Clinical trials in South Africa, key ethical issues in the process of realising a valid informed consent.

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Dedication

To my sons Joshua and Luke for questioning why I needed to study more as they thought adults knew everything. If they only knew as Socrates once said;

"The only true wisdom is in knowing you know nothing."
Socrates

My work is dedicated to the thousands of clinical trial participants who are enrolled in clinical trials in South Africa. Who are either knowingly are unknowingly involve themselves in research processes they often do not understand.

Abstract

A valid Informed consent (IC) is the cornerstone of good research ethics practice from clinical trials to social science research. My research report will explore the idea of IC from its first known beginnings to its many facets as now recognised in the literature. One of my focuses is on the Nuremberg Code which I consider to still carry the fundamental ethical ideals concerning research involving human participants. As I identify the many obstacles to achieving a valid informed consent, it will be clear that in the context of a developing or 'low income' country, that a valid informed consent should be taken very seriously as it involves much more than just a research participant putting his or her signature on a piece of paper. In research, particularly in clinical trials where the scientific or clinical impact is potentially very great and in which much money has been invested, researchers should be aware that often their participants hold different views of what participation involves. For example, some may view participation in a clinical trial as a means of obtaining medical treatment they would otherwise not receive. One of the many barriers to realizing a valid informed consent that I consider is the problem of the increasing length of informed consent forms. This, I will suggest represents a shift from the ethical ideal of protecting human participants in research.

Rather, it seems to represent as a protection from possible liability on the part of the industry-sponsor. In my research report, I also identify particular South African legislation and research ethics guidelines which should guide good research practice in South Africa. I point out that there are many laws, research ethics guidelines and regulations that have been implemented due to the atrocities of the past (and present) regarding using people in experimentation and the gross human right violations that accompanied these. Yet, in spite of these, I identify the many barriers that are present in obtaining a valid informed consent as well as the recognition that it is a *process.* A valid informed consent has at its ethical grounding respect for the dignity and worth of every human being. This research report hopes to add to the discussion concerning the importance of a valid informed consent in research involving human participants.

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Acronyms:

CIOMS……..Council for International and Medical Science

DH……Declaration of Helsinki

EU……European Union

FDA……Food and Drug administration

GCP……Good Clinical Practise

HPCSA……..Health Professional Council of South Africa

HPTN……HIV prevention trials network

IC……Informed Consent

ICH…… ……International Conference of Harmonisation

MRC……Medical Research Council

NC……Nuremberg Code

NCB……Nuffield Code of Bioethics

OHRP……Office of Human research Protection

PI……Principal Investigator

US……United States

WHO……World Health Organisation

Chapter 1. Before 'Consent'

1.1 Ancient clinical research and the quest for scientific knowledge

While conjecture, probably it is most likely that some humans were involved in different types of what we call 'research'[1] from the time of hominoid evolution. This is due to our species' intelligence and with it, curiosity.

One of the earliest examples of this comes from the works of Aristotle. At that time, what we now term 'philosophy' and 'science' were not separated. To try to understand 'how things work' Aristotle, in the fourth century B.C.E., not only observed animals, fish and insects, but also dissected many of them (Berkley 2002). In keeping with the norms of the era, at least as far as is known, the human body was not subject to the rigors of Aristotle's early zoological experiments (French 1978). Yet, it was to come.

According to Von Staten (1992), the history of science reveals the introduction of systematic human dissection and probably systematic vivisectory experimentation performed on condemned criminals by the physician Herophilus of Chalcedon in Alexandria in the early third century B.C.E. These 'criminals' were given to

[1] In this research report I will use the term 'research' to refer to medical or scientific research which includes clinical drug trails.

the philosopher-scientists when they visited Alexandria, the seat of learning, from the king. Von Staten (ibid) discusses this and includes writings of Celsus who, as a first-century Latin encyclopaedist are a great source of ancient Greek medical history. According to this record, the "Rationalists" justified human dissection and vivisection by claiming that both "hidden" and "evident" causes of diseases must be known, as must the "natural activities" of the internal parts, if one is to treat patients effectively. Celsus writes:

> *Moreover, since both pains and various types of diseases arise in the internal parts, they [the "Rationalists"] think that no one who is ignorant of these parts can apply remedies to them. It therefore is necessary to dissect the bodies of the dead and to examine their viscera and intestines. Herophilus and Erasistratus, they say, did this in the best way by far when they cut open people who were alive, criminals out of prison, received from kings. And while breath still remained in these criminals, they inspected those parts which nature previously had concealed, also their position, colour, shape, size, arrangement, hardness, softness, smoothness, connection, and the projections and depressions of each, and whether anything is inserted into another thing or receives a part of another into itself. For, they say, when pain occurs internally, it*

> *is impossible for one who has not learned in which part each internal organ or intestine lies, to know what hurts the patient. Nor can that part which is ill be treated by one who does not know what it is. And when a person's viscera are exposed by a wound, one who does not know the colour of an [internal] part in its healthy state, cannot recognize which part is intact and which damaged; thus he cannot even come to the aid of the damaged parts. External remedies also can be applied more suitably by people acquainted with the positions, shapes, and size of the internal parts ... Nor is it cruel, as most people maintain, that remedies for innocent people of all times should be sought in the sacrifice of people guilty of crimes, and of only a few such people at that.*

In application to an ethical theory, it could be said that Celsus recorded one of the first examples of utilitarian theory as applied to research on humans: ‘an act is right if it produces the greatest amount of happiness (good / pleasure) for the greatest number of people’ (Mill [1869] 1962). Importantly, this systematic dissection practice of humans was, according to Von Staten (1992), only practiced by the Greeks for about one generation. This is because the norms of society tended to prohibit the use of the human alive or dead, even in the quest for scientific knowledge.

Records of animal dissection appear in the influential works of Galen (129 - 210 AD), perhaps best known for his research and discourses on physiology and science. He developed new theories related to human body functioning and diseases based on his animal studies (Szasz, Knoff, and Hollender 1958: 523). Galen's medical research made him the earliest most notable anatomist and a great authority whose work influenced and dominated the western medicine and science for about 1500 years. Unfortunately, many of his observations were proven to be incorrect because they were based upon animal models which he had 'adapted' to the human form.

Brain (1986), who translated Galen's works, provides some evidence that Galen believed that Hippocrates practiced venesection freely when treating various diseases. This is because the Hippocratic physicians practiced blood-letting, emetics and purges as therapies to restore the body's four humours, as was the theoretical basis of their medical practice.

Advances in medical and scientific research continued to rapidly expand. The concept of dissection, or research justified on acquiring knowledge about the structure of human body was revised again only during the 14-15th centuries.

1.2 The use of the deceased human body for furthering the development of science and education

Born in 1514, Andreas Vesalius is considered as the founder of human anatomy. Before Vesalius, human anatomy was not learned by studying or dissecting human bodies. As such, much of the knowledge contributed by Galen long before, was incorrect. Vesalius (1514-1564) was the first to challenge Galen's theories and carried out dissection to closely observe the inner structure and construction of the human body. He also was one of the first medical students to dissect a cadaver and continued with cadaver use even as a professor (Rath and Garg 2006: 330). Based on direct observation, Vesalius discovered, recorded and published his works. He marked a new direction in scientific research and observation. His most famous work *De Humani Corporis Fabrica* (On the Fabric of the Human Body) revolutionised the science of medicine and laid foundation for modern human anatomy.

Since the Renaissance, doctors have been the force impelling the necessity for scientific research. This is understandable as, from at least a historical perspective, the physician was usually the patient's only attendant. As the betterment of the patient was mutually desirable, it is reasonable to assume that a physician would be interested in learning more e.g. concerning the disease, aspects of a particular disease process, possible cures and so forth. The works of such doctor-scientists usually involved, in keeping with the historical-social periods, studies by

a single individual or a small group of individuals who shared their research with others having the same or similar interests.

The doctors and scientists involved as well as the institutions of medical learning actively encouraged research and experimentation. This not only contributed to a greater scientific knowledge *per se*, but also resulted in the development of new medical equipment such as thermometers and microscopes, formulas and medicines. Prior norms considering all human bodies as sacrosanct were outweighed in the West as the idea of rational science began to take root. For example, the procurement of cadavers, in earlier times obtained from grave robbers and mortuaries, was legitimised by England's Anatomy Act of 1832 which enabled unclaimed bodies to be used for teaching and research in academic institutions. It was, though the Barber-surgeons who served as 'technicians'. They demonstrated various anatomical structures at command of the professors (Rath and Garg 2006: 330). [2]

From the 1000s to the 1700s, in keeping with the growth of medicine and science, the major sites for medical research went from individual practice or laboratory to specialized clinics to hospitals. Hospitals, particularly in the 1700s were places where

[2] Perhaps this might mean that the use of a human body, although legitimised in the name of education, still bore some vestiges of the sacred that the professors did not want to profane or that distinctions of medical rank were evolving along with the practice of medicine.

doctors could test the effects of e.g. different drugs or treatment procedures on a large number of 'captive' patients.

