

Stem cell tourism in South Africa: The legal position

S Mahomed, M Nöthling Slabbert

Department of Jurisprudence, University of South Africa; and the Special Interest Research Group on Biotechnology and Medical Law of the College of Law, University of South Africa, Pretoria

S Mahomed, BComm, LLB

M Nöthling Slabbert, BA, BA (Hons), MA, DLitt, LLB, LLD

Corresponding author: M Nöthling Slabbert (slabbn@unisa.ac.za)

Stem cell tourism has become a common phenomenon worldwide and is increasingly affecting South Africa, as is evident from recent media reports. We examine the South African legal framework regulating stem cell therapy, focusing first on the effects of unproven stem cell treatments, and provide recommendations that may assist in strengthening the legal position.

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Around the world, patients with a variety of diseases unresponsive to conventional medicines are travelling to various destinations to receive stem cell therapies – a phenomenon known as ‘stem cell tourism’. This raises significant ethical concerns, as patients receive treatments that are unproven, often unregulated, potentially dangerous, and often fraudulent.¹

Stem cell research remains at the experimental stage, with clinical trials uncommon. However, over 700 clinics are estimated to be operating in mostly developing countries such as Costa Rica, Argentina, China, India, Russia and South Africa (SA).² They have lured many patients, mostly from industrialised countries, whose desperation and hope are fuelling the growth of such tourism.³

Although most countries have regulations for conducting research with human subjects, as well as medical malpractice and licensing laws, some guidelines are not specific to stem cell therapy.¹ While international agreements may help close this regulatory gap, some countries don’t accept or abide by these.¹ Unscrupulous individuals may also evade these rules.¹

Increasing use of social media has made it easier for bogus doctors to advertise their ‘miracle’ cures as routine therapies and entice their victims with the promise that stem cells hold. Many services offered to medical tourists are legitimate, provided by reputable hospitals and health professionals. However, there is no evidence for the efficacy of most stem cell therapies, except for cell transplants for some blood disorders.³

For a medical innovation to be ethically responsible, it should be based on animal studies or other research that guarantees evidence of safety and clinical efficacy. Stem cell therapies offer hope for those in frantic need of a remedy. Therefore, what are the implications if an individual is administered a therapy that is unproven in an unregulated environment?

We examine the South African legal framework regulating stem cell therapy and the effects of unproven stem cell treatments, and conclude with recommendations that may help to strengthen the legal position. We focus on legal issues relating to stem cell

therapy and not stem cell research, where different legal and ethical considerations apply.

Effect of unproven stem cell therapies

In the late 1990s, two South African researchers at the University of Pretoria tested an experimental drug, Virodene P058, on human participants, without ethical review committee approval and proper peer review.⁴ Health professionals opposed to Virodene sparred with prominent political figures including Thabo Mbeki, then SA’s deputy president, who backed the researchers’ efforts.⁴ The University of Pretoria ultimately reprimanded the two doctors for conducting the trial without approval, and blocked further tests as the substance was potentially harmful and there was scant evidence it would work.⁴

This example emphasises the importance of peer review for health research and the importance of research ethics committees to safeguard human participants from unethical conduct. The National Department of Health’s 2004 Guidelines on Ethics in Health Research: Principles, Structures and Processes state that all health research must be approved by research ethics committees before the study begins.⁵

A dramatic example is that of a young boy who developed a multi-focal brain tumour following treatment in Russia, where human fetal neural (brain) stem cells were administered into his spinal cord.⁶ After several treatments, and four years after his first treatment, he developed tumours at the treatment sites.⁶ Here, the safety of the procedure was unproven and there was no experimental or pre-clinical evidence to suggest that it might work.⁶

SA has had its stem cell operators. Laura Brown (now deceased) and Steve van Rooyen fled to SA after their fraudulent stem cell operations were exposed in the USA. In 2002 they defrauded individuals suffering from ALS, multiple sclerosis and other incurable diseases, obtaining money from them by false and fraudulent pretences and representations.⁷ Their company, Biomark, claimed to provide miracle cures for many diseases through the use and injection of stem cells derived from cord blood, for fees ranging from US\$10 000 to US\$32 000 or at times negotiated by the customer.⁷ They recruited customers by claiming that the therapeutic power of stem cells was scientifically proven, and that Biomark was simply making it

available. However, these therapies were unproven and unlicensed. Furthermore, the same type and quantity of the same type of stem cells were injected into every patient, most of whom suffered from different illnesses.⁷ None of their patients were cured and many died from their illnesses during the course of their treatments.

