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**A COMPARATIVE ANALYSIS OF THE REGULATORY FRAMEWORK OF THE
THERAPEUTIC APPLICATION OF STEM CELL TECHNOLOGIES**

by

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ABSTRACT

Stem cell technologies as a branch of regenerative medicine are becoming increasingly popular as the science behind it evolves. Therefore, it is important that the regulatory framework pertaining to stem cell technologies be well defined and appropriate to prevent unethical and unscrupulous behaviour on the part of medical practitioners, which gives rise to stem cell tourism. South African legislation pertaining to stem cell technology is regarded as inadequate and dissonant with the Constitution, exacerbating the problem of stem cell tourism and denying patients access to certain stem cell therapies, which ultimately can be viewed as an infringement of their constitutional rights. The *United Kingdom* (UK) provides a clear-cut regulatory framework, which is not only centred around consent and patient safety but is also conducive to production of stem cell therapies. For such reasons, this dissertation finds the UK framework to be an appropriate benchmark against which the South African regulatory framework can be evaluated. By means of comparison and elaborating on the biology of stem cells in addition to pertinent ethical principles, legislation and human rights of both South Africa and the UK, an argument will be made out that South African legislation pertaining to stem cell therapy and related matters is wanting. Furthermore, analysis will be made of the definition of biological medicine as put forward by the *Medicines and Related Substances Control Act* 101 of 1965 to conclude that certain stem cell therapies are best excluded from such a definition as such stringent requirements and protocols encumbers access to stem cell therapies and inflates costs. Lastly, remedial measures are proposed to remedy these injustices by proposing for the institution of a specialist advisory committee to oversee stem cell and related activities.

Key Words: Regenerative Medicine; Stem Cells; Stem Cell Regulation; National Health Act; Medicines and Related Substances Control Act; Advanced Therapy Medicinal Product; Human Tissue Authority; Human Fertilisation and Embryology Authority; HTA; HFEA; Medicine and Healthcare Products Regulatory Agency; MHRA; European Medicines Agency; Tissue-engineered Products; Doctor-Patient Relationship; Medical Innovation Bill 2014; Experimental Treatments; Innovative Therapy; Hospital Exemption; Informed Consent; Special Exemption; Autologous Stem Cell Therapy; Stem Cell Transplants; Gene Therapy Advisory Committee.

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CHAPTER 1

INTRODUCTION

Akin to stem cell research, the global regulation of stem cell therapy and their therapeutic application is marked by legal uncertainty. Even though national policy is inspired by international and regional instruments, stem cell research and therapy remain within the domain of national policymakers. Variance in regulatory policy is a natural result of a heterogenic culture and, therefore, unintended and unanticipated consequences may arise if there are regulatory *lacunae*. If the regulatory framework is too authoritarian, it denies vulnerable members of society beneficial medical interventions and access to scientific progress. However, if the regulatory regime is too permissive or slapdash, it exposes vulnerable patients to unproven and possibly harmful stem cell treatments. This phenomenon has been characterized as “stem cell tourism” which originates from legal *lacunae* or a meagre national regulatory framework, which in turn translates into grave legal and ethical concerns due to the fact that patients receive unproven and often unregulated, potentially dangerous and fraudulent treatments.

To develop an efficacious regulatory framework in South Africa for the therapeutic application of stem cell technologies, due regard must be given to the international guidelines and the regulatory framework of the United Kingdom (UK). This can be ascribed to the fact that the UK has a well-vested system that conforms to international guidelines and standards for biotechnologies and stem cell therapy in particular, which provides surety for investors as well as a clear-cut environment to stimulate the production of such life-saving therapies.

Very few breakthroughs in science have inspired as much attention and debate in the biomedical sphere as stem cell research and the potential application thereof in fields such as cell and gene therapy, regenerative medicine and tissue engineering. Stem cells are self-renewing cell lines, which are essentially eternal due to their capacity to proliferate and differentiate indefinitely into any type of tissue. These cells have a wide variety of applications, one of which is to inject (or introduce rather) new stem cells into deteriorated and broken-down tissue, thereby allowing it to proliferate and divide into the specific type of broken tissue, resulting in a permanent rejuvenation of the failing tissue/organ. This new medical advancement changes the

scope of traditional medical science from slowing down degeneration of cells in the body by administering drugs and surgical therapies (call it damage control if you will) to all new heights into an era called “regenerative medicine”, where medical science has the ability to permanently restore proper cell function and therefore permanently cure or rejuvenate the affected tissue/organs.

The hope of stem cell therapy and applications may be to cure previously incurable diseases and may also provide for relief and remedies for people suffering from diseases and disorders such as diabetes; cardio vascular diseases, Parkinson’s, Alzheimer’s and spinal cord injuries, to name only a few. These cells may also serve to aid in the research and development of drugs and medicines. However, certain misconceptions regarding stem cells exist among the general public, and to a certain extent the medical fraternity, much of which can be resolved by a sound understanding of the basic biology of stem cells.¹ One of these misconceptions is, for instance, the promise stem cell therapy holds for curing diseases for which no current therapy exists, which is often translated into fact. Over the past few years, these common misconceptions have led to an increase in the number of unproven stem cell “treatments”. This enigma, called stem cell tourism, is characterised by suffering patients travelling to certain destinations where novel medical treatments such as stem cell therapies are made available, usually by phoney operators promoting various stem cell ‘treatments and cures’ who, in doing so, mislead vulnerable patients. Most popularly and due to their unique properties and the fact that they can be harvested with ease, Mesenchymal Stem Cells (MSCs) have become the most popular and sought-after product of these doubtful clinics. This phenomenon is brought about due to a lax regulatory system and it creates grave legal and ethical trepidations due to the fact that patients receive unproven, unregulated, often fraudulent and potentially dangerous treatments. As a result of a lax regulatory framework pertaining to stem cell therapy, South Africa has become such a destination.² Nöthling Slabbert *et al*³ rightly note that South Africa is particularly vulnerable in this regard, as limited information is available to inform the population of the status quo and the potential benefits and harms of stem cell

¹ Botes & Allesandrini “Legal implications of translational promises of unproven stem cell therapy” 2015 SAJBL 36.

² Nöthling Slabbert *et al* “Stem Cell Tourism in South Africa: A legal update” 2015 SAJBL 41.

³ Ibid.

treatments through relevant and trustworthy information. The fact that physicians and medical practitioners are often ill informed of recent global developments and of the South African legal implications exacerbates this problem.

Stem cell therapy in South Africa is governed mainly by the National Health Act⁴ (NHA), the MRSCA⁵ and the Consumer Protection Act⁶ (CPA). The latter regulates all agreements between patients and healthcare providers for the supply of healthcare goods, including biological medicine and marketing of stem cell therapies. The NHA, as it pertains to stem cell therapy, is characterised by numerous redundancies and inaccuracies. In addition to the various inaccuracies, misleading or unscientific language creates the need for resonance of definition, not only between the Act and regulations, but also among the regulations themselves. The MRSCA categorises stem cell technologies as medicine and prohibits the sale of unregistered medicines. The Medicines Control Council (MCC), which is charged with regulating all medicines in terms of its mandate via the MRSCA, requires that all medicines be subject to registration.

However, medicine will only be registered when the Registrar of Medicines is satisfied that the medicine is safe, efficacious, of good quality, appropriate for the purpose for which it is designed, complies with relevant standards and that registration of such medicine is in public interest.

Only after these requirements have been met, will the Registrar of Medicines issue the certificate of registration and only then, the medicine may be sold legally. Disregarding the aforementioned provisions may result in criminal liability, which is punishable with a fine and/or imprisonment not exceeding 10 years. Even though there are strict legislative prohibitions, these offences are widespread with very few convictions to date.

Stem cell technologies and law have different base points of knowledge and although they are developed side by side, they come into conflict with one another

⁴ National Health Act 61 of 2003 (NHA).

⁵ Medicines and Related Substances Control Act 101 of 1965 (MRSCA).

⁶ Consumer Protection Act 68 of 2008 (CPA).

more often than not. Sustainable solutions need to be found to resolve the conflict between the advancement of medical science and the legal and ethical aspect of the therapeutic application of stem cell technologies. Pepper and Nöthling Slabbert⁷ give several pillars for a successful cell therapy environment, which include a vigorous regulatory environment, quality assurance and accreditation, and a well-established informed consent process during which potential side effects are stipulated. The South African regulatory dilemma can be resolved, firstly, by giving due regard to the international guidelines and standards set out by their respective bodies and, secondly, by learning lessons from the UK's regulatory framework pertaining to stem cell therapy, while not disregarding the variance in social context and the values and rights vested in the Constitution of South Africa (Constitution).

This dissertation consists of seven chapters. Chapter 2 will set out the current and up-to-date scientific development regarding stem cell therapy. A clear understanding of the biological properties and therapeutic workings of stem cells is required, as the law pertaining thereto is instructed by the scientific advancement that creates the need for regulation. Before the pertinent legal rules can be set out, it is necessary to set out the workings of the doctor patient-relationship, which relationship is not only governed by law, but also by various ethical principles. Therefore, Chapter 3 will set out the nature of the doctor-patient relationship as well as the governing ethical principles that instruct its operation.

Despite the fact that the law and ethics are interlinked, the Constitution is the supreme law of the country, even though it is based on various ethical principles such as those elucidated in Chapter 3, therefore, the Constitution will form the base of and lens through which all legislative instruments pertaining to stem cell technologies must be viewed and analysed.

As stated above, this study intends to compare the legislation surrounding stem cell technologies of South Africa with that of the UK, in particular, and, therefore, it is necessary that an in-depth discussion of the laws of the European Union (EU) and the UK should be given, as is done in Chapter 5. Chapter 6 will set out the legal

⁷ Pepper & Nöthling Slabbert "Human tissue legislation in South Africa: Focus on stem cell research and therapy" 2015 *SAJBL* 5.

position of stem cell technologies in a South African context, weigh it up against the Constitution and expose the relevant gaps and inconsistencies in the South African legislation by means of comparison to the UK framework pertaining to stem cell technologies.

Lastly, Chapter 7 will be the final synthesis and conclusion of this dissertation. It will conclude that there are, in fact, instances where it is necessary to regulate stem cell technologies as medicine, but there are also instances where stem cell technologies, such as specific autologous bone marrow stem cell treatments, should be exempted from the ambit of medicines regulation and, accordingly, escape the high production cost associated with good manufacturing principles and clinical trials. Such exemption can be justified in terms of the Constitution and the faster delivery of life-saving treatments to patients in need.

To summarise, the conclusion of this study will indicate that the definition of biological medicine in the NHA needs to be updated in order to provide for such therapies to be exempted from medicines legislation and to provide legal certainty in the ever-growing field of regenerative medicine. Furthermore, it will expose the lurking consequences contained within the semantics of the Medical Innovation Bill 2014,⁸ as well as the possible effects that a certain exemption from registration as medicine in terms of the MRSCA might have on the occurrence and regulation of unproven and often dangerous stem cell therapies.

⁸ Medical Innovation Bill 2014, as published in GG 37349 2014-02-18.

CHAPTER 2

A MEDICAL PERSPECTIVE TO STEM CELL TECHNOLOGIES

2.1 Introduction

The laws pertaining to stem cell technologies are dictated by biological and medical advancements. Regulators often try to balance sufficient space for research and development and adequate patient safety. The complexity of this delicate balance leads to a labyrinthine regulatory framework. Much of the complexity, misconceptions and inconsistencies in the regulatory framework of stem cells can be ascribed to the misinterpretation of biological attributes and concepts. The biological capabilities of stem cells are the main rationale for how stem cells are being regulated. In other words, as science advances, new ethical and regulatory issues arise. Therefore, the regulatory framework can only be elucidated and evaluated after the biological attributes and advancements have been discussed.

This chapter will be compartmentalised into smaller, more manageable sections for a pertinent description of the therapeutic applications of the various stem cell technologies available. Firstly, the history of stem cell technologies will be discussed in general; secondly, the concept of regenerative medicine will be explained; thirdly, the classification of stem cell technologies will be set out to illuminate the definitive attributes of stem cells, cell potency and differentiation. Fourthly, the various sources of stem cells and alternative methods of deriving pluripotent stem cells will be discussed and lastly, the various therapeutic applications that are being explored and applied in contemporary medicine will be discussed.

2.2 History of stem cell technologies

Over the last few decades, stem cell therapies have become a momentous life-changing procedure, bearing in mind its humble origins. The initial applications of bone marrow were documented as early as the 19th century, sadly and quite obviously, they failed due to the oral route of administration.¹ A major stride forward was made when James Till and Ernst McCulloch collaborated at the Ontario Cancer Institute in Toronto where they studied the effects of radiation on the bone marrow of

¹ Vertes *et al* *Stem Cells in Regenerative Medicine: Science, Regulation and Business Strategies* (2015) 69.

rodents in the 1950s and 1970s.² This unique and influential contribution to science set the stage for all the present research on both adult and embryonic stem cells. This research unveiled the therapeutic and restorative “edge” of bone marrow transplantation, which can be narrowed down to a single type of cell that cannot only proliferate, but also differentiate into all the different types of blood cells, such as red blood cells, white blood cells and blood platelets. The first bone marrow transplantation took place in the 1960s, with the aim of replacing abnormal blood cells with stem cells that will produce healthy blood cells.³ Until this day, bone marrow transplantation is revered as a life-changing therapy and is routinely practised.

In the late 1990s, James Thomson from the University of Wisconsin isolated and cultured cells from the inner cell mass of an early human embryo, which gave rise to the first embryonic stem cell lines.⁴ These cells are self-renewing and have the capacity to give rise to all the cells in the body. Potentially, these cells can continuously repair failing organs or tissue of such organs and this brought about the era of regenerative medicine. Due to ethical considerations pertaining to the destruction of human embryos for the procurement of embryonic stem cells, other alternatives were explored. After much trial and error in the laboratory and experimenting with mice, two scientists, Shinya Yamanaka at Kyoto University and James Thomson at the University of Wisconsin, both independently reported in 2007 that they have managed to reprogram human fibroblast back to a pluripotent state, similar to that of a human embryonic stem cell. This marked the advent of the induced pluripotent stem cell and held many promises for the future.

2.3 Regenerative and personalised medicine

2.3.1 Regenerative medicine

Stem cells have the potential to repair a failing organ/tissue permanently and they can ameliorate diseases by introducing new and healthy cells into the body, either in their already differentiated state or in their unspecialised form to proliferate and

² Krimsky *Stem Cell Dialogues: A Philosophical and Scientific Inquiry into Medical Frontiers* (2015): In 2005, they were awarded the Albert Lasker Basic Medical Research Award to honour their unique and influential contribution. The Award Description noted that by the early 1970s, Till and McCulloch’s experimental observations were unclear.

³ *Idem* at 4.

⁴ *Idem* at 7.

differentiate only once they are introduced. Contrary to stem cell technologies, is the traditional pharmaceutical paradigm built upon orthodox drug-based therapy. Here the primary mode of action causes an alteration in the cell's metabolism in order to slow down its regression, excluding the regrowth or renewal of ailed tissue from its reach.⁵ Technology such as stem cell therapies, harnesses the body's own evolutionary regenerative powers and brought about a paradigm shift, changing the traditional scope of medicine completely and propelled us into an era of regenerative medicine, which not only improves debilitating diseases but also acts to restore the degenerated tissue or cells in the body.

2.3.2 Personalised medicine

Medicine has come a long way to develop into what it is today. It all started with a plant-based extract approach for the development of pharmaceuticals and therapies that treat ailments in humans and animals. There was a decrease in the application of plant-based extract therapies due to the upsurge of clearer and more precise modes of action in pharmaceuticals. Later years, the foundation of the pharmaceutical industry was laid by the application of pure chemical-based therapies. Chemical-based therapies were further enhanced by ancillary advances in other fields of science⁶ and set the stage for the rise of safer and more efficacious therapies, which could be aimed at treating various ranges of more complex ailments and medical disorders.⁷

One of the great (if not the greatest) challenges in medicine is to develop medicine in which the medical benefit factor outweighs the potential risk of an adverse reaction. Among the first applications of stem cell technologies was their application in the development and testing of safer and more efficacious pharmaceuticals. However, recently we have seen a shift to what we now call 'personalised medicine'. In essence, personalised medicine provides for the development of personal, tailor-made pharmaceuticals and medical therapies designed for maximum efficiency and reduced side effects. By acting on its precise mechanism, personalised medicine

⁵ Holland *et al* *The human embryonic stem cell debate: Science, ethics, and public policy* 3 (2001) 3-4.

⁶ Such as: pharmacology, molecular biology, cell biology, microbiology, genetics and bioinformatics.

⁷ Vertes *et al supra* n9 3.

exclusively hones in on the targeted area while, at the same time, excluding the healthy tissue or cells in the surrounding area from its onslaught.⁸

It is widely accepted that diseases are heterogeneous with variances in biological subgroups, each of which requires a specific pharmacological mode of action or response to cure the disease. Due to this specific and individual nature of diseases, a shift has taken place from the traditional large-scale production of a 'one size fits all' type of product, into a new era that requires a specifically individualised response. The ability to identify which patients would benefit from the proposed treatment would significantly reduce waste medical costs and is one of the substantiating arguments for the shift towards a paradigm of personalised medicine.⁹

2.4 Classification of stem cells

2.4.1 Definitive attributes of stem cells

From a clinical point of view, stem cells can be divided into two different types, namely adult stem cells¹⁰ and pluripotent stem cells, each with different cell potency and abilities to generate or regenerate different types of cells that make up the human body. Okarma¹¹ describes a stem cell as “a self-renewing cell line that gives rise to all cells and tissue of the body” or rather “Cells that can both renew themselves in the undifferentiated state as well as differentiate into descendent cells that have a specific function.”

The *American National Institute of Health* defines stem cells as “cells with the ability to divide for indefinite periods in culture and give rise to specialised cells.” Khan states “Stem cells are extremely specialized cells of the human body that are present in all mammalian species. These cells have two distinct features: their ability to renew through mitotic cell division and their ability to differentiate into all types of body cells.”¹² Stem cells have the following unique properties that distinguish them from normal cells:

⁸ *Idem* at 4.

⁹ *Idem* at 6.

¹⁰ Khan *Biotechnology in Medical Sciences* (2014) 163. Also known as somatic stem cells: One of the main roles of adult stem cells is that they remain in an undifferentiated state in the human body and multiply by cell division to replenish dying cells and restore damaged tissue and organs.

¹¹ Holland *et al supra* n13 3-4.

¹² Khan *supra* n18 153.

- They have the ability to proliferate for long periods of time and to self-renew.¹³
- Stem cells are not differentiated and therefore, unspecialised cells; and
- They possess the capability to differentiate into specialised cells.

2.5 Cell potency and differentiation

Cell potency refers to the level of plasticity a cell possesses. This in turn refers to a cell's capability of differentiating into various types of cells. The more a cell differentiates, the less potent that cell becomes. Therefore, as the cell differentiates, the cell's potency diminishes, in other words, the less specialised the cell is, the higher its potency. There are different levels of cell potency, depending on the stage of human development and the niche it originates from.

2.5.1 Totipotent stem cells

The human body is made up of germ cells, egg cells, sperm cells and somatic cells,¹⁴ all of which contain two sets of chromosomes, with the exception of germ cells. It is necessary to set out the developmental process of an embryo before totipotency, and lower potency cell levels will be explained below:

After fertilisation, the fertilised egg begins a process of cell division, each time doubling in the number of cells. Cell division takes place as the embryo migrates down the oviduct and into the uterus.¹⁵ At this stage, the formation of cells is all undifferentiated and the cells have no specific function yet. An exceptional ability of a pre-implantation embryo is its plasticity and the fact that it is totipotent. Totipotency refers to the ability of a cell to create an entire organism. In other words, if a pre-implantation embryo¹⁶ is split in half, each of its halves would be able to develop to term and create a separate entity. This is the case of twinning¹⁷

¹³ Holland *et al supra* n13 18: "[T]he hES [human embryonic stem] cell lines derived to date have a normal complement of chromosomes and are capable of prolonged proliferation. Normal (diploid) human somatic cells proliferate in culture for a characteristic number of times and then stop dividing (replicative senescence)... Because hES cell lines are derived from very early embryos, they naturally express high levels of the enzyme associated with cellular immortality, telomerase".

¹⁴ Better known as adult cells.

¹⁵ Prinsen *An analysis of the proposed regulatory framework for the procurement and distribution of stem cells* (LLM Dissertation 2010 UP) 13.

¹⁶ An embryo which has not yet been implanted into the uterus.

¹⁷ Monozygotic Twins <http://www.biology-online.org/dictionary/Monozygotic_twins> (Accessed 26 June 2016).

Totipotent cells have the capacity to differentiate into any type of tissue such as placenta and any type of tissue a body consists of. However, the plasticity of these cells are short lived and after three to five days of embryonic cell division, the first notable differentiation event occurs where an outer layer of cells, called the trophoblast, separates from the inner cell mass.¹⁸ At this first stage of differentiation of the developing embryo, the cells become more specialised, resulting in diminished potency, therefore, the cells are not totipotent anymore and thus become pluripotent.

2.5.2 Pluripotent stem cells

2.5.2.1 Embryonic stem cells

After the first differentiation phase, the three-to-five-day-old embryo is called a blastocyst and consists of cells normally referred to as the inner cell mass¹⁹. It is from the inner cell mass that embryonic stem cells are derived, which are pluripotent and can differentiate into all the different types of cells that make up an organism; however, they do not possess the ability to develop into a whole organism. This can be ascribed to the fact that these cells need a trophoblast layer (which ultimately develops into the placenta) to develop to term.²⁰ During the normal course of development of an implanted embryo, the cells of the inner cell mass would differentiate into more specialised cells with reduced plasticity. Therefore, the cells in the inner cell mass function merely as precursor cells and differentiate into tissue specific cells.²¹ The stem cells in the inner cell mass of the early-embryo are not totipotent anymore, but pluripotent.²²

The farming of the inner cell mass to procure pluripotent embryonic stem cells necessitates the destruction of the embryo as a whole and, therefore, once the inner cell mass has been farmed, it is impossible to implant the embryo into the uterus and carry the embryo to term to become a foetus. The destruction of human embryos for the gathering of pluripotent stem cells causes much ethical, religious and legal

¹⁸ *Holland et al supra* n13 16; *Khan supra* n18 9.

¹⁹ Consisting of blastomeres.

²⁰ *Holland et al supra* n13 16.

²¹ *Idem* at 17.

²² *Khan supra* n18 153-154.

debate around the world.²³ If pluripotent cells continue to develop, they become more specialised cells, which are defined as multipotent cells.

2.5.2.2 Induced pluripotent stem cells

The destruction of a human embryo causes for much ethical debate. However, the destruction of human embryos for the derivation of pluripotent stem cells can be circumvented by the direct reprogramming of somatic cells back into a pluripotent state.

In 2007, Shinya Yamanaka from the Kyoto University in Japan and James Thomson from the University of Wisconsin successfully managed to reprogram human adult fibroblast cells²⁴ back to a pluripotent state. This was accomplished by transfecting certain stem cell-associated genes into an adult non-pluripotent cell, like a skin cell. The gene transcription is accomplished by attaching them to retroviruses.²⁵ Among others, the dominant gene-transcriptional regulator Oct-3/4(Pou5f1) and Sox2 improved the efficiency of the inducement. After a few weeks, these gene-transfected cells react as if they are in a pluripotent environment and start to become as Khan²⁶ describes it “morphologically and biochemically comparable to pluripotent stem cells”. Subsequently, these cells can be isolated via morphological selection for further culturing and expansion. However, these induced pluripotent stem cells showed structural problems in the DNA methylation²⁷ and failed to create viable chimeras upon injection into developing embryos.²⁸ Viral transfection systems, which insert genes at random locations in the host’s genetic sequence, are oncogenic in nature. To overcome the oncogenic nature of the cells an Adenovirus was used for the transportation of the four indispensable genes. An Adenovirus does not pool its genes with those of the host and therefore the problem of tumorigenicity is solved.²⁹

²³ Khan *supra* n18 173.

²⁴ A fibroblast is a human skin cell.

²⁵ Devolder *The Ethics of Embryonic Stem Cell Research* (2015) 121.

²⁶ Khan *supra* n18 164.

²⁷ “DNA methylation is an epigenetic mechanism used by cells to control gene expression. A number of mechanisms exist to control gene expression in eukaryotes, but DNA methylation is a commonly used epigenetic signalling tool that can fix genes in the ‘off’ position”. Robertson “What is DNA methylation” <<http://www.news-medical.net/life-sciences/what-is-dna-methylation.aspx>> (Accessed 2 June 2016).

²⁸ Khan *supra* n18 164.

²⁹ *Idem* at 165.

This method has not been tested on human cells and other methods are also being explored such as the application of plasmid without viral transfection.³⁰

2.5.2.3 Multipotent stem cells

Multipotent or adult stem cells are formed in the foetal stage of development. The term 'adult stem cells' should not cause confusion, as these cells are present in both adults and children, therefore the term 'somatic stem cell' would be a more apt description. It was always thought that these cells are only able to produce cell types derived from the layer of the foetus in which it originated. For instance, if the stem cells originated from the middle germ layer, also called the mesoderm, they would only be able to produce cells from that layer.³¹ However, their plasticity is much greater than previously thought, as new research has disproven the notion that a cell, which is destined to produce blood cells, could not produce other types of cells, such as liver or pancreatic cells.³² It has been reported that neural stem cells, which are formed by the ectodermal layer, could become blood cells and muscle cells.³³ The main function of a multipotent cell is to repair and maintain the cells in the surrounding tissue or organ in which it is found.³⁴

2.5.3 Oligapotent stem cells

Somewhat more specialised than multipotent stem cells, oligapotent stem cells have the capacity to differentiate only into a few types of cells within specific tissue or organs such as adult lymphoid or myeloid stem cells.³⁵

2.5.4 Unipotent stem cells

A unipotent stem cell has a restricted capacity to differentiate and divide into a specific type of cell; however, it still retains the capacity to self-renew, which separates them from their non-stem cells counterparts. These cells are also termed

³⁰ *Ibid.*

³¹ The very early embryo consists of three primal germ layers such as the ectoderm (outer layer), the mesoderm (middle layer) and the endoderm (the most proximal of the three layers). The mesoderm differentiates into cells such as blood, muscle, cartilage, endothelial cells and cardiac cells.

³² Buratovich *The Stem Cell Epistles: Letters to my Students about Bioethics, Embryos, Stem cells, and Fertility Treatments* (2013) 16.

³³ Cohen *Renewing the stuff of life: stem cells, ethics, and public policy* (2007) 15.

³⁴ Khan *supra* n18 159.

³⁵ Vertes *et al supra* n9 28.

'precursor cells' and include progenitor cells, which are stem-like cells, but can only differentiate into a specific cell type and have a restricted capacity for differentiation.³⁶

The following illustration gives a terse description of the differentiation and potency of cells.³⁷

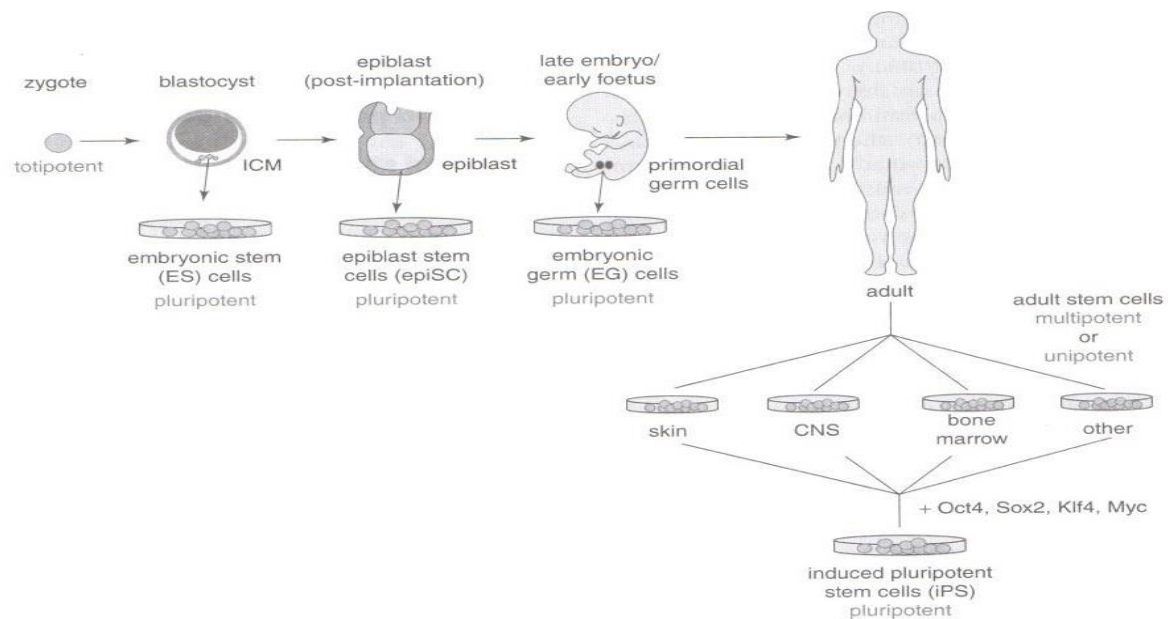


Figure 1: Cell differentiation and cell potency

Cells are described as totipotent if they possess the capacity to generate all the tissue in an organism, in addition to the extra-embryonic tissue. Pluripotent stem cells are when the cells are capable of forming any cell of an adult organism. Multipotent stem cells can differentiate into any cell type of a said tissue. In certain instances, tissue only contains stem cells, which are only able to produce and maintain a specific type of cells. These stem cells are thus unipotent. CNS =the central nervous system, ICM= inner cell mass.

³⁶ *Ibid.*

³⁷ Illustration available in Vertes et al (2015).

2.6 Sources of stem cells

2.6.1 Sources of pluripotent stem cells

2.6.1.1 Human embryonic stem cells

Human embryonic stem cells were the first source of pluripotent stem cells. These cells are derived from the blastocyst, which is the stage of development occurring three to five days after the union of the male and female gametes, called fertilisation. During this period, the blastocyst stage, the embryo is microscopic and smaller than a pinpoint.³⁸ The blastocyst consists of two layers of cells: on the outside, the trophoblast cells and, on the inside, the cells of the inner cell mass, which will develop into the embryo itself.³⁹ The cells from the inner cell mass are then separated from the cells of the trophoblast and cultured by placing the cells on feeder cells. Normally, the feeder cells are human or mouse fibroblasts, which provide the chemical environment for the survival of the inner cell mass as well and prevent cell differentiation. After a few days, these cells have divided without differentiating. This process is repeated by placing the cultivated cells onto a fresh feeder layer and gradually a stem cell line is born.⁴⁰ A stem cell line is a colony of cells that can divide perpetually, while maintaining its integrity by retaining its undifferentiated state. After the establishment of a stem cell line, these cells are frozen in batches and recovered by means of thawing when needed. It has been noted that by the year 2005 a total of 150 embryonic stem cell lines existed.⁴¹

These embryos are mainly made available for research through the donation of excess embryos subsequent to *in vitro* fertilisation and the creation of such embryos for research purposes.⁴² Many of these embryonic stem cell lines have been created by means of mouse feeder cells and may pose health risks to patients receiving cells that stem from these cell lines. In addition to patient safety reasons, those opposing the destruction of human embryos based on ethical and religious convictions are exploring other sources of pluripotent stem cells. Therefore, alternative sources of pluripotent stem cells should be discussed.

³⁸ Cohen *supra* n41 19.

³⁹ Buratovich *supra* n40 20.

⁴⁰ Cohen *supra* n41 20.

⁴¹ *Ibid.*

⁴² Origins, ethics and embryos: The sources of human embryonic stem cells
<<http://www.eurostemcell.org/factsheet/origins-ethics-and-embryos-sources-human-embryonic-stem-cells>> (Accessed 26 June 2016).

2.6.2 Alternative sources of pluripotent stem cells

2.6.2.1 Somatic cell nuclear transfer or ‘research cloning’

Many problems exist for the application of currently available embryonic stem cell therapies, particularly the problem of an immunological response that involves the rejection of stem cells by the immune system when they are transplanted into a body. Even though new research has indicated that the probability of immune rejection of pluripotent stem cells is less than that of adult stem cells, rejection is still a possibility.⁴³ To bypass this problem, scientists have to develop cells that are immunologically and genetically matched to that of the donor. One such a method is called somatic cell nuclear transfer or more commonly known as research cloning. Somatic cell nuclear transfer involves removing and replacing the chromosomes of a donated egg by a process called enucleation.⁴⁴ Researchers induce fusion of the patient nucleus and donated egg by means of chemical or electrical impulse, resulting in a human embryo. Subsequent to reaching the blastocyst stage, the embryo will be destroyed for the derivation of the stem cell located in the inner cell mass. After procurement of the embryonic stem cell, these cells can be cultured and directed to differentiate into cell types initially required for treatment by the donor. By following this route, the patient can be provided with genetically identical cells (except for their mitochondrial DNA) which would not be rejected by the patient’s immune system. Somatic cell nuclear transfer would not solve the issues regarding the destruction of what some call “nascent” human life, but it could resolve issues pertaining to immune rejection. Furthermore, the application of somatic cell nuclear transfer could be help to treat patients with gene-based conditions by combining nuclear transfer with gene transfer. The enucleated egg will be destroyed for the derivation of embryonic stem cells, whereafter these cells will be subjected to genetic modification. Subsequent to gene manipulation or alteration, the stem cells will be differentiated into the desired cell type and transplanted back into the patient to treat the genetic disorder by replacing the genetic shortfall.⁴⁵

⁴³ *Idem* at 34.

⁴⁴ Buratovich *supra* n40 23.

⁴⁵ Cohen *supra* n41 36.

2.6.2.2 Embryos via parthenogenesis

The term ‘parthenogenesis’ is derived from Greek, which translates into “virgin birth”, may provide an alternative source of human embryonic stem cells. Scientists have been familiar with this phenomenon for more than 100 years. In modern biology, parthenogenesis denotes a form of asexual reproduction in which an animal ovary can be induced into producing an embryo without being fertilised.⁴⁶ This is a naturally occurring phenomenon in some invertebrates such as bees and ants, as well as in some vertebrates such as reptiles and snakes. However, parthenogenesis does not occur naturally in mammalian development. This virgin birth can be induced in a laboratory environment by stimulating the unfertilized mammalian egg with chemical or electrical impulses to induce cell division and development into an early embryo. However, due to the fact that the egg did not receive male chromosomes, it fails to develop as it would have had it been fertilised.⁴⁷

In 2003, Winger and his team from Stemron of Maryland publicised⁴⁸ that they have grown human parthenotes (parthenogenesis on human eggs) and developed them into the blastocyst stage. This marked the first time where human stem cells were derived from human parthenotes. It should be noted that although the human parthenotes developed until the blastocyst stage, the embryos did not survive to become human organisms. In 2004, researchers from the Tokyo University declared the creation, birth and survival into adulthood of a mouse. This was done by means of parthenogenesis and gene alteration in the foetal stage of development that fluked the genetic material to react as if it had received its male genetic contribution.⁴⁹ In 2006, Italian scientists created human parthenotes from which they managed to procure pluripotent stem cells, and differentiated and cultured them into neurons.⁵⁰ However, the application of parthenogenesis in animal studies has shown that the animals have abnormal development and therefore should be treated with caution. The development of treatments using abnormal cells is troublesome and should be handled with great care.

⁴⁶ *Idem* at 43.

⁴⁷ Krimsky *supra* n10 46.

⁴⁸ Cohen *supra* n41 45.

⁴⁹ *Ibid.*

⁵⁰ Krimsky *supra* n10 46.

In short, the ersatz embryo certainly circumvents “embryocide” and serves as an alternative source of pluripotent stem cells. However, parthenogenesis is still not absolved from the ethical issues. As Krimsky⁵¹ states, even though we avoid the creation of a real human, we are acting within the realm of human engineering, which sequentially puts us firmly within the ethical debate of the creation of quasi-human life.

2.6.2.3 Human animal chimeras

A chimera is an organism which is an amalgamation of human and nonhuman cells. The creation of a non-viable chimera embryo could certainly circumvent the issue of destroying a human embryo and would provide for pluripotent stem cells generated by means of non-viable human-animal chimeric embryos. Another advantageous application could be when human embryonic stem cells or other specialised human cells are implanted into animals during the prenatal and postnatal stages of development. Subsequently, scientists might shed light on how human embryonic stem cells react and behave during the development of an organism.⁵² This type of research is further advocated by pointing out the fact that studying stem cells derived from animals such as mice can only take them so far. At some point in time, it becomes necessary to examine the idiosyncrasies of human stem cells in a living organism.⁵³ Because it would be unethical to conduct research on humans where the risks to the research participant is largely unknown, scientists have initiated research that involves inserting various types of stem cells into animals at different stages of development to explore the ways in which these cells might react. To many people it seems sickening and unnatural to develop creatures that are both beast and man. The main concerns spelling out the impermissibility of chimeras can be categorised by four ethical concerns as set out by Cohen⁵⁴:

It is impermissible because it

1. is unnatural;
2. crosses species boundaries;
3. is morally repugnant; and

⁵¹ *Idem* at 47.

⁵² *Idem* at 110.

⁵³ *Ibid.*

⁵⁴ *Idem* at 111.

4. violates human dignity.⁵⁵



Figure 2: Chimera

2.6.2.4 *Single cell embryo biopsy*

Preimplantation genetic diagnosis is a screening test for serious genetic and chromosomal conditions done on embryos created by means of *in vitro* fertilisation. The procedure involves removing one cell from the embryo during the blastocyst stage of development for purposes of assessing its composition and integrity. In the event that the cell shows genetic or chromosomal abnormalities, both the cell and the embryo are usually discarded. Conversely, if the cells turn up to show no abnormalities, the remainder seven-cell embryo is implanted into the woman's uterus with high hopes of initiating a pregnancy.⁵⁶ Because pre-genetic diagnosis shows that the embryo is capable of developing even though a cell has been removed,

⁵⁵ The chimera was a fearsome creature depicted in Greek mythology as an immortal, lion-headed goat in the middle and a serpent for a tail. This illustration was completed by Brian Barresi <http://www.brianbarresi.com/portfolio/chimera> (Accessed 2 June 2016).

⁵⁶ Cohen *supra* n41 50.

researchers asked: “Why not to use this technology for stem cell research and therapy in conjunction with pre-genetic diagnosis?”

Robert Lanza, chief scientific officer of Advanced Cell Technology, managed to create two human embryonic stem cell lines in 2006.⁵⁷ The study involved sixteen donated, thawed human embryos in the blastocyst stage of development, where 91 cells were derived from them. Of the 91 cells, only two managed to develop into human embryonic stem cell lines.⁵⁸ This method is not without ethical concerns, as these cells might be totipotent; however, a verification study cannot be undertaken, as it would require the cell to be transplanted into a woman’s uterus to test its developmental potential.

Despite the potential of the single cell being totipotent, it does provide a source of pluripotent stem cells without the destruction of a human embryo. Although the removal of a single cell from the early embryo might not cause the destruction of the embryo, people might not want the remaining seven-cell embryo for implantation. In the end, it might still just be donated for research if it has not been used for pre-genetic screening.

2.7 Source of adult stem cells

2.7.1 General

In contrast to human embryonic stem cells, adult stem cells are found in a fully developed human child or adult person. The origin of the stem cells is directly correlated to where it is situated. As an example, skin stem cells are present in the skin while neural stem cells are located in the brain. Adult stem cells are located in more types of tissue than was once thought.⁵⁹ Research has illuminated the fact that bone marrow contains two types of stem cells. Firstly, haematopoietic stem cells responsible for the formation of all types of blood cells in the body and, secondly, bone marrow stromal cells, widely known as mesenchymal stem cells that generate cartilage, fat and bone cells.⁶⁰

⁵⁷ Krimsky *supra* n10 47.

⁵⁸ Cohen *supra* n41 50.

⁵⁹ Khan *supra* n18 160.

⁶⁰ *Idem* at 160.

2.7.2 Stem cell *niche*

Stem cells are located in a particular area of each organ or tissue, called the stem cell *niche*. It has been proposed that certain types of adult stem cells are termed pericytes, meaning that they make up the outermost layer of blood vessels. *In vivo* these cells may remain undifferentiated for prolonged periods of time, until they are activated by an injury. Interestingly, these cells are found in small numbers in tissue and once they are procured, they do not perform well in culture.⁶¹

2.7.3 Cadaveric foetal tissue stem cells

These stem cells are obtained after an abortion, which may be either an elected abortion or a spontaneous abortion, including ectopic pregnancies and miscarriages. However, due to the flaws present in ectopic pregnancies and miscarriages, scientists favour the tissue and cells from electively aborted fetuses. The cells are withdrawn from fetuses that are aborted within the stage of five to nine weeks after fertilisation.⁶²

2.7.4 Placental and umbilical cord cells

There are various types of placental and umbilical cord stem cells. Everything that is transferred from a mother to her child is passed via the placenta. The placenta is an extremely specialised structure and is situated at the inner layer of the uterus and attaches to the baby's abdomen by a series of blood vessels tightly packaged in a rope-like structure, called the umbilical cord. The umbilical cord transports nutrients, oxygen and hormones in addition to serving as a return for waste products back into the mother. The developing baby is kept in suspension by means of amniotic fluid that fills the amniotic membrane or sac.⁶³

Both the placenta and the amniotic membrane hold at least four different cell types that might be used in cell therapies one day. These are amniotic epithelial cells, amniotic 'mesenchymal' cells, placental-derived mesenchymal stem cells and amniotic fluid stem cells. There is some difference of opinion regarding the ability of

⁶¹ *Ibid.*

⁶² Prinsen *supra* n23 19.

⁶³ Buratovich *supra* n40 148.

amniotic epithelial cells and amniotic mesenchymal cells to divide and differentiate perpetually; therefore, many will not term these cells as ‘stem cells’ per se.⁶⁴

2.8 Therapeutic application of stem cells

2.8.1 General

Scientists are culturing human stem cells *in vitro* with a number of different goals, one of which is to use stem cells as a base to develop new therapies for serious illnesses. These cells are grown with the hope of finding the correct signal to guide stem cells to differentiate into tissue-specific cells and transfer them to patients who suffer from serious conditions such as diabetes, spinal cord injury and heart failure.⁶⁵ As illuminated above, stem cells brought about an era of regenerative medicine and have the capacity to restore lost cellular tissue. The transferring of stem cell derivatives might also cure degenerative diseases associated with aging, such as Parkinson’s and Alzheimer’s.⁶⁶ Even more astonishing is the possibility that stem cells might lead to organ engineering such as hearts, kidneys or livers.⁶⁷ Researchers are merging efforts of genetic research with that of stem cell technologies in the hope to genetically modify and correct genes associated with hereditary diseases and disorders. This is done in order to reintroduce healthy genes into patients suffering from conditions such as haemophilia and muscular dystrophy.⁶⁸ A second major goal of scientists is to gain insight into the process of human development. The aim is to gain knowledge of how a single cell differentiates and grows into the millions of cells and vast number of different types of tissue that make up a body. Gaining this knowledge will bring about a deeper understanding of how healthy cells replace damaged ones and how cellular proliferation is controlled. These studies might shed light on abnormal cellular division within the first few days, which may lead to chromosomal and developmental disorders in neonates.⁶⁹ Stem cell research might aid in unfolding new knowledge regarding the cause of infertility and serve to eliminate premature pregnancy loss. Currently, researchers are determining the toxicity of new pharmaceuticals in animals before they commence

⁶⁴ *Ibid.*

⁶⁵ Cohen *supra* n41 11.

⁶⁶ *Ibid.*

⁶⁷ *Ibid.*: This would be a more effective way to repair tissue than the normal viral vectors and other means; Prinsen *supra* n23 18.

⁶⁸ *Ibid.*

⁶⁹ Prinsen *supra* n23 18; Holland *et al supra* n13 8.

human trials. This is done despite the major differences between human and animal physiology.⁷⁰

Due to the fact that stem cells are a source for all the different types of cells, it will in future be possible to produce cell lines that represent specific tissue and organs for testing of toxicity of new or existing drugs.⁷¹ This would help to eliminate non-viable and dangerous compounds before it is used in clinical trials. This would also eliminate the debate about animal testing, as, in future, it might not be necessary due to the new source of human tissue.

2.8.2 Application of adult stem cells

Despite the vast application of human embryonic stem cells (or pluripotent stem cells), adult stem cells still find application. Certain tissue in the body such as skin cells and blood cells are in need of constant rejuvenation due to wear and tear. Adult stem cells are formed during the foetal stage of development and are multipotent as a rule, and their plasticity is much greater than was once thought.⁷² This misconception was created due to the fact that most researchers were prone to investigate the application of pluripotent stem cells. In recent times, this does not have to be the case and multi-potency should not be a hurdle to be overcome. Studies have shown that women who received bone marrow transplants from male donors had Y-chromosomes in places other than their bone marrow such as their muscles, blood cells, hearts, brains, retinas, etc.⁷³ This is a strong indication that stem cells from bone marrow do much more than just create blood cells.⁷⁴ Researchers also managed to turn adult bone marrow cells into nerve cells by giving it the correct environment and stimulus, creating great expectation for the treatment of diseases such as Parkinson's and Alzheimer's, as well as certain spinal cord injuries. In the same spirit, stem cell scientists have coaxed human fat cells into cartilage, muscle and bone cells, which creates high hopes of cultivating replacement tissue.⁷⁵ Doctors can remove adult stem cells from healthy tissue and

⁷⁰ Cohen *supra* n41 16; Holland *et al supra* n13 6: "Stem cells may aid to identify a wide variety of potential teratogens compounds that induce fetal abnormalities".

⁷¹ Holland *et al supra* n13 7.

⁷² Buratovich *supra* n40 17-18.

⁷³ Males have both an "X" and a "Y" chromosome, while women have two "X" chromosomes.

⁷⁴ Buratovich *supra* n40 18.

⁷⁵ Cohen *supra* n41 15-17.

transplant it into the tissue that is compromised and degenerated so that new stem cells can regenerate and heal the tissue. This would allow people to be treated with their own cells and circumvent problems of immuno-rejection and ethical considerations regarding the use, derivation and application of human embryonic stem cells.⁷⁶

2.8.3 Application of human embryonic stem cells

Currently, human therapies based on the application of embryonic stem cell research are still in the experimental phase and far from being applied. Stem cell therapies mostly focus on exploring cures for debilitating diseases. This could be illustrated by researchers attempting to produce neurons from human embryonic stem cells by producing insulin to treat patients suffering from diseases such as Parkinson's and diabetes.⁷⁷ It is worth mentioning that treatments for diseases such as amyotrophic lateral sclerosis and multiple sclerosis will not be available within the next five years, but rather within ten years.⁷⁸

Other scientists believe that animal studies provide an adequate indication that certain human embryonic stem cell treatments might be effective for cell therapy. For instance, Geron Corporation, Menlo Park, California, has embarked on curing diseases such as spinal cord injury by means of embryonic stem cells.⁷⁹

2.8.4 Capita Selecta of recent stem cell therapies

2.8.4.1 Advocating stem cell therapies

The therapeutic potential of stem cell technologies is often translated into a fact it is not and it is relatively unsure when cell therapies will be available on the market. However, stem cell therapies should not be regarded as a passing fad, as the potential they hold is too great to ignore. Intuitively, an analogy can be drawn with the transformation of medicine with the advent of monoclonal antibodies in the late

⁷⁶ This type of treatment is called autologous transplantation and has been used to treat diseases such as lupus. Tissue from a compatible donor can also be used and this type of treatment is called allogeneic treatment; Khan *supra* n18 9.

⁷⁷ Krinsky *supra* n10 49-54.

⁷⁸ Cohen *supra* n41 23.

⁷⁹ Akst J Geron's Stem Cell Program Sold 2 October 2013
<<http://www.thescientist.com/?articles.view/articleNo/37749/title/Geron-s-Stem-Cell-Program-Sold/>> (Accessed 26 June 2016).

1990s.⁸⁰ In addition to stem cell transplants, cells can also be developed into medicinal products such as the allogeneic mesenchymal stem cell preparation Prochymal[®], which has been conditionally approved in Canada for the treatment of monoclonal antibody refractory paediatric acute Graft versus Host Disease.⁸¹ One of the first pioneering breakthroughs of cell therapy could be regarded as the treatment of inflammation and autoimmune diseases. Until the emergence of cytotherapeutics, orthodox medical treatment did not have the capacity to bring an improvement in such conditions. Mesenchymal stem cells have been shown to be effective in the treatment of Graft versus Host Disease, inflammatory bowel diseases and osteoarthritis.⁸² Furthermore, these kinds of therapies offer much greater efficacy and disease-modifying benefits while reducing side effects. This is the foundation on which cytotherapy is built. Contrary to traditional pharmaceutical modalities, cytotherapeutics are able to sense their environment, adapt and respond according to the stimulus they encounter. This characteristic is best explained by the paracrine effects of mesenchymal stem cells.⁸³ Furthermore, novel drug modalities are subject to patentability. Various patents have been granted for a wide range of stem cell products. However, it should be noted that embryonic stem cells are not patentable in every jurisdiction such as the EU, which states that no product that involves the destruction/prior destruction of an embryo shall be subject to patentability.⁸⁴

2.8.4.2 Adult stem cells in modern days

Undoubtedly and above all else, the future of cytotherapeutics lies with the therapeutic potential of adult stem cells such as haematopoietic and mesenchymal stem cells. Haematopoietic stem cells are regarded as the golden standard for treating diseases and disorders of the haematopoietic system and others such as immunosensitive malignancies. More than 50 000 first haematopoietic stem cell transplantations were performed with 43% as allogeneic donors and the rest

⁸⁰ Khan *supra* n18 6-7: Monoclonal antibodies first proposed by Paul Ehrlich who envisioned that medicinal compounds could be delivered accurately and precisely along with monoclonal bodies. Monoclonal antibodies are mono-specific antibodies as they are identical clones of a distinct parent cell.

⁸¹ Rattue *Prochymal – First stem cell drug approved* (2012)
<http://www.medicinalnewstoday.com/articles/24_5704.php> (Accessed 5 June 2016).

⁸² Vertes *et al supra* n9 12.

⁸³ *Idem* at 13; Paracrine signalling is a form of cell communication different from that of endocrine communication of hormones.

⁸⁴ *Idem* at 12.

autologous transplantation.⁸⁵ *Ex vivo* stem cell expansion techniques are being pursued due to the fact that the amount of umbilical cord blood cells is the limiting factor in such transplantations. If the amount of cells transplanted is too small, it may increase the risk of graft failure and delay the haematological recovery. The *ex vivo* cell expansion is focused on extrapolating the amount of CD34⁺ cells⁸⁶ from single cord blood units, which in turn could increase the chances of a successful transplantation.⁸⁷ This technique is currently applied by *Gamida Cell*, Jerusalem, which is in Phase II/III of the clinical trial. It uses copper chelator technology to generate substantial grafts from a single unit of umbilical cord blood. This generated graft is then amalgamated with the original unit and subsequently transplanted back into the patient.⁸⁸

Mesenchymal stem cells have the ability to avoid detection by the immune system. This particular characteristic opens the door for mesenchymal stem cells to be used allogeneically. Allogeneic applications would involve a sample containing mesenchymal stem cells to be expanded and cultured *ex vivo* and implanted into a different person than the one the stem cells were obtained from. A mesenchymal stem cell product, such as Cartistem[®], was developed by Medipost in Seoul, South Korea. Cartistem[®] is an allogeneic treatment derived from umbilical cord blood for knee cartilage regeneration and was approved in 2012.⁸⁹ It is worth mentioning that South Korea also approved the first stem cell therapy in 2011, Hearticellgram[®]-AMI, for treating myocardial infarction by means of a direct autologous bone marrow-derived mesenchymal stem cell injection into the ailing heart.⁹⁰

2.8.4.3 Pluripotent stem cells modern days

Given the capacity of a pluripotent stem cell to differentiate into almost any cell type, these cells are currently being researched for cellular replacement therapy. A cytotherapy derived from a human embryonic stem cell containing neural cells was first tested by Geron Corporation in a Phase I clinical trial with the hope of enhancing

⁸⁵ *Idem* at 17.

⁸⁶ CD34⁺ is a glycoprotein used as a substitute marker of haematopoietic stem cells and progenitor cells.

⁸⁷ Vertes *et al supra* n9 17.

⁸⁸ Gamida Cell – Nichord[®] (2016) <http://www.gamida-cell.com/products.asp?ID=4&t=Nicord%C2%AE> (Accessed 10 June 2016).

⁸⁹ Medipost Stem cell Drugs CARTISTEM[®] (2016) <<http://www.medi-post.com/cartistem/Medipost>> (Accessed 5 June 2016).

⁹⁰ Vertes *et al supra* n9 18.

remyelination and the promotion of motor functions to treat spinal cord injuries. Despite promising results, Geron Corporation ceased the study, claiming they had to reevaluate business factors.⁹¹ Asterias Biotherapeutics took over the study from Geron Corporation and continued the programme. In 2010, the programme was approved by the Swiss regulatory agency for therapeutic products, Swiss Medic. Approval was given for the initiation of a Phase I clinical trial of foetal brain-derived human nervous system stem cell population, which is being conducted by the University of Zürich at the Balgrist University Hospital.

One of the most exciting and promising applications of pluripotent stem cells is the development of retinal progenitor cells, which can be derived from both embryonic or induced pluripotent stem cells. Subsequent to successful pre-clinical experiments for the preservation of photoreceptors and visual function, sub-retinal transplantation procedures involving the replacement of dysfunctional retinal progenitor cells with healthy and operating ones were performed. Companies such as Pfizer, New York, in collaboration with the University of London, have undertaken to clinically test blinding diseases such as Advanced Macular Degeneration or Stargardt's macular dystrophy.⁹² The amalgamation of medical devices and cytotherapeutics may produce superior therapeutics such as a combination of limbal epithelial stem cells for the treatment of stem cell scarcities, or plasters, combined with stem cells, that have the ability to treat foot ulcers of a diabetic.⁹³ Pluripotent stem cells could also be used in the production and encapsulation of stem cell-derived insulin-secreting β -cells that could treat type 1 diabetes.⁹⁴

Many of the abovementioned technologies have a wide array of applications in the field of healthcare with proof of concepts already achieved pre-clinically for different functional elements, which is essentially a matter of replaced or artificially maintained organs or tissue. The four functional elements set out by Vertes *et al* are as follows:⁹⁵

1. Sourcing, isolating and manufacturing of pluripotent stem cells;

⁹¹ *Ibid.*

⁹² *Ibid.*

⁹³ Moura *et al* "Recent advances on the development of wound dressings for diabetic foot ulcer treatment – a review" 2013 *Acta Biomaterialia* 7093-7114.

⁹⁴ Vertes *et al supra* n9 19.

⁹⁵ *Ibid.*

2. Differentiation of pluripotent stem cells into the desired cell type;
3. Encapsulation of therapeutic stem cells in an implantable retrievable device;
and
4. Delivery of the therapeutic cells.

Technical difficulties are far from eliminated, such as: the avoidance of genetic or epigenetic abnormalities; the realization of confidence in safety and development of sophisticated differentiation practices, which is necessary to circumvent the remnant of the pluripotent stem cell in the final product, due to potential formation of teratomas of undifferentiated pluripotent stem cells.⁹⁶

2.9 Conclusion

As illuminated above, it is evident that stem cell technologies are marvellous and hold the capacity to bring about tremendous medical advancements that will cure numerous diseases and conditions. Despite the marvels of stem cells, many biomedical ethical issues come into contention when applying such technology, such as the application of embryonic stem cells, human animal chimeras to name only a few. When developing or applying stem cell technologies, there are numerous ethical issues that a stem cell researcher or practitioner should take cognisance of to ensure that they abide by the ethical rules of medical research and practice. The next chapter will give an exposition of the ethical rules that are pertinent to the development and application of stem cell technologies.

⁹⁶ *Ibid.*

CHAPTER 3

REGULATION OF THE DOCTOR-PATIENT RELATIONSHIP

3.1 Introduction and general remarks to the doctor-patient relationship

3.1.1 Introduction

Very few relationships are as unique as the one between a doctor and a patient. Since Hippocrates, the importance and necessity of a special relationship between a doctor and a patient has been a subject of discussion. Very few relationships, certainly not in law, are as tilted as the relationship between doctor and patient. During the normal course of events, a patient will see a doctor when he is ill and in need of medical care. Contrary to the patient, the doctor has the option of passing on the patient or, in certain circumstances, refusing to treat the patient. When dealing with stem cell technologies, we are dealing with novel medicinal modalities, which are sought by patients suffering from life-threatening or seriously debilitating conditions. It is due to this imbalance that the relationship between a doctor and patient should be clearly set out in relation to its regulatory framework consisting not only of national legislation, but also in professional ethical rules.

3.1.2 Definition of the doctor-patient relationship

The doctor-patient relationship could be defined in broad terms as the connection and association that amasses between a healthcare provider (the doctor) and the healthcare recipient (the patient). It is in the interest of both the doctor and the patient that they attain a symbiotic relationship based on mutual respect, knowledge, trust, collective values, and perspectives. The more the doctor-patient symbiosis thrives, the better the chance of medical success.¹ The doctor-patient relationship is built on a few core ethical principles such as veracity, privacy, confidentiality and fidelity. Each of these ethical principles will be discussed to give a broad ethical overview of what the doctor-patient relationship entails.

¹ Gupta "Humanity in Medicine" 2011 *Journal of Medical Ethics and History of Medicine* 3 <<http://jmehm.tums.ac.ir/index.php/jmehm/article/view/60/45>> (Accessed 26 June 2016).

3.1.2.1 *Obligation of veracity*

In healthcare terms, ‘veracity’ is the obligation a doctor has towards his patient to provide objective and comprehensive information, both accurately and timely. In addition to providing accurate and timely information, the doctor must nurture and provide an environment conducive to the patient’s understanding of this information. Beauchamp and Childress² make the following three arguments in support of an obligation of veracity:

The first argument is based on the respect owed to persons in contexts beyond informed consent. The second argument connects to obligations of fidelity, promise-keeping, and contract. When we communicate with others, we implicitly promise that we will speak truthfully and that we will not deceive listeners. By entering into a relationship in health care or research, the patient or subject enters into a contract that includes a right to receive information regarding diagnosis, prognosis, procedures, and the like, just as the professional gains a right to truthful disclosures from patients and subjects. The third argument is based on the role of trust in relationships between health professionals and patients and subjects. Its thesis is that adherence to rules of veracity is essential to the development and maintenance of trust in these relationships.

Veracity is just one obligation a healthcare practitioner must honour. A healthcare practitioner is charged with carefully managing what is disclosed to the patient and he or she may sometimes limit the extent of the disclosure; refrain from disclosing or, in certain circumstances, deceive or even lie to the patient if values like medical beneficence outweigh divulgence. In the context of a doctor’s obligation of veracity, the general ethical guidelines of the *Health Professions Council of South Africa* (HPCSA)³ require from a medical practitioner to act in accordance with principles such as respect for persons,⁴ beneficence,⁵ autonomy,⁶ integrity⁷ and, most importantly, truthfulness.⁸

² Beauchamp & Childress *Principles of Biomedical Ethics* (2013) 303.

³ Par 2 *Booklet 1: General Ethical Guidelines for the health care professions* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_1_guidelines_good_prac.pdf> (Accessed 29 June 2016).

⁴ *Idem* at par 2.3.1: “Respect for persons: Health care practitioners should respect patients as persons, and acknowledge, their intrinsic worth, dignity, and sense of value.”

⁵ *Idem* at par 2.3.3: “Best interest or well-being: Beneficence: Health care practitioners should act in the best interest of patients even when the interests of the latter conflict with their own personal self-interest.”

⁶ *Idem* at par 2.3.5: “Autonomy: Health care practitioners should honour the right of patients to self-determination or to make their own informed choices, and to live their lives by their own beliefs, values and preferences.”

3.1.2.3 ***Obligation of privacy and confidentiality***

There are various forms of privacy connected to the limited access to the person such as: informational privacy, often emphasised in the field of biomedical ethics; physical privacy, mostly referred to as locational privacy; decisional privacy, which pertains to personal choices; and relational or associated privacy, which includes family and other intimate relationships into the decisions an individual makes in conjunction with other people.⁹

When a patient or a research participant grants others access to personal information regarding his or her health, they usually surrender some degree of privacy. In doing so, the patient does not lose complete control over such information and usually retains substantial control over information that is given or generated in the course of diagnosis, research, and therapy.¹⁰ For example, a doctor is prohibited from divulging information regarding a patient or research participant to insurance companies or prospective employers without the patient or research participant consenting to such divulgence. In the event that others obtain such privileged information without authorisation, they are either infringing on a person's right to privacy or the person's right to confidentiality or both.¹¹ Beauchamp & Childress¹² clearly set out the difference between privacy and confidentiality.

The basic difference between the right to privacy and the right to confidentiality is that an infringement of a person's right to confidentiality occurs only if a person or institution to whom the information was disclosed in confidence fails to protect the information or deliberately discloses it to someone without first-party consent. By contrast, a person who, without authorisation, obtains a hospital record or gains access to a computer database violates the right to privacy, but does not violate the

⁷ *Idem* at par 2.3.6: "Integrity: Health care practitioners should incorporate these core ethical values and standards as the foundation for their character and practice as responsible health care professionals."

⁸ *Idem* at par 2.3.7: "Truthfulness: Health care practitioners should regard the truth and truthfulness as the basis of trust in their professional relationships with patients."

⁹ Beauchamp & Childress *supra* n104 312.

¹⁰ *Idem* at 316.

¹¹ *Ibid.*

¹² *Idem* at 317.

right of confidentiality. Only the person or institution who obtains information in a confidential relationship can be charged with violating the right of confidentiality.

There are two general types of justification for the principle of confidentiality, the first of which appeals to the principle of respect for autonomy. This is based on the fact that if a healthcare practitioner disregards the autonomy and privacy of a patient, they fail to uphold the confidentiality of the doctor-patient relationship.¹³ This is true irrespective of whether the healthcare practitioner explicitly recognised such a promise or not.¹⁴

The second justification is based on the premise that confidentiality must be maintained as a necessary condition for a healthcare provider to do his or her job properly.¹⁵ In the event that medical confidentiality is disregarded by a healthcare researcher or practitioner, patients or participants would feel discouraged to divulge sensitive information to the healthcare researcher or practitioner. In turn, such disregard would lead to faulty diagnosis and ultimately would have a negative impact on the patient's health.¹⁶ In short, the trust vested in a doctor-patient relationship would be placed in jeopardy if a doctor fails to maintain proper patient confidentiality.

Due to the fact that the second justification requires a healthcare practitioner to balance the consequences of divulgences to third parties and the maintenance of patient confidentiality, it has been at the centre of much controversy.¹⁷ As the second justification is based on consequentialism, it requires a healthcare practitioner to actively balance the potential benefits of upholding confidence with the benefits of revealing sensitive, confidential information to parties in need thereof.¹⁸

In the landmark decision in *Tarasoff v Regents of the University of California*,¹⁹ the court found that healthcare professionals have to weigh up the possible dangers contained in the confidential transmissions between doctors and their patients

¹³ Beauchamp *et al* *Contemporary issues in bioethics: International edition* (2014) 36.

¹⁴ *Ibid.*

¹⁵ *Ibid.*

¹⁶ *Ibid.*

¹⁷ *Idem* at 37.

¹⁸ *Ibid.*

¹⁹ *Tarasoff v Regents of the University of California* 1976 17 Cal 3d 425, 131 Cal Rptr 14, 551 P.2d 334 (hereinafter referred to as the "Tarasoff case").

against the duty of maintaining confidentiality. An immense ethical concern that emerged in this judgement is the question whether allowing doctors to disclose sensitive and confidential information to endangered third parties undermines the benefit of the medical system, which is designed to be conducive to an environment for patients to seek help.²⁰

At first glance, this problem could be solved by taking the first justification as an absolute and disregarding the broader social benefit brought about by disclosing confidential information. However, it is clear that the benefit of disclosing confidential information to endangered third parties would be lost when taking an absolutist approach. This is best illustrated when considering instances where a medical practitioner discloses information regarding contagious diseases, child abuse, gunshot wounds and sensitive genetic information to the relatives/parties of the patient or research participant.²¹

Beauchamp *et al*²² proposed that a “firm”, yet not absolute, stance of confidentiality be adopted, which would provide for special circumstances where confidential information regarding a patient may be disclosed to third parties. The general ethical guidelines for health care professions oblige healthcare practitioners to uphold and nurture the values of confidentiality²³ and community.²⁴ Furthermore, the ethical and professional rules of the HPCSA are tantamount to the “firm approach” as espoused in Beauchamp *et al*,²⁵ instead of an “absolute approach” to confidentiality by stating in rule 13 that:²⁶

²⁰ Beauchamp *et al supra* n115 37.

²¹ *Ibid.*

²² *Ibid.*

²³ *Booklet 1: General Ethical Guidelines for the health care professions* par 2.3.8 <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_1_guidelines_good_prac.pdf> (Accessed 29 June 2016): “Confidentiality: Health care practitioners should treat personal or private information as confidential in professional relationships with patients – unless overriding reasons confer a moral or legal right to disclosure.”

²⁴ *Idem at* par 2.3.12: “Community: Health care practitioners should strive to contribute to the betterment of society in accordance with their professional abilities and standing in the community.”

²⁵ Beauchamp *et al* n115 37.

²⁶ Rule 13 Booklet 2 of the Ethical and Professional rules of the HPCSA as promulgated in GG R717 of 2006 <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_2_generic_ethical_rules_with_anexures.pdf> (Accessed 29 June 2006).

- (1) A practitioner shall divulge verbally or in writing information regarding a patient which he or she ought to divulge only –
 - (a) in terms of a statutory provision;
 - (b) at the instruction of a court of law; or
 - (c) where justified in the public interest.

- (2) Any information other than the information referred to in subrule (1) shall be divulged by a practitioner only –
 - (a) with the express consent of the patient;
 - (b) in the case of a minor under the age of 12 years, with the written consent of his or her parent or guardian; or
 - (c) in the case of a deceased patient, with the written consent of his or her next-of-kin or the executor of such deceased patient's estate.

Akin to the *Tarasoff* case, rule 13 makes it clear that the doctor is permitted to divulge confidential information regarding the patient without the patient consenting thereto, if it is in terms of law, a court order or in public interest. Confidential information disclosed for any other reasons as those stated in subrule 1, without the express consent of the patient or research participant, is considered unethical.

3.1.2.4 Obligation of fidelity

The moment a healthcare professional enters into a relationship of significant fiduciary trust, a duty of fidelity arises. A significant fiduciary relationship is established in the event that a promise is exchanged to carry out instructions faithfully or to abstain therefrom. In context of research, an obligation of fidelity can differ greatly from clinical practice. Nevertheless, central to both contexts are the values of trustworthiness and loyalty. Even though this is a cornerstone of ethical medical practice, conflicts of interest often arise.²⁷ The effect of a conflict of interest will be elucidated later on in the chapter. As the principles upon which the doctor-patient relationship is built clearly illuminate, an examination of the recent shifts in the approach to the doctor-patient relationship will form the topic of discussion.

3.1.2.5 Development of the doctor-patient relationship

In the past, the doctor-patient relationship was characterised by medical paternalism. In laymen's terms, it can be described as the "doctor-knows-best" approach and the

²⁷ Beauchamp & Childress *supra* n104 324.

patient's role is only to answer the doctor's questions and faithfully comply with the doctor's instructions. However, this is no longer the case, as there has been a shift towards a more mutual decision-making, patient-based approach.²⁸ Nowadays, patients are encouraged to ask questions, while doctors are encouraged to see patients as having expertise. This approach has tilted the scales in favour of patient autonomy, as espoused by the case of *Castell v de Greef*.²⁹ The court's rationale for adopting a more patient-based approach was that such an approach is in line with the fundamental values and rights of autonomy and self-determination.³⁰

Before discussing the ethical rules and guidelines governing the medical professions relating to stem cell technologies, it is essential to be acquainted with the structure and legislative framework in which medical researchers and practitioners operate.

3.2 South African legislative framework of the doctor-patient relationship

3.2.1 The Health Professions Council

Despite the application of the Constitution and certain common-law principles that transcend the boundaries of the relationship between doctor and patient, the medical profession is primarily regulated by statute.³¹ Central to the statutory framework is the Health Professions Act (HPA).³² The HPA provides for the creation of the HPCSA. The HPCSA is the regulatory body charged with oversight of all matters pertaining to training and the manner in which doctors diagnose, treat or prevent physical or mental defects, illnesses or deficiencies in humankind.³³

²⁸ Herring *Medical Law and Ethics* 5th ed (2014) 10.

²⁹ *Castell v de Greef* 1994 4 SA 408 (C): In *Castell* the plaintiff consulted the defendant, a plastic surgeon, who advised that she should consider having a mastectomy as a precautionary measure. The operation was not a success and the plaintiff sued successfully for damages; See also Thomas "Where to from *Castell v De Greef*? Lessons from recent developments in South Africa and abroad regarding consent to treatment and the standard of disclosure" 2007 *SALJ* 188.

³⁰ *Idem* at 426.

³¹ Carstens & Pearmain *Foundational Principles of South African Medical Law* (2007) 249.³² Health Professions Act 56 of 1974 as amended by Act 89 of 1997 (hereinafter referred to as the "HPA").

³² Health Professions Act 56 of 1974 as amended by Act 89 of 1997 (hereinafter referred to as the "HPA").

³³ Coetzee & Carstens "Medical malpractice and compensation in South Africa" 2011 *Chi-Kent L Rev* 1263.

The HPA states that no person may practice as a medical practitioner unless they are registered.³⁴ Acting on the recommendation of the HPCSA and the relevant professional board, the Minister of Health may define the scope of a specific profession by means of promulgating a regulation.³⁵ This necessitates the specification of certain acts that are deemed to fall within the scope of the said profession. It should be noted that such a regulation may only be made after the relevant professional board was given an opportunity to submit recommendations regarding the scope of the said profession.

The HPA forbids any person from practising any profession, which has been defined by the minister as a health profession unless they are registered in accordance with the act.³⁶ Acting in contravention of this prescription constitutes an offence that is punishable by a fine or imprisonment for a period not longer than twelve months, or both a fine and imprisonment.³⁷

In *Veriava v President of the South African Medical and Dental*³⁸ the court ruled that the HPCSA is the individual source of power that has to decide on what is regarded ethical or unethical practice. Furthermore, the court held that the HPCSA is considered the custodian of the medical profession and public interest in the event that the conduct of a healthcare practitioner has an effect on the profession or the public.³⁹ Some of the far-reaching powers vested in the HPCSA are that it may: financially aid the professional boards in the performance of their functions, consider any matters that have an effect on a profession registered with the HPCSA or make representation or take action in connection with such matters as the council deems fit, make rules on any matter deemed necessary or pragmatic by the HPCSA for the furtherance of the objects of the HPCSA.⁴⁰ It is important to take cognisance of the fact that the HPCSA is allowed to establish committees as it deems necessary, together with disciplinary committees and ad hoc disciplinary appeal committees.⁴¹ In

³⁴ S 34 read with s 39 of the HPA.

³⁵ *Idem* at s 33(1).

³⁶ *Idem* at s 39(1)(b) read with s 33.

³⁷ *Idem* at s 49 of the HPA.

³⁸ *Veriava v President, South African Medical and Dental Council* 1985 2 SA 293 (T) at 307.

³⁹ *Ibid.*

⁴⁰ Carstens & Pearmain *supra* n133 252.

⁴¹ *Ibid.*

delegating powers to any committee, the HPCSA is by no means stripped from its powers after delegation and remains the custodian of the medical profession.

3.2.2 Health professional boards

The HPA provides for the creation of professional boards related to all the registered professions in terms of the act. The Minister of Health, guided by the recommendations of the HPCSA, may reconstitute the professional board of a specific profession and establish other boards.⁴² Of particular interest is the Medical and Dental Professions Board. Legally spoken, the professional boards are under the authority of the HPCSA; however, in practice they function mostly autonomously.⁴³ Professional boards are afforded extensive powers under the HPA,⁴⁴ such as the power to remove names from the register or restore names to it, to suspend a registered practitioner pending a formal enquiry⁴⁵ and to consider any matters affecting a profession within the jurisdiction of the professional board.⁴⁶ A professional board is allowed to institute an inquiry into any complaint, charge or allegation of unprofessional conduct of registered practitioners.⁴⁷ Any decision made by the professional board, which falls within the jurisdiction of the board's powers, shall not be subject to ratification. This can be ascribed to the fact that the HPCSA is charged with the duty to determine which matters will fall directly within the ambit of a professional board. A professional board has the power to inquire into any complaint, charge or allegation of unprofessional conduct of any registered person in terms of the HPA.⁴⁸ Upon a guilty conviction, the board may institute an appropriate penalty for such conduct.⁴⁹

⁴² S 15(2) of the HPA.

⁴³ Coetzee & Carstens 2011 *Chi-Kent L Rev* 1264; Professional Boards: Medical and Dental, Health Professions Council of South Africa <<http://www.hpcsa.co.za/Professionals/ProBoards.>> (Accessed 10 June 2016).