1.3 The use of human subjects for furthering the development of science and education

There are two positive aspects of early research which are important to note: 1) Generally, the existing ethos carried over from the classic doctor-patient relationship extended to the doctor/researcher-subject; and 2) there is evidence that in general, early doctor-researchers had the requisite scientific knowledge needed for their research. Negative aspects are present as well and include 1) The existing ethos carried over from the classic doctor-patient relationship extended to the doctor/researcher-subject inasmuch as the research subject was of e.g. the same ethnic, cultural, political religious, or identifiable class as that of the researcher, and 2) that the researcher could in some way justify his or her research in the 'name of science'.

Some examples of the use of humans as the subjects of research experiments were recorded during vaccination trials in the 1700s. [3] For example, although confident of previous results obtained through animal trials, Louis Pasteur "agonized over treating humans". He consented to treat a human only when he

[3] For example, John Hunter, an 18th-century surgeon and anatomist who put himself through a series of highly risky experiments, including taking various strengths of poison (*The Times* 2006).

was convinced that the death of his first test subject, the child Joseph Meister, "appeared inevitable" (Rothman1993). As an example of the need to build on prior knowledge, in this case the link of one infectious disease to another, Edward Jenner, heralded to be the father of the Smallpox vaccine, injected a healthy eight-year-old James Phillips first with cowpox then three months later with smallpox. His wisdom in the application of 'folk' knowledge – milk maids who developed cowpox from their contact with cow udders did not contract smallpox – served to protect millions from a disease that had scourged humans from antiquity (Barquet, and Domingo 1997).

In the United States of America (USA) from 1845 until 1849, J. Marion Sims, the "Father of Gynecology" performed multiple surgeries on enslaved African women most without the benefit of anaesthesia for the benefit of 'scientific knowledge concerning the female reproductive tract' (Avelsem 1985: 10). After suffering great pain, many lost their lives to infection. One woman endured 34 experimental operations for a prolapsed uterus (ibid: 12-13).

In this case, we can see connections to the example presented in the first section of this chapter both in perspectives and subjects: the "Rationalist" perspective and the subject's involved (criminals owned by the king and slaves owned by a master). In contrast, a few years later in 1865, French physiologist Claude

Bernard published an article titled "Introduction to the Study of Human Experimentation." In it, he stated:

> *Never perform an experiment which might be harmful to the patient even though highly advantageous to science or the health of others* (WL 2000).

In 1900, in the search for a Yellow Fever vaccine, Walter Reed injected 22 Spanish immigrant workers in Cuba with the agent for Yellow Fever paying them USA $100 if they survived and USA $200 if they contracted the disease. Walter Reed's well-known experiments, because they were carefully scrutinised - albeit after the fact - led to some advances in the protection of human subjects in research in the USA (Brady 1982). In the same year, the *Berlin Code of Ethics* was published by the Royal Prussian Minister of Religion, Education, and Medical Affairs. This Code of Ethics, now considered as the first code concerning human participation in research, set out to pledge that:

> ... *all medical interventions for other than diagnostic, healing, and immunization purposes, regardless of other legal or moral authorization are excluded under all circumstances if (1) the human subject is a minor or not competent due to other reasons; (2) the human subject has not given his unambiguous consent; (3) the consent is not preceded by a proper explanation of*

the possible negative consequences of the intervention (Vollmann and Winau 1996: 1446).

From these examples, we can see that there were both positive and negative approaches towards the treatment of humans involved research. Overall, the pretext of using medical experimentation for the advancement of scientific and medical knowledge has been and continues to be used as a justification for many research atrocities (Anspach 1993).[4] The idea of consent for participants in clinical research was considered by some but rarely formalised.

1.4 Concluding remarks

The few examples I have shown in this chapter come from various times and places in history. I have shown that during ancient times, with at least one know exception, the human and his or her body were considered 'taboo' as far as clinical research was concerned. Then later, as I showed, the development of science, medicine and technology, took precedence and there were both positive and negative views on research practices. In the next chapter, I will turn to the document which most significantly introduced the notion of consent for human participants in research, The *Nuremberg Code*.

[4] It is important to note that information concerning the positive and negative uses of humans in research comes mainly from open societies. In closed societies it is not possible to ascertain other types and places of research misconduct.

Chapter 2. The Idea of Consent: a Brief Background to Its Conception and the *Nuremberg Code*.

2.1 A brief background to the Nuremberg Code

To understand the importance of the *Nuremberg Code*, it is essential to provide a brief background into the circumstances that preceded its conception.

The eugenics movement in Germany was influenced by a number of factors including economic crisis, radical National Socialism, Nazi totalitarianism, and the medical profession's willing participation and attraction to Nazism for financial and ideological reasons (Sofair and Kaldjian 1999: 435).

It is agreed that for public health purposes, sometimes citizens must temporarily forego individual rights in the name of the public good. In Nazi Germany, the idea of *Volksgesundheit* or public health was so cleverly orchestrated by the Nazis that German citizens believed that the health of the State (viewed as body consisting of all of its citizens) was sick (Annas and Grodin1992). Viewed in this way, it was easy to negate the idea of an individual (Ridley 1998: 44-47).

Doctors as well as academics, many of whom were proponents of "racial hygiene," or eugenics, served to legitimate and put into action Nazi policies which had as their goal the ‘cleansing’ of their society of people considered as biologic and genetic threats to the health of the State (Micklos and Carlson 2000:153). In the name of ‘racial-hygiene’, measures began in Germany with the mass sterilization and murder of the ‘biologically and genetically diseased’. Not only ordinary citizens,

but doctors and medical researchers capitulated into this belief as well and began to view themselves as 'guides to a healthy, moral, industrious Germany' (Weindling 1989: 12).

As these ideas became rooted in the German psyche, particular groups of people were singled out as the 'causes' of the country's ailments. These groups were the Jewish people and the Roma ('gypsies). It was particularly the Jews who bore the brunt of the propaganda machines as they were labelled as 'vermin', 'less than human' and the cause of all the woes which the country faced. The Nazi racial hygiene programme took a major turn. It moved from controlling reproduction and marriage to the mass murder of persons regarded as genetic threats to the health of the State.[5] Lethal doses of drugs, starvation, and gassing were the methods of killing, administered by doctors and nurses (Friedlander 1995; Proctor 1998). Stringent laws were enacted which forbade Jews from attending schools and universities, their properties were confiscated, and they were subjected to all forms of abuse and humiliation. Part of Hitler's plan was to permanently annihilate European Jewry (Burleigh 1994). During the Nazi era in Germany, eugenics prompted the sterilisation of several hundred thousand people then helped lead to anti-Semitic programmes of euthanasia and ultimately to the death camps where over 6 million people, mainly European

[5] Proctor (1998) estimates that between 1939 and 1945, about 200,000 Germans, ranging from children with Down's syndrome and other birth defects, to the blind, to elderly psychiatric patients judged to be "incurably ill" were killed in euthanasia program.

Jews perished. Although the Berlin Code of Ethics stood as a legal document concerning research involving humans throughout the Nazi regime Vollman and Winau (1996: 1447) write:

> *Though no other nation seems to have had such ethically and legally advanced regulations at the time, these did not prevent crimes against humanity ...*

The Nazis lost the war against the Soviet Union, America and Britain. Based on evidence of the Nazi's deliberate, sustained and systematic intent – through starvation, work camps, torture and human experimentation to eradicate all Jews (as well as others considered racially inferior or deviant) the trial of the Nazi doctors (known as the *United States of America vs. Karl Brandt et al.*, the Medical Case, or the Nazi Doctors Case) began in Nuremberg, Germany on December 9, 1946 (Katz 1972).