Unproven therapies do not meet the minimal ethical, scientific or medical standards of safety and efficacy² and their alleged success is based on unreliable evidence^{8,9} and patients' self-reports.¹ No scientific rationale supports these unproven therapies and post-treatment care is seldom provided, which in itself could be detrimental.¹⁰

There is no medico-legal protection or coverage or medical practitioners' insurance for stem cell therapies.¹⁰ The treatments are rarely reviewed by ethics committees, data are not collected, research is not published in peer-reviewed journals and charges are exorbitant for treatments that are no more than experimental.¹⁰ Many treatments are offered in countries where there is no legal pathway for medical negligence claims.¹⁰ Often there is also no ethics review process to ensure proper conduct by a doctor or researcher, and protect patients from the unscrupulous use of unproven treatments. As their results are not published, which would subject them to international peer review, these scientists are unaccountable for their actions.¹⁰

The Health Professions Council of South Africa (HPCSA) and Medicines Control Council (MCC) have issued guidelines to regulate the good practice of healthcare professionals and researchers; protect patients and research subjects; and regulate the registration of medicines, including biological medicines.¹¹⁻¹⁶ International guidelines also protect the rights of patients, emphasise the need to safeguard vulnerable populations and stress the importance of reviews by accredited research ethics committees.¹⁷⁻²⁰ Unproven stem cell treatments contradict the guidelines and policies that form the framework of the medical profession.

The International Society for Stem Cell Research (ISSCR) offers its Guidelines for the Clinical Translation of Stem Cells,²¹ which were developed by a team of stem cell researchers, clinicians, ethicists, and regulatory officials from 13 countries. These condemn the administration of unproven applications of stem cells or their direct derivatives to a large series of patients outside of a clinical trial, particularly when patients are charged for such services.²¹ Scientists, clinicians and healthcare and research institutions may not ethically participate in such activities. Regulators in countries where such illegitimate therapies are offered have a responsibility to prevent exploitation of patients and, if necessary, to close fraudulent clinics and take disciplinary action against the clinicians involved.²¹ The ISSCR offers a guide²¹ to help individuals make informed choices when contemplating a stem cell-based intervention either locally or abroad. It points out that:

- There is a long process of laboratory studies and clinical research to show that a treatment is safe and effective. Like a new drug, stem cell therapies must be assessed and meet certain standards before national regulatory bodies approve their use.
- Doctors have been transferring blood stem cells by bone marrow transplant for >50 years, and advanced techniques are used clinically to collect blood stem cells. Umbilical cord blood is often collected as a source of blood stem cells, for experimental use as an alternative to bone marrow in

transplantation. Other tissue-specific stem cells, such as for skin and corneas, have played a role in tissue transplants for several years, contributing to long-term regeneration. Other stem cell treatments are still experimental.

- Unlike drugs, stem cells cannot necessarily be produced and tested for quality in large batches, and treatments may even be patient specific. For most diseases, it is still being determined which cells will best repair a particular damaged or diseased tissue, and how to get them to the right place in the body. Side-effects and long-term safety must also be determined, since transplanted cells may remain in patients' bodies for many years. Therefore, careful monitoring and extended follow-up of patients who receive stem cell treatments is extremely important.
- To test whether and how a new intervention may work for a particular disease or injury, studies are done first *in vitro* and, if possible, in animals with a disease or injury similar to those in humans. These preclinical studies should be reviewed by other experts, published and repeated before the research is extended to human subjects. After demonstrating a reasonable expectation that the treatment will work and be safe, permission is sought to conduct a clinical trial in humans, starting with a few individuals. New experimental treatments may sometimes be carried out on a very small number of people before a clinical trial is started. As the safety and side-effects are better understood and methods for delivery of the treatment to the correct part of the body improve, the number of patients may be gradually increased and the new intervention compared with existing treatments. Once safety and effectiveness is demonstrated, the relevant regional regulatory agency should approve the use of the treatment for particular diseases or conditions.
- No medical treatment can be described as completely safe as all may involve risk, albeit small. Even small risks should be explained clearly by a medical professional.
- Patients must be sure that there is good scientific evidence that the treatment is safe and effective, and that their rights are respected.
- Patients should be cautious if claims are based on anecdotal evidence; if multiple diseases are treated with the same cells; the source of the cells or how the treatment will be done is not clearly documented; practitioners claim there are no risks; or in cases of high or hidden treatment costs.

