS: United States and South Africa

6.1 INTRODUCTION

As was seen in the previous chapters, despite the very public Nuremberg Doctors' Trial which gave rise to the Nuremberg Code in 1947 and the World Medical Association setting its standards for ethics in research through its 1954 Resolution on Human Experimentation: Principles for those in Research and Experimentation and the Declaration of Helsinki in 1964, these guidelines did not prevent the chain of disasters in the United States during and following this period. Some of these were elaborately demonstrated in Beecher's publication in 1966[1]. Even after Beecher's exposé, there was a succession of tragedies including the Tuskegee Syphilis Study, news of which emerged in 1972[2,3], and the Gautemala STD research, news of which has emerged only recently[4].

In South Africa, prior to 1979, there were no national guidelines or policies for participant protections in research. As discussed in chapter 4, following the publication of Beecher's paper[1], the Committee for Research on Human Subjects (Medical), the first REC in SA, was established at the University of the Witwatersrand. From the seventies, tertiary institutions at which health research was conducted established local RECs. In 1979, the South African Medical Research Council (SAMRC), produced the first set of guidelines at a national level[5]. The protections espoused in those guidelines applied to any research being funded by the SAMRC or conducted by researchers affiliated to the SAMRC. These guidelines have undergone several revisions. While an important milestone in the participant protections endeavours in South Africa, the MRC guidelines did not have regulatory authority for non SAMRC associated research. Furthermore, there was no uniformity of functioning between

the local institutional RECs that had been set up. Standards of review ranged from exceptionally high at some RECs to very poor at others and some RECs even served as mere "rubber-stamping" committees. Hence, in my experience, anecdotal evidence of ethics "shopping" was not uncommon in the country and protectionism ranged from weak to strong depending on the institutional commitment to safeguards. The promulgation of the NHA brought about far-reaching changes, with research participant protections and the functioning of RECs now being regulated by the country's statutory laws.

The examination of protections from a national perspective will start off with an appraisal of the Belmont Report[6] , and the Code of Federal Regulations[7], both of which were outcomes of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research in the US. The Commission was appointed as a consequence of the Tuskegee Syphilis study. The US guidelines are discussed because, and as stated previously, a large proportion of international research conducted in SA is sponsored by funders from the United States[8,9]. Research in SA is primarily a combination of investigator driven, US federally funded initiatives and pharmaceutical multinational research where the parent company is, in the main, situated in the United States[9,10]. Only a small proportion of research is funded by sponsors in other countries in the West. Furthermore, as stated in the previous chapter, the Belmont Report is a key text that directed the development of the SA Ethics Guidelines[11]. An appraisal of the ethical and regulatory approach to research participant protections in South Africa will follow the discussion on the US documents. .

6.2 NATIONAL GUIDELINES AND REGULATIONS: THE UNITED STATES

Because of the disregard of codes and guidelines by prominent researchers during the sixties, several scholars developed an interest in research ethics through this decade. One of

them was Paul Ramsey, a theologian from Princeton. His landmark work in 1970, 'The Patient as Person"[12], underscored that where it was possible to obtain consent, "no man [sic] is good enough to experiment on another without his consent"[13]. In the context of research, he stressed the importance of establishing a partnership between the researcher and the subject in order to ensure that the subject would not be treated as a mere means to an end, a utilitarian approach, which he stated was morally indefensible. By 1970, the notion of consent was well established as a principle in research.

Just two years later though, press reports on the Tuskegee Syphilis Study (see chapter 4), where subjects were not informed participants, came to light[2]. It was clear now that consent was weakly implemented in practice. The US Department of Health, Education and Welfare stopped the research[3,14] and a federal panel, the Tuskegee Syphilis Study Ad Hoc Panel, was appointed to review the study. One of its recommendations was that Congress should establish a federal panel to regulate federally sponsored research on human subjects[13].

The Tuskegee Syphilis Study elicited quite a forceful influence on law and policy formulation in the United States. On 12th July, 1974, the National Research Act[15] (Pub. L. 93-348) was signed into law. The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research was established as a result of the Act. The Commission was charged, among others, to identify the basic ethical principles that should underlie the conduct of biomedical and behavioural research involving human subjects and to follow this with the development of guidelines to ensure that such research was conducted in accordance with those principles. In carrying out its mandate, the Commission was directed to consider[3]:

"(i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine,

(ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects,

(iii) appropriate guidelines for the selection of human subjects for participation in such research, and

(iv) the nature and definition of informed consent in various research settings."

The National Commission functioned between 1974 and 1978[3]. The 1979 Belmont Report[6], a statement of ethical principles to guide research involving humans, was one of its final outcomes. It was the result of a four-day period of rigorous discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Centre together with the monthly deliberations of the Commission that were held over a period of nearly four years[3]. The National Commission also influenced the development of the Code of Federal Regulations and the 1991 Common Rule, a set of regulations to govern research in the United States[7].

6.2(A) The Belmont Report[6]

The Belmont Report, while a brief document, exhibited outstanding vision and has "provided something of a textual bedrock for the succeeding decades"[3]. It identifies three comprehensive principles or general prescriptive statements that are relevant to research involving human subjects and incorporates them in an analytical framework to assist in the resolution of ethical dilemmas in research. It distinguishes between research and clinical practice in order to identify the activities that should undergo ethics review for protecting

humans involved in health research. It defines practice as interventions that are designed specifically to enhance the wellbeing of individual patients and that have a reasonable expectation of success. Research is defined as "an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge." The need for this distinction could denote that at that time most of research was done on patients with medical conditions. In the DoH, the distinction is between "clinical research combined with clinical care" and "non-therapeutic clinical research"(1964), which was changed to "Medical research combined with professional care (clinical research)" and "Non-therapeutic biomedical research involving human subjects (non-clinical biomedical research)" in 1975.

The Belmont Report is divided into three sections. Section A is specific to the boundaries between practice and research, section B, the three basic ethical principles and section C, the application of the principles. For the purpose of this chapter, only pertinent aspects of sections B and C which relate to vulnerabilities will be discussed.

According to section B of the Belmont Report, the three basic ethical principles, respect for persons, beneficence and justice, refer to "those general judgements that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions." All three make reference to vulnerabilities although the term is not used explicitly in this section.

Respect for persons has two separate moral requirements. The first is to acknowledge and respect the autonomy of those individuals capable of self-determination and the second is the requirement to protect those individuals with diminished autonomy who have decreased levels of or no capacity for self-determination. The principle draws to attention

that the capacity for self-determination matures during an individual's life. Illness, mental disability or circumstances that severely restrict liberty result in some individuals losing this capacity partially or completely. Protecting the immature while they mature and the incapacitated while they are incapacitated is necessary if these individuals are to be respected. The degree of protection required will range from extensive (to the point of excluding individuals from activities that may harm them) to very little where all that is necessary is to ensure voluntary participation and an awareness of possible adverse consequences. The extent of protection depends on the risk of harm and likelihood of benefit. The degree of autonomy should be periodically re-evaluated. The section further states that in some situations the application of the principle of respect for persons may not be obvious, and uses prisoners as research subjects as an example. The principle requires that prisoners are not deprived of the opportunity to volunteer for research. However, it should also be recognised that under prison conditions they may be subtly coerced or unduly influenced to partake in research activities that they would otherwise not normally involve themselves in. Respect for persons would prescribe that prisoners be protected and the resultant dilemma would be that of balancing the competing claims urged by the principle of respect itself, i.e., to allow prisoners to volunteer vs protecting them. This principle focuses on vulnerable individuals with diminished autonomy and correlates the amount of protections with the risk of harm and likelihood of benefit. From this it can be extrapolated that a meticulous benefit / risk analysis will be necessary when vulnerable individuals with diminished autonomy are to be involved in research. This principle further brings to light that prisoners are a vulnerable population or group.

Beneficence is described in the Report as an obligation to make efforts to secure the well-being of persons. It formulates two general rules as being complementary expressions of beneficent actions; the rule of "do not harm" and the rule of "maximize possible benefits and minimize possible harms". These two rules are both necessary to ensure adequate protections of vulnerable individuals and groups. The Report further states that the principle of beneficence often occupies a well-defined justifying role in many areas of research and illustrates this point by using children as an example. Dilemmas arise when research involving children presents more than minimal risk without immediate prospect of direct benefit to the children involved. While deontological arguments would stress that research of this nature should not be conducted, utilitarian arguments would highlight the consequences of this limitation as ruling out much needed research which could be of great benefit to children in the future. It is clear that when research is conducted on vulnerable groups the rules within the principle of beneficence come into conflict, challenging the researcher to make difficult choices. By using children as an example, this principle gives credence to children being a vulnerable group.

The principle of justice in the Report examines who ought to receive the benefits of research and bear its burdens. It goes on to explain that when a burden is unduly imposed or when a benefit to which a person is entitled is denied without good reason, an injustice results. Several examples of injustice are used in the Report to demonstrate the principle. During the 19th and 20th centuries, the burdens of serving as research subjects fell onto poor ward patients. However, the benefits of improved medical care were enjoyed primarily by private patients. This is an issue of concern for RECs in SA, especially in light of our two-tier health system. Additional concerns include issues of distributive justice in international

research. Other examples include the exploitation of unwilling prisoners as research subjects by the Nazis and the exploitation of disadvantaged rural black men in the Tuskegee Syphilis Study. According to the Report justice would require that the selection of research subjects must be meticulously examined to ensure that some populations are not systematically selected because of their easy availability, their compromised position, or their manipulability instead of reasons directly related to the problem under study. The populations used as examples in this section are welfare patients, particular racial and ethnic minorities, and persons confined to institutions. Furthermore, the principle elucidates that those persons from groups that are unlikely to be beneficiaries of the subsequent applications of research should not be unduly involved in the research. This principle designates welfare patients, particular racial and ethnic minorities, and persons confined to institutions as vulnerable groups / populations.

Section C of the Report is on the application of each principle to conflicts in research. Informed consent is discussed as an application of the principle of respect for persons, risk/benefit assessment as an application of the principle of beneficence and subject selection as an application of the principle of justice.

The elements of informed consent considered in Section C are information, comprehension and voluntariness. The latter two elements focus on protecting the interests of vulnerable individuals and groups. The comprehension element highlights the need to adapt the presentation of information to the subjects' capacity to understand because the latter is a function of intelligence, rationality, maturity and language. The greater the risk, the greater is the obligation on the investigator to ensure comprehension. To ensure this obligation is met in situations when comprehension is severely limited, special provisions may need to be

made where conditions of immaturity or mental disability exist in research subjects, either as individuals or as populations. Examples of populations that are considered incompetent are infants, young children, mentally disabled patients, the terminally ill and those that are comatose. Even in these situations, respect for persons places an obligation on the investigator to give them the opportunity to choose, to the extent that they are able, whether or not to participate and also to seek permission from other relevant parties to enrol them in the research. The latter should be those that are in a position to most likely understand the incompetent subject's situation and to act in that individual's best interests. In this way, these individuals will be protected against harm both by respecting their wishes and that of the surrogate decision-maker. This section of the Report clearly affirms the importance of respecting the moral status and human dignity of the research participant.

The voluntariness element stresses that there should be no coercion or undue influence when the subject participates in research. Coercion arises when an overt threat of harm is deliberately raised by one person to another so as to achieve compliance. Undue influence is when an excessive, unwarranted, inappropriate or improper reward or other overture is offered to a subject in order to gain compliance. It is highlighted that an inducement that is ordinarily acceptable may become undue if the subject is particularly vulnerable. The Report continues to explain that unjustifiable pressures usually occur when persons in positions of authority or commanding influence advocate a course of action for a subject, but because a continuum of such existing factors may be present, it is impossible to state at which precise point justifiable persuasion gives way to undue influence. Examples of undue influence cited in this section are actions that manipulate a person's choice through the controlling

influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

The application of the principle of beneficence as expressed by the risk / benefit assessment states that when vulnerable populations are involved, the appropriateness of involving them should be demonstrated. Such judgements are made using a number of variables including the nature and degree of risk, the condition of the particular population involved and the nature and level of the anticipated benefits. Many types of harms need to be taken into account. These include risks of psychological, physical, legal, social and economic harms.

Selection of subjects is the application of the principle of justice in the Report. Here there is a moral requirement that procedures and outcomes in the selection of research subjects be fair. This is relevant at both the individual and population levels. Potentially beneficial research should not be offered to only some patients because they are favoured by the researcher while only "undesirable" individuals are selected for risky research. The same would apply to populations. In addition, an order of preference is appropriate when certain populations are selected (e.g., adults before children). Furthermore, some populations may be involved only under certain conditions, if at all (e.g., the institutionalised mentally infirm or prisoners).

The section draws to attention that social, racial, sexual and cultural biases institutionalised in society could result in injustices. Furthermore, some populations, especially institutionalised ones, are already burdened in many ways because of their infirmities and environments and should not be involved in research that involves risks without a therapeutic component. In such situations, less burdened populations should be selected

unless the research is directly related to the specific burdened population. In addition, it is unfair that the economically disadvantaged population using public sector health care facilities should constitute a pool of preferred research subjects for the benefit of the more advantaged populations who are likely to be the recipients of proven interventions.

The section ends by discussing a special instance of injustice that results from the involvement of vulnerable subjects. It states that certain groups such as racial minorities, the economically disadvantaged, the very sick, and the institutionalised may continually be sought as research subjects because of their ready availability in settings where research is conducted. It cautions that they should be protected against the danger of being involved in research exclusively because of administrative convenience or because they are easy to manipulate for reasons of illness or socioeconomic conditions. They need protection because of their frequently compromised capacity for free consent and their dependant status. The principles in the Belmont Report, similar to the DoH, are greatly influenced by deontology and virtue ethics.

Table 4: VULNERABLE GROUPS AND CONDITIONS AS RELATED TO THE BELMONT PRINCIPLES

Respect for persons	**Beneficence**	**Justice**
• Illness • Mental disability • Circumstances that severely restrict liberty: coercion or undue influence • Immature (age): infants, young children • Incapacitated: severely limited comprehension, terminally ill, comatose • Prisoners	• Children : when research presents more than minimal risk without immediate prospect of direct benefit • People at risks of harm: physical, legal, social, economic	• Poor ward patients • Unwilling prisoners being exploited • Disadvantaged rural black men • Welfare patients • Particular racial and ethnic minorities • Persons confined to institutions • The economically disadvantaged • The very sick

The Belmont Report, as a statement of basic ethical principles and guidelines, assists in resolving ethical problems that may arise when conducting research with human participants. The Report describes its ethical principles in detail and refers to vulnerable groups and populations as an application of all three of its principles.

6.2(B) The Code of Federal Regulations[7]

The Belmont Report greatly influenced the current United States regulatory system for the protection of human subjects. Using this report to underpin their documents, in 1981 the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) revised their existing human subjects regulations to make them as compatible as possible under their respective statutory authorities. Fourteen other Federal departments and agencies, in 1991, joined the DHHS in adopting a uniform set of rules as the Code of Federal Regulations (CFR) for the Protection of Human Subjects in research[7]. The DHHS regulations, also known as 45 CFR 46, are made up of 4 subparts. Most collaborative research in South Africa, because of the sponsor being in the USA, needs to abide by the stipulations in these Regulations. Subpart A is also known as the Federal Policy or the "Common Rule", Subpart B is on additional protections for pregnant women, human foetuses and neonates, Subpart C, additional protections for prisoners and Subpart D, additional protections for children. The protections in Subparts B, C and D are in addition to the general protections imposed by the Common Rule. The Code of Federal Regulations was revised on 15th January 2009. This revised version became effective from July 2009.

6.2(B)I Subpart A - The Common Rule[7]

The Common Rule outlines the basic provisions for Institutional Review Boards (IRBs), informed consent and Assurances for Compliance. Vulnerability is mentioned in its section 46.111 under its criteria for IRB approval of research. Subsection (a)(3) states that selection of subjects should be equitable and in making this assessment, IRBs should take into account the purpose of the research and the setting in which the research is to be conducted and should be "particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons." Subsection B goes further to state that when all or some of the subjects in those populations are likely to be vulnerable to coercion or undue influence, additional safeguards must be included in the studies so as to protect the rights and welfare of these subjects. This section gives recognition to the fact that not all individuals within a population may share the population's vulnerability.