2.2 The 'Nazi Doctors'

In 1946 and 1947, the American Military Tribunal at Nuremberg tried 20 German physicians and 3 lay assistants for medical experiments using the prisoners of Nazi concentration camps. Twelve experiments were singled out for prosecution as war crimes. Extensive evidence was presented for each of them during the trial of the 'Nazi doctors' (Annas and Grodin 1992). These experiments, as described by the American Holocaust Museum (2000), included: 1) High-Altitude or Low Pressure

Experiments, [6] ; 2) Freezing Experiments,[7] ; 3) Malaria Experiments[8] ; 4) Mustard Gas Experiments [9] ; 5) Experiments with Drugs, Muscle and Nerve Regeneration, and Bone Transplantation[10] ; 6) Seawater Experiments[11]; 7) Epidemic Jaundice Experiments[12]; 8) Sterilization Experiments[13]; 9)

[6] From the US Holocaust Museum (2006) the following is reported:' Inmates of the Dachau concentration camp in 1942 were locked in an airtight pressure chamber and the pressure was altered to simulate atmospheric conditions at very high altitude without oxygen. In the words of the official report on this experiment, performed on a 37-year-old Jew: "After 4 minutes the experimental subject began to perspire, and wiggle his head; after five minutes cramps occurred; between 6 and 10 minutes breathing increased in speed and the experimental subject became unconscious; from 11 to 30 minutes breathing slowed down to three breathes per minutes, finally stopping altogether. Severest cyanosis developed in between and foam appeared at the mouth. About one-half hour after breathing had stopped, dissection was started´ the report then provides a detailed description of the autopsy.

[7] In experiments conducted in Dachau in 1942 and 1943 to learn how to re-warm German pilots downed in the North Sea, victims were forced to stand naked in freezing weather for nine to fourteen hours or in a tank of ice water for three hours. The official Nazi report notes, "The experimental subjects died invariably, despite all attempts at resuscitation." In October 1942, one of the defendants presented a paper, "Warming Up after Freezing to the Danger Point," based on these experiments to a conference held in Nuremberg on the prevention and treatment of freezing (Angell 1990: 1462-1464).

[8] Over 1,200 Dachau inmates were infected by mosquitoes or injected from the glands of mosquitoes and then treated with various drugs. As a consequence, thirty inmates died from malaria, and 300 to 400 more died from complications and overdoses of some of the drugs.

[9] Victims in Sachsenhausen, Natzweiller, and other camps were deliberately inflicted with wounds. These were subsequently infected by mustard gas, or were injected with the gas, or were forced to ingest it by inhaling or drinking. Nazi reports of these experiments in 1939 describe the swelling and intense pain the victims suffered.

[10] Chief Prosecutor Telford Taylor described these experiments as "perhaps the most barbaric of all"(ibid). They were performed primarily on women in Ravensbrück, and consisted in inflicting wounds to simulate battle injuries, into which a gangrene-producing culture was introduced to cause severe infections. Some victims were then treated with sulfanilamide, others with nothing. Bone transplantation was performed on other subjects. In Buchanwald, victims—usually Polish Catholic priests—were injured and then treated with polygal or sulfanilamide. Many died from these tests or from untreated blood poisoning and other infections.

[11] Conducted in Dachau in 1944, these experiments involved feeding the victims shipwreck rations. Some were given no water, others received ordinary seawater, or seawater in which the salty taste was concealed, or seawater that had been treated to remove the salt. The tests were performed primarily on Roma (Gypsies). The test subjects suffered deliriums and convulsions, and some died.

[12] Eight Jews of the Polish resistance were selected for this experiment in Sachsenhauser and Natzweiler camps. The experiment began in an effort to find an inoculation against epidemic jaundice and resulted in the torture and death of the subjects.

Typhus and Other Virus Experiments[14]; 10) Poison Experiments[15] ; 11) Incendiary Bomb Experiments[16];and12) Anthropology Experiments[17].

The trial of the Nazi doctors was officially named '*Case No. 1 of the Military Tribunal I, as Constituted on October 25, 1945'* (NC 1949). Telford Taylor, the Chief Counsel for the prosecution, charged the defendants with,

> *... murder, tortures, and other atrocities committed in the name of medical science* (Katz 1972).

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[13] These experiments, conducted on victims in Auschwitz, Ravensbrück, and other camps, were part of Nazi planning for genocide by the most efficient, scientific, and least conspicuous methods. The Nazi's goal was to eliminate Russians, Poles, Gypsies, Jews, and other undesirable populations by using medicinal rather than surgical sterilization, primarily through injection of caladium sequinum and other substances. In addition, gland transplantation was performed on fourteen inmates of Buchanwald, two of whom died. Others were subjected to sterilization by X-rays and castration. The aim was to prevent reproduction among Jews who were preserved from extermination in order to perform labour (Mitscherlich and Mielke 1992).

[14] For nearly five years, until the end of the war, medical experiments were performed on inmates of Buchanwald and Natzweiler to test vaccines for typhus, yellow fever, smallpox, paratyphoid A and B, cholera, and diphtheria. For the typhus experiments, hundreds of prisoners were infected with typhus. Some of these had received an anti-typhus vaccine to be tested; the others were used as the control group or simply infected to provide a supply of the virus for further testing (Weindling 2001).

[15]Russian inmates of Buchanwald were injected with poisons, sometimes administered through poison bullets. The tests were designed to permit the Nazi doctors to observe the victims' reactions to the poison up to the point of death.

[16]These experiments took place in Buchanwald in 1943. Five inmates were burned with phosphorous material taken from an English bomb and were severely injured as a result

[17] Two of the defendants in the Doctors' Trial were obsessed with racial theories and had collected skulls representative of "all races and peoples," but lacked those of the "Jewish race." In order to complete the collection, they had requested that Jewish victims be photographed and that "anthropological measurements" of their skulls be taken while they still lived. The victims were then killed and beheaded, and their heads were brought to the laboratory in a sealed tin filled with conserving fluid. In requesting this service from the *Wehrmacht,* one of the defendants had explained that he wanted skulls to "represent the prototype of the repulsive but characteristic subhuman." Prosecutor Taylor called these experiments "perhaps the most utterly repulsive charges in the entire indictment "(ibid).

There were four counts covered in his indictment: 1) Conspiracy to commit war crimes against humanity: The ordering, planning, and organization of the war crimes and crimes against humanity charged in counts two and three, 2) War crimes, 3) Crimes against humanity (Charged against all defendants.), and 4) Membership in a criminal organization (the SS).

The judgment was returned on August 19, 1947, and sentencing was pronounced on the following day.[18] Of the twenty-three defendants, seven were found guilty of war crimes and crimes against humanity and sentenced to death. Four of these were doctors (Weindling 2001: 37-71). Five other defendants were sentenced to life imprisonment. Seven were found not guilty and one was found guilty of the charge of belonging to the SS but not of crimes relating to medical experimentation. Thirty-one lesser officials were put on trial and found guilty, of whom twenty-two were sentenced to death (Mitscherlich 1992).

According to Katz (1972), Taylor gave the opening statement for the prosecution noting that,

> *... most of [the defendants] are trained physicians, and some of them are distinguished scientists ...*

The idea that doctors and scientists, considered not only as intellectuals but as the holder's of society's trust, would

[18] The tribunal met 139 times, heard 85 witnesses, and examined 1,471 documents (Annas and Grodin 1992).

wilfully be involved in obscene human experimentation tempered the idea of medicine and science as healing arts. Yet from the Tribunal of War Crimes there was a section called 'permissible medical experiments'. This section served to be the foundation of all research ethics principles, rules and guidelines which were to follow. It introduced globally the rule that all humans involved in research must first give 'consent'. It is known as The *Nuremberg Code*.

2.3 The Nuremberg Code

The tribunal judges enumerated ten principles[19] that

> *"must be observed in order to satisfy moral, ethical, and legal concepts."*

The principles have come to be known as the "*Nuremberg Code*," and have had far-reaching significance for medical and scientific research. The Code begins with the core principle that "the voluntary consent of the human subject is absolutely essential ..."

> *The voluntary consent of the human subject is absolutely essential. This means that the person involved should have the legal capacity to give consent; should be so situated as to exercise free power of choice, without the intervention of any*

[19] A Katz (1978) note that the judges' intention was to specify only legal requirements as they considered to dictate to the field of medicine was beyond their frame of reference.

> *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 subject matter involved so as to enable him, to make an understanding and enlightened decision. This latter element requires that before acceptance of an affirmative decision by the experimental subject there should be known to him the nature, duration and purpose of the experiment, the methods 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* (NC 1949: 181).

Other rules state that any experiment involving a human subject should be for the good of society; it should build on the results of animal experimentation. It clearly states that scientific knowledge and experimental research should

> *... avoid all unnecessary physical and mental suffering and injury* (ibid: 182).