⁴⁴ S 15B of the HPA: General powers of the professional boards.

⁴⁵ S 15B(1)(a) of the HPA.

⁴⁶ S 15B(1)(b) of the HPA.

⁴⁷ S 41 of the HPA.

⁴⁸ S 15(5)(f) of the HPA, read with the regulations published in GN R. 979 of 1999-08-13, allows for the establishment of such boards; S 41(1) of the HPA: Inquiries by professional boards into charges of unprofessional conduct; For further reading see Coetzee & Carstens 2011 *Chi-Kent L Rev* 1266.

⁴⁹ S 41(1) of the HPA.

Unprofessional conduct is in essence defined as *improper, disgraceful, dishonourable* or *unworthy* conduct.⁵⁰ It should be noted that the HPA makes no explicit reference to unprofessional conduct in section 42(1) of the HPA and only refers to improper or disgraceful conduct. This means that when an inquiry is held into the “unprofessional conduct” of a practitioner, it has to be determined whether the practitioner acted in an *improper* or *disgraceful* manner.

3.2.3 Unprofessional conduct

When considering whether a practitioner’s conduct is improper or disgraceful, simple semantics do not satisfy the test. In 1934, the case of *Groenewald v South African Medical Council*⁵¹ cited English case law for guidance as to what should be regarded as *improper* or *disgraceful* conduct. With reference to *Allinson v General Council of Medical Education and Registration*⁵² the court adopted the following definition:

If it is shown that a medical man, in pursuit of his profession has done something with regard to it, which would be reasonably regarded as disgraceful or dishonourable by his profession brethren of good repute and competency, then it is open to the General Medical Council to say that he has been guilty of ‘infamous conduct in professional respect. The question is not merely whether what a medical man has done would be an infamous thing for anyone else to do, but whether it is infamous for a medical man to do. An act done by a medical man may be ‘infamous’ though the same act done by anyone else would not be infamous, but, on the other hand, an act which is not done ‘in a profession respect’ does not come within this section. There may be some acts which although they would be infamous in any other person, yet if they are done by a medical man in relation to his profession, that is, with regard either to his patients or to his profession brethren, may be fairly considered ‘infamous conduct in a profession respect. I adopt that as good definition....⁵³

The opinion has been aired that improper or disgraceful conduct can be seen in four divisions namely: (a) medical malpractice, (b) improper or disgraceful conduct in relation to patients, (c) improper or disgraceful conduct in relation to fellow practitioners and (d) other improper or disgraceful conduct unfitting to a medical practitioner.⁵⁴

⁵⁰ S 1 of the HPA.

⁵¹ *Groenewald v South African Medical Council* 1934 TPD 404.

⁵² *Allinson v General Council of Medical Education and Registration* 1894 1 QB Div. 750.

⁵³ *Groenewald v South African Medical Council supra* n153 411.

⁵⁴ *Carstens & Pearmain supra* n133 263.

Medical malpractice can be described as medical treatment considered to be negligent, improper or dissonant with good medical practice. Improper or disgraceful conduct relates to acts that are regarded as unethical by members of the medical fraternity such as a breach of confidentiality, exploiting the relationship between the doctor and patient or that of the families, engaging in an illicit sexual relationship with a patient, charging of fees for medicine which has not been put through a clinical trial, over-servicing or the application of novel medical treatment or medical innovation without ethics clearance or informed consent.⁵⁵

3.3 Medico-ethical codes of conduct and unprofessional conduct

Given the fact that a court of law is clearly not bound by the medical ethical codes of conduct and medical practices when determining liability for medical malpractice, the dominant ethical principles and practice of the medical profession will weigh heavily in the consideration as to what constitutes medical malpractice.⁵⁶ Various national and international medical ethical codes of conduct regulate the medical profession.⁵⁷ In South Africa, to promote the ethical behaviour of medical practitioners, the Health Professions Council, in consultation with the professional boards, created a code of conduct that is in line with the provisions of the HPA, specifying conduct which constitutes unethical behaviour and would be subject to review.⁵⁸ The Ethical and Professional Rules of Conduct for Practitioners Registered under the HPA,⁵⁹ embody the most important national medical ethical codes of conduct. Cognisance should be taken of the fact that the specified acts or omissions listed in the rules for which the professional boards may institute an inquiry are by no means *numerus clauses*.

⁵⁵ *Idem* at 264.

⁵⁶ Coetzee & Carstens 2011 *Chi-Kent L Rev* 1267.

⁵⁷ In the United States of America, the American Medical Association Code of Medical Ethics <<http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics.page>> (Accessed 29 June 2016); In the United Kingdom, the General Medical Council's Guidance on Good Medical Practice <http://www.gmc-uk.org/guidance/good_medical_practice.asp> (Accessed 29 June 2016); Globally applicable is the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects <<http://www.wma.net/en/30publications/10policies/b3/17c.pdf>> (Accessed 29 June 2016).

⁵⁸ Ethical and Professional Rules of the Health Professions Council of South Africa R 717 as promulgated in GG 29079 of 2006-08-04 <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_2_generic_ethical_rules_with_anexures.pdf> (Accessed 29 June 2016).

⁵⁹ *Ibid*.

3.3.1 General ethical guidelines and standards for good practice

The medico-ethical rules and guidelines set out by the HPCSA have been incorporated into a collection of booklets, each related to a specific field of medicine and containing the binding ethical rules for the registered healthcare professions.⁶⁰ For purposes of this discussion, the guidelines for good practice for healthcare professionals will be used as a foundation, with references made to other instructive policy documents where necessary and appropriate.

A healthcare professional has an incumbent duty placed on him or her to abide by the core ethical values⁶¹ necessary for good clinical practice. This duty is multifaceted and includes a duty to patients, colleagues and other healthcare practitioners, towards themselves, the profession, society and the environment. The duty towards a patient will form the basis of the discussion from here on and includes the duties towards: the patient's best interest or well-being, respect for patients, ensuring informed consent, patient confidentiality, patient participation in their own healthcare decisions, impartiality and justice, access to medical care and avoiding potential conflicts of interest.

Solving ethical issues such as conflict of interest or a potential breach of patient confidentiality can be very difficult as many conflicting interests need to be considered to determine what will be ethical and good clinical practice. Therefore, an approach to identify and solve biomedical issues must be adopted. In the next section, the biomedical perspective of principlism will be suggested as a suitable standard for medical professionals to deal with an ethical conundrum.

⁶⁰ HPCSA Professional Conduct and Ethics <<http://www.hpcsa.co.za/Conduct/Ethics>> (Accessed 15 June 2016).

⁶¹ The purpose of this discussion is not to focus on all the different ethical values that form the foundation of the medical practice, but to highlight certain applicable ethical values as they appear in context of stem cell technology. However, the ethical values set out in the *General Ethical Guidelines for Health Care Professionals* are as follows: Respect for persons, beneficence, non-maleficence, human rights, autonomy, integrity, truthfulness, confidentiality, compassion, tolerance, justice, professional competence and self-improvement and contribution to the community. *Booklet 1: General Ethical Guidelines for Health Care Professionals* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_1_guidelines_good_prac.pdf> (Accessed 15 June 2016). For a broad and in-depth view of the different bioethical values, see the work of Beauchamp & Childress *supra* n104.

3.3.2 Solving bioethical issues

Health care has traditionally been based on the principle of *primum non nocere* or “do no harm”. In a contemporary setting, we rely on a more patient-orientated holistic approach.⁶² Among other bioethical perspectives such as *consequentialism* and *deontology*, *principlism* is regarded as one of the most influential approaches to bioethics, advocating an approach to solving ethical dilemmas by using the following four principles: autonomy, beneficence, non-maleficence and justice.

As espoused by the influential work *Principles of Biomedical Ethics* written by Beauchamp and Childress, these four principles represent a “common morality” that is respected around the world.⁶³ Although the authors regard all principles as equally valuable, autonomy has been regarded as “first amongst equals”.⁶⁴ Beauchamp and Childress submit that these principles do not readily provide a solution for the conflict between these values; however, they do provide a framework for identifying the moral issue.⁶⁵ The degree of conflict between the different principles fades as the four principles are defined more precisely⁶⁶. A discussion of the four principles will follow to give a terse overview of the values that a medical practitioner has to take into account when confronted with a moral conundrum.

3.3.2.1 Autonomy

Autonomy is revered as the primary principles of biomedical ethics.⁶⁷ Autonomy in the context of health care is concerned with respecting a patient’s right to make his or her own decisions regarding medical treatment. Against this backdrop, it is important for a healthcare practitioner to always obtain informed consent by sensitising the patient to both the benefits, possible side effects and alternatives to the proposed treatment.⁶⁸ Autonomy does not require respect for every choice the patient makes, but only those choices that are competent. Therefore, in certain circumstances, the decisions of children and the mentally ill can be overruled.⁶⁹

⁶² Moodley (ed) *Medical ethics, law and human rights: A South African perspective* (2014) 5.

⁶³ Beauchamp & Childress *supra* n104 6.

⁶⁴ Herring *Medical Law & Ethics* 6th ed (2015) 25

⁶⁵ Beauchamp & Childress *supra* n105 ch 1.

⁶⁶ Herring *supra* n166 25

⁶⁷ *Ibid.*

⁶⁸ Pepper & Nöthling Slabbert 2015 *SAJBL* 4, 5.

⁶⁹ Herring *supra* n166 26; For an in-depth discussion regarding the obtaining of informed consent pertaining to minors and mentally ill patients or research participants please see Prinsen *supra*

The importance of autonomy can be ascribed to the turn to human rights. In this light, “patients are not regarded as subjects of a higher authority but as individuals, each with their own rights.”⁷⁰Autonomy and self-determination are both enshrined in the provisions regarding the right to bodily and psychological integrity, the right to privacy, the right to life and human dignity.⁷¹

3.3.2.2 Beneficence

Beneficence is based on the premise that medical professionals must do good for their patients. According to the Hippocratic Oath, the physician promises to “follow that system of regimen which, according to my ability and judgement, I consider for the benefit of my patients”. This principle is focused on the positive ethical duty owed by a health professional towards the patient. Furthermore, it entails that before applying a specific therapy, it must be shown that the said therapy will be of benefit to the patient, preferably through well-controlled clinical trials.⁷² It should be noted that the law rarely places an obligation to act positively on someone. However, in ethics, the principle of seeking to benefit others, or at least acting to cause greater good than harm, is one that is revered among many as ethical thinking.⁷³

3.3.2.3 Non-maleficence

The Hippocratic Oath states: “I will use treatment to help the sick according to my ability and judgement, but I will never use it to injure or wrong them.”⁷⁴ This can be translated into a duty incumbent on medical professionals not to do harm to others.⁷⁵ Herring asked the question: “What, however, does it mean to be harmed?” and refers to the work of Harrosh who suggests certain aspects of humanity that could lead to harm:⁷⁶

n23 ch 5 as the onslaught of this dissertation is mostly concerned with *compos mentos* patients or participants. However, it cannot be ignored entirely and the reader has to take cognisance thereof.

⁷⁰ *Ibid.*

⁷¹ S 10, 11, 12, 14 & 27 of the Constitution.

⁷² Pepper & Nöthling Slabbert 2015 *SAJBL* 4, 5.

⁷³ Herring *supra* n166 28.

⁷⁴ Beauchamp & Childress *supra* n104 6.

⁷⁵ *Ibid.*

⁷⁶ Herring *supra* n166 27.

- (1) We are conscious beings and can have harmful negative experiences such as pain, discomfort, sadness, and a sense of worthlessness.
- (2) We are beings with a physical and psychological integrity which can be harmed through disease or improper functioning of the body.
- (3) We are rational beings who set goals and form values. We can be harmed if our plans for our life or values are hindered.
- (4) We are creatures of meaning and can be harmed if we cannot engage with the basic goods of life, such as relationships.

The harm should not be disproportionate to the benefits of the treatment. Whether or not the proposed treatment of therapy causes harm that exceeds the benefit thereof is a fact that is established in a clinical trial setting during phases I and II. Bearing this in mind, applying treatments that have not been shown to be efficacious would be dissonant with the principle of non-maleficence.

Non-maleficence must not be seen in isolation, but rather in relation to all the other ethical values. As stated above, these values are all equal and in case a medical practitioner wants to apply novel or innovative medical therapy, due consideration must be given to determine whether such conduct would be of more benefit to the patient than the imminent harm thereof.

3.3.2.4 Justice and fairness

The definition of justice is a contentious issue. It is often described in the context of what is regarded as fair, equitable or reasonable. In the context of health care, justice is particularly concerned with issues regarding the use and allocation of scarce resources.⁷⁷ At the heart of justice is the principle of substantive equality, which acknowledges the fact that everyone is not equal and therefore those that are “unequal” should be treated “unequally”, as opposed to the “one-size-fits-all approach”.⁷⁸

In South Africa, distributive justice will ensure that all South Africans will receive the benefits of stem cell technologies. Applying these four principles, which resonate

⁷⁷ *Idem* at 28.

⁷⁸ *Ibid.*

with the provisions in the Constitution, will promote ethical practices and will help to determine the criminal or professional liability of healthcare practitioners.

The following section is written from the point of view that stem cell technologies are, in most instances, regarded as either *innovative therapy* or *experimental research* and *medicine* for the purposes of the Medicines and Related Substances Act.⁷⁹ Throughout this dissertation, compelling arguments will be made to substantiate the claim that stem cell therapy is tantamount to medicine. A critical analysis of the ethical guidelines and rules pertaining to stem cell technologies and its applications follows.

3.3.3 Ethical guidelines pertaining to stem cell technologies

The fact that medical research has benefitted the well-being of thousands of people is uncontested. Alongside the power to save lives and ameliorate diseases, there is a concurrent duty to achieve these goals via ethical means and practices. When conducting health research, a researcher has to consider the possibility of an adverse reaction to the research subject and, at the same time, uphold his or her duty to protect the rights of research participants. Responsible health research is twofold and not only demands a scientific contribution for the good of humans and animals, but also that such contribution is brought about in an ethical way.

Health research ethics committees make use of a protocol review procedure for the consideration of all ethical questions relating to human and animal proposals and protocols. The NHA⁸⁰ requires that all proposals and protocols be authorised by an accredited health research ethics committee.⁸¹

The duties bestowed upon a health researcher towards a research participant include:⁸² to act in the best interest of the research participant, to respect the research participants, to adhere to principles of informed consent, to safeguard the

⁷⁹ S 1 of the Medicines and Related Substances Act 101 of 1965 as amended by the Medicines and Related Substances Amendment Act 59 of 2002 (hereinafter referred to as the "MRSCA").

⁸⁰ NHA.

⁸¹ *Idem* at s 72-73.

⁸² Par 6 *Booklet 6 Generic Ethical Guidelines for Researchers: Medical Biotechnology Research* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 7 July 2016).

research participant's confidentiality, to maintain impartiality conform to principles of justice, and to avoid conflicts of interests such as the unnecessary conflation of medical research and medical care.

South Africa is a developing country and therefore healthcare practitioners have a duty to be sensitive to cultural differences and perspectives relating to health and health care that might come into contention. It is of the utmost importance for healthcare researchers/practitioners to avoid the exploitation of the vulnerable and the weak for their own benefit and to act in the best interest of the research participant or patient.⁸³

3.3.3.1 Acting in the best interest of the research participant

As alluded to above, stem cell therapy and technologies are still in its infancy. Many of the current treatments available on the market have not been afforded marketing authorisation and are still in the clinical trial phase. This means that safety and efficacy still have to be proven before the product or therapy will be afforded marketing authorisation and prescribed to patients.

Acting in the best interest of the research participant is in line with the principle of beneficence and requires health researchers to place the life, well-being, health, privacy and dignity of the research participants before all other interests at all times.

Most patients/participants will primarily resort to conventional treatments and will only opt for experimental stem cell treatments as a last resort. When choosing a research subject, a health researcher should be aware of the fact that he or she is in a position of power over the research participant and should avoid abusing this power.

Stem cell-based interventions are not free from adverse medical effects such as tumour growth⁸⁴, immunological reactions⁸⁵, unexpected or unpredictable cell

⁸³ Par 3.1 *Booklet 7: Medical Biotechnology Research*
<http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_7_medical_biotechnology_research.pdf> (Accessed 10 June 2016).

⁸⁴ Pepper & Nöthling Slabbert 2015 *SAJBL* 23, 29.

⁸⁵ Krinsky *supra* n10 10.

behaviour and long-term health conditions.⁸⁶ However, before human experimentation can be initiated, appropriate animal models should be followed. A health researcher should refrain from engaging in stem cell therapy unless he or she is certain that the risks are or will be managed adequately throughout the duration of the research experiment. If the continuation of the research poses risks that are harmful or outweigh the potential benefit, the research project should be ceased immediately.

Furthermore, health researchers should abstain from offering any undue inducement or incentives to entice potential research participants to partake in the study. Even though research participants are allowed to be reimbursed for all the reasonable costs incurred as a result of participation such as loss of income, such payment should be specified in the proposal or protocol.⁸⁷ Clinical trials that involve experimental drugs such as stem cell treatments may also pose compensation claims for non-medical-related injuries, as was decided in the case of *Venter v Roche Products*.⁸⁸ Certain critical points of discussion emerged from this judgement and were set out by Nöthling Slabbert *et al*⁸⁹ as follows:

- Regulators are responsible for assessing and approving the nature of the compensation for research-related injuries when reviewing or approving a research proposal or protocol.
- An informed consent document is regarded as binding on the research participant as approved by the regulators, and any amendments should be in writing and liaised with the appropriate regulator in order to be legally binding.
- There is a need for implementing an adequate informed consent process that distinguishes between a health researcher and a sponsor and sets out the limits of compensation.

⁸⁶ Pepper & Nöthling Slabbert 2015 *SAJBL* 23, 29.

⁸⁷ Par 6.1 *Booklet 1: General Ethical Guidelines for the Health Care Professions* <http://hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_1_guidelines_good_prac.pdf> (Accessed 26 June 2016).

⁸⁸ *Venter v Roche Products (Pty) Ltd* A11/2014 2014 ZAWCHC 157.

⁸⁹ Nöthling Slabbert *et al* 2015 *SAJBL* 42.

- A delictual claim based on research-related injuries will fail in the event that a plaintiff has signed an informed consent document that limits his or her right to compensation.

It should be kept in mind that a health researcher is charged with the duty to respect his research participants and that, in all instances, should safeguard and avoid infringements on the human rights of the research participants.⁹⁰ One of the ways in which a researcher can make sure that he does not unduly infringe on rights such as dignity and privacy of participants is to have an ongoing discussion and obtain full and voluntary informed consent.

3.3.3.2 Informed consent

Before the initiation of health research or medical treatment, it is vital that informed consent is obtained from the patient or participant. This requirement resonates with the ethical and constitutional duty to respect the autonomy of the patient or research participant. In line with section 12(2)(c) of the Constitution, the NHA states that research on a living person may only be conducted with that person's informed consent.⁹¹ Research ethics committees are required to ensure adherence to principles of informed consent, which entail: (1) disclosure, (2) understanding or appreciation, (3) voluntariness and (4) the capacity to consent.⁹²

In applying a non-threatening approach, a researcher is required to supply any potential research participant with any information for the consent to be informed.⁹³ This means informing the potential participant of their rights to be informed about new findings and the consequences of withdrawal from the research project. Participants must be made aware of the availability of peer counselling for

⁹⁰ Par 6 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

⁹¹ S 71 of the NHA.

⁹² The HPCSA has set out guidelines on how a health practitioner must seek patients' informed consent in *Booklet 9: Informed Consent* http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_9_informed_consent.pdf (Accessed 2 June 2016).

⁹³ Par 7 *Booklet 9: Informed Consent* <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_9_informed_consent.pdf> (Accessed 7 July 2016).

assistance in making informed choices as well as the possibility of terminating their participation.

Disclosure of research proposals and protocols that affect the research participant either directly or indirectly in some instances is mandatory and should be communicated to participants in such a manner that there is no uncertainty regarding their rights in the study.⁹⁴ The World Medical Association developed the Declaration of Helsinki, which states the ethical principles that govern human medical research and identifiable human biological material.⁹⁵ The Declaration of Helsinki primarily addresses medical practitioners, but is commonly used by health researchers and fortifies the informed consent requirements for ethical approval. The ethical guideline for informed consent pertaining to research subjects was compiled with reference to the Declaration of Helsinki and the Constitution. In the case where new information is revealed or changes in the research procedures take place, informed consent must be obtained from the continuing participants anew.⁹⁶

The very nature of informed consent requires that the research participant should have sufficient information regarding the nature and effect of the research, particularly regarding the consequences, risks and benefits, in order for him or her to be able to make an informed choice.⁹⁷ The wellbeing of the patient is always vested in the health researcher and not in the participant and should be maintained even though the participant has consented to the experiment. The above information should be communicated in a language and manner that the participant understands, taking into account his level of literacy, understanding and values. Participation should remain voluntary at all times and should never be forced. ⁹⁸Informed consent

⁹⁴ Par 2.6.4.1 *Booklet 7: Medical Biotechnology Research*, states essential information that must be disclosed to biotechnology research participants in order to facilitate informed consent <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_7_medical_biotechnology_research.pdf> (Accessed 26 June 2016).

⁹⁵ World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects <<http://www.wma.net/en/30publications/10policies/b3/17c.pdf>> (Accessed 20 June 2016) (hereinafter referred to as the “Declaration of Helsinki”).

⁹⁶ *Ibid*; Par 3.1.3.10-11 *Booklet 9: Informed Consent* <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_9_informed_consent.pdf> (Accessed 7 July 2016).

⁹⁷ Par 3.1 *Booklet 9: Informed Consent* <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_9_informed_consent.pdf> (Accessed 7 July 2016).

⁹⁸ *Idem* at par 3.4.2.

is regarded as an ongoing process and the participant should be reminded that they could withdraw their consent at any given time.⁹⁹

Purposefully withholding information from the research subject is not in their best interest and the health researcher should allow competent research participants access to any material relating to the research study throughout the research period.¹⁰⁰ The principles of informed consent can be adhered to by keeping a proper record and ensuring that the research participant understands the information and freely gives his or her informed consent in writing in the presence of a witness.¹⁰¹

Both verbal and written informed consent must be obtained, except when there are compelling reasons to deviate.¹⁰² In the instance that the research participant is illiterate, verbal consent must be obtained in the presence of an independent, literate witness who corroborates the consent in writing.¹⁰³ In the event that the independent witness is illiterate, audio-visual confirmation must be recorded.¹⁰⁴

Stem cell research and treatments present great challenges for informed consent, such as problems that cannot be circumvented by the application of the standardised informed consent forms, for example, the application of induced pluripotent stem cells in research and treatment. This rapidly expanding field makes it almost impossible to provide accurate information regarding the scope of application for which a research participant's cells might be used for in future. Nevertheless, efforts should be made to convey information regarding controversial issues, such as the fact that the germ line derivatives and reproduction will not be attempted or developed with the generated induced pluripotent stem cells. However, assurance should be given that this is prohibited by the current legislative framework in South Africa, which will be discussed in the course of this dissertation.¹⁰⁵

⁹⁹ *Idem* at par 3.4.1.

¹⁰⁰ *Idem* at par 3.3: Withholding information from the patient.

¹⁰¹ *Idem* at par 13: Express consent.

¹⁰² *Ibid.*

¹⁰³ Par 6.3.13 *Booklet 6: General Ethical Guidelines for Health Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 7 July 2016).

¹⁰⁴ *Ibid.*

¹⁰⁵ S 57(1) of the NHA prohibits certain uses of biological samples.

South Africa is marked as a country that has many social challenges, for instance, a high rate of illiteracy among many of its citizens. This could pose great problems for informed consent regarding the fact that the procedure and techniques must be explained to research participants.

Greenberg *et al*¹⁰⁶ ask the question “How does one convey information to a layperson about the reprogramming of somatic cells back to their embryonic state?” and believes that “emphasis must be put on ensuring that the relevant information is imparted in a clear and simple manner and in the appropriate language.” The informed consent document serves as a record to ensure that all the relevant ethical information has been discussed. This document can never replace the transmissions between research staff and the providers of human biological material.

The *International Society for Stem Cell Research* (ISSCR) has proposed guidelines to enhance the obtaining of informed consent:¹⁰⁷

- (a) When obtaining informed consent, the person conducting the informed consent dialogue should have no material interest in the research protocol. If no other means exist, they should disclose their interest and take care to ensure that information is transparent and accurate.
- (b) Empirical research has shown that informed consent is more effective when obtained via an interactive, involving and dynamic process than a static one of admission. Therefore, researchers should provide sufficient opportunity for participants to discuss their role in the research.
- (c) Access to counselling services should be provided prior to the procurement of biomaterials.
- (d) The consent procedures should be reviewed against the backdrop of new information regarding informed consent for any type of human biological procurement research and, if relevant, the long-term effects of oocyte retrieval.

¹⁰⁶ Greenberg *et al* “Towards guidelines for informed consent for prospective stem cell research” 2015 *SAJBL* 47.

¹⁰⁷ ISSCR Guidelines for the Clinical Translation of Stem Cells (2016)
<<http://www.isscr.org/home/publications/2016-guidelines>> (Accessed 30 June 2016) 10-11.

The following table describes the information that should be provided in an informed consent document pertaining to stem cell therapy:¹⁰⁸

Informed consent and stem cell therapy

<u>SECTION</u>	<u>PARTICULARS</u>
Purpose of the study	Sets out what the study involves. The more specific the research protocol, the more detailed should the information be. The broader the study, the less the detail it should include.
Explaining concepts such as induced pluripotent stem cells / mesenchymal stem cells / haematopoietic stem cells / adult stem cells	Terse explanations and descriptions of the samples to be obtained should be provided as well as the potential application thereof such as drug discovery or therapeutic applications. The fact that the biomaterial may be destroyed during the derivation of totipotent or pluripotent stem cells. It should also contain statements saying that for the donation or creation of embryos, they will not be used to initiate a pregnancy or allowed to develop in culture for longer than 14 days from fertilisation.
Participant's involvement	Explain to the participants which samples will have to be obtained (skin, blood, hair, etc.), that the biomaterial might be stored and used in future

¹⁰⁸ The ISSCR provides sample informed consent for the procurement of human biomaterials for stem cell research in Appendix 2 of the ISSCR Guidelines for the Clinical Translation of Stem Cells (2016) <<http://www.isscr.org/home/publications/2016-guidelines>> (Accessed 30 June 2016) 32. This table was produced by using the work of Greenberg *et al* 2015 *SAJBL* 47 and Appendix 1 of the ISSCR *Guidelines for stem cell research and clinical translation 2016* <<http://www.isscr.org/docs/default-source/clin-trans-guidelines/isscrglclinicaltrans.pdf>> (Accessed 1 July 2016) 31.



	<p>studies, many of which is not anticipated at the time.</p> <p>For studies involving embryonic stem cell derivation, somatic cell nuclear transfer, somatic cell reprogramming, parthenogenesis or androgenesis, the derived material would be partially or completely identical to the genetic material of the donor.</p> <p>Explain that the donor and biomaterials derived therefrom will be screened for infectious and possible genetic diseases or markers of disease.</p>
Collection of medical information	<p>Explain the extent of medical information required such as age, sex, family disease history, etc.</p>
Amount and regularity of visits required	<p>State if a single sample will suffice or if multiple visits and samples will be required.</p> <p>State that the donation is done without restriction or direction regarding the recipient, except in the case of autologous treatment. This being the fact that no preference will be given to any further donations in terms of the recipient thereof.</p>
Re-contact	<p>Set out whether the participant will be contacted in future to obtain further consent for future projects or to obtain further medical particulars or update the participant's consent.</p>
Restrictions on the application of	<p>Describe to what extent the donated</p>



cells	cells will be used, as well as that all research will be within the bounds of ethical and statutory regulation, such as the use and derivation of pluripotent or totipotent stem cells.
Risks	Set out the risks associated with the applicable medical procedure.
Confidentiality	<p>Outline the plans and policies set out to protect the patient-participant confidentiality, such as password-protected databases, coding and restricted laboratory access.</p> <p>Also outline the fact that nucleic acid sequencing of a resultant stem cell line will be performed and such sequence will be stored in databases that will be available to the public or qualified researcher, subject to confidentiality provisions, and that this may compromise the anonymity of the donation.</p>
Benefits	<p>Explain whether the benefits of the research are purely for the gain of the scientific community or if the participants and their families will also benefit.</p> <p>The document should also disclose whether there is a plan to share relevant clinical information pertinent to the biomaterial donor incidentally during the course of the study.</p>
Possibilities	The participants should be informed that the study is voluntary.



Adjustments to consent	<p>Explain to the participants that they are entitled to change their minds, for instance they may withdraw their samples or de-attach the sample from the donor.</p> <p>Explain that neither consenting nor refusing to donate biomaterials will not affect the quality of health care provided to potential donors.</p>
Payment	<p>Include in this form a section regarding financial compensation for future commercial use as well as the compensation the participants will be entitled to. This should also be done within the confines of the law.</p>
Problems or questions	<p>Provide contact details for any person or group of persons that might have further questions.</p>

3.3.3.3 Confidentiality

Confidentiality could be regarded as a branch or subset of informational privacy. It prevents further disclosure of information initially disclosed within the confines of a confidential relationship, such as a relationship where the confider has a reasonable and legitimate expectation that the confidant will not divulge the confided information to anyone without the confider's consent.¹⁰⁹ Beauchamp and Childress¹¹⁰ note the nature of medical confidentiality as follows:

when one person discloses information to another whether through words or other means, and the person to whom the information is disclosed pledges, implicitly or explicitly, not to divulge that information to a third party without the confider's

¹⁰⁹ Beauchamp & Childress *supra* n104 316.

¹¹⁰ *Idem* at 318.

permission. Confidential information is private and voluntarily imparted in the confidence of trust.

Privacy is also recognised section 14 of the NHA,¹¹¹ which states:

- (1) All information concerning a user, including information relating to his or her health status, treatment or stay in a health establishment, is confidential.
- (2) Subject to section 15, no person may disclose any information contemplated in subsection (1) unless –
 - (a) The user consents to that disclosure in writing;
 - (b) A court order or any law requires that disclosure; or
 - (c) Non-disclosure of the information represents a serious threat to public health.

Therefore, whenever a patient authorises the release of information to third parties, no violation of confidentiality takes place, although a loss of confidentiality and privacy has occurred. The ethical guidelines pertaining to health research state that a research participant may expect that a health researcher would not pass on and would protect any personal and confidential information learnt in the course of their professional duties, unless the research participant consents thereto.¹¹² Furthermore, the guidelines state that a researcher would uphold confidentiality and not break it without sound reason and the knowledge and consent of the research participant.¹¹³ Precautions such as coding research participants' names instead of revealing their identities must be used.¹¹⁴

3.3.3.4 Disclosure or genetic information to third parties

In the context of stem cell research and therapy, the following problem might arise. A medical doctor or a researcher is charged with the task of performing a stem cell treatment. In completion of his task, he prepares stem cells using somatic cell

¹¹¹ S 14 of the NHA.

¹¹² Par 6.4 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

¹¹³ *Idem* at par 6.4.2.

¹¹⁴ Par. 2.6.5 *Booklet 7: Medical Biotechnology Research* <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_7_medical_biotechnology_research.pdf>(Accessed 7 July 2016); Department of Health Ethics in *Health Research: Principles, Structures and Processes* 34-35 <<http://www.mrc.ac.za/ethics/DOHEthics.pdf>> (Accessed 6 July 2016).

nuclear transfer or ‘research cloning’ techniques. In doing so, he makes use of the genetic material of the donor or the donor recipient and discovers the fact that the donor and his family members are particularly prone towards a certain genetic disorder or debilitating disease, such as Parkinson’s or Multiple Sclerosis. The question arises, ‘Does the doctor or researcher have a duty to disclose this information to third parties and risk being in breach of patient or participant confidentiality or does he have to uphold confidentiality at all times?’

An individual who learns that he or she has a serious genetic condition is morally inclined to share that information with at-risk parties, mostly their relatives, so that they can take action to reduce the risk to themselves or their offspring or to seek treatment. A healthcare practitioner or researcher should accentuate the importance of such a moral obligation to his patient or research participant.¹¹⁵ A genetic counsellor or stem cell researcher and therapist will have to overcome their predisposition towards nondirective counselling and pursue ways to sway patients or participants to disclose the sensitive information to at-risk parties.¹¹⁶ The Institute of Medicine Committee on Assessing Genetic Risks notes that genetic information may only be disclosed when:

- (1) attempts to elicit voluntary disclosure fail, (2) there is a high probability or irreversible or fatal harm to the relative, (3) the disclosure of the information will [likely] prevent the harm, (4) the disclosure is limited to the information necessary for diagnosis or treatment if the relative, and (5) there is no other reasonable way to avert the harm.¹¹⁷

The *General Medical Council of the United Kingdom* advises that:

[A] Patient might refuse to consent to the disclosure of information that would benefit other, for example, where family relationships have broken down, or if their natural children have been adopted. In these circumstances, disclosure might still be justified in the public interest. If a patient refuses consent to disclosure, you will need to balance your duty to make the care of your patient your first concern against your duty to help protect the other persons from

¹¹⁵ Beauchamp & Childress *supra* n104 323.

¹¹⁶ *Ibid.*

¹¹⁷ *Ibid.*

serious harm. If practicable, you should not disclose the patient's identity in contacting and advising others of the risk they face.¹¹⁸

As seen in the ethical guidelines of the HPCSA,¹¹⁹ a researcher has a *prima facie* duty to respect the confidentiality of the research participant and may not break this confidentiality without “sound reason and without the knowledge and consent of the research participants”.¹²⁰ What about the fact that they might have to disclose that information in certain circumstances to protect others from harm?

Beauchamp and Childress¹²¹ use an analogy of a bank account and state that genetic information is similar to that of a personal account, which resonates with the principles of autonomy, confidentiality, maintenance of trust in healthcare relationships, and good practice. Criticism of this model proposes that the familial nature of genetic information should be emphasised and is similar to that of a joint bank account.

In a joint account, the default position would be to make the genetic information available to all of its account holders and deviating from the norm would only be allowed if there are compelling reasons to do so, such as serious harm to the individual from whom the genetic information was generated. This joint account stems from concerns of justice and reciprocity-based beneficence. It is based on the premise that “one family member should not be able to benefit from jointly valuable information while excluding others from that information and its benefits.”¹²²

For the time being, in South Africa the guidelines make use of the personal account model and further states that when facts are revealed regarding a condition or factor affecting the research participant, which poses a serious risk to the third party, the researcher might be obliged to disclose such a fact to the third party. This is also in

¹¹⁸ General Medical Council: Good Medical Practice Rule 69 <http://www.gmc-uk.org/guidance/ethical_guidance/confidentiality_67_69_genetic_and_other_shared_information.asp> (Accessed 30 June 2016).

¹¹⁹ Par 6.4 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

¹²⁰ *Ibid.*

¹²¹ Beauchamp & Childress *supra* n104 324.

¹²² *Ibid.*

line with the principle of beneficence. It should be noted that a researcher may only disclose such a fact in the event that the participant/patient refuses to do so.¹²³

In the instance that conversion to a joint account model would take place, patients and research participants making use of genetic services must be informed from the point of entry so that they have the opportunity to decide whether to proceed or not. Beauchamp and Childress¹²⁴ indicate that it would be better to educate individuals in their duty to family members who could benefit from or avoid harm if they were to have access to discrete genetic information, instead of changing to a joint account model.

3.3.3.5 Genetic privacy and insurance

Insurance companies would go to any lengths to obtain the genetic information of an insured person to enable them to predict more accurately whether an insured person poses a risk to the company. This creates a moral dilemma, as some people would be unable to obtain life insurance, as companies would view them as a too high risk. Not being able to obtain life insurance will have severe implications for someone who, for instance, is more prone to disease and it would defeat the purpose life insurance seeks to address.

In 2001, the *Human Genetics Commission in the UK* imposed a three-year suspension on insurance companies to seek genetic test results in cases where the amount involved was less than £500 000.¹²⁵ The Association of British Insurers has voluntarily agreed to ban the request of genetic information by insurance companies for five years.¹²⁶ The question to ask is whether society is willing to pay a higher premium to keep genetic information out of the equation or whether each individual life-insurance policy should be evaluated individually? In effect, this would mean that, by luck of the draw, those with “bad” genetic make-up would pay a much higher

¹²³ Par 2.6.5.1 *Booklet 7: Medical Biotechnology Research* – This is similar to the duty imposed on healthcare practitioners by the HPCSA that they have to disclose to the sexual partner or spouse of their HIV positive patient the imminent danger if the patient/participant refuses to do so. <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_7_medical_biotechnology_research.pdf> (Accessed 21 June 2016).

¹²⁴ Beauchamp & Childress *supra* n104 324.

¹²⁵ Herring *supra* n130 256.

¹²⁶ *Ibid.*

insurance premium than those who have been endowed with a “healthy” genetic make-up.¹²⁷

Stem cell researchers and practitioners should take cognisance of the ethical rules pertaining to confidentiality¹²⁸ and adhere to the guidelines¹²⁹ set by the HPCSA.

3.3.3.6 Data and specimen storage

The security of data and specimens obtained during the course of research is of the utmost importance. A health researcher is obliged to keep data for a minimum period of two years after publication or six years in the case where the study has not been publicised.¹³⁰

3.3.3.7 Impartiality and justice

Stem cell therapy might either hold great potential medical benefits or grave dangers for the research participants. It is important to ensure that economically disadvantaged people are not exploited in this type of research. In this regard, the principles of justice play a vital role. Justice as an ethical principle consists of two elements – individual justice and social justice. Individual justice is concerned with the application of fairness in the selection of research participants, meaning that potentially beneficial research should not be offered only to patients who the researchers deem favourable or precarious and dangerous research studies should not be used on “undesirable” candidates only.¹³¹

On the other hand, social justice necessitates that a distinction should be made between classes of subjects who ought to and ought not to participate in a certain research study, based on the ability of each class to bear the burdens, and on

¹²⁷ *Ibid.*

¹²⁸ Rule 13 Booklet 2 of the Ethical and Professional Rules of the HPCSA as promulgated in GG R. 717 of 2006 <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_2_generic_ethical_rules_with_anexures.pdf> (Accessed 29 June 2006).

¹²⁹ Par 6.4 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

¹³⁰ Par 13. *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

¹³¹ Beauchamp *et al supra* n115 541.

whether it is appropriate to burden certain members of a class even more.¹³² Therefore, it can be seen as a matter of social justice when there is a preferential order for the selection of certain classes of potential research candidates.

The generic ethical guidelines for researchers state that a health researcher must take cognisance of the laws pertaining to unfair discrimination in the management of research participants or their families on the basis of race, culture, ethnicity, social status, lifestyle, perceived economic worth, age, gender, disability, communicable disease status, sexual orientation, religious or spiritual beliefs, or any condition of vulnerability such as contained in health-rights legislation.¹³³

Moreover, a researcher may not discriminate on the aforementioned grounds, except where the exclusion or inclusion of particular groups is critical to the research purpose or scientific intention.¹³⁴ Most important is the fact that researchers should actively attempt to distribute the burdens and benefits of the research within different population groups to avoid unfair discrimination.¹³⁵

Despite the fact that it is an offence for any person to receive financial consideration for the donation of tissue, gametes, blood or blood products, in excess of what is considered reasonable costs incurred by the donor to provide such donation, other coercive situations might still unduly entice potential research participants to partake in research studies.¹³⁶

Some people report feeling heavily pressured into taking part in clinical trials, despite the fact that their enrollment is classified as voluntary.¹³⁷ A typical situation would be the case where a person feels controlled by the constraints of severe illness, which is often the case in stem cell therapy, as most patients seeking stem cell treatments

¹³² *Ibid.*

¹³³ Par 6.5.1 Impartiality and Justice *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 7 July 2016).

¹³⁴ *Idem* at par 6.5.2.

¹³⁵ Par 6.5 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

¹³⁶ S 60 of the NHA.

¹³⁷ Beauchamp & Childress *supra* n104 268.

are most likely suffering from life-threatening conditions. Even though no one has intentionally “threatened” the person in order to acquire compliance and consent, the person might feel powerless and compelled to prevent or ameliorate the imminent danger of his or her condition.

A health researcher or practitioner conducting stem cell research or therapy should be mindful of this fact as they are charged with having the best interest and well-being of the patient at heart, in accordance with the principle of beneficence. Choosing patients who have no other option but to participate in the research experiment might amount to unfair discrimination on the ground of vulnerability and could be subjected to review.¹³⁸

3.3.3.8 Conflict of interest

Beauchamp and Childress¹³⁹ define a conflict of interest as follows:

A conflict of interest exists when an impartial observer would determine that a professional’s judgements, decisions, or actions are at risk of being unduly influenced by his or her personal interests, such as financial interests or friendship.

A conflict of interest often arises in medicine, health care and biomedical research. Despite the fact that inadequate attention is given to nonfinancial conflicts, such as professional advancement or friendship, various efforts have been made to address financial conflicts, such as fee splitting, self-referral, accepting gifts, accepting fees for recruiting patients for a research protocol.¹⁴⁰

A point to consider is the referral of patients. Healthcare practitioners often refer patients to institutions and facilities in which they have a financial interest. Such as the case where a healthcare practitioner in the field of stem cell technologies, for instance, refers a patient to a stem cell clinic in which he has a financial interest. With a self-referral, it is much more difficult for a patient to determine the financial

¹³⁸ *Ibid.*

¹³⁹ *Idem* at 328.

¹⁴⁰ The HPCSA has published ethical guidelines pertaining to overservicing, perverse incentives and related matters *Booklet 5: Perverse Incentives* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_5_perverse_incentives.pdf> (Accessed 21 June 2016).

interest that a healthcare practitioner has than in the case of fee-for-service unless it is explicitly disclosed to the patient.

The ethical guidelines pertaining to over-servicing, perverse incentives and related matters published by the HPCSA state that a healthcare practitioner may only refer patients or clients to an establishment in which the practitioner or his close family members or business associates have a material financial interest, if he declared the conflict of interest to the HPCSA and received subsequent approval, on condition that the healthcare practitioner discloses such interest to the patient.¹⁴¹ Furthermore, healthcare practitioners may not refer patients to any clinic or establishment if it would constitute over-servicing, which will be discussed below.

Conflicts of interests also transcend medical practice into the field of scientific research. Biomedical research vitally depends on interaction and partnership with the industry and government. Clinical trials for the development of medicine such as stem cell treatments are more often than not dependent on the financial support of pharmaceutical companies that are willing to assume the financial risk of the study. However, this mutually beneficial relationship created between health practitioner or researchers and corporations may induce motive for a healthcare researcher to find positive results or soften negative results, thereby compromising scientific objectivity.¹⁴² According to a report of the Institute of Medicine in the USA, researchers should not conduct research involving human subjects, if they have a significant financial stake in the outcome of that research.¹⁴³

The general ethical guidelines for healthcare researchers¹⁴⁴ state that healthcare researchers are obliged to disclose any conflict of interest they may have with

¹⁴¹ “A healthcare practitioner may only refer their clients or patients to any health establishment in which such healthcare practitioner or a close family member or business associate has a financial interest or a potential conflict of interest if such interest has been declared to and approved by the HPCSA and on condition that such interest is discussed and agreement reached with the patient prior to the referral for the patient’s consent.” Par 3.5.1 *Booklet 5: Perverse Incentives* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_5_perverse_incentives.pdf> (Accessed 21 June 2016).

¹⁴² Beauchamp & Childress *supra* n104 330.

¹⁴³ *Ibid.*

¹⁴⁴ Par 6.7 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

institutions, equipment and research sponsors. Healthcare researchers must also declare whether the research is being conducted for academic or therapeutic purposes. In addition to the former, healthcare practitioners must disclose any conflicts of interest to their research ethics committee prior to the initiation of such research and must design their studies to exclude any such potential conflicts of interest with sponsors or collaborators.

Stem cell technologies require large amounts of money to produce and the temptation might be looming for researchers to deliver false positives. This would be in contravention of the ethical guidelines. Any researcher conducting himself or herself in such a way also risks the wellbeing of the research participant, which is his main responsibility.

3.3.3.9 Conflating healthcare and health research

Biomedical ethics has drawn a line between clinical ethics and research ethics. This distinction is based on the difference between clinical practice and clinical research. In contrast to medical practice, research has been regulated vigorously due to the perception that it places certain subjects at risk for the benefit of others, in addition to exploring the unsupported hypothesis. While clinical practice, on the other hand, has been regulated minimally due the difference in intention between clinical practice and clinical research. Clinical practice aims to further the best interest of the patient and depends on interventions of proven benefit and acceptable risk.¹⁴⁵ It is this distinction between research and therapy that determines whether a specific research activity must be submitted for review by an ethics review board for the protection of human subjects in research. Beauchamp and Childress¹⁴⁶ rightly ask the question why there is a distinction between health research and practice when it comes to the safety of patients and research subjects.

Instinctively, the purpose of research is designed to test theory aimed at developing or contributing to what is referred to as general knowledge. Contrary to health research, medical interventions in practice are directed at diagnostic and preventative treatment or therapy that might bring about a therapeutic benefit to the

¹⁴⁵ Beauchamp & Childress *supra* n104 331.

¹⁴⁶ *Ibid.*

patient. Furthermore, in practice the risks are warranted by the potential benefit to the patient, while in research the benefit would usually be to society and sometimes both society and the patient.¹⁴⁷ The boundary between medical research and practice is described as porous, particularly where they occur in the same health institutions and are interdependent.¹⁴⁸

Although acceptable methods for gaining scientific knowledge in health research is contentious, it is “morally unsatisfactory to allow physicians to use treatments that are either new or unapproved on grounds that the doctor-patient relationship is a private transaction immune from regulatory interference and unaccountable to external oversight, such as a review committee.”¹⁴⁹

The ethical guidelines of the HPCSA state that health researchers may only combine health research with health care to the extent that the prophylactic, diagnostic or therapeutic value warrants it.¹⁵⁰ When doing scientific health research, researchers must ensure that research participants have access to the best prophylactic, diagnostic or therapeutic interventions and health research processes.¹⁵¹ Furthermore, in line with the principle of informed consent the researcher/practitioner should explain to the research participant/patient the fact that his or her role as a researcher differs from the role of a healthcare practitioner, as well as any potential conflict of interest that may exist. For example, the outcome of this research might benefit a researcher’s/practitioner’s career greatly, but they must ensure that this does not happen at the expense of the wellbeing of the patient/participant as the researcher/practitioner has an overarching duty to uphold the well-being of his patients/participants.

Cognisance should be taken of the fact that the same conditions apply to research that has no prospect of medical benefit for the subject, and research that may offer some sort of medical benefit to the patient/participant may be conducted during the

¹⁴⁷ *Idem* at 332.

¹⁴⁸ *Ibid.*

¹⁴⁹ *Ibid.*

¹⁵⁰ Par 6.6.1 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

¹⁵¹ *Idem* at par 6.6.2.

course of the patient's treatment. Beauchamp and Childress¹⁵² rightly note that the term *therapeutic research* commonly creates a misconception because it misplaces the focus from the fact that *research* is being conducted.

Health research must be distinguished from both *routine therapy* and *experimental or innovative therapy*, which focuses on the health of specific patients. Simply attaching the word *therapeutic* incorrectly construes the research proposal or protocol as therapy that will be directed at a specific patient, instead of health research that will generate generalisable facts.¹⁵³

Most of what are regarded as stem cell therapies are still research. Therefore, by implication, practice is not divorced from new research findings. Stem cell-based medical innovation interventions are mostly unproven and outside of the boundaries of a formal clinical trial. Innovative medicine falls short of the high validation standards that test for efficacy and safety in a randomised clinical trial.

The ISSCR published guidelines¹⁵⁴ that allow healthcare practitioners to attempt medical innovative stem cell treatments for seriously ill patients in very rare situations. This is done with amplified levels of cautiousness and with informed consent that states the experimental and preliminary nature of such clinical interventions.¹⁵⁵

Botes and Alessandrini¹⁵⁶ mention the case of Gordon Howie, a Canadian ice hockey player who suffered a stroke in 2014 and was subsequently allowed experimental stem cell treatment. Despite the fact that the CPA¹⁵⁷ is not applicable, therapeutic research in South Africa is covered by principles of informed consent, constitutional principles of autonomy and ethics review boards that review research proposals to ensure safety monitoring and management of harm that might be experienced by

¹⁵² Beauchamp & Childress *supra* n104 333.

¹⁵³ *Idem* at 333-334.

¹⁵⁴ ISSCR Guidelines for the Clinical Translation of Stem Cells (2016) <<http://www.isscr.org/home/publications/2016-guidelines>> (Accessed 30 June 2016) 26 (hereinafter referred to as the "ISSCR").

¹⁵⁵ Botes & Alessandrini 2015 *SAJBL* 39.

¹⁵⁶ *Ibid.*

¹⁵⁷ The CPA.

participants.¹⁵⁸ This overview by an ethics committee would also be done in matters of compensation for any research-related injuries and the providing of long-term care and observation of participants of innovative stem cell therapy.¹⁵⁹

The Medical Innovation Bill¹⁶⁰ purports to:¹⁶¹ codify the best existing practices pertaining to the decisions on the part of medical practitioners; to innovate in cases where evidence-based treatments or managements are not optimal or appropriate due to the uncertainty of the evidence, or the lack thereof; enhance certainty and clarity for healthcare practitioners and others regarding the criteria to be satisfied when determining whether to innovate or not; encourage responsible medical innovation and management by supporting legal clinical decisions; deter reckless, illogical and unreasonable departure from standard practice; legalise and regulate the use of cannabinoids for medical purposes and for beneficial commercial and industrial uses.

Section 4 of the Medical Innovation Bill would allow a medical practitioner to prescribe a treatment other than a generally accepted or legally authorised treatment. However, the practitioner may only do so if it is impossible or inappropriate to make an evidence-based decision regarding the proposed course of treatment, as the medical practitioner believes that no research, evidence or alternative treatments are available, or if the practitioner believes that such research or evidence is insufficient or uncertain. In making a decision to depart from what the practitioner believes to be the pre-existing range of acceptable treatments for the relevant condition, the medical practitioner must consider the following:¹⁶²

- (a) the reasons why the available research or other evidence is insufficient or unclear including, without limitation, whether such insufficiency can be referred to the nature of the condition or the limited number of patients subject thereto;
- (b) the relative risks that are, or can reasonably be expected to be, associated with the treatment the medical practitioner proposes to apply and other treatments;

¹⁵⁸ Par 2.16 Department of Health Ethics in Health Research: Principles, Structures and Processes 9. <<http://www.mrc.ac.za/ethics/DOHEthics.pdf>> (Accessed 6 July 2016).

¹⁵⁹ Botes & Alessandrini 2015 *SAJBL* 39; *Venter v Roche Products (Pty) Ltd supra* n190 157.

¹⁶⁰ The Medical Innovation Bill as published in GG 37349 of 2014-02-18.

¹⁶¹ *Idem* at s 2.

¹⁶² *Idem* at s 4(2).



- (c) the relative likely success rates of the treatment the medical practitioner proposes to apply compared to other treatments, and, in the medical practitioner's reasonable judgement, the relative likely consequences of applying, or failing to apply, the treatment the medical practitioner proposes to apply, and other treatments;
- (d) opinions or requests made by, on behalf of, or in relation to, the patient;
- (e) the informed consent of the patient or his guardian or other person legally entitled to provide such consent on behalf of such patient;
- (f) any other matter that appears to that medical practitioner to be reasonably necessary to be considered in order to reach a clinical judgement; and
- (g) what process or protocol should be adopted with a view to ensuring that the decision to innovate is made accountably, transparently and with full consideration of all relevant matters.

Even though, the Bill was created with the purpose of legalising and regulating the use of cannabinoids for medical purposes and for beneficial commercial and industrial uses, nothing in the wording of the bill would restrict its application to include within its ambit any other form of medical innovation, such as stem cell treatments to patients with no other hope. The bill has not yet been incorporated as an act and, therefore, the guidelines can only help a medical practitioner with the intention to innovate to make an ethical decision. However, such medical innovation be done in accordance with the rules of the HPCSA and be subject to ethical review.

3.3.3.10 Reporting misconduct

An ethical duty is bestowed upon health researchers and practitioners to report evidence of fraud and other crimes or scientific misconduct in research experiments to the HPCSA. Scientific misconduct is defined as fabrication¹⁶³, falsification¹⁶⁴ or plagiarism in proposing, performing or reviewing research, or in reporting research results.

Furthermore, scientific misconduct also includes failure to obtain informed consent, inappropriate disclosure of research participant data, deviation from approved

¹⁶³ "Fabrication" is making up data or results and recording or reporting them. Par 9.2 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

¹⁶⁴ *Ibid*: "Falsification" is the manipulation of research material, equipment or processes, or the changing or omitting of data or results such that the research is not represented accurately in the research record.

protocol, falsification of credentials and deception in the research proposal. However, scientific misconduct does not include honest errors or an honest difference of opinion.¹⁶⁵

3.3.3.11 Access to limited resources

A health researcher is obliged to work sparsely with healthcare resources and should refrain from wasting or duplicating research that has already been recorded. In conducting research, health researchers should refrain from entering into improper financial agreements that unduly inflate costs or disadvantage research participants, patients or institutions.¹⁶⁶

A human embryo is widely regarded as a scarce resource and therefore, when a stem cell researcher is of the intent to conduct stem cell research that involves using an embryo (mostly these embryos are donated leftover embryos from *in vitro* fertilisation), they should be mindful not to duplicate research and to handle the embryo responsibly.¹⁶⁷

The ISSCR encourages institutions engaged in human stem cell research, irrespective of whether they are public or private, to develop procedures to provide unhindered access to research materials, which are free from undue financial burdens and bureaucracy.¹⁶⁸ This entails that when an application is filed for patenting for commercial purposes, the research community would still be provided access. Furthermore, the ISSCR endorses the principle that before being granted the privilege to conduct stem cell research, the researcher must make their materials and findings readily available to the biomedical scientific community for non-commercial research.¹⁶⁹

¹⁶⁵ Par 9.2 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

¹⁶⁶ *Idem* at par 9.3.

¹⁶⁷ Bell & Davaney (2007) 33 *J Med Ethics* 621.

¹⁶⁸ Recommendation 2.3.6 ISSCR Guidelines for the Clinical Translation of Stem Cells (2016) <<http://www.isscr.org/home/publications/2016-guidelines>> (Accessed 30 June 2016) 12.

¹⁶⁹ *Ibid.*

3.3.3.12 Conforming to legal prescriptions

The ethical guidelines state that a health researcher must abide by legal regulation to ensure that the research conducted is lawful.¹⁷⁰ Furthermore, health researchers must adhere to ethical rules, even when they prescribe a higher standard than that of the law. A health researcher must always be able to guarantee that research is properly supervised by health researchers, that they are regarded as competent, ethical and approved by relevant legal bodies.¹⁷¹

3.3.3.13 Duty to animals

The normal course of medical research dictates that research must first be conducted on animals before the hypothesis can be tested on human research subjects. In conducting animal research, researchers have the responsibility to care for the animals and must be able to justify why the research is warranted. If it is possible to conduct the same research by means of less controversial means, it should be done so. The only time research conducted on a sentient animal will be justified, is when the potential benefit of the technology outweighs the moral and ethical conundrum raised by using such animals as a means to an end.¹⁷² If possible, researchers must make use of lower level animals that are less susceptible to pain and suffering, while still upholding the integrity of the research project. The research protocol must be designed to make use of the smallest number of animals possible to produce the answers of the research hypothesis.¹⁷³ A stem cell researcher must also abide by the ethical and regulatory guidelines that govern the use of animals in research.¹⁷⁴

Harnessing the capacity of pluripotent stem cells to differentiate into any type of tissue has brought about a potential revolution for drug discovery.¹⁷⁵ If it is possible to

¹⁷⁰ Par 9.4 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

¹⁷¹ *Ibid.*

¹⁷² Par 6. *Booklet 7: Medical Biotechnology Research* <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_7_medical_biotechnology_research.pdf> (Accessed 21 June 2016).

¹⁷³ *Ibid.*

¹⁷⁴ Par 11 *Booklet 6 Generic Ethical Guidelines for Researchers* <http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

¹⁷⁵ See ch 2 for a discussion regarding the potential of induced pluripotent stem cells.

produce the tissue on which the therapeutic substance is to have an effect, the need for animal experimentation might diminish. Certainly, this technology is still in very early developmental stages and the need to test the overall effect of a therapeutic substance or procedure on an organism is still of vital importance before the said technology can be made available to the public.

Despite the possibility of eliminating animals from the research equation, the use of animals is currently still a necessary evil for the greater good. Therefore, researchers have an obligation to minimise the amount of pain and suffering inflicted on animals until alternative means have been developed.

3.3.3.14 A duty to the environment and humankind

A health researcher must not conduct research that, in any manner, can be harmful to the health and well-being of the population, nature and the environment. It is of paramount importance that researchers ensure the safety of the environment, not only for the present, but also for future generations as is required by the Constitution.¹⁷⁶

Akin to the discovery of nuclear technologies which led to the creation of the atomic bomb, stem cell technologies, specifically induced pluripotent stem cells, have brought about issues of cloning and genetic engineering that have the capacity to disturb the evolutionary course humans were intended to take. The beauty of evolution is found in the diversity of genetic material so that when an external stress factor becomes a reality, mankind (or any other species) has the ability to deal with the problem and those with the necessary genetic adaptation will be able to survive. If we tamper with the current genetic pool, we risk putting humanity itself at stake. Therefore, when a researcher conducts research that has the ability to destroy humanity as we know it, it should be done with the utmost respect and care for ethical values and society.

¹⁷⁶ Par 12 *Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethicalrules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 26 June 2016).

3.3.3.15 *Capita Selecta of ethical issues in the context of stem cell technologies*

(a) *Overservicing¹⁷⁷, perverse incentives and related matters*

A healthcare practitioner shall not accept any payment, benefit or any other form of consideration, calculated to induce him or her to act in a way that is not scientifically, professionally or medically indicated or to underservice, overservice or overcharge patients.¹⁷⁸

The specific ethical guidelines relating to overservicing and perverse incentives state that such acts are impermissible and unethical.¹⁷⁹ In particular, a health practitioner may not provide or perform procedures on patients that are not indicated or scientific, or that have been shown to be ineffective, harmful or inappropriate through evidence-based medicine. A health practitioner may also not refer a patient to another practitioner to acquire services related to the former.¹⁸⁰

From a medical perspective, hematopoietic stem cells are regarded as the only form of globally accepted stem cell therapy. Looking at the global mesenchymal stem cell therapy landscape, more than a 100 different indications are currently being treated or will be treated.¹⁸¹ However, the only mesenchymal stem cell treatment that managed to reach the market is a mesenchymal stem cell treatment for Graft v Host Disease (GvHD), Prochymal[®].¹⁸²

Even though more than 100 indications are being treated in a research environment, none of them have been able to demonstrate sufficient benefit that outweighs the

¹⁷⁷ “Overservicing” means the supply, provision, administration, use or prescription of any treatment or care (including diagnostic and other testing, medicines and medical devices), which is medically and clinically not indicated, unnecessary or inappropriate under the circumstances or which is not in accordance with the recognised treatment protocols and procedures, without due regard to both the financial and health interests of the patient. *Booklet 5: Perverse Incentives* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_5_perverse_incentives.pdf> (Accessed 15 June 2016).

¹⁷⁸ Proc R. 717 in GG 29079 of 2006-08-04 Booklet 1 rule 7.3.

¹⁷⁹ Par 3.1 *Booklet 5: Perverse Incentives* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_5_perverse_incentives.pdf> (Accessed 15 June 2016).

¹⁸⁰ *Ibid.*

¹⁸¹ Botes & Alessandrini 2015 *SAJBL* 36.

¹⁸² *Ibid.*

harm.¹⁸³ This means that when doctors prescribe treatments such as stem cell therapies, they are only allowed to provide treatments or refer patients to other practitioners for treatments that are clinically indicated or scientific.

In the ethical guidelines, the word ‘scientific’ denotes an application of stem cell therapy in a clinical trial setting for which ethical clearance has been provided and which is not against good medical practice. This means that, currently, the only stem cell treatment available to patients outside a research setting is that of haematopoietic stem cell treatments, such as Prochymal[®] in Canada, which has been afforded marketing authorisation by the appropriate competent authority.

As early as the 17th century, Francis Bacon (1561–1626), a British philosopher of science and medicine, loathed the state of medical practice. He urged medical practitioners to base their concepts on what is today known as the scientific method, rather than on “experience”.¹⁸⁴ John Gregory, at the University of Edinburgh, applied Bacon’s logic and cautioned against ‘enthusiasm’ and excessive expectations for how rapidly and well medicine could expand its capacity.¹⁸⁵

More recently, the 2016 ISSCR guidelines applied the same logic of Bacon and Gregory regarding the clinical translation of stem cell therapy. These guidelines state concerns regarding the marketing of unproven stem cell-based therapies as follows:¹⁸⁶

The ISSCR condemns the administration of unproven stem cell-based interventions outside of the context of clinical research or medical innovation compliant with the guidelines in this document and relevant laws, particularly when it is performed as a business activity. Scientists and clinicians should not participate in such activities as a matter of professional ethics. For the vast majority of medical conditions for which putative “stem cell therapies” are currently being marketed, there is insufficient evidence of safety and efficacy to justify routine or commercial use. Serious adverse events subsequent to such procedures have been reported and the long-term safety of most stem cell-based interventions remains undetermined. The premature commercialization of unproven stem cell treatments, and other

¹⁸³ *Idem* at 37.

¹⁸⁴ Jones *et al* *The Ethics of Surgical Practice: Cases, Dilemmas, and Resolutions* (2008) 130.

¹⁸⁵ *Idem* at 131.

¹⁸⁶ ISSCR Guidelines for the Clinical Translation of Stem Cells (2016)

<<http://www.isscr.org/home/publications/2016-guidelines>> (Accessed 30 June 2016) 25.

cell-based interventions inaccurately marketed as containing or acting on stem cells, not only puts patients at risk but also represents one of the most serious threats to the stem cell research community, as it may jeopardize the reputation of the field and cause confusion about the actual state of scientific and clinical development. Government authorities and professional organizations are strongly encouraged to establish and strictly enforce regulations governing the introduction of stem cell-based medical interventions into commercial use.

It is clear that doctors should be cautious when advocating, providing, performing or referring patients to practitioners who will provide or perform stem cell treatments that fall outside the scope of routine practice or for which research ethical clearance has not been given. Such behaviour will not only be subject to review and the penalty for overservicing and perverse incentives, but will also ultimately lead to the detriment of the patient and give the stem cell community a bad reputation.

(b) Payment for research

Offering payment to persons to participate in a research experiment is a cause for much ethical debate. On the one hand, it might be perceived that not offering incentive would constitute taking advantage of research participants and a failure to recognize the contribution the research participants are making. On the other hand, offering sizable amounts of money may unduly influence the less fortunate into being a research participant.¹⁸⁷ Paying people to enlist as research participants, might be beneficial in the sense that it encourages participation and discourages withdrawal from the project later on in the study.

From an ethical perspective, paying the reasonable expenses incurred on the part of a research participant is not a problem. However, offering payment for research in a developing country such as South Africa could amount to exploitation, as numerous people do not have any other means of income and would put themselves at risk in order to put food on the table.

Akin to organ donation, offering payment for research involving stem cells is tantamount to the commodification of human tissue, which opens many ethical issues. The NHA prohibits anyone from obtaining financial gain, except for the

¹⁸⁷ Herring *supra* n166 623.

reimbursement of the reasonable costs incurred for the donation.¹⁸⁸ This prohibition is in harmony with the with the recommendation of the ISSCR guidelines¹⁸⁹, which state that if an individual stored biomaterial prior to the donation, they are not entitled to be reimbursed for storage costs prior to the donation.¹⁹⁰

In the case where fresh somatic cells or sperm are donated for research, the out-of-pocket expenses may be determined during the review process and reimbursed.¹⁹¹ For the provision of embryos or foetal tissue, it is recommended that no valuable consideration be paid of anything that exceeds the out-of-pocket expenses.

The recommendations pertaining to the procurement of oocytes outside of clinical treatment are very rigorous. When such a donation occurs, it is of paramount importance that the compensation for non-financial burdens does not amass to undue inducement.¹⁹²

(c) *Secret remedies*

A health practitioner may use forms of treatment, apparatuses or health technology that is not secret and is not claimed to be secret. Healthcare practitioners may only apply an apparatus or health technology, which, upon investigation, is capable of fulfilling the claims made with regard to the said treatment.¹⁹³

This means that if a stem cell therapy that has not been proven to be safe and efficacious through a clinical trial or evidence-based medicinal means, it can be regarded as a secret remedy in the sense that, upon closer investigation, might turn

¹⁸⁸ S 60(4) of the NHA.

¹⁸⁹ ISSCR Guidelines for the Clinical Translation of Stem Cells (2016) <<http://www.isscr.org/home/publications/2016-guidelines>> (Accessed 30 June 2016).

¹⁹⁰ *Idem* at 9: recommendation 2.2.4.

¹⁹¹ *Ibid.*

¹⁹² *Idem* at 9-10: Recommendations 2.2.5 This could be ascribed to the fact that women have to endure a more taxing procedure of procurement for their gametes, and women's efforts should be acknowledged accordingly. At the same time, precaution is important to avoid situations of exploitation. Furthermore, in-depth procedures are recommended for the payment involved in the donation of an oocyte.

¹⁹³ Par 19 Booklet 2 of the Ethical and Professional rules of the HPCSA as promulgated in GG R. 717 of 2006 <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_2_generic_ethical_rules_with_anexures.pdf> (Accessed 29 June 2006).

out to be ineffective and unable to substantiate the medical claims that were made in relation thereto.

(d) *Undue advertisement*

A healthcare practitioner is prohibited from advertising, endorsing or encouraging the use of a health establishment, medicine, complementary medicine, veterinary medicine, medical devices, scheduled substances or health-related products or services that unduly promote the practice of a practitioner or healthcare facility for the purpose of financial gain or other valuable consideration. It is often the case that doctors endorse or advocate the application of certain medical services such as stem cell therapy for the betterment of their own practices. In short, the advertising of stem cell medicine when other treatments are available, just for the betterment of the health practitioner's practice, would be dissonant with the ethical guideline and the principles of beneficence, and non-maleficence. Furthermore, the CPA¹⁹⁴ also prohibits false or misleading marketing, which will be illuminated in the statutory regulation of stem cell therapies in Chapter 6.

(e) *Allocation of resources*

South Africa has limited resources to be allocated for the purpose of biotechnology research, as it is still a developing country. Therefore, funds should be allocated to health care and agriculture that have a possibility to address the needs of the South African population directly and the sustainability of the environment. Issues such as HIV/AIDS, Tuberculosis (TB), Malaria, malnutrition and other poverty-related illnesses should be given prevalence over stem cell research.¹⁹⁵

The NHA sets out the health research priorities, which the National Health Research Committee must take into consideration when finding areas to which the Minister of Health should allocate resources.¹⁹⁶ These considerations include the burden of disease; the cost-effectiveness of the interventions aimed at relieving the burden of disease; the availability of human and institutional resources for the implementation

¹⁹⁴ S 29 of the CPA.

¹⁹⁵ Par 3.4 *Booklet 7: Medical Biotechnology Research*

<http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_7_medical_biotechnology_research.pdf> (Accessed 26 June 2016).

¹⁹⁶ S 70 of the NHA.

of an intervention at the level closest to the affected communities; the health needs of vulnerable people such as women, the elderly, children and people with disabilities; and the health needs of the communities.

It is well known that the development of stem cell technologies certainly does not come cheap. With matters such as TB, HIV, etc. affecting the general population, the allocation of state resources for the development of stem cell technologies is not a reality in a developing country such as South Africa, as there are more pressing issues to attend to. For now, the development of stem cell technologies relies on the private sector.

The ISSCR guidelines state that sponsors committed to developing stem cell-based interventions that target serious, debilitating or life-threatening medical conditions should seek to provide access to safe and efficacious therapies to everyone in need, irrespective of their financial means.¹⁹⁷ The guidelines also state that, in the case of private firms they should seek to develop and market stem cell-based interventions in conjunction with philanthropic organisations to provide safe, efficacious and affordable products to the less fortunate.¹⁹⁸

(f) *Intellectual property concerns*

Intellectual property rights in connection with stem cell research are filled with ethical controversy. In particular, the patentability of living things or products of nature is a big cause of contention. *Contra* to purified or isolated stem cells, which are generally patentable as research tools, including the techniques and reagents needed for the development of a stem cell line, disunity has flourished across different borders such as the USA, Japan and Europe.¹⁹⁹

Since 2008, the industrial or commercial application of human embryonic stem cell lines has not been subject to patent protection in Europe.²⁰⁰ This ruling was adopted

¹⁹⁷ Recommendation 3.5.2.2 ISSCR Guidelines for the Clinical Translation of Stem Cells (2016) <<http://www.isscr.org/home/publications/2016-guidelines>> 28 (Accessed 30 June 2016).

¹⁹⁸ *Ibid.*

¹⁹⁹ Pepper & Nöthling Slabbert 2015 *SAJBL* 14.

²⁰⁰ G 0002/06 (use of embryos/warf) of 25-11-2008 on 25 November 2008 <<http://www.epo.org/lawpractice/case-law-appeals/recent/g060002ex1.html>> (Accessed 22 June 2016).

by the European Court of Justice in 2011 in the matter of *Brüstle v Greenpeace*.²⁰¹ This case prohibits the patenting of procedures that involve the destruction/prior destruction of human embryos, including procedures applied for the derivation of human embryonic stem cell lines, even those developed before the judgement. This is a stark contrast to the position in the United States.²⁰²

Further concerns in the field of intellectual property relate to the rights of donors to retain a property or proprietary interest in their own tissues, embryos or genetic material. It is common for research participants to have no property interest in the donated biological material, despite the fact that their samples or specimens might lead to lucrative commercial applications. This could be seen as unethical when considering the continuing right of a donor regarding the use and secondary application of his or her tissue.²⁰³ The code of ethical practice for biotechnology research²⁰⁴ notes the following: when an application is lodged to register a patent, cognisance must be given to the provisions of the Patent Act²⁰⁵ and the National Environmental Management Biodiversity Act (NEMBA)²⁰⁶, with regard to benefit sharing with indigenous communities, and they must be adhered to.

The provisions further note that biopiracy may not be practiced in any form. Biopiracy relates to the situation where a third party usurps the developments or discoveries in the area of biological resources without consent. In this context, discoveries by indigenous communities must be respected and appropriately acknowledged. In the event that an application is lodged to patent stem cell technologies the applicant must take cognisance of and do the following:²⁰⁷

²⁰¹ *Brüstle v Greenpeace* 2011 ECR I 9821

<http://curia.europa.eu/juris/document/document.jsf?_afz=Jsessionid=9ea7d2dc30d50a5ec1080a4c4c41969e82aecd83bc4.e34KaxiLc3qMb40Rch0SaxuTbh90?text=&docid=111402&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=141650> (Accessed 1 July 2016).

²⁰² Pepper & Nöthling Slabbert 2015 SAJBL 14.

²⁰³ *Idem* at 15.

²⁰⁴ Par 9 *Booklet 7: Medical Biotechnology Research* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_7_medical_biotechnology_research.pdf> (Accessed 25 June 2016).

²⁰⁵ Patent Act 57 of 1978 (hereinafter referred to as "Patent Act").

²⁰⁶ National Environmental Management: Biodiversity Act 107 of 1998 (hereinafter referred to as "NEMBA").

²⁰⁷ Par 9 *Booklet 7: Medical Biotechnology Research* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_7_medical_biotechnology_research.pdf> (Accessed 25 June 2016).

The applicant must disclose in the application the following:

- The source of the genetic or biological material or the knowledge applied to produce the invention
- That non-disclosure or wrongful disclosure of preceding knowledge and traditional knowledge, oral or otherwise, is unethical and may have legal consequences in the sense that the application is refused or the patent is rescinded
- That the prospective applicant must obtain the informed consent of the owners or holders of traditional knowledge prior to lodging an application for patent protection of any element of indigenous knowledge or heritage, for the sharing of ownership, control, use and benefits
- That the informed consent must be properly recorded and subsequently submitted to the Registrar of Patents.

South African researchers must seek to develop new discoveries in ways that will provide appropriate returns to the state as far as possible so that it can maintain control over the intellectual property in South Africa.²⁰⁸

In the context of stem cell technologies, this is very hard to do, as most of the big pharmaceutical companies are situated in USA and Europe, particularly in Switzerland; therefore, health researchers should aim to licence instead of sell the intellectual property yielded by their research. Even though the costs of developing stem cell therapy are very high, researchers should not be discouraged from doing research that would have the potential to benefit the South African population, especially the poor and disadvantaged communities, and the costs associated with developing these therapies should not obstruct the vulnerable from having access to new stem cell technologies that may benefit them. This would also be in line with the duty to act ethically towards society and the research community.