6.2(B)II Subpart B – Additional Protection for Pregnant Women, Human Fetuses and Neonates Involved in Research

This Subpart details as part of the special protections, stringent conditions that need to be satisfied by researchers and that IRBs have to take into consideration when reviewing research involving pregnant women, their foetuses and neonates. Meticulous risk / benefit assessments are mandated. Only the woman's consent is required where the research involves both her and the fetus. In the case of research involving the fetus only, the consent of both the woman and the father must be obtained. Where the father is unavailable, incompetent, has temporary incapacity or the pregnancy resulted from incest or rape, his

consent need not be obtained. With regard to neonates who are of uncertain viability, research can only be conducted where it holds out the prospect of enhancing survival of the neonate to the point of viability and the risks are the least possible for achieving the objective or the biomedical knowledge from the research cannot be obtained by any other means and there will be no added risk to the neonate as a result of the research. Informed consent from either parent or legally authorised representative is requisite, except in the case of the pregnancy resulting from incest or rape where the father's consent is not deemed necessary.

6.2(B)III Subpart C – Additional Protections Pertaining to Biomedical and Behavioural Research Involving Prisoners as Subjects.

This subpart recognises that prisoners need additional safeguards because they may be under constraints as a result of their incarceration which could affect their ability to make truly voluntary and uncoerced decisions whether or not to participate in research. The additional safeguards include that the majority on the IRB have no association with the prison(s) involved except for their membership on the Board and that at least one member of the IRB is a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity. Where the research is reviewed by more than one IRB, only one Board need satisfy the latter requirement. Other safeguards focus on the principle of justice: fairness in subject selection, avoiding undue inducements and coercion, the risks of the research being commensurate with acceptable risks involving non prisoner volunteers and provision for post-study follow up examination or care that takes into consideration the varying lengths of individual prisoner sentences.

6.2(B)IV Subpart D – Additional Protections for Children Involved as Subjects in Research

In this Subpart, scrupulous attention is paid to risk with added safeguards provided for several categories of risk:

a. Research not involving greater than minimal risk ;
b. Research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects;
c. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or conditions; and
d. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Stipulations with regard to child assent and parent or guardian permission are also detailed.

In addition, regulations pertaining to children as wards of the state or any other agency, entity or institution are provided.

Where children are able to provide assent (affirmative agreement to participate in research), adequate provisions need to be made for obtaining the assent. The age, maturity and psychological state of the child must be considered when determining the child's ability to assent. This determination may be for all children or each child in a particular protocol as deemed appropriate by the IRB. Where the capability of some or all children is very limited and they cannot be reasonably consulted, or the research intervention or procedure holds out the prospect of direct benefit which is so important to the health and wellbeing of the children and is available only in the context of health research, the assent of children will not be a necessary condition for proceeding with the research and the IRB may waive the

assent requirement. Adequate provisions need to be made to obtain parent or guardian consent. Only one parent's consent is required when the research is no greater than minimal risk or when the research is greater than minimal risk but holds out the prospect of direct benefit to the child, or the monitoring procedure in the research is likely to contribute to the child's wellbeing. Should the IRB be of the opinion that parent or guardian permission is not reasonable to protect the child, the IRB may waive this requirement on condition an appropriate mechanism for protecting the children in the research is substituted.

When children who are wards of the state or any other agency, entity or institution are included in research, they can be enrolled if the research is related to their status as wards, or the research is conducted in schools, camps, institutions, or similar settings in which the majority of children are not wards. Where children as wards are enrolled in research, the IRB would require the appointment of a neutral advocate for each child to act in the best interests of the child even if there is a guardian or individual in the position of *loco parentis* acting on behalf of the child.

Table 5: VULNERABLE GROUPS IN THE CODE OF FEDERAL REGULATIONS

Subpart A	**Subpart B**	**Subpart C**	**Subpart D**
• Coercion or undue influence: children, prisoners, pregnant women, mentally disabled persons, economically or educationally disadvantaged persons.	• Pregnant Women • Fetuses • Neonates	• Prisoners	• Children

6.3 NATIONAL GUIDELINES AND REGULATIONS: SOUTH AFRICA

Although medical research had been conducted in South Africa since the 1800's[16], and despite oversight mechanisms being set up at individual institutional levels, there was no national guideline or policy until 1979. Even this document was limited in scope in that it applied only to researchers affiliated with the SAMRC, either as recipients of funding from the SAMRC or as researchers within its institutes, units or groups.

In the 19th century, Cape Town, Grahamstown, Durban, Pietermaritzburg and Kimberley were large thriving towns with many doctors in practice. They formed their own associations as branches of the British Medical Association (BMA). By the 1920's, these branches had spread throughout South Africa and in 1927, they joined to form a national association, the Medical Association of South Africa (MASA). The MASA later joined the WMA when it was established. The MASA was replaced by the South African Medical Association (SAMA) on the 21st May 1998.The SAMA as we know it today is the result of the unification of the fragmented pre-democracy medical groups[17]. Although there were no safeguards for participants in research at a national level for many decades, doctors involved in research were bound by the WMA's guidelines and declarations. At this juncture a brief history of health research in South Africa is appropriate for an understanding of the evolution of participant protections in this country.

6.3(B) History of Medical Research in South Africa

In South Africa, medical scientists were busy with discoveries and innovations as far back as the 1800s. Ova of bilharzia were discovered in the urine of a patient from Uitenhage by Dr John Harley in 1864. About 30 years later, in 1895, the cycle of nagana, a disease of cattle

spread by a species of tsetse fly, was uncovered by Sir David Bruce, of the British Royal Army Medical Corps in Zululand. Because of this, he was able to associate the disease with human sleeping sickness caused by a related parasite and transmitted by other tsetse flies. In 1912, the South African Institute for Medical Research (SAIMR) was established as a joint venture between the South African Government and the Chamber of Mines represented by the Witwatersrand Native Labour Association. While some research was conducted at the SAIMR, a major aspect of its activities was directed to routine screening and diagnostic work[16]. It has been argued that early medical research in South Africa was established to keep the mines in production and not to protect the population of miners against the high incidence of serious tropical diseases which the mine workers were succumbing to. It is suggested that the goal of medical research in South Africa at that time was based on narrow economic rather than humanitarian reasons[16], undoubtedly a utilitarian view.

The SAIMR played a substantial role in research involving pneumococci which subsequently resulted in the development of the pneumococcal vaccine. In addition, the SAIMR researchers determined the transmission cycle of plague and identified 2 species of anopheles mosquito, principally responsible for the transmission of malaria. As a result of rapid scientific and industrial development during the Second World War, research in many fields gained momentum in South Africa, especially at the University of Cape Town. In 1944, Dr Basil Schonland from the University of the Witwatersrand was requested by General Jan Smuts, then Prime Minister and Minister of Defence of the country, to create the legislative basis for scientific research and the Scientific Research Council Act was promulgated in 1945. This Act established the principle of overall government control of research and led to the establishment of the Council for Scientific and Industrial Research (CSIR) soon

thereafter. The CSIR controlled the practical administration of research in the country. Although the CSIR's brief, while broad, did not include medicine, it established a coordinating committee (Committee for Research in Medical Sciences) within the organisation to take forward medical research. It was this Committee that established several research units and sponsored research programs in medical schools. It also participated in collaborative research with institutes outside South Africa. The established and fully fledged universities at that time were the Universities of Cape Town, the Witwatersrand, Stellenbosch and Pretoria[16].

In December 1967, the historic first human heart transplant was done in Cape Town, South Africa. Although it is unclear how much research preceded this procedure, there is no doubt that the operation was done in a research setting[18] and it had far reaching impact. Spurred by this dramatic feat in therapy, Senator Walter Mondale of the USA that year introduced a Bill in Congress, the Senate Joint Resolution (SJRES 145) which called for a National Commission on Health, Science and Society to "evaluate the integrity and direction of research and to assess the impact of the technological advances on society including issues of social justice generated by research."[18] The Bill generated little support and was not enacted in the form that it had first been introduced. After several attempts by Mondale, only a few aspects of the Bill were incorporated into legislation some years later[18].

While most people around the world showered praise on South Africa, there were murmurs, although somewhat stifled, that research could have been better channelled in other directions towards the greater good for a greater number of South Africans and that the research was only possible because of South Africa's oppressive apartheid policies[16]. However, Barnard's heart transplant was undoubtedly a major medical achievement. It also

underscored the need for order in the organisation of medical research in the country. The need for this order led to the enacting of the Medical Research Act (No 19 of 1969), and the establishment of the Medical Research Council in 1969. Its most important mandate was promoting the improvement of health and the quality of life of the people in SA through research, development and technology transfer. The MRC was funded solely by an annual government grant. Initially there was no provision for the acceptance of funds from other sources. It was to co-ordinate medical research within the country and to determine the distribution of government funding for such research[16].

6.3(C) Participant Protections in South Africa: The SAMRC Research Ethics Guidelines.

In 1978, almost a decade after the establishment of the SAMRC, the then vice president of the SAMRC, de V Lochner, following a visit to the WHO in Geneva, wrote out the first set of guidelines for participant protections in research at a national level in South Africa. These guidelines have been revised and updated regularly so as to be in line with international research ethics standards[5].

6.3(C)I SAMRC Research Ethics Guidelines 1979[19]

In December 1979, the SAMRC published its first set of guidelines entitled "A Guide to Ethical Considerations in Medical Research."[19] While not mentioned explicitly in the text, the bibliography to these guidelines includes The DoH (1964), The Nuremberg Code and some proposed US Federal Policy documents[20]. The guidelines emphasised in the introduction that it was of paramount importance for any ethical code relating to medical research to err in the "... direction of stringency rather than laxity, and no man should find himself in the position of solely being judge of his own morals in research." The guidelines,

which also referred to itself as an “Ethical Code”, underscored that safeguarding the rights and welfare of human subjects involved in activities supported by grants or contracts from the SAMRC was of paramount importance and that the responsibility for this was to be borne by the investigator, the heads of departments and the institutions concerned. The guidelines further stated that it was the policy of the SAMRC that no grant or contract for an activity involving human subjects would be made without prior review and approval of the application by an appropriate “Institutional Committee” acceptable to the SAMRC. Substantial prominence was placed on the law and it was stressed that particularly relevant to the decision of the Committee were those rights of the subject that were defined by the law. The Committee was advised to familiarise itself with those statutes and common law precedents which could have bearing on its decisions. It was further stated that:

> “The provision of this Code may not be construed in any manner or sense that would abrogate, supersede, or moderate more restrictive applicable law or precedential legal decisions.”

Furthermore, in its Statement of Principles, it was affirmed that institutions should adopt a Statement of Principles that would assist in their discharge of responsibilities for the protection of rights and welfare of subjects. It went on to state that;

> “This official guide of the SAMRC may be used as a guideline for such a statement and care should be exercised to ensure that the principles outlined in the said statement do not supersede SAMRC policy or any legal rule.”

It was ironic that for the safeguarding of rights and dignities of participants, such importance was placed on the law, especially as this was in the context of the apartheid era where people of colour were oppressed and their rights trampled upon.

Section 4.3.9 of the Code listed a number of different subjects and activities that would require special consideration. Fetuses, pregnant women, minors and the institutionalised mentally infirm were included in the list.

In attaching "A Patient's Bill of Rights" as an appendix to the Code, it gave recognition to patients being particularly vulnerable. In its Appendix VI, it provided special safeguards for fetuses and pregnant women as research subjects, the institutionalised mentally infirm and minors. The protections for fetuses and pregnant women were very much in line with Subpart B of the Code of Federal Regulations. The mentally infirm included those in institutions who were mentally ill, mentally retarded, emotionally disturbed, or senile regardless of their legal status or basis of institutionalisation. It stated that additional safeguards were required for them because their freedoms and rights were potentially subject to limitation as they were confined to institutional settings; they might have been unable to sufficiently comprehend information to give an informed consent and they might have been legally incompetent to consent. Where possible, assent should be secured. There should be no undue inducements and procedures for subject selection, securing consents, protecting confidentiality and monitoring continued participation should be adequate. It is interesting to note that monitoring of research was a consideration even at that time.

On the issue of minors, it stressed that sufficient maturity should be ascertained and the minor given the opportunity to consent where appropriate; however, the consent of the guardian should also be obtained. It went on to state that normally, parents would be the

guardians with the *father having the final say* (my emphasis), but where the child was illegitimate, its mother alone was its legal guardian. The law applicable here was the then Children's Act (No 33 of 1960). The document further stated that the position was more complicated where Black Africans were concerned. Most "Bantu" women were usually in the position of minors and fell under the guardianship of their father or head of the kraal if unmarried, and under their husband if married. The guardianship of a "Bantu" child was difficult to establish as the South African Law and the State imposed Bantu Law were in conflict on that point. A customary union was not recognised as a lawful marriage according to South African Law. This created uncertainty as to whose consent would have to be obtained for a child born in a customary union. It recommended that the consent of the legal guardian recognised by each system be obtained in order to avoid any problems that might have arisen from this uncertainty. It is remarkable that the SAMRC placed such importance on the laws, especially considering there were two sets – the South African Law and the "Bantu" Law. The latter applied to indigenous Black South Africans, who clearly were not acknowledged as being on par with others in the country. They were considered a lesser form of life with no moral status or human dignity and hence did not qualify to benefit from the protections offered by South African Law. I have used the word "Bantu" in inverted commas as this term was used in a derogatory manner to describe Black South Africans during the period of apartheid. "Bantu" actually refers to more than 400 ethnic groups in Africa in countries ranging from Cameroon to South Africa. They form a common language group, the Bantu language family[21].

6.3(C)II SAMRC Research Ethics Guidelines 1987[22]

Eight years after the first edition, the SAMRC launched its "Ethical Considerations in Medical Research. Revised Edition: 1987." Again, while not explicitly mentioned in the text, the DoH of 1964 (despite the 1983 version being in force), the Nuremberg Code and the two Federal Documents listed in the Bibliography of the earlier Code were recorded in the Bibliography. There are no recorded external influences on the revised guidelines and the reason given for the revision was that medical science was progressing at a rapid rate and new ideas and questions that did not seem to be significant just a decade back had become part of the ordinary problems that researchers had to deal with regularly. Certain aspects, e.g., biohazards and the use of animals for experimentation were revised extensively and there was a more logical chapter arrangement. Of note, the focus on complying with the legal framework was carried through into the second edition. Appendix V, on Informed Consent, carried an additional safeguard which required that special care had to be taken when dealing with uneducated or underdeveloped communities to ensure that the subjects were not misled and their ignorance not exploited. Similar to the previous edition, it cautioned researchers to be cognisant of patients' mental and emotional conditions when discussing risks of research. With regard to individuals and groups requiring special considerations the only change in this guideline was to include prisoners and detainees. However, in Appendix VI all that was stated about this group was that although clinical experimentation was not legally forbidden with prisoners and detainees, the accepted government policy was that prisoners or detainees should not be used as subjects in such experiments under any circumstances. Hence, the SAMRC did not believe it was necessary to lay down any guidelines for that group. The other change to Appendix VI was that the section on Minors

referred to the Child Care Act (No 74 of 1963) and not to the Children's Act as it did in the first edition. However, the principles as regards protections remained unchanged. Additional changes included replacing the term "Bantu" with "Black" and expanding on Kwa-Zulu law for Black women living in Natal whose status upon acquiring majority at the age of 21 was no longer determined by a guardian. Moreover, the Kwa-Zulu Act on Medical and Surgical Treatment (No 11 of 1986) allowed for a married woman in certain circumstances to consent independently to treatment. The situation with regard to Black children born of a customary union was also clarified. According to indigenous law the consent had to be given by both the father and the head of the kraal. Where the child was illegitimate, consent had to be given by the mother and her legal guardian. The Code went on to state that these stipulations were valid only where the researcher and subject were both Black. Where the researcher was not Black, the ordinary principles of South African Law were valid and the legal incompetence of Black women according to traditional law did not apply. It is highly likely that these discriminatory distinctions between professionals created many tensions and conflicts and even confusion.

6.3(C)III SAMRC Research Ethics Guidelines 1993[23]

With the promise of transition from apartheid to democracy just around the corner, the early nineties in South Africa witnessed a flurry of activities towards change in laws and policies that took into consideration the rights and dignity of all South Africans. In the context of research, the Medical Research Act of 1969 was replaced by the Medical Research Council Act (No 58 of 1991) and the guidelines were further amended and replaced by "Guidelines on Ethics for Medical Research – Revised Edition, 1993". This edition was much more comprehensive than previously and drew substantially on reports

from the Royal College of Physicians of London. Some other documents that also influenced this edition included the DoH and the CIOMS Guidelines. Of note this set of guidelines made no reference to separate laws for Black population groups and South African Laws for other groups, as had been the case in the previous guidelines. The guidelines and laws referred to in this document applied to all South African equally, irrespective of colour. This is probably because SA was on the brink of liberation and a democratic government.