It declares that there should be no "*a priori* reason to believe that death or disabling injury will occur" (with the possible exception of the experimental physicians serving as subject) (ibid). Notable also is that the *Nuremberg Code* states that the degree of risk

should be proportionate to the humanitarian gain and that adequate precautions should be taken "to protect the experimental subject against even remote possibilities of injury, disability, or death" (ibid). The *Nuremberg Code* also says that only scientifically qualified persons should conduct experiments and that research subjects should be able to halt the experiment "if he has reached the physical or mental state where continuation of the experiments seems to him to be impossible" (ibid).

In the Code, responsibility is also placed on the principal investigator or lead scientist in that he or she should be prepared to end the experiment at any stage "if he has probable 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" (ibid).

The *Nuremberg Code* was considered as the first official document which sets forth rules or guidelines for the treatment of research subjects (or participants). As noted in the first chapter, this is not the case. Nonetheless, the great importance of the *Nuremberg Code* is twofold:

1) It provides a clear articulation of the rules which should govern good research practice and introduced globally, the idea

that humans prior to their involvement in research must knowledgeably and freely give their consent.

2) Understanding the context that gave birth to its origin should provide researchers, scientists and medical professionals with a greater understanding of the type of forces that can influence research practice and to be mindful of them. As Myers (1999: 284) puts it: 'What this indicates is that the Holocaust does not belong only to history but also to possibility. If we cannot affect its outcome, we can still do something about its meaning. Events mean nothing in themselves; they must be interpreted. But what this also indicates is that meaning arises from responsibility. The counterfactual possibility of doing something appropriate about the Holocaust is what creates our responsibility to it, and if what we want is to discover its meaning-that is, to interpret the Holocaust-then our interpretation must be shaped and guided by our responsibility.'

The responsibility of researchers is to ensure that their subjects or participants in scientific research are protected against harm. One of the ways in which this may be achieved is through the process of ensuring that a valid informed consent takes place before the commencement of research (Kaplan 1999: 43). At first glance, might appear to be straight-forward, as I will show in the next chapter, this is not the case.

Chapter 3 Towards a Valid Informed Consent

3.1 Beecher's admonition

In 1966, Henry Beecher, a Harvard anaesthesiologist, authored an exposé of numerous unethical experiments that had been published in prominent medical journals. According to Perlman (2004: 39-42), his article had major impact on the development

of new regulations.[20] Beecher (1996) did not furnish names or references to the research. His aim was not to encourage prosecution but rather to increase awareness of the broader ethical problems in human experimentation. He wanted to heighten awareness that unethical practises in the US were similar to those of Nazi Germany. Beecher (1966:1360) concluded making the following points:

- *Unethical treatment was not confined to the barbarism of the Nazis;*
- *Informed consent is a goal. It is something we may never be able to achieve, but we should strive for it;*
- *It is not enough to mention that consent was obtained; subjects must be informed and understand the risk;*
- *There should be a second safeguard: an intelligent informed, conscientious compassionate investigator.*

Beecher's important article was in keeping with the times. In clinical research and medical practice, the idea of informed

[20] One of these was the Belmont Report written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report discusses three key ethical principles and their application to the conduct of research (informed consent, assessment of risks and benefits, and selection of research subjects).

consent was part of the response to the paternalistic approach in the doctor-patient which was the manner of medical practice in most Western countries until around the 1970s. Recognising that there was a 'wrongful imbalance' in the doctor-patient relationship and researcher-participant relationship, there was a concerted effort made to change this (Faden 1996: 356). The idea was to give moral authority to patients and research participants to take part in medical decision-making by focussing on the idea of respect for persons. The way in which this was enacted was through the vehicle of informed consent (ibid: 358).

3.2 Components of a valid informed consent

Lindegger (2000:131-137) considers informed consent as incorporating four essential components:

1) *Disclosure* about all relevant information about the research;

2) *Comprehension* of the prospective participant of this information to make an informed decision;

3) *Freedom* from all coercion of the prospective participant; and

4) *Explicit and formal consent* by the participant usually in written form.[21]

[21] Differing, the Nuffield Council on Bioethics (2002) states verbal consent is acceptable if written consent is inappropriate. The Nuffield Council also recommends adopting the term "genuine consent" as opposed to "Informed consent". This is because it would make more sense in cases when the participant is illiterate and consent cannot be supported by a written document. While one may understand their motive, there may be some global confusion if the term "informed consent" is changed. Concerning the requirements for informed consent, the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*

In clinical research, as in all forms of research involving humans, basic information given during the consent process generally encompass major issues such as the nature of the research, the anticipated risks and benefits, possible alternatives, and the choice to withdraw at any time without prejudice (see major research ethics guidelines e.g. *Declaration of Helsinki*, the *Belmont Report* and *CIOMS*). While informational issues are required, there are other factors which are important to consider when attempting realising a valid informed consent. For example, ensuring that the participant receives truthful Information, has the capacity to understand and to make a decision, and that he or she freely chooses (voluntariness) to partake or not in scientific research are important.

When respect for persons is held as the primary ethos in the valid informed consent process, the researcher should consider that to be capable of making a decision includes the ability to communicate, understand, logically decipher information, and to appreciate within the circumstance of one's life (Appelbaum and Grisso 1988; Roberts 1998: 99-110).

(published in 1993, and since revised, by the Council for International Organizations of Medical Science) state: "The investigator must obtain the voluntary, informed consent of the prospective subject [or legally authorized representative]. . . . Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee."

The welfare of the participant should be the major responsibility of the researcher. In the next section, I outline their duties.

3.3 Researcher's responsibilities

The *Nuremberg Code* provided the descriptive characteristics of a free and voluntary decision. Later, the USA's *Belmont Report* states that a freely-taken or voluntary decision is one that is "free of coercion and undue influence"(BR 1975). 'Coercion' and 'undue influence' are defined in the *Belmont Report* as follows.

> *[Coercion is] ... an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence ...occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance.*

On the part of the researcher or principal investigator (PI), he or she must ensure that the participant is informed of and understands the following elements:

- The purposes or aims of the study;
- The study's procedures or interventions;
- The reasonably expected benefits to the participant, the community or society, and/or scientific knowledge;

- Any risks, discomforts, and inconveniences that the participant may expect;
- The way in which confidentiality of research records and information about individual participants is assured;
- The participant's right to refuse to participate and right to withdraw at any time without prejudice;
- The expected duration of the research;
- Any alternatives to study participation (e.g. any alternative treatments that may be available);
- Any treatment and/or compensation that will be provided in the event of study-related injury;
- The researcher's responsibility, if any, to provide *medical* care;
- The name of person and their contact details concerning the reporting of any ethical concerns, questions or research-related injury or illness;
- The conditions, if any, under which the researcher or principal investigator may ask the participant to leave the study;
- Any potential conflicts of interest;
- Whether/how biological specimens will be stored;
- Whether commercial products will be developed from stored specimens;
- How study results will be published/communicated to participants ; and

- Whether/how an intervention demonstrated to be effective will be made available to participants after the study.

Numerous national and international research ethics guidelines as well as legislations both support and sometimes require inclusion of these elements and set out the ethical imperatives concerning informed consent.[22] In spite of the clarity of terms, the available ideas for implementation and the ethical duty to realise a valid informed consent, research failings in this area continue.

In the European Union's *Report on Ethics, Research and Globalisation* (2007), the importance of communication in the process of obtaining a valid informed consent was also highlighted. Panel members from both 'North' and 'South' countries identified that in seeking a valid informed consent, if the information is given clearly, correctly and, most importantly, appropriately then communities both North and South can

[22] *The International Covenant on Civil and Political Rights* (international treaty became effective in 1976): "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation." *Declaration of Helsinki of the World Medical Association* (promulgated in 1964 and revised eight times since): "The physician should obtain the subject's freely-given informed consent, preferably in writing. . . . [But in clinical research] if the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to [an] independent committee." *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (published in 1993, and since revised, by the Council for International Organizations of Medical Science): "The investigator must obtain the voluntary, informed consent of the prospective subject [or legally authorized representative] ... Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee."

understand the research activity. Moreover, they pointed out that "the important factor in avoiding double standards in the process of informed free choice is to realise that the process is a continuous and interactive one, not simply requiring a signature on a document" (ibid). These ethical responsibilities fall under the researcher or PI's gambit.

To enhance understanding, it was also suggested that international or multinational research establish good practice guidelines which include thoughtful considerations of the factors which go into making a free choice, and that the delivery of the information to the proposed participant as well as ensuring that the process involve "patients' organisations and community groups" (EU Report 2007). Concerning the informed consent procedures, it was agreed that they must be "designed to protect the patient, rather than the researcher or the industrial sponsor" (ibid). It was emphasised that all documentation must be written in a lay-friendly language and must be designed to protect vulnerable and poorly educated patients.