²⁰⁸ *Ibid.*

3.3.3.16 Ethical review of healthcare researchers/practitioners

Before the initiation of a health research project, health researchers must seek approval from the authorities such as the MCC, provincial and hospital authorities and the national Department of Health. The NHA²⁰⁹ provides for the establishment of health research ethics committees who must approve any proposed research activity.²¹⁰

The main function of a research ethics committee is to safeguard ethical standards of practice in research, protect researchers and participants from possible harm or exploitation, uphold the rights of research participants which prevail over society's rights and provide a guarantee to the public that research is being conducted ethically.

In addition to a change in the research protocol, a health researcher is required to inform all the relevant review bodies when the risks to research participants outweigh the benefits of the research. Health researchers must also satisfy themselves about the health institutions with which they partner, in the sense that they must satisfy themselves regarding the partnering institution's accreditation by the National Health Research Ethics Council and that they have sufficiently provided access to an accredited health research ethics committee registered with the National Health Research Ethics Council.

Furthermore, healthcare researchers are required to report unsatisfactory or inappropriate research protocols to the HPCSA and are required to terminate the study prematurely if the research question has been answered or the research proves to be disproportionately harmful to participants. These guidelines are applicable to all healthcare practitioners registered with the HPCSA, irrespective of where they conduct their research.²¹¹

²⁰⁹ Ch 9 of the NHA.

²¹⁰ Par 9 *Booklet 7: Medical Biotechnology Research* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_7_medical_biotechnology_research.pdf> (Accessed 25 June 2016).

²¹¹ Par 10.1.1 *Booklet 7: Medical Biotechnology Research* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_7_medical_biotechnology_research.pdf> (Accessed 25 June 2016).

In addition to ethics review, the HPA provides for investigations into alleged unprofessional conduct of any health practitioners registered with the HPCSA. This investigation is a twofold enquiry: (a) a preliminary inquiry and (b) a disciplinary inquiry. Usually, a preliminary inquiry is instigated when an aggrieved patient or research subject lodges a formal complaint with the registrar of the council or the relevant professional board.

Upon receiving such complaint there are numerous steps that can be taken, such as the request for further particulars from the complainant and further correspondence with the accused for more information. After all the relevant information has been gathered, the registrar submits the matter to the Committee of Preliminary Inquiry.²¹² The registrar is also allowed to do so from the first instance. After duly considering the matter, the Committee of Preliminary Inquiry may:²¹³

- request any additional particulars from any party of interest and defer the matter to the following meeting;
- consult with either the accused or the complainant in terms of section 41(2);
- make a decision to inspect that practice of the accused;
- take cognisance of the explanation of the accused, which sets out the full reasons for such conduct and forward it to the accused to take note of; and
- refer the matter for an inquiry with/without the option of a fine.²¹⁴

The main task of the Committee of Preliminary Inquiry is to establish the fact of a *prima facie* case against the practitioner in question. In *Tucker v SA Medical and Dental Council*²¹⁵ the court held that the Committee of Preliminary Inquiry is only concerned with whether there should be a disciplinary hearing and should not concern themselves with whether the charge will be proven or not.²¹⁶

²¹² Carstens & Pearmain *supra* n133 270.

²¹³ *Idem* at 271.

²¹⁴ If the Committee of Preliminary Inquiry is of the opinion that all the documentation pertaining to the matter constitutes a transgression that is too trivial in nature to warrant a disciplinary inquiry, the Committee of Preliminary Inquiry must impose a penalty in terms of s 42(1)(a), (d), (e) and (f) of the HPA GN R765 dated 2005-08-24.

²¹⁵ *Tucker v SA Medical and Dental Council* 1980 2 SA 207 (T) at 212 F-G.

²¹⁶ Carstens & Pearmain *supra* n133 271.

When the matter is referred to a Committee of Professional Conduct, it can be regarded as a court matter.²¹⁷ The procedure is analogous to that of a court of law where the conduct of the accused health practitioner is closely examined by his or her peers serving on the professional conduct committee.²¹⁸ The Medical and Dental Professional Council is an administrative body and *quasi-judicial* by nature and is therefore bound by the Constitution and the Promotion of Justice Act (PAJA).²¹⁹ Due to the former, all respondent practitioners are afforded the right to fair administrative action that is lawful, reasonable and procedurally fair. The respondent practitioner is also entitled to receive reasons for the decision of the Professional Conduct Committee.²²⁰ It should be noted that the ordinary rules of evidence apply in a professional conduct inquiry.²²¹

It is widely acknowledged that when the Professional Conduct Committee considers a charge, it must first determine whether sufficient facts have been proven in its opinion to support the charge. After the charge has been substantiated with evidence, it must be decided if the charge constitutes improper or disgraceful conduct or conduct which, when regard is given to the respondent practitioner's profession, is improper or disgraceful.²²² The *pro forma*²²³ complainant is charged with the onus, balanced on a preponderance of probabilities to prove that the conduct of the respondent practitioner amounts to unprofessional conduct.²²⁴

The accused or *pro forma* complainant is entitled to appeal against the decision or penalty of the Professional Conduct Committee to the Appeal Committee.²²⁵ The possibility of an appeal to the High Court of South Africa is open to any aggrieved

²¹⁷ Strauss *Doctor, patient and the law: A selection of practical issues* (1991) 273.

²¹⁸ Carstens & Pearmain *supra* n133 274.

²¹⁹ Promotion of Justice Act 3 of 2000 (hereinafter referred to as "PAJA"); Carstens & Pearmain *supra* n133 274.

²²⁰ S 33 of the Constitution and the provisions of PAJA; Carstens & Pearmain *supra* n133 275.

²²¹ *McLoughlin v South African Medical and Dental Council* 1947 2 SA 377 (W).

²²² *De Beer v Health Professions Council of South Africa* 2005 1 SA 332 (T).

²²³ Similar to a state prosecutor in a criminal case.

²²⁴ Carstens & Pearmain *supra* n133 275.

²²⁵ This is a committee incorporated in terms of s 10(2) of the HPA for the purposes of conducting an appeal against the finding of an inquiry conducted by a professional conduct committee or professional board.

party to a decision of the council, a profession board or disciplinary appeal committee.²²⁶

Such an appeal only occurs in practice after the aggrieved party has exhausted all the internal remedies available. The Supreme Court of Appeal held in *De Beer v Health Professions Council of South Africa*²²⁷ that the appeal procedure created by section 20 of the HPA “is an appeal in the ordinary sense, that is a rehearing on the merits but limited to the evidence of information on which the decision under appeal was given, and in which the only determination is whether that decision was right or wrong.”²²⁸ It is important to remember that the Medical and Dental Practitioner’s Professional Board is a creature of statute and has limited jurisdiction to pass sentences. As stated above, the HPCSA is regarded as the *costos morum* of the medical profession and is charged with upholding the prestige and status of the profession, as well as with acting in public interest. Imposing an appropriate sentence is dependent on whether the practitioner was convicted of disgraceful or improper conduct, with disgraceful being more serious and worthy of more severe punishment.²²⁹ If the sentence or penalty is taken on appeal or review, it is unlikely that a court will deviate from the judgement of the council unless misdirection has been made or the sentence is strikingly inappropriate.²³⁰

In the absence of an appeal, when a practitioner is found guilty of professional misconduct, the committee may impose any of the following penalties:²³¹

- (a) A caution or a reprimand and a caution
- (b) A suspension for a specific period from practising or performing acts specifically pertaining to his profession²³²
- (c) Removal of his name from the registrar

²²⁶ S 20 of the HPA: Notice of appeal must be given within one month from the date on which the decision was made; Carstens & Pearmain *supra* n133 276.

²²⁷ *De Beer v Health Professions Council of South Africa supra* n324.

²²⁸ Carstens & Pearmain *supra* n133 278.

²²⁹ *Ibid.*

²³⁰ *De Beer v Health Professions Council of South Africa supra* n324 par 27.

²³¹ Carstens & Pearmain *supra* n133 268.

²³² Subsequent to suspension or removal from the register, the relevant person is disqualified from carrying on supplying professional services and his or her registration certificate is deemed cancelled until the expiry of the suspension period or until his or her name has been restored to the register of professional boards.

- (d) A fine
- (e) A compulsory period of profession service as may be determined by the professional board
- (f) The payment of the costs of the proceedings or restitution

3.4 Conclusion

Bearing in mind a healthcare practitioner's obligations of veracity, privacy and confidentiality, it is important that these obligations should be interpreted against the backdrop of principlism. This means that, before a healthcare practitioner or researcher acts, it is important for them always to reflect on what is regarded as ethical by making a value judgement. Such a value judgement can be made by balancing the principles of autonomy, beneficence, non-maleficence and justice to determine the most suitable route of action.

From an ethical perspective, administering or doing research that has not been proven by evidence-based methods or have not been afforded ethical clearance would be contrary to the principles of beneficence and non-maleficence. Choosing subjects or patients based on discriminatory criteria such as defencelessness might influence the informed consent process and would not be in line with the principles of justice and beneficence. Any such action would be subject to a review process of the HPCSA.

Besides the professional ethical regulation of the medical profession, a labyrinth of statutory provisions regulates the field of stem cell technologies. In terms of the multi-layered approach, before the statutory provisions pertaining to stem cell technologies can be set out, it is necessary to discuss the basis on which the statutory regulations are built. Therefore, the next chapter will outline the constitutional values that permeate all facets of law in the context of stem cell technologies.

CHAPTER 4

CONSTITUTIONAL ANALYSIS OF STEM CELL TECHNOLOGIES

4.1 Introductory remarks and application of the Constitution

4.1.1 Introduction

Even though the law and ethics are intimately intertwined, it is safe to say that the legal rule is normally preceded by the ethical rule it is charged to govern. In the previous chapter, the principles of autonomy, beneficence, non-maleficence and justice were elucidated. If these principles are complied with, they will further the realisation of the rights enshrined in the Constitution as well as aid in the prevention of possible criminal and unprofessional conduct in the context of stem cell therapy.

Chapter 2 of the Constitution, the Bill of Rights, was created in harmony with ethical principles that purport to protect the core of human life, the right to bodily and psychological integrity, privacy, freedom of religion belief and opinion, and access to health care, to name only a few. The aforementioned intends to limit the protection of the Constitution, but only to sketch the applicable constitutional principles that are relevant in the context of stem cell technologies.

This study intends to critically analyse the regulatory framework pertaining to the therapeutic application of stem cell technologies in both South Africa and the UK. In the context of a multi-layered approach, the constitutional principles have to be discussed before national legislation can be understood fully. This can be ascribed to the fact that the Constitution is the supreme law of the country and instructs all other legislation. Any conduct that is inconsistent with the Constitution is unlawful to the degree of dissonance therewith.¹

The Bill of Rights is binding on and applicable to the executive, the legislature, the judiciary and all organs of state,² and compels the state not to violate any of the fundamental rights when exercising its constitutional mandate. This is essential, as

¹ S 7(1) of the Constitution: This Bill of Rights is a cornerstone of democracy in South Africa. It enshrines the rights of all people in our country and affirms the democratic values of human dignity, equality and freedom.”

² *Idem* at s 8(1).

the government sets out the legislative framework for the regulation of stem cell technologies such as the methods of derivation, preparation, use and storage of stem cell technologies. Because the government has the power to set out the legislative policy regarding the use of stem cells, the Constitution will play a vital role in the validation and benchmarking of such legislation to test whether the national policy resonates with the intrinsic values of the Constitution.

As the stem cell debate unfolds, certain ethical and constitutional dilemmas emerge, often leaving members of society with an unsettling feeling or uncertainty about what is acceptable and what is not. This could include issues such as the application of untested and unregulated stem cell therapy, experimental treatment (often referred to as therapeutic or innovative research or expanded access programmes), the derivation of embryonic stem cells and the destruction of the embryo, the application of somatic cell nuclear transfer, parthenogenesis and induced pluripotent stem cells. All of the above issues and debates may violate and limit constitutional rights such as the right to freedom of religion, belief and opinion;³ life;⁴ dignity;⁵ equality;⁶ physical and psychological autonomy;⁷ privacy;⁸ and access to health care.⁹ When dealing with conflicting constitutional rights, section 36 (“the limitation clause”) plays a vital role to balance the conflicting constitutional principles and rights.

In the course of this chapter, the constitutional principles relating to stem cell technologies will be discussed. However, before doing so, the various forms of constitutional application need to be discussed to fully understand the impact the Constitution has on the application of stem cell technologies.

4.1.2 Application of the Constitution

4.1.2.1 Direct application of the Constitution

The Constitution provides for two different types of application of the Bill of Rights, namely direct application and indirect application. Direct application refers to

³ *Idem* at s 15.

⁴ *Idem* at s 11.

⁵ *Idem* at s 10.

⁶ *Idem* at s 9.

⁷ *Idem* at s 12.

⁸ *Idem* at s 14.

⁹ *Idem* at s 27.

conferment of a duty by the Bill of Rights on a specific party. If a party breaches the imposed duty, it is regarded as a violation of a constitutional right. Indirect application, is “[where] there is a provision of ordinary law (legislation, common law or customary law) that mediates between the Bill of Rights and the actors who are subject to that law.”¹⁰ The Constitution includes both natural and juristic persons as beneficiaries and concurrent duty-bearers of the rights enshrined in the Bill of Rights.¹¹ This would only be applicable if the constitutional right can be applied sensibly to juristic persons.

The Constitution not only finds application in a vertical sense, which regulates the unequal relationship between state and subject, but also provides for horizontal application between legal subjects. Section 8(1) of the Constitution contains the direct vertical application, setting out the circumstances under which the law and conduct of the state may be challenged due to being inconsistent with the Bill of Rights. On the other hand, section 8(2) of the Constitution deals with direct horizontal application, setting out the circumstances under which the conduct of private persons may be challenged due to being inconsistent with the Bill of Rights. Furthermore, section 8(3) of the Constitution confers the power to rectify such infringements to the courts, by conferring the duty on them to develop, limit or interpret the common law in such a way to ensure that it is in accordance with the Constitution.

The influence the Bill of Rights has on the rights and duties imposed by the common law or legislation is referred to as the indirect application of the Constitution, in both the horizontal of vertical axis. Since the case of *Du Plessis v De Klerk*,¹² the courts have routinely practiced an indirect application of the Constitution.¹³ This is also consistent with the doctrine of avoidance, which is preferred over the direct application of the Constitution.

¹⁰ Currie & De Waal *The Bill of Rights Handbook* (2014) 34.

¹¹ S 8(4) of the Constitution states that: “A juristic person is entitled to the rights in the Bill of Rights to the extent required by the nature of the rights and the nature of that juristic person.”

¹² *Du Plessis v De Klerk* 1996 3 SA 850 (CC).

¹³ Currie & De Waal *supra* n344 45.

As Currie and De Waal state:¹⁴ “The only cases where direct application seems to make sense is when common-law offences or rules are challenged with the purpose of ‘invalidating’ them.”

Additionally, private parties are reluctant to invoke the Bill of Rights directly due to the fact that the remedies for the private violation of fundamental rights are unattractive and tough to predict.¹⁵ However, when challenging state conduct or legislation, constitutional remedies are a more appealing option.¹⁶

4.1.2.1 Indirect application of the Constitution

The indirect application means that the Constitution does not directly bind the legal subjects. In contrast to the direct application of the Constitution, the influence of the Bill of Rights is mediated through the application of other laws, both statutory and common law. In terms of the doctrine of avoidance, a legal dispute should be decided in terms of existing principles or rules of ordinary law so interpreted or developed to agree with the values of the Bill of Rights, before considering the direct application of the Bill of Rights to the dispute.¹⁷ When applying this doctrine to statutory law, it simply means that a court must first attempt to interpret the legislation so that it agrees with the Bill of Rights, before considering whether to declare the legislation inconsistent and in conflict with the Bill of Rights.¹⁸

Therefore, the Bill of Rights can be seen as a standard which enshrines the values and norms to be respected in South Africa. This means that when a case is brought before a court to challenge the constitutionality of national legislation governing stem cell technologies, the court would first try to develop or limit the legislation in such a way that it agrees with the Bill of Rights, before declaring the legislation unconstitutional and invalid in terms of a direct approach.

Armed with a clear understanding of the various forms of constitutional application, it is evident that indirect application is the first line of entry when evaluating the

¹⁴ *Ibid.*

¹⁵ Currie & De Waal *supra* n344 45.

¹⁶ For an in-depth discussion of constitutional remedies see ch 8 of Currie & De Waal *supra* n344 172.

¹⁷ With regard to the doctrine of avoidance see *S v Mhlungu* 1995 (3) SA 867 (CC) [59]; *Ferreira v Levin* 1996 (1) SA 984 (CC) [199].

¹⁸ Currie & De Waal *supra* n344 57.

constitutionality of stem cell legislation. For instance, if the constitutionality of a prohibition of the application of a specific type of stem cell therapy is brought before the court, the court would first attempt to interpret the legislation in such a way so that it agrees with the values enshrined in the Constitution, before declaring the prohibitive section invalid and unconstitutional. The following section will shed light on the various constitutional rights applicable to the application of stem cell technologies.

4.2 Constitutional analysis

4.2.1 Equality

4.2.1.1 *Ethical and constitutional equality*

As stated in the previous chapter, the generic ethical guidelines for researchers state that a health researcher must take cognisance of the laws pertaining to unfair discrimination in the management of research participants or their families, on the basis of race, culture, ethnicity, social status, lifestyle, perceived economic worth, age, gender, disability, communicable disease status, sexual orientation, religious or spiritual beliefs, or any condition of vulnerability such as contained in health-rights legislation.¹⁹

The only time a researcher may discriminate on the above-mentioned grounds, is in the event that such discrimination is warranted due to its importance in the outcome of the research experiment.²⁰ Equality is regarded as a cornerstone of the ethical principles of justice and fairness and requires from a healthcare practitioner to apply the principles of substantive equality.²¹ This would acknowledge the fact that we are not all equal and therefore that different patients or participants should be treated differently to ensure an equal outcome, as opposed to a “one-size-fits-all approach” proposed by formal equality that could result in unsympathetic inequality between patients or research participants.

¹⁹ Par 6.5.1 *Impartiality and Justice Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 7 July 2016).

²⁰ *Idem* at par 6.5.2 “...except where the exclusion or inclusion of particular groups is critical to the research purpose and scientific design.”

²¹ See ch 3 regarding justice and fairness.

The ethical values of justice and fairness have not only been enshrined in section 9 of the Constitution, but also in section 36 (limitation clause) and section 39 (interpretation clause). This fact proves the importance of the right to equality and, therefore, the right to equality in the context of health care must be illuminated in the context of stem cell technologies.

4.2.1.2 Formal and substantive equality

To understand what substantive equality means, it has to be distinguished from formal equality. Formal equality means treating everyone the same, in other words, the law must treat everyone in the same circumstances the same.²² Substantive equality requires equal outcome in a situation and acknowledges the inequality between different persons, so that an equal outcome can be achieved.²³

In terms of a formal conception of equality, inequality is simply a digression that can be axed by affording the same rights to everyone based on an impartial standard.²⁴ Therefore, it disregards the social and economic disparities between groups of people, for instance the fact that the less fortunate might be more willing to participate in a dangerous and unproven stem cell research protocol than their blessed counterparts.

In contrast to formal equality, substantive equality necessitates the evaluation of the actual social and economic conditions of groups and individuals when determining whether their constitutional right to equality is being upheld. For instance: A stem cell researcher would have to evaluate the socio-economic position of each potential participant to determine whether the potential participant's involvement would be constitutionally sound with the right to equality, to ensure not only equal access to health care, but also that each participant's right to bodily and psychological integrity,

²² For an in-depth discussion regarding formal and substantive equality, see Freedman "Formal versus substantive equality and the jurisprudence of the Constitutional Court" (2000) 63(2) THRHR 314.

²³ Currie & De Waal *supra* n344 213, n 18: "For example, on a formal conception of equality, equality is achieved if all children are educated according to the same school curriculum. Substantive equality, on the other hand, would require equality of outcome. If children with disabilities (deaf children for example) undergo the same school programme as other children they may very well end up receiving an education that is inadequate for their special needs. To realise the right to equality of such children, it may therefore be necessary to treat them differently to everyone else."

²⁴ *Ibid.*

privacy, confidentiality and dignity is equally respected. Such an approach has been adopted by the Constitutional Court:²⁵

We need...to develop a concept of unfair discrimination which recognises that although a society which affords each human being equal treatment on the basis of equal worth and freedom is our goal, we cannot achieve that goal by insisting upon identical treatment in all circumstances before that goal is achieved. Each case, therefore, will require a careful and thorough understanding of the impact of the discriminatory action upon the particular people concerned to determine whether its overall impact is one which furthers the constitutional goal of equality or not. A classification which is unfair in one context may not necessarily be unfair in a different context.

Section 9(2) of the Constitution evidently supports a substantive conception of equality by stating “equality includes the full and equal enjoyment of all rights and freedoms”. In view of such semantics, a healthcare practitioner or researcher should be mindful of unfair discrimination and ethical considerations such as justice and fairness, but above all, they must uphold a patient’s or participant’s constitutional right to equality. Determining whether an infringement constitutes a violation of the constitutional right to equality is a multifaceted enquiry.

4.2.1.3 Unfair discrimination

A compliance test regarding the equality clause was set out in the *locus classicus* case of *Harksen v Lane* as follows:²⁶

- a) First, does the law or conduct in question differentiate between certain people or groups of people? In such a case, it has to be established whether the differentiation is logically connected to a legitimate government purpose. Despite bearing a rational connection to a legitimate government purpose, the said law or conduct might still amount to unfair discrimination.
- b) After it has been established that the conduct or rule amounts to differentiation, it has to be determined whether it equals to unfair discrimination, which is a two-step investigation:
 - (i) Firstly, is the *differentiation* equal to *discrimination*? If it is based on a listed ground, the differentiation is equal to discrimination. If the differentiation is not based on a specified ground, it must be determined objectively, whether the

²⁵ *President of the Republic of South Africa v Hugo* 1997 4 SA 1 (CC).

²⁶ *Harksen v Lane* 1998 1 SA 300 (CC) [53]; The case of *Hoffmann v South African Airway* 2000 12 BLLR 365 (CC) serves an example where the court applied this test to make a finding of unfair discrimination based on the grounds of a person’s HIV status; For a discussion regarding the “*Harksen v Lane* test” see Kruger R “Quality And Unfair Discrimination: Refining The *Harksen* Test” 2011 SALJ 479.

ground of differentiation is based on attributes or characteristics that have the potential to harm the fundamental human dignity of persons, or have an adverse effect in a comparably serious manner.

- (ii) If the differentiation is indeed discrimination, does it amount to *unfair discrimination*? If the discriminatory-ground is based on a listed ground, it will be presumed unfair discrimination. If it is based on an unlisted ground, the plaintiff bears the onus of proof, to show on a preponderance of probability that the discriminatory ground is indeed unfair. The test for unfairness is mainly concerned with the impact of the discrimination on the complainant and others in the same situation.

If it is found after the two-step enquiry that the discrimination is not unfair, the discrimination will not constitute a violation of section 9(3) and (4).

- c) In the event that the discrimination is found to be unfair, it will have to be determined whether as to whether the infringement is justifiable under section 36 of the Constitution.

As required by section 9(4) of the Constitution, national legislation has been incorporated to prohibit or prevent unfair discrimination, particularly in relation to private persons or institutions. This was realised by the Promotion of Equality and Prevention of Unfair Discrimination Act 4 of 2000 (Equality Act), which purports to eradicate social and economic inequalities.²⁷

The Equality Act hopes to succeed in its endeavour: by prohibiting the state and other persons (such as medical practitioners or researchers) to discriminate unfairly; by providing remedies to victims of unfair discrimination; and by promoting the achievement of substantive equality.²⁸ Akin to labour relations rights²⁹ and the rights to just administrative action,³⁰ any legislation aimed at the realisation of a constitutional right (such as the Equality Act) must be regarded by the courts as consistent with the provisions of the Constitution. Therefore, any claim stating that an infringement of equality has occurred must be decided in terms of the provisions and procedures of the Equality Act.³¹

²⁷ For instance, the eradication and prevention of unequal access to health care.

²⁸ Currie & De Waal *supra* n344 244.

²⁹ Employment Equity Act 55 of 1998 as amended by Act 47 of 2013.

³⁰ Promotion of Administrative Justice Act 3 of 2000.

³¹ *MEC for Education, Kwazulu-Natal v Pillay* 2008 1 SA 474 (CC).

After the incorporation of the Equality Act, any challenges based on equality must be based on section 9 of the Constitution. Direct reliance on section 9 of the Constitution will only be allowed in exceptional circumstances, such as the case where the conduct or legislation is beyond the reach of the Equality Act.³² This requirement resonates with the principle of subsidiarity, which states that before resorting to direct constitutional remedies, an aggrieved party must first exhaust all the available common law or legislative remedies so interpreted or developed to conform to the Constitution.³³

In terms of the Equality Act's objective to prevent unfair discrimination, it applies to both the state and all persons.³⁴ In general, the enquiry into what constitutes unfair discrimination in the Act would follow the Constitutional Court's reasoning, such as the courts rationale in *Harksen v Lane*.³⁵ In the event that an aggrieved party wishes to challenge conduct that might amount to unfair discrimination, it must be based on the rights, duties, procedures and remedies as set out by the Equality Act.³⁶ Only once all such remedies have been exhausted the aggrieved party may rely on the Constitution.

In the event that an action for relief is brought regarding discrimination based on an unlisted ground, the Equality Act provides greater protection than the Constitution by stating that discrimination on an analogous ground will be presumed unfair.³⁷ However, before this is presumption takes effect, it must be shown that the discriminatory ground either causes or perpetuates systemic disadvantage, undermines human dignity, or adversely affects the equal enjoyment of rights and freedoms in such a way that it is tantamount to a prohibited ground.³⁸

³² Currie & De Waal *supra* n344 245.

³³ *Ibid*; See also Du Plessis "Subsidiarity: What's in the name for constitutional interpretation and adjudication?" *Stell LR* 207 for a general discussion on the constitutional principles of subsidiarity.

³⁴ S 5 of the Equality Act states that a 'person' includes a juristic person, a non-juristic entity, a group or a category of persons.

³⁵ *Harksen v Lane* 1998 1 SA 300 (CC).

³⁶ For a discussion on the application and controversy surrounding the Equality Act, see Kok "The Promotion of Equality and Prevention of Unfair Discrimination Act: why the controversy?" 2001 *TSAR* 301.

³⁷ Definition of "prohibited grounds" can be found in s 1 read with s 13(2) of the Equality Act.

³⁸ Currie & De Waal *supra* n344 247.

4.2.1.4 Equality in context of stem cell technologies

Inequality is present in various facets of stem cell technologies, from the procurement of the stem cell up to the use of new stem cell therapies. It is vital that medical practitioners or researchers take cognisance of what is regarded as unequal, especially when dealing with vulnerable or socio-economically disadvantaged patients or participants. Therefore, researchers or practitioners should be mindful of what constitutes unfair discrimination and should not discriminate on the listed grounds or a differentiating factor that has the ability to diminish a person's intrinsic worth, such financial status. However, researchers must be careful to choose participants for a study who would not be able to bear the burdens that come with it.³⁹ Be that as it may, discriminating on a listed ground or an unlisted ground with the potential to undermine human dignity or to adversely affect the equal enjoyment of rights and freedoms, such as access to health care, would be in contravention of the Equality Act and therefore unconstitutional.

The right to equality should not be misconstrued by everyone seeking stem cell treatments. Akin to section 27 of the Constitution, which only grants a right to access to health care, section 9 of the Constitution only provides for equal opportunity, and not a right to be afforded stem cell treatments. Sadly, in a country suffering from many socio-economic issues, the state has limited resources to be made available for stem cell research. Therefore, for the most part, stem cell research is funded by the private sector and will only be offered to those who can afford it.⁴⁰

Chapter 5 of the Equality Act places a responsibility on the state to promote equality.⁴¹ Furthermore, it provides a list of the duties incumbent on the state to develop substantive equality and address unfair discrimination. In certain circumstances, even private institutions can be compelled to conform to equality measures.⁴² Also, the annexure to the Equality Act illustrates and emphasises

³⁹ Beauchamp *et al supra* n115 541: Social justice necessitates a distinction to be made between classes of subjects who ought and ought not to participate in a certain research study, based on the ability of each class to bear the burdens, and whether it is appropriate to burden certain members of a class even more.

⁴⁰ Nöthling Slabbert *et al SAJBL* 41: "Developing countries, such as SA, are facing many challenges in ensuring that basic medical services are established and maintained. The need for specialised forms of treatment, such as cell-based therapies, is therefore questioned."

⁴¹ S 24-29 of the Equality Act.

⁴² S 27(2) of the Equality Act.

practices which may be unfair, as well as when the state is charged with passing legislation or other means to address such inequalities.

Among nine others, health care is listed in point 3(b) of the annexure, read with section 29 of the Equality Act, which states that the unfair denial or refusal of access to healthcare facilities of any person, or failure to provide access to healthcare facilities to any person is one of the areas where the state is obliged to take reasonable measures to address unfairness. Therefore, it is submitted that, as stem cell treatments have the potential to cure debilitating life-threatening conditions or diseases, the state has a duty to make stem cell treatments available to the public if no other means of treatment are available, if reasonably and financially possible. It should be noted that this duty is not absolute and the state must only do so within its reasonable available means.⁴³

Based on the government's reasonable inability to provide stem cell treatments (as there are more pressing health issues that need care, such as HIV/AIDS and Tuberculosis),⁴⁴ an argument of unfair discrimination based on social status will have to remain. Until the state is in a position to reasonably provide financial means to support stem cell therapies to those in need, the inequality and divide between rich and poor, unfortunately, still prevails.

In the context of genetic discrimination, the right to equality is closely related to the right to medical confidentiality, which in turn is a subset of privacy.⁴⁵ In the event that a healthcare practitioner or researcher divulges a patient's or participant's genetic information to an insurance company, without the patient's or participant's prior

⁴³ In *Soobramoney v Minister of Health, KwaZulu-Natal* 1997 12 BCLR 1696 (CC), the court stated that the right to access to health care in section 27(1) of the Constitution is qualified by the wording of section 27(2) which states "The state has to take reasonable legislative and other measures within its available resources, to achieve the progressive realisation of each of these right." Due to this qualification, the court held that an unqualified obligation to fulfil the right envisaged in section 27(1) is currently not possible. Furthermore, the court is unlikely to interfere with the allocation of scarce resources that has been done in good faith.

⁴⁴ Tbfacts.org TB Statistics for South Africa – national & provincial <<http://www.tbfacts.org/tb-statistics-south-africa/>> (Accessed 8 August 2016). South Africa is one of the countries with the highest burden of TB with the WHO estimating 450 000 cases of TB in 2013. Out of the 450 000 TB cases about 60% also have HIV. TB continues to be the leading cause of death in South Africa; In South Africa approximately seven million people are living with Aids. <<http://www.unaids.org/en/regionscountries/countries/southafrica>> (Accessed 8 August 2016).

⁴⁵ See ch 3 regarding privacy.

informed consent, it will not only lead to a breach of patient confidentiality and the right to privacy as set out in the Constitution, but also to potential unfair discrimination based on genetic information. For example, in the event that the insured patient or participant was, by luck of the draw, endowed with a lesser set of genetic material and therefore more prone to disease, an insurance company might use it against the insurer to set a higher monthly premium, as the insured patient is a higher risk than someone else. Such differentiation could presumably constitute unfair discrimination.

Although section 9(3) of the Constitution makes no mention of “genetic make-up”, in terms of the Equality Act it could be construed as discrimination based on birth, ethnic or social origin or disability (if it could be interpreted to include genetic predisposition under the ambit of disease)⁴⁶ or on an analogous ground that it affects the intrinsic worth of the insured by undermining human dignity or adversely affecting the equal enjoyment of rights in the same way as a listed ground would.⁴⁷ Discriminating on the grounds of genetic make-up is something of the extremely personal sphere and violation of privacy.⁴⁸ This could be ascribed to the fact that a person’s genetic material dictates that person’s race and physical attributes, all by the luck of the draw. As stated by Nienaber and Van der Nest⁴⁹ “[the] results of genetic tests may cause shame, fear and resentment towards one’s ancestors and members of one’s family.” Discriminating on such grounds is presumably tantamount to unfair discrimination.

An insurance contract comes into being at the time of consensus between the parties to the contract⁵⁰ and the normal rules of contract pertaining to offer and acceptance are applicable. In the event of an insurance contract, the public is usually

⁴⁶ Nienaber & Van Der Nest “Genetic testing for the purposes of insurance risk assessment and the constitutional right to privacy” 2004 *THRHR* 446, 455.

⁴⁷ Based on the definition of ‘prohibited grounds’ in s 1 read with s 13(2) of the Equality Act.

⁴⁸ Nienaber & Van der Nest 2004 *THRHR* 446, 458.

⁴⁹ *Idem* at 447.

⁵⁰ *Idem* at 452; Peterson *Genetic Turning Points: The Ethics of Human Genetic Intervention* (2001) 207: “The traditional insurance system in the United States is based on actual fairness. If you choose to operate a business in a high-risk environment, the reward may be great but the cost of insurance will be too. The insurance company must charge higher premiums because of the greater likelihood that it will have to pay a claim...[The] free-market system requires the insurance company to tie premium levels to actual risk so that it can compete for customers yet not be overwhelmed by expensive claims.”

invited to make the offer by completing the proposal form.⁵¹ In terms of good faith, both parties have the right to rescind the agreement if the other party has misrepresented a material fact.⁵² This entails that, among other things, the insured is charged with disclosing all facts of interest for the determination of the risk, such as age, family history regarding breast cancer and so on.⁵³ If the potentially insured person answered affirmatively, the insurance provider may ask him or her to undergo genetic testing in order for them to accurately calculate their risk.⁵⁴

In the event that a voluntary disclosure has taken place on the part of the insured, regarding his or her genetic information that might make him or her prone to disease, an argument can be put forward to justify the higher premium to be paid.⁵⁵ This is akin to the voluntary disclosure regarding information such as previous medical records and in line with the right of an insurer to contract on fair terms.

It is clear that the right to equality is closely intertwined with the other rights contained in the Bill of Rights. For instance, unfair discrimination on the basis of a person's genetic endowments or any listed grounds in section 9(3) of the Constitution, has the capacity to infringe on a the most intrinsic facets of a person and therefore can be an infringement on a person's right to human dignity, privacy, access to health care and the right to life.

⁵¹ *Ibid.*

⁵² *Ibid.*; The concept of *uberrima fides* as the utmost degree of good faith has been abolished, as good faith has no degrees. The strongest criticism is found in Joubert's majority judgment in *Mutual and Federal Insurance Co Ltd v Oudtshoorn Municipality* 1985 1 SA 419 (A) where he states that: "...there is no magic in the expression *uberrima fides*. There are no degrees of good faith. It is entirely inconceivable that there could be a little, more or most (utmost) good faith. The distinction is between good faith or bad faith. There is no room for *uberrima fides* as a third category in our law...*Uberrima fides* is not a juristic term with a precise connotation."

⁵³ *Ibid.*; Herring *supra* n130 255 "An insurance company offering someone life insurance would dearly want to know genetic information about that person, so that a precise calculation can be made as to whether he or she is a good or a bad risk for life insurance purposes; For more information on the duty to disclose see Church (2013) "*Jerrier v Outsurance Insurance Company Ltd* 2013 JDR 0562 (KZP) The duty to disclose: An ongoing problem?" *De Jure* 859.

⁵⁴ *Ibid.*; Herring *supra* n130 256: It is interesting to note that the Human Genetic Commission in May 2001 imposed a moratorium preventing insurers to make use of genetic information in the event that the value was less than £500 000, except when testing for Huntington's chorea; Peterson *supra* n384 208 "If the insurer does not charge a higher premium for higher risk, people at high risk will notice that the company's premium is lower for them than that of competitors." This will cause a higher volume of claims than money coming in and is known as adverse selection, something that can bankrupt an insurer quickly. Therefore, it is imperative that insurance companies tie risk to the premium; Peterson *supra* n384 212: In North Carolina, Senate Bill 254 prohibits discrimination against any individual due to the results of a genetic test with regard to health insurance and employment, even though it does not address the issue of premiums.

⁵⁵ Peterson *supra* n384 209 "If insurance companies do not have access to the results of client genetic testing, they fear adverse selection."

4.2.2 Human dignity

Section 10 of the Constitution reads as follows: “Everyone has inherent dignity and the right to have their dignity respected and protected.”

4.2.2.1 Human dignity as a central value and right

The value of human dignity is embodied in the *General Ethical Guidelines for the Health Care Professions* of the HPCSA, which states that a healthcare practitioner should respect a patient as person, acknowledge their intrinsic worth, dignity and sense of value.⁵⁶ Furthermore, in terms of respect for persons, a healthcare practitioner should respect the privacy and dignity of patients.⁵⁷ Human dignity is also affirmed and incorporated in the Constitution as both, a value and a right and is arguably the most important right and value contained in the Bill of Rights.⁵⁸

In the case of *Charmichele v Minister of Safety and Security*,⁵⁹ the court stated that human dignity is a central value of the objective normative value system that was brought about by our Constitution and probably the most profound value on which the constitution is built.⁶⁰ As this right is central to the protection of all other rights, human dignity can be described as a “pre-eminent value in the Constitution, even more so than the right to life.”⁶¹ This is best illustrated by the fact that human dignity

⁵⁶ *Booklet 1: General Ethical Guidelines for the health care professions* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_1_guidelines_good_prac.pdf> (Accessed 29 June 2016).

⁵⁷ *Ibid.*

⁵⁸ S 1 of the Constitution states that South Africa is founded on the values of ‘human dignity, the achievement of equality, and the advancement of human rights and freedoms’; S 7 states: the Bill of Rights is an instrument that ‘affirms the democratic values of human dignity, equality and freedom’; S 36 (the limitation clause) provides that rights in the Bill of Rights may be limited, provided the limitation is ‘reasonable and justifiable in an open and democratic society based on human dignity, equality and freedom’. In addition, s 39 (the interpretation clause) states that, when interpreting the Bill of Rights ‘the values that underlie an open and democratic society based on human dignity, equality and freedom’ must be promoted.

⁵⁹ *Carmichele v Minister of Safety and Security* 2001 4 SA 938 (CC).

⁶⁰ Ackermann in *National Coalition for Gay and Lesbian Equality and Another v Minister of Justice and Others* 1998 2 ZACC 15 that: “...the right to dignity is a cornerstone of our Constitution.”

⁶¹ *S v Makwanyane* 1995 5 BCLR 666 (CC); Chaskalson “Human Dignity as a Foundational Value in our Constitutional Order” 2000 SAJHR 193, 196.

is imported into the text of several sections in the Bill of Rights where it functions as both a right and an important value upon which the Constitution is based.⁶²

4.2.2.2 Defining dignity

Human dignity and health care are closely related concepts, as health is essential to life and human dignity.⁶³ Additionally, decisions related to bodily integrity and the effect of those decisions are deeply personal and therefore affect one's right to human dignity.⁶⁴ Depending on one's definition of human dignity, stem cell technologies might either promote or impede on a person's human dignity. Therefore, it is important to have a clear and concise understanding of the term human dignity. It has been said that human dignity is indefinable and serves no purpose for an ethical analysis of medical technologies.⁶⁵ It is no secret that the concept of dignity is so vast and unclear that it is not much more than a rhetorical device.⁶⁶

This fact is best illustrated by the two different appeals to human dignity, such as when death-with-dignity organisations appeal to a loss of dignity when ending life support, as opposed to anti-euthanasia proponents who are also appealing to dignity, but in the context of respect for human life.⁶⁷ In the context of stem cell technologies, the proponents of embryonic stem cell research appeal to the furtherance of the human dignity of the potential beneficiaries of such research, while the opponents of stem cell research appeal to the protection of the human dignity of the early embryo.

⁶² For a general discussion on human dignity as a cornerstone of other rights in the Constitution see Ackermann *Human Dignity: Lodestar for Equality in South Africa* (2012); Currie & De Waal *supra* n344 251: Section 7(1)(the Bill of Rights) is an instrument which "...enshrines the rights of all the people in our country and affirms the democratic values of human dignity, equality and freedom"; Section 39: all the rights in the Bill of Rights must be interpreted so as to promote the Constitution's ambition of creating an "open and democratic society based on human dignity, equality and freedom"; Section 36 (rights can only be limited to the extent justifiable in such a society).

⁶³ Carstens & Pearmain *supra* n133 29.

⁶⁴ Verwey & Carstens 2014 30 *SAJHR* 91.

⁶⁵ *Idem* at 92.

⁶⁶ Moody "Why Dignity in Old Age Matters" 1998 *JGSW* 13, 14.

⁶⁷ Verwey & Carstens 2014 *SAJHR* 92.

Currie & De Waal⁶⁸ note that despite the critical role human dignity plays in the Constitution and in other international instruments, much is to be said about the meaning of this concept. Holland *et al* state:⁶⁹

Dignity has to do with the intrinsic value of a human person, and cannot be reduced to his or her instrumental worth. This means that we are always worth more than our stock market portfolios or our reputations or our function in the economy. As persons we dare not to be reduced to the subjective value of those who like or dislike us. We know we can claim our rights even when everyone around us dislikes us. As individuals we are always an end and never merely a means to some greater value. It is this dimension of intrinsic value that constitutes human dignity as we know it in the modern West.

Such a definition of dignity is in line with the Kantian notion⁷⁰ of respect for human beings, which has also been incorporated into the Constitutional Court's decisions. In *S v Dodo*,⁷¹ Ackermann noted that "...human beings are not commodities to which a price can be attached, they are creatures with inherent and intrinsic worth; they ought to be treated as ends themselves, never merely as means to an end."

In summary, acting with dignity towards patients involves the following as set out by Foster:⁷²

- (a) To treat the patient politely and respectfully in honour of his or her dignity and rights as an individual
- (b) To acknowledge a patient's participation in and responsibility for making autonomous decisions regarding his or her body
- (c) Principles of informed consent
- (d) To act fairly and in accordance with the law. To promote equal opportunity for all patients and to avoid unfair discrimination on grounds such as sex, age, race, ethnic origin, nationality, special needs or disability, sexuality, health, lifestyle, belief, or any other irrelevant consideration

⁶⁸ Currie & De Waal *supra* n344 251.

⁶⁹ Holland *et al supra* n13 133.

⁷⁰ The work of Immanuel Kant can be read in the translation of *the Groundwork of the Metaphysics of Morals* by H.J. Patton.

⁷¹ *S v Dodo* 2001 (3) SA 382 (CC).

⁷² Foster *Human dignity in bioethics and law* (2011) 71, with reference to clause 2.1-2.5 of the *Standards for dental professionals* of the General Dental Council of the United Kingdom <<http://www.gdc-uk.org/Dentalprofessionals/Standards/Pages/default.aspx>> (Accessed 18 July 2016).

- (e) To always furnish the patient with the relevant information, in a manner that will be to his or her benefit when he or she makes healthcare decisions
- (f) To establish and maintain appropriate boundaries in the doctor-patient relationship to ensure that the relationship is never exploited

4.2.2.3 Human dignity as incorporated in international instruments

Section 39 of the Constitution states that a court, tribunal or forum:

- (a) Must promote the values that underlie an open and democratic society based on human dignity, equality and freedom;
- (b) Must consider international law; and
- (c) May consider foreign law.

In terms of section 39(b) the court is obliged to take cognisance of various international instruments such as the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine Convention on Human Rights and Biomedicine (the Oviedo Convention);⁷³ the Additional Protocol to the Oviedo Convention, concerning Biomedical Research;⁷⁴ the Additional Protocol to the Oviedo Convention, on Transplantation of Organs and Tissues of Human Origin;⁷⁵ the Additional Protocol to the Oviedo Convention, on Genetic testing for Health Purposes;⁷⁶ the UNESCO Universal Declaration of Bioethics and Human Rights;⁷⁷ the UNESCO Universal Declaration on the Human Genome and Human Rights;⁷⁸ the World Medical Association Declaration

⁷³ Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine Oviedo 4 IV 1997 <<https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98>> (Accessed 18 July 2016).

⁷⁴ Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research Strasbourg, 25.I.2005 <http://www.coe.int/en/web/conventions/full-list//conventions/rms/09000016800837_1a> (Accessed 18 Jul 2016).

⁷⁵ Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin Strasbourg 2002-01-24 <<http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/186>> (Accessed 18 July 2016).

⁷⁶ Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes Strasbourg 2008-27-11 <<http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/203>> (Accessed 18 July 2016).

⁷⁷ Universal Declaration on Bioethics and Human Rights 2005 <http://unesdoc.unesco.org/images/0014/001428/1_42825e.pdf#page=80> (Accessed at 18 July 2016).

⁷⁸ Universal Declaration on the Human Genome and Human Rights 1997 <<http://unesdoc.unesco.org/images/0011/001102/110220e.pdf#page=47>> (Accessed 18 July 2016).

of Helsinki: Ethical Principles for Medical Research involving Human Subjects;⁷⁹ and the UNESCO International Declaration on Human Genetic Data,⁸⁰ to name only a few.

All of these treaties mention respect for dignity and some of them will be discussed as they pertain to stem cell technologies. It should be noted that most of these treaties have not been ratified by South Africa. Nevertheless, they may serve as instructive guidelines as to how the courts can interpret the right to dignity in the context of stem cell technologies.

4.2.2.4 Human dignity applied to stem cell technologies

In the context of stem cell technologies, various appeals to dignity arise such as: situations pertaining to the way in which healthcare practitioners or researchers treat their patients; the application of novel medical treatment as an autonomous decision; unfair discrimination between research participants on grounds that affect their intrinsic worth and value; the exploitation of the doctor-patient relationship for the benefit of the healthcare practitioner's or researcher's ulterior motive; when practitioners or researchers act in dissonance with the principles of informed consent and subsequently violate patient bodily and psychological integrity and privacy; the use of embryos for the derivation of pluripotent stem cells; the application of technologies such as somatic cell nuclear transfer and induced pluripotent stem cells. Each of these issues will be discussed accordingly

4.2.2.5 Treating patients with dignity

As noted by the Constitutional Court,⁸¹ human beings are not “commodities to which a price can be attached”, but rather “creatures with inherent and infinite worth that deserve to be treated as ends and not a means to an end.”⁸²

⁷⁹ WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects 2014 <[http://www.wma.net/en/30publications/10policies/b3/index.html.pdf?print-media-type&footer-right=\[page \]/\[toPage\]](http://www.wma.net/en/30publications/10policies/b3/index.html.pdf?print-media-type&footer-right=[page]/[toPage])> (Accessed 18 July 2016).

⁸⁰ International Declaration on Human Genetic Data 2003 <<http://unesdoc.unesco.org/images/0013/001331/133171e.pdf#page=45>> (Accessed 1 July 2016).

⁸¹ *S v Dodo* 2001 3 SA 382 (CC); Verwey & Carstens 2014 *SAJHR* 89, 93.

⁸² Liebenberg “The Value of Human Dignity in Interpreting Socio Economic Rights” 2005 *SAJHR* 1, 6.

More often than not, the lines between research and practice are obscured. Therefore, when researchers/practitioners apply novel medicinal modalities, such as stem cell technologies, to patients, they should assure themselves and the patient about fact that the best interest of the patient is always paramount and that there is no ulterior motive as the real reason for the research. Applying novel medical modalities to a patient in unwarranted cases would result in treating a patient merely as a means to an end that disregards the patient's intrinsic worth, all for the benefit of scientific research and the betterment of the medical research/practitioner. Article 11 of the Declaration of Helsinki safeguards the patient/participant by stating that:

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

Furthermore, the UNESCO Universal Declaration on Bioethics and Human Rights provide in Article 3 that: ⁸³

...human dignity, human rights and fundamental freedoms are to be fully respected. (2) The Interests and welfare of the individual should have priority over the sole interest of science or society

When researchers choose potential research participants, they should ensure that they do not unfairly discriminate between participants based on grounds such as those set out in section 9(3) of the Constitution or analogous grounds as set out in the Equality Act that have the potential to adversely affect the intrinsic value of the participant as a human being. The UNESCO Universal Declaration on Bioethics and Human Rights affirms this in article 10 by stating that "The fundamental equality of all human beings in dignity and rights is to be respected so that they are treated justly and equitably."

In the event that a medical practitioner or researcher fails to obtain informed consent throughout the duration of the treatment or the experiment, it has the potential to infringe on a patient or participant's human dignity. These medical procedures are

⁸³ Article 3 of Universal Declaration on Bioethics and Human Rights 2005 <<http://unesdoc.unesco.org/images/0014/001428/142825e.pdf#page=80>> (Accessed 18 July 2016).

often invasive and touch the very core of a person's health and enjoyment of life. When a medical practitioner or researcher performs a stem cell therapy without informing the patient of all the reasonably conceivable complications and side effects and the patient or participant consequently suffers such a complication, it would have the ability to infringe on the human dignity of that patient. This is due to the fact that failure to obtain informed consent infringes on a person's right to make an autonomous decision regarding their body and subsequently will infringe on the dignity of that person as this amounts to treating people as a means to an end. Moreover, failure to obtain informed consent is a violation of the constitutional right to bodily and psychological integrity and the patient's privacy.⁸⁴

4.2.2.6 Dignity and autologous stem cell treatment

In the context of autologous stem cell treatments, one would feel that human dignity, together with the right to bodily and psychological integrity, would allow for a patient to make autonomous decisions regarding his or her health care. However, this is not always the case, for example: When a patient's own stem cells are withdrawn, cultured *ex vivo* or mixed with therapeutic substances, and subsequently reintroduced into that patient, it might not be able to do so without restriction. Such restrictions would constitute an infringement on the right to human dignity as the autologous donor is denied the right to make autonomous decisions regarding his or her body and health care.⁸⁵

Even though there might be an infringement, it is possibly justified in terms of section 36 of the Constitution, which provides that no right in the Bill of Rights is absolute and that a limitation is justified if it is "in terms of a law of general application" and is "reasonable and justifiable in an open and democratic society based on human

⁸⁴ Verwey & Carstens 2014 SAJHR 89, 95: "Dignity therefore presupposes a sphere of personal autonomy, even though it is not exclusively synonymous with individual freedom and self-fulfilment."

⁸⁵ For instance, in the EU autologous stem cell therapies not applied for the same essential function qualify as a tissue-engineered product (TEP), thereby bringing such products into the ambit of the Advanced Therapy Medicinal Product Regulation 1394/2007/EC, which classifies TEPs as medicinal products. For an autologous stem cell therapy to be classified as an advanced therapy medicinal product, the therapy has to comply with much more stringent regulation regarding quality, safety and efficacy such as Good Manufacturing Practice and Good Clinical Practice, as opposed to traditional bone marrow stem cell transplants that are classified as transplants, before it can be administered to the patient.

dignity, equality and freedom.”⁸⁶ Such restrictive legislation, as will be argued in due course of this dissertation, includes the NHA and the MRSCA, which purport to regulate both allogeneic and autologous stem cell transplants as biological medicinal products. However, as will be discussed in due course of this dissertation, there are certain instances where it would be more beneficial to disregard certain stem cell therapies from medicines regulations.⁸⁷

Whether or not stem cell treatments should be regarded as medicine is an argument premised on the question whether the stem cells have been substantially manipulated, which will be discussed later in this dissertation.⁸⁸ For now, first consider an argument that if stem cells are cultured or mixed with therapeutic substances to the extent that they are regarded as substantially manipulated, they are to be regulated as medicinal products. Therefore, infringing on the dignity of an autologous donor is justified as medicines legislation purports to protect the health and safety of all the members of society whose rights weigh more heavily than the patient’s right to dignity.⁸⁹

In contrast to the above scenario, consider the following: If stem cell therapies are not regarded as substantially manipulated,⁹⁰ the following argument might be put forward: denying someone the right to such medical treatment would, unjustifiably, infringe on that person’s constitutional right to make autonomous decisions regarding his or her health care and subsequently deprive them of their right to human dignity. This is only if the patient has been duly informed and has consented to the autologous stem cell treatment, knowing the risks and possible adverse effects pertinent to such procedures, as well as the fact that the procedure is cleared by an ethics review committee and not contra to good clinical practice.

⁸⁶ S 36(1) of the Constitution.

⁸⁷ See ch 5.

⁸⁸ The criterion in the USA is whether or not the cells have been more than minimally manipulated.

⁸⁹ This is in line with the state’s duty to protect the health of the collective as was emphasised in the case between *Soobramoney v Minister of Health, KwaZulu-Natal* 1998 1 SA 765 (CC).

⁹⁰ See ch 5: “A cell will only be regarded as ‘substantially manipulated’ and fulfil the criteria for TEP, if the cell’s relevant biological characteristics, physiological functions, or structural properties have been changed.”

Allogeneic transplants are more complicated as these procedures involve the rights of more than one person as well as the fact that immunological rejection becomes a reality and therefore should be regulated with more caution. However, it is contradictory to exclude allogeneic bone marrow stem cell transplants (often for haematological restoration) from stringent quality controls as required by medicines legislations, but not a bone marrow stem cell transplant in an immunocompetent patient receiving his or her own stem cells.⁹¹

4.2.2.7 Dignity, embryos, cloning and induced pluripotent stem cells

Undoubtedly, embryonic stem cell research presents an array of ethical concerns. However, the question regarding the dignity of the embryo is by far the most complex. The former Commissioner of the US Food and Drug Administration (FDA) writes:

The devaluation of humans at the very commencement of life encourages a policy of sacrificing the vulnerable that could ultimately put other humans at risk, such as those with disabilities and the aged, through a new eugenics of euthanasia.⁹²

Furthermore, in opposing government-funded stem cell research that destroys embryos in the United States, groups like 'Do No Harm' argue that each human embryo is to be regarded as a tiny human being.⁹³ By implication, this means that they argue that each zygote is already a tiny human being, worthy of human dignity.⁹⁴ Therefore, in accordance with the principle of non-maleficence, medical practitioners should avoid the destruction of embryos, even if it leads to worthy scientific advancements.⁹⁵ Moreover, this agrees with the Kantian notion of respect, which advocates treating human persons as an end and never merely use them as means to an end.⁹⁶

⁹¹ Cuende *et al* "Concise review: Bone marrow mononuclear cells for the treatment of ischemic syndromes: Medical product or cell transplantation" 2012 *Stem Cell Trans Med* 403, 406, such as bone marrow mononuclear cells used for autologous neovascularization which are subject to the Advanced Therapy Medicinal Product Regulation 1394/2007/EC in the European Union.

⁹² Young 2000 *Science* 1424.

⁹³ Holland *et al supra* n13 129.

⁹⁴ *Ibid*; Swanepoel *Embryonic stem cell research and cloning: A proposed legislative framework in context of legal status and personhood* (LLM dissertation 2006 UP 16).

⁹⁵ *Ibid*; "This reflects the view of the Roman Catholic Church."

⁹⁶ *Ibid*; See Swanepoel (LLM dissertation 2006 UP 132) for arguments advocating against experimentation and research on human embryos.

Similarly, proponents of stem cell research also appeal to human dignity to justify stem cell research. The American Association for the Advancement of Science appeals to dignity by stating that even under favourable conditions these cells are still just pluripotent and not totipotent and do not have the capacity to form a trophoblast.⁹⁷

It is this distinction between pluripotency and totipotency that is the differentiating factor, because if cells are totipotent, they possess the capacity to develop into a human being and should therefore be treated with dignity. If cells are merely pluripotent, they do not have to be treated with dignity.⁹⁸ Such an approach honours the dignity of the future beneficiaries of the stem cell treatments, which flows from the research.⁹⁹

Assigning dignity to cells based on the cells' potency is not without problem. For instance, with cell reprogramming (induced pluripotent stem cells) and somatic cell nuclear transfer, any somatic cell can potentially give rise to a human baby. Subsequently, the question to ask is: ¹⁰⁰ "[w]hat then will determine whether one cell has actual potential for humanity and another does not?" The definitive factor will be the choices made by those who allowed for the development of a somatic cell, until it reached adult phase, a so-called "life journey".¹⁰¹

Even though worthy of respect, arguments that regard an embryo as a tiny human being have no substance when considering the changes brought about by the advent of pluripotent stem cells, and the broad notion of the potency of cells. This technology makes it possible for any cell to potentially become a human baby. Therefore, they cannot be regarded as tiny human beings as this would mean that

⁹⁷ Chapman *et al* (1999) *Stem Cell Research and applications* <http://www.aaas.org/sites/default/files/content_files/Stem%20Cell%20Research%20and%20Applications%20Report.pdf> (Accessed 19 July 2016).

⁹⁸ Holland *et al supra* n13 130.

⁹⁹ *Idem* at 136.

¹⁰⁰ *Ibid*; See Devolder "Human embryonic stem cell research: Why the discarded-created-distinction cannot be based on the potentiality argument" *Bioethics* 167; Devolder *supra* n33.

¹⁰¹ *Idem* at 137.

any cell should be treated with dignity.¹⁰² However, stem cell research provides the opportunity to improve the lives of those suffering from debilitating diseases and conditions radically, which cannot be denied. Peters states:¹⁰³

By no means do I make an appeal to crass utilitarianism here. Rather, I see the larger enterprise of dedicated scientific research serving the dignity of persons who will tomorrow benefit from difficult laboratory work today.

It is important to look at the scope of the constitutional right to dignity in order to determine whether an embryo is protection-worthy in terms of the Constitution. Section 12 states that “everyone” should be treated with dignity. Therefore, an embryo should also be treated with dignity. Considering this fact, the mother’s right to dignity, equality, bodily and psychological integrity and privacy will have to be balanced against that of the embryo. Only if an embryo is afforded the right to life, will this question pertaining to the dignity of the embryo be unravelled.¹⁰⁴

Whether or not the embryo is entitled to dignity, will be answered by whether the embryo can be afforded legal status.¹⁰⁵ Jordaan¹⁰⁶ states that there is no legal duty towards the embryo or a pre-implantation embryo.¹⁰⁷ McCreath states that if the drafters of the Constitution intended to protect the rights of the unborn child in the Bill of Rights, they would have done so explicitly in terms of section 28 of the Constitution, which would have resolved any uncertainty regarding the status of the foetus.¹⁰⁸ Considering this, the embryo cannot be regarded as having legal status and therefore be afforded the right to be treated with dignity. Taking such a stance is

¹⁰² *Ibid.*

¹⁰³ *Idem* at 138.

¹⁰⁴ Prinsen *supra* n23 59.

¹⁰⁵ Legal status denotes the level of protection the law confers upon a subject or embryo in this context.

¹⁰⁶ Jordaan “The legal status of the human pre-embryo in the context of the genetic revolution” 2005 *SALJ* 237, 240.

¹⁰⁷ Swanepoel (LLM Dissertation 2006 UP) 103: “According (to the common law position, live birth is an acceptable point for the beginning of personhood. Slabbert indicates that the question of the status of prenatal life has been left open. As the human embryo and fetus are neither full subjects of the law, nor things, nor tissue, the legal status of these entities can be described as special or differential”; Slabbert “The fetus and embryo: Legal status and personhood” 1997 *TSAR* 234 at 238.

¹⁰⁸ *Christian Lawyers Association of South Africa and Others v Minister of Health and Others* 1998 4 SA 1113 (T); Swanepoel (LLM Dissertation 2006 UP 104).

regarded as a reinforcement of the right to human dignity, as affording such a right to those without sentience would degrade the right of human dignity.¹⁰⁹

Dignity does not function independently and is intrinsically linked to the right to life and privacy. Without life, there can be no dignity, and without dignity, there can be no life.

4.2.3 Life

The rights to life and human dignity are seen as the most basic rights from which all other personal rights in the Bill of Rights stem.¹¹⁰ In the landmark case of *S v Makwanyane*,¹¹¹ Chaskalson P stressed the unconditional nature of the rights to life and dignity with reference to a Hungarian precedent, which held that other rights may be limited or taken away and be afforded again, but the absolute constraint of state power is vested in the safeguarding of the closely intertwined rights of life and human dignity.¹¹²

Section 11 of the Constitution states “Everyone has the right to life”. The section 11 right to life differs from that of other jurisdictions, in the sense that there is no internal limitation of the right.¹¹³ The only way that the right to life may be limited in a South African context, is in accordance with section 36 of the Constitution, which is an external limitation clause. The right to life has both a positive and negative aspect. Positively, it refers to the burden on the state to protect human life. Negatively, it refers to the duty incumbent on members of society not to take someone’s life.¹¹⁴

When considering the controversies surrounding stem cell technologies, the right to life comes into contention, amongst many others, in the following conflicts:

¹⁰⁹ Jordaan “Science versus anti-science: The law on pre-embryo experimentation” 2007 *SALJ* 618, 631.

¹¹⁰ *S v Makwanyane* 1995 3 SA 391 (CC).

¹¹¹ *Ibid.*

¹¹² *Idem* at par 83-85.

¹¹³ A right is internally qualified if the restriction is vested within the text of the clause itself, for example: The right to life may not be deprived arbitrarily or other than in accordance with a sentence of a court of law. This is true for jurisdictions such as the United States, Canada, Hungary, India and other international instruments such as the European Convention on Human Rights and International Covenant on Civil and Political Rights; Currie & De Waal *supra* n344 259.

¹¹⁴ *S v Makwanyane* 1995 3 SA 391 (CC) at par 193; Currie & De Waal *supra* n344 262.

- The right to access to health care and the right to life of an individual as against the duty of the state to safeguard the lives of others. Such as the case where a patient wants innovative or experimental treatment that is not yet regarded as routine practice or has shown to be efficacious and safe to use and accordingly afforded marketing authorisation.
- The right to life of the embryo as against the mother's right to bodily autonomy, reproductive freedom and privacy.

4.2.3.1 The right to research and experimentation and the right to life

Upon closer investigation of section 12(2)(c) of the Constitution, it is evident that an appeal to a right to research and experimentation can be best described if one examines the conflicting rights. On the one hand, the right to make autonomous decisions regarding one's own body and health care, which is closely linked to the rights of human dignity, and the right to life. On the other hand, the state's positive duty to ensure that no one is unjustly deprived of their right to life, by protecting patients or research participants from unethical and unwarranted medical treatments that have not been shown to be efficacious and safe.¹¹⁵

Healthcare researchers are not the only ones to gain benefit from the fruits of the research, but also those with a deep personal interest, such as those whose lives and health may be bettered by it.¹¹⁶ One might ask, does the loss of a chance at a therapy or experimental treatment deprive a patient/participant of his rights to life, access to health care, dignity and security of person? In the context of the prohibition of unproven medical treatments,¹¹⁷ we are dealing with potential medical treatments rather than existing medical practice.¹¹⁸ The question to answer relates to the question whether such research would have provided other useful treatments than existing medicinal modalities. In the eyes of the patient, he or she stands to lose a chance at beneficial therapy that could save his or her life or increase life quality.¹¹⁹

¹¹⁵ S 7(1) & (2) read with s 9, 10, 11, 12 & 27 of the Constitution.

¹¹⁶ Chandler "Does a patient have a constitutional right to the freedom of medical research? Regenerative medicine and therapeutic cloning research in Canada" 2012 *McGill JL & Health* 27.

¹¹⁷ S 14 of the Medicines Act: "Save as provided in this section or sections 21 and 22A, no person shall sell any medicine which is subject to registration by virtue of a resolution published in terms of subsection (2) unless it is registered.

¹¹⁸ Bearing in mind the ethical principle of do no harm above all else. See the previous chapter regarding the ethical principles that govern the medical profession.

¹¹⁹ Chandler 2012 *McGill JL & Health* 30.

This is true even though the precise value of the benefit is difficult to establish given the experimental nature of the therapy.

The potential benefit an experimental treatment can be plotted along a spectrum of increasing likelihood.¹²⁰ On the one end, a scientific enquiry that pursues knowledge and, on the other hand, advanced clinical trials that test specific therapeutic benefits.¹²¹ In a Canadian case between *Operation Dismantle v Canada*,¹²² it was made clear that where the harm of a law or an action such as experimental stem cell treatment amounts to speculation that is tantamount to guesswork, it will be impossible for a court to conclude that a deprivation of a section 7 interest will follow from the law in question.¹²³ It should be noted that the court does not opine that speculation will always infringe on a section 7 right and in order to have such a claim, something less than certainty is needed, such as where there is reasonable certainty for future harm.

The American case of *Abigail Alliance for Better Access to Developmental Drugs v Von Eschenbach*¹²⁴ illustrates this point. In this matter, the plaintiff claimed a right of access to an experimental drug prior to completion of clinical testing and subsequent government approval. The plaintiff's claim was based on the right of a terminally ill patient to gain access to experimental treatment if the treatment has passed limited safety tests.¹²⁵ However, the court rejected such an argument and concluded that there was no such right. Taking the judgements of *Abigail Alliance* and *Operation Dismantle* into consideration in the context of stem cell therapy, if the speculative

¹²⁰ *Ibid.*

¹²¹ *Ibid.*

¹²² S 7 of the Constitution Act, 1982, being Schedule B to the Canada Act 1982 (UK) c 11; *Operation Dismantle v The Queen* [1985] 1 SCR 44, 18 DLR 481; Chandler 2012 *McGill JL & Health* 32: In this case, the plaintiffs argued that the decision made by the Canadian Government to permit a US cruise missile testing in Canada violated their section 7 right, because it increased the risk of a nuclear war. The claim was dismissed on the basis that there was no reasonable cause of action. The case went on appeal, where the Supreme Court rejected the appeal and stated that claiming that the government has increased the risk of nuclear war was too much of a speculative nature, an argument which is not fit to hold up in court. In short, this case was dependent on the way both of the countries would react, which is something that cannot be said with certainty. The court stated that a remedy for future harm may well be appropriate in certain instances, but not those where the alleged harm is not capable of being proved.

¹²³ Chandler 2012 *McGill JL & Health* 15.

¹²⁴ *Abigail Alliance for Better Access to Developmental Drugs v Von Eschenbach* 445 F (3d) 470 (DC Cir 2006).

¹²⁵ Chandler 2012 *McGill JL & Health* 35.

benefit of the experimental treatment or innovative therapy is of such a nature that there is no level of certainty, the state's duty to protect its people from potentially harmful medicine, as envisaged by section 14 of the Medicines Act, trumps the rights of a patient to receive experimental treatment.¹²⁶

For time being, the Medical Innovation Bill 2014 (MIB) has not come into force. Therefore, patients claiming stem cell treatments that have not been afforded marketing authorisation cannot claim that their right to make autonomous healthcare decisions has been infringed upon and subsequently affected their human dignity and their right to life, as such an infringement is justifiable in terms of section 36 of the Constitution.

4.2.3.2 The embryo and the right to life

From an ethical perspective, some members of society, especially religious and anti-abortion groups, regard a blastocyst produced by the means of somatic cell nuclear transfer or obtained by the means of *in vitro* fertilisation as a human being with all of the accompanying rights. Seen from such a point of view, the destruction or biopsy for the production of stem cell lines constitutes the taking of a human life.¹²⁷ Exacerbating the problem and in support of their argument, opponents refer to the fact that it can take a total of 286 frozen blastocyst-stage embryos to derive a few stem cell lines.¹²⁸

In stark contrast, proponents of embryonic stem cell research argue that it does not involve the destruction of human life as the embryos obtained from leftover *in vitro* fertilisation clinics will either be discarded or frozen perpetually until they are no longer capable of producing human life.¹²⁹ In the context of embryos created by means of somatic cell nuclear transfer or "research cloning", proponents of stem cell research reject the moral status of embryos by contending that they are not human beings in any rational sense of the word and should not be treated as such.¹³⁰ It is

¹²⁶ This is also in line with the principle of non-maleficence, see ch 3.

¹²⁷ Amechi "Regulating developments in embryonic stem cell research in Africa: A third person's perspective" 2007 *AJICL* 87.

¹²⁸ *Ibid.*

¹²⁹ Philipkoski "Canada closes door on cloning" *Wired News* <<http://www.wired.com/2004/03/canada-closes-door-on-cloning/>> (Accessed 21 July 2016).

¹³⁰ Amechi 2007 *AJICL* 85, 87.

like saying all acorns become oak trees, but not all oak trees are acorns. As stated by Schüklenk & Lott:¹³¹

We have difficulty accepting positions that ask us to believe that an embryo consisting of a few hundred cells constitutes a person and that it should be treated as such. Given that the embryo does not have the capacity to suffer, we fail to see how such a being could possibly be harmed when it is destroyed in the process of stem cell research. Accordingly, we reject arguments defending the moral status of the embryo, for we believe it has none.

The legal position in South African law currently agrees that an embryo cannot be regarded as human life. This became fact after the case of *Christian Lawyers Association of South Africa and Others v Minister of Health and Others*.¹³² In this matter, an application was made regarding the constitutionality of the Choice of Termination of Pregnancy Act,¹³³ which provides for the destruction of early “human life”. The Constitutional Court rejected the applicant’s argument, premised on the fact that section 11 of the Constitution states “everyone has the right to life” and concluded that “everyone” does not include a foetus, as the words “everyone” and “every person” are used interchangeably.¹³⁴ McCreath stated that the change in the language of section 9 of the interim Constitution and section 11 of the final Constitution did not intend to create a new class of rights-bearers and that “everyone” is often referred to as “people” or “persons”.¹³⁵ In reaction to the argument of the opponents of abortion and the destruction of the early embryo, Holckeberg and Epstein’s words resonate with those of the Constitution by concurring that embryos cannot be afforded rights, in particular, the right to life:¹³⁶

...rights are not some supernatural construct, mystically granted by the will of the ‘God’ [but] are this-worldly principles of proper political interaction rooted in man’s rational nature...[they] exist to protect and further human life. Rights enable individual men to think, act, produce,

¹³¹ Schuklenk & Lott 2002 *Afr Med J* 783.

¹³² *Christian Lawyers Association of South African and Others v Minister of Health and Others* 1998 4 SA 1113 (T).

¹³³ Choice of Termination of Pregnancy Act 92 of 1996.

¹³⁴ For an opposing view of this approach see Meyerson “Abortion: The constitutional issues” 1999 *SALJ* 50, 59.

¹³⁵ *Christian Lawyers Association of South African and Others v Minister of Health and Others* 1998 4 SA 1113 (T); Prinsen (LLM Dissertation 2010 UP) 62.

¹³⁶ Holckeberg & Epstein “*The antilife opposition to embryonic stem cell Research, Ayn Rand Institute*” quoted in Amechi 2007 *AJICL* 85, 88.

trade, live and love freedom. The principles of rights are utterly inapplicable to tiny, pre-human clusters of cells that are incapable of such actions.

Furthermore, and resonating with the argument put forward by the proponents of stem cell research and therapies, the case of *Clarke v Hurst*¹³⁷ is important as it made a distinction between “biological life” and “human life”. “Biological life” denotes the continuation of bodily functions such as organs, including the person’s digestive and respiratory system, and “human life” refers to a person’s cognitive functions and includes additional elements such as self-awareness, awareness of surroundings, social interaction and registering of sensation.¹³⁸ The following dictum sets out the relation between human life and biological life: ¹³⁹

Life in the form of certain biological functions such as heartbeat, respiration, digestion and blood circulation but unaccompanied by any cortical and cerebral functioning of the brain, cannot be equated with living in the human or animal context.

This dictum indicates the fact that the court clearly attributes more moral value to “human life” than “biological life”. Where does human life begin? Several theories attempt to define the advent of human life:¹⁴⁰

1. The appearance of the “primitive streak”¹⁴¹
2. Feasibility of the foetus. The moment it can be sustained outside the womb, even be it by artificial life support
3. Brain birth. This is the developmental stage that distinguishes humans from animals as it signifies higher intelligence¹⁴²
4. Conception as the moment of “ensoulment”¹⁴³
5. The argument that human embryos and foetuses are not to be regarded as “things”, but rather as persons

¹³⁷ *Clarke v Hurst* 1992 4 SA 630 (D).

¹³⁸ *Idem* at 659A.

¹³⁹ *Idem* at 658F.

¹⁴⁰ For an in-depth discussion regarding the beginning and end of legal status and personhood see 3.4.2.1- 3.4.2.9 of Swanepoel (LLM Dissertation 2006 UP 77- 103).

¹⁴¹ Krimsky *supra* n10 14-15 “At the fourteenth day of its development, an embryo exhibits a “primitive streak”, a faint white trace that is the first evidence of the embryonic axis. It is a precursor of the neural tube and the nervous system. Without a neural tube... the embryo cannot have feelings or exhibit any level of consciousness.”

¹⁴² Jeeves (ed) *From cells to souls, and beyond: Changing portraits of human nature* (2004) 22.

¹⁴³ Davel & Jordaan *Law of persons* (2005) 11- 26.

Bearing in mind the judgements of *Clarke v Hurst*¹⁴⁴ and *Christian Lawyers Association of South Africa and Others v Minister of Health and Others*,¹⁴⁵ it is clear that the law affords no legal status to a foetus or early embryo. Taking these judgements to heart, opponents of embryonic stem cell research then argue that the pre-embryo is potential human life and should be protected. However, potential is just potential and still has a level of uncertainty. Jordaan¹⁴⁶ states that potential is not an absolute and, therefore, the protection of a pre-embryo is not worthy of legal status either.