Registration of medicines in SA

The registration of medicines in SA is governed by the provisions and requirements of the Medicines and Related Substances Control Act²² (MRSCA). The Guidelines for the Registration of Medicines²³ aim to help applicants prepare documentation for the registration of medicines for human use.²³ These guidelines are relevant only to human medicines, including biological and complementary medicines. Legislation requires that the MCC shall register every medicine before it may be sold or marketed,²² and an application for registration must be submitted for approval.

In terms of the National Health Act, it is often unclear whether stem cell therapy should be regarded as a 'health service', which includes medical treatment, 'therapeutic' or 'non-therapeutic research', or 'health services for experimental or research purposes'.²⁴ Each has different legal and ethical considerations, depending on whether cell-based therapy is viewed as medical treatment, experimental research or medicine.²⁵

Stem cell therapy – medicine?

The MCC prohibits the sale of medicine that is subject to registration but not registered.²² An exception would be where *inter alia* medical practitioners compound such medicine for a particular patient in the course of practising their profession, in a quantity not greater than that required for treatment, as determined by such medical practitioner.

The MRSCA defines a medicine as any substance or mixture of substances used, or purporting to be suitable for use, or manufactured or sold for use in:

- the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental states or the symptoms thereof in humans
- restoring, correcting or modifying any somatic or psychic or organic function in humans.

The MRSCA also applies to any veterinary medicine.²²

Biological medicines are a highly specialised class of medicine, produced using living organisms. They are complex protein structures typically much larger than traditional chemical medicines, and are mostly administered by injection. Biological medicines are more advanced than conventional therapies.²⁶ However, even though clinically effective, they are very expensive in SA.²⁶

The MRSCA does not define a biological medicine. The Guidelines,²³ however, categorise biological medicine as a type of medicine²³ and define it as a medicine where the active ingredient and/or key excipients have been derived from living organisms or tissues, or manufactured using a biological process. Biological medicines can be defined largely by reference to their method of manufacture (the biological process). These include *inter alia* medicines prepared from the following substrates: (i) microbial cultures (fermentation); (ii) plant or animal cell cultures (including those resulting from recombinant DNA or hybridoma techniques); (iii) extraction from biological tissues; and (iv) propagation of live agents in embryos or animals.

Biological medicines include, but may not be limited to: (i) plasma-derived products, e.g. clotting factors, immunosera, etc; (ii) vaccines; (iii) biotechnology-derived medicinal products (rDNA products), e.g. rHu-antithaemophilic factors, hormones, cytokines, enzymes, monoclonal antibodies, erythropoietins; and (iv) human gene therapy.

In SA, it has been the practice that the MCC can decide to exclude certain well-characterised, low-molecular weight medicinal biological compounds from biological medicine status, such as antibiotics, insulin, etc. These compounds are therefore not reviewed by the Biological Medicines Committee.²²

By these definitions, a stem cell product (or application) falls within the ambit of a biological medicine. The position of autologous stem cell therapy (ASC), however, is less clear. ASC involves the removal of the patient's own stem cells, which are cultured and often mixed with other therapeutic substances, stored or cryopreserved, then administered back to the patient, typically by injection. The question of whether ASC may be viewed as a biological medicine or not hinges on the nature of the 'product' thus created, and whether it is essentially still part of the person's body or something entirely new.

The autologous stem cell therapy Regenexx attracted worldwide attention when the USA regulatory authority, the Food and Drug Administration (FDA), filed suit against its developers, Regenerative Sciences. The FDA claimed that the stem cell-based product developed during the Regenexx procedure is a 'biological product' that, in addition to claims regarding its therapeutic use, makes it subject to FDA regulation.²⁷ The FDA calls the procedure the 'manufacturing, holding for sale, and distribution of an unapproved biological drug product', and in 2010, ordered Regenerative Sciences to stop offering the treatment.

The court noted that 'the biological characteristics of the cells change during the process', and that this, together with other factors, means the cells are more than 'minimally manipulated'. While the court held that 'maintaining the FDA's role as watchdog and regulatory authority is imperative',²⁷ Regenerative Sciences asserted that the FDA's mandate is to regulate mass production of drugs by pharmaceutical companies and not 'one-on-one' doctor-patient risks.