If the investigator is primarily interested simply recruiting participants, rather than ensuring what is really in their best interests, then the process of obtaining a valid informed consent will be flawed and fails to meet ethical standards.

This is a special consideration in multinational research involving participants from the developing countries; the importance of understanding barriers e.g. cultural, religious and economic to a valid informed consent must be contextualized. Respecting an individual's local tradition and cultural values should be integrated into the informed consent process. Finally, while some research misconduct is based on greed or other human misconduct,[23] others may be due to a failure to understand and appreciate the complex dynamics that feed into the idea of receiving a valid informed consent. In the next chapter, I will overview some of these factors.

[23] From Resnik (2010) some of the following are examples of research misconduct: "1932-1972 The Tuskegee Syphilis Study, sponsored by the U.S. Department of Health. Studied the effects of untreated syphilis in 400 African American men. Researchers withheld treatment even when penicillin became widely available. Researchers did not tell the subjects that they were in an experiment. Most subjects who attended the Tuskegee clinic thought they were getting treatment for "bad blood." 1944-1980s: The U.S. government sponsors secret research on the effects of radiation on human beings. Subjects were not told that they were participated in the experiments. Experiments were conducted on cancer patients, pregnant women, and military personnel; 1956-1980
Saul Krugman, Joan Giles and other researchers conduct hepatitis experiments on mentally disabled children at The Willowbrook State School. They intentionally infected subjects with the disease and observed its natural progression. The experiments were approved by the New York Department of Health; 1997: In an article published in N. Engl. J. Med., Peter Lurie and Sidney Wolfe accuse the NIH, WHO, UN and CDC of designing unethical studies on the prevention of mother-child transmission of HIV in developing countries. The dispute spurs a re-examination of international research ethics codes; 2005: Seoul University research Woo Suk Hwang admits to fabricating data in two papers published in the journal Science. In the papers, Hwang claimed that he had used nuclear transfer techniques to develop patient-specific human embryonic stem cells."

Chapter 4 Some Essential Barriers and Components for Researchers to Consider Concerning a Valid Informed Consent

4.1 Competencies and comprehension

In 1988, Appelbaum and Grisso set out the requisite components for competence in informed consent decision-making. These included the abilities to communicate,

understand, appreciate, and reason. Their works have shaped subsequent thought concerning an individual's capacity to consent. Subsequent to this publication, others have adapted or refined their model. (Kass, et. al: 1996: 25-29; Thomasma, DA. 1996 Grisso and Appelbaum 1998; Nedopil, *et al.* 1999).

While defining works exist concerning the components of competence in informed consent such as those of Appelbaum and Grisso (1998), a problem remains in testing an individual's comprehension of the information provided (James 2004; Fitzgerald 2002; Ancke 2001). Despite the use of memory-checks and other recommendations many articles that indicate that research participants have not understood the information given, particularly in terms of personal implications (Ballard, *et al.* 2011: 12-19; Oliver 2001).[24] To make an informed choice the information presented by the researcher must be retained by the participant. Work in this area has shown that participants do not fully understand or are unable to recall the information presented. This has relevance to the idea of a participant freely choosing to take part in research (Rogers, *et al.* 2000: 605-607; Macillop 1988: 355-358).

[24] According to James (2004) although not conclusive, available data suggests that research participants may frequently not understand disclosed information. For example, approximately 30% of participants in cross section oncology clinical trials believed that their treatment had been proven to be the best treatment for the cancer. Of the Ina randomized trial on ß-blocker drugs to prolong the lives of patients with a history of myocardial infarction, 44% of research participants interviewed did not know that they were assigned to treatment or placebo.

If potential research participants are not able to understand the risks of participating in a trial, then they will not be able to act in what they consider to be their own best interest (Lloyd 2001: 17-18; Grimes 1999). Moreover, studies have shown that even when research participants demonstrate understanding about the nature, purpose, risks, and alternatives of research activities, it is often quickly forgotten. This is a cause for concern as understanding and acceptance of the parameters of the research should have been the basis of their voluntary choice (Bowling and Ebrahim 2001: 2-8; Lloyd, *et al.* 1999).

4.2 Free choice or voluntary participation

A valid informed consent includes the mandate that individuals must be free to choose to participate or not in a research study. Broadly, in countries where individualism is promoted, the idea of making a decision freely is not a major issue as it is bound up in one's social identity (Beauchamp and Childress 1994; Boyd, Higgs and Pinching 1997). However, in other countries where this is not the case, the idea of making an individual decision unfettered by social and cultural upbringing and individual circumstances can be problematic. Moreover, in certain types of clinical research e.g. in the field of psychiatry, application of the idea of 'freely choosing to participate' runs into great difficulties regardless of the research participant's country of origin (Dresser 1996:67–72; Sugarman, *e t al.* 1999:S1–S42; Zaubler, Viederman and Fins, 1996; Levine 1986).

Choosing freely to participate or not of course relies on other factors such as the individual's capacity to understand, the information provided by the principal investigator (PI), how the information is shared, as well as his or her comprehension of the information provided. But the topic of freely choosing or volunteering has not been focused upon much in the literature.

To freely choose (e.g. volunteer) to participate or not in clinical research involves a persons' ability to act in keeping with what that particular individual believes to be good, right and best in the context of his or her own situation, values and prior history. It also assumes that the individual is not placed under any pressure or coerced for example, by a PI, any other person, or factor to participate or not.[25]

4.3 Developmental stages

To choose freely though is not simple. There are complex biological, psychological, and sociocultural factors that feed into the decision and they often overlap with other requisites for a valid informed consent. For example, an individual's development e.g. his or her cognitive capacity and emotional maturity affect the ability to freely choose. Children, it is generally

[25] Regarding this, The Declaration of Helsinki does include a provision saying that "[w]hen obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress." In these circumstances, "informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship"(DH 2000).

accepted, are unable to make self-determining cognitively complex evaluations. Yet as they mature and their intellect, self-understanding and awareness of personhood develops, children become increasingly able to express preferences that meet some tests of judgment, logic, coherence, and emerging personal values (Kohlberg 1971).

During late childhood and pre-adolescence, the capacity to accept or reject a choice is demonstrated in the acknowledgement of a child's ability to assent to research (Piaget 1970). As children mature, their capacity to think abstractly e.g. to think about the repercussions of decisions they have made based on their personal life experience develops further. In late adolescence, young people often are able to make decisions concerning their own safety and well-being and to also make sincerely committed unselfish choices (Kohlberg 1971). With increasing maturity, individuals develop the ability to identify their own personal values and beliefs based on learning and self-knowledge that accompanies life experience. In addition, adults usually have roles that include decision-making including freely made or voluntary decisions. Later in life, the capacity to make a free choice does not rely as much on developmental factors.

Research also supports that amongst individuals with moderate and severe developmental problems there is little comprehension of the nature of research and the informed consent process (Iacono and Murray 2003; Freedman 2001; Gunn *et al.* 1999; Morris *et al.* 1993). Overall, we can say that freely choosing to participate or not in research is influenced by an individual's developmental capacity. But there are other factors which also influence the requisite for voluntary choice in a valid informed consent. These are bound up in the participant's social and cultural values.

4.4 Social and Cultural values

The meanings of health, illness, disease, cures and healing are shaped by a society's cultural values (Warren 1997). Psychological issues and cultural and religious values influence an individual's ability to make a freely informed choice. On the one hand, such values may serve to enhance an individual's sense of individualism and their autonomy. On the other hand, they may do the opposite. This is because psychological issues and values derived from a person's own cultural and spiritual environment influence ideas about what is good and bad e.g. the community's perception of clinical research as a good or bad thing.

In the medical context, how a disease or illness is conceived (e.g. as a curse from the ancestors or as retribution for a past sin) may influence how illness is socially labelled and whether consenting to a treatment is acceptable. Applied to clinical research, such factors may either enhance or not the idea of voluntary choice. So the ways in which researchers understand how an individual's cultural values influence their ability to consent to research is vitally important (Katz 1995: 88-91; Kiev 1993: 61).

The difference in an individual's perception of self also is a variant affecting free choice dependent on the influence of one's culture. A moral agent able to decide and act as typified in Western society may be quite alien from the perspective of other societies where acting in a way that enhances the relationships in the family or defers to the judgment of elders has greater weight. In this view, an individual who defines a personal preference separate from the needs of others or different from the values of the society may be considered wrong or unthinkable.