With the advent of induced pluripotent stem cells and other big advancements in the field of adult stem cells, the whole ethical conundrum regarding the legal status and rights of foetuses and embryos can be circumvented, as these technologies do not involve the destruction or even the use of a human embryo. Rather than destroying embryos and potential human life, the application of induced pluripotent stem cells and adult stem cells would provide enormous medical benefit to those in need as well as improve and enable many human lives. As the right to make autonomous decisions regarding one's own body and health care flow from the right to freedom and security of the person, it shall be discussed accordingly in terms of stem cell technologies.

4.2.4 Freedom and security of the person

The rights as encompassed in section 12 of the Constitution safeguards the right to freedom and security of the person. Section 12(1) of the Constitution pertains to the protection of the physical liberty of a person. Section 12(2) of the Constitution furthers this purpose by safeguarding aspects of bodily self-determination.¹⁴⁷ In the matter between *Ferreira v Levin NO*, the majority's interpretation of section 11(1) of the Interim Constitution,¹⁴⁸ envisages a residuary role of the right, which is to protect

¹⁴⁴ *Clarke v Hurst* 1992 (4) SA 630 (D).

¹⁴⁵ *Christian Lawyers Association of South African and Others v Minister of Health and Others* 1998 (4) SA 1113 (T).

¹⁴⁶ Jordaan 2005 SALJ 237 at 243.

¹⁴⁷ Currie & De Waal *supra* n344 271.

¹⁴⁸ Constitution of The Republic of South Africa, Act 200 of 1993- Hereinafter referred to as the "Interim Constitution".

the intrinsic and essential freedoms which are not adequately or explicitly protected in the other section of Bill of Rights.¹⁴⁹

It is to be noted, that the inviolability of the person as purported in section 12(2)(b) has two components namely “security in” and “control over” one’s body.¹⁵⁰ These terms are not to be conflated. “Control over” refers to bodily autonomy or self-determination against interference that creates the right not to be hindered and to lead the life one chooses, for instance to make the decision to undergo stem cell therapy or research.¹⁵¹

In the context of stem cell technologies, the right to have security and control over one’s body plays a vital role in the following instances, such as: not to be subjected to medical or scientific experiments without informed consent; to make decisions regarding reproduction; the donation of an embryo for stem cell research; to undergo stem cell therapy or research.¹⁵²

4.2.4.1 Reproductive decisions and destroying embryos

In terms of section 12(2)(a) of the Constitution, read with the Choice of Termination of Pregnancy Act,¹⁵³ up to 12 weeks after fertilisation a woman has the right to decide whether to terminate her pregnancy freely by way of an abortion.¹⁵⁴ Akin to an abortion is the donation of a fertilised embryo for embryonic stem cell research and therapy, as it also involves the destruction of potential human life. Affording the same rights to an embryo as those afforded to a child would make all abortions unconstitutional, as the right to life of the embryo or foetus would outweigh the right to bodily autonomy of the mother. Many issues surround the abortion debate and one that is often overlooked, is the issue regarding a woman’s right to make autonomous decisions regarding reproduction.¹⁵⁵ One should never lose sight of the

¹⁴⁹ Currie & De Waal *supra* n344 271.

¹⁵⁰ *Idem* at 287; See also *Phillips v De Klerk* 1983 TPD (unreported as quoted in Strauss SA 1991 “Voluntary sterilization for convenience: The case of the unwanted child” *Consult* 93-97

¹⁵¹ *Ibid*; De Vries *The ethics in genetics – The legitimacy and application of stem cell research* (LLM Thesis 2006 UP 117).

¹⁵² This right is closely intertwined with the right to freedom of expression that allows for academic freedom of expression and research. See 3.5 of Swanepoel (LLM Dissertation 2006 UP 127-135).

¹⁵³ Choice of Termination of Pregnancy Act 92 of 1996.

¹⁵⁴ *Idem* at s 2(1)(a).

¹⁵⁵ Swanepoel (LLM Dissertation 2006 UP 109).

key issue that is buried underneath meticulously constructed semantics and the use of rhetoric, such as the issue of whether the state may force someone to bear a child and subsequently support such a child against their will.¹⁵⁶

Furthermore and in the context of the viability of a pre-implanted *in vitro* fertilisation embryo, the United States Court in *Roe v Wade*¹⁵⁷ stated that a pre-implantation embryo intended for *in vitro* fertilisation is not viable from the onset, as it would never be possible to save the embryo in the event that the decision was made not to implant the embryo.

With an abortion, the woman voluntarily decides to terminate the pregnancy before it becomes a viable foetus with protectable interests. The same can be said of a cryopreserved pre-implanted embryo donated for stem cell research. Therefore, it could be argued that allowing a woman to donate her fertilised embryo for the purpose of stem cell research is in line with the right to reproductive autonomy as envisaged by section 12(2)(a) of the Constitution.

4.2.4.2 Autonomous decision to undergo stem cell therapy

The right to make autonomous decisions regarding health care, such as the choice to undergo stem cell research or therapy, is closely related to the right to access to health care and the right to life. As explained in the discussion regarding the right to life, claims based on bodily autonomy to gain access to experimental or innovative treatment will fail, as the state's duty to protect all human life from harm will trump the section 12(2) constitutional right of the patient/participant.¹⁵⁸ However, claiming access to proven stem cell therapy is in accordance with the right to have security and control over one's body as set out in section 12(2)(b) of the Constitution. Therefore, the application of stem cell treatments that have been afforded marketing authorisation will be protected under section 12(2) of the Constitution.¹⁵⁹

¹⁵⁶ *Id* at 110; Prinsen L. (2010) LLM dissertation 70.

¹⁵⁷ *Roe v Wade* 410 US 113, 152 (1973).

¹⁵⁸ See Pieterse M. & Hassim A. (2009) "*Placing human rights at the centre of public health: A critique of Minister of Health, Western Cape v Goliath*" 126(2) SALJ 231,232: state that individual rights may only be limited in the interest of public health, for the benefit of the collective, and when it is the least intrusive option available to the state.

¹⁵⁹ For more detail about this matter, refer to the section regarding access to health care.

4.2.4.3 *Informed consent and stem cell therapy*

In both the clinical and the research environment, no one may be subjected to medical or scientific experiments without their informed consent as envisaged by section 12(2)(c) of the Constitution.¹⁶⁰ Beauchamp *et al* state:¹⁶¹

The idea of an informed consent suggests that a patient or subject does more than express agreement with, acquiesce in, yield to, or comply with an arrangement or proposal. He or she actively *authorizes* the proposal in the act of consent. John may assent to a treatment plan without authorizing it. The assent may be a mere submission to the doctor's authoritative order, in which case John does not call on his own authority in order to give permission, and thus does not authorize the plan. Instead, he acts like a child who submits, yields, or assents to the school principal's spanking and in no way gives permission for or authorizes the spanking. Just as the child merely submits to an authority in a system where the lines of authority are quite clear, so often do patients.

Informed consent can be defined as follows: It is an autonomous action by a patient or participant that authorises a professional to either involve him or her in a research protocol or treatment for the patient (in some cases both), consisting of the following elements: ¹⁶²

[Informed] consent... is given if a patient or subject with (1) substantial understanding and (2) in substantial absence of control by others (3) intentionally (4) authorized a professional (to do intervention).

¹⁶⁰ For a general argument that reads section 12(2)(c) and section 16(1) of the Constitution together to allow for scientific research as academic freedom of speech and a duty on the state to allow stem cell and genetic research, see Swanepoel (LLM Dissertation 2006 UP 127–135), on page 129: “The core of the right to academic freedom is the right to do research. This right vests in individual academics, not only in universities. Currie and De Waal point out that, if the state could prescribe to universities that no research critical of the government may be funded by the university or that no researchers critical of the government may be appointed, academic freedom would be left stranded. Currently, the area where freedom of scientific research contradicts most frequently with state regulation is in the field of human genetics. Here regulation, for example bans on embryonic stem cell research, human cloning or germ-line engineering, is motivated less by political than by ethical concerns – concerns that are frequently at odds with the impetus of scientific discovery. Section 16 implies a positive duty of the state⁴⁶⁴ to promote research and teaching by providing functional academic and scientific institutions, or at least the financial and organizational backup needed to exercise the right to academic freedom and scientific research.”

¹⁶¹ Beauchamp *et al supra* n115 79.

¹⁶² *Ibid.*

This was reiterated by Watermeyer in the case between *Stoffberg v Elliot*,¹⁶³ where he held that any procedure undertaken on a person without consent would constitute an unlawful infringement on a person's right to security and control of the body. For consent to be valid, the following constituents need to be present according to Van Loon and Lindegger:¹⁶⁴

- a) Disclosure of all appropriate information about the research study
- b) Ensuring that the prospective participants adequately comprehend the disclosed material
- c) Ensuring that the prospective participant has the legal and mental capacity to decide about and consent to participation in the research
- d) Ensuring that the decision about participation is freely given
- e) Formal consent with written documentation or an acceptable alternative

In *Rompel v Botha* the court held that consent was only given if the full scope of the procedure had been explained.¹⁶⁵ The information needed in health research differs from that of healthcare practice. In healthcare practice, informed consent includes information that would be materially relevant to a reasonable person. In a health research environment, the consent needs to be more comprehensive and includes full disclosure of all the anticipated material risks, including death.¹⁶⁶ Therefore, individuals must be duly informed of the purpose, methods, risks, benefits and alternatives to the research, and they must understand the information.¹⁶⁷

From a constitutional perspective, the right to informed consent is explicitly safeguarded in the Constitution.¹⁶⁸ Healthcare practitioners or researcher should be

¹⁶³ *Stoffberg v Elliot* 1923 CPD 148; Earle M "Informed consent: Is there room for the reasonable patient?" 1995 SALJ 629, 629.

¹⁶⁴ Van Loon & Lindegger "Informed consent in clinical trials: Perceptions and experiences of a sample of South African researchers" *Health SA Gesondheid*.

¹⁶⁵ *Rompel v Botha* 1953 (T) (unreported) as mentioned by Van Oosten FFW *The Doctrine of informed consent in medical law* (LLD Thesis 1989 Unisa 47).

¹⁶⁶ Moodley *supra* n164 332.

¹⁶⁷ Par 6.3 *Booklet 6: Informed Consent General Ethical Guidelines for Health Researchers* 2008 <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 9 August 2016).

¹⁶⁸ Section 12(2)(c) of the Constitution.

sure to act in accordance with the ethical principles of informed consent as set out in chapter 3.

4.2.5 Privacy

Section 14 of the Constitution reads as follows:

Everyone has the right to privacy, which includes the right not to have-

- (a) their person or home searched;
- (b) their property searched;
- (c) their possessions seized; or
- (d) the privacy of their communications infringed.

In terms of section 14 of the Constitution, the physical examination of a person in the context of health care constitutes an invasion of that person's privacy, which can only be lawful if the person has consented to the invasion of his privacy. Information pertaining to a patient's or participant's health status is also closely related to the patient's privacy.¹⁶⁹ This fact is best explained by examining the concept of a continuum of privacy, which was introduced for the first time in *Bernstein v Bester*.¹⁷⁰ The words of Sachs shed light on this concept: ¹⁷¹

The truism that no right is to be considered absolute, implies that from the outset of interpretation each right is always already limited by every other right accruing to another citizen. In such a context of privacy this would mean that it is only the inner sanctum of a person, such as his/her family life, sexual preference and home environment, which is shielded from erosion by conflicting rights of the community...Privacy is acknowledged in the truly personal realm, but as a person moves into communal relations and activities such as business and social interaction, the scope of personal space shrinks accordingly.

Evidently, certain elements of a person's life should not be eroded by the rights of others, such as his health status, which is truly in the inner sanctum of his personal life. This is affirmed in the Promotion of Access to Information Act (Information Act),¹⁷² which defines personal information as inclusive of issues relating to "pregnancy", "physical or mental health, well-being, disability", "medical, criminal or

¹⁶⁹ Carstens & Pearmain *supra* n133 32; *Seetal v Pravitha* 1983 3 SA 827 (D).

¹⁷⁰ *Bernstein v Bester* 1996 2 SA 751 (CC).

¹⁷¹ *Mistry v Interim National Medical and Dental Council of South Africa* 1998 4 SA 1127 (CC).

¹⁷² Promotion of Access to Information Act 2 of 2000.

employment history of the individual” and “blood type”.¹⁷³ In terms of the Information Act, any unreasonable disclosure of personal information about a third party is prohibited.¹⁷⁴

In the context of stem cell therapy there is ample of opportunity to divulge personal information that is closely related to the inner sanctum of a person’s life, such as his health status and his genetic information. ¹⁷⁵ In view of the judgement of *Bernstein v Bester*¹⁷⁶ it can be said that a person’s genetic information is the most private and intrinsic part of that person’s being. This position is also affirmed by the words of Nienaber and Van der Nest,¹⁷⁷ stating that the “truly personal realm” of a person is threatened when a person is compelled to reveal or undergo genetic testing and few intrusions on the self could be more severe.¹⁷⁸ For a discussion of the medical confidentiality and privacy, see Chapter 3.

4.2.6 Access to health care

Section 27(1) of the constitution reads as follows:

- (1) Everyone has the right to have access to-
 - (a) Health care services, including reproductive health care;
 - (b) Sufficient food and water; and
 - (c) Social security, including, if they are unable to support themselves and their dependants, appropriate social assistance.

4.2.6.1 A right to health and access to health care

The right to health and its constituent rights can often be very complex. In certain circumstances, the right to health and the right to access to health care are often conflicting. For instance, where a patient claims access to experimental stem cell therapy that has not yet been approved by the Medicines Control Council (MCC),¹⁷⁹

¹⁷³ *Idem* at s 1(a), (b) & (d).

¹⁷⁴ *Idem* at s 34.

¹⁷⁵ Carstens & Pearmain *supra* n133 32; Langa in *Bernstein v Bester*: “Privacy is a right which becomes more intense the closer it moves to the intimate personal sphere of the life of human beings, and less intense as it moves away from the core.”

¹⁷⁶ *Bernstein v Bester* 1996 2 SA 751 (CC).

¹⁷⁷ Nienaber & Van der Nest 2004 *THRHR* 446, 458.

¹⁷⁸ *Idem* at 460.

¹⁷⁹ About the MCC Overview: The Medicines Control Council applies standards laid down by the Medicines and Related Substances Act 101 of 1965, which governs the manufacture, distribution,



and therefore is potentially detrimental to the patient's health as is it has not yet been proven to be safe and efficacious.

It is with such claims to access to treatment that the conflict between the right to access to health care and the right to health is born. Because the same right can cause diametrically opposing results, it has to be determined whether the short-term benefit to the patient claiming to have access to stem cell therapy (often in an experimental phase) outweighs the long-term detriment caused to patients and the collective by allowing access to unapproved stem cell treatments. Allowing such access could infringe on the right to health and a safe environment for future generations. Therefore, it has to be determined whether the rights of those in the future outweigh the rights to life and human dignity of the present generation.¹⁸⁰ This example illustrates the importance of balancing the multifaceted right to health against its constituent rights, such as bodily and psychological integrity and the right to live in an environment that is conducive to good health or well-being.¹⁸¹

Following this logic, a person must be afforded the option of whether or not to exercise the right of access to healthcare services.¹⁸² By no means is it acceptable to argue that since there is a right of access to healthcare services, the holder has no choice regarding the nature or level of the services that are to be provided to him or her. Carstens and Pearmain state: ¹⁸³ "The right to accept or refuse health care services is an aspect of the right to health since it impacts upon a person's psychological well-being as much as his or her physical well-being." Reading the above in the context of the provisions of the MIB,¹⁸⁴ it affirms the right that a patient might have to undergo stem cell treatment that has not yet been proven and is still experimental, and possibly detrimental to his or her health. Taking such a stance would reaffirm a patient's rights to bodily and psychological integrity, human dignity and the right to life. However, all rights contained in the Bill of Rights are subject to

sale and marketing of medicines. The prescribing and dispensing of medicines are controlled by means of the determination of schedules for various medicines and substances.

<<http://www.mccza.com/About>> (Accessed 29 September 2016).

¹⁸⁰ Carstens & Pearmain *supra* n133 35.

¹⁸¹ *Ibid.*

¹⁸² *Ibid.*

¹⁸³ *Ibid.*

¹⁸⁴ As published in the GG 37349 of 2014-02-18.

limitation in terms of section 36 of the Constitution, and for this reason, the provisions of the MIB cannot reaffirm such rights just yet, as it is only a Bill and not yet of force.

Despite the fact that the right to health is not expressly provided for in the wording of the Constitution, it might exist due to the interaction of various constitutional rights.¹⁸⁵ Carstens and Pearmain¹⁸⁶ note, “[it] is not so much an element of the Bill of Rights as an inevitable result of the matrix formed by the interaction of the various rights contained therein.” Therefore, this right must not be overemphasised as it is a result of the interaction of rights explicitly provided for in the Constitution, rather than a requirement set by the Constitution.¹⁸⁷

4.2.6.2 The right to access to health care in South Africa

Stem cell therapy is often expensive and more often than not, it has not yet been approved or indicated for medical conditions by the MCC. The Constitution only provides for “access” to and not a direct right to health care.¹⁸⁸ The scope of the right to access to health care was defined in the Soobramoney case.¹⁸⁹ In this case it was found that the state is obliged to provide access to housing, health care, food, water and social security, insofar as it has available resources allocated for such means.

As stem cell technologies are regarded as very expensive and taking into consideration the economic disparities and difficulties present in South Africa, the

¹⁸⁵ Carstens & Pearmain *supra* n133 35.

¹⁸⁶ *Ibid*; Leary “The right to health in international law” 1994 *HHR* 39: “Human rights are interdependent. That is, particular rights may depend on other rights for their fulfilment. The right of freedom of association, for example, is closely related to that of freedom of expression. Many other examples could be cited. As has been frequently reiterated by human rights organizations, all human rights and fundamental freedoms are indivisible and interdependent. Therefore, the right to health cannot be effectively protected without respect for other recognized rights. These include, in particular, both prohibition of discrimination, and the right of persons to participate in decisions affecting them.”

¹⁸⁷ Carstens & Pearmain *supra* n133 36: In *S v Jordan (sex workers and advocacy task force as Amici Curiae)* 2002 6 SA 642 (CC) [53]: “While we accept that there is manifest overlap between the rights to dignity, freedom and privacy, and each reinforces the other, we do not believe that it is useful for the purposes of constitutional analysis to posit an independent right to autonomy. There can be no doubt that the ambit of each of the protected rights is to be determined in part by the underlying purport and values of the Bill of Rights as a whole and that the rights intersect and overlap one another. It does not follow from this however that it is appropriate to base our constitutional analysis on a right not expressly included within the Constitution.”

¹⁸⁸ *Idem* at 41.

¹⁸⁹ *Soobramoney v Minister of Health, KwaZulu-Natal* 1998 1 SA 765 (CC).

following quote made by Chaskalson P is applicable in the context of the allocation of scarce resources, such as stem cell technologies:¹⁹⁰

I have no doubt that in a perfect world any treatment which a patient, or a patient's family, sought would be provided if doctors were willing to give it, no matter how much it cost, particularly when a life was potentially at stake. It would however, in my view, be shutting one's eyes to the real world if the court were to proceed on the basis that we do live in such a world. It is common knowledge that health authorities of all kinds are constantly pressed to make ends meet. They cannot pay their nurses as much as they would like; they cannot provide all the treatments they would like; they cannot purchase all the extremely expensive medical equipment they would like; they cannot carry out all the research they would like; they cannot build all the hospitals and specialist units they would like. Difficult and agonising judgments have to be made as to how a limited budget is best allocated to the maximum advantage of the maximum number of patients. That is not a judgment which the court can make.

Chaskalson J then concluded that the government has to make difficult decisions at a political level pertaining to how healthcare resources should be spent, by considering factors such as the health budget and the priorities to be met. Furthermore Chaskalson J stated that a court would be hesitant to interfere with the *bona fide* rational decisions made by the government and medical authorities who are responsible for dealing with such matters.¹⁹¹ The Soobramoney case justifies favouring the interests of the collective community over those of individuals in certain circumstances. In the context of stem cell technologies, this is of particular importance. The state has a duty to protect the collective from possibly harmful substances (such as unproven stem cell treatments), as well as to provide the necessary medical treatments to the collective members of society. However, this duty is not unqualified, as the state is only obliged to provide such access within its reasonably available means.

In a country that struggles with high HIV/AIDS numbers and Tuberculosis, a claim to have access to stem cell therapy (often unproven and experimental) is not a

¹⁹⁰ Chaskalson P quoting *R v Cambridge Health Authority, Ex Parte B* [1994] ALL ER 129 (CA) in *Soobramoney v Minister of Health, Kwazulu-Natal* 1998 1 SA 765 (CC).

¹⁹¹ *Soobramoney v Minister of Health, KwaZulu-Natal* 1998 1 SA 765 (CC).

priority.¹⁹² Therefore, scarce resources will have to be allocated according to the state's priorities. The criterion for the courts to decide whether or not to interfere with a political organ's decision regarding the allocation of healthcare resources is whether or not it was made rationally and *bona fide*.¹⁹³ Subsequently, a claim based on access to stem cell therapy in the public health sector would not succeed.

In the context of private health care, if a stem cell treatment is clinically indicated, if the patient provides the resources and no other rational limitation is present, a prohibition of access to such experimental stem cell treatment or innovative therapy could be seen as an infringement on a person's right to access to health care. Such a prohibition would violate the constitutional rights of the patient/participant, such as the right to make autonomous healthcare decisions, human dignity and, ultimately, the right to life. This would only be true insofar as the speculative benefit outweighs concerns of patient safety as the MIB is not yet in force and therefore, in terms of section 36 of the Constitution, the state's duty to protect the collective from harm trumps an individual's right of access to experimental treatment.

4.2.6.3 Access to experimental treatment in the United States

Similar to the decision in the Soobramoney case,¹⁹⁴ the position in the United States also seeks to protect the collective from harmful treatments that have not been approved by the FDA.¹⁹⁵ After the FDA instructed that before marketing authorisation can be afforded to medicinal products, well-controlled clinical trials have to be initiated to show efficacy and safety, which in turn led to an increase from two and a half years to eight years to develop a medicinal product.¹⁹⁶

¹⁹² Tbfacts.org TB Statistics for South Africa- national & provincial < <http://www.tbfacts.org/tb-statistics-south--africa/>> (Accessed at 8 August 2016), South Africa is one of the countries with the highest burden of TB with the WHO estimating 450 000 cases of TB in 2013. Out of the 450 000 TB cases about 60 % of them have HIV as well. TB continues to be the leading cause of death in South Africa; In South Africa approximately seven million people are living with aids.<<http://www.unaids.org/en/regionscountries/countries/southafrica>> (Accessed 8 August 2016).

¹⁹³ Carstens & Pearmain *supra* n133 48; For a pertinent discussion regarding the rationing of state resources see *Government of the Republic of South Africa and Others v Grootboom* 2001 SA 46 (CC) as well as the case between *Minister of Health v Treatment Action Campaign* 2002 5 SA 271 (CC).

¹⁹⁴ *Soobramoney v Minister of Health, KwaZulu-Natal* 1998 (1) SA 765 (CC).

¹⁹⁵ The FDA reviews clinical trial data for new drugs and determines whether the benefit of these drugs outweighs the risks; Title 21 US Code § 355; Darrow *et al* 2015 *N Eng J Med* 279.

¹⁹⁶ Kaitin & DiMasi 2011 *Clin Pharmacol Ther* 183-188.

In reaction to the prolonged development cycle of a new medicinal product, the FDA permitted patients or physicians to petition to gain access to unapproved drugs.¹⁹⁷¹⁹⁸ Since 2009, there are three pathways, which can provide access to experimental treatment/innovative therapy (or expanded access as it is termed in the United States):¹⁹⁹

1. Request for individual use, which entails emergency circumstances and treatment, sometimes in the absence of a formal written request to the FDA.
2. Requests by intermediate-size groups of patients, who are eligible to receive the drug in its early development.
3. The preponderate use under a treatment protocol, which might occur after a successful research protocol of an experimental agent, but before it is afforded FDA approval.²⁰⁰

The 2009 US Regulations aim to balance the protection of vulnerable and sick patients from the application of products that may have no clinical effect or may worsen the patient's condition and a vulnerable patient's chances by means of experimental treatment, as authorisation might only come too late. Applicable to any of the routes to gain expanded access to an investigation medicinal product, the FDA must be satisfied that the condition is serious or immediately life threatening, as well as the fact that there are no similar or alternative therapies.²⁰¹ Furthermore, very important to the right of access to health care is that "the evidentiary threshold for this criterion increases with the number of patients who are involved and is higher for less serious conditions."²⁰² The position of the FDA pertaining to access to experimental treatment can be paralleled to that of the South African position as the government of the United States seeks to protect the collective from possibly harmful

¹⁹⁷ Darrow *et al* 2015 *N Eng J Med* 279: "These informal pathways were institutionalised in 1987 in the context of the growing AIDS epidemic and were substantially revised in 2009."

¹⁹⁸ *Ibid.*

¹⁹⁹ Similar to the "compassionate-use" exemption in the EU.

²⁰⁰ *Idem* at 280 for an interesting tabulated exposition of the criteria for gaining expanded access to investigation medicinal products.

²⁰¹ *Ibid.*; For a discussion on access to experimental treatment in the US, see Leonard "Right to experimental Treatment: FDA New Drug Approval, Constitutional Rights, and the Public's Health" *JL Med & Ethics* 269; See ch 5 regarding the application of the various exemptions from medicinal regulation in the EU.

²⁰² *Ibid.*: "For example, the FDA must find sufficient evidence of safety and effectiveness before it permits and expanded-access protocol involving large numbers of patients with serious disease"

substances that have not been afforded marketing authorisation. The bigger the danger, the more taxing the criteria for gaining expanded access will be. These FDA regulations are also in line with the propositions of the MIB which state in section 4(1):²⁰³

Where a medical practitioner believes that it is not possible or appropriate to make an evidence-based decision in determining how to treat a patient's condition, because in the medical practitioner's opinion there is no research or other evidence available in relation to the condition or alternative treatments thereof, or the available research or other evidence is insufficient or uncertain, that medical practitioner may, subject to this Act, administer or prescribe a treatment other than a generally accepted or legally authorised ones.

4.2.6.4 Access to experimental treatment in the European Union

As in South Africa and in the USA, the case of *Durisotto v Italy*²⁰⁴ illustrates where the collective was protected from unapproved or untested medicinal products over the right to gain access to such treatment.

The facts

The applicant's daughter (born in 1975) has been affected by a degenerative brain disease, metachromatic leukodystrophy, since her adolescent years. On 8 April 2013, the applicant as the legal guardian of his daughter applied for a summary judgement which required Brescia Hospital to initiate a stem cell treatment called "Stamina" method.²⁰⁵ In terms of a ministerial decree passed on 5 December 2006, such treatment was legal for patients whose lives or health was at risk as no other treatments were available, or if the patient suffered from an illness that progressed rapidly. The court found that the applicant's daughter risked irremediable harm as

²⁰³ S 4(1) of the Medical Innovation Bill 2014, as published in GG 37349 of 2014-02-18.

²⁰⁴ *Durisotto v Italy* (62804/13) May 6, 2014 (ECHR); Van Toor *Access to an experimental treatment according to the right to respect for private life* Medstra-online case note <http://www.medstra-online.de/pdf/medstra-online_casenote_3-2015.pdf> (Accessed 5 August 2016).

²⁰⁵ Macgregor *et al* "Patient access to unproven stem cell treatments: A human rights issue?" 13 December 2015 *EuroStemCell* <<http://www.eurostemcell.org/commentanalysis/patient-access-unproven-stem-cell-treatments-human-rights-issue>> (Accessed 4 August 2016): "The Stamina method was said to turn mesenchymal stem cells (MSC) from the patient's own bone marrow into neural stem cells in order to treat neurodegenerative conditions. Vannoni set up the Stamina Foundation to help advance the application of this therapy. Many patients were treated from 2006, first from a clinic in Turin, and then later San Marino and other cities across Italy, even though the safety and efficacy of the treatment were not established, and regulatory approval was not obtained from Italian authorities. Following the pattern of other clinics that sell unproven stem cell therapy (eg the X-Cell Center), online patient testimonials became a key tool in selling hope to desperate and frustrated patients."

she was suffering from progressive cerebral atrophy and her condition had degraded since the preceding year. On 10 April 2013, provisional access was granted and a hearing was scheduled for 6 May 2013, where the court would further consider the decision before allowing access to the “Stamina” therapy.²⁰⁶ On 3 May 2013, Brescia Hospital applied for a dismissal of the applicant's request on the basis that the applicant's request did not satisfy the requirements of a subsequent Legislative Decree No. 24/2013.²⁰⁷ This decree only allowed patients to receive access to Stamina therapy if they had either started or had been duly authorised to receive this therapy by the court before the decree was enacted on 27 March 2013. The applicant's request was subsequently revoked on 11 July 2013 and a review was sought from a larger panel of judges. On 30 August 2013, the larger panel of judges upheld the refusal due to the fact that the Stamina method was still in the experimental phase and the national public health services only guaranteed access to medicines or treatments that have been shown to be efficacious, safe and approved by scientific medical bodies. The applicant's daughter was denied access as she had not provided a sample or obtained judicial authorisation before 27 March 2013.

The applicant made reference to cases where the court authorised access to Stamina therapy, including instances where the treatment was still to be initiated and not yet authorised. This paved the way for an argument that the decree restricted access to the therapy on temporal grounds, constitutes unfair discrimination and refuses access to healthcare services.²⁰⁸ A scientific committee, appointed by the ministry of Health, concluded on 29 August 2013 that the Stamina treatment had no scientific basis.²⁰⁹ The applicant based his application on articles 2,²¹⁰ 8²¹¹ and 14²¹² of the European Convention on Human Rights (ECHR).²¹³

²⁰⁶ Press release issued by the registrar of the Court “A properly reasoned refusal by the courts to authorise access to experimental treatments was neither arbitrary nor discriminatory” 2014 *ECHR* <http://hudoc.echr.coe.int/app/conversion/pdf/?library=ECHR&id=003-4774464-5811888&filename=003-4774464-5811888.pdf> (Accessed 4 August 2016).

²⁰⁷ *Ibid.*

²⁰⁸ *Medicine: terminally ill patient – experimental stem cell treatment: Case Comment* 2014 *EHRLR* 527.

²⁰⁹ *Ibid.*

²¹⁰ S 2: Right to Life.

²¹¹ S 8: Right to respect for private and family life. This right pertains to bodily and psychological integrity. However, this right specifically mentions in subsection (2) that a public authority is not allowed to interfere with the enjoyment of the right, except if it is in terms of law and is necessary in

Decision

The court found that as the application was brought in terms of a prohibition to access to Stamina therapy, it had to be examined in terms of article 8 of the ECHR as it pertained to “private life”, which is concerned with notions of personal autonomy and quality of life. In this instance, the interference with the article 8 right was in terms of a legislative decree. As the court considered the proportionality of the measures taken to restrict access to the Stamina method, it reiterated that the member states have a wide discretion in cases concerning companionate care. As the decree only allowed access to persons who had already started or had received authorisation before 27 March as well as the fact that Stamina therapy was still in the experimental phase, the court rejected the applicant’s request on 30 August 2013.²¹⁴ Based on the negative opinion from the scientific committee, the court reiterated that it was not its task to determine, in the place of the Italian Medicines Agency, whether the Stamina therapy posed an acceptable level of risk for patients who want access to experimental (compassionate) therapy.²¹⁵ Following this logic, the court found that the interference with the applicant’s daughter’s right to respect for private life in terms of article 8 of the ECHR could be considered necessary in a democratic society. Therefore, the court rejected the application, as it was manifestly ill founded.²¹⁶

Regarding whether the temporal differentiation between Stamina candidates amounted to unfair discrimination, the court stated that a mere difference in treatment of persons in a relevantly similar situation is not enough, the impugned

a democratic society in the interest of national security, public safety ... for the protection of health or morals, or for the protection of the rights and freedoms. This right differs from the South African Constitution and can be seen as the amalgamation of section 12(2)(b) rights and section 27 of our Constitution. It also differs in the sense that the Article 8 right is internally limited, unlike the South African Constitution that has an overall external limitations clause (section 36).

²¹² Article 14: Prohibition of Discrimination, similar to section 9 of the South African Constitution.

²¹³ European Convention for the Protection of Human Rights and Fundamental Freedoms, as amended by Protocols 11 and 14 <http://www.echr.coe.int/Documents/Convention_ENG.pdf> (Accessed 4 August 2016).

²¹⁴ *Medicine: terminally ill patient – experimental stem cell treatment: Case Comment 2014EHRLR 528.*

²¹⁵ Press release issued by the registrar of the court “A properly reasoned refusal by the courts to authorise access to experimental treatments was neither arbitrary nor discriminatory” 2014 *ECHR* <<http://hudoc.echr.coe.int/app/conversion/pdf/?library=ECHR&id=003-4774464-5811888&filename=0034774464-5811888.pdf>> (Accessed 4 August 2016).

²¹⁶ *Ibid.*

difference in treatment must also be discriminatory.²¹⁷ A difference in treatment would only amount to discrimination if it had no objective and reasonable justification, meaning that it did not pursue a legitimate aim or that there was no reasonable proportionality between the means to achieve the aim and the actual aim to be realised.²¹⁸ As the decree has a legitimate aim of protecting health and it is proportional, the court found that although there was a difference in treatment, it did not amount to discrimination under article 14 of the ECHR. The application was subsequently dismissed on the basis that it was manifestly ill founded.²¹⁹

Synthesis

It is clear from the international and South African case law referred to above, that legislation that prohibits the application of novel or experimental medicinal therapies or products can be seen as a reasonable and justifiable infringement on the right of a patient of access to health care. In such an instance, the state's duty to protect the collective from harmful substances will triumph over the rights of the individual, as emphasised by the *Soobramoney* case²²⁰

Similar to the MIB,²²¹ the UK has passed a Medical Innovation Act 2016.²²² This Act provides extra legal protection to doctors who are open to treating terminally ill patients with experimental therapies or products, including the off-label and unlicensed use of medicines.²²³ In South Africa, however, the MIB has not yet come into force. Therefore, in terms of the *Soobramoney* case and the Medicine's Act which establishes the MCC,²²⁴ an infringement on a desperate patient's right to access to health care is justifiable as the legislation aims to protect the collective from harmful medical substances which have not been validated and approved by

²¹⁷ Press release issued by the registrar of the court "A properly reasoned refusal by the courts to authorise access to experimental treatments was neither arbitrary nor discriminatory" 2014 *ECHR*. This can be equated to the test that was put forward in the *locus classicus* case between *Harksen v Lane* 1998 1 SA 300 (CC). See the constitutional section regarding the right to equality above.

²¹⁸ *Ibid.*

²¹⁹ *Medicine: terminally ill patient – experimental stem cell treatment: Case Comment* 2014 *EHRLR* 529.

²²⁰ *Soobramoney v Minister of Health, KwaZulu-Natal* 1998 1 SA 765 (CC).

²²¹ As published in the GG 37349 of 2014-02-18.

²²² Access to Medical Treatments (Innovation) Act 2016 c 9 <http://www.legislation.gov.uk/ukpga/2016/9/pdfs/ukpga_20160009_en.pdf> (Accessed 4 August 2016).

²²³ Section 1(a) & (b) Access to Medical Treatments (Innovation) Act 2016 c 9 <http://www.legislation.gov.uk/ukpga/2016/9/pdfs/ukpga_20160009_en.pdf> (Accessed 4 August 2016); *Medicine: terminally ill patient – experimental stem cell treatment: Case Comment* 2014 *EHRLR*. 530.

²²⁴ S 2 of the Medicines Act.

the MCC.²²⁵ However, as will be argued in Chapter 6, there are instances where the inclusion of certain stem cell therapies under the auspices of medicine might amount to an infringement of a vulnerable patients constitutional rights.

4.3 Conclusion

Taking into consideration all of the various constitutional rights pertaining to stem cell technologies, it is clear that these rights often overlap or conflict with each other. The concept of a right to health could be assumed by the overlapping rights of security of person, dignity, access to health care and life. One should rather base a claim on the constituent rights of a right to health rather than ascribing too much value to the formed right to health itself.²²⁶

Furthermore, a patient should be wary to claim an infringement on their right to access to health care in the event that the state has denied them access to innovative and experimental therapy that has not been approved by the MCC. This can be ascribed to the fact that, in certain circumstances, the duty of the state to protect the concomitant rights of the collective to be protected from unproven and possibly harmful unproven stem cell treatments outweighs the rights of an individual to undergo such treatments, as it is justified in terms of a law that purports to protect the society from harm.²²⁷ However, the provisions of the MIB could change this perspective. If assented to, it would provide legislative protection of the rights to access to health care and strengthen the rights of security of person, human dignity, access to health care and the right to life, as it allows a healthcare practitioner to make use of innovative therapy if the medical practitioner is of the opinion that there are is no alternative treatment available or the research is either insufficient or uncertain.²²⁸

²²⁵ *Idem* at s 14.

²²⁶ Carstens & Pearmain *supra* n133 227.

²²⁷ Pepper & Nöthling Slabbert 2015 *SAJBL* 20-21.

²²⁸ *Idem* at s 4(1). S 4(2) states that when making such a decision, the medical practitioner, has to consider certain important factors “(a) the reasons why the available research or other evidence is insufficient or unclear including, without limitation, whether such insufficiency can be referred to the nature of the condition or the limited number of patients subject thereto; (b) the relative risks that are, or can reasonably be expected to be, associated with the treatment the medical practitioner proposes to apply and other treatments; (c) the relative likely success rates of the treatment the medical practitioner proposes to apply compared to other treatments, and, in the medical practitioner’s reasonable judgement, the relative likely consequences of applying, or failing to apply, the treatment the medical practitioner proposes to apply, and other treatments; (d) opinions



As Carstens and Pearmain state:²²⁹

It is impossible not to take cognisance of the Constitution when making decisions involving the delivery of health care services to be provided whether in terms of rationing of health care, the nature and extent of the health care services to be provided, the right of health care professionals to practice their professions or questions of intellectual property in health care goods.

In terms of the multi-layered approach to this study, the pertinent ethical values as incorporated in the Bill of Rights have been discussed in the previous and current chapter. This has set the foundation so that the national legislation regulating stem cell technologies in both South Africa and the UK can be critically discussed and compared. The following chapter will set out the position in the UK as part of the EU as it pertains to the therapeutic application of stem cell technologies, whereafter the South African regulatory framework will be discussed and compared to that of the UK.

or requests made by, on behalf of, or in relation to, the patient; (e) the informed consent of the patient or his guardian or other person legally entitled to provide such consent on behalf of such patient; (f) any other matter that appears to that medical practitioner to be reasonably necessary to be considered in order to reach a clinical judgement; and (g) what process or protocol should be adopted with a view to ensuring that the decision to innovate is made accountably, transparently and with full consideration of all relevant matters.”

²²⁹ Carstens & Pearmain *supra* n133 227.

CHAPTER 5

STEM CELL TECHNOLOGY IN THE UNITED KINGDOM

5.1 Introduction

Ever since the UK¹ joined the EU, European law became an important source of law. In terms of the European Communities Act 1972,² European law takes precedence over the domestic laws of the UK and, therefore, all domestic law should be interpreted and effected under the supremacy of European law.

On 23 June 2016, the UK held a referendum to separate from the EU, commonly known as the Brexit Referendum. Should the UK leave the EU, it would have various legal implications for the UK. In this case, the European Communities Act, which keeps UK law subservient to EU law, would be repealed as a necessary consequence of the Brexit Referendum. This would entail that all EU Regulations, such as the Advanced Therapies Medicinal Product Regulation (EC) 1394/2007 (ATMP Regulation), would have to be explicitly enacted into UK law before they can take effect.³ However, EU Directives first have to be enacted by Parliament before they take effect, such as the *Human Tissue (Quality and Safety for Human Application) Regulations* SI 2007/1523 (Q & S Regulations),⁴ which ensure compliance with the EU Directives on the Safety of Tissue and Cells (EUTCD).⁵ However, currently, the European Communities Act still stands and, therefore, all EU legislative documents are still in force and will not have an impact on the UK's regulatory framework governing stem cell technologies.

This chapter will set out the UK's regulatory framework pertaining to stem cell technologies in two parts – Part I: The procurement, use and storage of stem cells as start-up materials; and Part II: Stem cell technologies in clinical trials and their subsequent marketing authorisation as medicinal.

¹ Throughout this dissertation, any reference made to the UK will refer to the legislation as it stands in England and is not inclusive of the UK's other members.

² S 2(4) of the European Communities Act 1972 ch 68.

³ S 2(1) of the European Communities Act 1972 states that provisions that are directly applicable or have direct effect, such as a regulation, are incorporated without further enactment and are binding in member-state countries.

⁴ The Human Tissue (Quality and Safety for Human Application) Regulations SI 2007/1523 (Q and S Regulations).

⁵ EU Directive 2004/23.

5.2 Part I: The procurement, storage and use of stem cells

After the medical practitioner has proposed stem cell treatment, the stem cells necessary to prepare the stem cell therapy have to be procured. Depending on whether the stem cells are procured from a living donor, from a cadaver, blood, an embryo, or by means of an existing stem cell line, various legal instruments and authorities have an impact on the legality of such procurement and use, especially in the field of consent and safety.

In the EU, three EU Directives have been passed to regulate the procurement and use of human tissues and cells for human application.⁶ EU Directive 2004/23 of 31 March 2004, also known as the “mother directive” and ⁷ two accompanying technical directives, which provide detailed requirements regarding quality and safety standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells,⁸ together with the EUTCD, were incorporated into the UK’s legislation via the Q & S Regulations.⁹ The Q & S Regulations work alongside the Human Tissue Act 2004 (HTAct),¹⁰ which primarily deals with consent for the storage and use for a specific purpose of human tissues and cells after they have been procured.¹¹

There are three main regulatory agencies incorporated in the UK to regulate the entire series of activities regarding human tissue and cells, which are the following:¹²

⁶ Mahalatchimy *et al* “The legal landscape for advanced therapies: Material and institutional implementation of European Union rules in France and the United Kingdom” 2012 *J Law & Soc* 135.

⁷ Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells *OJ L* 102/48 2004-04-07.

⁸ Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC regarding certain technical requirements for the donation, procurement and testing of human tissues and cells *OJ L* 38/40 2006-02-09, and Directive 2006/86/EC of 24 October 2006, implementing Directive 2004/23/EC as regards traceability requirements, notification of serious adverse reactions and events, and certain technical requirements for the coding, processing, preservation, storage, and distribution of human tissues and cells *OJ L* 294/32, 25-10-2006.

⁹ Q and S Regulations.

¹⁰ The HTA ch 30.

¹¹ Mahalatchimy *et al* 2012 *J Law & Soc* 137: “The overwhelming weight of the provision in the United Kingdom’s Human Tissue Act is devoted to elucidating the principles of informed consent by patients.”

¹² *Idem* at 136.

the Human Tissue Authority (HTA),¹³ charged with regulating human tissue and cells, except gametes and embryos intended for human application, and hair and nails from a living person; the Human Fertilisation and Embryology Authority (HFEA),¹⁴ mandated to regulate activities regarding gametes and embryos intended for human use; and the Medicinal and Healthcare Products Regulatory Authority (MHRA) for medicinal products, such as Advanced Therapy Medicinal Products (ATMP).¹⁵

In 2006, the UK government proposed that the HTA and the HFEA be abolished and a single Regulatory Authority for Tissues and Embryos should be formed by their coalescence.¹⁶ On 1 February 2011, this coalescence was once again the topic of discussion.¹⁷ Mahalatchimy *et al*¹⁸ rightly note that it could be advantageous to distinguish between the applicable sets of rules pertaining to human tissues either as raw materials or as medicinal products once transformed by a bio-manufacturing process. However, this creates a labyrinthine regulatory framework often leaves researchers and manufacturers with uncertainty of which statutory authority's remit is applicable.¹⁹

Due to this complexity, the remit of the HTA as incorporated and extended by the Q & S Regulations will now be discussed.

¹³ Part II of the Human Tissue Act 2004 ch 30.

¹⁴ As Incorporated by the Human Fertilisation and Embryology Act 2008 ch 22, incorporated to amend the Human Fertilisation and Embryology Act 1990. In 2015, The Human Fertilisation and Embryology Regulations 2015 were passed as an instrument to enable mitochondrial donation techniques to be used as part of *in vitro* fertilisation (IVF) treatment to prevent the transmission of serious mitochondrial diseases from a mother to her child; HFEA at <http://www.hfea.gov.uk/> (Accessed 20 September 2016).

¹⁵ Article 2 of the ATMP Regulations EU Regulation 1394/2007, states in par (a) that “Advanced therapy medicinal product’ means any of the following medicinal products for human use: a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, a somatic cell therapy medicinal product as defined in Part IV Annex I to Directive 2001/83/EC, or a tissue engineered product”; Mahalatchimy *et al* 2012 *J Law & Soc* 136.

¹⁶ Department of Health, Review of the Human Fertilisation and Embryology Act: Proposals for revised legislation, including establishment of the Regulatory Authority for Tissues and Embryos) <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/272391/6989.pdf> (Accessed 18 August 2016).

¹⁷ Howe 724 *HL Deb col GC* 313 (1 February 2011) <<http://www.publications2.parliament.uk/pa/ld201-011/ldhabsred/text/110201gc0001.htm#11020174000137>> (Accessed 20 September 2016).

¹⁸ Mahalatchimy *et al* 2012 *J Law & Soc* 137.

¹⁹ *Ibid*.

5.2.1 Functioning of the Human Tissue Act and Quality and Safety Regulations

5.2.1.1 History and purpose of the Human Tissue Act and the Quality and Safety Regulations 2007

The HTAct was passed after the scandals at Bristol Royal Infirmary and the Royal Liverpool Children's Hospital (Alder Hey) in 1999-2000, as set out in the Kennedy and Redfern Inquiries.²⁰ These inquiries unveiled that the retention of body parts and organs from dead children was rampant and not uncommon. The retention of these organs often took place without the consent or knowledge of the parents. In some instances, parents were misled as to what they were consenting to and sometimes the conditions of the consent were disregarded. This gave rise to massive public outrage and something had to be done to put a stop to this practice. As a response, the HTAct was incorporated.²¹ The government explained the purpose of the Act as follows:²²

The purpose of the Human Tissue Act is to provide a consistent legislative framework for issues relating to whole body donation and the taking, storage and use of human organs and tissue. It will make consent the fundamental principle underpinning the lawful storage and use of human bodies, body parts, organs and tissue and the removal of material from the bodies of deceased persons. It will set up an over-arching authority which is intended to rationalise existing regulation of activities like transplantation and anatomical examination, and will introduce regulation of other activities like post mortem examinations, and the storage of human material for education, training and research. It is intended to achieve a balance between the rights and expectations of individuals and families, and broader considerations, such as the importance of research, education, training, pathology and public health surveillance to the population as a whole.

The HTAct does not intend to regulate the removal of human materials from humans, but rather the subsequent use and storage of such removed material, with emphasis

²⁰ Herring *supra* n130 414; Price "The Human Tissue Act 2004" 2005 *Mod L Rev* 798: "The Act is principally a response to the furore generated by revelations about practices relating to the retention and use of human tissue in the Bristol Royal Infirmary (Kennedy) and Alder Hey Children's Hospital in Liverpool (Redfern) Inquiry Reports, and more latterly the Isaacs Report 4, in particular 5. These Reports catalogued local practices resulting in relatives, principally parents of dead children, lacking appreciation of subsequent tissue retention and use for research following (generally coroners')6 post-mortem examinations, often resulting in the burial or cremation of loved ones without the realisation that they were not 'complete', and some further burials or cremations of body parts."

²¹ See Herring *supra* n130 414-417 regarding the events surrounding and giving rise to the HTAct.

²² Par 4 of the HTAct ch 30: Explanatory notes.

on the requirement of consent thereto.²³ It does not purport to regulate the situation where a doctor has improperly performed an operation or did so in the absence of proper consent, which is dealt with separately by the tort of negligence.²⁴

The Q & S Regulations were incorporated into UK law in order to comply with the EUTCD.²⁵ The Q & S Regulations were introduced to ensure common safety and quality standards for human tissues and cells across the EU as well as to facilitate a safer and easier exchange of tissues and cells, including human eggs and sperm, between member states and to improve the safety standard for European Citizens.²⁶ Where the HTAct is primarily concerned with issues regarding consent for the storage and use of relevant material,²⁷ the Q & S Regulations ensure that the scheduled uses for such tissues and cells conform to the prescribed quality and safety measures.²⁸ To oversee the application of human tissues or cells and to safeguard the public from harm during this application, the HTA is charged with protecting and promoting safe and consensual use of human tissues and cells.²⁹

5.2.1.2 The remit of the HTA

The remit of the HTA is set out in section 14. In terms of section 14, the HTA is charged with overseeing activities that relate to the removal, use, storage, import or export, or disposal of a human body or the relevant material from a human body (alive/deceased if applicable).³⁰ However, ever since the incorporation of the Q & S

²³ Mahalatchimy *et al* 2012 *J Law & Soc* 131,137: “The overwhelming weight of the provision in the United Kingdom’s Human Tissue Act is devoted to elucidating the principles of informed consent by patients”; Herring *supra* n130 ch 8, 414.

²⁴ Furthermore, Directions 003/2010 came into force on 12 November 2010. In total, these directions consolidate and clarify standards required under the Q & S Regulations; See Herring *supra* n130 417 for more information regarding consent and medical negligence in terms of the UK’s common law; see Herring *supra* n130 ch 3 & 4 101-214.

²⁵ Stipulating that imports of tissues and cells from non-European Area states must meet the standards of quality, safety and traceability equivalent to those provided in the regulations.

²⁶ Human Fertilisation and Embryology Authority (EUTCD) <<http://www.hfea.gov.uk/2072.html>> (Accessed 18 August 2016).

²⁷ S 53 of the HTA: “‘relevant material’ means material, other than gametes, which consists of or includes human cells. (2) In this Act, references to relevant material from a human body do not include- (a) embryos outside the human body, or (b) hair and nail from the body of a living person.”

²⁸ Price 2005 *Mod L Rev* 798, 800, states in relation to the HTAct that “...its central provisions radiate around consent and the creation of a new regulatory regime to oversee the retention of such material.”

²⁹ Ch 2, specifically, s 14 of the HTAct, sets out the remit of the HTA.

³⁰ S 53 of the HTAct defines ‘relevant material’ as material, other than gametes, that consists of or includes human cells, however, in terms of s 14(5) ‘relevant material for purposes of

Regulations, the remit of the HTA has been extended to also apply to tissues and cells that are procured outside the body,³¹ such as existing cell lines.³² Furthermore, the remit of the HTA excludes the use of gametes and embryos outside the human body, which are regulated separately by the HFEA and will be discussed later on.³³

Therefore, the HTA operates in terms of two main pieces of legislation (the HTAct and the Q & S Regulations) to ensure compliance with the EUTCD. The HTA's remit only continues up to the stage where the stem cells have been processed or manipulated to the extent that they are so far along the chain of production that the ATMP Regulation is applicable and the cells or therapy falls under the scope of medicinal product legislation where the remit of the MHRA is applicable.

5.2.1.3 Procurement, storage and use of stem cells from a human body

In terms of the HTAct, it is only lawful to perform certain listed acts with a body or relevant materials of such a body (deceased or alive), if appropriate consent has been obtained.³⁴

For the procurement of stem cells to fall within the ambit of the HTAct, it has to satisfy three elements:

1. It has to be regarded as relevant material for the purposes of the Act
2. It has to be applied for a Schedule 1 purpose³⁵

transplantation does not include blood or anything that is derived from blood. The definition of relevant material will be discussed later on in this dissertation.

³¹ S 30(2) of the Q & S Regulations: "At the end of subsection (1) insert- '(h) the procurement, processing, preservation, testing, storage, distribution, import or export of tissues and cells, in so far as those are activities to which regulation 7(1) or (2) of the 2007 Regulations applies and are not within the remit of the Authority by virtue of paragraph (a) to (g)".

³² S 54(7) of the HTAct states: "For the purposes of this Act, material shall not be regarded as from a human body if it is created outside the human body."

³³ S 53(2) of the HTAct; The Human Fertilisation and Embryology Act 2008 ch 22, incorporated to amend the Human Fertilisation and Embryology Act 1990. In 2015, the Human Fertilisation and Embryology Regulations 2015 were passed as an instrument to enable mitochondrial donation techniques to be used as part of IVF treatment to prevent the transmission of serious mitochondrial diseases from a mother to her child.

³⁴ S 1 of the HTAct.

³⁵ Schedule 1 specifies the purposes that require consent in terms of s 1 of the HTA. Part 1: "(1) Anatomical examination, (2) Determining the cause of death, (3) Establishing after a person's death the efficacy of any drug or other treatment administered to hum, (4) Obtaining scientific or medical information about a living or deceased person which may be relevant to any other person (including a future person), (5) Public display, (6) Research in connection with disorders, or the functioning, of the human body, (7) Transplantation; Part 2: (8) Clinical audit, (9) Education or

3. Appropriate consent must be obtained

Only once these elements have been satisfied will there be compliance with the HTAct. However, one should never lose sight of the fact that, alongside the requirements of consent set out in the HTAct, the Q & S Regulations have to be complied with at all times.

Before embarking on a discussion as to which tissues and cells are regarded as *relevant material*, it is important to note that if a person uses relevant material for a purpose other than one approved in Schedule 1, the HTAct will not apply;³⁶ however, such a situation will not render such an act(s) legal or illegal.³⁷ Therefore, it is submitted that the HTAct should be amended to set out how such instances should be dealt with.

‘Relevant material’ is defined in section 53 as material other than gametes that consists of or includes human cells.³⁸ Excluded from the definition are any embryos outside the human body, or hair and nails from the body of a living person.³⁹ Furthermore, the use of existing cell lines is also excluded, along with any other material created outside the human body.⁴⁰

Therefore, if done with appropriate consent, it shall be lawful to remove, store or use relevant material originating from a human body for a scheduled purpose.⁴¹ In the HTAct, the concept of relevant material is further qualified in that it states that the

training relating to human health, (10) Performance assessment, (11) Public health monitoring, and (12) Quality assurance.”

³⁶ Herring *supra* n130 421; Explanatory notes to the HTAct <<http://www.eui.eu/Projects/InternationalArtHeritageLaw/Documents/NationalLegislation/UnitedKingdom/humantissueact2004explanatorynotes.pdf>> (Accessed 18 August 2016).

³⁷ *Ibid.*

³⁸ S 53(1) of the HTAct.

³⁹ *Idem* at s 53(2)(a) & (b); Price 2005 *Mod L Rev* 798, 800 N.21: “Hair and nails were excluded on the account of their ‘natural discardability’.”

⁴⁰ S 54(7) of the HTAct 2004 states: “For the purposes of this Act, material shall not be regarded as from a human body if it is created outside the human body”; The Q & S Regulations define ‘cells’ and ‘tissue’ in s 5 as follows: ‘cells’ means “individual human cells or a collection of human cells when not bound by any form of connective tissue, including cell lines grown outside the human body but not including- (a) gametes, (b) embryos outside the human body, or (c) blood and blood components”, ‘tissue’ means “all the constituent parts of the human body formed by cells, but does not include – (a) gametes, (b) embryos outside the body, and (c) organs or parts of organs if it is their function to be used for the same purpose as the entire organ in the human body”.

⁴¹ S (1)(1)(c), (d), (e), (f) of the HTAct.

remit of the HTA does not extend to include blood or anything derived from blood.⁴²
Yet, Price states:⁴³

The definition highlights the breadth of the statute, extending as it does to blood (although not a cellular serum and plasma), as well as sputum, lung washouts and urine ('including', although not 'consisting', of human cells).

5.2.1.4 Procurement, storage and use of stem cells not from a human body

Parallel to the HTAct, the Q & S Regulations state in Regulation 7(1) & (2) read with 7(3) that no person shall procure, test, process, distribute, import or export, or store tissues or cells intended for human application without a licence from the HTA or in pursuance of a third-party agreement.⁴⁴ The Q & S Regulations set out the quality and safety standards for tissues and cells intended for human use and can find application even when the HTAct is not applicable.

The following definitions in the Q & S Regulations are noteworthy:⁴⁵

- **Blood** means whole human blood collected from a donor and processed either for transfusion or for further manufacturing;
- **Blood component** means a therapeutic constituent of human blood (red cells, white cells, platelets and plasma) that can be prepared by various methods, but does not include lymphocytes intended for use for the purpose of haematopoietic stem cell transplantation;

⁴² *Idem* at s 14(5) & 16(7) "'relevant material' in relation to use for the scheduled purpose of transplantation, does not include blood or anything derived from blood."; Directives 2002/98/EC and 2004/33/EC via the *Blood Safety and Quality Regulations 2005* and its amendments (SI 2005/50, 2005/1098 and 2006/2013) set out the standards for quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, aspects of the regulations apply to blood establishments (the UK Blood Services) and hospital blood banks. All the above fall within the remit of the MHRA, who is responsible for the control and authorisations that apply to blood establishments and controls that apply to hospital blood banks and sites that collect, test and supply blood or blood components intended for transfusion; Explanatory notes to the HTAct <<http://www.eui.eu/Projects/InternationalArtHeritageLaw/Documents/NationalLegislation/UnitedKingdom/humantissueact2004explanatorynotes.pdf>> (Accessed 18 August 2016).

⁴³ Price 2005 *Mod L Rev* 800 states that drawing the line at cellular material has caused some arbitrary exclusions, such as the fact that hair is excluded even though it contains keratin-producing cells.

⁴⁴ Reg 7(1), (2) & (3), read with reg 6(1), of the Q & S Regulations sets out the requirements of a third-party agreement.

⁴⁵ Reg 5 of the Q & S Regulations.

- **Cells** means individual human cells or a collection of human cells when not bound by any form of connective tissue, including cell lines grown outside the human body but not including— (a) gametes, (b) embryos outside the human body, or (c) blood and blood components;
- **Tissue** means all constituent parts of the human body formed by cells, but does not include— (a) gametes, (b) embryos outside the human body, or (c) organs or parts of organs if it is their function to be used for the same purpose as the entire organ in the human body.

Taking a closer look at the provisions and definitions of the HTAct, the use of an existing cell line will not be regulated by the HTAct, as it was not obtained from a human body, but from a stem cell bank. Therefore, existing cell lines will be regulated by the Q & S Regulations as it falls under the definition of a cell. Moreover, the way induced pluripotent stem cells are produced disqualifies them from regulation under the HTAct; however, the Q & S Regulations are still applicable.⁴⁶

Another example where the HTAct would not apply is instances where sections 7 and 8, read with section 9, apply, which state that consent will not be needed for the storage or use of relevant material for the purpose of research into disorders or the functioning of the human body if:

1. the material is from a living donor; and
2. the research falls within section 9, which means, it is ethically approved and will be carried out under such circumstances where the researcher is not in possession or is unlikely to obtain information regarding the person from whom the relevant material was obtained from so-called “donor de-identification”.

Therefore, the section 1 consent requirement can only be disregarded in the event that the relevant material was obtained from a living donor who cannot be identified

⁴⁶ However, the skin cell obtained from a living donor or the deceased must be obtained with the necessary consent and therefore the HTAct will be applicable in that sense. However, strictly speaking, an induced pluripotent stem cell is formed by cell reprogramming that happens outside the body and therefore the HTAct does not apply to it directly, only the Q & S Regulations will be applicable; See ch 2 on the production of induced pluripotent stem cells.

by the researcher.⁴⁷ However, the Q & S Regulations will still find application in such a situation.⁴⁸

As the concept of relevant material and the application of the Q & S Regulations are explained, the next topic of discussion will be the appropriate consent required to lawfully perform a schedule 1 purpose as set out in the HTAct.

5.2.1.5 Consent in terms of the Human Tissue Act

The notion of consent can be seen as the unifying theme of the HTAct as it has been described in Parliament as its “golden thread”.⁴⁹ ‘Appropriate consent’ is defined in sections 2 and 3 of the Act.⁵⁰ Consent must be given to store or use relevant material for a particular schedule 1 purpose. However, if that person has consented to the use or storage of his or her relevant material for research purposes, there is no need to obtain such consent for each individual research project.⁵¹ In this context, consent means positive consent and, therefore, failure to object is insufficient.⁵² The HTA’s Codes of Practice on Consent state that:⁵³

To give consent, the individual (or the person with parental responsibility) should understand the nature and purpose of what is proposed and be able to make an informed decision. They should be told of any ‘material’ or ‘significant’ risks inherent in the way the sample will be obtained, how the tissue will be used and any possible risks or implications of its use, e.g. genetic tests. If the person concerned is not a patient, and is volunteering samples purely for research, the general principles of providing appropriate information still apply.

Whether or not a person has the capacity to consent to the removal, storage for use, or use of his or her human tissue or cells, is a matter regulated by the general law on consent.⁵⁴ The HTAct gives specific prescriptions as to who may give consent.⁵⁵

⁴⁷ Recall that s 1 of the HTAct states that “relevant material may be used or stored for research purposes in connection with disorders and the function of human bodies, only if appropriate consent is given”; S 7 & 8 read with s 9 of the HTAct.

⁴⁸ Reg 7(1) – (3) of the Q & S Regulations.

⁴⁹ Price 2005 *Mod L Rev* 805; Ladyman, HC Standing Committee col 66 of 2004-01-27 and col 142 of 2004-01-29.

⁵⁰ S 2 of the HTA: Appropriate consent for children, and s 3: Appropriate consent for adults.

⁵¹ Herring *supra* n130 418.

⁵² *Ibid.*

⁵³ Par 158 of the HTA Code of Practice 1: Consent (Accessed 20 August 2016).

⁵⁴ *Idem* at par 30: “Consent to treatment and examination is covered by the common law and the Mental Capacity Act (MC Act) 2005, where appropriate. Trusts should have local policies in place for obtaining consent to treatment and the legal position is set out in the Department of Health's

(a) *Consent from a living person*

In respect of a living person, *consent* means that person's consent.⁵⁶ In the event where such a person is still a minor,⁵⁷ appropriate consent means that of the child. However, if the child is alive and fails to make a decision on whether to consent or not, or is incompetent to deal with the issues of consent related to the activity, or even though competent to deal with such issue, the child fails to deal with the issue of consent, appropriate consent refers to the consent of a person with parental responsibilities over the child.⁵⁸ Nonetheless, it was emphasised in parliament that the notion of Gillick competency will apply, which states that parental consent will continue to apply, even after the child has acquired adult status, subject to the now adult (previously minor's) revocation.⁵⁹ It should be noted that there is no legal duty on either of the parents or the relevant trust to inform the new adult (previously minor) that his or her stem cells are still being stored.⁶⁰ Where an adult lacks the capacity to give consent, it can be deemed given under certain circumstances, as set out in the HTAct (Persons who Lack Capacity to Consent and Transplants) Regulations of 2006.⁶¹ The conditions where consent can be deemed as given by the person lacking capacity are as follows:

1. If the relevant material of "P" who lacks mental capacity is stored or used for certain scheduled purposes⁶² by a person who is acting in what he or she reasonably believes to be in the best interest of P⁶³

guidance. Guidance for healthcare professionals in Wales is available in the Welsh Assembly Government's *Reference guide to consent for examination and treatment*. The Department of Health, Social Services and Public Safety (DHSSPS) (Northern Ireland) has published its own *Reference guide to consent for examination, treatment or care*."

⁵⁵ S 2 & 3 of the HTAct.

⁵⁶ *Idem* at s 3(2).

⁵⁷ *Idem* at s 54(1).

⁵⁸ *Idem* at s 2(2) read with s 2(3).

⁵⁹ Price 2005 *Mod L Rev* 805 N.44.

⁶⁰ *Ibid*; Par 153 of the HTA Consent Code of Practice.

⁶¹ The HTA (Persons who Lack Capacity to Consent and Transplants) Regulations 2006/1659; Par 135-150 of the HTA Consent Code of Practice.

⁶² Par 4-7 of Part 1 of Schedule 1 of the HTA: "(4) obtaining scientific or medical information about a living or deceased person which may be relevant to any other person (including a future person), (5) Public display, (6) Research in connection with disorders, or the functioning, of the human body, (7) Transplantation."

⁶³ S 3(2)(a) of the HTA (Persons who Lack Capacity to Consent and Transplants) Regulations 2006.

2. If the relevant material of “P” who lacks mental capacity is stored or used for the purpose of a clinical trial which is authorised and conducted in accordance with the clinical trials regulations⁶⁴ or
3. In accordance with sections 30-34 of the Mental Capacity Act 2005 (MC Act),⁶⁵ that allows for the storage and use of relevant material from the person lacking capacity for research purposes provided for in that Act.

(b) *Consent from a deceased person*

In the case of a deceased adult, consent or non-consent of the deceased can be obtained in various instances. Firstly, if the deceased has expressed his or her views, expression must be given to such wishes. In the event that the body or relevant material from the body of the deceased is used or stored for the purpose of anatomical examinations or public display, explicit consent is required.⁶⁶ Such a decision must have been made prior the death of the deceased. Therefore, if the deceased expressed his or her willingness to allow his or her body to be used for medical research, but shortly before death revoked such views, there will be no effective consent.⁶⁷ For all other purposes, consent need not be in writing.⁶⁸

In the event that a person passed away without making a decision regarding the use or storage of his bodily material and the deceased has appointed a representative, the representative may make representations on behalf of the deceased.⁶⁹ Lastly, if the person died without appointing a representative, the person who is in the closest qualifying relationship may make such decisions regarding the deceased’s bodily material.⁷⁰ In terms of section 27(4), the closest qualifying relationship is as follows: in descending order (a) spouse or partner; (b) parent or child; (c) brother or sister; (d) grandparent or grandchild; (e) child of a person falling within paragraph (c); (f) stepfather or stepmother; (g) half-brother or half-sister; and (h) friend of long standing.

⁶⁴ *Idem* at s 3(2)(b).

⁶⁵ MC Act ch 9.

⁶⁶ S 3(3) read with s 3(4) of the HTAct.

⁶⁷ S 3(6)(a) of the HTAct; Herring *supra* n130 419.

⁶⁸ Price 2005 *Mod L Rev* 806.

⁶⁹ *Idem* at s 3(6)(b) read with s 4. The representative can be appointed orally or in writing.

⁷⁰ *Idem* at s 3(6)(c).

If there are two people of the same rank, the consent of only one of them is required.⁷¹ The relation between a person and the deceased is to be disregarded if a person either does not wish to deal with or is unable to deal with the issue of consent, or the activity for which consent is sought makes it practically unreasonable to communicate with the person of qualifying relation within the time available for consent to be obtained.⁷²

(c) *Storage and use without consent*

As stated above, the “golden thread” of the HTA is vested in the principle of consent. However, there are a few scenarios where consent need not be obtained for the storage and use of relevant material, such as:

1. Part II of Schedule 1 of the HTAct sets out various purposes for which consent will not be required regarding the storing for use and use of human material from a living person (LP) for purposes in relation to a clinical audit, education and training in relation to human health, performance assessment, public health monitoring, or quality control.⁷³
2. The HTA has the power to deem that consent was given, if it is impossible to trace the individual from whom the material originated. The HTA has such powers if it is satisfied that the relevant material originates from an LP and that the storage or use would be in the best interest of another person (including a future person) in order to obtain scientific or medical information from an LP, and that there is no reasonable belief that the LP has died or has refused to consent.⁷⁴ The HTA may also deem consent to have been given if reasonable attempts have been made to oblige the LP to decide whether or not to consent to the storage or use of his or her tissue.⁷⁵

⁷¹ The list seems to neglect uncles and aunts, which could cause major problems.

⁷² As stated by Price 2005 *Mod L Rev* 808: “This last requirement obviates some of the difficulties under the 1961 Act where it was not certain whether the phrase ‘such reasonable enquiries as may be practicable’ was expected to take into account the limited time frame in which the enquiries could be made if organs were to remain viable for transplantation.”; Herring *supra* n130 419.

⁷³ The reason for these exceptions is that the use of material for such purposes is vital to the proper conduct of a patient’s treatment or the health of the nation.

⁷⁴ S 7(1) - (d) of the HTAct.

⁷⁵ *Idem* at s 7(2)(c).

3. In terms of section 7(4) of the HTAct, the High Court may issue an order deeming appropriate consent for the purposes of research on tissue from living or deceased persons in connection with disorders or the functioning of the human body.⁷⁶
4. In terms of section 1(7) & 1(8) of the HTAct, consent for the storage for use, or the use of relevant material from an LP may be disregarded, if
 - a. the research is ethically approved in terms of regulations made by the Secretary of State (mostly research ethics committees); and
 - b. it is to be, or is, carried out in circumstances such that the person carrying out is not in possession, and is not likely to come into possession, of information from which the person from whose body the material has come can be identified.⁷⁷
5. Surplus material may be removed in the course of medical treatment, diagnostic tests or research, whereafter such material will be dealt with as medical waste.⁷⁸
6. The consent provision of the HTAct does not apply to relevant material that has been imported from overseas.⁷⁹ However, in terms of section 1(13), if a body or relevant material was exported solely for the purpose of re-

⁷⁶ Price 2005 *Mod L Rev* 801: "The Minister however described such potential scenarios as 'truly exceptional', for example an unexpected outbreak of the Ebola virus where relatives of deceased persons might not be available to give consent, or in a case of bioterrorism"; Herring *supra* n130 422.

⁷⁷ *Ibid*: "This is an extremely important provision. Notably, it permits the use of material for research even where the patient positively objects. Hopefully, where a patient has voiced an objection, the researcher will choose not to use his or her material. Note that this does not justify the removal of material without the consent of the patient. It therefore covers material that has been removed with consent, for example material removed during an operation."

⁷⁸ Nuffield Council on Bioethics "Human tissue: Legal and ethical issues" 1995 *Nuffield Council on Bioethics* 67: the Nuffield Council on Bioethics took the stance that surplus tissue may be used without consent as the patient can be seen to have abandoned it. This was also the position taken by the Supreme Court of California in the USA in *Moore v Regents of the University of California* 1990 793 P 2d 479 Cal Sup Ct with respect to a removed cancerous spleen, that was subsequently used to produce a commercial cell line. However, the court held that the patient had a right to be informed about future use of the spleen, based on a fiduciary duty towards the patient; Price 2005 *Mod L Rev* 802; Herring *supra* n130 422.

⁷⁹ S 1(6)(b) of the HTAct states that s 1(1) - (3) does not apply in the event that the body has been imported, meaning that consent requirements can be ignored.

importation, consent requirements will have to be fulfilled.⁸⁰ This is done solely to prevent the export and subsequent re-importation of bodies and material for the purpose of defying principles of consent.⁸¹

7. If a hospital or medical practitioner has bodies or relevant material that was held for a Schedule 1 purpose prior to the implementation of the HTAct, consent can be disregarded.⁸²

8. Coroners' activities are also not covered by the Act.⁸³

As was stated earlier, relevant material in the HTAct excludes any material such as a gamete, embryo or tissue derived from an embryo. Such tissues fall under the remit of the HFEA.

5.2.2 Operation of the Human Fertilisation and Embryology Act and the Quality and Safety Regulations

5.2.2.1 History of the Human Fertilisation and Embryology Act

The Human Fertilisation and Embryology Act of 1990 (HFE Act) was enacted after the Dame (now Baroness) Mary Warnock inquiry was published in 1984. The report considered the social, ethical and legal implications of developments in the field of human reproduction.⁸⁴ The HFE Act regulates the creation, storage and use of embryos outside the human body, as well as gametes to create embryos.⁸⁵ The HFE Act prohibits certain activities from being performed without a licence, as well as

⁸⁰ The HTA considers it good practice for mechanisms to be in place that provide assurance that human tissue that was imported is obtained with valid consent. This is also applicable where the object is to analyse DNA in the material.

⁸¹ See the HTA Code of Practice 8: Import and export of human bodies, body parts and tissue, for guidance on the regulation of the import and export of human material <https://www.hta.gov.uk/sites/defaultimport_andexport_of_human_bodies.body_parts_and_tissue.pdf#pag/files/Code_of_practice_8_-e=2> (Accessed 20 August 2016).

⁸² S 9(1) read with 1(1) & 9(4) of the HTAct; Price 2005 *Mod L Rev* 801; Herring *supra* n130 423; The HTA Code of Practice 5: Disposal of relevant material deals with the storage, use, and disposal of existing holdings.

⁸³ Herring *supra* n130 423.

⁸⁴ Human Fertilisation and Embryology Act 2008 Explanatory Notes: "Most notably the birth of the first child conceived through *in vitro* fertilisation in 1978, named Louise Brown", hereinafter referred to as the "2008 Explanatory Notes" <<http://www.legislation.gov.uk/ukpga/2008/22/notes>> (Accessed 22 August 2016); see Gomez 2011 "The Special Status of the Human Embryo in the Regulation of Assisted Conception and Research in the United Kingdom" *MLJ* 6.