The report addressed vulnerability extensively in its sections on Special groups (sec 6.2), Research on patients (sec 7) and Consent (sec 8). It also made a strong statement on vulnerability in its section on Considerations in risk assessment (sec 5.4.2) where it states that particular care should be exercised when identifying risk in vulnerable population groups because some patients would already have been exposed to extreme risk and it would be unacceptable to increase that degree of risk by adding to it the physical and emotional risks of being a research subject. While this could have resulted in such populations being therapeutic orphans and the perception that it would have been inappropriate to exclude them from reaping the benefits of research, added protections had to be afforded these groups in order to ensure a just distribution of risks as well. It stressed that the burden of proof had to be on why it was necessary to study a particular vulnerable group and that institutionalised individuals could only be research subjects if the research was pertinent to their problems. Section 7 on patients was quite extensive as regards protection of patients as research subjects.

Women, children, the elderly, the mentally handicapped, prisoners, students, junior colleagues and others were listed under its Special Groups (sec 6). Studies were not to be conducted on these groups if they could have been equally done on other adults to obtain

the same information. With regard to women, all the guidelines stated was that special consideration should be paid to the risk of damage to the fetus which was a possibility in women of child-bearing potential. Clearly this indicates that the fetus was part of a special group and not women. Protection for children was approached from the perspective of therapeutic and non-therapeutic research and in the latter situation, greater emphasis should be placed on risk assessment. As regards the elderly, the guidelines stipulated that particular care had to be paid to the subject's ability to comprehend what participation in research entailed. It also recognised that it would be appropriate to conduct physiological and pharmacological studies on the elderly that were relevant to their age provided that particular care was taken to confirm their fitness for the proposed study. Research on the mentally handicapped would be acceptable on condition that precautions similar to those that applied to children were taken. Research on prisoners, although controversial, was not considered unethical and these guidelines allowed for such research, a very different stance as compared to the previous guidelines. However, it cautioned that particular care had to be taken to avoid coercion and any impression that inducements like reductions in sentence or pardon or other favours would result from their participation. It also stated that for some prisoners the opportunity to contribute positively to the well-being of society could be of help in re-establishing self-esteem and rehabilitation. It stipulated that RECs should pay critical attention when reviewing protocols involving prisoners so as to ensure that they would not be exploited. Students were recognised as being particularly vulnerable to academic, personal and financial pressures. When students were to be involved in studies, the investigator should not be involved in recruitment and negotiations about remunerations if he was in any way involved in the student's tuition. There should be no impression created that participation in the study would benefit the student or that non-

participation would result in discrimination against him. Junior colleagues were considered vulnerable because over-enthusiasm or lack of enthusiasm could impact his future career positively or negatively respectively. Under other groups, the unemployed were used as an example. It cautioned that researchers needed to be aware that financial rewards would be a particular incentive for them and that they should not be enrolled in an excessive number of studies.

Section 8 explained in detail the added requirements for informed consent for the special groups mentioned above. In addition, it included informed consent procedures from proxies for two other groups: research into sudden unexpected events and research on the severely ill or unconscious patient.

The 1993 Guidelines were a remarkable improvement on the previous sets both from the perspective of substantive considerations and a greater application of the principles of ethics in its recommended guidance points. The influence of deontology and virtue ethics is also obvious in these guidelines.

6.3(C)IV SAMRC Research Ethics Guidelines 2002[24]

Almost a decade after the SAMRC's 3rd edition of guidelines were published, the next set of revisions were issued. This was because of a number of important factors including major socio-political reform in South Africa and great interest globally in the field of ethics in research, especially as a resurgence of transgressions around the world were getting exposed[25]. For its 4th edition, the SAMRC placed emphasis on South African needs and incorporated the principles of the Bill of Rights of the South African Constitution, 1996 into its guidelines[26]. In addition, developing country concerns were also stressed. The current

edition comprises 5 booklets of guidelines. Booklet I is on general ethical principles on medical research[24]; Booklet 2 is on ethics in reproductive biology and genetic research[27]; booklet 3 is on ethics in the use of animals in research[28], booklet 4 is on ethics in the use of biohazards and radiation[29]; and booklet 5 is on ethics in HIV vaccine trials[30]. For the purpose of this chapter, only Booklet 1 will be described and analysed.

The importance of consent is highlighted in section 5 in Booklet 1. Additional safeguards as regards consent are provided for the following groups: the mentally ill or mentally handicapped, the elderly, pregnant women, unconscious patients, the dying, minors, patients and members of vulnerable communities in international collaborative research (sec 5 and 11). Special groups are discussed in section 7. Pregnant women, children, prisoners, people with mental impairment, the elderly, students, persons in dependant relationships and vulnerable communities are discussed. Most of the guidance points for these groups are similar to those in the 1993 edition. Persons in dependent relationships are described as those occupying junior or subordinate positions in hierarchically structured groups e.g., employees and employers, wards of State and guardians, and patients and healthcare professionals. The characteristics of a vulnerable community are described as including one or more of the following:

"i. limited economic development;

ii. inadequate protection of human rights;

iii. discrimination on the basis of health status;

iv. inadequate understanding of scientific research;

v. limited availability of healthcare and treatment options;

vi. limited ability of individuals in the community to provide informed consent."

This section underscores that South Africa is home to a large number of vulnerable communities and particular caution must be taken prior to permission being given by RECs for research to be undertaken here. The above characteristics are also used in the SA Ethics Guidelines to define vulnerable "communities" and the SA Guidelines[11] state that this is the definition used by UNAIDS.

One of the important aspects of this edition is the stress on vulnerable communities, especially in the context of international research.

6.3(D) Participant Protections and the South African Department of Health

In 2000[31], the National Department of Health's Guidelines on Good Clinical Practice in Clinical Trials was published. This was followed by a revised edition in 2006[32]. These guidelines are an adaptation of the International Conference on Harmonization's Good Clinical Practice Guidelines (ICH-GCP) which was discussed in detail in the previous chapter. The most significant milestone in the history of participant protections in South Africa was the inclusion of research and experimentation in the Bill of Rights of the Constitution[26] and the statutory legislation of protections in the NHA. Section 12(2)(c) of the Bill of Rights, on Freedom and Security of the Person, affirms everyone's right to bodily and psychological integrity including the right "not to be subjected to medical and scientific experiments without their informed consent."

Other protections for research in the Bill include the rights to equality (sec9), human dignity (sec10), life (sec11), and privacy (sec14).

The NHA and its protective instruments will be discussed in the section that follows.

6.3(D)I The National Health Act (No 61 of 2003)

For the first time in the history of South Africa, protections for participants in research were made mandatory by statutory law in 2003, hence strong protectionism as mandated by legislation. Health research in terms of section 1 of the NHA includes:

> "... any research which contributes to the knowledge of –
>
> *(a)* the biological, clinical, psychological or social processes in human beings;
>
> *(b)* improved methods for the provision of health services;
>
> *(c)* human pathology;
>
> *(d)* the causes of disease;
>
> *(e)* the effects of the environment on the human body;
>
> *(f)* the development of new applications of pharmaceuticals, medicines and related substances; and
>
> *(g)* the development of new applications of health technology."

This definition is very broad and covers a wide range of research activities, which, in terms of section 73 of the Act, will need to be reviewed by health research ethics committees which are registered with the National Health Research Ethics Council (NHREC). Section 71 of the Act affirms that written consent from a research participant is requisite prior to involvement in health research. This section includes special safeguards for minors (anyone less than 18 years of age). It also uses the therapeutic / non-therapeutic distinctions for minors. Where minors are involved in therapeutic research, the consents of the parent or guardian and of the child where s/he is capable of understanding are necessary. As regards non-therapeutic research, not only will the consents of the parent / guardian and child be

necessary, but the Minister will need to give consent too. No mechanisms have been instituted by the Department of Health to facilitate the process of obtaining consent from the Minister. This stipulation is unreasonably restrictive and will serve to obstruct necessary research involving children to their disadvantage as a vulnerable group. Hence, in my experience, it would seem that most RECs in South Africa have chosen to ignore this specification in the Act and it is "business as usual" at the level of RECs when it comes to reviewing non-therapeutic research in children.

The establishment of the NHREC is provided for in section 72 of the Act. The function of the NHREC includes, among others, that of determining guidelines for the functioning of health RECs. "Ethics in Health Research: Principles, Structures and Processes"[11] is the guideline book from the NHREC which all RECs and researchers in the country need to abide by as regards health research.

6.3(D)II Ethics in Health Research: Principles, Structures and Processes[11]

This is the guideline document for ethical conduct of research in the country as determined by the law. Interestingly, section 5 is specific to groups and research requiring additional attention.

Groups requiring additional attention include:

"1.Minors

2.Persons with intellectual or mental impairment

3.Disabled persons

4.Persons in dependant relationships

5.Persons participating in research as groups (collectivities)

6.Pregnant women”

Research that requires additional attention includes:

“1. Research involving indigenous medical systems

2. Emergency care research

3. Innovative therapy or interventions

4. Research necessitating ambiguity of information for participants”

Special mention of research requiring additional attention is probably made because the degree of risk associated with the research could be quite high and this in itself could initiate vulnerability in research participants who otherwise may not be vulnerable.

The stipulations on minors is very similar to Subpart D of the DHHS Regulations (45 CFR 46) in that the research can only be conducted if it is minimal risk, more than minimal risk but provides possible benefit with the degree of risk being justified by the potential benefit or if greater than minimal risk with no prospect of direct benefit but high probability of providing significantly generalizable knowledge. However, it differs in that the research mentioned includes observational research, and research with greater than minimal risk but no direct benefit must be justified by a “risk-knowledge ratio” and the risk must be no more than a minor increase over minimal risk. This aspect is unclear and somewhat inelegantly written in that “greater” is equated with “no more than minor increase”. Provisions for assent and parent or legal guardian consent or permission are also similar in some aspects to Subpart D of the DHHS Regulations (45 CFR 46). RECS need to ensure that the protocol outlines

adequate steps to obtain the child's assent. The permission of one parent is sufficient when the research does not involve more than minimal risk, or involves greater than minimal risk but presents the likelihood of direct benefit to the child. Permission from both parents is required when the research is greater than minimum risk or is of no direct benefit to the child but is likely to produce generalizable knowledge. Unlike the DHHS Regulations, there is no allowance made for waiver of parent or guardian permission and child assent. An additional difference is the stipulation that when only one parent is available for reasons including death, incompetence or disappearance, or where the court has placed the child in the sole custody of one parent, then the permission of that one parent is sufficient for participation in the greater than minimum risk with no direct benefit research. Additionally, when views between parents conflict, the best interests of the child take precedence. However, there is no guidance on who determines the child's best interests. Researchers will probably need to consult with RECs or the Courts in making this determination.

The SA Guidelines have drawn extensively from Subpart C the DHHS Regulations (45 CFR 46) when it discusses prisoners. The only difference is the addition of the stipulation that RECs need to consider the extent to which research facilitates the empowerment of prisoners as a vulnerable group.

The groups designated as vulnerable are extensive and the guidelines seem to have drawn from the various versions of the DoH up to 2008, CIOMS (2002), ICH-GCP, the Belmont Report and the DHHS Regulations (45 CFR 46) and additional groups not included in these documents. The groups include minors, adolescents, persons in dependant relationships, women, pregnant women, fetuses, those requiring emergency care, prisoners, vulnerable communities, collectivities, persons highly dependent on medical care, patients in intensive

care units, neonates, those at the end of life requiring terminal care, those with impaired capacity to communicate, the unconscious person, and other special groups.

Those in dependent relationships are listed as:

1. older persons and their caregivers;
2. persons with chronic conditions or disabilities and their caregivers;
3. wards of State and guardians;
4. patients and health-care professionals;
5. students and teachers;
6. prisoners and prison authorities;
7. persons with life-threatening illness;
8. employees and employers, including farm workers and their employers, and members of uniformed services and hospital laboratory staff and their employers.

The Guidelines use the same definition as the MRC to characterise vulnerable groups, but refers to them as "vulnerable communities". The Guidelines, in section 5.12, state that where factors relating to vulnerability are an aspect of the research, the researchers need to demonstrate how they will try to "redress" that vulnerability. This places a huge burden on the researcher whose duties are now extended to that of reparative justice. While the intention of the Guideline is laudable, this is highly aspirational and not really practical. The Guidelines go on to say that particular caution must be exercised prior to enrolling participants from such communities in research and that RECs should ensure:

> "● persons in these communities will not ordinarily be involved in research that could be carried out in the non-vulnerable communities;

● the research is relevant to the health needs and priorities of the community in which it is to be carried out;

● research participants should know they are taking part in research and the research should be carried out only with their consent. This requires that particular attention be paid to content, language and procedures used to obtain informed consent."

The first two stipulations are quite similar to those found in the international guidelines discussed earlier and the Belmont Report. These stipulations, while specific to consent in the DoH of 2000 and 2008, appeared in the 2013 version of the DoH for the first time as applicable to all vulnerable groups, years after the SA Guidelines had been promulgated. Although consent protections are required in all the other documents, additional obligations are placed on the researcher to ensure that consent is informed.

Table 6: VULNERABLE GROUPS AND DEPENDANT RELATIONSHIPS IN ETHICS IN HEALTH RESEARCH: PRINCIPLES, STRUCTURES AND PROCESSES

Vulnerable groups	**Dependent Relationships**
• Minors • Adolescents • Women • Pregnant women • Fetuses • Those requiring emergency care • Prisoners • Vulnerable communities • Persons highly dependent on medical care • Patients in intensive care units • Neonates	• Older persons and their caregivers • Persons with chronic conditions or disabilities and their caregivers • Wards of State and guardians • Patients and health-care professionals • Students and teachers • Prisoners and prison authorities • Persons with life-threatening illness • Employees and employers, including farm workers and their employers, and members of uniformed services and hospital laboratory staff and their

• Those at the end of life requiring terminal care • Those with impaired capacity to communicate • The unconscious person • Other special groups.	employers.

As can be seen from above there are a number of different but relevant vulnerable groups to be considered for special protections in research in the SA Ethics Guidelines, similar to the CIOMS

Table 7: VULNERABLE GROUPS IN INTERNATIONAL AND NATIONAL GUIDELINES

Vulnerable groups	International			National		
	A	B	C	D	E	F
Patients	X	x		X		X
Patients with incurable diseases		x				
Those with serious life-threatening diseases		x		X		X
Those at the end of life requiring terminal care				X		X
The unconscious/comatose				X		X
Those requiring emergency care		x				X
Persons with chronic conditions or disabilities						X
Persons highly dependent on medical care						X
Patients in intensive care units						X
Challenges with informed consent	X		x			X
Consenting under duress	X					
Coercion or undue influence				X	x	
Elderly persons with limited capacity to consent		x				X
Those with impaired capacity to communicate				X		X
Mentally disabled persons				X	x	
Children				X	X	X
Wards of State						X
Neonates					x	X
Women						X
Pregnant women					X	X

Fetuses					x	X
Groups with hierarchical structuring			x			
Juniors / subordinates		x				
Students		x				X
Employees						X
Persons in dependant relationships	X					X
Persons confined to institutions				X		
Residents of nursing homes		x				
Prisoners		x		X	x	X
Those on welfare/social assistance		x		X		
Those that are unemployed		x				
Unfamiliar with modern medical concepts		x				
Those at risk of harm: physical, legal, social, economic		x		X		
Ethnic / Racial minority groups		x		X		
Homeless persons		x				
Refugees/displaced persons		x				
Nomads		x				
Disadvantaged rural black men				X		
Racial and ethnic minorities		x				
Politically powerless		x				
Economically disadvantaged persons				X	X	
Educationally disadvantaged persons					X	
Vulnerable communities						X
Other			x			X

A: DoH(2013); **B**: CIOMS (2002); **C**: ICH-GCP; **D**: Belmont Principles;
E: Code of Federal Regulations (US); **F**: Ethics in Health Research: Principles, Structures and Processes (SA)

6.4 CONCLUSION

The comparison between the international and national guidelines above illustrates clearly that the SA Ethics Guidelines has generated the greatest number of vulnerable groups with the CIOMS Guidelines close on its heels. There is overlap of vulnerable groups between the guidelines. The SA Ethics Guidelines overlaps with all the different guidelines. In addition,

the ICH-GCP and SA Ethics Guidelines, by having a category called “other” unambiguously indicates that the list of groups is limitless. The groups are currently so extensive that it would seem as though almost anyone participating in research in the country would be vulnerable. The concern that arises is that for the small number that escapes being categorised into one or other group and who may have unnamed vulnerabilities, there is no requirement in the guidelines for special protections. The danger here is that these individuals may be made even more vulnerable by the mere fact that they are not considered for special protections. In addition, a major challenge is the ever present tensions experienced by RECs between protecting these vulnerable groups and facilitating ethical research and in the SA situation, this is quite daunting as almost everyone is considered vulnerable.