Included in cultural perspectives is also the use of language. Dialogue with individuals concerning e.g. the research process and informed consent should be given in the language that is understood by the participant. Yet, in spite of this is possible that

misunderstanding and misinformation has the potential to occur due to inadequate language translations. This is particularly a problem in scientific research as the meanings of terms often do not have an adequate equivalent in an individual's local language so the quality of the interpretation is vitally important. Research has shown that the use of untrained translators in clinical and research settings has lead to frequent errors that in some cases result in dangerous misinterpretations (Appelbaum, *et al.* 2002: 139-147).

4.5 Physical and mental factors

Physical factors also may impact on free choice. For example, when an individual is in great pain a valid informed consent is not possible (Helman 1994). This is because an individual in pain is consumed with the idea of relief and will agree to anything that will relieve his or her suffering (Nickel 2006: 245-264). As an example of this, in research concerning pain-control and end of life decision-making, researchers have found that adequate pain relief modifies the consent decisions previously voiced by patients (Larson and Tobin 2000: 1573-1577; Teno, Byock and Field 1999: 75-82).

This then indicates that freely chosen or voluntary consent may be influenced by physical factors. In addition, recent work in the field of psychiatry also points out that e.g. depression, substance

abuse, and other types of mental illnesses present a variety of challenges to the idea of freely choosing or voluntarily given informed consent (Gunn *et al.* 1999; Ganzini, *et al.* 1993: 337-340).

4.6 Poverty, resource limitation and lack of healthcare

There are other influences that impact on a obtaining a valid informed consent. In some countries there may be local or national laws which set out parameters for individual decision making. One area of particular concern to research in developing countries is resource limitations inherent in many health care settings. This fact opens the door for potential abuse of obtaining a valid informed consent as trial participants often look upon research as a means to receive healthcare that would otherwise not be possible. Because of this, an individual may agree to participate in clinical research not really caring about whether or not information is provided.

This also has relevance to incentives or strongly reinforcing pressures within the research context which may also impact on an individual's voluntary choice to participate or not. In addition, unethical researchers may knowingly take advantage of

particular circumstances such as disease outbreaks to exploit the idea of a free and voluntary valid informed consent.[26]

4.7 Institutional settings

Institutional settings also place a limit on the idea of free choice. This has been shown in countless ways throughout the history of research misconduct. Institutionalised individuals because of their external situations, have an altered experience of freedom that the possibility of ever receiving a genuine, uncoerced choice from them is debatable (Brody 1998). Individuals who are living in institutionalised settings are considered as 'vulnerable persons'. [27] In research, vulnerable persons and groups are afforded special protection.

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[26] A now considered classic example of this is summarised by Annas (2009:2052): "In late 2000, the Washington Post broke the story of a 1996 medical experiment conducted by Pfizer researchers in Kano, Nigeria, during a major meningitis epidemic. The story created a sensation, especially with its lead, which described the slow death of a 10-year-old girl known only as Subject 6587-0069. The researchers, who were working for Pfizer, monitored her dying without modifying her treatment, following the protocol designed to test their antibiotic Trovan (trovafloxacin) in children. *The Post* noted that its investigation had uncovered other such corporation-sponsored experiments "in Africa, Asia, Eastern Europe, and Latin America" that were "poorly regulated" and "dominated by private interests"- studies, it remarked, that "far too often betray" their promises to research subjects and consumers. After the exposé was published, the families of the Kano subjects brought suit against Pfizer in Nigeria and, later, in the United States, charging the company with conducting medical experiments without informed consent. Until recently, Pfizer had successfully argued in court both that there was no international norm requiring its physicians to obtain informed consent for the use of experimental drugs and that any lawsuit against them by subjects and their families should be tried in Nigerian courts, not U.S. courts. Pfizer abandoned this latter claim when, in 2006, an internal report by the Nigerian Ministry of Health was made public. The report concluded that the study violated Nigerian law, the Declaration of Helsinki, and the United Nations' Convention on the Rights of the Child. The Nigerian government then filed both a criminal and a civil suit against Pfizer in Nigeria. A settlement in this case was reached."

[27] The CIOMS International Ethical Guidelines for Biomedical Research define "vulnerable persons" as "those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power,

4.8 Roles and relationships

The relationship with a researcher as e.g. both an individual's doctor and a trial investigator presents hidden coercive effects that may present when such multiple roles or overlapping relationships exist. For example, in a participant observation study done by Taylor (1988), the time at which the diagnosis of cancer was given to the patient was used by her personal doctor (and drug trial PI) to instigate talk about the clinical trial.

> *Doctor / PI: We don't really know which surgery is best. We do not have any real answers. We are collecting data to help us with these questions. Let me tell you about this clinical trial...*

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intelligence, education, resources, strength, or other needed attributes to protect their own interests" (Macklin 1999: 474). Therefore, there are specific guidelines designed to protect the rights and welfare of vulnerable persons by requiring special justifications for involving them. In research, there is a tension between trying to balance both protection from abuse and access to new, experimental treatments for the vulnerable. The CIOMS guidelines include a guideline pertaining to research involving vulnerable persons. It states that, "special justification is required for inviting vulnerable individuals to serve as research subjects, and, if they are selected, the means of protecting their rights and welfare must be strictly applied" (ibid). For individuals and groups, the most important characteristic is that they have "limited capacity or freedom to consent or to decline participation in research." Prisoners, Women, Children, Mentally incapacitated, Refugees, the Poor, Elderly, Sexual minorities and Addicts are all examples of groups considered vulnerable.

> *Patient: Doctor, I am asking YOU what you think is best for me. For God's sake you are a doctor ... I don't want my breast off ... but then I want to live ...* (Taylor 1988: 118).

When an act is performed voluntarily, it means that an individual chooses for him or herself what is believed to be the best or right action in view of their personal circumstances. To freely choose also includes the capacity to make a decision without fear, intimidation or under duress. Thus far in this chapter, I have shown some of the barriers which should be considered in the process of realizing a valid informed consent. If researchers take the idea of a valid consent seriously then they will realise that there are many factors which must be considered in the attempt to realise this goal.

4.9 The increasing problem about informed consent forms

Various concerns about the growing globalisation of clinical research trials has resulted in calls for more effective ethical and legal regulations to protect both research participants and scientific integrity. It is a fact that research in developing countries is tainted with many instances of unethical conduct and the precepts found in e.g. the *Nuremberg Code* and *The Declaration of Helsinki* were flaunted. With the increasing

emphasis on legal measures to protect industry-sponsored clinical trials and research,[28] one of the results has been the increasingly complicated and legalistic revisions of the required informed consent forms.

Concerns have arisen that the increasing length and complexity of consent forms are inhibiting information disclosure and impeding understanding (Grossman *et al.* 1994: 2211-2215). Consequently, critics worry that the informed consent process does not accomplish the goal of adequately informing prospective participants about the nature of a study and its potential risks and benefits (Dresden and Levitt 2001: 241; Murphy, O'Keefe and Kaufman 1999).

A recent study concerning the informed consent forms provided to researchers engaged in HIV/AIDS trials in the US and internationally pointed out some of the rising problems concerning the length of informed consent forms (Kass *et al.* 2011). In their review, they report the analysis of 124 informed consent forms which included descriptions of research procedures, risks and benefits. used by the US government-sponsored, multinational HIV/AIDS research conducted in 2006. The researchers identified that on average the informed consent

[28] This is in addition to other international changes in views on research such as the US's Food and Drug Administration (FDA) decision that research studies submitted to it for review need no longer be bound by the Declaration of Helsinki. According to Annas (2009: 2050-2053), "they need only follow the industry-sponsored Guidelines for Good Clinical Practice outlined by the International Conference on Harmonisation".

forms were 22 pages in length with a median for adult participants at 27 pages (ibid).

In their 2006 study,[29] Loverde, Prochazka and Byyny state that "… [Informed] consent forms are often long and incomprehensible." They (ibid) also identified that there was a 58% increase in the length of forms since 1982, a factor known to impair comprehension. For these reasons they conclude that many informed consent forms are incomprehensible. Their recommendation are that researchers "be brief, use plain English, and write consent forms at appropriate reading levels, and receive training on how to obtain a valid consent "(ibid). This study supports the findings of others that suggest that decreasing the length and complexity of consent forms may improve understanding, satisfaction with the informed consent process, or both.