⁸⁵ *Idem* at par 6.

other activities which are absolutely forbidden, such as the placing of non-human embryos or gametes inside a woman.⁸⁶

However, it is possible to obtain a licence for the purposes of fertility treatment, storage and research, as well as for non-medical fertility services⁸⁷ after the Q and S Regulations were incorporated.⁸⁸ The activities in the HFE Act are overseen by the HFEA, which is the statutory licensing authority for activities that fall under the scope of the Act.⁸⁹

Following deliberations in the government, the HFE Act was reviewed in 2004 subsequent to scrutiny by a joint committee of both Houses of Parliament, whereafter the Human Fertilisation and Embryology Act 2008 (HFEA Act) was ordained.⁹⁰ The HFEA Act brought about changes to enable same-sex couples to be granted legal parenthood; the regulation of admixed embryos “hybrids”; the barring of sex selection for social reasons; provisions explicitly regulating embryo testing; and the replacement of the concept of the need for a father with that of the concept “supportive parenting” with regard to the welfare of the child. The amendments relating to the definition of an embryo and gametes that have been introduced in the HFE Act are important in the regulation of stem cell technologies.

5.2.2.2 The remit of the Human Fertilisation and Embryology Authority

In terms of section 8 of the HFE Act, as amended by the HFEA Act, the HFEA shall:⁹¹ keep under review, any information about embryos and any subsequent development of embryos and about the provision of treatment services and activities

⁸⁶ *Ibid.*

⁸⁷ In some cases, the activities may be performed by a third party, under a contractual agreement between the a licence holder and the third party; Non-medical fertility services are defined as any services that are provided in the course of a business, for the purpose of assisting women to carry children, but which are not medical, surgical or obstetric services. For example, internet-based businesses that arrange for donated sperm to be delivered to women at home for self-insemination.

⁸⁸ The Human Fertilisation and Embryology (Quality and Safety) Regulations (SI 2007/1522) implementing the EU Tissue and Cell Directives 2004/23/EC.

⁸⁹ Created by s 5 HFE Act, the Authority is an executive non-departmental public body sponsored by the Department of Health.

⁹⁰ HFE Act ch 22, which received Royal Assent on 13 November 2008.

⁹¹ S (8)(1) of the HFE Act, as amended by the HFEA Act; The HFEA was established in terms of the HFE Act. The HFEA subjects all embryo research in both the private and public sector to a robust system of case-by-case review before any licence is issued to permit research. No research is allowed on embryos older than 14 days. At the time of the HFE Act, embryo research was restricted to the study of infertility, miscarriage and congenital disease.

governed by the Act and advise the Secretary of State on such matters, if required; publicise the services provided to the public by the Authority or provided in pursuance of licences; provide, as it deems appropriate, information and advice to persons to whom licences apply, who are receiving treatment or are providing (or are potentially providing) embryos or gametes for the purposes of activities governed in this Act; maintain a general statement of general principles, which it considers to be followed when carrying out activities governed by the Act or in carrying out its function in relation to such activities; and promote compliance with requirements imposed by, or under, this Act and the code of practice under section 25 of this Act, in relation to activities governed by the Act.

5.2.2.3 Procurement, storage and use of embryonic stem cells

(a) Procurement, storage and use of embryonic stem cells

The HFE Act states the various activities that are prohibited, as well the activities that may only be performed in pursuance of a licence.⁹² As this Act's rationale is to regulate the use of embryos and gametes, it is important to have a clear understanding of what these terms mean, as this affects the remit of the HFEA.

(b) Defining embryos and gametes

Originally, in the HFE Act, reference to an "embryo" meant any live human embryo where fertilisation was complete, which includes an egg in the process of fertilisation.⁹³ Furthermore, as far as the creation of an embryo is concerned, this only applies to embryos created outside the human body, and references to embryos created *in vitro* include those embryos where fertilisation began outside the human body, irrespective whether or not it was completed there.⁹⁴ If the embryo was taken from a woman, it does not qualify as an embryo that was created *in vitro*.⁹⁵

After the enactment of the HFEA Act, "embryo" now means a live human embryo and does not include a human admixed embryo as set out by section 4(A)(6),⁹⁶ and

⁹² *Idem* at s 3 & 4 of the HFE Act.

⁹³ *Idem* at s 1(b): "For such purposes, fertilisation was not complete until the appearance of a two cell zygote."

⁹⁴ *Idem* at s 1(2)(a).

⁹⁵ *Idem* at s 1(2)(b).

⁹⁶ S 4(A)(6) of the HFE Act defines a "human admixed embryo", as "(a) an embryo created by replacing the nucleus of an animal egg or of an animal cell, or two animal pronuclei, with—(i) two

references to an embryo include an egg that is in the process of fertilisation or is undergoing any other process capable of resulting in an embryo.⁹⁷

The scope of this definition was drafted to include eggs that are induced to behave as if they were fertilised, cell nuclear transfer, and eggs that are undergoing processes leading to limited (if any) development, such as zygotes created from an enucleated egg equipped with male or female pronuclei and parthenotes.⁹⁸ If such eggs are to qualify as embryos, a licence from the HFEA will have to be obtained before research and the subsequent derivation of stem cell lines from such embryos can be undertaken.⁹⁹

As the HFEA Act allows for a licence for treatment storage and research on embryos (as defined above) or human admixed embryos, it is important to know what is meant by human admixed embryos (HAE).¹⁰⁰ An HAE includes the following categories:¹⁰¹

1. Cytoplasmic hybrid¹⁰²
2. True hybrid¹⁰³
3. Transgenic human embryo¹⁰⁴
4. Chimeric human Embryo¹⁰⁵

human pronuclei, (ii) one nucleus of a human gamete or of any other human cell, or (iii) one human gamete or other human cell, (b) any other embryo created by using— (i) human gametes and animal gametes, or (ii) one human pronucleus and one animal pronucleus, (c) human embryo that has been altered by the introduction of any sequence of nuclear or mitochondrial DNA of an animal into one or more cells of the embryo, (d) a human embryo that has been altered by the introduction of one or more animal cells, or (e) any embryo not falling within paragraphs (a) to (d) which contains both nuclear or mitochondrial DNA of a human and nuclear or mitochondrial DNA of an animal (“animal DNA”) but in which the animal DNA is not predominant.”

⁹⁷ S 1 HFE Act, as amended by the HFEA Act, which was prompted by the avoidance of fertilisation in a well-known sheep, Dolly.

⁹⁸ Vertes *et al supra* n9 126; See ch 2 for a discussion regarding parthenogenesis.

⁹⁹ *Ibid.*

¹⁰⁰ S 11 of the HFE Act, as amended by the HFEA Act.

¹⁰¹ Medical Research Council Code of Practice for the use of Human Stem Cell Lines April (2010) <http://www.mrc.ac.uk/documents/pdf/code-of-practice-for-the-use-of-human-stem-cell-lines/> (Accessed 22 August 2016). Hereinafter referred to as the “MRC Code of Practice 2010.”

¹⁰² Created by replacing the nucleus of an animal egg or cell with a human nucleus, cell, gamete or two pronuclei.

¹⁰³ Created from human and animal gametes or pronuclei.

¹⁰⁴ A human embryo that has animal nuclear or mitochondrial DNA inserted into it.

¹⁰⁵ A human embryo, altered by the insertion of one or more animal cells. See ch 2 regarding human-animal chimeras.

5. Any embryo not falling under (1) – (4) that contains both nuclear and mitochondrial DNA of a human and nuclear or mitochondrial DNA of an animal, but in which the animal DNA is not predominant.

The above definition of an “embryo”, seen in the light of the definition of a “human embryo”, as set out by the European Court of Justice in 2011 in the matter between *Brüstle v Greenpeace*,¹⁰⁶ which stated that no development was required, makes it clear that such entities which are created by parthenogenesis or by means of enucleated eggs, will fall under the definition of a live human embryo in terms of the amendments to the HFE Act.¹⁰⁷

However, in the case of *R v (Quintavalle) v Secretary of State for Health*¹⁰⁸ the court ruled on the correct interpretation of the original definition of “embryo.” The court found that it would only consider male-only and female-only zygotes and parthenotes to be embryos if parliament meant to do so when passing the amended definition, had it been aware of such things at the time.¹⁰⁹ Vertes *et al* note the following in relation to parliament:¹¹⁰

It certainly should have known of such things because when UK Parliament debated the revised definition of the term ‘embryo’, it was well known that a double complement of maternally imprinted genes and the absence of paternally imprinted genes render human development impossible. Moreover, Elena Revazova and her colleagues at the International Stem Cell Corporation had only recently (in 2007) demonstrated the potential of parthenotes as a source of therapeutic stem cells.

Taking this into account, the definition that materialised in parliament aims only to regulate entities that have the capacity to develop into a human being.¹¹¹ However, it

¹⁰⁶ *Brüstle v Greenpeace supra* n303

¹⁰⁷ In the United States, the National Institute for Health Guidelines and federal laws include parthenotes under the definition of “embryos”; Vertes *et al supra* n9 123.

¹⁰⁸ *R v (Quintavalle) v Secretary of State for Health* 2003 2 All ER 113.

¹⁰⁹ Vertes *et al supra* n9 126.

¹¹⁰ *Ibid.*

¹¹¹ *Ibid*; EU Court of Justice in *International Stem Cell Corporation v Comptroller General of Patents* Case-364/13 2014-12-18; MRC Code of Practice 2010 <<http://www.mrc.ac.uk/documents/pdf/code-of-practice-for-the-use-of-human-stem-cell-lines/>> (Accessed 22 August 2016) in par 3.3 takes the view that the potential life is what is to be protected: “The special regulations which govern the creation and use of human embryonic stem cells reflect the fact that the human embryo has a special moral status. The position adopted by Parliament in this legislation is that the

is most likely that the definition of embryos is being interpreted otherwise and would include the application of eggs such as those created by parthenogenesis within the ambit of the HFE Act.

(c) *Licence for research under the Human Fertilisation and Embryology Act*

The HFEA can only licence the *in vitro* creation, storage¹¹² and use of human embryos (including HAE) for research purposes, if it is satisfied that the proposed use of embryos or human admixed embryos is necessary for the purpose of the research.¹¹³

In terms of Schedule 2, paragraph 3(A)(1) of the HFEA Act, the HFEA cannot authorise any activity, unless the activity (such as stem cell research) appears to be necessary or desirable for a principle purpose, as set out in paragraph 3A(2). The principle purposes include most importantly “increasing knowledge about serious disease or other serious medical conditions” and “developing treatments for serious disease or other serious medical conditions”.¹¹⁴

Furthermore, the HFEA may also grant a licence for research on embryos, if it deems such research necessary or desirable for the purpose of providing knowledge that, in its view, could be applied for principle purposes.¹¹⁵ Therefore, after the insertion of section 3A(2)(b), which allows for research into the development of treatments for serious diseases or other serious conditions, research may be conducted to initiate the growth of specific tissues that were derived from stem cells,

embryo, unlike an infant, does not have the full rights of a person. However, its human potential gives it intrinsic value which implies that neither its creation nor its destruction is to be treated casually”. Therefore, it can be said that any entity that lacks such capabilities, that is, to develop into human life, cannot be afforded the same protection and therefore falls outside the remit of the HFE Act.

¹¹² S 2(1) & 2(1A) of Schedule 2 of the HFE Act, as amended by the HFEA Act.

¹¹³ *Idem* at s 11, read with par 3(1) & 3(5) of Schedule 2 of the HFEA Act.

¹¹⁴ *Idem* at par 3(A)(2)(a) & (b) of Schedule 2 of the HFEA Act. Par 3(2)(A) also includes: “(c) increasing knowledge about the causes of any congenital disease or congenital medical condition that does not fall within paragraph (a), (d) promoting advances in the treatment of infertility, (e) increasing knowledge about the causes of miscarriage, (f) developing more effective techniques of contraception, (g) developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation, or (h) increasing knowledge about the development of embryos.”

¹¹⁵ *Idem* at s 3(A)(1)(b).

which in turn, could lead to advances in the regeneration or repair of tissue damage caused by disease or trauma.¹¹⁶

As the HFEA Act provides for the creation of HAE, licences may now be issued for the creation, keeping and use of HAE.¹¹⁷ They may also be used in the derivation of embryonic stem cell lines; however, it must be necessary for the purpose of the research.¹¹⁸ Furthermore, the amended Schedule 2 provides time limits and conditions that must be complied with in terms of a research licence, such as the fact that the licence itself may impose further conditions that must be complied with in order for the activities performed under the licence to be lawful,¹¹⁹ and the fact that a licence may not be granted for a period exceeding three years, specified in the licence itself.¹²⁰

(d) *Licence for storage*

In terms of the HFEA Act, the storage of gametes and embryos (including HAE) is permitted.¹²¹ However, the licence will still be subjected to the normal time limits and conditions as set out in paragraphs 2(2) and (3) of Schedule 2 as licences to store and use embryos.¹²² The following conditions shall be applicable to any licence for the storage of gametes, embryos or HAE:¹²³

- i) That the gametes of a person shall only be placed in storage if they are received from that person under the circumstances set out in paragraphs 9 and 10 of Schedule 3 and that person's consent is not required;¹²⁴

¹¹⁶ The MRC Code of Practice 2010 <<http://www.mrc.ac.uk/documents/pdf/code-of-practice-for-the-use-of-human-stem-cell-lines/>> (Accessed 22 August 2016).

¹¹⁷ Par 3(3) of the HFEA Act allows for HAE, as defined by s 4A(5)(a) - (e), to be created, kept and used.

¹¹⁸ *Idem* at par 3(5).

¹¹⁹ *Idem* at par 3(6).

¹²⁰ *Idem* at par 3(8).

¹²¹ Par 2(2) of the HFE Act, as amended by the insertion of the new subparagraph 1A, that allows admixed embryos to be stored (irrespective of whether the license holder already possesses a licence to store embryos or gametes).

¹²² HFE Act 2008: Explanatory notes 9 <<http://www.legislation.gov.uk/ukpga/2008/22/notes/division/6/2/17/1/13>> (Accessed 22 August 2016).

¹²³ S 14 HFE Act, as amended by the HFEA Act.

¹²⁴ S 9, as inserted into the HFE Act by the HFEA Act: "9(1) The gametes of a person ("C") may be kept in storage without C's consent if the following conditions are met. (2) Condition A is that the gametes are lawfully taken from or provided by C before C attains the age of 18 years. (3) Condition B is that, before the gametes are first stored, a registered medical practitioner certifies in writing that C is expected to undergo medical treatment and that in the opinion of the registered medical practitioner- (a) the treatment is likely to cause a significant impairment of C's fertility, and

- ii) That an embryo may only be taken from a woman for the purpose of storage, if it (1) was received from that woman, or (2) if it was acquired from a licence holder or in terms of a third party agreement;
- iii) In the event that an embryo was created *in vitro*, not in the pursuance of a licence, it shall only be stored if it was acquired from someone who has a licence or where a third-party agreement applies. The same applies to HAE; however, only in the event that paragraph 2 or 3 of Schedule 2 applies;¹²⁵
- iv) That all information should be maintained in pursuance of a storage licence, until it has expired as set out in direction for the keeping records of such sort;
- v) That gametes and embryos or HAEs may only be stored for a period not exceeding ten years, as specified in the licence. However, regulations may prolong or shorten this period.

As discussed above, the Q & S Regulations will only find application once the cellular material or, in this particular instance, the stem cells, have been derived from the embryo. However, the HFE Act provides certain criteria in section 14A that have to be met before the storage of, or research on, gametes or embryos is permitted.¹²⁶

A licence for research purposes may not authorise the storage, procurement, testing, processing or distribution of gametes or embryos, unless it complies with the conditions of Schedule 3A of the HFE Act.¹²⁷ If any embryos or gametes are imported into the UK from another European Economic Area (EEA) state, excluding the UK or Gibraltar, compliance with the EUTCD, as incorporated by that state's

(b) the storage of the gametes is in C's best interests. (4) Condition C is that, at the time when the gametes are first stored, either- (a) C has not attained the age of 16 years and is not competent to deal with the issue of consent to the storage of the gametes, or (b) C has attained that age but, although not lacking capacity to consent to the storage of the gametes, is not competent to deal with the issue of consent to their storage. (5) Condition D is that C has not, since becoming competent to deal with the issue of consent to the storage of the gametes- (a) given consent under this Schedule to the storage of the gametes, or (b) given written notice to the person keeping the gametes that C does not wish them to continue to be stored.”; S 10 is similar to s 9, however, it deals with the instances where consent can be disregarded for the storage and use of gametes.

¹²⁵ In terms of par 2(1A) of Schedule 2 of the HFEA Act, a licence may be provided for the storage of HAEs, and par 3(3) applies to licences issued for research on HAEs.

¹²⁶ S 14A(1)(b) & (c), which states that “every licence under paragraph 3 of that Schedule, so far as authorising activities in connection with the derivation from embryos of stem cells that are intended for human application.”; For the purpose of this dissertation, the discussion regarding the application of gametes, embryos or HAEs will not reach as far to include licences for treatment other than for the purpose of the derivation of embryonic stem cells as this forms part of the discussion.

¹²⁷ Schedule 3A was an insertion into the HFE Act by SI 2007/1522.

legislation or any other legislation will be assumed, to comply with Schedule 3A.¹²⁸ Schedule 3A was incorporated to amend the HFE Act to ensure compliance with the EUTCD on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. It is submitted that, if done with consent, paragraph 3 of Schedule 2, read with section 14 and 14A, as set out above, will provide for the storage of embryos that were created *in vitro*, but donated to be used for research experiments that are lawfully sanctioned. Such a donation(s) can be regarded as the basis upon which embryonic stem cell research is built.

(e) *The general conditions of licences*

In addition to the above conditions of a research licence, section 12 of the HFE Act, as amended by the HFEA Act, sets out the general conditions to be complied with for all licences issued by the HFEA. The licenced activities, such as research, in terms of section 11(1)(c), read with Schedule 2 of the HFE Act that provides for research projects on embryos, have to comply with the following conditions:¹²⁹

- i) Such research shall only be carried out on the premises as specified in the licence under the supervision of the person responsible, except where the activities fall under sections 3(1A)(b)¹³⁰ or (1B)¹³¹ or 4(1A);¹³²
- ii) Any member of the Authority, if he or she wishes, should be permitted upon the premises and inspect them (including the records and equipment or the observing any activity);
- iii) The provisions of informed consent, as set out in Schedule 3, will be complied with;
- iv) The licence holder will maintain proper records, as prescribed by the HFEA. In terms of the amended HFE Act, every licence must have a condition that states that any information that is necessary with regard to the traceability,

¹²⁸ S 14A(3) of Schedule 3A of HFE Act, as amended by SI 2007/1522.

¹²⁹ *Idem* at s 12.

¹³⁰ No person shall keep or use an embryo- except (b) in the case of the keeping, without storage, of an embryo intended for human application, or the processing, without storage of such an embryo, in pursuance of a third party agreement.

¹³¹ "No person shall procure or distribute an embryo intended for human application except in pursuance of a licence or a third party agreement."

¹³² "No person shall procure, test, process or distribute any gametes intended for human application except in pursuance of a licence or a third party agreement."

quality and safety of gametes or embryos, as far as they are being stored, must be kept and provided to the HFEA upon request.¹³³

- v) No remuneration (including any other benefit) will be given or received for the supply of gametes, embryos or HAEs, unless as authorised by the directions of the HFEA;¹³⁴
- vi) In the event that gametes, or embryos or HAEs are supplied to a person subject to another licence, such a person (to whom such other licence applies) will be provided with information as set out by the Directions of the Authority; and
- vii) The HFEA must be provided with copies or extracts of records or other information, in the form that it prescribes in the directions.

5.2.2.4 Consent in terms of the Human Fertilisation and Embryology Act

(a) General conditions of consent

Just as research concerning human tissue / cells requires consent under the HTAct, consent is a prerequisite for research on gametes and embryos or HAEs and is regulated by the HFE Act and the HFEA Act.¹³⁵ Schedule 3 of the HFE Act sets out the consent requirements for the storage of gametes, embryos or HAEs.

For consent to be valid, varied or withdrawn in terms of the HFEA Act, it must be in writing and signed by the person giving it.¹³⁶ In the event that a person is unable to consent, vary or withdraw consent due to illness, physical disability or injury, that person would be regarded to have given consent if the consent document has been signed under the direction of the person unable to sign, in the presence of the

¹³³ S 13(3), read with 1s 3(2), of the HFE Act, as amended by the Q & S Regulations.

¹³⁴ Par 72 of the Human Fertilisation and Embryology Act 2008: Explanatory Notes states that s 12, as amended, ensures that “no money or other benefit can be given or received for the supply of human admixed embryos (unless authorised by directions) and that if human admixed embryos are supplied to a person to whom another licence applies, they must be provided with any information that the HFEA may specify in conditions.” These amendments ensure that any research licence granted in connection with human admixed embryos will be subject to the same relevant licence conditions.

¹³⁵ S 12 of the HFEA Act introduces the amendment of the HFE Act Schedule 3, which relates to the storage and use of embryos to create an embryo *in vitro*: “(1)...(c) except in relation to the use of gametes in the course of providing basic partner treatment services, that the provisions of Schedule 3 to this Act shall be complied with”.

¹³⁶ Par (1)(1) of the HFEA Act.

person unable to sign and at least another witness who can attest to that signature.¹³⁷

In the context of the development of stem cell therapy, paragraph 2(1)(c) of Schedule 3 provides that the consent must specify that the embryo may be used for research purposes, subject to conditions for which the embryo may be used.¹³⁸ In the event that the gamete, embryo or HAE that was procured is to be stored, the consent must be qualified by stating the maximum period allowed for storage (if less than the statutory period). Furthermore, the consent must state what is to be done with the gamete, embryo or HAE if the consenting individual dies or loses capacity to do so, varies the terms or withdraws consent.¹³⁹

Before giving consent as set out in Schedule 3 of the HFEA Act, a person must be given a suitable opportunity to receive both relevant and proper information regarding the implications of taking the proposed steps such as undergoing *in vitro* fertilisation and subsequently donating “left over” embryos for the purpose of stem cell research.¹⁴⁰ The donor must be informed of his right to vary or withdraw consent in terms of paragraph 4 and 4A of Schedule 3.¹⁴¹ However, if the donor donated an embryo or HAE and consented to the use of that embryo or HAE, the consent cannot be varied or withdrawn if the donated embryo or HAE has been used to create a subsequent embryo or HAE for research purposes.¹⁴²

(b) *Consent requirements for in vitro fertilisation and subsequent use of embryos or human admixed embryos*

¹³⁷ *Idem* at par 1(2) read with (1)(1).

¹³⁸ *Idem* at par 2(1)(c); Par 4 of Schedule 3 sets out the various purposes for which consent is applicable in this schedule, therefore the whole Act: “(a) to the use or storage of a particular embryo or human admixed embryo, or (b) in the case of a person providing gametes or human cells, to the use or storage of – (i) any embryo or human admixed embryo whose creation may be brought about using those gametes or those cells, and Schedule 3 Consent to use or storage of gametes, embryos or human admixed embryos, etc. (ii) any embryo or human admixed embryo whose creation may be brought about using such an embryo or human admixed embryo.”

¹³⁹ If consent is given by virtue of par 8(2ZA) or 13(2) of Schedule 3 of the HFE Act, as amended.

¹⁴⁰ *Idem* at par 3(1).

¹⁴¹ *Idem* at par 4.

¹⁴² *Idem* at par 4(2)(b) read with 4(3) - (5) of Schedule 3 of the HFE Act, as amended by the HFEA Act; Similar to withdrawal of consent for the use of an embryo, consent for the storage of an embryo may be withdrawn. Consent to the storage of a permitted embryo, which was created *in vitro*, may be withdrawn and, subsequently, the person or institution storing such an embryo must take reasonable steps to notify all parties of interest regarding the withdrawal of consent.

A person's gametes or cells may not be used for the creation of an embryo to be used for research purposes without effective consent from each relevant person in relation to the embryo for that specific purpose.¹⁴³ Therefore, and similar to the consent requirements in the HTAct, consent needs to be specific.¹⁴⁴ The consent given for the creation of an embryo by means of donated gametes or human cells is in addition to the consent requirements for the use of gametes as set out in paragraph 5 of Schedule 3.¹⁴⁵ Embryos created by means of *in vitro* fertilisation may only be stored if effective consent was given by all relevant persons in accordance with the consent given.¹⁴⁶

(c) *Cases where consent is not required for storage*

Similar to the HTAct, the HFEA Act provides for instances where embryos and gametes may be stored in the absence of consent from the relevant persons involved.¹⁴⁷ This is true:

1. if the gametes have been lawfully withdrawn from a person under the age of 18 years;
2. if, prior to the initial storage, a medical doctor certifies in writing that the patient is about to undergo treatment that would impair the patient's fertility or that it would be in the patient's best interest;¹⁴⁸

¹⁴³ *Idem* at par 6(1) read with par 2(1)(c) of Schedule 3 as amended by the HFEA Act; "Effective consent" is regarded as consent under Schedule 3 that has not been withdrawn as set out in par 1(3) of Schedule 3 of the HF EAct; Par 12(1) of Schedule 3 of the HFEA Act; Par 6(3) HFEA Act; A relevant person is described in par 3E as follows: "(a) each person whose gametes or human cells were used to bring about the creation of embryo A, (b) each person whose gametes or human cells were used to bring about the creation of any other embryo, the creation of which was brought about *in vitro*, which was used to bring about the creation of embryo A, and (c) each person whose gametes or human cells were used to bring about the creation of any human admixed embryo, the creation of which was brought about *in vitro*, which was used to bring about the creation of embryo A."; Par 12(3) of Schedule 3 states that an HAE may not be used for research without effective consent of each relevant person as prescribed by such consent.

¹⁴⁴ See consent under the HTA as set out above.

¹⁴⁵ See also par 7 of Schedule 3 that refers to the procurement of embryos by means of lavage and sets out similar conditions for consent as those of the use of embryos created by means of IVF.

¹⁴⁶ *Idem* at par 8(2C), which sets out who qualifies as a relevant person in this regard.

¹⁴⁷ Par 9 - 11 of Schedule 3 of the HFEA Act.

¹⁴⁸ Par 9(3), read with par 10(2) & (3), which states that the gametes of a person [P], who is under the age of 16, may be stored without consent, if a registered medical doctor certifies in writing that P will undergo medical treatment that is likely to affect P's fertility and that P currently lacks the capacity to consent to the storage of his or her gametes, but is likely in future to gain such capacity and that it is in the best interest of the patient to store his or her gametes. Furthermore, consent may be disregarded when P, subsequent to storage attained the capacity to consent, has in fact

3. if, when the gametes were first stored, the donor has not attained the age of 16 years and is therefore incompetent to deal with issues of consent regarding the storage of gametes, or even though the donor is 16 years old, lacks the capacity to deal with consent; and
4. consent for the storage of gametes may be disregarded in the event that the minor has attained competency and has not given consent to the storage thereof or if the minor has not given a written notice which bars the person storing the gametes from continuing to do so.¹⁴⁹ It is interesting to note that the 2008 Act provides that no person's gametes may be stored, irrespective of their prospective use, by virtue of paragraph 9 or 10 after that person has passed.

These sections are particularly important where a parent or the child himself or herself wishes to store the minor's gametes. This would be applicable in instances where they might need to create an embryo by means of *in vitro* fertilisation for future purposes to one day derive stem cells from it and subsequently culture stem cells for transplant, or to develop them into a medicinal product, in the event that the minor falls ill with an otherwise untreatable disease or condition.

(d) *Creating, using and storing human admixed embryos*

As illuminated above, the HFEA Act allows for the creation, use and storage of an HAE. HAEs can accomplish two tasks, as they can provide for the derivation of embryonic stem cells, while avoiding arguments of the destruction of a potential human life because these embryos are from the onset not regarded viable to develop into a human being (or at least for now).¹⁵⁰ The consent requirements for such purposes are set out in Schedule 3 of the HFEA Act.

The *in vitro* creation of an HAE for research purposes is prohibited, unless effective consent was given by the person whose gametes were used¹⁵¹ and it may not be

given consent, or has not given written notice to the person storing P's gametes that he or she does not wish such storage to continue.

¹⁴⁹ *Idem* at par 9(5)(a) & (b).

¹⁵⁰ For more information see Savulescu *The Ethics of Human Admixed Embryos: Concerns and Responses* <<http://blog.practicaethics.ox.ac.uk/2008/05/the-ethics-of-human-admixed-embryos-concerns-and-responses/>> (Accessed 5 September 2016); See MacKellar "Differentiating between human and non-human interspecies embryos" 2014 *J Med Ethics* 284 for a discussion regarding the differentiation between human and non-human interspecies embryos.

¹⁵¹ Par 12(1) of Schedule 3 of the HFEA Act.

received by any person, unless effective consent from all relevant parties has been obtain in relation to the HAE to be used for research purposes.¹⁵² Similar to the creation, use and storage of human embryos, consent needs to be specific and the HAE may not be used in discord with the qualifications of the consent. This means, it may only be used for purposes that were consented to, hence, consent to use an HAE for infertility treatment does not warrant the subsequent storage or use for research projects.¹⁵³

In the event that the gametes of a person under the age of 18 are to be used for the creation of an HAE, consent is further qualified in paragraph 15 of Schedule 3, which sets out the parental conditions of consent, which, in such circumstances, is to be regarded as the effective consent.¹⁵⁴ However, in the event that the minor turns 18 or acquires the capacity to consent to the creation of an HAE, effective consent given becomes that of the now major.

(e) *Exemption of consent conditions for adults lacking capacity to consent*

The Authority may authorise the use of human cells to create an embryo or an HAE *in vitro* for research purposes or the storage thereof, if certain conditions are met, irrespective of whether the human cells were used during the donor's lifetime or after the donor has passed. These conditions are as follows: ¹⁵⁵

1. If the donor suffers from or is likely to develop a serious disease or physical or mental disability or any other serious medical condition.
2. If the donor lacks mental capacity to consent to the use of his or her human cells to create an embryo or HAE.
3. If the person responsible for the licence has no reasonable belief that there was any objection to the use of the donor's cells to create an embryo or HAE.
4. If it appears unlikely that the donor will at some point obtain/re-obtain capacity to consent.
5. The human embryo or HAE created *in vitro* for research purposes must be used to increase knowledge about the disease, disability or medical condition

¹⁵² *Idem* at par 12(2).

¹⁵³ *Idem* at par 12(3)(a) & (b).

¹⁵⁴ *Idem* at par 12(4) read with par 12(5).

¹⁵⁵ *Idem* at par 17(1).

of the donor, or the treatment of the donor or care of the persons affected by that disease, disability or medical condition or any similar disease, disability or medical condition.

6. If there are reasonable grounds to believe that research of comparable effectiveness will not be possible if the only human cells (that will be used for the creation of embryos and HAEs *in vitro* for the research project) are those human cells that have been attained from a person 18 years of age with the capacity to consent to such matters, or a person under the age of 18, who is nevertheless competent to consent to such use of his or her human cells.

In the event that the adult donor (P) lacks the capacity to consent to the use of his or her human cells for the creation of a human embryo or an HAE for the purposes of a research project, the following conditions must be complied with by the person who is responsible under the licence (R):¹⁵⁶

1. R must take reasonable steps to identify a person who cares for P or is interested in P's welfare, other than in a professional capacity or for remuneration and is prepared to be consulted by R for such purposes.
2. If R is unable to identify such a person, R must nominate such a person who is prepared to consult with R and has no connection with the research project.
3. R must provide the nominated candidate or the person identified with information regarding the use of the human cells for the purpose of creating a human embryo or HAE and ask such a person, in their opinion, what P's wishes and feelings would likely be regarding such uses of his or her human cells if P had the capacity to consent to such matters.
4. Human cells obtained from P may only be used for the creation of human embryos or HAEs if the identified or nominated person has not advised R that P's opinion and feelings would most likely lead to the decline of such consent.

Neither of these sets of requirements will apply if, at any time before the use of the human cells, the donor becomes competent to consent and gives a written notice to

¹⁵⁶ *Idem* at par 18; Par 17(8) of Schedule 3 of the HFEA Act states the following in relation to who is to be regarded as a the 'person responsible' "In this paragraph and par 18 references to the person responsible under the licence are to be read, in a case where an application for a licence is being made, as references to the person who is to be the person responsible."

the person keeping the cells, stating that he or she does not wish for their human cells to be used in such a manner.¹⁵⁷

Furthermore, a human embryo or HAE may not be used for research purposes without the donor's consent if, at any time before the commencement of the research project, the donor has the capacity to consent to the storage or use thereof and gives a written notice to the person keeping the embryo or HAE that he does not wish for them to be used or stored for such purposes.¹⁵⁸

(f) *The use of cells or existing cell lines before the relevant commencement date of the HFE Act*

Consent of a person to use or store human cells for the creation of an embryo or HAE may be disregarded if the cells were lawfully stored for research purposes, as prescribed by HFE Act. In addition, if such research is to be conducted under an HFEA licence, appropriate research ethics approval is required.¹⁵⁹ A licence authorising the application of human cells may only be issued if:

1. the Authority is satisfied that if they deny the use of human cells for the creation of embryos or HAEs for research purposes, it will have a significantly adverse effect on scientific; and
2. the conditions below are met before an embryos or HAE may be created for research purposes.¹⁶⁰

This is also true if the cells were obtained by someone who is unable to consent and a nominated or identified person has been appointed to express the likely

¹⁵⁷ Par 19 of Schedule 3 of the HFEA Act: The purposes for which consent of the donor can be disregarded in such instances are set out in section par 16(2)(a) & (b): "(a) to the use (whether during P's lifetime or after P's death) of P's human cells to bring about the creation *in vitro* of an embryo or human admixed embryo for use for the purposes of a project of research, (b) to the storage or the use for those purposes (whether during P's life or after P's death) of an embryo or human admixed embryo in relation to which P is a relevant person by reason only of the use of P's human cells."

¹⁵⁸ *Ibid.*

¹⁵⁹ Par 9.2.2(i) of the HTA Consent Code of Practice.

¹⁶⁰ *Idem* at par 21(1)(b).

views and opinion of the donor lacking capacity to consent.¹⁶¹ The conditions applicable to such a licence are as follows:¹⁶²

1. Condition A:

- a) If it is not reasonable for the person who is responsible for the licence (R) to identify a person in terms of paragraph 16 of Schedule 3, who is either nominated by R or identified by virtue of his or her relation to the donor.
- b) None of the information available to R (whether de-identified or not) must indicate that the donor would not have consented to the use of his or her human cells for the purpose of creating an embryo or HAE for research purposes.

2. Condition B:

- a) If the donor whose cells are to be used for the purposes of a research project, is either dead or R reasonably believes that the donor is dead.
- b) If the information regarding the donor who is dead (or presumed dead), should not suggest that that donor would have objected to the use of his or her cells to create an embryo or HAE for the purposes of a research project.
- c) If a person who stood in a qualifying relationship with the deceased donor gave consent in writing for the use of the donors cells to bring about an embryo or HAE for research purposes, immediately before the donor had passed.

3. Condition C:

- a) If R has taken all reasonable steps to contact the donor or, in the case where the donor has passed (or believed to have passed), R has taken steps to contact the persons who stood in a qualifying relationship with the donor, who could consent in writing and has not yet done so
1. b) If the information regarding the donor available to R does not suggest that the donor would have objected to the use of his or her cells to bring about an embryo or HAE for research purposes. The consent requirements regarding the consent of a person who stood in a qualifying relationship are the

¹⁶¹ As required by par 16 of Schedule 3 of the HFEA Act.

¹⁶² *Idem* at par 17.

requirements set out in 3(6)(c) of the HTAct.¹⁶³ Furthermore, subsection (4), (5), (6), (7) and 8(a) & (b) of section 27 of the HTAct is applicable.

5.2.2.5 The UK Stem Cell Bank and its principle operation

(a) Background

In 2002, the UK Stem Cell Bank was established to provide an ethically approved and guaranteed quality controlled repository of embryonic, foetal and adult stem cell lines. Jointly funded by the Medical Research Council and the Biotechnology and Biological Sciences Research Council, the Bank provides human embryonic stem cell lines for clinical research, as well as stem cell lines for use as starting materials for the development of cellular therapies, which comply with the EUTCD.¹⁶⁴ The Bank plays a vital role in the governance of human embryonic stem cell research, as it requires from everyone with an HFEA licence who is deriving embryonic stem cells to deposit any unused cells from licenced research projects at the UK Stem Cell Bank.¹⁶⁵

Even though the UK Stem Cell Bank stores and distributes stem cell lines, the ownership of any intellectual property embodied in the stem cell lines remains with the discoverer.¹⁶⁶ To obtain a stem cell line deposited after April 2010, the supplicant is obliged to sign a Research Use licence, which will set out the terms of use for that specific stem cell line. If the stem cell line was deposited before April 2010, the cell line will only be released to the supplicant in terms of an agreement or licence

¹⁶³ In terms of s 27(4) of the HTAct the closest qualifying relationship is as follows in descending order: (a) Spouse or partner; (b) Parent or child; (c) Brother or sister; (d) Grandparent or grandchild; (e) Child of a person falling within paragraph (c); (f) Stepfather or stepmother; (g) Half-brother or half-sister; and (h) Friend of long standing. In the event that there are two people of the same rank, only the consent of one of them is required.

¹⁶⁴ MRC Code of Practice 2010.

¹⁶⁵ R. 30 "Where this licence authorises the derivation of human embryonic stem cell lines: (a) a sample of all stem cell lines derived must be deposited in the UK Stem Cell Bank in accordance with any relevant Bank guidelines, and (b) the remainder of all stem cell lines (in so far as not used or destroyed as part of or in the course of the research project) must be deposited in the UK Stem Cell Bank or distributed in accordance with any relevant guidelines issued by the UK Stem Cell Bank." Eighth HFEA Code of Practice <[http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition\(Oct_2015\).pdf](http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition(Oct_2015).pdf)> (Accessed 9 September 2016).

¹⁶⁶ *Ibid.*

between the supplicant and the discoverer or originator, which regulates all intellectual property and aspects of ownership regarding that stem cell line.¹⁶⁷

It is important to note that this requirement means: that in the absence of intellectual property rights, human embryonic stem cells can be made available to anyone in the world. As the decision in *Brüstle v Greenpeace*¹⁶⁸ now prohibits the patentability of stem cell lines that are traced back to the destruction of an embryo in the EU, the only registered intellectual property rights that are available to the depositors of cells will be patents that are enforceable outside the EU.¹⁶⁹

Inside the EU, the steering committee provides access to valuable stem cell lines produced by those incautious enough to produce stem cell lines, without stating that the deposited cell “must be made available”, instead, they use the words “may be made available”.¹⁷⁰ This makes it clear that the final discretion to distribute the stem cells rests with the steering committee.¹⁷¹

The activities of the UK Stem Cell Bank are overseen by the steering committee, an independent national committee. The role of the steering committee is to support stem cell research and to ensure ethical and transparent practices.¹⁷² The steering committee is a non-statutory body that reports to the Medical Research Council annually and works closely with the Department of Health, HFEA, HTA and the MHRA.¹⁷³ Any legal force the steering committee has regarding the distribution of deposited stem cell lines is derived from section 26 of the HFE Act.¹⁷⁴ Even though

¹⁶⁷ Vertes *et al supra* n9 127 opine that the steering committee mistakenly conflates commercial rights with intellectual property rights by defining exploitation as ‘the process of turning patented invention into a commercial success’.

¹⁶⁸ *Brüstle v Greenpeace supra* n303

¹⁶⁹ Vertes *et al supra* n9 127.

¹⁷⁰ MRC Code of Practice 2010.

¹⁷¹ *Ibid*; MRC Code of Practice 2010.

¹⁷² UK Stem Cell Bank <<http://www.mrc.ac.uk/research/policies-and-resources-for-mrc-researchers/uk-stem-cell-bank-steering-committee/>> (Accessed 9 September 2016).

¹⁷³ MRC Code of Practice 2010.

¹⁷⁴ S 26 HFE Act: “(1) The Authority shall send a draft of the proposed first code of Procedure for practice under section 25 of this Act to the Secretary of State within twelve months of the commencement of section 5 of this Act. (2) If the Authority proposes to revise the code or, if the Secretary of State does not approve a draft of the proposed first code, to submit a further draft, the Authority shall send a draft of the revised code or, as the case may be, a further draft of the proposed first code to the Secretary of State. (3) Before preparing any draft, the Authority shall consult such persons as the Secretary of State may require it to consult and such other persons (if any) as it considers appropriate. (4) If the Secretary of State approves a draft, he shall lay it before

the HFE Act empowers the HFEA to authorise the derivation of stem cell lines from embryos intended for human application,¹⁷⁵ it does not empower the HFEA to licence activities related to the downstream derivation of cells from isolated human embryonic stem cells in general.¹⁷⁶

(b) Operation of the Bank

The storage of stem cell lines is well defined and documented.¹⁷⁷ It must take place under conditions that prevent the deterioration and cross-contamination of the stored material as far as possible.¹⁷⁸ The Bank further requires that all depositors and users of stem cell lines and other third-party service providers must have procedures in place (in compliance with the Q & S Regulations) for adverse events and the reporting thereof.¹⁷⁹

Therefore, it is imperative that all stem cells lines must have been tested for viability before accession to the Bank. On completion of the banking process, the depositor is offered a sample to evaluate the Bank's stock. Any deviation from the original sample will be discussed and an appropriate course of action will be decided on.¹⁸⁰

Parliament and, if he does not approve it, he shall give reasons to the Authority. (5) A draft approved by the Secretary of State shall come into force in accordance with directions.”

¹⁷⁵ S 12(2)(c) HFEA Act, amending the HFE Act.

¹⁷⁶ Vertes *et al supra* n9 128; Medical Research Council Code of Practice for the use of Human Stem Cell Lines 2010 <<http://www.mrc.ac.uk/documents/pdf/code-of-practice-for-the-use-of-human-stem-cell-lines/>> (Accessed 22 August 2016): “Unlike human embryos, embryonic stem cells do not have the potential to become a human person and do not therefore have the moral status of human embryo. Accordingly, the Government has passed legislation that establishes that research involving established stem cell lines does not need the same regulation to which embryo research is subjected by the HFEA. However, as the generation of embryonic stem cell lines involves the destruction of human embryos, oversight in the form of a steering committee was recommended to ensure that research performed is in keeping with the HFEA Regulations.”

¹⁷⁷ The bank ensures that for each cell line accessioned there is evidence of approval by the steering committee and that it is traceable with its steering committee reference number, and that any constraints imposed by the depositor regarding the use and release are well documented. Furthermore, the Bank requires evidence that informed consent has been obtained, as set out in section 9 of the MRC Code of Practice 2010.

¹⁷⁸ Medical Research Council *Code of Practice for the use of Human Stem Cell Lines April 2010* <<http://www.mrc.ac.uk/documents/pdf/code-of-practice-for-the-use-of-human-stem-cell-lines/>> (Accessed 22 August 2016).

¹⁷⁹ MRC Code of Practice 2010: This procedure entails the prevention of distribution of affected cell lines, communication of recall notices to all relevant parties, reconciliation of returned lines, storage quarantine and disposal of returned samples, and assuring appropriate action in relation to adverse event reporting in compliance with the above regulation.

¹⁸⁰ *Ibid.*

Once banking and testing has been completed, all information pertaining to the depositing, processing, testing, storage and distribution of each cell is held in the Cell Line Master File, which must be reviewed before the cell line's release for use.¹⁸¹ All the stem cell lines approved by the steering committee are listed in the "Stem cell Catalogue" on the UK Stem Cell Bank website, along with information regarding the depositor, the cell line and any ethical or consent restraints imposed by the depositor or donor.¹⁸²

5.2.3 Prohibitions and offences related to human tissue and stem cells

In terms of section 3 of the HFEA Act, no person shall bring about the creation, keep or use an embryo, except if it is done in pursuance of a licence. The HFEA Act amended section 3(2) of the HFE Act by saying that no person shall place in a woman any embryo, eggs or sperm, except for a permitted embryo, or permitted sperm or eggs.¹⁸³

Therefore, the derivation, keeping or use of embryonic stem cell lines without a licence (irrespective of whether the embryos contained genetic material from human origin or not) will be regarded as an offence in terms of section 29 of the HFEA Act. However, if the defendant acted under the direction of another with reasonable belief that the other person was at all material times the person responsible under the licence,¹⁸⁴ and had reasonable belief that he or she was authorised by virtue of a

¹⁸¹ *Ibid.*

¹⁸² *Ibid.*: "Once a cell line has been banked, tested and approved for release to researchers, its listing in the stem cell catalogue is amended to include scientific information and test data as well as any other pertinent information. The Bank's catalogue is different to the Steering Committee UK Stem Cell Line Registry which lists all the lines that have been approved by the Steering Committee for use in the UK, regardless of whether they are available from the Bank."; The website to the stem cell registry <<https://www.mrc.ac.uk/documents/pdf/uk-stem-cell-line-registry/>> (Accessed 9 September 2016).

¹⁸³ HFE Act 2008: Explanatory Notes par 29: "...permitted embryo is defined as an embryo which has been formed by the fertilisation of a permitted egg by a permitted sperm, whose nuclear or mitochondrial DNA has not been altered and which has not had cells added (except by division of the embryo's own cells). Permitted eggs are defined as eggs produced by or extracted from the ovaries of a woman and permitted sperm as sperm produced by or extracted from the testes of a man. These eggs and sperm must also not have been subject to any alterations to their nuclear or mitochondrial DNA. This clause ensures embryos created by artificial gametes or genetically modified gametes could not be placed in a woman. Similarly, genetically modified embryos or embryos created by cloning cannot be placed in a woman. This prevents reproductive cloning and supersedes the Human Reproductive Cloning Act 2001."

¹⁸⁴ A designated person by virtue of s 17(2) of the HFEA Act is a person to whom a licence applied, or a person who received directions under s 24(5A) to (5D).

licence or directions to perform the deed in question, he or she will be pardoned from a fine or imprisonment for a period not exceeding 10 years.¹⁸⁵

In terms of the section 8 of the HTAct, it is an offence to use donated material for a purpose which is not a qualifying purpose. In terms of section 16 of the HTAct, no person may remove or store relevant material from a human body (irrespective of whether the person is deceased or not) without an HTA licence.¹⁸⁶

Section 25(1) of the HTAct states that anyone performing any licenced activities (such as the removal of tissue from a human body in order to derive stem cell from it) in the absence of an HTA licence commits an offence, unless he or she reasonably believes that the activity is not covered by section 16 (in other words, the removal from or storage of relevant material from a human body or from a deceased body for purposes other than transplantation) or that he or she acted under the authority of an HTA licence.¹⁸⁷ If a person is found guilty of a section 25(1) offence, that person will be liable to a fine not exceeding the statutory maximum or imprisonment for three years, or both.¹⁸⁸

The primary offence in section 5 of the HTAct is aimed at the storing and using of tissues and cells. This offence is committed where a person commits a scheduled activity without the necessary specific consent required. However, no offence is committed if the person concerned reasonably believed that the activity was completed with appropriate consent or that the activity is not one requiring appropriate consent.¹⁸⁹

¹⁸⁵ S 29(10) of the HFEA Act.

¹⁸⁶ *Idem* at s 16(1) read with 16(2) of the HTAct; however, an activity is excluded if it relates to the body of a person who died before the day on which this section came into force or to material which comes from the body of such a person, and at least one hundred years have elapsed since the date of the person's death.

¹⁸⁷ *Idem* at s 25(1)(a) & (b).

¹⁸⁸ *Idem* at s 25(2).

¹⁸⁹ S 5(1)(a) & (b) of the HTA; Price 2005 *Mod L Rev* 809: "It was assumed that the main consent-based offences will not need to be invoked in practice, but considerable consternations were incited both outside and within parliament about the maximum penalties for these offences, which are punishable on conviction on indictment to a term of imprisonment of up to three years, a fine, or both. These were however perceived to be necessary to cater for flagrant and egregious breaches, characterised by the activities of Professor van Velzen, although intended almost exclusively as a deterrent."



Upon closer examination, it is evident that ambiguity strikes at the heart of the HTAct: Section 5(1) states that it is an offence for a person to perform an activity to which section 1(1) – (3) applies and section 1(1) states “The following activities shall be lawful if done with appropriate consent... (d) the storage for use for a purpose specified in Part 1 of Schedule 1 of any relevant material which has come from a human body.”

The problem arises when a person stores relevant material for a purpose that is not listed as a Schedule 1 purpose.¹⁹⁰ For example, in terms of section 1(1)(d), it should be decided whether the activity is simply the storage of relevant material of a human body, in which case the defendant would be guilty; or is it storage for a Part 1 Schedule 1 purpose, in which case the defendant would not be guilty under section 5 of the HTAct.¹⁹¹

Furthermore, the HTA Code of Practice for Consent describes the offences regarding the removing, storing or using of human tissue for scheduled purposes without appropriate consent.¹⁹² This makes it apparent that if the act is done for a scheduled purpose, an offence would have been committed; however, if not, no offence would have been committed.¹⁹³ Furthermore, the use of the word “lawful” in section 1 of the HTAct is unclear.

As Herring states¹⁹⁴ “Presumably the section means that the act will not be unlawful as contrary to the other provisions of the Act, and does not mean that an act under section 1 cannot be unlawful under other legislation or other parts of the law...”

In addition to the above offences, the HTAct has a number of other offences such as a false representation of consent, failure to obtain a death certificate, the analysis of DNA without consent and the trafficking of human tissue for transplantation.

¹⁹⁰ Herring *supra* n130 427.

¹⁹¹ *Ibid.*

¹⁹² HTA Consent Code of Practice.

¹⁹³ Herring *supra* n130 427.

¹⁹⁴ *Idem* at 428.

5.2.4 Summary for the procurement, storage and use of stem cells

Taking a step back to look at the overall framework that regulates the procurement, storage and use of stem cells, it is clear that the UK government's attempts to unify and simplify stem cell legislation achieved the opposite, which is the creation of a complicated maze-like regulatory framework. With various legal instruments and authorities playing a vital role in the development of stem cell therapies, researchers are often left with uncertainty as to where the remit of the HTA, the HFEA and the MHRA starts and ends.

It is clear that the removal of tissue for the procurement of stem cells is allowed in terms of the HTAct, which requires such acts to be performed with appropriate consent and in compliance with the quality and safety standards of the procurement, storage, processing and distribution, as set out in the Q & S Regulations.

For the derivation of embryonic stem cells, the HFE Act, the HFEA Act and its further amendments are applicable, in addition to the Q & S Regulations. The HFEA is concerned with the protection of potential human life. Therefore, the derivation of any stem cells involving the use or destruction of an embryo will fall within the remit of the HFEA.¹⁹⁵

Once the stem cells have been procured, the Q & S Regulations will find application regarding the further use, storage and distribution, etc. to ensure compliance with the necessary quality and safety standards for the use of human cells.¹⁹⁶ Furthermore, it is important to remember the function of the UK Stem Cell Bank as operated by the steering committee via their Code of Practice, which sets ancillary consent requirements and the condition that a sample of each embryonic stem cell line derived by research should be deposited in the Bank.

¹⁹⁵ Created by s 5 of the HFE Act, the Authority is an executive Non-Departmental Public Body sponsored by the Department of Health.

¹⁹⁶ Bell & Devaney 2007 *J Med Ethics* 621: "Once consent has been given to make the embryos available for research, however, two different standards may apply, first in relation to their handling in the laboratory and second in relation to any subsequent uses. If the stem cells are being derived for potential human application, then specific and very high laboratory standards regarding air quality, handling, temperature and quality control are imposed."

To clarify the uncertainties regarding the remit of each of the various authorities that regulate the whole production chain of stem cell therapies, the HTA, the HFEA and the MHRA issued a joint statement on 3 May 2007,¹⁹⁷ aiming to ensure the highest standards for the derivation of stem cells and their clinical application.¹⁹⁸ In this statement, the HFEA, HTA and the MHRA set out the bounds for each authority's remit stating that the HFEA is responsible for regulating the procurement of gametes and the associated processing involved in the creation of an embryo, including the derivation of stem cell lines, but it does not include the regulation of the stem cell lines themselves.

The HTA, under the Q & S Regulations, regulate the processing, storage and distribution of stem cell lines for human application. When deriving an embryonic stem cell line, the embryo is destroyed and the cells are separated from the embryo. At this junction, the remit of the HTA will find application and the HFEA regulatory remit ceases. After the embryonic stem cell line is established, it is a condition of all HFEA licences that a sample should be deposited in the UK Stem Cell Bank.¹⁹⁹

Up to this point in the discussion, stem cell lines have not come into contact with medicines regulation. However, once Master Cell Banks have been created with a reasonable prospect of clinical application in a medicinal product, these cells will fall within the remit of the MHRA.²⁰⁰

¹⁹⁷ HTA Position statement on regulating human embryonic stem cell lines for human application, as updated in August 2015 <http://www.biolink.org/home2/sites/files/hta_position_statement_on_regulating_humanembryonic_stem_cell_lines_for_human_application.pdf> (Accessed 9 September 2016).

¹⁹⁸ The abolishment of the HTA and the HFEA and the formation of a single, unified regulating authority was discussed in the UK (spring 2011). However, the opinion of Mahalatchimy *et al* 2012 *J Law & Soc* 137 is that the existence of two different authorities presents an advantage in differentiating between the different sets of rules applicable to human tissues and cells either as raw materials or as medicinal products once transformed by a bio-manufacturing process.

¹⁹⁹ R. 30 UK Stem Cell Bank 8th HFEA Code of Practice <[http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition\(Oct_2015\).pdf](http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition(Oct_2015).pdf)> (Accessed 9 September 2016).

²⁰⁰ *Ibid*; A master stem cell bank is a culture of fully characterised cells distributed into containers in a single operation, processed together in such a manner to ensure uniformity and stored in such a manner (usually – 70 degrees Celsius) to ensure stability. See the EU Guidance of Good Manufacturing Practice 2007 <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp> (Accessed 9 September 2016).

As the derivation, processing, use and storage of stem cells have been elucidated, the human application of such stem cells, as incorporated into medical products and therapies, will now be discussed.

5.3 Part II: Stem cells as advanced therapy medicinal products, clinical trials and marketing authorisation

5.3.1 Introduction

In the previous section of this dissertation, the procurement, storage and use of stem cells were discussed. At the point where the stem cells have been isolated and prepared to serve as medical starting material, the application of such cells for the production of medicinal products or therapies will bring such activities under the remit of the MHRA. In 2007, the EU adopted a *lex specialis*, Regulation (EC) NO 1394/2007 on advanced therapy medicinal products, which applies to the ATMPs prepared industrially or manufactured in such a way that it involves an industrial process.²⁰¹ As regenerative medicines such as ATMPs are considered to be high-risk products, they need to undergo clinical trials before they can be placed on the market. The next section will be dedicated to the exposition of the UK laws pertaining to clinical trials.

5.3.2 Clinical trials involving stem cell therapies and products

5.3.2.1 Authorising a clinical trial

EU Directive 2001/20/EC, as implemented in the UK by the UK Medicines for Human Use (Clinical Trials) Regulation 2004 No. 1031 (2004 UK CTR), primarily sets the standard and procedures for all clinical trials conducted in the UK to ensure quality, safety and efficacy in all medicinal products.

As of 28 May 2016, the new Clinical Trial Regulation 536/2014/EC (2014 EU CTR) was enacted by the European Commission to standardise safety and quality measures across the entire EU. However, as a transition period was established, all UK-based clinical trials will be regulated under UK 2004 CTR for three years after 28

²⁰¹ Article 2(1) of the ATMP Regulation: 'Advanced therapy medicinal product' means any of the following medicinal products or human use, which includes (1) a gene therapy medicinal product; (2) a somatic cell therapy product; and (3) tissue engineered product as set out by article 2(1)(b).

May 2016, if the application was submitted before 28 May 2016 or within one year after entering the application process and the sponsor opted for the old system.

Therefore, most of the therapies currently undergoing clinical trials will be regulated by the 2004 UK CTR, which implements the EU Directive 2001/20/EC into UK law.²⁰² The key changes brought about by the 2014 EU CTR will be highlighted in further on in this dissertation. However, emphasis is placed on the requirements of the 2004 UK legislation, as most of the current clinical trials in process are regulated under the EU Directive 2001/20/EC as incorporated by the 2004 UK CTR. The 2004 UK CTR institutes the establishment of Research Ethics Committee (REC) and states that no clinical trial may be initiated without a favourable opinion of an REC and the authorisation of the MHRA.²⁰³ Two central rules apply to clinical trials involving ATMPs. Firstly, the 60-day decision period regarding an opinion from an REC subsequent to a valid trial application may be extended to 90 days if the product is based on human body elements and may be extended by a further 90 days if consultation with the MHRA is deemed necessary.²⁰⁴

Secondly, the decision regarding the success of the clinical trial application has to be communicated to the sponsor of the clinical trial. While the non-opposition of the MHRA is usually sufficient to initiate a clinical trial, an explicit written authorisation is required for trials regarding ATMPs, as they are perceived to be of high risk.²⁰⁵

²⁰² Commission Directive 2005/28/EC of 8 April regarding good clinical practice with respect to the investigation of medicinal products for human use, as well as the requirements for the authorisation of manufacturing or importation of such products, will find application until the end of the transitory period.

²⁰³ Reg 12(1) & (2) read with sub-reg 12(3) of the 2004 UK CTR; In terms of Article 4 of the 2014 EU CTR: "A clinical trial shall be subject to scientific and ethical review and shall be authorised in accordance with this Regulation. The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7 as appropriate for each Member State concerned."

²⁰⁴ *Idem* at reg 15(1) states that an ethics committee shall give an opinion in relation to the clinical trial within the specified period, which, in the case of somatic cell therapy or a gene therapy product, can be 180 days if a specialist group or committee is consulted, or if no such consultation has to be made, is 90 days; Vertes *et al supra* n9 131: "...in the case of a xenogeneic cell therapy, there is no time limit to the authorisation period."

²⁰⁵ *Idem* at reg 19(2): "Subject to the following provisions of this regulation, the licensing authority may, within the period of 30 days from the date of receipt of a valid request for authorisation of a clinical trial to which this regulation applies- (a) issue a written authorisation to the sponsor; or (b) give a notice in writing to the sponsor setting out the grounds for not accepting the request; Mahalatchimy *et al* 2012 *J Law & Soc* 138.

In the United Kingdom, a specialist advisory committee, the Gene Therapy Advisory Committee (GTAC), is the appropriate committee charged with the ethical oversight of research involving gene therapy, embryonic stem cell therapy, cell therapies based on existing stem cell lines, the therapeutic use of genetically modified cells or therapeutic xenotransplantation.²⁰⁶

By now, it should be apparent that stem cell technologies do not fall under the regulation of conventional medicinal modalities. Therefore, the 2004 UK CTR requires a separate authorisation procedure for medicinal products involving gene therapy, somatic cell therapy (including xenogeneic cell therapy) and genetically modified organisms.²⁰⁷ This can be done by using the new Integrated Research Application System [IRAS], which is a single system for application and approval of health care research in the UK.²⁰⁸

After the GTAC and the MHRA have authorised a clinical trial involving embryonic stem cells, existing stem cell lines, gene therapy and xenogeneic cells, the clinical trial may be conducted lawfully, on condition that it should comply with the prescriptions of good manufacturing practice, pharmacovigilance, etc. as set out below.

5.3.2.2 Clinical trial requirements relating to good clinical practice, pharmacovigilance, manufacture and importation of investigational medicinal products in the UK

(a) Good clinical practice

In terms of Part IV of the 2004 UK CTR, all clinical trials must be conducted in terms of the conditions and principles of good clinical practice (GCP).²⁰⁹ In doing so, the sponsor must install and maintain arrangements to ensure compliance with the

²⁰⁶ Reg 12(3)(a) states that a favourable opinion is required from an ethics committee or an appeal panel appointed in terms of Schedule 4 of the 2004 UK CTR. Furthermore, reg 19(5) of the 2004 UK CTR states: "An application for an ethics committee opinion in relation to a clinical trial involving medicinal products for gene therapy, other than a trial falling within paragraph (4), shall be made to the Gene Therapy Advisory Committee."

²⁰⁷ *Idem* at reg 19 of the 2004 UK CTR.

²⁰⁸ The IRAS system is provided throughout the UK by the Health Research Authority and its partners, such as the HFEA, MHRA, GTAC to name only a few. <<http://www.hra.nhs.uk/resources/applying-for-reviews/integrated-research-application-system-iras/>> (Accessed 17 September 2016).

²⁰⁹ Reg 28(1) of the 2004 UK CTR.

requirements of GCP.²¹⁰ This translates into the fact that no person may conduct a clinical trial outside the terms of the protocol for that clinical trial,²¹¹ the request for authorisation to conduct that trial, the application made for a favourable ethical opinion, any other conditions imposed by the MHRA,²¹² and particulars or documents other than the protocol which supplemented the application or request for authorisation.²¹³ The sponsor and the medical investigator may take urgent safety measures to protect the subjects of the trial against any immediate health or safety hazard. In doing so, the sponsor must inform the licensing authority and appropriate REC of such measures within three days from taking such measures.²¹⁴

If the MHRA is not satisfied that the stem cell clinical trial is being conducted in terms of all conditions, restrictions or limitations applicable to the clinical trial, it may give written notice that the trial or certain conduct in terms of the trial may be suspended or terminated.²¹⁵ However, before issuing such a notice, the MHRA must inform the sponsor or the investigator of its intention of suspension or termination of the trial, setting out reasons for such termination.²¹⁶ After issuing a notice of suspension or termination of the clinical trial, the MHRA is charged with informing the competent authorities of each EEA (other than the UK), the relevant ethics committee, the European Medicines Agency (EMA) and the European Commission.

Schedule 1 of the 2004 UK CTR sets out the conditions and principles of GCP and the protection of clinical trial subjects. It is mostly designed to comply with the Principles of the International Conference of Harmonisation GCP Guideline.²¹⁷ In addition to ensuring the credibility of the clinical trial data, compliance with GCP

²¹⁰ *Idem* at reg 28(2).

²¹¹ As may be amended in terms of reg 22 to 25 of the 2004 UK CTR.

²¹² In terms of reg 18(2) or (6), 19(8), 20(5), 24(4) or Schedule 5 of the 2004 UK CTR.

²¹³ *Idem* at reg 29.

²¹⁴ *Idem* at reg 30.

²¹⁵ *Idem* at reg 31, this is also true if the licensing authority has information that raises doubt regarding the safety of scientific validity of the trial, or the conduct of the trial at a particular trial site.

²¹⁶ This requirement may be disregarded if the Authority feels that the trial poses an imminent risk to the health and safety of any of the subjects of the clinical trial.

²¹⁷ ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 R. 1 of 10 June 1996, was incorporated to provide a unified set of standards for the EU, Japan and the USA to facilitate the mutual acceptance of clinical data by the regulatory authorities
<http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf> (Accessed 17 September 2016).

standards guarantees protection of the rights, safety and well-being of research participants in accordance with the Declaration of Helsinki.²¹⁸

In addition to revolutionising the existing rules on clinical trials, ATMPs require from the European Commission to produce all-encompassing guidelines pertaining to GCP for ATMP, after which they set out the detailed guidelines at the end of 2009 (ATMP GCP Guidelines).²¹⁹ The ATMP GCP Guidelines supplement rather than replace the Good Clinical Practice Directive 2005/28/EC of 8 April 2005 and should be read in conjunction with the detailed guidelines as set out in Volume 10 of *Eudralex* (the Rules governing Medicinal Products in the European Union). The ATMP sets the tone for the ATMP Regulation as it sets out legislative boundaries for the remit of different authorities, such as the fact that the Q & S Regulations will only find application to the donation, procurement and testing of advanced therapy investigational medicinal products (IMP). Furthermore, the ATMP GCP Guidelines provide a concise method for understanding the regulatory requirements for the protocol and follow up.²²⁰

(b) *Pharmacovigilance*

Pharmacovigilance (PV) is related to the detection, assessment, understanding and prevention of adverse effects. Part 5 of the 2004 UK CTR sets out the requirements for PV. If a serious adverse event takes place, the investigator is obliged to notify the sponsor immediately, which should be followed by a written report of the serious adverse event.²²¹ The sponsor of the clinical trial is obliged to keep all records of all adverse events relating to the clinical trial, which may be requested by the MHRA by way of a notice. Moreover, the sponsor must also ensure that all relevant information regarding a serious adverse reaction is recorded and reported to the MHRA and the

²¹⁸ *Ibid.*

²¹⁹ European Commission *Detailed guidelines on good clinical practice specific to advanced therapy medicinal products* <http://ec.europa.eu/health/files/eudralex/vol-10/2009_11_03_guideline.pdf> (Accessed 19 September 2016).

²²⁰ Vertes *et al supra* n9 132.

²²¹ *Idem* at reg 3: a “serious adverse event”, “serious adverse reaction” or “unexpected serious adverse reaction” means any adverse event, adverse reaction or unexpected adverse reaction, that- (a) results in death, (b) is life threatening, (c) requires hospitalisation or prolongation of existing hospitalisation, (d) results in persistent or significant disability or incapacity, or (e) consists of a congenital abnormality or birth defect.

competent authorities of all other EEAs, as well the relevant ethics committee, as soon as possible within seven days after becoming aware of the reaction.²²²

After each reporting year,²²³ in relation to each IMP tested in a clinical trial,²²⁴ the sponsor must furnish the MHRA and the relevant ethics committees (in this case the GTAC) with a list of all the suspected adverse reactions that have occurred and submit a report on the safety of the subjects of those trials.²²⁵

(c) Manufacturing and supply of investigational medicinal products

According to the 2004 UK CTR, an IMP is defined as:²²⁶

a pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorization but is, for the purposes of the trial- (a) used or assembled (formulated or packaged) in a way different from the form of the product authorized under the authorization, (b) used for an indication not included in the summary of product characteristics under the authorization for that product, or (c) used to gain further information about the form of that product as authorised under the authorization.

Like all medicinal products, IMPs are subject to manufacturing and importation requirements. Therefore, any new medicinal modality to be developed, such as a stem cell therapy, falls within the definition of an IMP and should comply with the provisions of Regulation 13 and Part 6 of the 2004 UK CTR regarding the

²²² *Idem* at reg 33(1); The sponsor can fulfil his duty to report by entering the report or information in the European database established in terms of Article 11 of Directive 2001/83/EC.

²²³ *Idem* at reg 35(2) states: The “reporting year”, in relation to an IMP, means “the year ending on the anniversary of- (a) in the case of a product which has a marketing authorization, the earliest date on which any such authorization relating to that product was granted or issued; or (b) in any other case, the earliest date on which any clinical trial- (i) relating to that product, and (ii) for which the person responsible for making the report was the sponsor, was authorised in an EEA State.”

²²⁴ Reg 2 of the 2004 UK CTR: “investigational medicinal product” means a pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorization but is, for the purposes of the trial- (a) used or assembled (formulated or packaged) in a way different from the form of the product authorized under the authorization, (b) used for an indication not included in the summary of product characteristics under the authorization for that product, or (c) used to gain further information about the form of that product as authorized under the authorization.”

²²⁵ *Idem* at reg 35(1).

²²⁶ *Idem* at reg 2.

manufacturing and importation of IMPs.²²⁷ In terms of regulation 36(1) of the 2004 UK CTR, no person may manufacture, assemble or import any IMP if they do not have a manufacturing authorisation.²²⁸ It is further a general requirement of all clinical trials and an obligation upon the holder of a manufacturing authorisation that there should be compliance with the principles and guidelines of good manufacturing practice (GMP).²²⁹

As stated in Regulation 2 of the 2004 UK CTR, the principles and guidelines of good manufacturing practice mean those principles and guidelines as set out by Commission Directive 2003/94/EC.²³⁰ These guidelines were published by the Commission's Directorate General of Health and Consumers (DG SANCO) as Volume 4 (which consists of three parts) of the labyrinthine *Rules Governing Medicinal Products in the European Union*.²³¹ The first part of Volume 4 pertains to the basic GMP requirements for medicinal products; the second part pertains to the GMP for *active substances used as starting materials* and the third part is a set of GMP-related documents. The GMP rules for ATMPs as medicinal products are stated in Annex 2, as incorporated by means of the ATMP Regulation, which required from the European Commission to set up guidelines for GMP relating to ATMP. Annex 2 is entitled *Manufacture of Biological Active Substances and Medicinal Products for Human Use* (the ATMP GMP guidelines).²³²

²²⁷ Vertes *et al supra* n9 129: "EU Member States are obliged to "take all appropriate measures to ensure that the manufacture of the medicinal product within their territory is subject to the holding of an authorisation."

²²⁸ However, reg 36(1) provides a caveat, stating that if it is done in terms of the marketing authorisation of that specific product, no manufacturing authorisation is required, and if it is done in terms of reg 37, there is exemption for hospitals and health centres, which will be discussed in due course.

²²⁹ Par 12(a) of Part 2 of Schedule 1 of the 2004 UK CTR.

²³⁰ Article 47 of Directive 2003/94/EC mandates compliance with Good Manufacturing Practice and it requires the Commission to publish detailed supplementary guidelines and to revise them as necessary to take account of all technical and scientific progress.

²³¹ Vertes *et al supra* n9 130.

²³² The ATMP GMP is divided into two parts. Part A sets out general considerations pertaining to the manufacturing of biologically active substances and medicinal products. It provides detailed instructions regarding personnel, the premises and the equipment to be used, the production and starting materials, appropriate seed lot and bank systems, operation principles and quality control. Part B is centred around specific types of bio-active substances and medicinal products, setting out each class of ATMP, including areas where new ATMP could emerge <http://ec.europa.eu/health/files/eudralex/vol-4/vol4-an2__2012-06_en.pdf> (Accessed 19 September 2016).

Furthermore, regulation 13 of the 2004 UK CTR states that no person shall sell or supply any IMP to an investigator or a healthcare practitioner forming part of an investigator's team, anyone under the direction or control of such medical practitioners or investigators, or a subject of a clinical trial with the aim of administering such IMP in a clinical trial, without complying with the following conditions:

1. The MHRA should have authorised the clinical trial for the purpose of which the IMP is sold or supplied.
2. If the IMP is manufactured or assembled in an EEA other than in accordance with marketing authorisation of that product, or imported into such EEA, that product will have to be manufactured, assembled or imported in terms of manufacturing authorisation as set out by Part 6 of the 2004 UK CTR, or in terms of authorisation granted by a competent authority of another EEA other than the MHRA, as set out in Article 13 of Directive 2001/20/EC.²³³

Regulation 37 of 2004 UK CTR makes a very important exemption regarding the need for manufacturing authorisation as envisaged by regulation 36(1) by stating that the need for marketing authorisation can be disregarded:²³⁴

1. if the IMP is assembled in a hospital or healthcare centre,
2. by a doctor, a pharmacist, or a person acting under such supervision, and
3. if the IMP is assembled for the exclusive use in that hospital or health centre, or any other hospital or health centre that is regarded as a clinical trial site for which that product will be used.

5.3.3 The 2014 EU Clinical Trial Regulation

5.3.3.1 Rationale for the adoption of the 2014 EU Clinical Trial Regulations

The 2014 EU CTR was enacted on 16 June 2014. However, it only came into force on 28 May 2016. One of the key changes to the existing regime is that the 2014 EU

²³³ If an IMP has been manufactured or imported prior to 1 May 2004- (a) the manufacturing authorization will only apply in relation to the assembly of that product which takes place on or after that date, and there will be no need to verify and certify the production batch.

²³⁴ This exemption is in line with the ATMP Regulation.

CTR strives to improve the EU's continued focus on market optimisation.²³⁵ Experience under Directive 2001/20/EC (CTD), the EU clinical trials directive and its varying application across the now 28 member states (which were only 15 at the time of the CTD's incorporation) showed that it undermines the progress of scientific research, which warranted a change.²³⁶

Due to the regulatory differences in the various member states, clinical trials operating at various trial sites in the different member states had to comply with different regulatory requirements, which undermined both academic and non-academic research.²³⁷ Science is advancing in the direction that requires a large number of patient populations, for instance based on certain genomic information.

Therefore, to include a sufficient number of research participants in the study, it may be necessary to operate across many or all of the member states.²³⁸ The adoption of the 2014 EU CTR, being a regulation and not a directive, would provide a distinct advantage for clinical trial sponsors and investigators, as multi-state trials can now rely on the provisions of the regulation directly.²³⁹

In summary, the 2014 EU CTR provides uniformity and enhances efficacy across the EU. In the event that a clinical trial is carried out in a non-EEA and the therapy or product is intended for EU marketing authorisation, that trial has to comply with the 2014 EU CTR and subsequent marketing authorisation procedures of the EU.²⁴⁰

²³⁵ Flear "The EU Clinical Trial Regulation: key priorities, purposes and aims and the implications for public health" 2016 *J Med Ethics* 192. In his paper, Flear argues that the fact that the 2014 EU CTR optimises the pharmaceutical production pipeline is a cause for concern, as this fact causes concern for the achievement of public health objectives.

²³⁶ *Idem* at reg 193.