The following chapter will review and analyse contemporary research ethics literature which considers the complexities that have arisen in research and at the level of RECs in the context of vulnerable groups and communities in research.

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Chapter 7: TOWARDS A PRACTICAL DEFINITION OF VULNERABILITY AND ITS APPLICATION IN HEALTH RESEARCH

7.1 INTRODUCTION

As evidenced from the previous chapters, protecting vulnerable individuals against exploitation and other harms is at the heart of research ethics. It has been shown in the previous two chapters that, with the expansion of protective guidelines, the focus on vulnerability protections shifted from individuals to groups. Group and subpopulation terminology firmly entrenched itself into the complex tapestry of research participant protections. The guidelines have put the onus of protection of these vulnerable groups onto RECs, without suitable direction to these committees as to how to do so. As the group approach unfolded, so have its challenges. It has become clear from the preceding chapters that there are so many different vulnerable groups that the term 'vulnerable' could have lost its significance with regard to who requires special protections, as almost anyone participating in research belongs to one or other group and would need the protections that are focussed at the specific group. On the other hand, participants with particular vulnerabilities that do not fall into any of the groups outlined in the guidance documents do not qualify for special protections and are at risk of harm because of insufficient protections. In addition, the guidelines are silent on the fact that vulnerabilities can differ between individuals within groups, i.e., that there are differing degrees of vulnerabilities between individuals within groups. Hence, while it is clear that the notion of vulnerability is obviously appreciated in the discipline of research ethics, adequate and appropriate analysis of the notion is lacking, the criteria for designating vulnerable populations are vague and its correct application in the field has not been suitably pieced together.

It is therefore not surprising that the scholarly literature over the past decade has been replete with criticisms of the group and subpopulation approach. Moreover, several journals have devoted complete issues or special sections to the subject[1-3]. While there have been a number of recommendations as to how the approach to vulnerable populations should be addressed, none has thus far managed to offer a comprehensive, yet uncomplicated, solution that could protect all vulnerable participants in health research.

The aim of this chapter is to review, analyse and critique the literature on the group and subpopulation approach utilized by the guidelines with a view to constructing a comprehensive and practical definition, the application of which could assist REC members to identify vulnerabilities within the research context. This would then assist them with determining the most appropriate protections where required.

7.2 CRITICISMS OF THE GUIDELINES APPROACH TO VULNERABILITY IN HEALTH RESEARCH

Many authors express the concern that how and when vulnerable individuals are involved in research remain challenging questions in the 21st century[4-7]. The concept remains nebulous and vague and as yet there is no cogent definition. At best the definition of vulnerability in health research remains an unanswered question[8-10].The source of much unease is that of finding the best balance between adequate protections and excluding vulnerable people from research. Excluding vulnerable people could result in obstructing valuable research, a social good that in actual fact should be promoted and not impeded. The controversies around the use of the term 'vulnerable' in the guidelines and regulations, both international and national include the fact that although the CIOMS guidelines, the latest version of the DoH and the SA Ethics Guidelines define the term, albeit inadequately, none of the other guidelines offers a definition. In addition, while the lists of groups are extensive, they are

not exhaustive, they are paternalistic in nature, in that they could at times be overprotective, and they could be demeaning and "sexist"[11]. The guidelines and various authors describe vulnerability by stipulating lists of characteristics and it is these lists of characteristics that create the perception that groups are more likely to be harmed as compared to the rest of the population.

From an international guidelines perspective, vulnerability as an important concept did not surface explicitly in the Nuremberg Code[12] or the early versions of the Declaration of Helsinki [13]. It was the 2000 version of the Declaration of Helsinki that first made direct reference to the term. The objective of these documents to protect vulnerable individuals that were involved in research is clearly unquestionable. The most significant protection emanating from these documents was the requirement of informed consent to protect participants against research-related harms and exploitation. It is this fundamental protective intervention of informed consent that has informed safeguards for vulnerable groups in guidelines and regulations that have subsequently followed. Informed consent has been carried through those documents to inform the understanding of how vulnerable participants in research should be protected against being harmed. Moreover, this theme of informed consent has been used to guide the unfolding of the group and subpopulation focus of vulnerability in these documents.

The Belmont Report[14], which has, as previously discussed, had a major influence on international guidelines and has been a key text directing the development of the SA Ethics Guidelines, introduced "vulnerability" and the "group" or "subpopulation" lexicon into research ethics guidance documents. The SA Ethics Guidelines, it seems, adopted the Belmont approach to vulnerability without much question. The Report can be criticised for

being the root cause of the confusion and the "labelling" of people created in this arena. It mentions protections for vulnerable individuals in its Applications section and does this three times. "Vulnerable" is drawn into the discussions on the voluntariness aspect of informed consent. It is extended further into the risk and benefits section and the justice section and in the latter, the labelling of groups emerge for the first time in research ethics guideline documents as examples of vulnerable groups that require added protections. Moreover, it highlights that participants falling into these categories are potentially limited in their capacity to make informed decisions and hence also places informed consent problems as pivotal to the notion of vulnerability. Rogers, Mackenzie and Dodds[15] claim that the approach in the Belmont Report created a "... dual approach to, and confusion about, vulnerability in research that continues to permeate the literature." They say that confusion arises because the Belmont Report combined the general claim that all participants in research require protection by the use of informed consent with the more specific claim that additional duties of special protection against exploitations and other forms of harms are necessary for some participants who are more vulnerable than others. Because the relationship between universal vulnerability and special vulnerability has not been adequately examined, labelling some as especially vulnerable has led to the slippery slope of unjustifiable paternalism. The Belmont Report started the "labelling" approach by identifying certain groups as vulnerable in line with the existence or lack of certain characteristics[16]. The Belmont Report distinguishes at least three characteristics that point to members of designated groups being vulnerable: lack of capacity to consent, increased susceptibility to being exploited or coerced and being at increased risk of harms. The Report does not go further to explain the relationship between these characteristics.

According to Nickel[17], the Belmont Report offers two related and overlapping notions of vulnerability. The first deals with the capacity to give autonomous and informed consent and the second relates to fairness. The fairness aspects focus on concerns that disadvantaged or dependant groups who lack the power to refuse to participate may be faced with an unfair burden of research participation. Additional fairness concerns revolve around the benefits of research being distributed unfairly and, in particular, the injustices that result as a consequence of being excluded from research are underscored. The Belmont recommendation that people with vulnerabilities be excluded from research as a blanket guidance leads to potential injustices and Nickel recommends that instead of using informed consent to remedy this injustice , benefit sharing should be brought into play.

Nicholson[18], in defence of the guidelines and regulatory instruments approach to vulnerability, claims that even if vulnerability is not explicit, as a concept it has been implicit since the earliest attempts to regulate medical research and that the approach in these documents is such that almost every research subject could fall into the category of vulnerable. He goes on to state that despite it being vague, it is nevertheless a useful concept and every research subject should be regarded as vulnerable "unless and until proven otherwise on an individual basis"[18]. The danger of this approach is that this could result in the systematic exclusion of some populations from research, thereby leading to missed opportunities to acquire valuable knowledge that could assist them and others in similar contexts[10,19].

Underlying the guidelines and regulations is the basic notion that certain categories of people are more likely to be misled, manipulated and mistreated in the research context as compared to others. It is the individuals in these categories that are considered to be

vulnerable. According to Levine *et* al., the status of being vulnerable creates the moral obligation of provision of special protections for them by RECs, regulators and researchers[16]; hence a strongly protectionist approach is recommended for individuals with vulnerabilities. In the early parts of the last decade, much of the discussion centred on whether or not certain groups should be added to the vulnerable category. The types of special protections were also considered, but to a lesser degree[20,21].

From the middle of the last century, with rapid advances in science and technology and expansion of projects globally, research has evolved to include multidisciplinary, multinational approaches. However, the guidelines and regulations have lagged behind on the issue of how vulnerability in different settings should be addressed. The term 'vulnerable populations' has also been criticised for implying that vulnerability is fixed and immutable and it risks labelling people who are vulnerable as "other" and the vulnerable "other" could be viewed as an object of pity or resentment[22] and of a lower or no moral status. An additional concern here is that this could result in stigmatising the vulnerable "other", and hence increasing the negative impression towards these people even further. The guidelines' and regulations' focus on vulnerability has ignored the fact that many participants, despite being vulnerable, possess agency[23] and for those who do not possess agency, e.g., children and severely demented individuals, most jurisdictions allow for "agency by proxy" While these documents have played a major role in giving recognition to the concept of vulnerability and the need for protections, by not giving credence to the agency of participants, they have unwittingly introduced paternalism into REC functioning in that RECs could turn down projects or request unreasonably overprotective measures based on the fact that "vulnerable populations" would be enrolled. Respecting the agency of

participants allows for RECs to introduce ways in which their agency and hence autonomy can be strengthened, thereby leading to their empowerment and reducing the power-imbalance gap between the researcher and participant.

7.3 RECOMMENDED APPROACHES TO ADDRESS VULNERABILITY IN HEALTH RESEARCH

7.3(A) Inability to Protect One's Interests

Broadly speaking, vulnerability is defined as an inability to protect one's own interests. This, in the context of research, would indicate that being vulnerable implies that one (or many) are at higher risk of being harmed by the study as their capacity to protect their own personal interests is decreased[4,6,24,25]. This simple and appealing approach views vulnerability as a condition whereby one will not be able to protect his or her own interests. While this straightforward, uncomplicated approach is attractive, it could end up being problematic as there could be several different interests that could require safeguarding by RECs who would need to be alert to these.

7.3(B)The Risks and Harms Approach

Risk exists in almost all research studies for all research participants and there is a wide range of risks in this context. Risk is exacerbated when research involves vulnerable people and the possibility of a significant burden on the research participants will inevitably arise. A helpful analysis and categorisation of research related risk was proposed by Charles Weijer in 2000[26]. This categorization would also be of assistance when considering vulnerability and the definition and assessment scale that is to be developed. The four broad risk categories are physical, psychological, social and economic:

1. Physical risks would be risks of bodily harms as a result of participating in the research and could range from minor to serious and immediate to delayed. This range, in my opinion is true for all categories of risk.
2. Psychological risks would include risks to perceptions of self, feelings of anxiety or shame, i.e., emotional suffering, and behavioural and thought deviations.
3. Social risks would be risks of being exposed to discrimination or other forms of social stigmatization as a result of participating in the research.
4. Economic risks would be risks of having to bear financial costs related to research participation either directly or indirectly.

The US National Bioethics Advisory Commission in 2001[27] listed six broad categories of harms to research participants that could arise as a result of their involvement in research. These include Weijer's four categories as recorded above together with a further two, legal and dignitary. Legal ramifications as a result of research participation could arise when law enforcement agencies would use research data to prosecute participants, e.g., in regions of human rights abuses or where participants are illegal immigrants. Dignitary harms would result when people are not treated as persons, e.g., violating their privacy or not obtaining their informed consent. These two additional categories would also be of assistance when considering the tools to be developed in this thesis. The focus on protections should involve a balancing of the concepts of vulnerability and special risks of harms[27].

Similar to other authors, Hoffmaster[28], in his analysis, made the point that most literature defines vulnerability as being at increased risk of harm and/or having a decreased capacity to protect oneself, and in the context of research ethics the term denotes greater than ordinary vulnerability while acknowledging that individuals differ in their exposure to risk

and in their abilities to deal with risks. When such vulnerabilities are identified, specific moral obligations and greater duties of justice are owed to these research participants.

Ballantyne and Rogers[4] state that because the potential to be harmed, i.e., risk is present in all research and hence all research participants are potentially vulnerable, it would be important to recognise that vulnerability "exists as a broad spectrum, rather than a simple, absent / present dichotomy." The significance of their claim could be that as one moves along the spectrum, the potential of harm could increase and this could determine the type of vulnerability. They further claim that vulnerability is related to power inequalities in the researcher-participant relationship. The power imbalance arises in different ways and could result in researchers deliberately or unintentionally misusing power inequalities to coerce participation in research, even if this is against the best interests of participants. In addition, the misuse of power could result in the benefits of research not being shared fairly with the research participants. Integrating conceptions of risk and harms stratification when dealing with vulnerable people in research is a useful move away from the strictly vulnerable population approach utilised in research ethics guidelines.

7.3(C) Source-based Approaches to Vulnerability

Protecting the vulnerable participant has evolved from an emphasis being placed on safeguarding participants from being used in research without their consent to include the justice principle towards invoking a balance of access to benefits and protection from exploitation. What makes participants vulnerable is a matter of needs, promise and risk[29]. Justice would involve balancing the need for protection against the need to access new and needed therapies[29] and the promise of novel and innovative treatments for future

wellbeing. Justice would also entail ensuring empowerment, especially in the context of the power imbalances in the researcher-participant relationship.

According to Ballantyne and Rogers[4] two sources of vulnerability should be discerned at a conceptual level: extrinsic and intrinsic. They state that extrinsic vulnerability arises from external circumstances, e.g., lack of socio-economic power, education or resources, and that intrinsic vulnerability emerges because of certain internal qualities of individuals themselves, e.g., mental illness, intellectual disability, severe illness, or extremes of age. Complex ethical issues appear in the research context as a result of these two types of vulnerabilities. In addition, these two types may be present independently, may coexist or at times may be interrelated. They maintain that in particular, those with intrinsic vulnerability are often extrinsically vulnerable because they lack power or live in poor resource settings with limited access to education and other social goods. According to them, it would be good for RECs to distinguish between these two types of vulnerabilities in order to consider the different mechanisms to best protect the interests of research participants. There is merit in the conceptual distinction they propose and also in the recognition of the overlaps and interrelatedness of the two types of vulnerabilities.

Schroeder and Gefenas[5] claim that for a definition of vulnerability to be meaningful, it needs to include two elements, internal and external. The external element is the exposure to the possibility of harm, i.e., the danger. The internal element to vulnerability is the substantial lack of ability to protect oneself. Just the exposure to harm is not adequate for vulnerability to materialise because one could have the power to protect oneself against this harm. Therefore, a definition of vulnerability will require *both* external and internal elements. The internal element is further broken down into intrinsic and contingent categories to explain

why some research subjects are unable to protect themselves. Intrinsic factors arise when there is an inherent lack of decision-making capacity resulting in a lack of ability to protect themselves, e.g., little children and severely mentally ill individuals. Contingent vulnerability to exploitation arises when people are competent enough to exercise self-determination but because of social, economic or political factors are unable to do so. In other words, they lack the means to protect themselves. As circumstances change, means change and so does vulnerability. Using this analytic process, Schroeder and Gefenas define vulnerability as[5]:

> "To be vulnerable means to face a significant probability of incurring an identifiable harm while substantially lacking ability and / or means to protect oneself."

The problem with this definition is that while the harm must be identifiable, there is no direction as to who is responsible for identifying the harm and a cogent definition ought to give direction on an approach to application of the concept defined. If identifying the harm is the responsibility of the REC, there is then an assumption that all RECs function at a basic level of competence that would allow for the identification of harms. This unfortunately is not necessarily the situation, especially for many RECs in developing countries[30-33]. Therefore, a definition of this nature without an additional guide to RECs that would assist implementation may not be of use to many RECs. The definition does not take into consideration that exposure to the possibility of harms comes in degrees and overemphasising danger could lead to an unnecessary expansion of vulnerable groups as has occurred in particular in the CIOMS and SA Ethics Guidelines. Everyone is not exposed to the same dangers and within each protocol different degrees of exposure and different dangers need to be identified. This is quite a problem with the external element in this definition. The authors do recognise that having a concise definition of this nature could

result in practical obstacles. However, on a positive note, this definition would safeguard against false categorisation of vulnerabilities, a severe criticism against group categorisations[34]. An example of false categorisation that could commonly arise in South Africa, which is viewed by many as a developing country, is as follows: Research participants in developing countries are categorised as vulnerable in the guidelines and by several authors that we have looked at already. However, a judge from the Constitutional Court in South Africa, while belonging to a developing country, does not face the same risks of identifiable harms as indigent men, women, children or even illegal immigrants living in either urban or remote rural areas. Furthermore, there are differing degrees of vulnerability between and within these groups.