In Norway, Berger, *et al.* (2009 379-385) reviewing the increasing length of oncology informed consent forms over the last 20 years note,

> *The legal aspect of medicine is getting even more important. However, one might speculate that it could seem the trend in today's society towards increased*

. [29] "The authors (ibid) studied 88 consecutive research consent forms generated at the USA Denver Veterans Administration Medical Center, evaluating the reading levels of the forms using the Fry Readability Scale and recording the numbers of lines of text. The mean grade reading level required for comprehension was 13.4 years of schooling. Twenty-two percent of all text passages scored were at the postgraduate level of readability. This difficult readability level has not improved since the forms were last tested in 1982. The mean length of the forms was 84.6 lines".

number of insurance arrangements has a defensive purpose to hold a retreat open and to protect oneself from lawsuits. This trend might influence the different authorities' requirements to patient's information to prevent misunderstandings and lawsuits in posterity.

As early as 1969, Epstein and Lasagna pointed out that informed consent forms should be ethically substantial as opposed to the emphasis on its 'form'. Others such as Young, Hooker and Freeberg (1990: 1-5) and Rogers, *et al.* (1998) have written concerning the trend towards using longer and complex wording of informed consent forms.

The 2011 study by Kass *et al.* also showed that commonly misunderstood research concepts such as 'randomisation' and 'placebo' seemed to be explained with far less attention. For instance, whereas confidentiality sections had a median length of about two pages, randomisation was treated to just 53 words. Randomisation is one of science's most trusted tools for minimising biases in studies. However, when informed consent forms spend so much time explaining why they are testing a new drug and so little on the concept of randomisation itself, participants may be left not understanding that half of them will get a different drug or perhaps no drug at all. The failure to understand clinical trial terms and methodology remains a major concern.

Another example of this comes from Joffe *et al.* (2001: 172-177). They (ibid) report a study of 287 adult cancer patients who participated in a clinical trial showing that that 70% of the patient-participants did not recognise that the study drug was of an unproven nature.

While it is true that research regulations do not require that forms explain concepts, it still remains part of an investigators ethical duty to ensure that the research participant is provided with the information necessary to make an informed and freely chosen decision concerning research participation. Kass *et al.*'s study shows that researchers spend considerable time on the key concepts that the legal regulations require them to cover, such as purpose, procedures and risks (Ibid). This fits in with the increasing worry of industry-sponsored research concerning liability.

In most of these studies, all of the consent forms were based on templates provided by the funder. This is the current procedure for international-industry sponsored research. Investigators themselves may have had little authority to change or shorten them. Pertaining to the trial consent forms reviewed by Kass *et al.* (2011), the forms that researchers were given by their sponsors as templates were very long. Data on literacy rates in both the US and internationally were compared to the informed

consent forms used in the clinical trials. [30] The sponsors of the research, of course are mindful of the legal issues concerning informed consent. It is likely that because of such legal concerns that the templates are designed to ensure sufficient coverage (Beardsley, Jefford and Mileshkin 2007: 13-14)

As Davis *et al.* suggest in findings from their study,

> *... too much attention is spent on the details of consent forms, possibly as a result of legal liability issues*.

They also point out that time spent revising the small details and specific wording of informed consent documents does not appear to impact on participant comprehension (Davis *et al.* 1998: 668-674). Menikoff (2008: 11-12) reports that shorter, more readable consent forms appear to have no adverse effect on the quality of informed consent. As his research identifies "... In the future, it would be acceptable for institutional review boards (IRBs) to approve shorter forms for use in human subject's research".

The majority of the consent forms that Kass *et al.* (2011) reviewed required readers with at least a USA's ninth-grader comprehension. Such findings, while still not meeting commonly agreed-upon standards, demonstrate lower readability than

[30] The authors (ibid) report that literacy rates in India, Bangladesh and Senegal are 63, 55 and 42 percent, respectively. Almost half of Americans read at or below the eighth-grade level.

consent form studies from decades past, a point made by Loverde, Prochazka and Byyny in 2006. By making informed consent documents so long and complex, researchers neglect their ethical duty to describe their research in ways that help participants truly understand.

4.10 Concluding remarks

Although a valid informed consent is a fundamental ethical requirement for research with humans, many studies indicate that research participants often do not understand critical aspects of the research in which they are participating, suggesting that the "informed" part of consent to participate is imperfectly realised (Fortun *et al.* 2008: 625-629; Lynoe, *et al.* 1991).

Moreover, it can be suggested that sponsors, investigators, or researchers fail to appreciate that their primary ethical obligation - to keep the protection of human participants in research at the forefront of their concern as realised in the process of informed consent - should trump all other considerations. Allowing and assisting an individual to make an informed choice is part of the idea of respect for persons because it includes understanding that each individual has his or her unique understanding of the world and his or her place in it. If this is disregarded or diminished, then any choice made is ethically compromised or unauthentic. In the process of realising a valid informed consent

researchers should be aware of both internal and external influences that affect a free choice. In understanding them, greater support mechanisms may be developed such as the identification of what the individual considers as valuable to him or her.[31]

Developmental, psychological, physical, institutional, economic, cultural, and linguistic factors are only some of the barriers hindering an individual to make a free choice to participate in research. An addition, as I have shown are the increasingly complex informed consent forms. These may take time away from the researcher which should be devoted to his or her research participants. In this chapter I have shown that realisation of a valid informed consent is complex and many considerations must be kept in mind. Through identifying some of the issues, it is hoped that a greater understanding of issues may be seen.

[31] One interesting method which has been developed in this regard is *The Values History* developed by Lambert, Gibson, and Nathanson (1989: 202-212) see also ideas in Murphy, O'Keefe and Kaufman (1999).

Chapter 5. South African Regulatory Guidelines and Legislation Concerning Informed Consent

5. 1. National research guidelines and legalisation

The *South African National Health Act 38 of 2005* defines 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". [32] Clinical trials then include not only drugs or medicines, but also other types of research such as treatment methods (e.g. psychological and behavioural research).

In South Africa, all clinical trials are required to be registered by the *South African National Research Registry* based at the National Department of Health.

South Africa has regulations regarding the ethical conduct of research. These were influenced by internationally recognised

[32] Clinical Trials are divided into phases as follows (NIH 2010) Phase I trials "evaluate the safety of diagnostic, therapeutic, or prophylactic drugs, devices, procedures, or techniques in healthy volunteer subjects or in patients." They involve few participants and aim to "determine pharmacologic and pharmacokinetic properties, structure/activity relationships, safe dosage range, toxicity, metabolism, absorption, elimination, or preferred route of administration. Phase II trials also involve relatively few subjects (perhaps a few hundred) and aim to determine the safety, efficacy, or optimum dosage schedule of one or more diagnostic, therapeutic, or prophylactic drugs, devices, or techniques. Phase III trials involve larger groups of participants (hundreds to thousands) aim to determine if there are clinically significant responses if Phase II trials suggest effectiveness. Phase IV trials are intended to obtain additional data about the safety and efficacy of diagnostic, therapeutic, or prophylactic drugs, devices, or techniques that have been approved for general use.

codes and declarations such as the *Nuremburg Code* and the *Declaration of Helsinki.*

The South African National Department of Health (2004), the Health Professions Council of South Africa (HPCSA) (2008) and the Medical Research Council (MRC) (2002-2004) are the bodies which publish research ethics guidelines for South Africa. The National Health Act 38 of 2005 includes as mandatory that that all research performed in South Africa is first approved by a research ethics committee (REC). In addition, the *Constitution of the Republic of South Africa of 1996* in 12 (2) c includes the dictum of informed consent as a requisite to participate in research. It states

> *Everyone has a right ... not to be subjected to medical or scientific experiments without their informed consent.*

Research related to human health is defined in the *National Health Act 61 of 2003,* Section 1 as "any research that contributes to the knowledge of 1) the biological, clinical, psychological or social processes inhuman beings; 2) improved methods for the provision of healthcare services; 3) human pathology; 4) the causes of diseases; 5) the effects of the environment on the human body; 6) the development or new application of pharmaceuticals, medicines, and related

substances; and 7) the development of new applications of health technology". In their research ethics guideline publication (2004), the *National Health Act* also provides a definition of research 'as the systematic search or inquiry for knowledge.

5. 2 Research in South Africa and informed consent

According to the *National Health Act 61 of 2003* Section 71,

> *... notwithstanding anything to the contrary in any other law, research and experimentation on a living person may be conducted only in the prescribed manner, and with the written consent of the person after he or she has been informed of the objects of the research or experimentation and any possible positive or negative consequences of the research to his or her health. Where the potential subject is a child (e.g. less than the legal age of 18 years), consent from the parent or guardian and from the child are required.*

Because the *National Health Act* Section 8(1) provides that healthcare users have the right to participate in any decision concerning their health and treatment, informed consent included, If the informed consent is given by an individual other that the individual user, then the user must be consulted before giving the required consent (Section 8 (2) (a)).