²³⁷ European Commission 10 December *Safe, innovative and accessible medicines: a renewed vision for the pharmaceutical sector* COM 2008 666 <<http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52008DC0666&from=en>> (Accessed 27 September 2016).

²³⁸ Jackson *Law and the regulation of medicines* (2012) ch 8.

²³⁹ Article 288 of the Treaty on the Functioning of the European Union states the definition of a *directive* and a *regulation*: "To exercise the Union's competences, the institutions shall adopt regulations, directives, decisions, recommendations and opinions; a regulation shall have general application. It shall be binding in its entirety and directly applicable in all Member States; a directive shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods; a decision shall be binding in its entirety. A decision which specifies those to whom it is addressed shall be binding only on them; Recommendations and opinions shall have no binding force."

²⁴⁰ Such as the ATMP Regulation.

5.3.3.2 Summary of changes under the 2014 EU Clinical Trial Regulation

As the rationale of the 2014 EU CTR was based on both ethical and scientific grounds, in an attempt to protect human research subjects and to facilitate the production pipeline of medicinal products within the EU, the 2014 EU CTR introduces a few key changes in the regulation of clinical trials in the EU.²⁴¹

First, the 2014 EU CTR introduces a centralised application procedure with a single portal for the submission of a clinical trial application for authorisation by a reporting member state.²⁴² The application is based on a single set of documents, split into two parts. Part I focuses on the necessity of the trial and a risk-benefit assessment regarding human participation in the trial.²⁴³ Part II focuses on compliance with the principles of informed consent, the recruitment of subjects, compensation and remuneration, data protection, and the suitability of those conducting the trial and trial sites.²⁴⁴

The Regulation also provides more legal certainty for small- and medium-sized enterprises and academics by extending the tacit agreement principle to the entire authorisation process.²⁴⁵ As previously stated, in terms of the CTD, as transposed into UK law by the 2004 UK CTR, the express written authorisation of the MHRA was required before a trial regarding ATMPs can commence. In terms of the 2014 EU CTR, if the reporting member state has not notified the sponsor of the success of the application within 10 days of submission, the clinical trial applied for shall be deemed to fall within the scope of the 2014 EU CTR and the application dossier shall be considered complete.²⁴⁶

²⁴¹ Reg 19(2) of the 2004 UK CTR: “Subject to the following provisions of this regulation, the licensing authority may, within the period of 30 days from the date of receipt of a valid request for authorisation of a clinical trial to which this regulation applies- (a) issue a written authorisation to the sponsor; or (b) give a notice in writing to the sponsor setting out the grounds for not accepting the request; Flear 2016 *J Med Ethics* 194.

²⁴² Article 2(12) of the 2014 EU CTR: “‘Member State concerned’ means the Member State where an application for authorisation of a clinical trial or of a substantial modification has been submitted under Chapters II or III of this Regulation respectively”; Article 5 of the 2014 EU CTR “Submission of an application, Article 16 “Authorisation procedure for a substantial modification of a clinical trial”, Article 80 “EU portal” of the 2014 EU CTR.

²⁴³ Article 6 read with Chapter V of the 2014 EU CTR- Part 1 is led by the reporting member state and jointly assessed by all member states that have trial sites.

²⁴⁴ Flear 2016 *J Med Ethics* 194.

²⁴⁵ *Ibid.*

²⁴⁶ Article 5(4) of the 2014 EU CTR: “Where the reporting Member State has not notified the sponsor within the period referred to in the first subparagraph of paragraph 3, the clinical trial applied for shall be deemed to fall within the scope of this Regulation and the application dossier shall be considered complete.”; Unlike the 2004 UK CTR, the 2014 EU CTR states in article 6(4) read with

The reporting of clinical trial results are also made easier by submitting them via the EU portal for storage on the EU clinical trial database, improving transparency by means of public availability.²⁴⁷ It is also important to note that the oversight and enforcement of EU law on clinical trials outside the EU have been strengthened by means of Chapter XIII of the 2014 EU CTR.²⁴⁸ Furthermore, authorisation applications for clinical trials referring to data derived from trials conducted outside the EU must ensure that those trials conducted outside the EU comply with the standards similar to those found in the 2014 EU CTR.²⁴⁹

5.3.3.3 Marketing authorisation of advanced therapy medicinal products

Anyone aiming to put an ATMP on the market will need marketing authorisation. Although the authorisation of an ATMP is similar to that of other biological medicinal products, the unique attributes of ATMPs provide for the consequential difference in marketing authorisation from the more orthodox chemical entities and their marketing authorisation.

On 13 November 2007, the EU adopted a *lex specialis*,²⁵⁰ the ATMP Regulation, to amend the existing Medicinal Product Directive, Commission Directive 2001/83/EC, to insert a new category of medicinal products, called ATMP.²⁵¹ The ATMP Regulation rationale is to provide uniform technical standards on quality and safety

sub-article (7) that the reporting member state must submit the final Part 1 of the assessment report and its conclusion to the sponsor within 45 days of the validation date, which may be extended for a further 50 days if the clinical trial involves ATMP for the purpose of consulting with experts where the clinical trial involves an ATMP IMP, a medicinal product as defined in point 1 of the Annex to Regulation (EC) No 726/2004 for the purpose of consulting with experts. In such case, the periods referred to in paragraphs 5 and 8 of this article shall apply *mutatis mutandis*.

²⁴⁷ Article 37(4) of the 2014 EU CTR: “Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. The content of that summary is set out in Annex IV.”

²⁴⁸ Chapter XIII “Supervision by Member States, Union Inspections and Controls” of the 2014 EU CTR.

²⁴⁹ Article 25(5) of the 2014 EU CTR.

²⁵⁰ In Latin, “*lex specialis*” comes from the legal maxim “*lex specialis derogate legi generali*”. A “*lex specialis*” is a “law” pertaining to a specific subject matter. The Maxim means that a law governing a specific matter should take precedence over a law that governs general application. Therefore, in terms of ATMP, Regulation 1394/2007 will override general EU pharmaceutical legislation, such as Directive 2001/83/EC relating to medicinal products for human use.

²⁵¹ Mahalatchimy *et al* 2012 *J Law & Soc* 140; Favale & Plomer 2009 “Fundamental Disjunctions in the EU Legal Order on Human Tissue, Cells & Advanced Regenerative Therapies” *Maastricht J Eur & Comp L* 89, 109; Vertes *et al supra* n9 133.

for bioengineered products; centralised procedures for marketing authorisation through the EMA;²⁵² and uniform procedures on post-authorisation PV.²⁵³ Furthermore, the ATMP Regulation institutes a new interdisciplinary advisory expert committee on ATMPs, the Committee for Advanced Therapies (CAT)²⁵⁴ that is responsible for preparing scientific expert opinions regarding the quality, safety and efficacy of each ATMP for final approval by the EMA²⁵⁵ and for consulting with the committee for Medicinal Products for Human Use.²⁵⁶

It should be noted that the ATMP Regulation was not introduced to clamp down on improper conduct or products, but rather to harmonise the approach to ATMPs throughout the EU and to facilitate Europe as a location for the development of ATMP.²⁵⁷

Most of the arrangements in the ATMP Regulation are aimed at harmonising technical standards on health and safety across member states.²⁵⁸ Since the

²⁵² Ch 3 ATMP Regulation; Mahalatchimy *et al* 2012 *J Law & Soc* 140: This centralised authorisation procedure entails that, once authorised, products may be made available throughout member states without recourse to separate national marketing authorisations.

²⁵³ *Idem* at ch 5.

²⁵⁴ *Idem* at ch 7.

²⁵⁵ *Idem* at article 8(2).

²⁵⁶ *Idem* at article 8(1) & 8(3); Klug *et al* "Regulatory Structures for Gene Therapy Medicinal Products in the European Union" 2012 *Methods Enzymol* 342: "When developing the ATMP Regulation, it was realized that ATMPs pose new questions and challenges to both developers and regulators and that expertise to review ATMPs is not specifically represented in the main scientific committee at the EMA. Therefore, the ATMP Regulation identifies the necessary expertise, relevant to ATMPs, to be represented in the CAT: ..., tissue engineering, gene therapy, cell therapy... The CAT is the first scientific committee where the legislation requires that certain specific scientific expertise be represented. This is a clear acknowledgement of the specific nature of the ATMPs and the need for a multidisciplinary expert Committee to provide for an adequate, high-level evaluation of ATMPs."

²⁵⁷ The main objectives of the ATMP Regulation as set out in the commission staff working document - Annex to the proposal for a regulation on advanced therapy medicinal products impact assessment, are to guarantee a high level of health protection for European patients treated with advanced therapies, to harmonise market access for advanced therapies and improve the functioning of the internal market by establishing a tailored and comprehensive regulatory framework for the authorisation, supervision and post-authorisation vigilance of these products, to foster the competitiveness of European undertakings operating in this field, to provide overall legal certainty, while allowing for sufficient flexibility at technical level in order to keep the pace with the evolution of science and technology. <<http://eur-lex.europa.eu/legal/content/EN/TXT/?uri=celex%3A52005SC1444>> (Accessed 19 September 2016); Vertes *et al supra* n9 133.

²⁵⁸ Faulkner 2016 "Opening the gateways to market and adoption of regenerative medicine? The UK case in context" *Regen Med* 323: "The safety standards differ somewhat from the accepted pharmaceutical regime, partly because of the novel modes of action of regenerative products and the need to take account of aspects such as potency;"

adoption of the ATMP Regulation, four different biological medicinal products are regulated at EU level:

1. Gene therapy Medicinal Products (GTMPs)
2. Somatic cell therapy medicinal products (CTMP)
3. Tissue-engineered products (TEP)
4. Combined ATMP, which is a combination of an advanced therapy with a medical device.

For help with the classification of such products, the EMA provides informal scientific recommendations.²⁵⁹

5.3.3.4 Scope of the ATMP Regulation

The ATMP Regulation will find application in the following instances:

1. If the cells are human
2. If the cells are viable
3. If the cells are either classified as a TEP, a GTMP or a CTMP
4. If these products are prepared industrially or manufactured by a method involving an industrial process²⁶⁰
5. If the products are placed on the market²⁶¹

As the first two requirements are not in contention, the following section will rather focus on the last two requirements as set out by points 3, 4 and 5 above.

(a) Industrial process?

Unsurprisingly, there are some difficulties in determining whether a product falls under the Regulation or not. In an effort to clarify what is regarded as an “industrial process”, the European Commission said the following:

This should cover, inter alia: any ‘mass production’ of advanced therapy products for allogeneic use (batch production, ‘on the shelf’ products, etc.); any advanced therapy

²⁵⁹ Article 17 of the ATMP Regulation.

²⁶⁰ *Idem* at Preamble (6); Faulkner 2016 *Regen Med* 323.

²⁶¹ Article 2 of the Medicinal Products Directive 2001/83/EC.

product for autologous use which, although being patient-specific by definition, is manufactured in accordance with a standardised and industrial process

Closer investigation of the definition of an industrial process revealed certain instances where the production of stem cell therapies would not constitute an industrial process. Therefore, this classificatory distinction is decisive in terms of the status and responsibilities of the producers of stem cell products and therapies.²⁶² Very little is said about what is to be regarded an industrially produced product. However, the *travaux préparatoires*²⁶³ and decisions from the CAT indicate clearly that this is a legislative requirement.²⁶⁴ It would appear that this definition implies that some therapies may be produced outside the scope of conventional pharmaceutical productions, which gave rise to the infamous hospital exemption.²⁶⁵

(b) *Placed on the market?*

Before a stem cell therapy can qualify as an ATMP, it must be intended for the market. In terms of medical devices, “‘placing on the market’ means the first making available in return for payment or free of charge... with a view to *distribution and/or use in the community market.*”²⁶⁶ There is no definitive law stating what could be regarded as placed on the market for medicinal products.

However, the Guide to the Implementation of Directives Based on the New Approach and the Global Approach (Blue Guide)²⁶⁷ provides some assistance by stating that:²⁶⁸

Placing on the market takes place when the product is transferred from the stage of manufacture with the intention of distribution or use on the Community market... The transfer can consist of a physical hand-over or be based on a legal transaction. It can

²⁶² Mahalatchimy *et al* 2012 *J Law & Soc* 140.

²⁶³ French for “preparatory works.”

²⁶⁴ Vertes *et al supra* n9 135-136.

²⁶⁵ Faulkner 2016 *Regen Med* 323: “The ‘industrial’ definition implied that some therapies would be allowed to be produced outside the conventional pharmaceutical batch production, and thus the famous, if not by now infamous, ‘hospital exemption’ was created.”

²⁶⁶ *Ibid*; Article 1(2)(h) of the Medical Device Directive 92/42/EC.

²⁶⁷ Commission Notice the ‘Blue Guide’ on the implementation of EU product rules 2016 <<http://ec.europa.eu/DocsRoom/documents/12661/attachments/1/translations/en/renditions/native>> (Accessed 20 September 2016).

²⁶⁸ Vollebregt & Klümper 2011 “To place on the market (or not)?” *Regulatoryaffairsmtech.com* <<http://www.gtlaw.com/portaresource/vollebregtmeddevice2>> (Accessed 20 September 2016); Vertes *et al supra* n9 136.

relate to the ownership, the possession or any other right transferred from the manufacturer to a distributor or to the end user. A transfer of a product is considered to have taken place e.g. when it is sold, leased, given as a gift, rented or hired. Where a manufacturer operates its own distinct distribution chain, the transfer can also occur to that distribution chain.

A more unequivocal definition for “placing on the market” is provided by the Market Surveillance Regulation 765/2008 of 9 July 2008, which states that it is the “first making available of a product on the community market”, which is defined as “any supply of a product for distribution, consumption or use on the Community market in the course of a commercial activity whether in return for payment or free of charge.”²⁶⁹

(c) *Tissue-engineered product?*

Since the passing of the ATMP Regulation, it was reiterated that it should not apply to transplants. Even though efforts were made to narrow down the exact definition of TEPs, it is still unclear when bone marrow transplants and other stem cell transplants are regarded as TEPs.²⁷⁰ This is evident when looking at the number of TEPs that have been centrally approved in the EU, both of which are autologous cartilage cells used in adults to repair damage of the cartilage in the knee.²⁷¹ The definition of TEP can be found in the Medicinal Products Directive, Article 2 of the ATMP Regulation, which states:

A TEP means a product that: contains or consists of engineered cells or tissue, and is presented as having properties for, or is used in or administered to human beings. A tissue engineered product may contain cells or tissues of human or animal origin, or both. These cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, bio-materials chemical substances, scaffolds or matrices.

²⁶⁹ Article 1 of the Market Surveillance Regulation 765/2008 of 9 July 2008; Recital 8 of the ATMP Regulation emphasises this fact as it states that: “in accordance with the principles of a *lex specialis*, this Regulation should apply only in so far as there are no specific provisions with the same objective, nature or effect in other existing or future rules of Community harmonisation legislation.”

²⁷⁰ Vertes *et al supra* n9 133.

²⁷¹ One is Chondrocelect, a TEP indicated for repairing single symptomatic cartilage defects of the femoral condyle of the knee in adults and is a suspension of cultured autologous cartilage cells. The second, MACI, is a combined ATMP indicated for the repair of symptomatic, full thickness cartilage defects of the knee in skeletally mature adult patients, consisting of autologous cartilage cells cultivated on a collagen membrane.

Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

It should be noted that it is the intended mode of action, such as the treating, preventing or diagnosis of a disease of CTMPs, as opposed to the regeneration of TEP that will distinguish it as either a TEPs or a CTMPs.²⁷² Granting the fact that autologous stem cells are administered to patients with the purpose of regenerating, repairing or replacing human tissue or cells, the question to ask is if the cells were engineered? Cells or tissues shall be considered engineered if they fulfil at least one of the following conditions:²⁷³

- a. If the cells or tissues have been subjected to substantial manipulation so that the biological characteristics, physiological functions or structural properties relevant for intended regeneration, repair or replacement are achieved;²⁷⁴ or
- b. If the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

Notably, the ATMP Regulation applies to cells used in an autologous manner, notwithstanding the use of wording such as “donor” and “recipient” in Article 2(3) of the ATMP Regulation and Part IV of Annex 1 to the Medicinal Product Directive 2001/83/EC.²⁷⁵ The list of excluded manipulations set out in Annex 1 of the ATMP Regulation suggests that isolated or concentrated cell populations would not suffice to constitute “substantial manipulation” to fall under a TEP.²⁷⁶

²⁷² Ram-Liebig *et al* “Regulatory challenges for autologous tissue engineered products on their way from bench to bedside in Europe” 2015 *Advanced Drug Delivery Reviews* 182 : “While somatic cell therapy medicinal products are intended to treat or prevent a disease or to make a diagnosis through pharmacological, metabolic, and/or immunological action, the claim of TEP is to regenerate, repair, or replace human tissues.”

²⁷³ Article 2(1)(c) of the ATMP Regulation.

²⁷⁴ Jekerle *et al* “Legal Basis of the Advanced Therapies Regulation” 2010 *Bundesgesundheitsblatt* 4-8; Excluded from substantial manipulation, is the listed Annexure 1 Manipulations of the ATMP Regulation, such as “cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification.”

²⁷⁵ Vertes *et al supra* n9 134.

²⁷⁶ *Ibid*.

In making classificatory decisions regarding TEPs, the CAT held, on occasion, that the extraction of sub-populations of stem cells for autologous use (such as CD133+ bone marrow cells) does not constitute substantial manipulation, but if the cells are not for homologous use (such as haematological restoration), the cells will be regarded as engineered (see the section below).²⁷⁷ A cell will only be regarded as substantially manipulated and fulfil the criteria of TEP if the cell's relevant biological characteristics, physiological functions or structural properties have been changed and are applied for a non-homologous use. In view of the above, it is evident that, in most cases of autologous stem cell therapies, the deciding factor regarding the criteria will not be *the change in characteristics per se*, but rather whether the cells are to be used for the same essential or primary function in the recipient as in the donor.²⁷⁸

(d) *Autologous stem cell therapies and procedures and the Advanced Therapy Medicinal Regulation*

Autologous tissues and cells extracted and processed within the same surgical procedure are often regulated in terms of a surgeon's professional obligation towards the patient.²⁷⁹ Even with laws in place for the regulations of medical devices used in such procedures,²⁸⁰ laws regulating medical practitioners and the cells themselves often create confusion as to which regulatory framework is applicable for an individual autologous stem cell therapy. Rightly noted by Vertes *et al*, "the lack of certainty itself undermines confidence in the development of these therapies." In many instances, if some of these products are to be treated as ATMP, many well-established procedures will unnecessarily be governed by the ATMP Regulation, for

²⁷⁷ Scientific recommendation on classification of advanced therapy medicinal products EMA EMA/920913/2011 <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/11/WC500118207.pdf> (Accessed 20 September 2016); Scientific recommendation on classification of advanced therapy medicinal products EMA/920913/2011 <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/11/WC500118208.pdf> (Accessed 21 September 2016).

²⁷⁸ Vertes *et al supra* n9 134; Cuende *et al* 2012 *Stem Cells Trans Med* 404: "The procedure to obtain BM-MNCs and CD133+ cells includes only manipulations considered nonsubstantial (cell separation, concentration, or purification). Therefore, their consideration or not as medicinal products will depend exclusively on the essential functions of the cells and their intended use."

²⁷⁹ *Idem* at 132.

²⁸⁰ As set out for each category of medical devices in Directives 93/42/EC and 98/79/EC regarding *in vitro* diagnostic medical devices, and Directive 90/385/EC on the approximation of laws of the member states relating to active implantable devices.

instance: standard coronary arterial bypasses or bone grafts will be deemed to have been “placed on the market” and, consequently, in contravention of the law.²⁸¹

In terms of article 2(2)(a) of the EUTCD, “tissues and cells used as an autologous graft within the same surgical procedure” are excluded from the ambit of its regulation. Consequently, its UK implementation states in regulation 7 of the Q & S Regulations that no person shall store tissues or cells intended for human application, which, by definition in terms of regulation 4, excludes “autologous grafts”.

In view of such provision, the Competent Authorities for Tissues and Cells had a meeting on 23 and 24 June 2011 to discuss why the use of the Celution device in reconstructive surgery should be exempted.²⁸² The exemption of the Celution device can be ascribed to its technique of procuring the stem cells from the same individual, in the same operating room, during the same procedure, to be applied for the same essential function, which is adipose-derived regenerative cells in order to restore the adipose mass of the breast, subsequent to a mastectomy for breast cancer.²⁸³

As the quality and safety measures applicable to cells and tissues of autologous grafts are different from those intended for medicinal application, an argument can be put forward that such autologous procedures should also be disregarded from medicines legislation. The ATMP Regulation was intended to be read in conjunction with the EUTCD as well as the Medicinal Product Directive 2001/83/EC by incorporating several of their definitions. For instance, article 12(a) of the ATMP Regulation requires the unique donation and product codes as referred to in article 8(2) of the EUTCD.²⁸⁴

Clearly, because tissue and cells used as an autologous graft in the same surgical procedure are exempted from the EUTCD, there would be no such codes.

²⁸¹ Vertes *et al supra* n9 132.

²⁸² The Celution device is a manufactured by Cytori Therapeutics Inc. for the purpose of extracting and concentrating stem cells from fat tissue for autologous re-implantation or reinfusion, commonly used in reconstructive surgery, see Fraser *et al* “The Celution® System: Automated Processing of Adipose-Derived Regenerative Cells in a Functionally Closed System” 2014 *Adv Wound Care* 38-45.

²⁸³ Vertes *et al supra* n9 132-133.

²⁸⁴ This is again replicated in par (m) of Annexure 3 of the ATMP Regulation.

Interestingly, Vertes *et al* make the observation that although paragraph (n) of Annex 3 and regulation 12(b) state that, in the case of an ATMP for autologous use, the unique patient identifier and the statement “[f]or autologous use only” should appear on the product; however, no conjunction was used between the sub-regulations and therefore the observation stands.²⁸⁵ Had there been an insertion immediately prior to article 12(b) such as “*and*” or “*or*”, it could be construed that these provisions should be read as alternatives. Similarly, regulation 14(5) of the ATMP Regulation states that:

...if serious adverse events or reactions occur in relation to a combined advanced therapy medicinal product, the Agency shall inform the relevant national competent authorities responsible for implementing Directives 90/385/EC, 93/42/EC and 2004/23/EC.

Therefore, if the tissue and cells used in an autologous procedure are exempted from the EUTCD, the EMA would not be able to contact the HTA and, as such, human materials have been exempted from their remit. It is clear that the ATMP Regulation is based on the premise that the various tissues and cells are governed by the EUTCD and that only such cells could constitute an ATMP. As a result of such reasoning, cells and tissues exempted by means of article 2(2)(a) of Directive 2004/23/EC shall be exempted from ATMP Regulation, such as the Celution device.

As noted above, an all-encompassing, rather strict interpretation of the ATMP Regulation could render some well-established surgical procedures criminalised, such as tissues used for coronary artery bypass graft. In such procedures, veins are extracted and grafted to bypass the coronary arteries that have narrowed in order to improve blood supply to the heart. Although removing the vein is autologous, it runs the risk of not being used in same homologous manner, as these veins now carry

²⁸⁵ Vertes *et al supra* n9 137; Article 12 of the ATMP Regulation reads as follows: “In addition to the particulars mentioned in Article 55(2) and (3) of Directive 2001/83/EC, the following particulars shall appear on the immediate packaging of advanced therapy medicinal products: (a) the unique donation and product codes, as referred to in Article 8(2) of Directive 2004/23/EC; (b) in the case of advanced therapy medicinal products for autologous use, the unique patient identifier and the statement ‘For autologous use only’.”

oxygenated blood away from the heart, as opposed to its original function, which was to carry deoxygenated blood away from the periphery.²⁸⁶

As an alternative interpretation, the ATMP Regulation was not designed to include therapies such as coronary artery bypasses and bone procedures. This necessitates the need for a robust interpretation of what is to be regarded as “the same essential function.”²⁸⁷

(e) *Case discussion: Bone marrow mononuclear cells and CD133+ cells*

Close to the end of 2011, the CAT published two scientific recommendations, classifying autologous bone marrow mononuclear cells [BM-MNCs]²⁸⁸ and CD133+ stem cells²⁸⁹ as medicinal products in terms of the ATMP Regulation, specifically as TEPs.

Both these recommendations were based on the products’ intended uses, which were to improve the heart function of patients with ischemic heart disease, post-acute myocardial infarction and chronic ischemic heart disease.²⁹⁰ The CAT’s conclusion that the therapies constituted ATMPs, was made based on the fact that the products were not intended for the same essential function (orthodoxly classified as haematological restoration) and that the products were intended for regeneration via stem cell-induced angiogenesis in ischemic heart tissue by non-haematological differentiation of bone marrow cells into vascular cells or by the paracrine effects of the stem cells.²⁹¹

More than ten years ago, the concept that bone marrow is exclusively dedicated to haematopoietic functions became obsolete, as it has been demonstrated that bone

²⁸⁶ *Ibid*; See also Astori *et al* 2010 “Bone marrow derived stem cells in regenerative medicine as advanced therapy medicinal products” *AM J Transl Res* 285-295 for a case discussion regarding the minimal manipulation of bone marrow cells as cell therapies.

²⁸⁷ *Ibid*.

²⁸⁸ Scientific recommendation on classification of advanced therapy medicinal products <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/11/WC500118208.pdf> (Accessed 21 September 2016). The term BM-MNCs is used to collectively denominate all the cells present in bone marrow.

²⁸⁹ Scientific recommendation on classification of advanced therapy medicinal products EMA 24 November 2011 <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/11/WC500118207.pdf> (Accessed 20 September 2016).

²⁹⁰ Cuende *et al* 2012 *Stem Cells Trans Med* 404.

²⁹¹ *Ibid*.

marrow carries out further regenerative functions of remote tissues under homeostatic conditions. As the legal definition of a TEP states that the tissue or cells should not be intended for the same essential function or functions in the recipient as in the donor, it stands to reason that the recommendation by the CAT regarding BM-MNCs and CD133+ cells is wrong.

These therapies should not be regarded as ATMP when they are applied to promote angiogenesis and ischemic tissue regeneration, as modern evidence clearly indicates their physiological role in postnatal neovascularization.²⁹² The only difference between the “therapy” and that of the physiological recruitment of CD 133+ cells lies in the fact that, instead of the process being cumulative recruitment over time, these cells are now collected from the bone marrow and administered intra-arterially.²⁹³

As BM-MNCs consist of a combination of different types of progenitor cells, as well as the fact that all the cellular subtypes included in BM-MNCs have not been classified, it can be argued that neovascularization is not the primary function of BM-MNCs.²⁹⁴ However, in a bone marrow transplant consisting of various subtypes of cells, the cells are considered to be a transplant and not a medicinal product.²⁹⁵ It is clear that the definition allows for more than one essential function of cells and the Regulation does not state that the intended use should be for the main essential function or that the essential function should be exclusive to those cells.²⁹⁶

The classification of BM-MNCs and CD133+ stem cells as medicinal products is important because medicinal products are subject to more stringent regulation. The strict regulation of medicinal products sets higher standards for processing, quality

²⁹² Takahashi *et al* 1999 “Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization.” *Nat Med* 434; Kocher *et al* “Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function” 2001 *Nat Med* 430; Kamihata *et al* “Implantation of bone marrow mononuclear cells into ischemic myocardium enhances collateral perfusion and regional function via side supply of angioblasts, angiogenic ligands, and cytokines” 2001 *Circulation* 1046; Gneocchi *et al* “Paracrine mechanisms in adult stem cell signaling and therapy” 2008 *Circ Res* 1204.

²⁹³ Cuende *et al* 2012 *Stem Cells Trans Med* 405- 406.

²⁹⁴ *Ibid.*

²⁹⁵ *Ibid.*

²⁹⁶ Article 2(1)(c) of the ATMP Regulation.

control and compliance with GMP as opposed to institutions that are authorised to do bone marrow transplants. This has a serious economic impact that cannot be justified by patient safety.²⁹⁷ Using only reason it is clear that, if using bone marrow for allogeneic transplants does not necessitate the stringent quality control requirements as set out by the ATMP Regulation, it cannot be justified to subject BM-MNCs used for autologous neovascularization to the taxing regulatory requirements of the ATMP Regulation.²⁹⁸

If such therapies were to be regarded as medicinal products (*status quo*), it would take much longer to make it available to a patient due to its experimental nature and would only be available after marketing authorisation has been obtained. On the other hand, if these therapies were to be regarded as transplants, medical institutions could offer them, just like they offer bone marrow transplants.

Evidently, there are occasions where stem cell therapy should be disregarded from the definition of a TEP and escape the ATMP Regulation.²⁹⁹ Stem cells, such as CD133+ and BM-MNC cells, are not just limited to haematological regeneration and have more than one essential function.³⁰⁰ Accordingly, it could be helpful for the CAT to provide a table of essential functions of all the 200-300 human cells, to help bring effective therapies to patients in need in a cost-effective and safe way. For now, as it stands, bone marrow stem cell therapies, which are not used for haematological regeneration are regarded as ATMPs and are to be regulated as medicine.

(f) *Exemptions from medicinal regulation*

ATMP, such as a stem cell therapies are mostly produced on a small scale, often in academic settings or small enterprises. This places an unnecessary regulatory burden on the developers of such therapies.³⁰¹ However, there are two explicit

²⁹⁷ Cuende *et al* 2012 *Stem Cells Trans Med* 405- 406.

²⁹⁸ *Ibid.*

²⁹⁹ As discussed earlier, it certainly was not the intent of the Commission to include transplants in the ambit if the ATMP Regulation.

³⁰⁰ For a discussion on the production and legal requirements regarding the production of an autologous TEP, see Ram-Liebig *et al* 2015 *Advanced Drug Delivery Reviews* 182.

³⁰¹ Blassime & Rial-Sebbag 2013 "Regulation of Cell-Based Therapies in Europe: Current Challenges and Emerging Issues" *Stem Cells & Dev* 14, 15; Von Tigerstrom "Regulation of Stem Cell-Based Therapies" 2015 *Food & Drug LJ* 315, 326; Pearce *et al* "Regulation of Advanced Therapy Medicinal Products in Europe and the Role of Academia" 2014 *Cytotherapy* 289, 290-291.

exemptions to the requirement of marketing authorisation for a product that would otherwise be regulated as medicine under the ATMP Regulation. It is worth mentioning that these exemptions will only be applicable if the product or therapy is a medicinal product or an ATMP that is not placed on the market.³⁰²

These exemptions are (1) The “specials exemption” (SE) in terms of the Medicinal Products Directive 2001/83/EC, allowing certain medicinal products to get marketing authorisation to fulfil special needs³⁰³ and (2) the “hospital exemption” (HE), specifically catering for the exemption of ATMP.³⁰⁴

These exemptions were included in UK legislation by means of Part X of the Human Medicines Regulation 2012,³⁰⁵ together with various other exemptions. In addition to these two exemptions, a medicinal product subject to the centralised community authorisation procedure may be exempted from the requirement of marketing authorisation, if such a product is made available for compassionate reasons to a group of patients with a chronic or seriously debilitating or life-threatening disease, who cannot be adequately treated by an authorised medicinal product.³⁰⁶ For now, the discussion turns to the specials exemption.

(i) Special exemption

SE is warranted as some patients may have special clinical needs that cannot be met by licensed medicinal products. To cater for the individual special needs of such patients, the law permits the manufacture and supply of unlicensed medicinal products, commonly known as *specials* subject to certain conditions.³⁰⁷ Regulation 167 of the Human Medicines Regulation 2012, flowing from Article 5(1) of the Medicinal Products Directive 2001/83/EC, states that such special medicinal products must only be:

1. supplied in response to an unsolicited order;

³⁰² Vertes *et al supra* n9 144.

³⁰³ Article 5 of the Medicinal Product Directive 2001/83/EC.

³⁰⁴ Article 28 of the ATMP Regulation.

³⁰⁵ *The Human Medicines Regulation* (2012) 1916.

³⁰⁶ Article 83 of Reg 726/2004 laying down community procedure for the authorisation and supervision of medicinal products for human and veterinary use and establishing the EMA.

³⁰⁷ The supply of unlicensed medicinal products (specials) MHRA Guidance Note 14 2014 <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf> (Accessed 22 September 2016).

2. formulated in accordance with the specifications of an authorised healthcare professional;
3. for use by an individual patient under the healthcare professional's direct personal responsibility; and
4. that the following conditions are met:
 - (a) The medicinal product must be supplied to a doctor, dentist, nurse or pharmacist; or that the product must be supplied for use under the supervision of a pharmacist in a registered pharmacy, hospital or health centre.
 - (b) No person may publish any advertisement relating to the medicinal product.
 - (c) The manufacture and assembly must be carried out under such supervision; precautions must be taken to ensure compliance with the specifications of the doctor nurse or pharmacist.

Aside from being exempted from the centralised marketing authorisation requirement, if a *special medicine* is manufactured in the UK, the manufacturer must hold a manufacturer's (special) licence issued by the MHRA.³⁰⁸ The UK has taken a broad interpretation of "special need", which means that it is a special need if no pharmaceutical equivalent medicinal product with marketing authorisation is available. Therefore, regarding an unlicensed medicinal product, the SE ceases if a pharmaceutical equivalent medicinal product receives marketing authorisation in the UK.

On the other hand, HE is designed to cater for the innovative use of ATMPs in the treatment of individual patients, free from the centralised marketing authorisation requirement.³⁰⁹

(ii) Hospital exemption

The HE is applicable to an ATMP that is:³¹⁰

³⁰⁸ Reg 167(5) of the Medicines for Human Use Regulations 2012; The supply of unlicensed medicinal products ("specials") MHRA Guidance Note 14 2014 <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf> Accessed 22 September 2016).

³⁰⁹ Von Tigerstrom 2015 *Food & Drug LJ* 326.



...prepared on a non-routine basis according to specific quality standards and uses within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

An ATMP included in such an exemption must be authorised by the MHRA, who is charged with overseeing the national traceability and pharmacovigilance requirements, as well specific quality standards that are equivalent to products subjected to the centralised authorisation procedures. Unlike the SE, HE does not include a “special needs test”, which makes for its perpetual application, even if a pharmaceutical equivalent ATMP has received marketing authorisation.³¹¹

In addition to the ATMP Regulation and consistent with the UK implementation of the SE, two additional restrictions are applicable to HE in the UK. Firstly, no advertisement may be published and, secondly, the sale or supply of the ATMP may only be in response to an unsolicited order.³¹²

GMP standards create challenges for ATMP in general, which are exacerbated for ATMP included in the HE, since they will be individualised therapies produced on a non-routine basis for specific patients with rare diseases or other specialised needs.³¹³ This raises the question regarding how strictly quality standards should be complied with, particularly products under HE. Some argue in favour of a risk-based approach as long as product safety is not compromised,³¹⁴ while others argue that all applicable quality and safety standards, including GMP, are applicable to HE therapies.³¹⁵ The ATMP Regulation makes no mention that the quality standards of HE therapies should be that of other medicinal products. Therefore, this would

³¹⁰ MHRA guidance on “non-routine” <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397739/Non-routine_guidance_on_ATMPs.pdf> (Accessed 22 September 2016); MHRA guidance on the UK’s arrangements under the Hospital Exemption Scheme <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397738/Guidance_on_the_UK_s_arrangements_under_the_hospital_exemption_scheme.pdf> (Accessed 22 September 2016).

³¹¹ Vertes *et al supra* n9 140.

³¹² *Ibid.*

³¹³ Von Tigerstrom 2015 *Food & Drug LJ* 328.

³¹⁴ *Ibid*; Pirnay *et al* 2013 “Business Oriented EU Human Cell and Tissue Product Legislation will Adversely Impact Member States’ Health Care Systems” *Cell Tissue Bank* 549.

³¹⁵ Alliance for Advanced Therapies 2013 “Focus Hospital Exemption on Developing Innovative and Safe Treatments for Patients” *Regenerative Med* 121.

include GMP for ATMP.³¹⁶ Furthermore, HE therapies are not required to show evidence of safety and efficacy, as, in reality, this would be almost impossible due to the small numbers involved.

An important question to consider is whether autologous ATMP fall under the HE by definition, as they are custom made.³¹⁷ Much of the answer is based on the interpretation of “non-routine production”, since autologous products can be produced by means of standard protocols for a large number of patients, even though each one is individually tailored to the individual patient’s own cells.³¹⁸ Therefore, if an autologous stem cell therapy is produced by means of a standardised procedure, it will fall under the ambit of the ATMP Regulation.³¹⁹ Furthermore, HE does not override clinical trial laws and therefore an IMP, which is also an ATMP under the HE, may not be used for clinical trials.³²⁰

In the UK, HE has only been granted in a few exceptional circumstances due to the possibility that manufacturers could confuse HE with the SE.³²¹ It is clear that some ATMP manufacturers see this as an attractive solution to the stringent regulatory requirements.³²² The EMA voiced their concern regarding patient safety and market distortion, as the HE is currently being abused.³²³ Furthermore, it would not be fair to expect centrally authorised products to compete with HE products, as the standards

³¹⁶ Von Tigerstrom 2015 *Food & Drug LJ* 329.

³¹⁷ *Ibid.*

³¹⁸ *Ibid.*

³¹⁹ Mahalatchimy “Access to Advanced Therapy Medicinal Products in the EU: Where do We Stand?” 2011 *EU J Health L* 313; Commission Staff Working Document – Annex to the proposal for a regulation on advanced therapy medicinal products impact assessment <COM/2005/567/final/SEC/2005/1444<[http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex %3A52005SC1444](http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A52005SC1444)> (Accessed 23 September 2016).

³²⁰ *Ibid.*

³²¹ Faulkner 2016 *Regen Med* 324; Von Tigerstrom 2015 *Food & Drug LJ* 331.

³²² *Ibid.*

³²³ EMA. Concerns over unregulated medicinal products containing stem cells (2010) <http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/04/news_detail_001016.jsp&mid=WC0b01ac050004d5c1> (Accessed 22 September 2016); Von Tigerstrom 2015 *Food & Drug LJ* 331: “Depending on how HE products are defined and regulated, however, it is possible that the exemption could allow those developing ATMP to circumvent the usual requirement for marketing authorisations. This was a widespread concern among industry respondents in the public consultation.”

would be less stringent and the prices of the HE would be lower, which would make it even harder for licenced products to reach the market.³²⁴

(iii) Comparison for exemptions of medicines legislation

Because there is confusion regarding the application of HE and SE, a table setting out the main differences and applicability of each of the exemptions is given below:

Comparison of medicinal legislation exemptions

Hospital exemption	Specials exemption	Comments
Applies only to ATMP	Applicable to all medicinal products, including ATMP	Even though HE does not create an exemption from clinical trial laws, it has been reported that certain competent authorities are encouraging the use of HE to produce ATMP, which allows for the data from the first inhuman cases to form part of the IMP dossier for trial applications.
Applicable to custom-made ATMP to suit individually tailored needs and must be made on a non-routine basis.	No such restriction on the manner of manufacture of a medicinal product in terms of SE. As a practical matter, regulators would prefer the routine production of products under SE. ³²⁵	Bearing in mind that HE does not automatically apply to autologous stem cell therapies, as they do not automatically fall under HE and are often produced by means of an industrial process. See also the

³²⁴ This will reduce the incentive for industry to develop ATMP and apply for marketing authorisations. See EC Health and Consumers Directorate-General Public Consultation Paper on the Regulation on Advanced Therapy Medicinal Product (2012) <http://ec.europa.eu/health/files/advtherapies/2012_12_12_public_consultation.pdf> (Accessed 22 September 2016).

³²⁵ Vertes *et al supra* n9 140.



		MHRA guidance on what is regarded as non-routine. ³²⁶
Specific quality requirements must be equivalent to those under the conventional marketing authorisation procedures, such as GMP.	No specific requirements regarding the quality, except those standards and safety requirements set out by the medical practitioner.	This could make SEs a more attractive route for the production for of ATMP, as the quality and safety standards are fewer than with ATMPs
Pharmacovigilance and traceability standards are the same as for conventional medicinal modalities.	No such specific requirement is present regarding pharmacovigilance and traceability.	
Must be prepared in the same EU member state.	Any product that meets the requirements of the SE scheme can be manufactured in, or imported into, the UK from another member state	
The ATMP must be used in a hospital.	Can be supplied or received by a doctor, pharmacist or nurse in a pharmacy, hospital or health centre	
The ATMP must be commissioned by a medical practitioner.	These products may be prescribed by doctors, dentists and supplementary prescribers.	

³²⁶ MHRA guidance on “non routine” <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397739/Non-Routine_guidance_on_ATMPs.pdf> (Accessed 22 September 2016).

Figure 3: Comparison of Medicinal Product Exemptions

5.4 Summary and conclusion

The procurement of start-up materials for the production of stem cell therapies is regulated by various authorities. Mostly in the UK, the HTA, mandated under the HTAct and the EUTCD as transposed into UK law by the Q & S Regulations, regulates the procurement, processing, storage, distribution, import and export, etc. to ensure compliance with adequate safety and quality measures and to ensure that the tissues or cells were procured by means of appropriate consent. Should the cells procured fall within the definition of an “autologous graft” (tissue or cells used in the same surgical procedure, which must perform the same essential function of the original cells), they will be excluded from the Q & S Regulations and, subsequently, medicinal regulation.

Furthermore, should the base material of a stem cell therapy involve the use of gametes, the creation or destruction of an embryo for the production of an embryonic stem cell line, such activities will be regulated by the HFEA. The remit of the HTA takes effect the moment an independent stem cell line has been established and banked according to the UK Stem Cell Bank Steering Committee’s instruction, whereupon the remit of the HFEA ceases.³²⁷ Once a master cell bank has been created with a reasonable prospect of clinical application, these cells will fall under the remit of the MHRA.³²⁸

If these cells are to be used as a therapy in a clinical trial as an IMP, they have to comply with the CTD as transposed into UK Law by the 2004 UK CTR or, more

³²⁷ R. 30 UK Stem Cell Bank. 8th HFEA Code of Practice <[http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition\(Oct_2015\).pdf](http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition(Oct_2015).pdf)> (Accessed 9 September 2016): “Where this licence authorises the derivation of human embryonic stem cell lines: (a) a sample of all stem cell lines derived must be deposited in the UK Stem Cell Bank in accordance with any relevant Bank guidelines, and (b) the remainder of all stem cell lines (in so far as not used or destroyed as part of or in the course of the research project) must be deposited in the UK Stem Cell Bank or distributed in accordance with any relevant guidelines issued by the UK Stem Cell Bank.”; 8th HFEA Code of Practice <[http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition\(Oct_2015\).pdf](http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition(Oct_2015).pdf)> (Accessed 9 September 2016); HTA position statement on regulating human embryonic stem cell lines for human application, as updated August 2015 <http://www.biobank.org/home2/sites/files/hta_position_statement_on_regulating_human_embryonic_stem_cell_lines_for_human_application.pdf> (Accessed 9 September 2016).

³²⁸ *Ibid.*

recently the 2014 EU CTR, setting out the standards for compliance with clinical trial laws, such as GCP, GMP and certain specific requirements for the production of IMPs. In addition, if the IMP is also an ATMP, the ATMP Regulation will also apply.

After an evidence base has been created by means of a clinical trial, anyone intending to place a medicinal product on the market has to comply with the Medicinal Product Directive, as amended by the ATMP Regulation, in order to obtain marketing authorisation. However, as alluded to above, the inclusive nature of the ATMP Regulation can have a negative and restricting effect on the delivery of vital treatments, such as including certain types of autologous stem cell therapies in the definition of TEPs.

Apart from such incidences, the Medicinal Product Directive and the ATMP provide certain exemptions, making it possible for a medicinal product to be used without marketing authorisation. In terms of the Medicinal Products Directive, SE allows for any medicinal product in the EU to be exempted from medicines legislation to cater for the individual special needs of a patient or a specific group of patients subject to certain requirements, if there is no pharmaceutical equivalent available on the market. Furthermore, this exemption was augmented by the ATMP Regulation and created the infamous HE.

HE is designed to make provision for the innovative use of ATMPs in treating individual patients, free from the centralised marketing authorisation requirement, if the product is manufactured on a non-routine basis to be used in the same member state, in a hospital under the sole responsibility of a medical practitioner, in order to cater for the tailored needs of an individual patient.³²⁹

These exclusions offer attractive means to develop ATMPs without the burden of stringent medicinal regulation. Unlike the SE, there is no “special needs” requirement

³²⁹ MHRA guidance on “non routine” <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397739/Non-routine_guidance_on_ATMPs.pdf> (Accessed 22 September 2016); MHRA guidance on the UK’s arrangements under the Hospital Exemption Scheme <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397738/Guidance_on_the_UK_s_arrangements_under_the_hospital_exemption_scheme.pdf> (Accessed 22 September 2016).



and no requirement stating that it has to be for a certain number of people.³³⁰ Therefore, manufacturers are lured by the thought of manufacturing ATMPs under the HE as it poses means to collect vital data to submit at the clinical trial authorisation application. However, in terms of the HE, compliance with GMP, PV and traceability is mandatory as with all other medicinal products, whereas products manufactured under the SE need not comply with such stringent quality control regulations.

Taking the above into consideration, it is clear that even though certain exemptions are in place, some definitions are still unclear, such as the meaning of “same essential function” and “non-routine” basis, etc., which causes confusion and ultimately discourages investors to produce ATMPs such as stem cell therapies.

Despite the minor discrepancies, the influence and regulation remit of several regulatory authorities, the harmonisation brought about by the 2014 EU CTR and the ATMP Regulation provide a clear and consistent regulatory framework for the production and subsequent marketing authorisation of stem cell therapies in the EU and the UK. The harmonisation of quality and safety standards not only protects patients and research subjects from harm, but also provides an environment conducive to the production of stem cell therapies across all member states, including the UK.

The next chapter will give an exposition of the current South African regulatory landscape as it pertains to stem cell technologies, whereafter the UK position will be compared to that of the South African regulatory framework so that recommendations can be made.

³³⁰ See the definition of non-routine as set out by the MHRA guidance on “non routine” <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397739/Non-Routine_guidance_on_ATMPs.pdf> (Accessed 22 September 2016).

CHAPTER 6

STEM CELL TECHNOLOGIES IN SOUTH AFRICA

6.1 Introduction

The regulation of stem cells in South Africa is regulated primarily by the NHA,¹ the MRSCA and their ancillary regulations as set out by the minister in terms of the primary legislation. The NHA provides the basic framework for the regulation of stem cells, specifically Chapter 8 “*Control of Use of Blood, Blood Products, Tissue and Gametes in Humans.*”² The regulations, on the other hand, purport to fill the body and the practical rules of such removal and subsequent uses of stem cells, whether it is the production of a medicinal product or a stem cell transplant.³

Various issues arise when analysing pertinent definitions as set out in section 1 of the NHA. Firstly, the absence of definitions for “biological material”, “cells”, “stem cells”, “competent person”, and, secondly, incorrect definitions of certain crucial definitions, such as a “blood product”,⁴ “gamete”, “oocyte”,⁵ and, particularly, “tissue”, which definition makes no mention of whether it includes “cells” or only means “human tissue” and includes “flesh, bone, a gland, an organ, skin, bone marrow or bodily fluid”, but excludes “blood” or a “gamete.” Pepper and Nöthling Slabbert⁶ propose that the definition of human tissue should also exclude stem cells from its

- 1 Matters pertaining to human tissue were previously regulated under the HTAct, which was repealed by the enactment of the final section of the NHA in 2012.
- 2 However, the title makes no mention of stem cells, or any kind of cells, whereas Chapter 8 is the proposed legislative tool by which stem cells should be regulated.
- 3 Prinsen “Flawed law: A critical analysis of the faults and shortcomings of Chapter 8 of the National Health Act of 2003” 2013 *Obiter* 524: “The NHA provides the framework for a structured and uniform health system under which the various elements of the South African national health system may be united in the common goal of improving universal access to quality health services by taking into account the obligations imposed by the Constitution.”
- 4 S 1 of the NHA: “Blood product means any product derived or produced from blood, including circulating progenitor cells, bone marrow progenitor cells and umbilical cord progenitor cells”, progenitor cells are not regarded as blood, as they are a form of multipotent stem cells. See ch 2 regarding a definition for multipotent stem cells. “Blood products” should rather be defined as “the constituents of whole blood such as plasma or platelets that are used in therapy”; See ch 12.1 Meyer *et al* Human Physiology: *Chemical physical and physiological principles* (1997).
- 5 Rather unsettling, an oocyte is defined as a “developing human egg cell”, which rather suits the definition of a zygote, being the union of a male and female gamete. Whereas an oocyte is defined as “A diploid cell from which an egg or ovum develops by meiosis. A primary oocyte divides to produce a polar body and a secondary oocyte, which divides again to produce the ovum and another polar body” in the Miller-Keane Encyclopaedia and Dictionary of Medicine, Nursing, and Allied Health 7th ed (2003) <<http://medical-dictionary.thefreedictionary.com/oocyte>> (Accessed 26 October 2016).
- 6 Pepper & Nöthling Slabbert 2015 *SAJBL* 5-6.

ambit, which will then be regulated under the definition of biological material as set out in the Regulations Relating to the Use of Human Biological Material 2012.⁷

Similarly, in an attempt to rectify the mistakes made in the NHA and the accompanying regulations in terms of section 68 of the NHA, the legislator failed to repeal certain regulations or explicitly regulate which regulations would remain in force and which were to be repealed. For example, there are four sets of Regulations Relating to Artificial Fertilisation: In 2007, the minister made the Regulations Regarding Artificial Fertilisation and Related Matters,⁸ in 2011, the Regulations Relating to Artificial Fertilisation of Persons,⁹ in 2012, the Regulations Relating to Artificial Fertilisation of Persons,¹⁰ and, more recently, in 2016, the Regulations Relating to Artificial Fertilisation of Persons (Regulations Relating to AF 2016).¹¹

As there are four sets of regulations regulating the same area, the expectation exists that they are connected or that the latter sets repeal the former sets. However, this is not the case, as these regulations are materially the same, mostly verbatim. The law of interpretation states that in the event of two pieces of legislation being the same, but not in conflict, such pieces of legislation are to be read in conjunction with each other.¹² However, if the pieces of legislation are conflicting and the latest piece does not repeal its predecessor, the court will be likely to choose the most recent legislation. Such a decision will be based on the reasoning that the legislator intended to rectify himself, but merely omitted to insert a repealing clause.

To be precise, if legislation such as the first versions of the Regulations Relating to Artificial Fertilisation is not explicitly repealed, it would still be in force and should be read together. Therefore, an argument can be made that the legislator intended to repeal it, but merely forgot; therefore, the regulations will repeal each other implicitly.¹³

⁷ Regulations Relating to the Use of Human Biological Material R. 177, as published in GG 35099 of 2012-03-02.

⁸ R. 8, as published in GG 29527 of 2007-01-05.

⁹ R. 8, as published in GG 34159 of 2011-04-01.

¹⁰ R. 175, as published in GG 35099 of 2012-03-02.

¹¹ R. 1165, as published in GG 40312 of 2016-09-30.

¹² See Part 1 and Part 2 of Botha Statutory Interpretation: An Introduction for Students (2012).

¹³ The same problem arises with the Regulations Relating to Tissue Banks R. 237, as published in GG 35099 of 2011-04-01; Regulations Relating to Tissue Banks R. 182, as published in GG 35099 of 2012-03-02; Regulations Relating to Stem Cell Banks R. 183, as published in GG 35099 of 2012-03-02; Regulations Relating to Blood and Blood Products R. 269, as published GG 34159 of 2011-04-01; Regulations Relating to Blood and Blood Products R. 179, as published in GG 35099

This chapter will be divided into three main parts. Part I: The regulatory framework regarding the procurement, storage and use of stem cells; Part II: The regulation of stem cells research in human participants; and Part III: The application of stem cells as medicinal products. It is important to note that, for purposes of this dissertation, this chapter will only focus on the procurement and use of stem cells procured from living persons and embryos or material originating therefrom.

6.2 Part I: The procurement, storage and use of stem cells

6.2.1 Authorised institutions

Before debating the legality of the various uses of stem cells, it is necessary to establish which institutions or persons are allowed to obtain or remove stem cells from a living person. Throughout the NHA and the regulations, there are several uncertainties regarding who is an authorised institution or a competent person to withdraw or use stem cells for their various applications. The following section will set out the uncertainty and redundancies regarding who is an authorised institution or a competent person to withdraw and, ultimately, develop stem cell therapies.

In terms of section 54 of the NHA, the minister may authorise certain institutions that are not yet authorised in terms of section 63¹⁴ to: acquire, use or supply the body of a deceased person for any purpose as set out in section 64;¹⁵ obtain or use any tissue imported or removed from either a living or a dead person for the purposes referred

of 2012-03-02; Regulations Regarding the use of Human DNA, RNA, Cultured Cells, Stem Cells, Blastomeres, Polar Bodies, Embryos, Embryonic Tissue and Small Tissue Biopsies for Diagnostic Testing, Health Research and Therapeutics R. 7, as published in GG 29526 of 2007-01-05; Regulations Relating to Human Biological Material R. 263 as published in GG 34159 of 2011-04-01; Regulations Relating to Human Biological Material R. 177, as published in GG 35099 of 2012-03-02; Regulations relating to Human Stem Cells R. 376, as published in GG 29840 of 2007-05-04; Regulations Relating to Stem Cell Institutions or Organisations R. 265, as published in GG 34159 of 2011-04-01; Regulations Regarding the General Control of Human Bodies, Tissue, Blood, Blood Products and Gametes R. 268, as published in GG 34159 of 2011-04-01; Regulations Regarding the General Control of Human Bodies, Tissue, Blood, Blood Products and Gametes R. 180, as published in GG 35099 of 2012-03-02 (Regulations Regarding the General Control of HBM).

¹⁴ Dealing with human material donated to an authorised institution whether from a deceased or a living person.

¹⁵ S 64(1) of the NHA sets out the purposes for which a donation of a body, tissue, blood or blood products of a deceased person may be used, which relate to education; health research; the advancement of health sciences; therapeutic purposes, including the use of tissue in any living person; or for the production of a therapeutic, diagnostic or prophylactic substance, which would be regulated under section 14 of the Medicines Act.

to in section 56 or 64;¹⁶ supply any preserved tissue to an institution or person as envisaged by section 63;¹⁷ and acquire, use and supply blood products for any of the purposes referred to in section 56 or 64. However, the execution of such functions may be subject to certain conditions, as set out by the minister by means of a notice in the Government Gazette.¹⁸

6.2.2 Competent persons

6.2.2.1 Competent person(s) in the RSA

As stated above, much ambiguity arises when deciphering which institutions are to be regarded as “authorised institutions”, knowing what type of authorisation is required, as well as which persons are to be regarded as “competent persons”. In terms of section 68 of the NHA, the minister may impose regulations relating to tissue, cells, organs, blood, blood products and gametes. However, in doing so, instead of harmonising and giving body to the broadness of the NHA, the opposite was achieved.

Among others, a problem arises as to who is competent to remove and use stem cells. Section 59 of the NHA can be used as a starting point, which reads as follows:

For the purpose of this Chapter, only a registered medical practitioner or dentist may remove any tissue from a living person, use tissue so removed for any of the purposes contemplated in section 56 or transplant tissue so removed into another living person.

However, when reading section 59 in conjunction with section 56(1) of the NHA, which states that “A person may use tissue or gametes removed or blood or blood product withdrawn from a living person only for such medical or dental purposes as may be prescribed”, it is clear that only a medical practitioner or dentist may use stem cells for medical or dental purposes as may be prescribed. Firstly, the wording of “[a] person” creates confusion, as the regulations refer to a person as being a “competent person.”

¹⁶ S 56 and s 64 of the NHA each relates to the use of the body of a deceased person, tissue, blood, blood products, gametes of living person, respectively.

¹⁷ S 63 states that a human body, tissue, blood, blood products or gametes may be donated by any person contemplated in section 55(a) (dealing with the removal of from such material from a living person), or s 62 (dealing with the donation of the body or tissue from a deceased person) for purposes as set out in s 56 and s 64.

¹⁸ *Idem* at s 54(3).

Secondly, section 59 precludes everyone, except medical practitioners or dentists, from removing tissue,¹⁹ and not only from removing stem cells, but also from their subsequent use. The following situation arises: Imagine a world-class stem-cell researcher, schooled in genetics and microbiology. Not only is he or she not allowed to remove stem cells (as the NHA states that only a medical or dental practitioner may remove or use tissue for section 56 purposes²⁰), section 59 also prohibits him or her from using it after it had been removed, as it prohibits the subsequent use of stem cells by persons other than medical or dental practitioners, despite the stem cells having been lawfully removed by a medical or dental practitioner. To add to the confusion created by the NHA, contradictions in the regulations make the clear understanding of the regulatory framework almost impossible. In terms of regulation 2(1), read with 2(3)(i) of the Regulations Relating to Stem Cell Banks 2012,²¹ no person (which should rather read, 'no competent person' to achieve harmony across the regulatory plane) shall remove, acquire or import human stem cells from any living or deceased person, unless they are authorised as a stem cell bank by the director-general.²²

However, in terms regulation 2(1), read together with regulation 2(2)(a) of the Regulations Relating to Blood and Blood Products 2012 (which should not regulate

¹⁹ As the legislator omitted to define tissue in the NHA, subordinate legislation as made by the minister will have to provide a definition. Throughout ch 8 of the NHA, references are made to tissue, which, after reading the Regulations Relating to Stem Cell Banks R. 183, as published in GG 35099 of 2012-03-02, can be interpreted to include cells, as it reads as follows: "'tissue' means a functional group of cells. The term is used collectively in Regulations to indicate both cells and tissue."

²⁰ Reg 5(b) of the Regulations Relating to Human Biological Material R. 177, as published in GG 35099 of 2012-03-02, specifically provides for health research as set out in section 69(3) of the NHA, which can be regarded as a prescribed medical and dental purpose; S 56(2) of the NHA states that certain tissue, blood, blood products or gametes may not be removed without ministerial consent. In the case of such restricted human material, ministerial consent would be in addition to the compliance with s 55 that states that such removal for the use of s 56 purposes must take place with informed consent of the donor and under prescribed conditions

²¹ Regulations Relating to Stem Cell Banks R. 183, as published in GG 35099 of 2012-03-02. The aforementioned regulation is the latest regulation that requires registration as a stem cell bank, whereas its predecessors, which have not yet been explicitly repealed, require registration as a "stem cell institution" in terms of the Regulations Relating to Stem Cell Institutions or Organisations R. 265, as published in the GG 34159 of 2011-04-01, and in terms of the Regulations Relating Human Stem Cells R. 376, as published in the GG 29840 of 2007-05-04. Also, as tissue and cells are used synonymously, the Regulations Relating to Tissue Banks R. 182, as published in the GG 35099 of 2012-03-02, require that registration as a human tissue bank would also be required in terms of regulation 3(3)(c).

²² *Idem* at reg 3(3)(c).

stem cells at all),²³ no other organisation, institution or person, except a blood transfusion service, as contemplated in section 53 shall be involved in the withdrawal of stem cells, except for embryonic stem cells, from any living person for the later administration thereof to that person or to any other living person.²⁴ This creates a unique contradiction, as, in terms of the Regulations Relating to Human Stem Cells 2012, authorisation by the director-general as a stem cell bank is required, but, in terms of the Regulations Relating to Blood and Blood Products 2012, only a blood transfusion service may remove stem cells. However absurd, due to the inconsistency and dissonance of the regulatory plane, every registered stem cell bank removing stem cells, etc., which is not a blood transfusion service as contemplated in terms of section 53 of the NHA, is acting in contravention with the Regulations Relating to Blood Products 2012, which is punishable by a fine or imprisonment not exceeding 10 years, or both.²⁵ The only exception would be embryonic stem cells.²⁶

Furthermore, the regulation of stem cells under the Regulations Relating to Blood and Blood Products is a clear indication of the chaos and ineptness of and within the legislator, as stem cells should only be regulated by the Regulations Relating to Human Biological Material 2012.²⁷ For instance, in terms of the NHA, the definition of “blood products” includes circulating progenitor cells, bone marrow progenitor cells and umbilical cord progenitor cells, which are by nature stem cells and should rather read “as the whole constituents of blood”. It is submitted that these irregularities should be addressed, as it is not only medical practitioners or the South African

²³ Regulations Relating to Blood and Blood Products R. 179, as published in GG 35099 of 2012-03-02.

²⁴ S 53 of the NHA: “(1) The Minister must establish a blood transfusion service for the Republic by granting a licence to a non-profit organisation, which is able to provide a blood transfusion service throughout the territory of the Republic. (2) The holder of the licence granted in terms of subsection (1)(a) must comply with prescribed norms and standards and must provide the prescribed blood transfusion and related services (b) may establish regional units, for the delivery of blood transfusion services, which must function under the control of the licence holder; and (c) has the sole right to provide a blood transfusion service in the Republic. (3) Any person other than the holder of the licence granted in terms of subsection (1) who is a blood transfusion service in the Republic, is guilty of an offence and liable on conviction to a fine or to imprisonment for a period not exceeding five years or to both a fine and such imprisonment.”

²⁵ Reg 14 of the Regulations Relating to Blood and Blood Products R. 179, as published in GG 35099 of 2012-03-02.

²⁶ *Idem* at reg 2(2)(a).

²⁷ Regulations Relating to the Use of Human Biological Material R. 177, as published in GG 35099 of 2012-03-02.

National Blood Services, as the designated blood transfusion service in South Africa, who partake in the removal of stem cells and the subsequent stem cell research, as such research is mostly conducted through collaboration of various fields of science, including genetics, microbiology, medicine. Such limitations would have a negative impact on the development of life-saving stem cell therapies and should be addressed.

6.2.3 Oversight and requirements of authorised institutions

6.2.3.1 Accreditation as an authorised institution

Depending on the type of stem cells to be used for transplantation, research or the production of a therapy, a competent person should bring an application to the director-general to be authorised as a stem cell bank, a fertility clinic, a tissue bank, a blood transfusion service (even though there may only be one) or a combination of these.²⁸ In bringing such an application, the applicant must include the name and nature of the applicant, the location of the premises where business would be conducted, an indication of how records and data would be kept, the quality management system that would be used, details of the responsible person and any other information the director-general may consider necessary for the consideration of the application.²⁹

In terms of such an application, the director-general may cause the applicant to be investigated, may seek to obtain further information as deemed necessary for consideration of the application, and may authorise the applicant as either a human tissue bank, fertility clinic, stem cell bank or tissue bank, subject to such conditions as the director-general may determine.³⁰

²⁸ Regulations Relating to Tissue Banks R. 182, as published in GG 35099 of 2012-03-02; Regulations Relating to Stem Cell Banks R. 183, as published in GG 35099 of 2012-03-02; Regulations Relating to AF 2016; Regulations Relating to Blood and Blood Products R. 179, as published in GG 35099 of 2012-03-02.

²⁹ Reg 3 of the Regulations Relating to Tissue Banks R. 182, as published in GG 35099 of 2012-03-02; Reg 3 of the Regulations Relating to Stem Cell Banks R. 183, as published in GG 35099 of 2012-03-02; Reg 3 of the Regulations Relating to AF 2016;

³⁰ *Ibid.*

6.2.3.2 Withdrawal and suspension of authorisation

In terms of the Regulations Relating to Stem Cell Banks 2012, if the director-general is of the opinion that there are reasonable grounds based on a report or recommendation of a health officer that the premises or equipment used by an authorised institution is hazardous to health, the authorised institution is not complying with the provisions of the NHA or the regulations thereto, donor or recipient rights are being violated, and after the relevant institution has been afforded an opportunity to present its case as to why it should not be suspended or lose its accreditation, but fails to do so, the director-general may suspend or withdraw the authorisation.³¹ Such suspension or withdrawal shall have the effect that the authorised institution must cease to carry out any activity.³²

6.2.3.3 Regulation of authorised institutions

(a) Institution of health officers

To ensure compliance with the regulatory framework requirements such as quality, safety and ethical oversight of authorised institutions, the legislator instituted the appointment of health officers in terms of the Regulations Regarding the General Control of Human Bodies, Tissue, Blood, Blood Products and Gametes R. 180, as published in Government Gazette 35099, 2 March 2012 (Regulations Regarding the General Control of HBM 2012) and the Regulations Relating to Blood and Blood Products 2012.³³ However, these two regulations contradict each other, as the health officer referred to in terms of the Regulations Regarding the General Control of HBM 2012 derive his powers from the member of the executive council for that province,³⁴ whereas the Regulations Relating to Blood and Blood Products 2012 state that the health officer is appointed by the minister.³⁵

(b) Duties of health officers

Despite the difference in where a health officer derives his or her mandate from, the Regulations Relating to Blood and Blood Products 2012³⁶ and the Regulations

³¹ Regulation 4(1) of the Regulations Relating to Stem Cell Banks R. 183, as published in GG 35099 of 2012-03-02.

³² *Idem* at reg 4(3).

³³ Regulations Relating to Blood and Blood Products R. 179, as published in GG 35099 of 2012-03-02.

³⁴ Regulations Regarding the General Control of HBM 2012.

³⁵ Reg 4(1) of the Regulations Relating to Blood and Blood Products R. 179, as published in GG 35099 of 2012-03-02.

³⁶ *Idem* at reg 5.

Regarding the General Control of HBM 2012 agree on the duties of health officer. In terms of the Regulations Regarding the General Control of HBM 2012, a health officer may enter any premises: in which human tissue (cells) is used or stored or is reasonably suspected to be used for any purpose in terms of the Act or the regulations; in which a therapeutic, diagnostic or prophylactic substance, or the supply of such substances so produced is carried on or suspected to be carried on; where the artificial fertilisation of any person is effected or suspected to be effected; on which a prescribed activity or process is carried on or is reasonably suspected to be carried on; or which are reasonably connected with or suspected to be connected with any of the aforementioned activities.³⁷

This holds true as long as a health officer has not been appointed in terms of the Regulations Relating to Blood and Blood Products 2012. If a health officer has been appointed, the health officer appointed by the minister shall have authority over the one appointed by the member of the executive council in terms of the Regulations Regarding the General Control of HBM 2012 in terms of the Regulations Relating to Blood and Blood Products 2012.³⁸ Furthermore, a health officer may examine any such premises, tissue, products or substances found therein, and may open any package or container located on such premises or is suspected to contain such tissue, products or substances, to ascertain whether the provisions of the NHA and its regulations have been complied with.³⁹

A health officer may demand that a register, record or other documents in the custody or under the control of that person be examined, copied or seized if the health officer deems it to be possible evidence for an offence and may require, if necessary, that an explanation of anything appearing therein be given by the person from whom it was seized or copied.⁴⁰ Most importantly, any person (authorised institutions and competent persons) in charge of any activity or process as set out in regulation 22(1) of the Regulations Regarding the General Control of HBM 2012, shall at all reasonable times render assistance to the health officer in the exercise of

³⁷ Reg 22(1) of the Regulations Regarding the General Control of HBM 2012.

³⁸ *Ibid.*

³⁹ *Idem* at reg 22(1)(b).

⁴⁰ *Idem* at reg 22(1)(c) read with 22(1)(d); The above functions of the health officer are the most important, among others; however, due to space constraints for the purpose of this dissertation, only the most important regulations are set out.

his or her duties, as he or she and the member of the executive council deems fit.⁴¹ In addition, the Regulations Relating to Stem Cell Banks 2012 state that, as far as stem cells or any matter relating thereto is concerned, a health officer may take samples of tissue of any tissue product or of any reagent or other special material used in the preparation of tissue or tissue products, or instruct for it to be taken and delivered to whomever it is deemed necessary to be tested; mark or seal any container with stem cells or any device, test reagent or substance; request information or registers from the management of the stem cell bank and interrogate any member of staff of the stem cell bank regarding (1) any premises, equipment or methods used or being used by the authorised stem cell bank; (2) any tissue or tissue product or any test reagent or substance referred to in the regulations; or (3) any applicable operating procedures; place under embargo or seize any stem cells or documentation that could in the health officer's opinion serve as evidence for a crime possibly committed in terms of the NHA or the Regulations;⁴² and, upon request, show the written authority to any person affected by the exercise of his or her powers, duties or functions in terms of the NHA or the regulations.

(c) *Quality and safety prescriptions*

(i) Organisational structure and responsible person(s)

To maintain the integrity of the production of stem cell research and subsequent therapies, various checks and balances relating to quality and safety, storage, protection of information, and accountability of stem cell institutions have been instituted. The different regulations setting out these checks and balances will be set out below.

To ensure compliance with the Regulations Relating to Stem Cell Banks 2012, a responsible person shall be appointed for each authorised stem cell bank.⁴³ A responsible person must ensure compliance with the regulations, provide the director-general with information as required and ensure that stem cells are handled

⁴¹ *Idem* at reg 22(2)(a)-(c).

⁴² Reg 7(c) and (d) of the Regulations Relating to Stem Cell Banks R. 183, as published in GG 35099 of 2012-03-02.

⁴³ Regulations Relating to Stem Cell Banks R. 183, as published in the GG 35099 of 2012-03-02: "Responsible person' means a person who is authorised to be a medical director of a stem cell bank".

according to the standards as set out in the regulations.⁴⁴ Furthermore, the Regulations Relating to Tissue Banks 2012 are applicable in any sense relating to cells and therefore compliance therewith is necessary.⁴⁵ In terms of the Regulations Relating to Tissue Banks 2012, a “designated person” shall be appointed to be in command of policymaking.⁴⁶ In addition, a registered medical practitioner, experienced in human transplantation must fulfil the duties of “medical director” to advise and oversee the organisation’s medical activities.⁴⁷ In addition, the medical director, also known as the “responsible person”, must implement the policies of the governing body, take charge of all operations, including compliance with the NHA and the ancillary regulations thereto, and provide information to the director-general as required in the regulations.⁴⁸

(ii) Traceability

“Traceability” in the Regulations Relating to Tissue Banks 2012 means “the ability to locate cells and/or tissue during any step of its donation, collection, processing, testing, storage, distribution or disposition. It implies the capacity to identify the medical facility receiving the cells and/or tissue and, at the medical facility, the ability to identify the recipient.”⁴⁹ Both stem cell banks and tissue banks must ensure that all the activities performed are traceable in terms of the donor and the recipient. Each donation of tissue or cells or associated product should be given a unique identification code so that all tissues or cells can be identified by means of a label containing the appropriate references to allow for the flow of information.⁵⁰

⁴⁴ *Idem* at reg 12; In terms of reg 5(3) of the Regulations Relating to Tissue Banks R. 182, as published in GG 35099 of 2012-03-02, a tissue bank must have a designated person(s) responsible for policymaking, unless it is provided for by the institution it forms part of.

⁴⁵ Regulations Relating to Tissue Banks R. 182, as published in GG 35099 2012-03-02.

⁴⁶ *Idem* at reg 5(3).

⁴⁷ *Idem* at reg 5(4); It is submitted that someone who is only qualified in the field of tissue transplantation is not necessarily qualified in the derivation of stem cells or the production of such medicinal therapies. Therefore, the appointment of a “medical director” should be applicable to various uses of tissues and cells, and should vary according to the medical practitioner’s field of speciality.

⁴⁸ Both a stem cell bank and a tissue bank shall be inspected at least every year to ensure compliance with the regulations and any other relevant requirements in terms of reg 8 of the Regulations Relating to Stem Cell Banks R. 183, as published in the GG 35099 of 2012-03-02, and reg 8 of the Regulations Relating to Tissue Banks R. 182, as published in GG 35099 of 2012-03-02.

⁴⁹ Reg 1 of the Regulations Relating to Stem Cell Banks R. 183, as published in GG 35099 of 2012-03-02.

⁵⁰ *Idem* at reg 9; Reg 14 of the Regulations Relating to Tissue Banks R. 182, as published in GG 35099 of 2012-03-02.

Furthermore, it is a requirement that data, which is essential for traceability, be kept for a minimum of 30 years after donation or clinical use in an electronic format.⁵¹

(iii) Quality and safety standards of practice

All authorised stem cell and tissue banks should have an updated quality control and safety system in place that resonates with the principles of best laboratory practice (BLP) and good manufacturing practice (GMP).⁵² However, the Department of Health has not recommended or published any set of standards of practice in the field of human tissue and cells. In response to such a need, professionals and organisations working in the field of human tissue and cells have resorted to self-regulation and have published their own guidelines. It should be noted that, at the time of writing this dissertation, the national standards for cellular therapy product collection, processing, storage and distribution have been drafted and, hopefully, would be published in the near future.⁵³ However, these standards of practice do not explicitly include stem cells; therefore, for the time being, the South African Stem Cell Transplantation Society standards will have to cover such matters. In addition, Pepper and Nöthling Slabbert⁵⁴ state that when drafting such guidelines, due consideration must be given to “national professional bodies, as well as international bodies such as the Foundation for the Accreditation of Cellular Therapy, the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and the European Society for Blood and Marrow transplantation (EBMT) and the American Association of Blood Banks.” Organisations such as the newly formed South African Tissue Bank Association (SaTiBA),⁵⁵ the South African Stem Cells Transplantation Society (SASCeTS)⁵⁶ and the South African transplantation Society (SATS)⁵⁷ have published guidelines in an attempt to self-regulate the production of stem cell therapies and associated matters.