Some markers for identifiable harms offered in the paper by Schroeder and Gefaenas[5] are an unfavourable benefit/risk ratio, breach of confidentiality or privacy, invalid consent, and lack of access to the benefits of research. They stress that some vulnerable participants may face a significant probability of incurring more identifiable harms in the same study as compared to other vulnerable participants. While this method of approaching the issue of vulnerability has merit, the authors have confounded the arguments by conflating individual and group protections. Although the importance of avoiding false categorisations is brought up, an adequate application of this notion is not carried through in the paper.

Rogers, Mackenzie and Dodds make the argument that research ethics needs an adequately theorised and nuanced conception of vulnerability[15]. They go on to explain that while most bioethics discourse associates vulnerability with risk of harm and exploitation and limited capacity for autonomy, there are several challenges to this approach. Challenges include not differentiating between universal human vulnerability and context-sensitive specific types

and origins of vulnerability and difficulties with balancing protections of the vulnerable with respecting their autonomy. In line with others, they also state that substantial ambiguities and tensions in the understanding and use of the term 'vulnerability' have led to issues of paternalistic overprotection of those considered to be vulnerable and neglect of those who are vulnerable but under existing classifications unrecognised as such.

7.3(D) The Bioethical Taxonomy Approach

One of the first articles in which a substantive critical analysis of vulnerability was achieved was that of Kipnis in 2001[8], in a commissioned paper for the US National Bioethics Advisory Commission (NBAC). Clearly the NBAC must have been concerned with the nebulous approach to such an essential concept. Kipnis, like many other authors, challenges the group and subpopulation focus and starts off his paper by stressing that the concept of vulnerability has been[8]:

> "... grandfathered into the lexicon, lore, and literature of research ethics without undergoing stringent clarification."

He acknowledges that the subpopulation approach is an improvement in the way research ethics has unfolded but states that because of the many different types within a group or subpopulation, it is unclear what the common characteristic is that holds them together and it is not generically apparent how researchers respond when faced with a vulnerable subject. Approved standards for identifying and responding to vulnerability are absent. He also emphasises the existing guidelines are sufficient only to deal ethically with the "paradigmatic" research subject and fails the vulnerable one because, for the latter, ethical consideration has to go beyond the baseline. The baseline, he states is "... a mature,

respectable, moderately well-educated, clear-thinking, literate, self-supporting US citizen in good standing, that is, a man who could understand a 12-page consent form and act intelligently on the basis of its contents."[8]

Kipnis proposes an analytic approach in which he considers the circumstances that directly signal the vulnerabilities researchers should take into account. He claims that the concept of vulnerability points in two directions. One is a characteristic threat in the subject's condition, that of being exposed to something that could harm the subject and therefore would be undesirable. The other is that there are those that are prone to take advantage of this exposure either intentionally or negligently and use others merely as a means to an end. The objective of the analytic approach would be to provide a checklist of circumstances in which, based on vulnerability, the permissibility of research could be questioned. The analysis would also recommend, based on intellectual reasoning, responses to the checklist questions and a determination of supplementary measures in light of the vulnerabilities. Thirdly, the analysis would provide a basis for a justifiable finding that a researcher has either intentionally or unintentionally taken unfair advantage of the vulnerabilities of research subjects[8].

Using this analytic approach, he distinguishes six discreet types of vulnerability applicable in the research context that form a "Bioethical Taxonomy"[8]. The types of vulnerabilities in this taxonomy are cognitive, juridic, deferential, medical, allocational, and infrastructural. Each of these is conceived as a cautionary signal signifying the need for safeguards, and not as a sign for exclusion. Each one is distinguished by a positive response to a distinctive question regarding the candidate subject (C-S)[8]:

- Cognitive: Does the C-S have the capacity to deliberate about and decide whether or not to participate in the study?
- Juridic: Is the C-S liable to the authority of others who may have an independent interest in that participation?
- Deferential: "Is the C-S given to patterns of deferential behaviour that may mask an underlying unwillingness to participate?"
- Medical: "Has the C-S been selected, in part, because he or she has a serious health condition for which there are no satisfactory remedies?"
- Allocational: "Is the C-S seriously lacking in important social goods that will be provided as a consequence of his or her participation in research?"
- Infrastructural: "Does the political, organizational, economic and social context of the research setting possess the integrity and resources needed to manage the study?"

In a subsequent paper, Kipnis introduces a seventh type of vulnerability[9], that of social. The question to be considered with this type is: "Does the C-S belong to a group whose rights and interests have been disvalued?"

While distinct types of vulnerability comprise this taxonomy, individuals and groups could display several types of vulnerabilities and hence an overlap and interrelatedness of vulnerabilities. Kipnis's approach has moved beyond consent-based vulnerabilities to vulnerabilities where the ability to avoid exploitation by the participant is limited, but the problem with Kipnis's approach is that anyone corresponding to the categories is vulnerable. Moreover, he implies that anyone able to provide a truly informed consent is

not. His taxonomy is interesting and attractive for use in research ethics, but it also suffers from being somewhat ubiquitous and falls into Levine et al.'s account of vulnerability in health research as being too broad and too narrow at the same time[20]. Furthermore, from the practical perspective, this taxonomy could be seen as more of an academic exercise than an operational tool that could assist REC members during the review process.

7.3(E) The Special Scrutiny Rubric

Levine et al.[20] have criticised the categorization of vulnerability by groups as resulting in the concept itself becoming too broad and at the same time too narrow. Many of those criticisms are relevant today, i.e., ten years later. They viewed the concept of vulnerability as having three basic related problems. To begin with, like many other authors, they stressed that too many categories of research subjects were deemed to be vulnerable. However, for many of these categories, the only guidance was that of special attention or consideration without clear direction on what these would comprise. They also stated that because of the many growing numbers of categories, almost anyone in research was vulnerable and hence RECs had to pay special attention to almost all protocols submitted for review. Furthermore, if RECs were to focus narrowly and almost unequivocally on consent as the underlying basis of group characteristics, attention would be deflected from features of the research itself, the institutional environment, and the socioeconomic context that could put participants at risk for harm. Consideration would not be given to the reality that there are many other factors that can put participants at risk of harm and not just the fact that they belong to a particular vulnerable group. Finally, whole categories of individuals would be stereotyped by the concept of vulnerability. No room was made for distinguishing

between those in the group that had the special characteristics that needed to be taken into account and those that did not.

They also made reference to certain circumstances which were not included in the group categories that made people vulnerable. These included timing of research (e.g., pregnant women in labour), the emotional impact of research, prior experiences, and other personal factors. Similar to other authors, they made a compelling argument that the need for special protection requires consideration beyond group categorization and has to take into account the particular features of the research project and the environment in which it is conducted[20]. They have offered a rubric to assist RECs carry out a more focussed review in order to provide more targeted forms of protections for research participants which they call "special scrutiny". The three criteria to be used in their rubric are[20]:

> "(1) the research involves initial experiences of translating new scientific advances into humans, especially when the intervention is novel and / or irreversible;
>
> (2) there is a known or credible risk of significant harm (death or serious disability being the clearest examples) *and* there is no potential of offsetting direct medical benefit; or
>
> (3) the protocol raises ethical questions about research design or implementation for which there is no consensus."

They claim that the special scrutiny rubric should provide appropriate protection for all research participants and not only those that are considered to be vulnerable. This claim is flawed as the rubric is restricted to the scientific aspects of research only and the risks that have been considered are no more than those that cause physical harms. Social and other

related aspects of research participation and the research context have not been considered at all. This approach is somewhat narrow and restrictive.

7.3(F) Context Dependent Vulnerability

Context-dependant vulnerabilities, because of their consequences within specific settings, require ethical responses. Rendtorff includes social, political, environmental, and cultural sources of vulnerability in his approach to the subject[35]. Vulnerabilities have also been defined in political terms in that people are particularly open to exploitation in situations where they lack basic rights and liberties[36]. Suitable moral responses to vulnerability will be facilitated by recognising its sources and the various modes in which the latter manifest. This could also assist in avoiding responses that are too broad (false categorisation leading to paternalistic protections) or too narrow (not identifying a source that would warrant a response)[15]. Rendtorff further elaborates that an adequate conception of vulnerability will also respond to how the developmental capacities for robustness and the social conditions for advancing agency and autonomy are to be met[35].

Ruth Macklin, whose arguments focus more on multinational research in resource poor or developing countries, claims that vulnerability is a concern in bioethics because vulnerable individuals and groups are subject to exploitation and exploitation is morally wrong[24]. She affirms, however, that this in itself is a somewhat simplistic approach because while there is agreement almost everywhere that exploitation is wrong, there is distinct divergence of opinion as to what constitutes exploitation. Not all acts that are wrong are necessarily exploitative and some situations may involve the inflicting of harm on vulnerable people without exploiting them. She also claims that acts of protection could be interpreted as being paternalistic and questioned by those that one is trying to protect. It is therefore

necessary to examine what criteria are necessary to determine vulnerability (group or individual) and exploitation. Moreover, it is also important to appraise when actions with good intent could be construed as paternalistic and hence questionable from an ethical point of view. Macklin highlights three main ethical concerns when international research is conducted in developing countries. Research participants might be vulnerable "... by virtue of their low educational level or lack of familiarity with modern scientific concepts, their poverty or powerlessness and therefore open to exploitation in some manner."[24] Macklin has noticeably placed significant reliance on the categorization of vulnerability in the CIOMS guidelines.

The lack of basic health services in some of these countries could mean that subjects enrol in research as a means of accessing care. They could also fall prey to the therapeutic misconception. While she states that RECs are mandated to ensure special protections for the vulnerable she does acknowledge that in many developing countries effective mechanisms for research oversight are absent or where present they may not be of an adequate standard[24]. In such situations, effective processes for identifying and sanctioning researchers who exploit vulnerable subjects would be lacking. Because of this, in her opinion, all research subjects in those contexts would be vulnerable. She defines exploitation as the situation that occurs when "... wealthy or powerful individuals or agencies take advantage of the poverty, powerlessness, or dependency of others by using the latter to serve their own ends (those of the wealthy or powerful) without adequate compensating benefits for the less powerful or disadvantaged individuals."[24], a definition that could be supported by utilitarian arguments. Macklin provides valuable analyses on vulnerability and moves beyond the consent-based approaches to include justice

considerations of fairness and equity. While her approach is attractive, it is lacking in that it is silent on other social problems that could be associated with vulnerability, e.g., discrimination that could arise as a result of privacy and confidentiality violations during research participation. Neither does she provide clear recommendations on how special protections should be approached. Furthermore, she also falls into the trap of using the vulnerable population approach, similar to the guidelines.

7.3(G) A Wrongs Approach

An interesting approach proposed by Samia Hurst[10] is that if vulnerability is a claim to special protections then it should be understood as "an identifiably increased likelihood of incurring additional or greater wrong". Vulnerability is therefore understood as extending beyond an inability to consent or to protect one's own interests. In addition, using "wrong" recognises that participants who are harmed as a result of their involvement in research are not necessarily always wronged. "Wrong" denotes greater moral burden and significance as compared to "harm". It indicates a moral transgression[10]. A criticism of the definition is that one would expect special protections when there is a likelihood of incurring any wrong. According to this definition, special protections are only necessary when "additional" or "greater" wrongs are expected to be experienced. This could be perceived as existing or lesser wrongs and reduced degrees of moral transgressions do not require special safeguards. Any wrong, irrespective of whether existing or of a lesser degree, is a moral transgression and special safeguards must be established-to protect research participants from such wrongs.

Hurst recommends the following four step approach when applying this definition of vulnerability in research[10]:

"1) Are any potential research subjects at risk of being wronged in any way by this research project?

2) Are some potential subjects identifiably more likely than other persons to incur this wrong, or likely to incur it to a greater degree?

3) Is our IRB among those who share in the duty to minimize, or avoid, this wrong?

4) If yes, what should we do to avoid this wrong, or minimize this increased likelihood or degree, or ensure it is compensated in ethically justifiable ways?"

This approach is somewhat out of line with her definition as it includes wrongs that are not necessarily additional or greater. It is also flawed in that step 3 allows for "task-shifting" by the REC and condones an evasion of its duty to protect the participant against being wronged. While there are often others who would share in the duty to minimise or avoid wrong, the REC always has a duty to protect potential research participants. After all, this is the moral purpose of the REC.

7.4 SUMMARY

It is clear that despite vulnerability remaining an abstract concept; it has concrete effects both on those who are labelled vulnerable and those who are not. It is imperative that researchers and RECs are able to identify who is vulnerable in order to qualify for special protections and fair benefit[37,38]. The term "special" protections is appropriate as currently RECs protect all research participants, even those who are not affected by specific vulnerabilities and do not have any particular interests that require protection. This overall oversight role of RECs is an essential minimum or basic standard afforded to all participants in light of the universal vulnerability that we all have by virtue of being human as discussed

in chapter 3. Where specific vulnerabilities are detected by RECs, “special” protections will be necessary as an additional requirement to the basic standard. Vulnerability in itself raises a valid moral claim for protections and safeguards. RECs are the ones who play a critical role in efforts to achieve the balance between protections, scientific progress and access to fair benefits[39]. Moreover, RECs need to identify when their efforts at protections result in paternalistic practices and exclusions. Protection should be viewed not as exclusion but as allowing participants to volunteer without the risk of abuse[40]. Hence, it is necessary to develop a robust, focussed and comprehensive definition of vulnerability that, when applied in the research ethics review process, will allow for a recognition of potential participants who could be vulnerable and of their degrees of vulnerability, a building of moral responses (aimed at duties of protection) and an identification of the situations in which the moral responses towards improving the plight of vulnerable individuals are justified.

7.5 TOWARDS A DEFINITION OF VULNERABILITY IN HEALTH RESEARCH

The several different suggestions outlined above towards the approach to vulnerability in health research, while individually lacking in some aspect or the other, taken together jointly complement each other and aspects of these approaches have been used to develop the practical working definition of vulnerability and its application that follow. Earlier chapters of this thesis have also informed this process. The objective of this activity is to create a harmonized approach towards protecting the vulnerable research participant when RECs review research proposals.

7.5(A) A Practical Working Definition of Vulnerability and its Application in Health Research

"Vulnerability is an inability or decreased ability of a research participant to sufficiently safeguard her/his own needs and interests resulting in her/him being at an increased likelihood of being identifiably wronged in varying degrees if special safeguards to protect her/him are not invoked by the Research Ethics Committee"

The baseline protective safeguards essential to this definition are the basic protections for all participants that are enrolled in research. The use of deontological and virtue principles combined with Beauchamp and Childress's four principles approach and direction from the guidelines will adequately protect universal vulnerability. Implicit in this definition is the distinction between universal vulnerability and increased vulnerability.

This definition is also a substantial improvement over the definition in the current version of the DoH which reads: "… may have an increased likelihood of being wronged or of incurring additional harm" as it brings in the inability to protect one's interests as a necessary component to being vulnerable which the DoH does not.

It also takes into consideration degrees of abilities or inabilities to protect oneself as not all participants in research are equally vulnerable. In addition, the potential wrong must be identifiable in order to allow the REC to position the special safeguards. The definition also establishes the obligation of the REC to develop the special safeguards. It moves away from being consent-based, access-based, or harms and risks based and hence it is not narrowly restrictive. Neither is it too broad as it avoids categorisation of vulnerability into numerous groups and is quite specific as to what the criteria are for a research participant to be vulnerable. A definition of this nature would avoid situations whereby participants who are vulnerable but do not fall into particular categories would not qualify for special protections by the REC. This definition could be easily utilised in practice by RECs if aided by a simple but

focussed and routinely applied “Vulnerability Assessment” Scale which asks relevant questions in sequential order.

7.5(B) The “Vulnerability Assessment” Scale

This scale would assist RECs implement the definition of vulnerability developed above during the review of protocols. As has been seen in chapter 3, vulnerabilities are firmly linked to correlative responsibilities. The more vulnerable the person, the greater is the agent’s responsibility to protect the individual’s interests. Vulnerability is seen as a matter of degree dependant on the number of needs arising in the researcher-participant relationship and the amount of assistance that would be required to meet those needs. To optimise protections, RECs would need to answer the questions posed in sequential order.

1. Has the essential minimum standard afforded all participants in light of universal vulnerability been met?
2. Has the baseline for respecting human dignity been met?
3. Will any participant be used in the research as a means to an ends she/he may not endorse?
4. Will all the research participants in this study be able to safeguard their own needs and interests?
5. If no, is there an increased likelihood of any of them being identifiably wronged as a result of their participation in the study?
6. Is there an increased likelihood of any participant being identifiably wronged to a greater degree than other participants?
7. Have the identifiable wrongs been recognised?