Healthcare users must be capable of understanding and must be informed about their health and treatment even though they may lack the legal capacity to give their informed consent (Section (2) (b)). Concerning those individuals who are unable to participate in decisions about their health (e.g. in emergency circumstances) they must be informed about any provision of treatment unless the disclosure of such information would be contrary to the individual's best interest (Section 8(3)).

Section 7(1) (e) of the *National Health Act* states that in emergency situations when an individual is not able to give consent such as in situations of irreversible damage to health, then emergency treatment may be provided without their consent (Stoffberg v Elliot 1923 CPD 148). Pertaining to this, embedded in the *South African Constitution of 1996,* Section 27(3) and the *National Health Act,* Section 5 are regulations that nobody can be refused medical treatment.

5. 3.The South African Constitution and informed consent

The *Constitution of the Republic of South Africa* 1996, states that everyone has "the right to bodily and psychological integrity which includes the right to security and control over their body" (Section 12 (2)). In keeping, this means that individuals have

free choice concerning what happens to them [33] (this would also involve the idea of informed consent (or refusal) to participate in research). Because of the right to bodily and psychological integrity, a spouse is given the right to individual consent to medical even if he or she are married in 'community of property'. Under the *South African Choice of Termination of Pregnancy Act* Section 1, consent of the male party is not required for an abortion.

5. 4 Informed consent and children

Concerning children under the age of 18 years as prescribed by law, consent of the child's parent or guardian is required in general. However, exceptions to this rule are found in the *Children's Act Number 38 of 2005* and the C*hoice of Termination of Pregnancy Act of 92 of 2006*. The *Children's Act Number 38 of 2005* provides "that children may consent to their own medical treatment or to the medical treatment of their children if the following conditions are met: 1) that they are over the age of 12 years; and 2) that they have sufficient maturity and have the mental capacity to understand the benefits and risks and social and other implications of the treatment (Section 129(2)).

[33] There is within the Constitution a provision for the limitation of rights provided that they are "reasonable and justifiable in an open and democratic society" (Section 36).

Concerning surgical procedures, children may consent under the *Children's Act,* Section 129 (3) if "they are over twelve years of age ; 2) that they have sufficient maturity and have the mental capacity to understand the benefits and risks and social and other implications of the surgical operation; and 3) they are duly assisted by their parent or guardian.

Special provision is made in the *Children's Act Number 38 of 2005* concerning HIV testing. Consent, it is stated may be given by a child under the following conditions: 1) "such a test is in the best interests of the child; and 2) the child is 12 years of age or older, or if the child is under the age of 12 and is of sufficient maturity to understand the benefits, risks and social implications of such test".

Others may consent on behalf of children to HIV testing if they are 1) the parent or caregiver 2) the provincial head of social development or 3) a designated child protection organisation arranging the placement of a child where the child is under the age of 12 years and is not of a sufficient maturity to understand the benefits, risks and social implications of such a test."

The *Children's Act* further states that "in the case where the child has no parent or caregiver, and where there is no designated child protection organisation, the superintendent or person in

charge of the hospital may give consent. If the child of the above persons unreasonably withholds consent, or the child or the caregiver of the child is incapable of giving consent, consent may be given by a children's court" (Section 132 (b-f)).

5. 5. Informed consent and mentally ill persons

The *Mental Health Care Act Number 17 of 2002* outlines the regulations concerning consent on the behalf of mentally incompetent persons. It provides that "healthcare practitioners or an establishment may provide care, treatment and rehabilitation services or admit an individual in need only if the following conditions are met: :1) The user consented to the care, treatment, rehabilitation services or admission; 2) the practitioner or institution is authorised by a court order or review board; pr 3) due to mental illness any delay in providing care, treatment or rehabilitation services or admission may result in: a. death or irreversible harm to the user or b. The user inflicting harm to himself or herself or others ; or the user causing serious damage to or loss of property belonging to him or her or others "(Section 9 (1)).

5. 6. Concluding remarks

As shown, South African research guidelines and well as its legislation takes into account research practice as well as

incorporating the idea of the value of individual informed consent. National research guidelines and the national registration of research conducted in South Africa are all vitally important.

However, there are also some problems in that research activities may evade the national register and institutional research ethics committees as well. Another problem is oversight on the part of research ethics committees. Although in clinical research, particularly international or multinational collaborative research, oversight is often sought by way of e.g. the *US Office of Human Research Protection* (OHRP) when US federal funds are involved, (likewise this applies to other countries such as those in the EU). However, there are often difficulties faced in collaborative research. This is particularly true when considering the issue of obtaining a valid informed consent. As previously noted, it is often assumed that all individuals share the same idea of individual autonomy conceived in the West which prohibits mutual understanding.

A final comment concerning the meaning of words and terms should also be mentioned. The *National Health Act 61 of 2003* in paragraph 6.7 says that the meaning of the term "sufficient maturity" [to consent] is linked to the child's mental capacity to "understand the benefits, risks and social implications of

treatments, surgical and testing procedures". As noted in my previous chapter, concerning barriers to a valid informed consent, 'sufficient maturity' in reality may be quite difficult to discern.

Chapter 6. Conclusion

I began this research report showing, in Chapter 1, that in ancient times generally there were social, cultural or religious barriers in using human individuals or their bodies in scientific research. I also illustrated with some examples of how, when the emphasis shifted to the idea of scientific knowledge and research as the ultimate aim of society, the idea of respect for persons diminished or because an individual was of a different race, ethnic group or class was disregarded.

In the following chapter, I presented a brief background about the social, cultural and economic factors that lead to the Holocaust. Arising from the US Military Tribunal Trials that followed I emphasised the document which achieved international recognition as setting forth the idea of consent in medical; and scientific research. My major points were that: 1) It provides a clear articulation of the rules which should govern good research practice and introduced globally, the idea that humans prior to their involvement in research must knowledgeably and freely give their consent; and 2)

Understanding the context that gave birth to the *Nuremberg Code*'s origin should provide researchers, scientists and medical professionals with a greater understanding of the type of forces that can influence research practice and to be mindful of them.

Then in Chapter 3, I outlined the responsibilities of researchers and investigators in obtaining a valid informed consent. Following the *Nuremberg Code*, another major international move towards developing guidelines for the ethical regulation of research was developed in 1964. The World Medical Association's *Declaration of Helsinki* and the subsequent development of guidelines by CIOMS (developed in collaboration with the World Health Organization) are widely regarded as coming closest to consensus-driven international guidelines for the ethical conduct of research (Bhutta 2004: 72). In spite of rules and guidelines as Emanuel, *et al.* (2003) describes and as I pointed out, major cases of research misconduct continue to occur.

Chapter 4 concerned the identification of many of the factors and elements that researchers and investigators should be aware of when aiming to realise a valid informed consent. I consider these all vital to be considered by ethically-minded investigators. In that chapter I also included a section concerning the increasing length of informed consent forms and suggested that

these are constructed more to protect the sponsor from liability than in the spirit of respect for persons.

In Chapter 5, I set out the South African guidelines and legislation concerning research and informed consent. The protection of human participants is entrenched in all our legislation given the gross human rights violations that were endured by some of our people in the country. Despite having some of the best laws in the world to protect human rights we as a country were also disgraced by our esteemed Prof Bezwoda who produced falsified data at an international congress, regarding a trial he conducted in women with breast cancer, (MRC-2005).

As a demonstration of our ethical duty to respect others, the doctrine of informed consent is the cornerstone of ethical medical practice, both in the clinic and clinical research setting (Screenivasa 2003). In this view, informed consent consists of two parts: a duty to obtain the freely chosen or voluntary agreement of the research participant before enrolment and a duty to disclose adequate information to the participant before seeking this agreement. This interpretation has an ethically weighty implication; that the validity of individuals consent depends on their actual comprehension of the information disclosed, which as I identified, is a difficult process.

Because it is the ethical duty of investigators to take all reasonable steps to ensure that the information they have disclosed has been adequately understood. As Screenivasa (ibid) argues, “successful communication should be a shared relationship between the investigator and the participant”. Related to this, we should remember Beecher’s (1966:1360) admonition as well:

> *There should be a second safeguard: an intelligent informed, conscientious compassionate investigator.*

Annas (2009: 2053) writes,

> *Post–World War II ethical standards of clinical research have not effectively protected subjects or ensured scientific integrity.*

We should take this seriously, and see that there is an identifiable need for ongoing discourse between sponsors, researchers, investigators, ethics experts, research ethics committee members, research participants and participant groups to enrich the ethical quality and meaning of a valid informed consent. I hope my research report has contributed to this.

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