⁵¹ *Ibid.*

⁵² *Idem* at reg 11(1)(a).

⁵³ Pepper & Nöthling Slabbert 2015 *SAJBL* 9.

⁵⁴ *Ibid.*

⁵⁵ Standards of Practice for Cellular Therapy: COLLECTION, PROCESSING, STORAGE AND DISTRIBUTION (DRAFT) <<http://www.satiba.org.za/documents/resources/standards-of-practice-for-cellular-therapy.pdf>> (Accessed 8 November 2016)

⁵⁶ The South African Stem Cell Transplantation Society <<http://www.stemcell.org.za/patients.htm>> (Accessed 8 November 2016).

⁵⁷ The South African Transplantation Society <<http://www.sats.org.za/Guidelines.asp>> (Accessed 8 November 2016).

It is strongly recommended that the Department of Health attend to this matter and adopt foreign standards in terms of which stem cell and tissue banks should operate or publish their own guidelines and standards of practice. For a South African stem cell therapy to be sold in the UK, compliance with their standards of practice or a standard that is essentially the same or more rigorous will have to be shown.⁵⁸ Currently, due to misconceptions and faulty definitions in the legislation, the definition of a blood product as set out in the NHA includes certain progenitor cells and, therefore, such stem cells included under this definition, will also be subjected to the mandatory test for blood and blood products, as set out in the Regulations Relating to Blood and Blood Products 2012. This is true, despite the definition of blood in the regulation not being inclusive of progenitor cells. Nevertheless, any inconsistency between the NHA and the regulations thereto would be solved by using the wording of the empowering legislation. Therefore, it follows that such progenitor stem cells must also comply with the Regulations Relating to Blood and Blood Products, as the NHA includes them in the definition of a blood product. In addition to the above requirements, there are also certain prescriptions regarding labelling, documentation and packaging of stem cells,⁵⁹ as well as certain ethical requirements relating to the protection of sensitive patient information, which will be discussed now.

(iv) Donor and recipient information and confidentiality

All authorised institutions performing genetic research or producing embryonic stem cells must record such information in separate registers and submit it to the minister.⁶⁰ All authorised stem cell institutions or tissue banks should at all times ensure that all data, including genetic information collected within the scope of their duties, remain confidential, and for such purposes ensure that safety measures are in place to prevent unauthorised data additions or deletions to, or modifications of, donor files, deferral records or a transfer of information.⁶¹ Furthermore, an authorised

⁵⁸ Reg 15 and 16 of the UK Q & S Regulations.

⁵⁹ Reg 16 of the Regulations Relating to Stem Cell Banks R. 183, as published in the GG 35099 of 2012-03-02; Regulation 13 of the Regulations Relating to Tissue Banks R.182, as published in GG 35099 of 2012-03-02.

⁶⁰ By the end of March each year. See reg 12 of the Regulations Relating to HBM 2012.

⁶¹ Reg 15 of the Regulations Relating to Tissue Banks R. 182, as published in GG 35099 of 2012-03-02; Reg 10 of the Regulations Relating to Stem Cell Banks R. 183, as published in the GG 35099 of 2012-03-02.

stem cell or tissue bank should ensure that no unauthorised disclosure of information occurs, while guaranteeing the traceability of such donations, as well as the anonymity and privacy of the donors.⁶²

In the event that an authorised institution keeps or discloses genetic material for records and other individually identifiable or related health information, that authorised institution must at all times ensure that:⁶³

- a) the information is treated confidentially;
- b) the patient is given a clear explanation of how their information will be used, kept and disclosed;
- c) the patient has access to their records;
- d) written informed consent is obtained before information is released to health insurers, other healthcare providers or any other relevant person;
- e) the information is being used for the purpose it was originally intended for;
- f) written informed consent is obtained for the long-term storage of genetic material, stem cells or research findings;
- g) the records are destroyed after they have fulfilled their intended purpose;
- h) the information is treated as anonymous when used for research purposes.

Now that the operation, structuring, quality and safety requirements of the authorised institutions operating in the field of stem cell technologies have been elucidated, this dissertation turns its focus to the manner and purposes for which such institutions may remove and use stem cells.

6.2.4 Removal and use of stem cells

6.2.4.1 Removal of adult stem cells and induced pluripotent stem cells

The removal of stem cells is primarily regulated by section 55 of the NHA, which states that:

A person may not remove tissue, blood, a blood product or gametes from the body of another person living person for the purposes referred to in section 56 unless it is done— (a) with the written consent of the person from whom the tissue, blood, blood

⁶² *Ibid.*

⁶³ Reg 13 of the Regulations Relating to HBM 2012.

product or gametes are removed granted in the prescribed manner; and (b) in accordance with prescribed conditions.

The “prescribed conditions” referred to in section 55 are set out in the Regulations Relating to Human Biological Material 2012 (Regulations Relating to HBM 2012),⁶⁴ the Regulations Regarding the General Control of HBM 2012,⁶⁵ the Regulations Relating to Stem Cell Banks (The Regulations Relating to Stem Cell Banks 2012)⁶⁶ and, as will be argued for induced pluripotent stem cells, the Regulations Relating to Tissue Banks (The Regulations Relating to Tissue Banks 2012).⁶⁷ The removal of embryonic stem cells will be discussed briefly, but this study focuses on the removal of adult stem cells, such as bone marrow stem cells.

As the definition of “biological material” in terms of the Regulations Relating to HBM includes tissue biopsies (from which stem cells could be derived) as well as stem cells itself, it is safe to say that stem cells or the tissue they are derived from, may only be removed by a competent person for the purposes of genetic testing, genetic health research or therapeutic purposes (which could include the development of a stem cell therapy) in an authorised institution or prescribed institution.⁶⁸ In addition to such requirements, the removal of human biological material for the aforementioned purposes may only be affected:⁶⁹ (a) if written consent was obtained from the donor; or (b) in the event that the donor is under the age of eighteen years, as defined by section 129 of the Children’s Act 38 of 2005 with (i) the informed consent by a child over the age of twelve years with sufficient mental capacity and maturity to understand the benefits, risks, social and implication of the procedure; (ii) the written informed consent of a parent, guardian or caregiver, if the child is younger than twelve years, or older than twelve but lacks sufficient maturity and the necessary mental capacity to understand the outcome of such procedures; (iii) consent of the head of the health establishment, in the case of an emergency; (iv) consent by the minister if the parent, guardian, or caregiver of the child: unreasonably refuses to

⁶⁴ Regulations Regarding the General Control of HBM, as published in the GG 35099 of 2012-03-02.

⁶⁵ Regulations Relating to HBM 2012.

⁶⁶ Regulations Relating to Stem Cell Banks R. 183, as published in the GG 35099 of 2012-03-02.

⁶⁷ Regulations Relating to Tissue Banks R. 182, as published in the GG 35099, 2012-03-02.

⁶⁸ Reg 2(a) & (b) of the Regulations Relating to HBM 2012.

⁶⁹ See s 55 of the NHA. Taking a closer look at sub-article (b) as set out above, it is clear that reg 2(a) & (b) of the Regulations Relating to HBM 2012 intends to set further “prescribed conditions” as referred to in the empowering NHA.

give consent or to assist the child in giving consent; is incapable of giving or assisting in the giving of consent; cannot be readily traced; or is deceased.⁷⁰ Similar to such consent requirements, regulation 2(1) of the Regulations Regarding to the General Control of HBM 2012: Amendment and the Regulations Regarding the General Control of Human Bodies, Tissue, Blood, Blood Products and Gametes: Amendment⁷¹ state that the removal of tissue, blood or gametes from the body of another person may only be effected with the written consent of that person, given that the person is older than eighteen years and, if not, by the parents or guardian of that person.

As induced pluripotent stem cells are produced by the reprogramming of a somatic cell, it does not per se require the removal of a stem cell itself, but the removal of somatic cells from a human body, which cells will ultimately be reprogrammed to a more primal state.⁷² It is submitted that, not only the Regulations Relating to HBM 2012 will apply but also the Regulations Relating to Tissue Banks 2012, as tissue and cells are used synonymously. In terms of sub-regulation 1(1)(a) and (c), read in conjunction with 1(d)(i), no person may remove, acquire or import human tissues from a living or deceased person or use human tissue or its therapeutic products (such as an induced pluripotent stem cell) for a therapeutic, research or educational purpose, unless he or she is registered with the Department of Health as a human tissue bank. It is unclear whether the derivation of a pluripotent stem cell would require authorisation from the director-general as both a stem cell bank and a human tissue bank. Furthermore, the regulations make no mention of the production of an induced pluripotent stem cell and its subsequent applications, which would indicate that the legislation is lagging behind the technology currently available on the market. However, one could argue that the production of an induced pluripotent stem cell would be governed by sub-regulation 1(1)(a) of the Regulations Regarding the General Control of HBM 2012, which states that tissue/cells may be used for medical and dental purposes, which would include “the production of a therapeutic, diagnostic, or prophylactic substance”.

⁷⁰ Reg 3 of the Regulations Relating to HBM 2012; Reg 6 of the Regulations Relating to HBM deals with the removal of biological material from deceased person, which falls outside the ambit of this chapter.

⁷¹ The Regulations Regarding the General Control of Human Bodies, Tissue, Blood, Blood Products and Gametes: Amendment R. 515, as published in GG 39982 of 2016-05-11.

⁷² See ch 2 regarding induced pluripotent stem cells.

More pertinent to human stem cells, the Regulations Relating to Stem Cell Banks 2012 state in sub-regulation 2(1) that no person may remove, acquire or import human stem cells from any living or deceased person; or preserve, screen, test, process, store, separate, label, pack, supply...; or release any stem cell product for therapeutic use, unless it is done at an authorised institution as contemplated by section 54 of the NHA and laboratory tests for infectious agents which may cause transplantation transmitted diseases have been completed and the results of each are available.⁷³ However, there is no need for such tests if the stem cells are for autologous use.

6.2.4.2 Removal of embryonic stem cells

Various regulations have been proclaimed in terms of Chapter 8 of the NHA regarding the use and removal of gametes used for artificial fertilisation.⁷⁴ Most recently, the Regulations Relating to AF 2016⁷⁵ were published on 30 September 2016, which explicitly repeal the 2012 Regulations Relating to Artificial Fertilisation of 2012. For purposes of this discussion, even though the regulations of 2007 and 2011 are still in force technically, only the Regulations Relating to AF 2016 will be discussed, as it was argued earlier that the legislator did in fact intend to repeal the preceding regulations, but negligently omitted to do so.

As most embryonic stem cells are leftover IVF embryos,⁷⁶ it is necessary to discuss how these embryos should be treated. In terms of the Regulations Relating to AF 2016, only a competent person⁷⁷ may remove or withdraw a gamete or cause it to be

⁷³ These diseases are syphilis, Hepatitis B, Hepatitis C and Human Immunodeficiency Virus types 1 and 2.

⁷⁴ Such as the Regulations Regarding Artificial Fertilisation and Related Matters R. 8, as published in GG 29527 of 2007-01-05, Regulations Regarding Artificial Fertilisation and Related Matters R. 262, as published in GG 34159 of 2011-04-01, Regulations Regarding Artificial Fertilisation and Related Matters R. 175, as published in GG 35099 of 2012-03-02.

⁷⁵ Regulations Relating to Artificial Fertilisation of Persons R. 1165 as published in GG 40312 of 2016-09-30.

⁷⁶ In terms of reg 11(c) of the Regulations Relating to AF 2016, a competent person has the authority to destroy any embryo in storage as soon as the recipient for whom embryo transfer has been affected conceives or as soon as that recipient decides not to proceed with the embryo transfer. This provision is essential as it opens the door for embryonic stem cell research, which requires the destruction of an embryo so that the inner cell mass of the blastocyst can be harvested.

⁷⁷ Due to negligence, which led to the omission of a precise definition of a competent person in the Regulations Relating to AF 2016 and the NHA, the definition of the Regulations Relating to Artificial Fertilisation R. 262, as published in GG 34159 of 2011-04-01 (which have not been

removed,⁷⁸ in an authorised institution,⁷⁹ from the donor for the purpose of artificial fertilisation.⁸⁰ Once such an embryo is removed, it must be stored in a frozen state or cryopreserved.⁸¹ Various restrictions on the donation of gametes, prerequisites pertaining to the withdrawal of gametes and the recording of information have to be complied with before embryonic stem cells may be withdrawn from an early IVF embryo. It should be noted that these restrictions are all related to the maximum number of births allowed to be effected using a specific gamete donor's gametes, which is not really applicable in the line of stem cell research and therapy, as the derivation of embryonic stem cells necessitates the destruction of an early embryo.⁸² Before removing a gamete from a donor, a competent person must:

- a) open a gamete donor file to which a unique identification number is allocated in respect of the gamete donor, if no such file has been opened yet;
- b) submit such information to the central data bank as contemplated in regulation 6;
- c) in the event of a known donor, ensure that no more than twelve births, by means of artificial fertilisation, have been realised with the gametes of that specific donor;
- d) obtain a signed statement from the donor regarding previous gamete donations and, if there were previous donations, where and when those donations took place;
- e) obtain informed consent from the donor regarding:
 - i) a physical examination and questioning by a competent person;
 - ii) the removal or withdrawal of a gamete for testing, analysing or other processing as the competent person may deem necessary;

repealed), contrary to its follow-up 2012 regulations, states that a competent person in relation to artificial fertilisation means a person registered with the HPCSA – who is a medical practitioner specialising in gynaecology with accredited training in reproductive medicine, or a medical scientist, medical technologist, clinical technologist, with training in reproductive biology and related laboratory procedures. Interestingly, it escapes the ambit of section 59 of the NHA, which is discussed above.

⁷⁸ For conciseness and flow of argument, reference to the removal of gametes will refer to both the removal and the cause to remove a gamete.

⁷⁹ Reg 10 Regulations Relating to AF 2016.

⁸⁰ *Idem* at reg 4(1).

⁸¹ *Idem* at reg 4(2).

⁸² Reg 7 of the Regulations Relating to AF 2016.



- ii) particulars regarding certain hereditary features, physical attributes, and personal information of the donor, such as: age, height, mass, nationality, colour, educational background, etc.,⁸³
- iii) the particulars of medical tests for genetically transmissible disorders or infectious diseases, or genetic evaluation of the gamete donor,⁸⁴ psychological suitability of the gamete donor,⁸⁵ results of certain tests as contemplated in (e) to (g);
- vi) the particulars contemplated in regulation 9(2)(c) must be submitted to the central data bank, relating to the unique identification number of the gamete donor's file, the number of donations and their respective dates, and the number of live births reached through the artificial fertilisation from the gametes of that specific donor;
- f) ascertain the age of the of the gamete donor;
- g) determine whether the gamete donor has on two occasions, not more than four months apart, and one month prior to the donation of gametes, undergone:
 - i) medical tests for sexually transmissible diseases;
 - ii) a semen analysis in the event of a male donor;
- h) in the case of a female gamete donor, ascertain if she has undergone a gynaecological examination prior to stimulation for the withdrawal of gametes;
- i) ask questions regarding the gamete donor's family history, especially regarding genetic conditions or carries status and mental illness in respect of any child, brother, sister, parent or grandparent of the gamete donor; and
- j) in the event of the recipient and the donor being acquainted, ensure that there is
 - i) written confirmation by both parties that they know each other;
 - ii) a psychological evaluation of both parties.

Furthermore, no gamete imported or removed in terms of the NHA or the Regulations Regarding the AF 2016 from a gamete donor whose test results as contemplated in regulation 8(e) to (g) are not yet available or if the gamete donor is

⁸³ *Idem* at reg 9(1)(a)(ii) of the Regulations Relating to AF 2016.

⁸⁴ *Idem* at reg 9(1)(b).

⁸⁵ *Idem* at reg 9(1)(c).

under the age of eighteen may be used for artificial fertilisation, except if it is medically indicated.⁸⁶ Moreover, a competent person may only effect *in vitro* fertilisation for the purposes of embryo transfer and, therefore, the creation of embryos for the sole purpose of research and the development of stem cell research is forbidden.⁸⁷ However, Regulation 7 of the Regulations Relating to HBM 2012 states that: ⁸⁸ “Excess embryos obtained from *in vitro* fertilisation may be used to produce embryonic stem cell lines for the purpose of research, provided that a competent person obtains written informed consent from the embryo donor.”

Once the stem cell line has been established, the same regulations stating the purposes for which adult stem cells and induced pluripotent stem cells may be procured will be applicable. This argument is around the constructed definition of “biological material” as set out in the Regulations Relating to HBM 2012, which includes “cultured cells”⁸⁹, “gametes”, “progenitor cells” and “embryos”,⁹⁰ as well as the definition of a “stem cell”, which is wide enough to include all types of stem cells (whether induced, adult or embryonic stem cells) and reads as follows:⁹¹ “‘Stem cell’ means a cell that has the capacity to self-renew and to differentiate into mature, specialised cells. Therefore, once the embryo has been destroyed, the “left-over”

⁸⁶ Reg 11(1) of the Regulations Relating to AF 2016; In terms of s 56(2) of the NHA, in addition to being medically indicated, ministerial authorisation is needed for the removal of gametes from a person under the age of eighteen years.

⁸⁷ *Idem* at reg 11(2). This is also in line with the Regulations Regarding the General Control of HBM, as published in the GG 25099 of 2012-03-02, which states in regulation 3(1)(c) that tissue, blood and gametes removed or withdrawn from living persons may only be used for medical and dental purposes, including the artificial fertilisation of another person, in the case of gametes.

⁸⁸ Reg 7 Regulations Relating to Human Biological Material R. 177, as published in GG 35099 of 2012-03-02.

⁸⁹ Reg 1 Regulations Relating to HBM 2012: “Cultured cells” means cells that have been grown outside the body, such as cell multiplication on a feeder layer. See ch 2 for the culturing of stem cell lines.

⁹⁰ Reg 1 Regulations Relating to HBM 2012.

⁹¹ *Ibid*; Reg 1 of the Regulations Relating to Stem Cell Banks 2012; Reg 1 of the Regulations Relating to Blood and Blood Products R. 179, as published in GG 35099 of 2012-03-02 (even though stem cells and blood are not alike, blood is the result of hematopoietic stem cells that have differentiated to blood); At least, these definitions are scientifically more sound than its predecessors, considering that the Regulations Relating to Blood and Blood Products R. 269, as published in GG 34159 of 2011-04-01, defined a stem cell as “any embryonic stem cell, circulating progenitor cell, bone marrow progenitor cell, umbilical cord progenitor cell, hematopoietic progenitor cell or any cell that is capable of replicating (proliferating) and giving rise to a differentiated cell”, which, upon examination of the NHA, concurs with that of the definition of “blood products”. Strictly speaking, as the NHA is the empowering legislation, it will enjoy precedence over the subordinate legislation; Regulations Regarding the Use of Human, DNA, RNA, Cultured Cells, Stem Cells, Blastomeres, Polar Bodies, Embryos, Embryonic Tissue and Small Tissue Biopsies for Diagnostic Testing, Health Research and Therapeutics R. 7, as published in GG 29526 of 2007-01-05.

embryonic stem cells will qualify as biological material and will be regulated accordingly.

6.2.4.3 Compensation for the removal of tissue, stem cells or gametes from a donor

Pepper and Nöthling Slabbert note that there is a distinction between altruistic donation of human material and those that are commercially incentivised.⁹² Furthermore, that any commercial activity directly related to stem cells provided for by an altruistic donor should be done on a not-for-profit cost-recovery basis with publically accessible accountability regarding resource management.⁹³ All other activities that are not for altruistic reasons should be run on a for-profit basis, which would include costs such as storage, manipulation of cells on a fee-for-service basis, tissue culture (including equipment) and medical devices (such as those required for stem cell harvesting and purification).⁹⁴ The ISSCR made a recommendation, stating that it is ethically justifiable to pay women in cash for providing eggs for research as a means of compensating them for their time, inconvenience, willingness to accept some risk, and as reimbursement for reasonable expenses incurred on the women's behalf.⁹⁵ This is not to be misinterpreted as payment for the eggs themselves, which is prohibited, as it provides an unethical incentive for women to donate their eggs, which could ultimately lead to the devaluation of certain genetic traits as could possibly lead to eugenics.⁹⁶

In South Africa, the payment for human biological material, such as stem cells and oocytes, is regulated by section 60 of the NHA titled *Payment in connection with the*

⁹² Pepper & Nöthling Slabbert 2015 *SAJBL* 10.

⁹³ *Ibid.*

⁹⁴ *Ibid.*

⁹⁵ Haimes *et al* "Position statement on the provision and procurement of human eggs for stem cell research" 2013 *Cell Stem Cell* 285-291.

⁹⁶ Holland *et al* n13 80: "If market forces dictate that the demand for oocytes used in reproduction is greater than the demand for oocytes used in research, the price for the latter will be lower than that of the former...If some body parts are worth more than others, and in this case, if some eggs are worth more than others..., any two-tiered system of egg donation creates an inequitable and unethical situation of supply and demand. It pits two groups of women against each other in terms of market desirability on the basis of market-supported eugenics. The eggs of well-educated Caucasians at Ivy League universities as obviously worth considerably more on the reproductive-fertility market than eggs of non-Caucasian, less educated, nonaffluent women. Might the eggs of these less valued women become a future source of research-only oocytes in the private sector?"

importation, acquisition or supply of tissue, blood, blood products or gametes'. This section reads as follows:

- (1) No person, except-
 - (a) a hospital or an institution contemplated in section 58(1)(a), a person or an institution contemplated in section 63 and an authorised institution or, in the case of tissue or gametes imported or exported in the manner provided for in the regulations, the importer or exporter concerned, may receive payment in respect of the acquisition, supply, importation or export of any tissue or gamete for or to another person for any of the purposes contemplated in section 56 or 64;
 - (b) a person or an institution contemplated in section 63 or an authorised institution, may receive any payment in respect of the importation, export or acquisition for the supply to another person of blood or a blood product.
- (2) The amount of payment contemplated in subsection (1) may not exceed an amount which is reasonably required to cover the costs involved in the importation, export, acquisition or supply of the tissue, gamete, blood or blood product in question.
- (3) This section does not prevent a health care provider registered with a statutory health professional council from receiving remuneration for any professional service rendered by him or her.
- (4) It is an offence for a person-
 - (a) who has donated tissue, a gamete, blood or a blood product to receive any form of financial or other reward for such donation, except for the reimbursement of reasonable costs incurred by him or her to provide such donation; and for in this Chapter.
 - (b) to sell or trade in tissue, gametes, blood or blood products, except as provided
- (5) Any person convicted of an offence in terms of subsection (4) is liable on conviction to a fine or to imprisonment for a period not exceeding five years or to both a fine and such imprisonment.

In accordance with section 60 of the NHA, the Regulations Relating to AF 2016 give further instruction. Sub-regulation 5 of the Regulations Relating to AF 2016 states that if gametes are removed from a person, the person may be reimbursed for any reasonable expenses incurred as contemplated in terms of section 60(1)(4).

Additionally, the 2008 guidelines of the Southern African Society for Reproductive Medicine and Gynaecological Endoscopy (SASREG) provide further guidance on

payment for gametes.⁹⁷ Regarding the donation of gametes, the compensation should reflect the time, inconvenience and financial costs to the donor (e.g. travelling costs, loss of income, childcare costs, physical and emotional burden costs) and should be of such a nature that it reduces the possibility of undue inducement and the misinterpretation that the compensation is for the oocyte itself.⁹⁸ The compensation should not be dependent on the outcome of the procedure, but rather on fair compensation of the donation procedure. In terms of an amendment of the 2008 SASREG guidelines, donors may only be compensated for a maximum of R7 000 per procedure as of 1 January 2015.⁹⁹

6.2.4.4 The purposes for which stem cells may be used, induced pluripotent stem cells and research cloning

(a) Uses of adult and embryonic stem cells

As the legality regarding the procurement of stem cells have been discussed, the purposes for which such removal is sanctioned should be discussed now. As stated above, the terms “biological material” and “stem cells” are so wide that it includes within their definition all types of stem cells, including embryonic and induced pluripotent stem cells. However, as induced pluripotent stem cells can be derived from skin cells or tissue, the purposes for which such stem cells may be used will have additional regulations that come into play, such as the Regulations Relating to Tissue Banks.¹⁰⁰ Furthermore, discrepancies in the NHA make for an interesting debate as to whether somatic cell nuclear transfer (SCNT) is admissible on embryonic stem cells.¹⁰¹ Before evaluating the regulations ancillary to the NHA in the context of which uses of stem cells are sanctioned, it is necessary to discuss the empowering provisions of the NHA, section 56, titled *Use of tissue, blood, blood products or gametes removed or withdrawn from living persons*, which reads as follows:

⁹⁷ Southern African Society of Reproductive Medicine and Gynaecological Endoscopy South African Society of Reproductive Science and Surgery. Guidelines for Gamete Donation 2008 <[http://www.fertilitysa.org.za/Egg Donation/](http://www.fertilitysa.org.za/Egg%20Donation/)> (Accessed 5 January 2017).

⁹⁸ Pepper, Nöthling Slabbert & Gouveia “Legislation governing pluripotent stem cells in South Africa” 2015 *SAJBL* 26.

⁹⁹ Southern African Society for Reproductive Medicine and Gynaecological Endoscopy 25 November 2014 Amendment to Gamete Donation Guidelines of 2008 Egg Donor Compensation <<http://www.fertilitysa.org.za/EggDonation/Egg%20donor%20compensation%20-0November%202014.pdf>> (Accessed 5 January 2017).

¹⁰⁰ Regulations Relating to Tissue Banks R. 182, as published in the GG 25099 of 2012-03-02.

¹⁰¹ S 57 of the NHA.

- (1) A person may use tissue or gametes removed or blood or a blood products withdrawn from a living person only for such medical or dental purposes as may be prescribed.
- (2) (a) Subject to paragraph (b), the following tissue, blood, blood products or gametes may not be removed or withdrawn from a living person for any purpose contemplated in subsection (1):
 - (i) Tissue, blood, a blood product or a gamete from a person who is mentally ill within the meaning of the Mental Health Care Act, 2002 (Act 17 of 2002);
 - (ii) Tissue which is not replaceable by natural purposes from a person younger than 18 years;
 - (iii) A gamete from a person younger than 18 years; or
 - (iv) Placenta, embryonic or foetal tissue, stem cells and umbilical cord, excluding umbilical cord progenitor cells.
- (b) The Minister may authorise the removal or withdrawal of tissue, blood, a blood product or gametes contemplated in paragraph (a) and may impose any conditions which may be necessary in respect of such removal or withdrawal.

When analysing this section, it is clear that no stem cells may be withdrawn without ministerial consent, with umbilical cord progenitor cells being the imperceptible exclusion. This means that every bone marrow transplant, even though regarded as established medical practice, will be subject to ministerial authorisation.¹⁰² Furthermore, in terms of section 59 of the NHA, no person may remove tissue from another living person for transplantation in another person or carry out the transplantation of such tissue, unless it is done in a hospital or authorised institution and on the written authority of the medical practitioner in charge of the clinical services in that hospital or authorised institution, or any other medical practitioner authorised by him or her.¹⁰³

¹⁰² Pepper & Nöthling Slabbert 2015 *SAJBL* 6: “This implies that HSC transplantation, which has been practiced for several decades in SA, requires ministerial authorisation, as will all future applications of stem cell therapy requiring removal or withdrawal of stem cells from a living person. The exception appears to be umbilical cord progenitor cells, which implies that other cells harvested from cord blood (i.e. earlier primitive stem cells that are not progenitors and non-haematopoietic stem cells) will also require ministerial authorisation. The legislator’s reason for making this distinction is not apparent. On the other hand, no mention is made of the requirement for ministerial approval in the Regulations Relating to the Use of Human Biological Material, which provide that biological material – which includes progenitor stem cells – may be removed or withdrawn from living adult persons with their informed consent. It is suggested that section 56(2)(a)(iv) above be changed to refer only to ‘embryonic or foetal tissue’.”

¹⁰³ S 58(b)(ii) of the NHA also provides: “...in the case where there is no medical practitioner in charge of the clinical services at the hospital or authorised institution, a medical practitioner authorised thereto by the person in charge if the hospital or authorised institution.”

In terms of regulation 5(a) – (d) of the Regulations Relating to HBM 2012, stem cells or the biological material from which they are derived, may only be withdrawn for medical and dental purposes, such as, among others, DNA, RNA and chromosome-based genetic testing and health research referred to in section 69(3) of the NHA.¹⁰⁴ As research is often done for the production of medicinal modalities, it is submitted that the legislator omitted wording that would explicitly regulate and sanction the production of stem cell therapies. However, as set out above, by applying a “shotgun approach”, which can only be ascribed to incompetence and a lack of attention to detail, the legislator managed to explicitly include “...in case of tissue, the transplanting thereof in the body of another living person or for the production of a therapeutic, diagnostic or prophylactic substance” in the Regulations Regarding the General Control of HBM 2012, which would provide for the production of stem cell therapies.¹⁰⁵ Nevertheless, this creates two contradicting pieces of legislation as the Regulations Regarding the General Control of HBM 2012 provide that tissue, blood and gametes may only be removed or withdrawn from living persons for medical and dental purposes, including the transplantation of tissue/cells or its use such as for the production of a stem cell therapy, whereas the Regulations Relating to HBM 2012 only sanctions the prescribed medical and dental purposes in sub-regulations 5(1)(a) to (d), this is a contradiction that needs to be addressed as researchers are unsure as to what may and what may not be done with regard to human biological material and, in particular, whether stem cell therapies may be produced after research has been conducted. Despite this discrepancy, the Regulations Relating to HBM 2012 provide that research may be done on excess *in vitro* fertilisation embryos for the production of stem cell lines for research purposes¹⁰⁶ and on primordial germ cells obtained from aborted fetuses.¹⁰⁷ In terms of regulation 9 of the Regulations Relating to HBM¹⁰⁸ “Any competent person who wishes to utilise embryonic, adult,

¹⁰⁴ Reg 5 of the Regulations Relating to HBM 2012.

¹⁰⁵ Reg 3(1) of the Regulations Regarding the General Control of HBM 2012.

¹⁰⁶ Reg 7 of the Regulations Relating to HBM 2012.

¹⁰⁷ *Idem* at reg 8.

¹⁰⁸ Pepper & Nöthling Slabbert 2015 *SAJBL* 9: Similarly, the use of transgenic cells shall only be used for stem cell therapy in humans provided: (a) clinical validity and utility of the cells have been demonstrated; and (b) prior permission is obtained from the council. The definition of transgenic cells define cells as ‘derived from species other than human.’ However, the universally accepted definition of cells derived from a species other than human is ‘xenogeneic’, whereas ‘transgenic’, on the other hand means an organism whose genome has been altered by the transfer of a gene

foetal or umbilical cord stem cells for stem cell therapy must obtain written informed consent from the donor of such stem cells.”

Bearing regulation 5 in mind, it now becomes clear that the legislator must have intended to include stem cell therapy in the ambit and negligently omitted to do so, as regulations 9 and 10 provide for the therapeutic application of stem cells. Considering this, it would seem that not only sub-regulations 5 and 9 are dissonant in relation to each other, but also in relation to the Regulations Regarding the General Control of HBM 2012. Furthermore, yet another inconsistency arises when reading the Regulations Relating to HBM 2012 alongside the NHA, in that no ministerial authorisation is needed for the removal and use of biological material (which includes progenitor cells), whereas the NHA states that ministerial authorisation must be obtained for the removal of stem cells and umbilical cord, excluding umbilical cord progenitor cells.¹⁰⁹ Therefore, due to the rules of legal interpretation, the enabling NHA will take precedence over the subordinate legislation and subsequently render the provisions of the Regulations Relating to HBM 2012 invalid.

(b) The production of induced pluripotent stem cells

For the production of induced pluripotent stem cells, additional regulations might come into play, as they are mostly derived from somatic cells such as skin cells, which, for instance, can be harvested from a sample of skin tissue.¹¹⁰ Therefore, in addition to the Regulations Relating to HBM 2012 and the Regulations Regarding the General Control of HBM 2012, the Regulations Relating to Tissue Banks 2012 give an additional requirement – that a person may not release any human tissue products for transplantation in the body of a person; or use human tissues or its products (such as induced pluripotent stem cells) for therapeutic, research or educational purposes unless he or she is authorised as a human tissue bank.¹¹¹ This would mean, when producing an induced pluripotent stem cell line, researchers and medical practitioners will have to be accredited as both a stem cell bank and a

or genes through recombinant DNA techniques from another species or breed using recombinant DNA techniques, such as transgenic mice.

¹⁰⁹ Pepper & Nöthling Slabbert 2015 *SAJBL* 6.

¹¹⁰ See ch 2 for the production of induced pluripotent stem cells.

¹¹¹ Reg 1(1) read with 3(3)(c) of the Regulations Relating to Tissue Banks R. 182, as published in GG 25099 of 2012-03-02.

human tissue bank, as it complies with both definitions and none of the Regulations Relating to HBM 2012, Regulations relating to Stem Cell Banks 2012 and Regulations Relating to Tissue Banks 2012 make mention of one another or exclude some of each other's provisions.

(c) *The use of therapeutic cloning*

“The procedure of SCNT can be described as the removal of the chromosomes (constituted as meiotic spindle complex) from an oocyte, followed by the transfer and fusion of a donor somatic cell nucleus followed by the transfer to the enucleated oocyte.”¹¹² There are two ways in which a blastocyst derived by means of SCNT can be used: Firstly, if the blastocyst is implanted into a uterus and develops to term, the offspring will be genetically identical to the somatic cell donor, which is a process called *reproductive cloning*. Secondly, if the cells from the inner cell mass of that blastocyst are derived and are grown *ex vivo* to form an embryonic stem cell line, it is referred to as *therapeutic cloning*.¹¹³ In terms of section 57(1) of the NHA, reproductive cloning is strictly forbidden, which states that no person may manipulate any genetic material, including human genetic material of human gametes, zygotes or embryos, or be involved in the nuclear transfer or embryo splitting for the purpose of reproductive cloning.¹¹⁴ Section 57(2) of the NHA states that the minister may allow therapeutic cloning, which employs adult or umbilical cord stem cells. It would appear that the legislator omitted to include embryonic stem cells and gametes in the ambit of this section. Such an omission effectively renders the production of genetically compatible embryonic stem cells by means of cell nuclear transfer, intended to produce identical cells or tissues for the production of therapeutic substances or transplantations, impermissible. This holds true despite the wording of section 57(4) of the NHA, which provides that the minister may permit research on stem cells and zygotes not older than fourteen days on a written application, if the applicant undertakes to document the research for record purposes and has

¹¹² “SCNT” is an abbreviation for “somatic cell nuclear transfer” – see Pepper, Gouveia & Nöthling Slabbert 2015 *SAJBL* 25.

¹¹³ *Idem* at 27.

¹¹⁴ S 57(6)(a) of the NHA: “‘Reproductive cloning of a human being’ means the manipulation of genetic material in order to achieve the reproduction of a human being and includes nuclear transfer or embryo splitting for such purpose”.

obtained informed consent from the respective donors, due to the fact that “research” does not necessarily include therapeutic cloning.¹¹⁵

The difference between reproductive cloning and therapeutic cloning lies only in the purpose for which the subsequently fertilised egg will be used.¹¹⁶ Interestingly, the NHA makes no mention of the legality pertaining to research on embryos of between fourteen days and eight weeks of gestation, such as the removal of a cell biopsy. Contravening section 57 is a serious offence and, upon conviction, is punishable with a fine or five years’ imprisonment, or both such a fine and imprisonment, in terms of subsection 5.

6.2.5 Comparison with the UK framework

6.2.5.1 Regulatory authorities in RSA and the UK

From the legislation in the UK, it is clear that there are two main regulatory authorities responsible for oversight regarding the procurement, storage and use of stem cells. Stem cells removed as “relevant material” from a human body will fall under the remit of the HTA.¹¹⁷ However, since the Q & S Regulations were incorporated in 2007, the remit of the HTA has been amended to apply to tissue and cells that were procured outside the human body, such as existing stem cell lines.¹¹⁸ Moreover, relevant material excludes embryos created outside of the human body and, therefore, excludes the procurement of embryonic stem cells.¹¹⁹ The procurement of embryonic stem cell lines is regulated separately by the HFEA in terms of the Acts of 1990 and 2008.¹²⁰ However, once a stem cell line has been established, such a cell line will fall within the ambit of the Q & S Regulations and, therefore, under the remit of the HTA. The HFEA remit ceases to exist when the moment the embryo is destroyed and the cells from the inner cell mass of the

¹¹⁵ Pepper, Gouveia & Nöthling Slabbert 2015 *SAJBL* 27.

¹¹⁶ Pepper & Nöthling Slabbert 2015 *SAJBL* 6: “Strong opposition globally to cloning led to a world-wide ban on reproductive cloning in humans, and as a consequence has cast a shadow on the use of SCNT, without distinguishing between ‘therapeutic cloning’ and ‘reproductive cloning’. As a technique, SCNT may produce a cloned embryo, but the purpose of the process (e.g. research, therapy or reproduction) is a separate matter.”

¹¹⁷ S 14 of the HTA.

¹¹⁸ Before the incorporation of par 30 of the Q & S Regulations, s 54(7) of the HTA excluded all material if it had been created outside the human body.

¹¹⁹ S 53(2)(a) of the HTA.

¹²⁰ Human Fertilisation and Embryology Act 1990. Human Fertilisation and Embryology Act 2008 ch 22.

blastocyst are removed, as the HFEA is only concerned with the creation of an embryo outside the human body.¹²¹ However, since the 2008 Act, the definition of an embryo was broadened to include HAEs.¹²²

Taking a step back to evaluate the South African position regarding the regulatory authorities charged with overseeing such matters, it is clear from an examination of all the regulations that, in order to obtain accreditation as an authorised institution, an applicant stem cell bank/tissue bank/blood bank (thanks to faulty definitions and lack of clarity and harmonisation of the regulatory framework) will have to apply to the director-general, which in turn reports to the Minister of Health. Contrary to the South African position, despite being highly sophisticated, the UK model seems complicated due to the various regulatory authorities in which such researchers have to operate. The separation of power between the HFEA and the HTA is clear, free from political agenda and, most importantly, they are both armed with leading scientists and advisors to lessen the burden of decision-making on one particular uniformed individual.¹²³ Adding to the former, having an institution such as the HFEA or the HTA is beneficial as it protects patients, eases public concern, provides for an environment conducive to scientific research and protects medical practitioners from unethical behaviour. All of this is done by protecting the interests of the embryo, the patients, the public as well as the medical practitioners themselves.¹²⁴

As has been proven by the UK regulatory model, there is a definite need for the establishment of an independent government organisation, charged with overseeing the regulation of human tissue and cells. Alternatively, as with the establishment of the National Health Insurance Advisory Committee, such a committee should be

¹²¹ S 1(2) of the 1990 Act.

¹²² In terms of s 4A(6) of the 2008 Act, an HAE includes: cytoplasmic hybrids, true hybrids; transgenic human embryos; chimeric human embryos; and any embryo not qualifying under the aforementioned, but containing both nuclear and mitochondrial DNA of a human and nuclear or mitochondrial DNA of an animal, but in which the animal DNA is not predominant; *R (Quintavalle) v HFEA* 2008 EWHC 3395 (Admin) found that the creation of hybrids was permissible even before the 2008 Act came into effect.

¹²³ Herring *Medical Law and Ethics* 6th ed (2016) 380: "...the UK's regulation of this area is well established and is regarded by many in the world as a model system. But what is the justification for regulation? The advantage of regulation is that it provides a flexible approach to this controversial area. The HFEA can respond reasonably quickly to advances in medical technology or novel moral issues, whereas it can be slow for Parliament to pass legislation in response to changing circumstances. The HFEA is also able to provide regulations that are free from political pressure: it is less likely to be influenced by a campaign from the tabloid press than political might."

¹²⁴ *Ibid.*

established for stem cell and related matters to ensure the harmonisation and clarification of a currently broken legal framework. Furthermore, the harmonisation of definitions and terms such as “tissue” and “cells” in the UK ensures an easy transition between the reading of the HTAct and the HFEA, arming researchers with the knowledge of the applicable legal boundaries within the field of stem cell research and therapy. However, taking into consideration the faulty definitions and confusion across the regulatory plane in South Africa, the NHA does not have a definition of “cells” or “stem cells”, and it is unclear as to whether “tissue” was meant to include “cells” and, by proxy, also “stem cells”. Adding to the former, certain progenitor cells are included in the definition of blood products, which would mean that only an organisation that is a not-for-profit organisation and allocated in terms of section 53 of the NHA as a blood transfusion service (of which there can only be one) may remove such stem cells, with the exclusion of embryonic stem cells. On the contrary, in the UK, the HTAct refers to “relevant material”, which includes “cells”, as well as the Q & S Regulations, which provide a concise definition of “cells”, to the exclusion of gametes, embryos outside the body, and blood and blood components. Therefore, the legislator needs to address the confusion created by the definitions or the lack thereof, as it does not only create confusion as to what is permissible for researchers and medical practitioners to do with stem cells, but also who has the authority to regulate matters pertaining to stem cells.

6.2.5.2 The removal and use of stem cells in RSA and the UK

(a) Purposes

As stated above, the UK framework pertaining to stem cells is complicated, yet clearly defined and harmonised. The same cannot be said about the South African framework. There are roughly 20 regulations that overlap and contradict each other. In addition, failure to explicitly repeal previous versions lead to legal uncertainty and redundancy, reducing the incentive to develop stem cell technologies; for instance, who is regarded as a “competent person” qualified to remove and work with stem cells? This because the empowering NHA refers to “no person” or “a person” that may remove tissue, gametes, blood or blood products from a living person, whereas the subservient regulations refer to a “competent person”. This causes unnecessary confusion and needs to be rectified, as only a competent person, who is either a medical or dental practitioner, may remove and use stem cells as envisaged by

sections 55 and 56 of the NHA. However, when reading section 59 of the NHA, it is clear that it precludes any other person, such as a medical scientist or any other stem cell researcher who is not registered as a medical or dental practitioner, from conducting research and developing life-saving therapies with the tissue/cells so removed. This issue can be addressed by amending section 59 to omit the words “...use tissue so removed for any purpose contemplated in section 56...”, as this would mean that only medical practitioners may remove such tissue and cells, but such tissue and cells may subsequently be used by other qualified persons to conduct research on such tissue or cells.

Furthermore, regarding the removal and use of stem cells, in terms of section 56 of the NHA, certain tissue, blood or blood products, and gametes may only be removed with overarching ministerial authorisation. For some unapparent reason, no ministerial authorisation is required for the removal or use of umbilical cord progenitor stem cells;¹²⁵ whereas, in the UK, this would seem redundant as any person, who has been afforded a licence from the HTA, as well as a licence from the HFEA, may procure and handle stem cells according to the prescribed purposes when deriving embryonic stem cells. Evidence of the legislator’s lack of keeping abreast of scientific development, is the fact that even though the Regulations Relating to HBM 2012 provide for the use of “transgenic cells” (which was meant to be “xenogeneic cells”), the legislator never explicitly sanctioned the production of HAEs in the Regulations Relating to AF 2016, which means that such cells may only be imported and not produced in South Africa. On the contrary, the UK legislator provided for the production of HAE in 2008, which is an indication that the separate regulatory authorities works well to provide the legislator with up-to-date insight pertaining to the development of stem cell technologies.

In the UK, when embryonic stem cells are derived, all unused cells from licensed research projects must be deposited at the UK Stem Cell Bank. The establishment of a stem cell bank in South Africa will help to provide ethically approved stem cells and guarantee a quality-controlled repository of embryonic, foetal and adult stem cell

¹²⁵ S 56(2)(iv) read with 56(2)(b) of the NHA.

lines, which in turn will provide for an environment that is conducive to the production of stem cell technologies.

(b) *Consent*

Consent can be regarded as a core value to both the HTA and the 1990 Act and its successors, such as the 2008 Act. Although consent is central to the HTA, there is no definition thereof in the Act. However, in terms of the HTA Code of Practice on Consent “[f]or consent to be valid it must be given voluntarily, by an appropriate informed person who has the capacity to agree to the activity in question.”¹²⁶ Furthermore:¹²⁷

For consent to be valid, the person should understand what the activity involves and, where appropriate, what the risks are. When seeking consent, healthcare professionals or other suitably experienced people should ensure that it is appropriate for the intended purpose.

In terms of South African common law, as set out by *Castell v De Greef*,¹²⁸ for consent to have been properly solicited, a patient must have been fully informed regarding the nature or extent of the harm or associated risks, must appreciate and understand the nature of the harm or associated risks and, when duly informed and comprehending the nature of the harm or risks associated, must consent to such medical intervention. Much of these requirements have been codified in sections 6, 7 and 8 of the NHA.

Section 6 of the NHA states that the health user should be informed of (except if there is substantial evidence to show that it is not in the best interest of the health user) his or her health status; the range of diagnostic procedures and treatment options available; the benefits, risks and consequences generally associated with each option; the user’s right to refuse the health services and to receive an explanation of the implications, risks and obligation of such refusal.¹²⁹ All the above must be set out in a language that the user understands and in a manner that takes

¹²⁶ Par 30 of the HTA Code of Practice Consent <https://www.hta.gov.uk/sites/default/files/Code of Practice_1-Consent.pdf#page=3> (Accessed 20 August 2016).

¹²⁷ *Idem* at par 32.

¹²⁸ *Castell v De Greef* 1994 4 SA 408 (CC).

¹²⁹ S 6(1) of the NHA.

into consideration the user's level of literacy.¹³⁰ Furthermore, section 7 of the NHA states that informed consent means "consent for the provision of a specified health service given by a person with legal capacity to do so and who has been informed as contemplated in section 6."¹³¹

These principles are further embodied in the Regulations Relating to AF 2016, the Regulations Relating to HBM 2012, and others.¹³² For instance, the Regulations Relating to HBM 2012 state that a competent person may not remove any biological material from a living person for a therapeutic purpose, unless written informed consent of that person has been obtained.¹³³ However, in terms of the Regulations Relating to Stem Cell Banks 2012, written informed consent is required even in the case of residual donor tissue. The term "residual tissue" is not defined in the NHA or the ancillary regulations and, therefore, it could be interpreted that the legislator intended to implement a system of continuous consent, for instance, leftover skin cells lawfully obtained by means of informed consent may not be used for the production of induced pluripotent stem cells without the further consent of the donor.¹³⁴ Even though the HTA is based on the principles of consent, it also provides for instances where consent may be disregarded. Most notably, the HTA provides that relevant material from living bodies may be stored for research purposes connected with disorders or the functioning of the human body, provided that the research project has ethical clearance and the material has been anonymised so that the person from which such material originates cannot be traced.¹³⁵ Furthermore,

¹³⁰ S 6(2) of the NHA.

¹³¹ *Idem* at 7(1): "Subject to section 8, a health service may not be provided to a user without the user's informed consent, unless- (a) the user is unable to give informed consent and such consent is given by a person-(i) mandated by the user in writing to grant consent on his or her behalf; or (ii) authorised to give such consent in terms of any law or court order; (b) the user is unable to give informed consent and no person is mandated or authorised to give such consent, and the consent is given by the spouse or partner of the user or, in the absence of such spouse or partner, a parent, grandparent, an adult child or a brother or a sister of the user, in the specific order as listed; (c) the provision of a health service without informed consent is authorised in terms of any law or a court order; (d) failure to treat the user, or a group of people which includes the user, will result in a serious risk to public health; or (e) any delay in the provision of the health service to the user might result in his or her death or irreversible damage to his or her health and the user has not expressly, impliedly or by conduct refused that service."

¹³² Regulations Relating to Tissue Banks 2012, Regulations relating to Stem Cell Banks 2012.

¹³³ Reg 5 of the Regulations Relating to HBM 2012.

¹³⁴ Reg 2(3)(iii) of the Regulations Relating to Stem Cell Banks R. 183, as published in GG 35099 of 2012-03-02.

¹³⁵ S 1(7) to (9) of the HTA; Herring *supra* n787 438: "This is an extremely important provision. Notably, it permits the use of material for research even when the patient positively objects."

consent is not required if the material was imported from abroad and, therefore, it will not be the responsibility of the English researcher to ensure that consent was obtained, as there is a presumption that foreign law provides adequate protection for their citizens' rights.¹³⁶ Being more protective of patient rights regarding autonomy and privacy, the South African position creates a possible restriction for the flow of scientific research; however, it is submitted that such restriction resonates with the principles of the Constitution and therefore is permissible.

After evaluating the regulatory framework regarding the removal of and purposes for which stem cells may be removed in Part I and Part II of the discussion, the focus will turn to the South African regulatory framework relating to human clinical trials for stem cell technologies. This area particularly is filled with ethical conundrums and therefore it is of paramount importance that South Africa should maintain a rigorous regulatory regime when it comes to human subjects involved in ethically debatable and experimental research, such as stem cell research.

6.3 Part II: The regulation of clinical trials in South Africa

6.3.1 General background

When producing a therapeutic substance, it is vital that it should be evaluated for quality, safety and efficacy. Most importantly, such validation must be done by means of an ethically approved clinical trial.¹³⁷

All research in South Africa, being a member of the World Health Organisation (WHO), should conform to the Declaration of Helsinki. As a result of the Declaration of Helsinki, an analysis was done of the research procedures, as unethical practices

Hopefully, where a patient has voiced an objection, the researchers will choose not to use his or her material. Note that this does not justify the removal of material without the consent of the patient. It therefore covers material that has been removed with consent, for example material removed during an operation."

¹³⁶ The HTA prohibits the intentional exportation of material with the intention just to reimport it back into the UK, as set out in s 1(13) of the HTA: "In this section, the references to a body or material which has been imported do not include a body or material which has been imported after having been exported with a view to it subsequently being re-imported."

¹³⁷ Department of Health 2006. Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa: "The value of carefully constructed clinical trials as the optimum methodology for the testing and evaluation of new treatments and medicines is well recognised within the South African research community."

were still taking place all over the world.¹³⁸ Following the Declaration of Helsinki, in order to put a stop to such unethical research practices, the FDA in the United States instituted guidelines on informed consent, as well as investigational new drugs and the ethical review and approval system, which collectively became known as good clinical practice (GCP). Since the early 1990s, a joint effort of the United States, the EU and Japan developed the International Conference of Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, and after that, the ICH Harmonised Tripartite Guideline for Good Clinical Practice in 1997 was brought into existence.

In order to ensure compliance with the standards of good clinical practice and the credibility of research, and to provide the public with the assurance that their rights and safety will be protected, the Department of Health drafted the RSA GCP Guidelines.¹³⁹ These guidelines are based on and guided by the ICH Guideline for Good Clinical Practice, ICH Harmonised Tripartite Guidelines (ICH GCP), the Declaration of Helsinki, as well as various other instructive WHO guidelines.¹⁴⁰ To ensure ethical practices, due regard must be given to the respect for autonomy of the research participant, the principle of beneficence and non-maleficence, as well as the principles of Justice and Fairness. For such requirements to be fulfilled, each clinical trial should comprise a few essential components, such as:¹⁴¹

- (a) a relevant and appropriate study rationale;¹⁴²
- (b) optimal study design;¹⁴³

¹³⁸ Moodley *supra* n164 322: “However, in the 1970s fraud in research was still continuing in the US. In the 1970s and early 1980s, the FDA (the equivalent of the Medicines Control Council (MCC) in South Africa) developed regulations on informed consent, Institutional Review Boards (IRB) or Ethics Committee review and approval, and investigation new drugs. Collectively, these regulations, along with various guidelines, became known as good clinical practices or GCPs.”

¹³⁹ Department of Health 2006. Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa: “The value of carefully constructed clinical trials as the optimum methodology for the testing and evaluation of new treatments and medicines is well recognised within the South African research community.” (hereinafter referred to as the RSA GCP guidelines).

¹⁴⁰ *Idem* at par 1.3.

¹⁴¹ *Idem* at par 1.2; Moodley *supra* n164 328-336 as to what makes research ethical.

¹⁴² To avoid unethical practice, the study must ask relevant and important questions that have not yet been substantially answered.

¹⁴³ The study design must be of such a nature that there is a high probability of providing the answers to the questions asked in the trial. Trial population and size must be adequately substantiated, and the variances in social context must be accounted for. Merely taking these issues into account would not be enough, as researchers must take adequate steps to overcome such issues in order to ensure the furtherance of the participants’ dignity, safety and welfare.

- (c) investigator competence;¹⁴⁴
- (d) a balance of risks and benefits for participants;¹⁴⁵
- (e) transparency;¹⁴⁶
- (f) patient privacy;¹⁴⁷ and
- (g) ethical review and impartial oversight of consent procedures: Ethical review provides an objective assessment of the research proposal and the effect it will have on the prospective participants. To ensure compliance with the former, research ethics committees¹⁴⁸ and data and safety monitoring committees have been established.¹⁴⁹

6.3.2 Consent to research and critical issues to be addressed

As discussed in Chapter 3, research could be either *therapeutic* or *non-therapeutic*. Therapeutic research can be defined as research of which the object is to be of benefit to the patient, meaning to prevent or treat a medical condition. It is submitted that most patients opting for stem cell research will fall into this category, as most of the patients/participants opting for stem cell research are suffering from a debilitating or life-threatening disease or condition. On the other hand, non-therapeutic research

¹⁴⁴ Par 1.2.3 of the RSA GCP guidelines: "The Principal Investigator's (and other investigators') competence is assessed by two major parameters: technical and humanistic. Technical competence which includes research competence is assessed by education, knowledge, certification and experience such that the investigator is able to assume responsibility for the proper conduct of a trial, should meet all the qualifications specified by applicable regulatory requirement(s), and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor and/or regulatory authorities. Humanistic parameters require compassion and empathy. This is provided by a proper clinical and research environment, encompassing good research mentoring. In all cases the Principal Investigator for each site must be a South African-based scientist (resident in South Africa)."

¹⁴⁵ Before commencement of the trial, the investigators need to do a benefit-to-risk analysis, particularly in cases of chronic life-threatening conditions, such as Parkinson's and Alzheimer's, which are regular subjects of stem cell clinical trials. For the therapeutic applications of stem cells, revisit ch 2.

¹⁴⁶ All clinical trial data must be reported honestly and unbiasedly. For this reason, the South African National Clinical Trial Register (SANCTR) (which is a central, publicly accessible clinical trial register) was established: to promote collaboration between researchers by easing the sharing of research information; to assist potential participants in finding trials to participate in; to decrease publication bias; to reduce redundant research projects; and to institute a requirement that all clinical trial sponsors are required to register their trials on the SANCTR at www.saclinicaltrials.gov.za. In the event of there not being a sponsor, the principal investigator must register the trial accordingly.

¹⁴⁷ For more information regarding patient privacy, refer to ch 3.

¹⁴⁸ RECs usually consist of lawyers, medical practitioners, bio-ethicists and community representatives.

¹⁴⁹ These committees are charged with overseeing ongoing clinical trials with respect to treatment, efficacy and safety. If it is clear that the study is detrimental to the health of the participants, these committees may ethically terminate the research project prematurely.

refers to research experiments that do not directly benefit the research participant and are mostly to the benefit of society and the furtherance of science.¹⁵⁰

In terms of the Constitution, nobody may be subjected to medical or scientific experiments without their informed consent.¹⁵¹ In promoting this right and in addition to Chapters 2 and 8 of the NHA, section 71(1) states that research or experimentation may only be conducted on a living person, if it is done in the prescribed manner and with the written informed consent of that person, prior to being informed of the object of the research, as well as the possible associated risks and benefits of the research for his or her health. Adding to the former, if research is done on a minor, it must also be done: ¹⁵² in the best interest of the child; according to prescribed conditions; with the consent of the parent or legal guardian of the child; and with the consent of that child, if he or she is capable of understanding the effects of his or her consent.

In an attempt to protect minors from unscrupulous research endeavours, additional ministerial consent is required in the event of non-therapeutic research being conducted on minors, although it is not a requirement for therapeutic research on minors.¹⁵³ The rationale for this distinction is unclear, as the dangers posed by non-therapeutic research are not necessarily greater than the risks of therapeutic research; however, argument could be made that the inherent potential benefit that the therapeutic research holds is in line with the principle of beneficence, and could potentially outweigh the potential harm of the research.

The NHA further states that the minister has the discretion to prevent such research from being conducted if, among other reasons, the research “poses a significant risk” to the health of the child or “some risk” to the health of the child, which does not significantly outweigh the benefit of the proposed research. Even though such

¹⁵⁰ McQuoid-Mason & Dada *A-Z of Medical Law* (2011) 101.

¹⁵¹ S 12(2)(c) of the Constitution; For an in-depth discussion of the principles of the autonomy and the constitutional right to autonomy, refer to ch 3 (Regulation of the Doctor-Patient Relationship) & ch 4 (constitutional analysis of stem cell technologies); McQuoid-Mason & Dada *supra* n814 101: “Logic suggests that for the purposes of the Constitution ‘experiments’ include research”.

¹⁵² S 71(2) of the NHA.

¹⁵³ *Idem* at s 71(3)(a)(ii); Reg 7 of the Regulations Relating to Research with Human Participants R. 719, as published in GG 38000 of 2014-09-19 (hereinafter referred to as the “Human Research Regulations”). Form A sets out the application for ministerial consent for non-therapeutic research with minors.



requirements were recorded with good intentions, the absence of a clear and concise definition of what constitutes a “significant risk” or “some risk”, creates confusion instead of providing the sought after additional protection for minors. Furthermore, such requirements are discordant with those set out in the Department of Health Code of Ethics.¹⁵⁴

The voluntariness of informed consent to a clinical trial may be influenced by various factors,¹⁵⁵ one of which may be if the treatment sought can only be obtained by means of a clinical trial.¹⁵⁶ It is submitted that, as most stem cell technologies are still in the experimental phase, most patients seeking such remedies will have to consent to therapeutic research in the hope of amelioration.¹⁵⁷ In the context of a research participant opting to withdraw from the clinical trial, a serious inconsistency arises between the general scope and the purpose of section 12 of the Constitution, the RSA GCP and the ICH GCP.¹⁵⁸ Both the ICH GCP and the RSA GCP require from a researcher to at least attempt to ascertain the reasons for the withdrawal from the trial, even though it is not a requirement for the participant(s) to furnish such reasons.¹⁵⁹ Such an inquisition can be seen as disrespectful towards the participant’s voluntarily decision and wishes, as it might be intimidating and therefore compel the participant not to withdraw from the research experiment. Moreover, being adequately informed about the research before consenting thereto is pivotal to the realisation of personal autonomy. Therefore, the Department of Health Code of Ethics¹⁶⁰ and the Declaration of Helsinki require that the prospective research participants must understand the information provided before consenting to the research experiment. However, the RSA GCP contains no requirement to ensure

¹⁵⁴ Department of Health: Ethics in Health Research: Principles, Structures and Processes (2004) <<http://www.nhrec.org.za/docs/Documents/EthicsHealthResearchFinalAused.pdf>> (Accessed 21 November 2016).

¹⁵⁵ Britz & Le Roux-Kemp 2012 “Voluntary informed consent and good clinical practice for clinical research in South Africa: Ethical and legal perspectives” *SAMJ* 747: “Other factors such as pain and psychological, such as altruism or social and economic situations like poverty. Prospective participants may also be influenced by the power difference between themselves and the research investigators that threaten truly voluntary informed consent.”

¹⁵⁶ *Ibid.*

¹⁵⁷ For instance, ChondroCelect®, a TEP. Refer back to ch 5 for information regarding tissue-engineered products that have been afforded marketing authorisation in the EU.

¹⁵⁸ Britz & Le Roux-Kemp 2012 *SAMJ* 747.

¹⁵⁹ *Ibid.*

¹⁶⁰ Department of Health: Ethics in Health Research: Principles, Structures and Processes (2004) <<http://www.nhrec.org.za/docs/Documents/EthicsHealthResearchFinalAused.pdf>> (Accessed 21 November 2016).

that the patient understands the research to be conducted. Since the judgement in *Castell v De Greef*,¹⁶¹ which necessitates a patient-centred approach, a health researcher should disclose all information and risks that a reasonable person in the prospective research participant's position would need to be able to attach significance to the research.¹⁶² It stands to reason that the RSA GCP is inadequate, as it does not conform to the appropriate standard to be applied when considering whether sufficient information was divulged and whether the prospective research participant truly fathomed the information before consenting to taking part in the research experiment.¹⁶³

“Informed consent” in itself is a vast topic. In this section and in Chapter 3, the goal was to sensitise the reader to the applicable principles of informed consent in the context of stem cell research and therapies, as well as the unique issues that arise in such a context, which can be ascribed to the novelty of such medicinal therapies and products. The discussion will now turn to the authorisation of a clinical trial and the governmental instruments that are pivotal to the authorisation of a clinical trial.

6.3.3 Authorisation of a clinical trial and the current regulatory environment

Before a clinical trial can be conducted in South Africa, the following steps have to be complied with:

- (a) Authorisation by the National Regulatory Authority, which, in South Africa, is the MCC
- (b) Research Ethics Approval
- (c) Inscription in the South African National Clinical Trials Register (SANCTR)¹⁶⁴

6.3.3.1 Clinical trial authorisation by the MCC

All clinical trials of non-registered medicinal substances and of new indications of registered medicinal substances must be reviewed by the MCC.¹⁶⁵ The MCC, as

¹⁶¹ *Castell v De Greef* 1994 4 SA 408 (CC).

¹⁶² Thomas 2007 *SALJ* 196.

¹⁶³ Britz & Le Roux-Kemp 2012 *SAMJ* 747.

¹⁶⁴ Baird & Van Niekerk 2004 “The Regulation of Clinical Trials in South Africa” *Qual Assur J* 36: This register was brought about by the continuing collaborative effort of both the MCC and the Clinical Trials Task Group, representing the South African pharmaceutical industry, to assist with the high volume of applications. It contains information on investigators, sponsors and site details. Furthermore, it will serve to track approved protocols, amendments, investigational sites, trial progress, safety reporting and other relevant aspects of clinical trials.

incorporated by the MRSCA, has a statutory obligation to ensure that medicines released on the market are compliant with the necessary safety, quality and efficacy standards. In the event of a serious breach of GCP occurring, the MCC may terminate the trial. As a cluster working under the authority of the Department of Health, the MCC consists of nine subcommittees,¹⁶⁶ one of which is the Clinical Trials Committee (CTC) responsible for the review and evaluation of all clinical trial applications. The MCC operates through external experts who are members of the council committee structures.¹⁶⁷ The Clinical Trial Authorisation Application Form (CTF1 form) was designed to assist members of the CTC to determine the answers to the following questions:¹⁶⁸

- (a) Does the proposed trial contribute to new knowledge in a scientific way?
- (b) Are all aspects of the trial in accordance with ethical principles?
- (c) Can patient safety be assured?
- (d) Is there a reason for the trial to be conducted in South Africa?

Furthermore, the application is divided into three sections. Firstly, a checklist of required documentation – in the event of the information being incomplete, such an application will not be processed any further. Secondly, administrative and supplementary details and, thirdly, the applicant's report or presentation regarding the trial.

6.3.3.2 Research ethics approval

In the past, ethical oversight of clinical trials by the MCC was a cause for concern because many of the existing ethics committees complied with the International Conference on Harmonisation and the FDA, but not necessarily with the RSA GCP

¹⁶⁵ Reg 34(1) of the General Regulations Made in Terms of the Medicines and Related Substances Act 101 of 1965 R. 510, as published in GG 24727 of 2003-04-10, as amended (hereinafter referred to as the "MRSCA General Regulations"): "A person desiring to initiate or conduct a clinical trial in respect of an unregistered medicine, a new indication or new dosage regimen of a registered medicine or substance, shall apply to the Council on a form determined by the Council for authority to conduct such a clinical trial."

¹⁶⁶ The Clinical Committee, Pharmaceutical and Analytical Committee, Clinical Trials Committee, Names and Scheduling Committee, Veterinary Clinical Committee, Pharmacovigilance Committee, Biological Medicines Committee, Complementary Medicines Committee, and Legal Committee.

¹⁶⁷ The skills among the MCC and its subcommittees are written into law and include expertise in toxicology and medicine safety, clinical pharmacology, biotechnology, pharmaceuticals, internal medicine, virology, pharmaceutical chemistry, neonatology, paediatrics, immunology, veterinary science, complementary medicine and law.

¹⁶⁸ Reg 32(2) of the MRSCA General Regulations; Refer back to the essential components of a clinical trial above.

guidelines.¹⁶⁹ Accordingly, the Department of Health addressed the issue by appointing the National Health Research Ethics Council (NHREC) in terms of the NHA.¹⁷⁰ The NHREC has the overall responsibility to ensure that health research ethics committees comply with the prescribed legislation, regulations and guidelines. This is done by means of an accreditation and auditing system regarding the performance of research ethics committees.¹⁷¹ In the event of an ethical (or potential) transgression, the NHREC must refer the matter to the HPCSA and must institute disciplinary action against anyone who contravenes the norms, standards and guidelines for research in terms of the NHA.¹⁷²

In terms of section 73 of the NHA, every institution, health agency and health establishment where health research is to be conducted must establish or have access to a health research ethics committee (REC), which is registered with the NHREC. RECs are charged with ensuring the protection of and respect for the rights, safety and wellbeing of participants in clinical trials, and with providing public assurance by reviewing, approving and providing comment on clinical trial protocols, and the suitability of investigators, facilities, methods and procedures used to obtain informed consent.¹⁷³

6.3.3.3 The South African National Clinical Trial Register

In terms of regulation 3(f) of the Human Research Regulations, a researcher (sponsor) conducting health research involving human participants, must register the research project with the SANCTR if the research is classified as a clinical trial. The NHA defines a clinical trial as¹⁷⁴ “A systematic study involving human subjects, which aims to answer specific questions about the safety or efficacy of a medicine or method of treatment.”

Such an application may be made in conjunction with the application for authorisation for the clinical trial. Should there not be a sponsor, it is the duty of the principle investigator (PI) to register the trial. Once the trial has been registered, it

¹⁶⁹ Baird & Van Niekerk 2004 *Qual Assur J* 35.

¹⁷⁰ S 72 of the NHA.

¹⁷¹ Par 1.5.4 of the RSA GCP.

¹⁷² S 72(6)(e) - (f) of the NHA.

¹⁷³ Par 1.5.4 of the RSA GCP; Reg 3 of the Human Research Regulations.

¹⁷⁴ S 72(7) of the NHA.

will be afforded a unique study number within two working days of receipt, whereafter the trial may commence, provided all other requirements have been met.

6.3.4 Comparison to the UK framework for clinical trials

Because the South African regulatory regime regarding clinical trials requires approval by the MCC, research ethics approval and an inscription into the clinical trial register, it is very similar to the process in the UK. Furthermore, the principles of GCP in both countries are vested in the Declaration of Helsinki, which brings further harmony between the regulatory environments. Notwithstanding the fact that the bases of the clinical trial regulatory regime of both countries are the same, it seems that there is a difference in the way it is applied. In the UK and throughout Europe, the focus of the 2014 CTR was incorporated not only to improve patient safety, but also to enable the production of such medicinal products so that smaller businesses would be able to produce them. In contrast to this, the South African regime does not cater for such purposes and is focused solely on patient safety. Furthermore, UK legislation provides for a particular kind of exemption regarding manufacturing authorisation of an IMP, which does not exist in South Africa. In terms of regulation 36(1) and regulation 37 of the 2004 UK CTR, the need for marketing authorisation can be disregarded if an IMP (for instance an autologous stem cell therapy) is assembled in a hospital or healthcare centre by a doctor or pharmacist for its exclusive use in that hospital or healthcare centre or any other centre that is regarded to be a clinical trial site in which the IMP is to be used.

Translated into the South African paradigm, such an exemption would mean that revolutionary new stem cell therapies would be exempted from harsh medicine and clinical legislation if there is an allocated medical centre where a medical practitioner would be allowed to administer, under very strict and controlled conditions, stem cell therapy to those in need and left with no other option. However, in a country that has many vulnerable populations, one should not lose sight of the ethical values governing these types of treatments, and should always strive for absolute compliance with the GCP as set out by the MCC. Interestingly, such an exemption is not the only way to achieve the ends sought by the UK exemption.

In terms of the Medical Innovation Bill 2014 (MIB), there might be instances where unproven and innovative stem cell therapy may be applied without compliance with

clinical trial and medicines legislation. The Bill purports to codify the existing best practices pertaining to decisions by medical practitioners to innovate in cases where evidence-based treatment or management is not optimal or appropriate due to insufficiency and unavailability of the current available evidence. In terms of section 4 of the MIB, a medical practitioner may prescribe or administer a treatment other than a generally accepted or legally authorised one, if he or she is of the opinion that there is no research or other evidence available.¹⁷⁵ However, similar to the position in the UK, the MIB will only apply to a pilot health centre, which is a private or government-owned hospital or other health service provider identified and authorised by the minister by means of a proclamation published in the government gazette. If this Bill were to be passed, it would provide much desired medical treatment in instances where there is none, especially in life or death cases.

Now that the regulatory regime regarding clinical trials has been elucidated, the attention is turned to the use of stem cell therapy on a bigger scale and the subsequent marketing authorisation thereof, such as instances where stem cell therapies have passed the rigorous tests of clinical trials to show quality, safety and efficacy, and are, accordingly, put on the market for the public. Part III of this chapter is dedicated to the exposition of the legislation regarding the use of medicine and the marketing approval thereof.

6.4 Part III: Stem cells as medicine

6.4.1 Background to medicines legislation

The authorisation of medicinal products is regulated by the MCC as incorporated by the MRSCA. The MCC is charged with governing the manufacture, distribution, sale and marketing of medicines, as well as with ensuring that the prescription and dispensing thereof are controlled through the determination of schedules for various medicines and substances. In short, the purpose of the MRSCA is stated very well in *Administrator, Cape v Raats Röntgen and Vermeulen (Pty) Ltd*:¹⁷⁶

¹⁷⁵ S 4(1) read with 4(2) of the MIB 2014 as published in GG 37349 of 2014-02-18, which sets out the specific considerations to be taken into account when deciding to deviate from existing medical practice.

¹⁷⁶ *Administrator, Cape v Raats Röntgen and Vermeulen (Pty) Ltd* 1992 1 SA 245 (A) 254B-E.

It would be advisable to pause for reflection lest the wood become obscured by the trees. Manifestly, the Act was put on the statute book to protect the citizenry at large. Substances for the treatment of human ailments are as old as mankind itself; so are poisons and quacks. The technological explosion of the twentieth century brought in its wake a flood of pharmaceuticals unknown before and incomprehensible to most. The man in the street – and indeed many medical practitioners – could not cope with the cornucopian outpourings of the world-wide network of inventors and manufacturers of medicines. Moreover, the marvels of advertising, marketing and distribution brought such fruits within the grasp of the general public. Hence, an Act designed, as the long title emphasises, to register and control medicines. The enactment created a tightly meshed screening mechanism whereby the public was to be safeguarded: in general any medicine supplied to any person is, first, subject to stringent certification by experts; then it has to be clearly, correctly and comprehensively packaged and labelled and may only be sold by certain classes of persons and with proper explanatory information; to round it out detailed mechanisms for enforcement are created and ancillary measures are authorised.

This was confirmed in a much more concise manner in *Treatment Action Campaign v Rath*,¹⁷⁷ where the court found that the purpose of the MRSCA is to “protect the public against quackery through assessing and controlling the quality [and] efficacy of... medicines”.¹⁷⁸ Bearing this in mind, it is evident that treatments such as stem cell therapy, with the potential to not only alleviate or heal, but also to cause great harm, should be strictly regulated to ensure the state’s constitutional burden to safeguard the public against danger and to provide an environment that is conducive to living safely and harmoniously, is upheld.

However, in the third part of this chapter an argument will be made that there are certain instances where certain stem cell therapies should be exempted from the strict regulatory environment in order to provide an environment that provides lifesaving treatments to patients in need, such as instances where they either have no other option, or in other situations where scientific progress indicates that long-

¹⁷⁷ *Treatment Action Campaign v Rath* 2008 4 ALL SA360 (C) (hereinafter referred to as the “TAC case”).

¹⁷⁸ *Idem* at par 42.

lasting stigmas should be removed and that a new perspective regarding the regulation of stem cell therapies should be taken. Such a case would be that of bone marrow stem cells and certain autologous stem cell procedures. It will be submitted in the argument that South Africa must conform to the UK model, which dictates that the cell therapy should be classified based on the degree of manipulation, rather than an all-inclusive approach based on the type of therapy.

In certain cases, it would be more advantageous for stem cell therapy to be classified as medicinal products due to concerns arising from the quality, safety and efficacy of the treatment. However, the opposite is also true, as there are instances where patient safety is outweighed by the constitutional right to access to health care, read with the right to bodily autonomy, which would provide for a patient to have access to novel medical modalities. This is also true for instances where new research has the potential to dispel superannuated notions that certain stem cell treatments should be regulated as medicinal products, such as the purpose of certain bone marrow stem cells. Before making such an argument, it is important to note that the definition of medicine put forward should be clear and concise, after which it must be determined whether stem cell therapy can be classified as medicine and, if so, which type of medicine.