8. Have special safeguards been developed to protect those participants in need of such safeguards?

The REC would also be assisted by developing clusters of pertinent easily identifiable wrongs. These could be categorised for ease of reference as follows:

Table 8. IDENTIFIABLE WRONGS: Clusters and Examples

Cluster of Wrongs	**Examples**
Physical Wrongs	Medical physical risks outweighing benefits, non-medical physical wrongs, e.g., pain, discomfort
Consent Wrongs	Exploitation because of, e.g., : Lack of capacity (e.g., extremes of age, mental disorders, anxiety, emergency) Understanding barriers (e.g., language, low levels of literacy) Diminished freedom or voluntariness (e.g., manipulation, coercion)
Social Wrongs	Confidentiality breach / inappropriate dissemination of results of research (e.g., stigmatisation, stereotyping, discrimination, physical / gender-based violence, job loss, legal sanction)
Psychological Wrongs	Anxiety, stress, emotional suffering (e.g., could be triggered by research tool, e.g., sensitive questions in interview schedule)
Justice Wrongs	no post study access to proven intervention, inequitable standards of care usually with international research, no provision for compensation for research-related injuries.

7.6 CONCLUSION

The “Vulnerability Assessment” Scale and the clustering of identifiable wrongs to specific contexts could aid RECs in the review process such that they would be able to plan directed protections for the potential research participants. In this way, both RECs and research participants benefit from the use of these tools. It could be stated that the guidelines

categorization and sub- categorization of research populations is a convenient approach for RECs in that it makes their task much simpler than the "Vulnerability Assessment" Scale offered. However, the pitfalls of the former approach and the resultant wrongs have been clearly illustrated. The Scale offered will require RECs to execute focussed and comprehensive wrongs assessments from the protocol to include the scientific aspects, social context and moral implications of the study and in so doing guide the researcher on how potential participants ought to be protected based on their individual needs and capabilities. RECs make the decisions on how participants in research are to be protected but the actual implementation of the safeguards is the responsibility of the professionals that conduct the research. This is why the researcher-participant relationship in which the moral status of the participant is respected and her / his human dignity is upheld is so important. This approach in no way detracts from the key duty of the REC which is to protect participants in research. It essentially enhances protections by assisting RECS in guiding researchers on its implementation and hence strengthens and enriches strong protectionism.

This chapter has culminated in the definition of the concept of vulnerability in health research and the tool for its application to facilitate participant protection. In the following chapter I will apply these tools to two Court Judgements involving research participants to demonstrate that their utility extends beyond the REC review process.

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Chapter 8: APPLYING THE DEFINITION AND VULNERABILITY SCALE TO CASE STUDIES

8.1 INTRODUCTION

Researchers and RECs in South Africa, despite our relatively early history of research participant protection programmes and our robust ethico-regulatory framework for participant protections, have been heavily criticised both in the scholarly literature and lay media for our inability to adequately protect participants in research[1,-4]. At times, participants have resorted to the Courts for protections, however, with morally disappointing results as judgements have been based on strictly legal criteria rather than moral obligations[5,6, 7].

In this chapter I describe pertinent aspects of two judgements[5,7] by the South African Courts, and then proceed to show how research participants have been wronged, using the definition of vulnerability and the Vulnerability Scale that I have developed. These wrongs could have been averted, or "righted" had there been a definition and Scale in place for use along the lines that I have developed.

It will become clear at the end of this chapter that the tools developed in this thesis are simple and uncomplicated, yet robust and comprehensive, and if used appropriately would optimise the protection of research participants with vulnerabilities and also be of great value as an adjudication instrument.

8.2 CASE STUDY 1: *NM AND OTHERS v SMITH AND OTHERS (FREEDOM OF EXPRESSION INSTITUTE AS AMICUS CURIAE)* 2007 (5) SA 250 (CC)[5]

A synopsis of the evidence and information contained in the judgement in this complex case is described below and then analysed using the vulnerability instruments developed in this

thesis. Dr M Botes, head of the Immunology Clinic in the University of Pretoria Medical Faculty, enrolled participants into the FTC 302 Trials at the Kalafong Hospital, Pretoria. These were HIV clinical trials, the objective being that of testing the efficacy of a combination of drugs that could decrease viral loads. The trials commenced in August 1999. At enrolment, potential participants were required to sign informed consent forms to participate.

Participants brought up concerns about illnesses and mortality in the trials soon after the trials had started. This was eventually brought to the attention of the then Minister of Health who, in April 2000, called for the South African Regulator, the Medicines Control Council (MCC), for a report. The MCC found that a causal association between the drugs and deaths was probable and suspended further enrolment of participants while additional investigation and full reports could be compiled on the serious adverse events and deaths associated with the trial interventions.

While at a support group meeting for people with HIV/ AIDS, participants and in particular three women complained to the leader of the group, Johan Viljoen, a former priest, about their adverse experiences in the trials. In March 2000, Viljoen approached Patricia De Lille, a member of Parliament at that time, and who was well known as an activist in relation to the rights of people living with HIV/AIDS, for assistance as he was quite concerned at the large numbers of participants that were getting ill while on the trials. De Lille met with members of the support group on the 28th March 2000 where the clinical trial participants complained that the consent form was never properly explained to them and that Dr Botes attributed their adverse symptoms to their illness and not to the side effects of the drugs. They also complained that she was unsympathetic to their complaints. This was followed by a meeting

with the REC, Dr Botes, De Lille, journalists and a representative from the South African Broadcasting Corporation at which the REC requested signed statements from the participants. These were obtained from the three women participants by Viljoen and sent to the REC in May 2000. The statements were also subsequently sent to the South African Human Rights Commission. With pressure now mounting, the Pretoria Academic Hospital set up an internal investigation, headed by a medical practitioner, to consider the complaints. The report of this internal investigation was submitted to the REC and the University Registrar, Professor Grove, in July 2000 and to De Lille in October 2000. She was satisfied that the participants' complaints were included and expressed in the report.

In August of the same year, Pretoria University appointed Professor SA Strauss, a leading legal academic, to conduct an external enquiry to complement the internal one. The three participants who had signed the statements and others involved in the clinical trials were invited to this enquiry. The three participants retracted their statements during the external enquiry. Nowhere in the Strauss Report were the reasons for this about-turn made available. Professor Strauss's report, which was delivered to the University on 30th May 2001, exonerated the Medical Faculty and stipulated that there was no substance in the three statements and no evidence of improper conduct on the part of Dr Botes. The Strauss Report was sent to De Lille without its annexures. The latter comprised the consents furnished to Strauss, the informed consents at enrolment of the trials and copies of statements sent by De Lille to the REC. The Report was also sent to several journalists. The Report included the names and HIV status of the three women. The introductory section of the Report stated that their names had been published in terms of the consents they had

given but did not highlight that this was for the purposes of the Report only. The Report did not state that the contents were confidential; neither was the Report marked “confidential”.

In March 2002, 5000 copies of an authorised biography of De Lille were published and distributed to various bookshops in the country. A journalist, Charlene Smith, had been commissioned by De Lille to write the biography. One of the chapters in the book was on De Lille’s activism on the rights of people living with HIV / AIDS. The chapter included information on her involvement with the issues raised in the FTC 302 trials. The internal report and the Strauss Report had been given to Smith, who after many unanswered attempts at obtaining the annexures to the Strauss Report from Strauss, the REC and the University, included the names of the three trial participants who had signed the statements of complaint, together with their HIV positive status in the chapter. The three women, who were unemployed, lived in informal settlements and had little to no formal education, were informed of this disclosure by Dr Botes. They feared that their families and lovers would now discover their HIV status and that they would be thrown out of their homes. At that time, and even perhaps today, the stigma and subsequent maltreatment associated with an HIV positive diagnosis were entrenched in South African society. Hence, because of serious personal and social consequences as a result of inappropriate disclosure, protection of privacy and confidentiality as to HIV status were at that time and even today are necessary and justified.

Dr Botes directed the women to the University of Pretoria’s Law Clinic and an application to interdict further publication of the book was lodged in the Pretoria High Court. This application was opposed and ultimately withdrawn. In the meantime, one of the women had her shack burned down by her lover who subsequently left her. She later attempted

suicide by dousing herself in flammable liquid and setting herself on fire. A second informed her mother of the disclosure. She was rejected and thrown out of the house. The third woman had retreated from society and had not informed her family of her HIV status and the disclosure in the book. She experienced serious fears that her family would find out. In July of that year, the women sent a letter to Smith's, De Lille's and the publisher's attorneys requesting the removal of their names from the book. This request was rejected by the former two and not responded to by the latter. They were subsequently sued for damages by the women in the Johannesburg High Court[6]. The claim was that their rights to privacy, dignity and psychological integrity had been violated.

The women (Applicants) claimed for:

a) a private apology from Smith, De Lille and the publishers (Respondents 1, 2 and 3 respectively);
b) removal of their names from all unsold copies of the book;
c) payment of R200 000 to each of them; and
d) costs of the suit.

In May 2005, the High Court dismissed with costs the action against the 1st and 2nd respondents. Some of the reasons for the dismissal contained in that judgement were that the women were illiterate in and claimed no understanding of English and that there was no possibility of confrontation in the future by anyone in their community as to the disclosure of their HIV status in the book (quite inappropriate reasoning in my opinion as lack of literacy is no reason for not protecting dignity and moral status). However, the 3rd respondent was ordered to pay each of the women a sum of R15000 and their costs. The 3rd respondent was also ordered to delete the women's names from all copies of the books that

it still had in its possession and not to sell any further copies of the book until such deletion was made. The women applied to the Supreme Court of Appeal to appeal against the judgement in terms of Respondents 1 and 2. This was dismissed without reasons being specified. They subsequently approached the Constitutional Court[5] of South Africa on Appeal.

The Constitutional Court held that the High Court was incorrect in its findings that Respondents 1 and 2 were not liable for any damage suffered by the women at the time of publication of the book and that the publication of their HIV status constituted wrongful publication of a private fact and that the rights to privacy of the women had been breached by all the respondents. In addition, as it was an affront to disclose their HIV status without their consent, and because of the indignity of the public stigma, degradation and indiscrimination that accompanied being HIV positive, their dignity and psychological integrity had been violated. The application for leave to appeal was granted and the quantum of damages was set at R35 000 per woman as this was considered a fair assessment of damages suffered. The women's names were to be deleted from all copies of the books that had not been sold, the High Court decision was set aside and each party was to pay its own costs.

8.2(A) Analysis of the Case

The definition of vulnerability as formulated in the previous chapter will be employed to start off the analysis.

"Vulnerability is an inability or decreased ability of a research participant to sufficiently safeguard her/his own needs and interests resulting in her/him being at an increased

likelihood of being identifiably wronged in varying degrees if special safeguards to protect her/him are not invoked by the Research Ethics Committee"

Using the definition of vulnerability above, it would need to be determined as to whether these women would be vulnerable and if so why?

Hence, the question to start off with is: *Was there an inability or decreased ability of the research participant to sufficiently safeguard her or his own needs and interests?*

This was an HIV clinical trial which started in the late nineties when access to antiretroviral therapy was not available to the poor and indigent in the country. Some of the participants, who joined the trial as a means of accessing therapy towards their needs and interests, would have not been in a position to sufficiently safeguard their own interests from the perspective of access to care. In addition, poverty is usually associated with lack of access to education[8] and hence poor research participants as in the case of these three women would have been more likely to be illiterate or have low levels of literacy. This would mean that their interests as autonomous decision-makers would be affected should they not understand the content of the informed consent forms and if there were weaknesses in the informed consent process. Poverty in South Africa was also associated with a negative social context in terms of having HIV with potential for stigma, intolerance, discrimination and violence against the individual should there be indiscriminate disclosure[9,10]. Because of the social context they would not be in a position to adequately safeguard their own interests.

Would this result in her / him being at an increased likelihood of being identifiably wronged in varying degrees if special safeguards to protect her / him are not invoked by the Research Ethics Committee?

The answer here is an unequivocal yes. The wrongs would include physical should they suffer side effects of the intervention being tested and there was no provision for monitoring and treatment. If the informed consent process was not appropriate, the participants may not have been in a position to realise that they were experiencing side effects and report this to the study team on time. Moreover, in this case, the physician researcher was dismissive of the Applicants' complaints of illness after joining the trial. The three participants were aggrieved enough to have taken their concerns to Viljoen at a support group meeting. Furthermore, the enrolment into the trial was suspended by the MCC because of a probability of a causal association between the interventional drugs and deaths. Hence there was an increased likelihood of experiencing physical wrongs if the REC did not invoke special safeguards to protect the participant. Because of poverty coupled with low levels of literacy and resultant understanding barriers and diminished voluntariness as a consequence of the so-called promise of much-needed healthcare within the context of the trials, the 3 participants would have been at an increased likelihood of consent wrongs. Moreover, because of the South African social context, inappropriate disclosure of the participant's HIV status would have resulted in stigmatization, discrimination and violence resulting in them being at an increased likelihood of social wrongs, and as a consequence, in a violation of dignity and an undermining of moral status. Several special safeguards to protect the three participants were required to be instituted by the REC.

It is clear that the three women would be defined as vulnerable.

The "Vulnerability Assessment" Scale is applied as follows:

9. *Has the essential minimum standard afforded all participants in light of universal vulnerability been met?*

   It is not possible to comment on this as this information was not available nor contained in the Judgement. However, it is worth mentioning that at that time, in the late nineties and at the turn of this century, there was no national basic standard as determined by the law in South Africa, as there is today. Nevertheless, it is possible that the University of Pretoria's REC could have derived its basic standards to protect universal vulnerability of participants from the DoH and SAMRC Guidelines that have been discussed in previous chapters.

10. *Has the baseline for respecting human dignity been met?*

    The intrinsic worth of the 3 participants had been violated by the Dr Botes who seemed not to take their concerns as regards the side effects of the drugs seriously. It is also of concern that they may not have understood the contents of the informed consent documents with resultant disrespect to their rights to bodily integrity. Their rights to privacy and confidentiality had also been violated by the Strauss Report and the biography.

11. *Will any participant be used in the research as a means to an ends she/he may not endorse?*

    Without ensuring proper consent, both for participation in the study and for disclosing their HIV status, and by not taking their concerns as regards the side effects seriously they were used as a means to an ends they did not endorse.

12. *Will all the research participants in this study be able to safeguard their own needs and interests?*

In terms of the situation in South Africa at that stage, not all research participants in the FTC 302 Trials would have been able to safeguard their own interests as this would depend on the social backgrounds of participants. Some participants could have been from contexts of social privilege, with access to education, adequate levels of literacy secure jobs and support of family and friends and hence be in a position to safeguard their interests[11]. This would differ from the participant on the opposite end of the social ladder, like the three women who came forward with complaints during the trials.

13. *If no, is there an increased likelihood of any of them being identifiably wronged as a result of their participation in the study?*

    In the case of these three women, the identifiable wrongs that they were at increased likelihood of were physical, consent social and psychological.

14. *Is there an increased likelihood of any participant being identifiably wronged to a greater degree than other participants?*

    Yes. This would depend on the socio-economic status of each participant, the level of literacy of each participant and the social contexts in which the different participants found themselves, as in the case of the three women.

15. *Have the identifiable wrongs been recognised?*

    It does not seem that the REC successfully identified the wrongs that could arise and hence the lack of adequate protections for these three women.

16. *Have special safeguards been developed to protect those participants in need of such safeguards?*

    No. This opinion is based on the almost silence of the REC to respond to the women's needs and concerns. When the women felt that their complaints regarding

their illnesses since joining the trials were not being taken seriously by Dr Botes, they complained to Viljoen rather than to the REC. Without having access to the informed consent form that they signed, one can only speculate as to its contents, and as to whether each participant did indeed receive a signed copy of the document. It is possible that the REC did not ensure that its contact details were made available to participants on the form should there have been a complaint or concern that they would have had in terms of their rights as research participants. It is also possible that the REC did not advise the researchers of the need for this information to be included in the informed consent forms or of the problems of social context and the specific safeguards required. One also wonders whether the REC did receive reports on adverse events and how it responded to these. The suspension of enrolment was determined by the MCC. The REC, as part of its post-approval responsibilities, should have also been appraising the adverse events reports and making recommendations to researchers. Protections of participants by an REC does not terminate once a protocol is reviewed and approved. The REC continues its protections role throughout the study through to dissemination of results. There is no evidence that the REC instituted an investigation as to the concerns of the three women despite the meeting with the 2nd Respondent. It was only after copies of the women's statements were sent to the Human Rights Commission that the Pretoria Academic Hospital, and not the REC, responded by conducting an internal investigation. The report of this investigation was submitted to the REC and University in July 2000. The women's complaints were included in this report. It is unclear how the REC responded to this report nor why the University instituted an "external" investigation to "complement" the internal one. It is also surprising that the women

would after all this time suddenly repudiate their statements during the external investigation without explanation for this being recorded in the Report. It is expected that the REC, as an entity in the University, would have been presented with the Strauss Report which contained the names of the three women and their HIV status. It is also expected that the REC ought to have raised concerns as to disclosures in the Report which did not carry a clear statement declaring that it was confidential nor that the consents obtained from the women as regards disclosure of their identities were qualified and limited. There is no record of the REC intervening because of the implications of inappropriate disclosure of the women's information even at that stage.