If the MRSCA and the Guidelines for the Registration of Medicines are interpreted strictly, stem cell products similar to Regenexx must be registered as a biological medicine in SA. For this to happen, the MCC should be convinced of their efficacy, safety and quality.^{22,23} The harvesting of stem cells, as well as their isolation, cryopreservation and any other activity affecting them, must also comply with the relevant requirements stipulated in Chapter 8 of the National Health Act and the 2012 Regulations Relating to the Use of Human Biological Material.²⁸

In contrast to the NHA, which requires ministerial authorisation for the removal of stem cells from living persons,²⁷ these regulations refer only to the informed consent of the patient whose cells are removed. This oversight creates practical obstacles for routine procedures, particularly bone marrow transplantation.²⁹

Regulation 2(1) of the 2012 Regulations Relating to Stem Cell Banks³⁰ also states that no person may *release stem cell products* for therapeutic use unless this is authorised in terms of section 54 of the National Health Act and, where relevant, laboratory tests for certain transmissible diseases have been performed. However, Regulation 2(1)(2) stipulates that this may not be required where the stem cells are for autologous use. In addition, Regulation 2(1)(3) states that no person may *use stem cell products* for therapeutic use unless they are registered with the Health Department and, among other things, relevant written (and duly documented voluntary) consent has been obtained from the donor of the cells, even in the case of residual tissue, blood or blood products.

Registration of a biological medicine with the MCC

Since the MRSCA requires that the MCC shall register every medicine before it may be sold and marketed, an application for such registration should be submitted for evaluation and approval.^{22,23} Applications to register medicine for humans are divided into different types to determine fees and allocate reviewers for evaluation.²³ One of these types is biological medicine. It is legally required that data submitted for evaluation should substantiate all claims and meet the technical requirements.

The MCC refers to international guidelines to be read in conjunction with the South African guidelines, in particular the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH aims to achieve greater harmonisation to ensure that safe, effective and high-quality medicines are developed and registered in the most resource-efficient manner.³¹ It promotes public health, prevents unnecessary duplication of clinical trials in humans, and minimises the use of animal testing without compromising safety and effectiveness.³¹ Therefore, applications to register a medicine must ensure that the product meets the technical requirements of quality, safety and efficacy for its intended use.

After the administrative steps for registration have been submitted,²³ biological medicines require primary evaluation by the Biological Medicines Committee, in addition to other committees of the MCC. The MCC may choose to accept, defer or reject the application. Should the application be deferred, the applicant will be required to produce additional information and re-submit the application. Once the application is accepted, the biological medicine is registered with the MCC and may be sold and marketed.

Failure to register a stem cell therapy as prescribed contravenes section 14(1) of the MRSCA and is an offence in terms of section 29, punishable by a fine or imprisonment of a period not exceeding 10 years.

Conclusion

The increasing demand for stem cell therapies should be countered by efforts to raise public awareness about the types of treatments that are scientifically sound and safe. To date, proven stem cell treatments include bone marrow transplants, bone and skin grafts, and treatments for blood and immune disorders, leukaemia and corneal disease. Patients must be informed that multiple diseases cannot be treated with the same type of stem cells.

Weak legal enforcement of the MRSCA permits the emergence of medically unsound and unethical practices that may exploit emotionally vulnerable patients.⁶ The only trusted sources of evidence confirming that a treatment is safe and effective are (i) independent clinical trials, approved by government regulatory agencies; (ii) evidence of ethical clearance; (iii) publication and peer review assessment in international scientific journals; and (iv) replication of results by other laboratories.

False advertisement and promises of miracle cures should be banned. Stringent rules are needed to ensure that pre-clinical studies and well-controlled clinical trials have been conducted before introducing cells into the patient.⁶ There must be well-proven records which indicate that the desired therapeutic effect will, under normal circumstances, be achieved.⁶ The person who administers such therapies must be medically qualified and familiar with stem cell therapies for a prescribed number of years. Furthermore, any work involving stem cells that will be (re)introduced into patients must be conducted in accredited or authorised institutions only, under strictly controlled conditions⁶ to ensure that this material is not contaminated and that no adverse effects will be produced under normal conditions.

Despite the legal requirements for the registration of biological medicines, the MCC has capacity problems and an ineffective law

enforcement arm.³² The most recent example is the inability of the MCC's law enforcement unit to deal with the so-called 'snake doctors' who offer bogus medical cures, including for HIV and AIDS. To compound the existing situation, the legal framework relating to the regulation of human tissues is generally unsatisfactory.³³

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