6.4.2 The definition of medicine

6.4.2.1 General definition

The MRSCA defines medicine as follows:

- [A]ny substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in –
- (a) the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or
 - (b) restoring, correcting or modifying any somatic or psychic or organic function in man, and includes veterinary medicine

An argument was made out in a constitutional challenge in the case of *Reitzer Pharmaceuticals (Pty) Ltd v Registrar of Medicines*¹⁷⁹ that the definition was overboard as “restoring somatic function in man” can be equated to “water used

¹⁷⁹ *Reitzer Pharmaceuticals (Pty) Ltd v Registrar of Medicines* 1998 4 SA 660 (T).

merely to quench thirst”.¹⁸⁰ However, the court refused to strike down the definition of medicine as “it is reasonable and justifiable for ‘medicine’ to be defined widely”, as its rationale is “to achieve the widest and most efficient form of regulation and control of medicines in the interest of the public”,¹⁸¹ without including the everyday eating of food by setting medical parameters to the definition.¹⁸² The Reitzer case achieved such a purpose by neither deletion nor reconstruction of the definition, but by setting out threshold criteria before a “substance” can qualify as medicine, such as an actual or purported medical use.¹⁸³ Therefore, if the stem cells do not have a specific medicinal use or purpose, it shall not be regulated as such. The use of the word “substance” justifies further investigation, as it would appear that it was inserted to confine the definition of medicine to traditional inorganic chemical substances to the exclusion of biological material such as cells.¹⁸⁴ However, such an argument can be dispelled when considering the fact that the court concluded in the Reitzer judgement that *saccharomyces boulardii* (a live micro-organism) should be regulated as medicine.¹⁸⁵ Therefore, biological matter, such as stem cells, arguably can fall within the ambit of the term “substance” and therefore should be regulated as medicine. As the regulatory framework regarding medicine evolved, different medicinal product categories emerged through various notices and regulations published in the Government Gazette. One such a category is “biological medicine”, which, without a doubt, would include stem cells under the definition of “medicine.”

6.4.2.2 Stem cells as biological medicine

In terms of the MCC Guidelines for the Registration of Medicines, biological medicines are categorised as medicinal modalities in which the active ingredient or key excipients have been derived from living organisms or tissues, or manufactured using a biological process.¹⁸⁶ Even though these guidelines do not strictly constitute a

¹⁸⁰ *Idem* at 662.

¹⁸¹ *Idem* at 684.

¹⁸² Jordaan 2012 SAJHR 37.

¹⁸³ *Ibid.*

¹⁸⁴ Jordaan 2012 SAJHR 38; *Reitzer Pharmaceuticals (Pty) Ltd v Registrar of Medicines supra* n843 664H.

¹⁸⁵ *Ibid.*

¹⁸⁶ Botes & Alessandrini 2015 SAJBL 37; MCC Guidelines for the Registration of Medicines: General Information 2012 <<http://www.kznhealth.gov.za/research/mccinfo.pdf>> (Accessed 14 Dec 2016).

source of law, “they do provide insight into the regulatory intent of the MCC and how the MCC officially interprets the ambit of its regulatory mandate”.¹⁸⁷

The MCC’s *Guidance Document: Good Manufacturing Practice for Medicines in South Africa 2010*¹⁸⁸ (MCC GMP Guidelines) defines biological medicine as follows:

- 15.1.1 Biological medicines comprise those derived or extracted from living organisms or tissues and those which contain living or inactivated organisms in the end product.
- 15.1.3 The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture. Biological medicinal products prepared by the following methods of manufacture will fall under this chapter.
 - (a) Microbial cultures, excluding those resulting from r-DNA techniques.
 - (b) Microbial and cell cultures, including those resulting from recombinant DNA or hybridoma techniques.
 - (c) Extraction from biological tissues.
 - (d) Propagation of live agents in embryos or animals.

Similar to the MCC GMP Guidelines, the MCC’s General Information Document for Human Medicines¹⁸⁹ concurs by defining biological medicine as set out above. From this definition, it is clear that as the ancillary regulations made in terms of the NHA, the term ‘tissue’ is used synonymous with the term ‘cells’ in the Regulations Relating to Tissue Banks 2012. Therefore, it follows that, due to the definition of biological medicine being inclusive of “cell cultures” and “biological tissues”, it is evident that stem cell therapy would constitute biological medicine, which is subject to registration in terms of the MRSCA.

6.4.2.3 The registration of biological medicine

Section 14(1) of the MRSCA prohibits the sale of any unregistered medicine that has been called up for registration. All biological medicines have been called up for

¹⁸⁷ Jordaan 2012 SAJHR 39.

¹⁸⁸ As published in GG 24785 of 2003-05-02.

¹⁸⁹ MCC *Guidelines for the Registration of Medicines: General Information 2012*
<<http://www.kznhealth.gov.za/research/mccinfo.pdf>> (Accessed 14 December 2016).

registration and are listed as scheduled substances under Category A, Classification 30.¹⁹⁰ As such, stem cell therapy is subject to registration under the Medicines Act. Prior to such registration, all biological medicine would be evaluated for safety, quality and efficacy by the Biological Medicines Committee as well as the standard MCC Committees.¹⁹¹ In doing so, the MCC will take both national and international guidelines such as the ICH GCP (focusing the global harmonisation of safety, efficacy and quality standards resulting from Good Manufacturing Practices and properly designed and conducted clinical trials) into consideration.¹⁹²

6.4.2.4 Stem cell tourism and the Consumer Protection Act 68 of 2008

As noted by Botes and Alessandrini,¹⁹³ even though the “selling of unregistered medicine is an offence punishable with a fine and/or imprisonment not exceeding 10 years, prosecutions and convictions are extremely rare.”¹⁹⁴ This creates a problem called stem cell tourism, where patients flock to countries with lax regulatory frameworks in order to obtain stem cell therapies that are often unproven and dangerous. It has been recorded that, on average, such treatments could amount to R122 500 and, in some instances, the stem cell tourist received stem cells from animals such as sheep or rabbits.¹⁹⁵ Administering such unproven therapies to patients and then even charging for them are regarded as highly unethical and, therefore, the ISSCR published guidelines that condemn the administration of unproven therapies outside the scope of a clinical trial.

Closely related to the patient safety, the MRSCA states that the director-general must be informed of the therapeutic efficacy and effect of any medicine as soon as practically possible after registration with the MCC, including its purpose as well as the manner and circumstances in which it is to be used.¹⁹⁶ Therefore, subsequent to registration, any advertisement that makes any false claims regarding the

¹⁹⁰ Notice in terms of s 14(2) of the MRSCA, R. 510 as published in GG 24727 (as amended) of 2003-05-02.

¹⁹¹ MCC *Guidelines for the Registration of Medicines: General Information* 2012 <<http://www.kznhealth.gov.za/research/mccinfo.pdf>> (Accessed 14 December 2016).

¹⁹² Botes & Alessandrini 2015 *SAJBL* 36, 37.

¹⁹³ *Ibid.*

¹⁹⁴ *Ibid.*; S 29 of the MRSCA.

¹⁹⁵ Pepper “Partial relief from the regulatory vacuum involving human tissues through enactment of Chapter 8 of the National Health Act and regulations thereto” 2009 *S Afr Med J* 736-737.

¹⁹⁶ S 22(1) of the MRSCA.

therapeutic effect and efficacy of the medicine is prohibited due to being false and misleading.¹⁹⁷ Any sale of medicine between a healthcare provider and a patient, including that of biological medicine, as well as the marketing thereof, and services in exchange for consideration, is subject to the provisions of the CPA.¹⁹⁸ In terms of section 29 of CPA, misleading, fraudulent or deceptive marketing is prohibited, which includes deceptions regarding the nature, properties, advantages or uses of goods or services, the conditions under which and the prices at which goods or services can be supplied or any other material aspect.

Therefore, offering unproven stem cell therapy and making therapeutic claims without any proof thereof are misleading and in contravention of the CPA. In addition, these patients are often left with no other option, as they are suffering from debilitating life-threatening diseases or conditions, and are most likely unable to protect their own interests, which would make the sale of such therapies highly unethical and unlawful. If the supplier sells such goods to a patient who fails to appreciate the language of the terms agreed upon and does not correct the patient's seemingly false impression, such a sale would constitute a false and misleading or deceptive representation in terms of section 41 of the CPA. Any agreement between a patient and a supplier of a stem cell product or a therapy based on fraudulent behaviour that violates the CPA, or purports to limit or exempt a supplier from liability for any loss due to the gross negligence of the supplier or any of its representatives, is forbidden.¹⁹⁹ Accordingly, liability of a stem cell therapy supplier/healthcare service provider may not be escaped contractually. Adding to the former, section 61 of the CPA states that a supplier is strictly liable for any harm caused where the product was either unsafe, hazardous or defective or was supplied to a patient without adequate warning of the associated risks related to the administration of such therapy. Any such contraventions of the CPA that result in serious illness, disability or death of a patient could warrant a direct application to court for the redress of

¹⁹⁷ *Idem* at s 20(1).

¹⁹⁸ Botes & Alessandrini 2015 *SAJBL* 37; Nöthling Slabbert *et al* "The application of the CPA in the health care context: Concerns and Recommendations" 2011 *Compar Int Law J SA* 168-203.

¹⁹⁹ S 51 of the CPA; With reference to s 48 of the CPA, Botes & Alessandrini 2015 *SAJBL* 38 note: "The agreed price for the therapy as well as the manner in which the therapy will be administered must also be fair, reasonable, just and may not waive any liability of suppliers or rights of patients, Liability resulting from stem cell therapy can accordingly not be escaped through contractual terms."

money spent as well as compensation for losses or expenses relating to harm suffered as a result of the said stem cell therapy, including legal costs.²⁰⁰ In assessing such a claim based on a contravention of the CPA due to a misrepresentation made by a healthcare supplier to a healthcare user, the court will, among other things, take into consideration the fact that the parties bound by the contract were not contracting on an even plane, which is influenced by factors such as both parties' capacity to enter into contractual agreements, level of education and intelligence, experience and bargaining position, whether the patient should reasonably have been aware of the existence and extent of the unfairness or unjustness contained in the agreement, the prevalence of identical or similar medical treatment from other medical suppliers and whether the biological medicine was supplied under special orders of the patient.²⁰¹

Depending on its findings, the court may order the supplier of stem cell technologies to cease all practices related thereto, to avoid further incurrence of such bad conduct in an effort to ensure the safety of other patients. Should the MCC be of the opinion that the stem cell technology does not serve the best interest of the public, it may order that such medicine be disposed of.²⁰² It is of vital importance that the suppliers of stem cell therapies and products provide validated treatments, as the "premature translation of unproven stem cell therapy resulting in such court and disposal orders can destroy people's trust in stem cell therapy and negatively impact on current translation research, future funding and development of this promising biological medicine."²⁰³

6.4.2.5 Stem cells as medicine?

As stated above, in most instances, stem cell products or treatments will fulfil the definition of medicine and constitute biological medicine in terms of the MRSCA. Despite the fact that the MCC prohibits the sale of unregistered medicine which has been called up for registration, two existing exemptions are applicable:

²⁰⁰ S 52 of CPA; The CPA makes no mention of restrictions pertaining to the heads of damages and therefore as rightly pointed out by Botes & Alessandrini 2015 *SAJBL* 38: "it is arguable that the patient will also be entitled to claim for general damages."

²⁰¹ *Ibid.*

²⁰² S 23 of the MRSCA.

²⁰³ Botes & Alessandrini 2015 *SAJBL* 38.

1. Stem cells used for haematological stem cell transplantation, which has been practiced for decades as part of the treatment of certain haematological disorders and cancers are not subject to registration in terms of the MRSCA. However, such transplants do require ministerial consent in addition to the written informed consent of the patient.
2. In terms of section 14(4) of the MRSCA, where medicine is compounded in the course of the medical practitioner's professional capacity "in a quantity not greater than that required for treatment as determined by the medical practitioner."

Before a substance can be regarded as medicine, it must be used relatively widely for therapeutic purposes and not only on a single occasion.²⁰⁴ When considering the ambit of the second exemption, the specific characteristics of an autologous stem cell therapy come to mind. The very nature of an autologous stem cell is vested in the fact that it is patient specific. According to the definition of biological medicine, such therapies or products will constitute medicine and should be registered and regulated as such. However, knowledge of foreign policy and case law would dictate that, despite autologous stem cell therapy or medicinal products satisfying the definition of medicine, there are other factors at stake. Therefore, the next section will be dedicated to clarifying the variables and will pose arguments for whether or where autologous stem cell therapies are in fact regarded as medicine. This will be done with reference to American case law and European policy, which govern stem cell legislation in the UK.

6.4.2.6 *United States v Regenerative Sciences LLC*

Whether autologous stem cell therapies do in fact constitute medicinal products subject to regulation as such, is a question that was put to the United States District Court for the district of Columbia (*United States v Regenerative Sciences LLC*).²⁰⁵ Before elaborating on the court's findings and applying it to the South African context, in conjunction with European policy, it is necessary to set out the facts of the case and the way in which the autologous stem cells before the court are applied.

²⁰⁴ *Reitzer Pharmaceuticals (Pty) Ltd v Registrar of Medicines supra* n843 660 (T).

²⁰⁵ *US v Regenerative Sciences, LLC*, 741 F.3d 1314 (DC Cir 2014).

Regenerative Sciences prepared a stem cell therapy by means of withdrawing small amounts of bone marrow or synovial fluid samples from the back of the patient's hip, whereafter these samples were used to withdraw and isolate mesenchymal stem cells to be cultured and grown in greater numbers by means of using natural growth factors found in the patient's blood. After the appropriate cell population has been cultured, it is combined with an antibiotic doxycycline, which is used to prevent bacterial contamination. Once quality tests have been completed and passed, these cells are then reintroduced/injected into the patient's injured area, such as the knee, hip or rotator cuff. After it has been injected, the patient's own cells begin to repair the damaged tissue in the injured area.²⁰⁶ Regenerative Sciences claims that this autologous mesenchymal stem cell therapy aids in the regeneration of bone and cartilage by publishing a study based on 227 patients and another study based on 339 patients that show that this type of stem cell therapy is dramatically safer than more invasive surgical procedures.

The FDA monitored the trademarked mesenchymal stem cell therapy, Regenexx™, based on how the company described it on the website. On 25 July 2008, the FDA sent a letter to Regenerative Sciences stating that the Regenexx™ therapy qualifies as a "drug" under the Federal Food, Drug and Cosmetic Act.²⁰⁷ After inspection by the FDA, it was found that the laboratories did not conform to GMP, upon which the FDA filed suit. After the FDA filed suit, Regenerative Sciences filed a counterclaim, claiming that the FDA was exceeding its mandate and did not have jurisdiction to regulate such stem cells. It was put before court that the methods applied to claim success were weak, as well as the fact that there were no substantial numbers to validate the findings and no control methods.²⁰⁸ Regenerative Sciences further argued that it was within the mandate of the FDA to regulate drugs produced for and administered to patients, which were standardised and mass produced, where Regenexx's™ stem cells were patient-specific autologous stem cells and not mass produced.

²⁰⁶ Krimsky *supra* n10 173.

²⁰⁷ Federal Food, Drug and Cosmetic Act 21 USC 9.

²⁰⁸ Krimsky *supra* n10 176.



Regenerative Sciences went on to argue that such stem cells are not to be regarded as a medicine, but merely as a process that forms part of medical practice over which the FDA has no authority.²⁰⁹ The FDA made a counterargument stating that it is irrelevant in terms of law whether a product is individualised for a patient, by referring to the definition of a “drug”²¹⁰ and a “biological product.”²¹¹ If Regenexx™ does indeed escape the grasp of FDA regulation it would have a seemingly lower regulatory oversight, but for it to be regulated as such it must be concluded that the stem cells were minimally manipulated. Bearing in mind the workings of the Regenexx™ therapy, Regenerative Sciences contended that the treatment does in fact constitute minimal manipulation of the cells. This is because, despite being subjected to additives and nutrients and environmental changes, such as humidity and temperature, these cells remain the cells of the patient and therefore should be classified as minimally manipulated. Regenerative Sciences further substantiated its argument by stating that in the event of the FDA being granted regulatory authority over autologous stem cell treatments, it will have a huge impact on the cost of production, and will only be available to the very rich.²¹²

Such regulation would therefore also deny hopeless and vulnerable patients the much needed treatment and would give rise to stem cell tourism in addition to hampering the production of such therapies and limiting small companies’ opportunity to compete against major drug companies. Lastly, Regenerative Sciences based their argument on the value of the doctor-patient relationship by stating that such regulatory oversight over autologous stem cell therapies by the FDA would infringe on a patient’s right to autonomy, which would include the right to use his or her own stem cells to be withdrawn, cultured and reintroduced.²¹³ Both the court *a quo* and the US appeals court decision in 2014 found that Regenexx’s™ therapy satisfies the definition of a drug and biological product and that these cells are not minimally manipulated.

²⁰⁹ *Idem* at 177.

²¹⁰ “Drug” is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animals, or articles other than food intended to affect the structure or any function of the body of man or animals.

²¹¹ “Biological product” is defined as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component, or analogous product applicable to the prevention, treatment, or cure of disease or condition of human beings

²¹² *Krimsky supra n10 178.*

²¹³ *Idem* at 179.

6.4.2.7 Minimal and substantial manipulation

Whether stem cells are minimally manipulated or not would determine whether medicines legislation in the USA would apply or not and, therefore, set the product upon an expensive clinical trial path before broad use may be authorised. In terms of the FDA guidelines on minimally manipulated cells,²¹⁴ which were instituted after the decision of the Regenexx™ therapy, the isolation and expansion of cells would in future be regarded as more-than-minimally manipulated, as the original cell characteristics have been changed.

Similar to the position in the USA, the ATMP Regulation in Europe and the UK states that cells or tissues will constitute TEPs, if the cells or tissues have been subjected to substantial manipulation so that the biological characteristics, physiological functions or structural properties relevant for intended regeneration, repair or replacement are achieved or if the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.²¹⁵ However, despite the fact that these cells do not constitute substantial manipulation, if they are used in a non-homologous fashion they will constitute a TEP and therefore be subject to registration as medicine.

6.4.2.8 Comparison to South African law

It is clear from the above construction of South African law and the analysis of the Regenexx case, in conjunction with UK law, that there is no doubt as to whether or not stem cell products would constitute biological medicine that has been called up for registration in terms of the MRSCA. However, contrary to the all-inclusive policy in South Africa, the UK and the USA provide for another threshold test, namely whether the cells have been “substantially manipulated” or “more-than-minimally manipulated” and whether they are for homologous use. On the other hand, the MRSCA does not provide for such a criterion, which in turn translates into the fact

²¹⁴ FDA Draft Guidance – Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (2014)

²¹⁵ Jekerle *et al* 2010 *Bundesgesundheitsblatt* 4-8; Excluded from substantial manipulation is the listed Annexure 1 manipulations in the ATMP Regulation, such as “cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification.”

that all stem cell therapies, including homologous minimally manipulated autologous stem cell therapies, should be registered with the MCC as biological medicinal products. Such an “all-inclusive approach” can be seen as an outright infringement of patients’ right to bodily autonomy. However, argument could be made that the state’s duty to protect society from harmful substances trumps such a right. Furthermore, such strict regulation would translate into high costs for the production and testing of such therapies and products, which would discourage investors and investigators and, ultimately, deny vulnerable patients hope.

It should be noted that, according to the *status quo*, there is no such a criterion in the MRSCA pertaining to the *degree of manipulation* of cells as a determining factor of whether the therapy qualifies as medicine, and the medical practitioners currently preparing autologous or even allogeneic stem cell therapies on a non-routine basis in quantities determined by the medical practitioner as necessary may be exempted in terms of section 14(4) of the Act.

(a) *Exempting certain autologous stem cell therapies from medicines legislation*

As stated earlier in Chapter 5, the CAT published two scientific recommendations classifying BM-MNCs and CD133+ stem cells as TEPs, both of which were based on the intended use, which was to improve heart function of patients with ischemic heart disease, post-acute myocardial infarction and chronic heart disease.²¹⁶ The concept that bone marrow is exclusively dedicated to haematopoietic functions is completely outdated, as bone marrow has been demonstrated to carry out further regenerative functions of remote tissues under homeostatic conditions.

Bearing in mind that the criteria for a TEP require that it should not be used for homologous purposes, the following argument can be made out: It stands to reason that, based on the new evidence that bone marrow has other regenerative functions in addition to haematological functions, it is outdated and wrong to include such therapies in the ambit of the ATMP Regulation, as it is now proven to be a

²¹⁶ Cuende *et al* 2012 *Stem Cells Trans Med* 404.

homologous function of bone marrow stem cells to regenerate heart tissue.²¹⁷ The only difference between the therapy and that of the natural recruitment of CD133+ cells is the fact that, naturally, these cells are cumulatively recruited over time, whereas, by means of the stem cell therapy, these cells are now collected from the bone marrow, cultured and administered intra-arterially.²¹⁸ With these facts in mind, argument can be put forward that the MRSCA creates an unreasonable inclusion of such therapies by using this all-inclusive approach brought about by a feeble definition of biological medicine, which translates into an infringement on a patient's right to bodily autonomy by unreasonably denying a patient access to health care (which should be regarded as standard medical practice) and the right to bodily autonomy.

Logically, it makes no sense to argue that a bone marrow transplantation, which is usually an allogeneic transplant, should escape the stringent medicines legislation; but applying the same bone marrow stem cells in an autologous manner (without the risk of immune rejection) for a different essential or homologous function, such as heart tissue regeneration, should be included under the definition of medicine, and, therefore, should comply with the higher standards for processing, quality control and GMP. Including this type of treatment under the umbrella of biological medicine, subjects such stem cell therapies to more stringent clinical trial regulation that cannot be justified in terms of patient safety. If these therapies are regarded as transplants and not as medicine, they would not only be much more cost-effective, but would also be more readily available to patients in need.

It is submitted that the MCC should review the scope of the MRSCA to determine its stance on the matter. As it stands, the exemption in terms of section 14(4) of the MRSCA would provide a way out for medical practitioners to provide such therapy to patients.

²¹⁷ Takahashi *et al* 1999 *Nat Med* 434; Crosby *et al* "Endothelial cells of hematopoietic origin make a significant contribution to adult blood vessel formation" 2000 *Circ Res* 728; Kocher *et al* 2001 *Nat Med* 430; Kamihata *et al* 2001 *Circulation* 1046; Gneccchi *et al* 2008 *Circ Res* 1204.

²¹⁸ Cuende *et al* 2012 *Stem Cells Trans Med* 406.

6.5 Conclusion

To summarise, the legislation regarding the procurement, storage and purposes for which stem cells may be used must be amended as it gives rise to vast legal uncertainty, especially in terms of the NHA. Despite broadly similar regulatory requirements and procedures regarding pre-market approval of medicines, such as clinical trials, GCP and GMP, as set out by the ICH GMP guidelines, various disparities remain, such as issues regarding donor eligibility and the suitability of stem cell lines for use in clinical trials and subsequent commercialisation.²¹⁹ Upon proper investigation of the MRSCA, it would appear that, similar to the USA and the UK, stem cell technologies would constitute biological medicine and is subject to registration. However, in terms of section 14 of the MRSCA, it is possible for a medical practitioner to produce such a stem cell therapy on a small scale for patient-specific needs, without complying with clinical trial and medicines legislation. Furthermore, when passed, the MIB could provide medical practitioners in authorised institutions with the means to deviate from standard practice and pursue treatment of a more experimental nature.

Furthermore, it is submitted that the MCC should clarify the definition of biological medicine because the *status quo* limits patients' right to access to certain medical therapies, in addition to hampering of therapy production due to rising costs. This limitation can be ascribed to a vague and wide definition of what constitutes biological medicine. As illustrated by the example of BM-MNCs and CD133+ cells, there are instances where it would be beneficial for certain stem cell technologies to be disregarded from the ambit of medicines legislation as it would provide a faster and more cost-effective cure or treatment to patients in need, in addition to a furtherance of their rights of bodily autonomy and access to health care.

However, taking the history and the current population landscape into account, the MCC should keep a watchful eye on stem cell treatments current readily available to the public, which, more often than not, are unproven and part of the ever-growing problem of stem cell tourism.²²⁰ In order to provide for an environment that ensures

²¹⁹ Pepper & Nöthling Slabbert 2015 *SAJBL* 4, 5-6; Feigal *et al* 2014 "Proceedings: International regulatory consideration on development pathways for stem cell therapies" *Stem Cells Transl Med* 879-887

²²⁰ Nöthling Slabbert *et al* 2015 "Stem cell tourism in South Africa: A legal update" *SAJBL* 45: "Close scrutiny of Chapter 8 of the MHA, including regulations promulgated in terms of the Act relevant to

both patient safety and provides access to stem cell technologies, these often-conflicting values must be weighed up and balanced, all of which must be done through the lens of the Constitution, which is the supreme law in South Africa. This can be achieved by learning from the UK regularity model regarding stem cell therapies. Despite its complexity, the UK model provides for an environment that is conducive to the production of life-saving stem cell technologies by creating an environment that instills trust in investors and investigators by means of a clear-cut regulatory framework, of which the procurement and use are regulated by the HTA and the HFEA, quality and safety of cells so procured are regulated by the HTA and, lastly, all medicinal products in the UK are regulated by the MHRA and the EMA. All of this is done without compromising patient safety, which requires compliance with the principles of consent as set out by the HTAct and the HFEA as well as the overarching EUTCD, which regulates the quality of the treatment and the ATMP Regulation, which provides for stem cell therapies to be regulated as medicine, and which provides for certain instances where such legislation should be exempted, such as HE.

Currently, stem cell therapy constitutes biological medicine and is subject to the control by the MCC. In addition to medicines legislation, the CPA also influences the way in which stem cell therapies may be provided and prohibits the supply of such therapies that were made available by means of false representation, or any agreement that waives a supplier's responsibility to provide a hazardous or harmful medicinal product to a patient. However, the MIB and section 14 of the MRSCA provide loopholes for the application of unproven stem cell therapies.

stem cell research and therapy, is required to close any regulatory gaps that may facilitate the promotion of unproven cell therapies. Inconsistent or conflicting statutory provision, regulations and guidelines governing both research and clinical applications may inadvertently expose vulnerable patients to possible exploitation by bogus stem cell therapy operators... some physicians are already practicing unregulated cell therapy in SA, with grave potential consequences. Access to novel therapies also raises pertinent issues regarding distributive justice and access to these treatments in a developing country where access to basic healthcare services is already severely compromised.”

CHAPTER 7

CONCLUSION AND RECOMMENDATIONS

This dissertation discussed a wide range of topics related to the biology of stem cell therapy, ethics and the constitutional rights and regulatory framework that govern the production and prescription of stem cell technologies. At first glance, the regulatory framework might be overwhelming and, as discussed in the previous chapters, quite confusing and contradictory in certain instances.

In Chapter 3 of this dissertation, the foundation of the medical profession, namely the ethical regulation of the doctor-patient relationship was discussed. It set out a healthcare practitioner's obligations towards a patient and concluded on what is most important for a healthcare practitioner when deciding which therapy to administer to a patient. In doing so, a medical practitioner is charged with a duty to always reflect on what is regarded as ethical by making a value judgement by weighing up various ethical principles like autonomy, beneficence, non-maleficence and justice, to determine the most suitable course of action.

In terms of medical ethical rules, such as those of the HPCSA, it would be regarded as unethical to administer a treatment that has not been proven safe, efficacious and of good quality as it would be in contrast to the principles of beneficence and non-maleficence. Furthermore, medical practitioners are charged not to choose vulnerable participants for their research experiments or experimental treatment, such as those in financial need or the very sick, as this might be dissonant with the principles of informed consent and, ultimately, against the principles of justice and beneficence. It is important to remember that any unethical action, despite not being illegal, could be subjected to a review process by the HPCSA, which could lead to a medical practitioner being struck from the roll. As a rule of thumb, the ethical rule presupposes the legal rule, which is best illustrated by the Bill of Rights of the South African Constitution, which embodies various ethical principles in a variety of rights afforded to everyone in South Africa.

Chapter 4 set out to discuss the various constitutional rights pertaining to stem cell technologies, which often overlap or compete with one another. It discussed the

concept of a right to health of a patient seeking stem cell therapy (often in experimental phase), which right does not exist in itself, but is the product of the overlapping rights to security of person, dignity, access to health care and the right to life. However, it is important not to place too much emphasis on such a right, but rather on its constituent rights. If a patient is denied treatment that has not yet been approved by the MCC, he or she should be careful to base their claim on the denial of their constitutional right to access to health care, as the competing duty of the state to protect and provide a safe environment, as well as the concomitant rights of the collective (to be protected from unproven and harmful stem cell therapy) will outweigh the patient's right to access to health care. However, if the MIB is assented to as an Act, it would provide for a legislative framework where medical practitioners may deviate from standard medical practice. Medical practitioners will be able to provide innovative and experimental treatment if they are of the opinion that there are no alternative treatments available or if the research is either insufficient or uncertain. If the MIB is assented to, it will be viewed as the fortification of a patient's rights to security of person, human dignity, access to health care and the right to life. However, such a Bill is not without problems, as it would open the door to unscrupulous behaviour on the part of medical practitioners and might lead to unethical practices where patients are receiving dangerous treatments and ultimately further contribute to the problem of stem cell tourism. However, such dangers should not hinder desperate patients to receive medical care and it is bestowed upon the South African government and the HPCSA to ensure that such practices are conducted within the law.

Turning a blind eye to the Constitution is impossible when making decisions regarding the delivery of healthcare services, irrespective of the healthcare questions at hand. The ethical and constitutional values and rights are the backdrop against which one must view the regulatory framework pertaining to stem cell technologies. Ultimately, the Constitution not only instructs the scope and content of the legislation, but is also serves as the benchmark against which the validity of stem cell legislation (or any legislation for that matter) will be tested. As South African legislation pertaining to stem cell therapy fails the public, which leads to an infringement of their constitutional rights, this dissertation set out to propose that certain principles and mechanisms of the UK's regulatory framework pertaining to stem cell technologies

should be incorporated, which form the topic of discussion in Chapter 5. In the United Kingdom the procurement of start-up materials for the production of stem cell therapies is regulated by various authorities. In terms of the HTAct and the EUTCD, as transposed into the UK by means of the Q & S Regulations, the HTA regulates the procurement, processing, storage, distribution, import, export, etc. to ensure compliance with adequate safety and quality measures and that the tissues or cells were procured by means of appropriate consent.

If the cells procured are classified as an “autologous graft”, these cells will fall outside the ambit of the Q & S Regulations as well as subsequent regulation in terms of medicines legislation. Should the start-up material involve gametes, or the destruction/creation of embryos or HAEs, such activities will be regulated by the HFEA. However, once an independent stem cell line has been established and banked according to the UK Stem Cell Bank Steering Committee’s instruction, the remit of the of the HFEA ceases.¹ Once an independent cell line has been created with a reasonable prospect of clinical application, such a cell line will fall within the remit and regulation of the MHRA.² In the event that these cells are to be used as medicinal products or therapies, compliance with clinical trial laws, such as GCP, GMP and various requirements relating to the production of an IMP is mandatory. In addition, if such an IMP is also an ATMP, compliance with the ATMP Regulation is also necessary. In order to place such an ATMP IMP on the market it needs to comply with marketing authorisation requirements as set out by the Medicinal Product Directive as amended by the ATMP Regulation. However, the width of the definition of an ATMP is too wide and therefore it accidentally and unintentionally includes certain stem cell therapies within its ambit to be regulated as medicine, such as certain autologous bone marrow stem cell therapies that have to comply with the stringent medicinal product marketing authorisation requirements as set out

¹ R. 30 8th HFEA Code of Practice http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition_Oct_2015.pdf (Accessed 9 September 2016): “Where this licence authorises the derivation of human embryonic stem cell lines: (a) a sample of all stem cell lines derived must be deposited in the UK Stem Cell Bank in accordance with any relevant Bank guidelines, and (b) the remainder of all stem cell lines (in so far as not used or destroyed as part of or in the course of the research project) must be deposited in the UK Stem Cell Bank or distributed in accordance with any relevant guidelines issued by the UK Stem Cell Bank.”; HTA *Position Statement on regulating human embryonic stem cell lines for human application*, as updated in August 2015 <http://www.biobank.org/home2/sites/files/hta_position_statement_on_regulating_human_embryonic_stem_cell_lines_for_human_application.pdf> (Accessed 9 September (2016).

² *Ibid.*

in the ATMP Regulation, which could be circumvented if the width of the definition of an ATMP was amended to exclude such therapies.

Despite the ATMP Regulation's inclusive nature, there are a few exemptions to medicinal product regulation in the EU and the UK, such as SE, which allows for any medicinal product in the EU to be exempted in order to cater for individual special needs of a patient or a specific group of patients if there is no pharmaceutical equivalent on the market. Alongside this exemption is HE, which provides for the innovative use of ATMPs that are free from marketing authorisation requirements if the product is manufactured on a non-routine basis, used in the same member state, in a hospital, under the sole responsibility of a medical practitioner in order to cater for the tailored needs of an individual.

Notwithstanding minor discrepancies and the regulatory framework's intricacy, the UK framework can be seen as clear and consistent and providing a harmonised regulatory plane for the production and subsequent marketing authorisation of medicinal products. This directly translates into the protection of patients' and their rights and the provision of an environment that is conducive to the production of stem cell technologies.

Lastly, in Chapter 6, as the title presupposes, a comparison was made between the South African legislation pertaining to stem cell technologies and that of the UK. In stark contrast to the UK framework, an examination of the legislation relating to the procurement, storage and purposes for which stem cells may be used indicated much legal uncertainty, especially brought about by the instrument that sought to bring about the opposite, the NHA. Despite conformity of procedures regarding pre-market approval, clinical trial requirements such as GCP and GMP which conform to the ICH GMP guidelines, various disparities are still present such as issues regarding donor eligibility and the suitability of stem cell lines for use in clinical trials and subsequent commercialisation.³

³ Pepper & Nöthling Slabbert 2015 *SAJBL* 4, 5-6; Feigal *et al* 2014 *Stem Cells Transl Med* 879-887.

In South Africa, stem cell therapy qualifies as biological medicine and is subject to registration as such. However, similar to HE and SE in terms of section 14 of the MRSCA, it is possible for a medical practitioner to produce a stem cell therapy on a small scale for patient-specific needs, without complying with medicines legislation. Furthermore, as elucidated above, the provisions of the MIB could provide medical practitioners in an authorised pilot site the opportunity to deviate from standard practice and pursue more innovative and experimental means of treatment. Currently, stem cell technology constitutes biological medicine and is subject to the control of the MCC. In addition to medicines legislation, the CPA influences the way in which stem cell therapies may be provided and prohibits the supply of such therapies by means of false representation or any agreement that waives or supplies responsibility for providing hazardous or harmful medicinal product to a patient.

Finally, this study concludes that it would be beneficial for the South African legislation to be amended and expanded in order to achieve the following:

1. The definition of *medicine* and specifically *biological medicine* should be amended as it is currently too inclusive due to the legislator's lack of scientific knowledge and therefore it includes various therapies that should rather be exempted from medicines legislation. Including such therapies in the definition of medicine causes the cost of production to rise, thereby delaying the production and ultimately denying patients in need vital therapies.
2. Chapter 8 of the National Health Act and its regulations should be amended as it is unclear to researchers which type of authorisation is needed as well as who must authorise them to perform stem cell-related activities. In addition to the confusion, due to a lack of knowledge, various regulations forbid certain actions and contradict each other. For instance, in terms of regulation 2(1), read with article 2(2)(a) of the Regulations Relating to Blood and Blood Products 2012, no organisation, institution or person, other than a blood transfusion service, as contemplated in section 53 of the NHA, shall be involved in the withdrawal of stem cells, except for embryonic stem cells from any living person for the later administration thereof to that person or to any other living person. This creates a unique contradiction, as, in terms of the Regulations Relating to Human Stem Cells 2012, authorisation from the

director-general as a Stem Cell Bank is required, but in terms of the Regulations Relating to Blood and Blood Products 2012, only a blood transfusion service may remove stem cells.

3. In executing points one and two above, the legislator must give due regard to the UK framework pertaining to stem cell technologies, as it provides a clear and harmonised framework with which stem cells are regulated, which, in addition to patient safety, also makes it possible for smaller businesses to compete with big pharmaceutical companies. If smaller companies are given the opportunity to develop such products in South Africa, it will not only stimulate our economy, but also translate into the delivery of life-saving therapies to desperate patients who had no other option available previously.
4. Instead of providing the Minister and the Director-General of Health with the power to authorise institutions as Authorised Institutions to conduct activities pertaining to stem cells, it is proposed that a separate legal entity, such as the HTA and the HFEA be instituted, for instance the CTAC. The CTAC should be an independent regulatory body, which is jointly governed by the HPCSA and the MCC. It should consist of ethicists, legal scholars, politicians, medical practitioners and various scientists all working in the field of regenerative medicine, such as stem cell therapy and gene therapy. Such an authority will not only safeguard the public from unproven/hazardous treatments and unethical behaviour, but will also remove any political agenda from the production of such therapies which often only serve their own agenda and might prevent the expansion of stem cell technology in South Africa.

BIBLIOGRAPHY

Primary Sources

Legislation

Primary Legislation: South Africa

Choice of Termination of Pregnancy Act 92 of 1996

Consumer Protection Act 68 of 2008

Employment Equity Act 55 of 1998 as amended by Act 47 of 2013

Health Professions Act 56 of 1974 as amended by Act 89 of 1997

Human Tissue Act 65 of 1963

Medical Innovation Bill 2014 Government Gazette 37349, 2014-02-18

Medicines and Related Substances Control Act 101 of 1965

National Health Act 61 of 2003

Promotion of Access to Information Act 2 of 2000

Promotion of Administrative Justice Act 3 of 2000

Promotion of Equality and Prevention of Unfair Discrimination Act 4 of 2000

The Constitution of the Republic of South Africa Act 200 of 1993

The Constitution of the Republic of South Africa, 1996

Secondary Legislation and Instructive documents: South Africa

MCC's *Guidance Document: Good Manufacturing Practice for Medicines in South Africa 2010* Government Gazette 24785, 2003-05-02

Notice in terms of section 14(2) of the Medical and Related Substances Control Act (Regulation 510) Government Gazette 24727 (as amended), 2003-05-02

Regulations Regarding Artificial Fertilisation and Related Matters (Regulation 8)

Government Gazette 29527, 2007-01-05

Regulations Regarding the General Control of Human Bodies, Tissue, Blood, Blood Products and Gametes (Regulation 268) Government Gazette 34159, 2011-04-01

Regulations Regarding the General Control of Human Bodies, Tissue, Blood, Blood Products and Gametes (Regulation 180) Government Gazette 35099, 2012-03-02

Regulations Regarding the use of Human DNA, RNA, Cultured Cells, Stem Cells, Blastomeres, Polar Bodies, Embryos, Embryonic Tissue and Small Tissue Biopsies for Diagnostic Testing, Health Research and Therapeutics (Regulation 7) Government Gazette 29526, 2007-01-05

Regulations Relating to Artificial fertilisation of Persons (Regulation 262) Government Gazette 34159, 2011-04-01

Regulations Relating to Artificial Fertilisation of Persons (Regulation 175) Government Gazette 35099, 2012-03-02

Regulations Relating to Artificial Fertilisation of Persons (Regulation 1165) Government Gazette 40312, 2016-09-30

Regulations Relating to Blood and Blood Products (Regulation 179) Government Gazette 35099, 2012-03-02

Regulations Relating to Blood and Blood Products (Regulation 269) Government Gazette 34159, 2011-04-01

Regulations Relating to Human Biological Material (Regulation 263) Government Gazette 34159, 2011-04-01

Regulations Relating to Human Biological Material (Regulation 177) Government Gazette 35099, 2012-03-02

Regulations relating to Human Stem Cells (Regulation 376) Government Gazette 29840, 2007-05-04

Regulations Relating to Research with Human Participants (Regulation 719) Government Gazette 38000, 2014-09-19

Regulations Relating to Stem Cell Banks (Regulation 183) Government Gazette 35099, 2012-03-02

Regulations Relating to Stem Cell Institutions or Organisations (Regulation 265)
Government Gazette 34159, 2011-04-01

Regulations Relating to the Use of Human Biological Material (Regulation 177)
Government Gazette 35099, 2012-03-02

Regulations Relating to Tissue Banks (Regulation 182) Government Gazette 35099,
2012-03-02

Regulations Relating to Tissue Banks (Regulation 237) Government Gazette 35099,
2011-04-01

South Africa (2006) Ethical and professional rules of the Health Professions Council
of South Africa (Proclamation R. 717), 2006-08-04

European Union

*Additional Protocol to the Convention on Human Rights and Biomedicine, concerning
Biomedical Research* Strasbourg 25.01.2005 <[http://www.coe.int/en/web/
conventions /full-list/-/conventions/rms/090000168008371a](http://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168008371a)> (Accessed 18 July
2016)

*Additional Protocol to the Convention on Human Rights and Biomedicine, concerning
Transplantation of Organs and Tissues of Human Origin* Strasbourg 24/01/2002
<<http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/186>> (Accessed
18 July 2016)

Advanced Therapy Medicinal Product Regulation EU Regulation 1394/2007.

Commission Directive 2005/28/EC laying down principles and detailed guidelines for
good clinical practice as regards investigational medicinal products for human use,
as well as the requirements for authorisation of the manufacturing or importation of
such products (Good Clinical Practice Directive)

Council of Europe *Convention for the Protection of Human Rights and Dignity of the
Human Being with regard to the Application of Biology and Medicine: Convention on
Human Rights and Biomedicine* Oviedo, 4. IV. 1997
<[https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/
090000168007cf98](https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98)> Accessed 18 July 2016

Council of Europe 1950 *Convention for the Protection of Human Rights and Fundamental Freedoms, as amended*

Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices *Official Journal* L189

Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells

Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC regarding certain technical requirements for the donation, procurement and testing of human tissues and cells, *Official Journal* L38/40

Directive 2006/86/EC of 24 October 2006, implementing Directive 2004/23/EC as regards traceability requirements, notification of serious adverse reactions and events, and certain technical requirements for the coding, processing, preservation, storage, and distribution of human tissues and cells, *Official Journal* L294/32

Directive 92/42/EEC of 5 September 2007 Amendment to the Medical Device Directive

Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices *Official Journal* L331 of 7 December 1998

European Communities Act of 1972 chapter 68

International Declaration on Human Genetic Data 2003

<<http://unesdoc.unesco.org/ima ges/0013/001331/133171e.pdf#page=45>>

(Accessed 1 July 2016)

Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency *Official Journal* L136

Regulation (EC) 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products, and repealing Regulation (EEC) 339/93 *Official Journal* L218

Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC *Official Journal* L158

Universal Declaration on Bioethics and Human Rights 2005

<<http://unesdoc.unesco.org/images/0014/001428/142825e.pdf#page=80>> (Accessed 18 July 2016)

WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects 2014. [http://www.wma.net/en/30publications/10policies/b3/index.html.pdf?print-media-type&footer-right=\[page\]/\[toPage\]](http://www.wma.net/en/30publications/10policies/b3/index.html.pdf?print-media-type&footer-right=[page]/[toPage])> (Accessed 18 July 2016)

United States

Title 21 Food and Drugs USC, Chapter 9, Subchapter V, Part A§ 355 – New Drugs

United Kingdom

Access to Medical Treatments (Innovation) Act 2016 Chapter 9

Human Fertilisation and Embryology (Quality and Safety) Regulations 2007 (SI 2007/1522)

Human Fertilisation and Embryology Act 1990

Human Fertilisation and Embryology Act 2008 c 22

Human Fertilisation and Embryology Regulations 2015

Human Reproductive Cloning Act 2001 c 23

Human Tissue (Quality and Safety for Human Application) Regulations 2007 (SI 2007/1523)

Human Tissue Act 2004 (Persons who Lack Capacity to Consent and Transplants)
Regulations 2006 (SI 2006/1659)

Human Tissue Act 2004 c 30

Human Tissue Authority Directions 003/2010 implementing the 'Guide to Quality and
Safety Assurance for Human Tissues and Cells for Patient Treatment'

Mental Capacity Act 2005 c 9

Case law

South Africa

Administrator, Cape v Raats Röntgen and Vermeulen (Pty) Ltd 1992 1 SA 245 (A)
254B-E

Bernstein v Bester 1996 2 SA 751 (CC)

Carmichele v Minister of Safety and Security 2001 4 SA 938 (CC)

Castell v de Greef 1994 4 SA 408 (C)

*Christian Lawyers Association of South Africa and Others v Minister of Health and
Others* 1998 SA 1113 (T)

Clarke v Hurst 1992 4 SA 630 (D) *De Beer v Health Professions Council of South
Africa* 2005 1 SA 332 (T)

Du Plessis v De Klerk 1996 3 SA 850 (CC)

Ferreira v Levin 1996 1 SA 984 (CC)

Government of the Republic of South Africa and Others v Grootboom 2001 SA 46
(CC)

Groenewald v Sout African Medical Council 1934 TPD 404

Harksen v Lane 1998 1 SA 300 (CC)

Hoffmann v South African Airways 2000 12 BLLR 1365 (CC)

McLoughlin v South African Medical and Dental Council 1947 2 SA 377 (W)

MEC for Education, KwaZulu-Natal v Pillay 2008 1 SA 474 (CC) *Minister of Health v Treatment Action Campaign* 2002 5 SA 271 (CC)

Mistry v Interim National Medical and Dental Council of South Africa 1998 4 SA 1127 (CC)

Mutual and Federal Insurance Co Ltd v Oudtshoorn Municipality 1985 1 SA 419 (A)

National Coalition for Gay and Lesbian Equality and Another v Minister of Justice and Others 1998 2 ZACC

Phillips v De Klerk 1983 TPD (unreported)

President of the Republic of South Africa v Hugo 1997 4 SA 1 (CC) *Reitzer Pharmaceuticals (Pty) Ltd v Registrar of Medicines* 1998 4 SA 660 (T).

Rompel v Botha 1953 (T)

S v Dodo 2001 (3) SA 382 (CC)

S v Jordan (sex workers and advocacy task force as Amici Curiae) 2002 6 SA 642 (CC)

S v Makwanyane 1995 5 BCLR 666 (CC)

S v Mhlungu 1995 3 SA 867 (CC)

Seetal v Pravitha 1983 3 SA 827 (D)

Soobramoney v Minister of Health, KwaZulu-Natal 1997 12 BCLR 1696 (CC)

Soobramoney v Minister of Health, KwaZulu-Natal 1998 1 SA 765 (CC)

Stoffberg v Elliot 1923 CPD 148

Treatment Action Campaign v Rath 2008 4 ALL SA 360 (C)

Tucker v SA Medical and Dental Council 1980 2 SA 207 (T)

Venter v Roche Products (Pty) Ltd A11/2014 2014 ZAWCHC 157

Veriava v President of South African Medical and Dental Council 1985 2 SA 293 (T).

United Kingdom

Allinson v General Council of Medical Education and Registration 1894 1 QB Div. 750

R v Cambridge Health Authority, Ex Parte B 1994 ALL ER 129 (CA) *R v (Quintavalle) v Secretary of State for Health* 2003 2 All ER 113

The United States of America

Tarasoff v Regents of the University of California 1967 17 Cal. 3d 425, 131 Cal. Rptr. 14, 551 P.2d 334

Abigail Alliance for Better Access to Developmental Drugs v Von Eschenbach 2006 445 F 3d 470 DC Cir

Roe v Wade 1973 410 US 113, 152

Moore v Regents of the University of California 1990 793 P 2d 479 Cal Sup Ct

Canadian Case Law

Operation Dismantle v The Queen 1985 1 SCR 44, 18 DLR 481

European Union

Brüstle v Greenpeace 2011 ECR I 9821

<<http://curia.europa.eu/juris/document/document.jsf?jsessionid=9ea7d2dc30d50a5ec1080a4c4c41969e82aecd83bc4.e34KaxiLc3qMb40Rch0SaxuTbh90?text=&docid=111402&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=141650>>
(Accessed 1 July 2016)

Durisotto v Italy (62804/13) 6 May 2014 (ECHR)

EU Court of Justice in International Stem Cell Corporation v Comptroller General of Patents Case-364/13 2014-12-18

G 0002/06 (Use of embryos/WARF) of 25-11-2008 <<http://www.epo.org/law-practice/case-law-appeals/recent/g060002ex1.html>> (Accessed 22 June 2016)

Secondary Sources

Textbooks

Ackermann L *Human Dignity: Lodestar for Equality in South Africa* (2012) Kaapstad: Juta

Beauchamp T & Childress J *Principles of Biomedical Ethics* (2013) New York: Oxford University Press

Beauchamp T et al *Contemporary Issues in Bioethics: International edition* 8th ed (2014) California: Wadsworth

Botha CJ *Statutory Interpretation: An Introduction for Students* 5th ed (2012) Cape Town: Juta

Buratovich MA *The Stem Cell Epistles: Letters to my Students About Bioethics, Embryos, Stem cells, and Fertility Treatments* (2013) Wipf and Stock Publishers

Carstens P & Pearmain D *Foundational Principles of South African Medical Law* (2007) Durban: LexisNexis

Cohen CB *Renewing the stuff of life: stem cells, ethics, and public policy* (2007) Oxford University Press

Currie I & De Waal J *The Bill of Rights Handbook* 6th edition (2004) Cape Town: Juta
Davel CJ & Jordaan RA *Law of Persons* (2005) Cape Town: Juta

Devolder K *The Ethics of Embryonic Stem Cell Research* (2015) Oxford University Press

Foster C *Human dignity in bioethics and law* (2011) Bloomsbury Publishing

Herring J *Medical Law and Ethics* 5th ed (2014) Oxford: Oxford University Press

Herring J. *Medical Law and Ethics* 6th (2016) Oxford: Oxford University Press

Holland S Lebacqz K & Zoloth L *The human embryonic stem cell debate: science, ethics, and public policy* (Vol. 3) (2001) MIT Press

Jackson E *Law and the regulation of medicines* (2012) Oxford: Hart Publishing

Jeeves MA (ed) *From cells to souls, and beyond: Changing portraits of human nature* (2004) Wm B Eerdmans Publishing

Jones J *et al* *The Ethics of Surgical Practice: Cases, Dilemmas, and Resolutions* (2008) New York: Oxford University Press

Khan FA *Biotechnology in Medical Sciences* (2014) CRC Press

Krimsky S *Stem Cell Dialogues: A Philosophical and Scientific Inquiry into Medical Frontiers* (2015) New York: Columbia University Press

McQuoid-Mason D & Dada D *A-Z of Medical Law* (2011) Cape Town: Juta

Meyer BJ *et al* *Human Physiology: Chemical physical and physiological principles* 3rd ed (1997) Cape Town: Juta

Moodley K (ed) *Medical Ethics, Law and Human Rights: A South African Perspective* (2014) Van Schaik: Pretoria

Peterson J *Genetic Turning Points: The Ethics of Human Genetic Intervention* (2001) Wm B Eerdmans Publishing

Strauss S *Doctor, Patient and the Law: A selection of practical issues* 3rd ed (1991) Van Schaik: Pretoria

Vertes *et al* (eds) *Stem Cells in Regenerative Medicine: Science, Regulation and Business Strategies* (2015) John Wiley & Sons

Theses & Dissertations

De Vries *The ethics in genetics – The legitimacy and application of stem cell research* (LLM Dissertation 2006 University of Pretoria)

Prinsen *An analysis of the proposed regulatory framework for the procurement and distribution of stem cells* (LLM Dissertation 2010 University of Pretoria)

Swanepoel *Embryonic stem cell research and cloning: A proposed legislative framework in context of legal status and personhood* (LLM Dissertation 2006 University of Pretoria)

Van Oosten *The Doctrine of informed consent in medical law* (LLD Thesis unpublished 1989 University of South Africa)

Journal Publications

Alliance for Advanced Therapies “Focus Hospital Exemption on Developing Innovative and Safe Treatments for Patients” 2013 *Regenerative Medicine* 121

Amechi “Regulating Developments in Embryonic Stem Cell Research in Africa: A Third Person’s Perspective” 2008 *African Journal of International and Comparative Law* 85

Astori *et al* “Bone marrow derived stem cells in regenerative medicine as advanced therapy medicinal products” 2010 *American Journal of Translational Research* 285-295

Baird & Van Niekerk “The Regulation of Clinical Trials in South Africa” 2004 *Quality Assurance Journal* 33

Bell & Devaney “Gaps and overlaps: improving the current regulation of stem cells in the UK” 2011 *Journal of Medical Ethics* 621

Blassime & Rial-Sebbag “Regulation of Cell-Based Therapies in Europe: Current Challenges and Emerging Issues” 2013 *Stem Cells and Development* 14

Botes & Alessandrini “Legal implications of translational promises of unproven stem cell therapy” 2015 *South African Journal of Bioethics and Law* 36

Britz & Le Roux-Kemp “Voluntary informed consent and good clinical practice for clinical research in South Africa: Ethical and legal perspectives” 2012 *South African Medical Journal* 747

Chandler “Does A Patient Have A Constitutional Right To The Freedom Of Medical Research? Regenerative Medicine and Therapeutic Cloning Research in Canada” 2012 *McGill Journal of Law and Health* 1

Chapman *et al* “Stem cell research and applications: Monitoring the frontiers of biomedical research” 1999 *American Association for the Advancement of Science*

Chaskalson A “Human Dignity as a Foundational Value in our Constitutional Order” 2000 *South African Journal for Human Rights* 193

Church J “Jerrier v Outsurance Insurance Company Ltd 2013 JDR 0562 (KZP) The duty to disclose: An ongoing problem?” 2013 *De Jure* 85

Coetzee L & Carstens P “Medical malpractice and compensation in South Africa” 2011 *Chicago-Kent Law Review* 1263

Crosby JR *et al* “Endothelial cells of hematopoietic origin make a significant contribution to adult blood vessel formation” 2000 *Circular Research* 728

Cuende N *et al* “Concise Review: Bone Marrow Mononuclear Cells for the Treatment of Ischemic Syndromes: Medical Product or Cell Transplantation” 2012 *Stem Cells Translational Medicine* 403, 404

Darrow J, Sarpatwari J & Kesselheim S “Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs” 2015 *New England Journal of Medicine* 279

Devolder K “Human embryonic stem cell research: Why the discarded-created-distinction cannot be based on the potentiality argument” 2005 *Bioethics* 167

Du Plessis L “Subsidiarity: What's in the name for constitutional interpretation and adjudication?” 2006 *Stellenbosch Law Review* 207

Gomez D “The Special Status of the Human Embryo in the Regulation of Assisted Conception and Research in the United Kingdom” 2011 *Medico-Legal Journal of Ireland* 6

Howe E “The Legal Landscape for Advanced Therapies: Material and Institutional Implementation of European Union Rules in France and the United Kingdom” *HL Debs, GC* 313

Earle M “Informed consent: Is there room for the reasonable patient?” 1995 *South African Law Journal* 629

Faulkner A “Opening the gateways to market and adoption of regenerative medicine? The UK case in context” 2016 *Regenerative Medicine* 321, 323

- Favale M & Plomer A “Fundamental Disjunctions in the EU Legal Order on Human Tissue, Cells and Advanced Regenerative Therapies” 2009 *Maastricht Journal of European and Comparative Law* 89, 109
- Feigal EG *et al* “Proceedings: International regulatory consideration on development pathways for stem cell therapies” 2014 *Stem Cells Translational Medicine* 879-887
- Flear ML “The EU Clinical Trial Regulation: Key priorities, purposes and aims and the implications for public health” 2016 *Journal of Medical Ethics* 192
- Fraser JK *et al* “The Celution® System: Automated Processing of Adipose-Derived Regenerative Cells in a Functionally Closed System” 2014 *Advances in Wound Care* 38-45
- Freedman W “Formal versus substantive equality and the jurisprudence of the Constitutional Court” 2002 *Tydskrif vir Hedendaagse Romeins-Hollandse Reg* 314
- Gnecchi M *et al* “Paracrine mechanisms in adult stem cell signaling and therapy” 2008 *Circulation Research* 1204
- Greenberg J *et al* (2015) “Towards guidelines for informed consent for prospective stem cell research” 2015 *South African Journal of Bioethics and Law* 46
- Gupta P “Humanity in Medicine” 2011 *Journal of Medical Ethics and History of Medicine*
- Haimes E *et al* “Position statement on the provision and procurement of human eggs for stem cell research” 2013 *Cell Stem Sel* 285-291
- Jekerle V *et al* “Legal Basis of the Advanced Therapies Regulation” 2010 *Bundesgesundheitsblatt* 4-8
- Jordaan D “The legal status of the human pre-embryo in the context of the genetic revolution” 2005 *South African Law Journal* 237
- Jordaan D “Science versus anti-science: The law on pre-embryo experimentation” 2007 *South African Law Journal* 618

Jordaan D “Autologous stem cell therapy: an analysis of the South African regulatory regime” 2012 *South African Journal on Human Rights* 31

Kaitin K & DiMasi J “Pharmaceutical Innovation in the 21st Century: New Drug Approvals in the First Decade, 2000–2009” 2011 *Clinical Pharmacology & Therapeutics* 183

Kamihata H *et al* “Implantation of bone marrow mononuclear cells into ischemic myocardium enhances collateral perfusion and regional function via side supply of angioblasts, angiogenic ligands and cytokines” 2001 *Circulation* 1046

Klug B *et al* “Regulatory Structures for Gene Therapy Medicinal Products in the European Union” 2012 *Methods in Enzymology* 337, 342

Kocher AA *et al* “Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodelling and improves cardiac function” 2001 *Nature Medicine* 430

Kok A “The promotion of equality and prevention of unfair Discrimination Act: Why the controversy?” 2001 *Tydskrif vir Suid Afrikaanse Reg* 301

Kruger R “Quality and Unfair Discrimination: Refining the Harksen Test” 2011 *South African Law Journal* 479

Leary V “The Right to Health in International Law” 1994 *Health and Human Rights* 24

Liebenberg S “The Value of Human Dignity in Interpreting Socio Economic Rights” 2005 *South African Journal for Human Rights* 1

MacKellar C “Differentiating between human and non-human interspecies embryos” 2014 *Journal of Medical Ethics* 284-285

Mahalatchimy A “Access to Advanced Therapy Medicinal Products in the EU: Where do We Stand?” 2011 *European Journal of Health Law* 305, 313

Mahalatchimy *et al* “The legal landscape for advanced therapies: Material and institutional implementation of European Union rules in France and the United Kingdom” 2012 *Journal of Law and Society* 131-149

Meyerson D "Abortion: The Constitutional Issues" 1999 *South African Law Journal* 59

Moody H "Why Dignity in Old Age Matters" 1998 *Journal of Gerontological Social Work* 13

Moura LI *et al* "Recent advances on the development of wound dressings for diabetic foot ulcer treatment – A review" 2013 *Acta Biomaterialia* 7093-7114

Nienaber AG & Van Der Nest D "Genetic testing for the purposes of insurance risk assessment and the constitutional right to privacy" 2004 *Tydskrif vir Hedendaagse Romeins-Hollandse Reg* 446

Nöthling Slabbert M & Pepper M "A global comparative overview of the legal regulation of stem cell research and therapy: Lessons for South Africa" 2015 *South African Journal of Bioethics and Law* 12

Nöthling Slabbert M *et al* "The application of the Consumer Protection Act in the health care context: Concerns and Recommendations" 2011 *Comparative and International Law Journal of South Africa* 168-203

Nöthling Slabbert M *et al* "Stem Cell Tourism in South Africa: A legal update" 2015 *South African Journal of Bioethics and Law* 42

Nuffield Council on Bioethics "Human tissue: Legal and ethical issues" 1995 *Nuffield Council on Bioethics* 67

Pearce F *et al* "Regulation of Advanced Therapy Medicinal Products in Europe and the Role of Academia" 2014 *Cytotherapy* 289, 290-291

Pepper M & Nöthling Slabbert M "Human tissue legislation in South Africa: focus on stem cell research and therapy" 2015 *South African Journal of Bioethics and Law* 4

Pepper MS, Nöthling Slabbert & Gouveia "Legislation governing pluripotent stem cells in South Africa" 2015 *South African Journal of Bioethics and Law* 23

Pepper MS “Partial relief from the regulatory vacuum involving human tissues through enactment of chapter 8 of the National Health Act and regulations thereto” 2009 *South African Medical Journal* 736-737

Pirnay *et al* “Business oriented EU human cell and tissue product legislation will adversely impact member states’ health care systems” 2013 *Cell Tissue Bank* 525, 549

Price D “The Human Tissue Act 2004” 2005 *Modern Law Review* 798-821

Prinsen L. “Flawed law: A critical analysis of the faults and shortcomings of chapter 8 of the National Health Act of 2003” 2013 *Obiter* 522, 524

Ram-Liebig G *et al* (2015) “Regulatory challenges for autologous tissue engineered products on their way from bench to bedside in Europe” 2015 *Advanced Drug Delivery Reviews* 181, 182

Schuklenk U & Lott J “Ethics, politics and embryo stem cell research in South Africa” 2002 *South African Medical Journal* 782

Slabbert M “The Fetus and Embryo: Legal Status and Personhood” 1997 *Tydskrif vir Suid-Afrikaanse Reg* 234

Takahashi T *et al* “Ischemia-and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization” 1999 *Nature Medicine* 434

Thomas R “Where to from *Castell v De Greef*: Lessons from Recent Developments in South Africa and Abroad Regarding Consent to Treatment and the Standard of Disclosure” 2007 *South African Law Journal* 188

Van Loon K & Lindegger G “Informed consent in clinical trials: Perceptions and experiences of a sample of South African researchers” 2009 *Health SA*

Von Tigerstrom B “Regulation of Stem Cell-Based Therapies” 2015 *Food and Drug Law Journal* 315, 326

Young E “A Time for Restraint” 2000 *Science* 1424

Websites and e-Publications

American Medical Association *Code of medical ethics* <<http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics.page> > (Accessed 29 June 2016)

Commission staff working document <<http://eur-lex.europa.eu/legal/content/EN/TXT/?uri=celex%3A52005SC1444>> (Accessed 19 September 2016)

Department of Health Review of the Human Fertilisation and Embryology Act: Proposals for revised legislation (including establishment of the Regulatory Authority for Tissues and Embryos) <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/272391/6989.pdf> (Accessed 18 August 2016)

Department of Health *Ethics in Health Research: Principles, Structures and Processes* 2004 <<http://www.mrc.ac.za/ethics/DOHEthics.pdf>> (Accessed 6 July 2016)

Department of Health *Ethics in Health Research: Principles, Structures and Processes* Pretoria 2004 <<http://www.nhrec.org.za/docs/Documents/EthicsHealthResearchFinalAused.pdf>> (Accessed 21 November 2016)

European Commission *Detailed guidelines on good clinical practice specific to advanced therapy medicinal products* <http://ec.europa.eu/health/files/eudralex/vol-10/2009_11_03_guideline.pdf> (Accessed 19 September 2016)

European Court of Human Rights Press release issued by the Registrar of the Court 2014 A properly reasoned refusal by the courts to authorise access to experimental treatments was neither arbitrary nor discriminatory <<http://hudoc.echr.coe.int/app/conversion/pdf/?library=ECHR&id=003-4774464-5811888&filename=003-4774464-5811888.pdf>> (Accessed 4 August 2016)

European Commission *Health and Consumers Directorate-General Public Consultation Paper on the Regulation on Advanced Therapy Medicinal Product* 2012 <http://ec.europa.eu/health/files/advtherapies/2012_12_12_public_consultation.pdf > (Accessed 22 September 2016)

European Medicines Agency *Concerns over unregulated medicinal products containing stem cells* 2010 <http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/04/news_detail_001016.jsp&mid=WC0b01ac050004d5c1> (Accessed 22 September 2016)

European Medicines Agency *Scientific recommendation on classification of advanced therapy medicinal products* 24 November 2011 <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/11/WC500118207.pdf> (Accessed 20 September 2016)

European Medicines Agency *EU Guidance of Good Manufacturing Practice* 2007 <http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp> (Accessed 9 September 2016)

Explanatory Notes to the Human Tissue Act 2004 <<http://www.eui.eu/Projects/InternationalArtHeritageLaw/Documents/NationalLegislation/UnitedKingdom/humantissueact2004explanatorynotes.pdf>> (Accessed 18 August 2016)

Manufacture of Biological Active Substances and Medicinal Products for Human Use <http://ec.europa.eu/health/files/eudralex/vol-4/vol4-an2__2012-06_en.pdf> (Accessed 19 September 2016)

Medical Research Council *Code of Practice for the use of human stem cell lines* April (2010) <<http://www.mrc.ac.uk/documents/pdf/code-of-practice-for-the-use-of-human-stem-cellines/>> (Accessed 22 August 2016)

Medical Research Council Code of Practice April 2010 <<http://www.mrc.ac.uk/documents/pdf/code-of-practice-for-the-use-of-human-stem-cell-lines/>> (Accessed 22 August 2016)

MHRA guidance on “non routine” <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/397739/Non-routine_guidance_on_ATMPs.pdf> (Accessed 22 September 2016)

MHRA guidance on the UK’s arrangements under the Hospital Exemption Scheme <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/3977>

38/Guidance_on_the_UK_s_arrangements_under_the_hospital_exemption_scheme.pdf> (Accessed 22 September 2016)

Gamida Cell *NiCord*® 2016 <<http://www.gamida-cell.com/products.asp?ID=4&t=NiCord%C2%AE>> (Accessed 10 June 2016)

General Dental Council *Standards for dental professionals of the General Dental Council of the United Kingdom* <<http://www.gdc-uk.org/Dentalprofessionals/Standards/Pages/default.aspx>> (Accessed 18 July 2016)

General Medical Council *Guidance on Good Medical Practice* <http://www.gmc-uk.org/guidance/good_medical_practice.asp> (Accessed 29 June 2016)

Health Professions Council of South Africa *Guidelines on the Ethical rules: Ethical rules, regulations and policy guidelines* <<http://www.hpcsa.co.za/Conduct/Ethics>> (Accessed 4 July 2016)

Health Professions Council of South Africa *Informed Consent Booklet 6 General Ethical Guidelines for Health Researchers* 2008 <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rule>

Health Professions Council of South Africa *Booklet 1: General Ethical Guidelines for the health care professions* http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_1_guidelines_good_prac.pdf 2008 (Accessed 7 July 2016)

Health Professions Council of South Africa 2008 *Impartiality and Justice Booklet 6: Generic Ethical Guidelines for Researchers* <http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 7 July 2016)

Health Professions Council of South Africa *Informed Consent Booklet 6 General Ethical Guidelines for Health Researchers* 2008 http://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/conduct_ethics/rules/generic_ethical_rules/booklet_6_gen_ethical_guidelines_for_researchers.pdf> (Accessed 9 August 2016)

Human Fertilisation & Embryology Authority European Union Tissues and Cells Directives <<http://www.hfea.gov.uk/2072.html>> (Accessed 18 August 2016).

Human Fertilisation and Embryology Act Explanatory Notes 2008 <<http://www.legislation.gov.uk/ukpga/2008/22/notes>> (Accessed 22 August 2016)

Human Fertilisation and Embryology Act Explanatory Notes 2008 <<http://www.legislation.gov.uk/ukpga/2008/22/notes/division/6/2/17/1/13>> (Accessed 22 August 2016)

Human Tissue Authority *Code of Practice 1 – Consent* <https://www.hta.gov.uk/sites/default/files/Code_of_Practice_1-Consent.pdf#page=3> (Accessed 20 August 2016)

Human Tissue Authority Code of Practice 8: Import and export of human bodies, body parts and tissue for guidance on the regulation of the import and export of human material <https://www.hta.gov.uk/sites/defaultimport_andexport_of_human_bodies.body_parts_and_tissue.pdf#pag/files/Code_of_practice_-_e=2> (Accessed 20 August 2016)

Human Tissue Authority *Position statement on regulating human embryonic stem cell lines for human application* as updated in August 2015 <http://www.biolink.org/home2/sites/files/hta_position_statement_on_regulating_human_embryonic_stem_cell_lines_for_human_application.pdf> (Accessed 9 September 2016)

Human Tissue Authority Code of Practice 1: Consent <<https://www.hta.gov.uk/guidance-professionals/codes-practice/code-practice-1-consent>> (Accessed 20 August 2016)

Information on the IRAS system <<http://www.hra.nhs.uk/resources/applying-for-reviews/integrated-research-application-system-iras/>> (Accessed 17 September 2016)

International Society for Stem Cell Research *Guidelines for the Clinical Translation of Stem Cells* 2016 <<http://www.isscr.org/home/publications/2016-guidelines>> (Accessed 30 June 2016)

Macgregor C *et al Patient access to unproven stem cell treatments: A human rights issue?* 13 December 2015 *EuroStemCell* <http://www.eurostemcell.org/commentanalysis/patient-access-unproven-stem-cell-treatments-human-rights-issue>> (Accessed 4 August 2016)

Medicines Control Council *Guidelines for the Registration of Medicines: general Information* 2012 <<http://www.kznhealth.gov.za/research/mccinfo.pdf>> (Accessed 14 December 2016)

Medipost *Stem Cell Drugs | CARTISTEM* 2016 <<http://www.medipost.com/cartistem/>> (Accessed 10 June 2016)

Miller-Keane & O'Toole *Miller-Keane Encyclopaedia and Dictionary of Medicine, Nursing, and Allied Health* 7th ed 2003 <<http://medical-dictionary.thefreedictionary.com/oocyte>> (Accessed 26 October 2016)

Philipkoski K *Canada Closes Door on Cloning, Wired News* <<http://www.wired.com/2004/03/canada-closes-door-on-cloning/>> (Accessed 21 July 2016)

Professional Boards: Medical and Dental, Health Professions Council of South Africa <<http://www.hpcsa.co.za/Professionals/ProBoards>> (Accessed 10 June 2016)

Rattue P *Prochymal – First stem cell drug approved* 2012 <<http://www.medicalnewstoday.com/articles/245704.php>> (Accessed 10 June 2016)

Savulescu J *The ethics of human admixed embryos: Concerns and responses* <<http://blog.practicaethics.ox.ac.uk/2008/05/the-ethics-of-human-admixed-embryos-concerns-and-responses/>> (Accessed 5 September 2016)

South African National Human Research Ethics Council *South African National Clinical Trial Register* www.saclinicaltrials.gov.za

Southern African Society of Reproductive Medicine and Gynaecological Endoscopy South African Society of Reproductive Science and Surgery *Guidelines for Gamete Donation* 2008 <http://www.fertilitysa.org.za/Egg_Donation/> (Accessed 5 January 2017)

South African Stem Cell Transplantation Society <<http://www.stemcell.org.za/patients.htm>> (Accessed 8 November 2016)

South African Transplantation Society <<http://www.sats.org.za/Guidelines.asp>> (Accessed 8 November 2016)

Standards of Practice for Cellular Therapy: Collection, Processing, Storage and Distribution (DRAFT) <<http://www.satiba.org.za/documents/resources/standards-of-practice-for-cellular-therapy.pdf>> (Accessed 8 November 2016)

Tbfacts.org *TB Statistics for South Africa – National and provincial* <<http://www.tbfacts.org/tb-statistics-south-africa/>> (Accessed 8 August 2016)

UK Stem Cell Registry <<https://www.mrc.ac.uk/documents/pdf/uk-stem-cell-line-registry/>> (Accessed 9 September 2016)

UK Stem Cell Bank <<http://www.mrc.ac.uk/research/policies-and-resources-for-mrc-researchers/uk-stem-cell-bank-steering-committee/>> (Accessed 9 September 2016)

UK Stem Cell Bank. 8th HFEA Code of Practice <[http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition_\(Oct_2015\).pdf](http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edition_(Oct_2015).pdf)> (Accessed 9 September 2016)

US Food and Drug Administration *Draft guidance – Minimal manipulation of human cells, tissues, and cellular and Tissue-Based Products* (2014) <<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM427746.pdf>> (Accessed 11 January 2017)

Van Toor D *Access to an experimental treatment according to the right to respect for private life* 2015 Medstra-online case note <http://www.medstra-online.de/pdf/medstra-online_casenote_3-2015.pdf> (Accessed 5 August 2016)

World Medical Association *Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects* <<http://www.wma.net/en/30publications/10policies/b3/17c.pdf>> (Accessed 29 June 2016)

UK Government

Howe E 724 HL Deb col. GC 313 (1 February 2011) <<http://www.publications2.parliament.uk/pa/ld201-011/ldhabsred/text/110201gc0001.htm#11020174000137>> (Accessed 20 September 2016)

Ladyman, HC Standing Committee col 66 of 27 Jan 2004 and col 142 of 29 January 2004

Vollebregt E & Klümper M *To place on the market (or not)?* 2011

Regulatoryaffairsmedtech.com <<http://www.gtlaw.com/portalresource/vollebregtmeddevice2>> (Accessed 20 September 2016)