8.2(B) Discussion

Section 14 of the South African Constitution[12] affirms the right to privacy which includes the right not to have the privacy of one's communications infringed (14d). The right to privacy basically is the right to limit access to, or control data about one's self. Other people having unauthorised access to that personal information may result in negative emotional reactions like fear, embarrassment and humiliation, and also stigmatization and discrimination. Limiting informational resources about one's self is important in shaping relationships, e.g., differing amounts of information are shared with family members, friends, healthcare practitioners and researchers. Very importantly, once unauthorised information about one's self is disclosed by a third party, the loss of privacy in that context is irreversible. In the case of these women, their medical information as regards HIV status was personal and highly sensitive and public disclosure would have the potential to result in negative repercussions. As the Strauss Report was not marked confidential, the REC had a

moral obligation to intervene and request that the women's identities be removed. It was an affront to the dignity and psychological integrity (also a Constitutional protection in section 12[12]) of the women for their HIV status to be made public without their consent. Because of the many years of indignities suffered as a result of the oppression of the majority of people in South Africa that were not of the white racial category, a constant theme in our Constitution is the importance of restoring human dignity. Apartheid was a denial of our common humanity, and the aim of the struggle against apartheid was that of restoring human dignity. Because human dignity is foundational in the Constitution it must be aggressively safeguarded and protected. Section 10 of the Constitution makes dignity a justiciable and enforceable right. It is unfortunate that the stigma associated with HIV undermines dignity in that it denies those living with HIV a life without shame, humiliation and fear. For privacy to be adequately protected it must be respected by others – and this was what the REC should have ensured. It is my opinion that as the REC failed to safeguard the vulnerabilities of these three participants from the commencement of their participation in the trials. It is unlikely that the REC had considered their specific vulnerabilities during the review of the research.

The case also highlights that problems of access faced by the research participants went beyond medical treatments to include lack of access to adequate and competent legal advice. The women were harmed by the inappropriate disclosure which resulted in them being wronged. The question that should have been considered by their legal team was: *"Who was the source of the harms and wrongs?"* Clearly, the response would be the original author of the document and the University. However, the women were being assisted by staff of the Law Clinic of the University who may not have been totally objective in the

assistance given. It is my opinion that the application ought to have been brought against Professor Strauss and the University in the first instance, and if this had been the case, the women would not have had to endure the anxieties and stresses of having to appeal to the Supreme Court, and the Constitutional Court thereafter.

8.3 CASE STUDY 2: *VENTER V ROCHE PRODUCTS (PTY) LTD ET AL* (11285/08) [2013] WCHC 7 MAY 2013

This case was heard in the High Court of South Africa and the judgement which is described below was delivered on 7 May 2013. In 2005, Mr Venter, the plaintiff, after signing a patient information leaflet and informed consent document (PIL ICON), was enrolled into a phase III multi-national clinical trial, the aim of which was to evaluate the efficacy and safety of a cancer intervention in patients with non-metastatic carcinoma of the colon, breast or lung. The study was initiated by Hoffman-La Roche AG (FHLR), a pharmaceutical company based in Switzerland. FHLR developed the study protocol. Roche SA (1st defendant) was contracted by FHLR to conduct the SA arm of the trial and to make the necessary applications to the regulatory body, the MCC and the RECs. The RECs that reviewed and approved the trials were Pharma-Ethics and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (HREC). Dr L Gouws and Partners Inc, also known as GVI Oncology (2nd defendant), was contracted by Roche SA to be principal investigator on the trial. The trial commenced once all the necessary approvals had been obtained. The plaintiff, because he satisfied the criteria for inclusion, was enrolled into the trial five days after he took the PIL ICON home to discuss with his wife and after the document had been gone through with him "point by point" as highlighted in paragraph 17 of the judgement. The PIL ICON provided for *inter alia* the payment of compensation to a participant in the event of him or

her suffering a trial-related injury. As will be seen below, a proper construction of the terms of the PIL ICON was central in the adjudication of the issues between the parties.

Nine days after randomisation to the intervention arm of the study, the plaintiff experienced acute abdominal pain, was hospitalised, and underwent a laparotomy and repair of a bowel perforation. Bowel perforation was a side effect described in the PIL ICON as occurring in up to one in ten patients. A month later, he underwent a cholecystectomy. These events were reported by GVI Oncology as trial related serious adverse events (SAE) and FHLR approved payment of costs. The plaintiff thereafter contended that he suffered damages as a direct result of the trial-related injury. A dispute arose subsequently between the parties as to whether the plaintiff was entitled to claim compensation for pain, suffering, and loss of income and general damages over and above medical costs. It was recommended by FHLR that the issue be submitted to an independent expert for an opinion but because the parties could not reach agreement in this regard, the matter proceeded to litigation.

The plaintiff's causes of action arose from the meeting between him and GVI at which he signed the PIL ICON. He advanced that a tacit contract was concluded in terms of which Roche SA represented by GVI gave a contractual undertaking to him that compensation would be awarded for trial-related injuries equivalent to the damages that would normally be awarded to a plaintiff by South African or British Courts for similar injuries where liability is accepted. This was based on the compensation clause in the PIL ICON.

The plaintiff's claims were dismissed with costs with the judgement entered into being in favour of the defendants. In determining his judgement, the Judge felt it necessary to

ascertain who the actual entity was in terms of the tacit contract and exactly what the offer of compensation entailed.

As the sponsor was FHLR and this is made clear in the PIL ICON in which FHLR is mentioned many times and because section 4.5 of the SAGCP guidelines allows for a sponsor to transfer trial-related functions to a local organisation, FHLR was the contracting party and not Roche SA or GVI Oncology. In fact Roche SA was not mentioned in the PIL ICON at all. Furthermore, section 4.11 of the SAGCP guidelines provides that it is the sponsor who has the obligation to provide compensation.

As regards compensation, the clause in the PIL ICON read as follows:

> "COMPENSATION IN CASE OF RESEARCH-RELATED INJURY
>
> The investigational medications will be given to you free of charge and you will not have to pay for any study visits or any tests required by the study. F Hoffman-La Roche Ltd will pay for the cost of medical treatment with the study medications when used as stated in the study protocol. The compensation available is in accordance with the 'Clinical Trial Compensation Guidelines' published in 1991 by the Association of the British Pharmaceutical Industry (ABPI)
>
> You may obtain a copy of these ABPI guidelines from your doctor. No other compensation is offered. "

The interpretation of this clause in the PIL ICON was considered in detail by the Judge. The heading of the clause referred to "compensation" but the body stated that FHRL would pay the cost of medical treatment for trial-related injuries only and in accordance with the ABPI Guidelines. Compensation and costs denoted different concepts, with the former conveying

a broader interpretation to include damages to which the individual may be entitled which could include an award for pain, suffering and loss of income. This wording was revisited against the background section of the ABPI Guidelines which did not lay down any legal obligations in terms of compensation. The guidelines were in fact only guidelines that made recommendations to the sponsor of the trial. According to the Judge, incorporation of "… in accordance with … (ABPI)," did not elevate compensation to a legally enforceable obligation and hence, the compensation clause in the PIL ICON did not provide a legal basis for the plaintiff's claim for damages.

8.3(A) Analysis of the Case

Definition

"Vulnerability is an inability or decreased ability of a research participant to sufficiently safeguard her/his own needs and interests resulting in her/him being at an increased likelihood of being identifiably wronged in varying degrees if special safeguards to protect her/him are not invoked by the Research Ethics Committee"

With the assistance of the use of the criteria in the definition of vulnerability, it is obvious that the plaintiff as a research participant was vulnerable in that he was not able to understand the content of the PIL ICON. This is evident from his lack of comprehension of its compensation clause. I am of the opinion that although his physical illness may have resulted in research-related vulnerability, he was not wronged from this perspective as special safeguards constituting treatment of research-related injuries had been instituted to protect him in this regard.

The Vulnerability Scale

1. *Has the essential minimum standard afforded all participants in light of universal vulnerability been met?*

   As the participant agreed in 2005 to participate in the trial, the expectation is that the REC would have been conducting its reviews in line with the SA Ethics Guidelines which have been discussed in chapter 5, and which were in use in the country at that stage and hence ought to have met this basic standard of safeguards.

2. *Has the baseline for respecting human dignity been met?*

   I am of the opinion that this was not achieved in light of the participant's lack of understanding of the implications of participating in the trial. In this way his bodily integrity had been violated.

3. *Will any participant be used in the research as a means to an ends she/he may not endorse?*

   Because the participant was enrolled in the research without his understanding of the PIL ICON being ascertained, he was used in the study as a means to an ends he did not endorse.

4. *Will all the research participants in this study be able to safeguard their own needs and interests?*

   No. This was an oncology trial involving participants with non-metastatic carcinoma. Participants' abilities to safeguard their own interests could differ in terms of socio-economic need, medical need, physical response to the intervention, anxiety and stress over their current medical condition and the ability to understand what participation in the trial would entail.

5. *If no, is there an increased likelihood of any of them being identifiably wronged as a result of their participation in the study?*

Yes. This would depend on their individual particular vulnerabilities.

6. *Is there an increased likelihood of any participant being identifiably wronged to a greater degree than other participants?*

   Yes. This would be the case if participants were not able to adequately protect themselves and special safeguards were not initiated by the REC towards their particular vulnerabilities. In the case of the plaintiff he was at an increased likelihood of experiencing consent wrongs.

7. *Have the identifiable wrongs been recognised?*

   It is clear in the case of this participant that both the RECs did not identify the potential for consent wrongs and hence did not respond accordingly.

8. *Have special safeguards been developed to protect those participants in need of such safeguards?*

   There had been consent wrongs to the participant as both the RECs approved the research without proper and adequate clarification on the meaning and implications of compensation in accordance with the ABPI Guidelines. It must be highlighted from my personal experience that this situation remains currently unchanged. It would be important for the potential participant to understand exactly what is and what is not covered by insurance for research-related injury and that this cover is provided on a moral basis without any legally binding obligations. An examination of the ABPI Guidelines[13] reveals that it is recommended that compensation should only be paid for the more serious injury of an enduring and disabling character and not for pain or

discomfort or less serious or curable complaints (s1.4). The Guidelines do not apply to phase I trials either (2.2). I have not seen this type of information included in the information to participants in the fifteen years that I have reviewed clinical trials on the several different RECs that I have served on, and currently serve on, both locally and nationally. Participants who require this type of knowledge are not having their needs and interests safeguarded by RECs in the country.

In the case of the plaintiff, despite him having the PIL ICON with him for about five days together with a member of GVI Oncology taking him through all the points in the document, it is clear that he did not understand that compensation in that clause was limited to the cost of treatment only and was not broad as it is commonly understood to be. Despite FHRL being mentioned in the PIL ICON many times and no reference being made to Roche SA, it would seem that he did not understand that Roche SA was not the sponsor.

8.3(B) Discussion

This case highlights the importance of ensuring that information in the informed consent documentation is clearly understood and is comprehensive. Participants' abilities to understand differ and cautioning researchers that going through all the points in the document is not sufficient is a necessary safeguard to guide researchers. It would also be necessary to ascertain from the participants how much they really understand. Furthermore, it is possible that the plaintiff, because he was literate and from a privileged social background, as he was able to engage legal counsel at his own costs, unlike the three women in the above case, may have not been considered vulnerable from the perspective of a lack of understanding of the informed consent document. This is because the norm in

research as a result of the effect of the guidelines' emphasis on vulnerable populations is that lack of understanding would be a feature of a vulnerable group that was poor and disadvantaged. This is an example of how vulnerability can be overlooked because the participant does not fall into a particular subgroup.

Compensation for research-related injuries was recognised as a moral requirement as early in 1900 as discussed in chapter 4. Walter Reed and his Yellow Fever Board, in a written contract for local workers in Cuba that explicitly explained the risks if involved in the research proposed by the Board, offered a payment of $100 compensation for those who became ill with yellow fever[14]. The Belmont Report[15], however, is silent on the issue of research-related injuries. In 2013, the DoH[16] stressed the importance of compensating injured participants by, for the first time including compensation in its "General Principles". Section 15 states that, "Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured". It goes on further under "Scientific Requirements and Research Protocols" to state, in section 22 that protocols should contain, "… information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study." The DoH contradicts itself in that in its principles it is explicit that both compensation *and* treatment must be ensured. However in the implementation it provides for "… treating *and/or* compensating … " (itallics – my emphasis), and in so doing, weakens its newly introduced principle considerably. However, the DoH does differentiate between the two different concepts of compensation and cost as discussed above and does make allowance for both.

The CIOMS[17] states in Guideline 19 that "Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for

such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation." Hence these guidelines provide for two well-defined entitlements, that of free medical treatment and compensation for accidental injury; and that of dependants to material compensation. This guideline takes into consideration that compensation and costs denote two different concepts.

The ICH GCP Guidelines[18], in section 5.8 on "Compensation to Subjects and Investigators", states that the sponsor should provide insurance if required by the applicable regulatory requirements and the method and manner of compensation should comply with these requirements. The sponsor's policies should address the costs of treatment in the event of trial-related injuries. These guidelines are quite feeble and watered down in terms of ensuring protections for injuries as a result of trial participation, and in my opinion has failed to differentiate between compensation and cost.

The principal motivation for ensuring participants that are injured in research are taken care of involves the principles of justice and fairness, and more specifically compensatory justice as discussed in chapter 2. Participants involved in research, where the informed consent process is above reproach, accept risks associated with the research and at times place their lives on the line. Because it is usually society that benefits from the participants' acceptance of the risks, it is only fair that participants are protected from the harms that may arise. Not doing so would result in participants being used as a means to the sponsor's, researchers', or society's ends. The SA Ethics Guidelines[19] fails research participants in this regard as all it states on the issue is in section 2.6 on "Informed Consent". It outlines some points that

participants *may* (my emphasis) find useful in the informed consent, with one of them being, “Explanation as to whether compensation will be given for research-related injuries”. This Guideline does not make explicit the need for compensation and treatment as a moral entitlement to research participants and it infringes the principle of justice and fairness. While the SAGCP[20], as mentioned in the judgement above includes the principles of the ABPI Guidelines, the South African ethical and regulatory framework is only weakly protectionist in this regard. It is therefore imperative that RECs ensure appropriate and adequate strong protections in the event of research-related injuries. Currently, it would seem that the best way to do this is by ensuring that participants truly understand the information given to them during the informed consent process.

8.4 CONCLUSION

In this chapter I have utilised two Court Judgements to test the utility of the definition and Vulnerability Assessment Scale developed in the previous chapter. In the first case the tools demonstrated clearly that the participants had suffered consent, social, physical, and psychological wrongs. With the use of the tools, it was also established that different types of access require consideration in contexts of social deprivation, and that lack of access to competent legal advice and guidance could also result in participants being wronged. In the second case the tool assisted in highlighting the importance of the understanding element of informed consent being satisfied for consent to be deemed valid. It also brought to light and made material the concern with the subgroup classification of vulnerability in the guidelines in that a participant who is not categorised into a particular vulnerable group may not be considered as needing special protections. Health research in S A, as defined by the NHA (see chapter 1) is quite broad and includes not only medical interventional studies but

also research into the biological, clinical, psychological or social processes in human beings, health service provision research, and epidemiological studies. These tools could be easily applied to any of these studies by RECs during the review process. The tool is of immense value in that it can be utilized during the review process, during the course of the research and even after the research is over to assist RECs to guide researchers, sponsors and even political authorities on optimizing protections for participants in research. Moreover, it could also be used as an adjudication tool should a dispute arise.

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Chapter 9: CONCLUSION

I concluded chapter 7 with the advancement of a definition of vulnerability in health research and a Vulnerability Assessment Scale to assist RECs guide researchers on focussed protections of vulnerable individuals. In chapter 8, I was able to demonstrate the utility of these tools. These instruments recognise heterogeneity between individuals and unlike the guidelines' subpopulations approach to vulnerability, they steer away from arbitrary distinctions. They adopt a holistic approach which addresses both the individual and structural causes of vulnerability and makes positive action to prevent wrongs to research participants with vulnerabilities morally obligatory. Hence, the definition and Scale confer a responsibility to address vulnerability.

The definition and Scale have benefitted by being derived from a combination of a normative, metaethical and historical inquiry. Using this method of analysis, in which the major ethical theories of deontology, utilitarianism and virtue ethics together with the four principles of medical ethics have assisted substantially, I have been able to deduce that the categorization of people into vulnerable groups is not justified and that RECs have responsibilities derived from common morality to ensure special protections for research participants who are vulnerable in order to safeguard them from being wronged. I have also been able to demonstrate that despite vulnerability remaining an abstract concept, it has concrete effects both on those who are labelled vulnerable and those who are not and that it is imperative that researchers with guidance from RECs are able to identify which vulnerable individuals qualify for special protections without paternalistic impositions.

I have argued earlier that vulnerability is an ontological condition of our humanity. This ordinary or universal human vulnerability is also linked to the inherent sociality of human

life in that embodied social beings are both dependant on the care and support of others and also vulnerable to their actions. It is unambiguous that the human condition in itself implies vulnerability. The definition and Scale consider safeguards for universal vulnerability for all participants in research as a basic minimum standard and provide additional protections for participants with more than universal vulnerability. I have made the argument that research ethics mandates special protections for participants considered to be vulnerable because of the danger of exploitation by researchers and the need to respect the intrinsic value and dignity of those who do not have the means and/or ability to protect themselves. Exploiting the vulnerabilities of participants is one of the ways in which justice as fairness is violated in research. I have demonstrated that these concerns over vulnerabilities have been intricately linked with issues of moral status and human dignity of the research participant and that the recognition and respect of the moral status of the research participant is important because it supports essential moral protections in the context of vulnerability. Respecting the moral status of the participant with vulnerabilities in health research would serve to caution that safeguarding her or him against exploitation would be a morally justifiable action that would also give regard to protecting her or his dignity as a human being. As inferred in chapter 3, human dignity is an articulation of a fundamental value that is widely accepted as seen by the fact that reference to and reliance on human dignity is found in most leading international documents. In the Constitution of South Africa, the supreme law of the land, human dignity is a constant refrain.

Respecting human dignity translates to respecting the intrinsic worth of the research participant, independent of the individual's capacity of rational autonomy. This in turn translates to how the researcher as one moral agent treats the vulnerable research

participant, another moral agent with reciprocal moral status. Coercive acts are incompatible with respect for the dignity of participants. Being demeaned or humiliated as a result of participation in research clearly violates the dignity of participants. This type of lack of respect could destroy or reduce the self-respect that is so necessary to the intrinsic worth of being human. Respect for intrinsic worth of the research participant recognises that she or he is entitled to her or his own beliefs, attitudes, ideas and feelings. Physical or psychological coercion is as striking an affront to human dignity as physical abuse or mental torture both within and outside the research context. Human beings are morally important because they have dignity, which is the inviolable core of being human and also of what gives one moral status. I have made an argument in my analysis on the link between moral status, human dignity and vulnerability that respect for human dignity and moral status are indispensable components of ethical standards for the treatment of participants in health research and that every human being, regardless of the degree to which he or she is autonomous, or vulnerable, has intrinsic worth. Human dignity and moral status are natural properties of research participants which must be recognised by researchers and REC members. Respecting human dignity and moral status is core to protecting the vulnerable research participant against exploitation and other forms of harms and wrongs. Moreover, this ensures that because of her or his inherent worth they are protected from being treated as a means to an end they may not endorse. Exploitation of vulnerability unequivocally results in violation of human dignity and disrespect of moral status.

From a historical perspective, as has already been discussed, because of the disasters and disgrace in medical research generated by the Nazi doctors during the 2nd World War, protectionism in health research emerged, with the Nuremberg Code of 1947 being the first

protectionist international document in research ethics. This was followed by the DoH in 1964 and as science and technology advanced, the DoH was revised and the WMA in October 2013 published the eighth version of the Declaration. The DoH is recognised as the leading research ethics guideline internationally. After many other abuses of vulnerable subjects in research in the United States, the Belmont Report was produced and Federal Rules were established for protecting vulnerable participants enrolled in studies. In SA establishing protections for participants of research commenced in the late sixties at the level of individual institutions. The protectionist approach was not as a response to scandals and tragedies inflicted on vulnerable participants by South African researchers but because of a sense of moral agency, moral responsibility and moral accountability of researchers in this country towards people they enrolled in research, especially since sponsors and researchers from well-resourced countries, and in particular the US, had started finding less resourced areas highly attractive for the conduct of clinical research.

I have indicated earlier that the Belmont Report which had a major influence on international and the SA Ethics Guidelines, introduced “vulnerability” and the “group” or “subpopulation” lexicon into research ethics guidance documents. The Report is therefore the root cause of the confusion and the labelling of people created in this arena. From an international guidelines perspective the 2000 version of the Declaration of Helsinki first made direct reference to the term. The themes of justice and informed consent were used to guide the unfolding of the group and subpopulation focus of vulnerability in these documents. While the objective of the early documents to protect vulnerable individuals that were involved in research is clearly unquestionable, the challenges created by the subpopulation and group approach have been vigorously articulated in this thesis.

It became clear during the analysis that protection should be viewed not as exclusion but as allowing participants to volunteer without the risk of abuse and of being wronged and that what was actually required was a robust, focussed and comprehensive definition of vulnerability to start off with. This definition, when applied in the research ethics review process, would allow for the REC to provide guidance to researchers on how:

a. to recognise vulnerability in potential participants
b. to recognise their degrees of vulnerability
c. to build moral responses (aimed at duties of protection) and
d. to justify these moral responses.

Not only has an appropriate operational definition been developed but a Vulnerability Assessment Scale has also been extracted from it. The Scale essentially enhances protections by assisting RECs in guiding researchers on the implementation of the definition and hence strengthens and enriches strong protectionism.

The utility of the definition and the Vulnerability Assessment Scale was tested in the previous chapter through reference to two court judgements. The value of the definition and Scale was clearly demonstrated to extend beyond the review process. These instruments can also be used during the course of research, after the research is over and as an adjudication tool should a dispute arise. The tools developed in this thesis offer a guide on the moral obligations of RECs and researchers in terms of avoiding wrongs to research participants with vulnerabilities by respecting them or their proxies (where relevant) as autonomous agents; guarding against them being harmed; behaving justly and fairly towards them and optimizing benefits to them. The definition and Scale are strongly protectionist and are compatible with all the moral philosophical systems described in this

thesis. Despite rejecting the subpopulation and group approach, they are also in line with the principles as articulated in the DoH and other international and national guidelines, including those from South Africa.

I conclude this thesis by establishing that this ethical inquiry has resulted in the concept of vulnerability in health research no longer being nebulous and vague and that there is now a cogent definition that assists with finding the best balance between adequate protections and excluding individuals that need to be excluded from research. The definition of vulnerability is no longer an unanswered question. Neither can it be criticised for being an extensive albeit non-exhaustive list that at times could be paternalistic and demeaning. Moreover, this approach towards recognising and instituting protections for the vulnerable participant would safeguard against the participant in research being used as a means to an end that she or he may not endorse. Furthermore, should this practice become the norm in health research, it would go a long way in easing the suspicions that the public has against researchers, improve respect from the public towards REC functioning and promote a researcher-participant relationship built on trust.

The definition and Vulnerability Assessment Scale (Annexure IV: Guidelines for Protecting a Research Participant who is Vulnerable) will be offered to RECs in South Africa and further afield for use in advancing the most appropriate and ethical approach towards vulnerable participants in health research.

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Annexure 1: Research Ethics Committee Waiver

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: Medical School Room 10M07, 10th Floor. Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265

Ref: W-AW-140909-1 09/09/2014

TO WHOM IT MAY CONCERN:

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).

Investigator: Professor A Dhai

Project title: **A STUDY OF VULNERABILITY IN HEALTH RESEARCH.**

Reason: This study involves a combination of normative, metaethical, historical and legal inquiry and did not involve empirical research. As such this research does not involve any human or animal participants.

Professor Angela Woodiwiss

Co-Chair: Human Research Ethics Committee (Medical)

Copy: Zanele Ndlovu, Research Office, Senate House, Wits

Annexure 2: The Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. 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.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Annexure 3: Circular of the Reich Minister of the Interior Concerning Guidelines for New Therapy and Human Experimentation, 28 February 1931.

(As Reprinted in History and Theory of Human Experimentation. Eds Schmidt U, Frewer A. Franz Steiner Verlag. Germany (2007): 333-335)

The Reich Health-Council (Reichsgesundheitsrat) has set great store in ensuring that all physicians receive information with regard to the following Guidelines. The Council has agreed that all physicians in open and closed healthcare institutions should sign a commitment to these guidelines when entering their employment.

Final Draft of Guidelines for New Therapy and Human Experimentation

1. Medical science, if it is not to come to a standstill, cannot refrain from introducing in suitable cases New Therapy using as yet insufficiently tested agents and methods. Also, medical science cannot dispense completely with Human Experimentation. Otherwise, progress in diagnosis, therapy, and prevention of disease would be hindered or even rendered impossible.

   The special rights to be granted to the physician under these new guidelines must be balanced by the special duty of the physician to be aware of the grave responsibility which he bears for the life and health of each individual undergoing New Therapy or Human Experimentation.
2. The term *New Therapy* used in these Guidelines defines therapeutic experimentation and modes of treatment of humans which serve the process of healing, i.e., pursuing in specific individual cases the recognition, healing or prevention of an illness or suffering, or the removal of a bodily defect, even though the effects and consequences of the therapy cannot yet be adequately determined on the basis of available knowledge.
3. The term *Human Experimentation*, as defined in the Guidelines, means operations and modes of treatment on humans carried out for research purposes which are non-therapeutic; it includes the side-effects and consequences which cannot yet be adequately determined on the basis of available knowledge.
4. Any New Therapy must be in accord with the principles of medical ethics and the rules of the medical arts and sciences, both in its design and in its realization.

   A consideration and calculation of possible harms must be undertaken to determine whether they stand in a suitable relationship to expected benefits.

   New Therapy may only be initiated after being tested in animal experimentation, where this is at all possible.
5. New Therapy may only be applied if consent or proxy consent has been given in a clear and undebatable manner following earlier appropriate information.

   New Therapy may only be introduced without consent if it is urgently required, and cannot be postponed because of a need to save life or prevent severe

damage to health, and if prior consent could not be obtained owing to special circumstances.

6. Introduction of New Therapy in the treatment of children and minors under eighteen requires especially careful examination.
7. Medical ethics rejects any exploitation of social and economic need in conducting New Therapy.
8. New Therapy using living micro-organisms requires heightened caution, especially in the case of live pathogens. Such therapy may only be considered permissible if a relative degree of harmlessness in the procedure can be assumed, and if the achievement of equal benefits by other means cannot be expected under any given circumstances.
9. In medical ethics, polyclinics, hospitals or other health care institutions, New Therapy may only be conducted by the chief physician himself or, at his specific request and with his full responsibility, by another physician.
10. A written report on any new therapy is required, containing information on therapy design, its justification and execution. Such a report shall state especially that the subject, or his legal representative, has been adequately informed and has given consent. If New Therapy is applied without consent, according to (5.2), the report must clearly outline these pre-conditions.
11. Publication of results of New Therapy must respect the patient's dignity and the commandments of humanity.
12. Numbers 1 through 11 of these Guidelines are equally applicable to Human Experimentation (Art.3). In addition, the following requirements for such experimentations apply:
    a) Without consent, non-therapeutic research is under no circumstances permissible.
    b) Any human experimentation which could as well be carried out in animal experimentation is not permissible. Only after all basic information has been obtained, should Human Experimentation begin. This information should first be obtained by means of scientific biological or laboratory research and animal experimentation for reasons of clarification and safety. Given these presuppositions, unfounded or random Human Experimentation is impermissible.
    c) Experimentation with children or minors is impermissible if it endangers the child or minor in the slightest degree.
    d) Experimentation with dying persons conflicts with the principles of medical ethics and therefore is impermissible.
13. Assuming that, in accordance with these Guidelines physicians and, in particular, responsible directors in charge of medical institutions will be guided by a strong sense of responsibility toward the patients entrusted to them, it also is to be hoped that they will maintain a readiness responsibly to seek relief, improvement,

protection or cure for the patient along new paths, when the accepted and actual state of medical science, according to their medical knowledge, no longer seems adequate.

14. In academic teaching, already, every opportunity should be used to stress the special duties of a physician undertaking New Therapy or Human Experimentation; these special responsibilities also apply to the publication of the results of New Therapy and Human Experimentation.

Annexure 4: Guidelines for Protecting a Research Participant who is Vulnerable

RECs make the decisions on how participants in research are to be protected but the actual implementation of the safeguards is the responsibility of the professionals that conduct research. This is why the researcher-participant relationship in which the moral status of the participant is respected and her / his human dignity is upheld is so important. The Definition of vulnerability and the Vulnerability Assessment Scale below, together with the example of clustering of identifiable wrongs to specific contexts could aid RECs in the review process such that they would be able to plan directed protections for the potential research participants. In this way, both RECs and research participants benefit from the use of these tools. The Scale offered will require RECs to execute focussed and comprehensive wrongs assessments from the protocol to include the scientific aspects, social context and moral implications of the study and in so doing guide the researcher on how potential participants ought to be protected based on their individual needs and capabilities.

A Practical Working Definition of Vulnerability and its Application in Health Research

> *"Vulnerability is an inability or decreased ability of a research participant to sufficiently safeguard her/his own needs and interests resulting in her/him being at an increased likelihood of being identifiably wronged in varying degrees if special safeguards to protect her/him are not invoked by the Research Ethics Committee"*

The baseline protective safeguards essential to this definition are the basic protections for all participants that are enrolled in research. This definition is quite specific as to what the criteria are for a research participant to be vulnerable takes into consideration degrees of abilities or inabilities to protect oneself in research. The REC is mandated to develop focussed safeguards to protect participants against identifiable wrongs.

A simple but focussed and routinely applied "Vulnerability Assessment" Scale which asks relevant questions in sequential order is a necessary complement to the definition in determining vulnerability.

The "Vulnerability Assessment" Scale

This scale assists RECs implement the above definition of vulnerability during the review of protocols. Vulnerabilities are firmly linked to correlative responsibilities. The more vulnerable the person, the greater is the agent's responsibility to protect the individual's interests. Vulnerability is seen as a matter of degree dependant on the number of needs arising in the researcher-participant relationship and the amount of assistance that would be required to meet those needs. To optimise protections, RECs would need to answer the questions posed in sequential order.

1. Has the essential minimum standard afforded all participants in light of universal vulnerability been met?
2. Has the baseline for respecting human dignity been met?
3. Will any participant be used in the research as a means to an ends she/he may not endorse?
4. Will all the research participants in this study be able to safeguard their own needs and interests?
5. If no, is there an increased likelihood of any of them being identifiably wronged as a result of their participation in the study?
6. Is there an increased likelihood of any participant being identifiably wronged to a greater degree than other participants?
7. Have the identifiable wrongs been recognised?

8. Have special safeguards been developed to protect those participants in need of such safeguards?

The REC would also be assisted by developing clusters of pertinent easily identifiable wrongs. These could be categorised for ease of reference in the example below:

IDENTIFIABLE WRONGS: Clusters and Examples

Cluster of Wrongs	**Examples**
Physical Wrongs	Medical physical risks outweighing benefits, non-medical physical wrongs, e.g., pain, discomfort
Consent Wrongs	Exploitation because of, e.g., : Lack of capacity (e.g., extremes of age, mental disorders, anxiety, emergency) Understanding barriers (e.g., language, low levels of literacy) Diminished freedom or voluntariness (e.g., manipulation, coercion)
Social Wrongs	Confidentiality breach / inappropriate dissemination of results of research (e.g., stigmatisation, stereotyping, discrimination, physical / gender-based violence, job loss, legal sanction)
Psychological Wrongs	Anxiety, stress, emotional suffering (e.g., could be triggered by research tool, e.g., sensitive questions in interview schedule)
Justice Wrongs	no post study access to proven intervention, inequitable standards of care usually with international research, no provision for compensation for research-related injuries.