

# Legal implications of translational promises of unproven stem cell therapy

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The promise stem cell therapy holds for curing diseases for which no therapy currently exists is often translated as fact. Unfortunately, enforced misconceptions between fact and promise often also translate into exploitation and harming of patients. This article aims to clear up misconceptions about the biological promise and legal consequences of insisting on promises not based on scientific facts.

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Stem cells hold great promise for treating and potentially curing many diseases for which no therapy currently exists. However, several misconceptions of stem cells exist among the general public and, to an extent, among the medical fraternity. Most of these misconceptions can be resolved by understanding the basic biology of stem cells, which would be critical to address prior to arguing the associated ethical and legal implications that arise from the use of stem cells for therapeutic purposes.

A stem cell has the unique ability to both replicate and develop into specialised tissues with specific functions. Different forms of stem cells exist, each with varying capacity or potency. The potency refers to the extent to which the stem cell is able to replicate and differentiate into multiple tissues. When the female egg cell is fertilised by the male sperm, a totipotent stem cell is created, from which a complete human body and placenta develops. On the fourth day of development, the embryo forms an outer layer of cells and an inner cell mass. The outer layer develops into the placenta, while the inner cell mass develops into the human body/fetus. Embryonic stem cells (ESCs) are derived from the inner cell mass and are referred to as pluripotent stem cells. Somatic stem cells (often referred to as adult stem cells) are stem cells that reside in tissues and organs of the developed human body for the purpose of providing a renewal and regenerative capacity. This capacity is generally limited to the tissue-group within which these stem cells reside. These stem cells are referred to as multipotent stem cells. Best known examples of multipotent stem cells are haematopoietic stem cells (HSCs), which give rise to all of the cellular components of blood; mesenchymal stem cells (MSCs), which are able to develop into bone, cartilage, muscle and fat; and neural stem cells (NSCs), which develop into cells of the nervous system.

From a therapeutic point of view, HSCs are the only form of globally accepted stem cell therapy. These cells are used for the treatment of blood and blood-related disorders, and are common practice in nearly 80 countries. This is a well-described and rational approach where 'blood-making' stem cells are used specifically in the context

of replacing defective blood cells. Of the more than 60 000 HSC transplants that take place globally per annum, approximately 90% are for treating blood cancers (leukaemia, lymphoma and myeloma), while the remaining indications include solid tumours and non-malignant conditions such as thalassaemia, sickle cell disease and immune disorders. In each of these cases, the HSCs are used to replenish blood cells that are depleted in a chemotherapy regimen received prior to the transplantation.

Over the past decade, the potential benefits of MSCs for treatment purposes have gained tremendous interest. There are several reasons for this, including the fact that these cells:

- Can be procured fairly easily (particularly from fat)
- Have the unique ability to migrate to the site of injury once injected
- Do not require genetic matching when obtained from a donor (as is the case with HSCs).

By investigating the global clinical trial landscape of MSCs, it was possible to identify over 100 different indications that have been or are currently being treated with MSCs (manuscript in preparation). These include diseases such as arthritis, heart attacks, multiple sclerosis, diabetes and spinal cord injuries. However, although widespread interest in this area of research exists, only one MSC product has successfully achieved market approval from regulatory authorities – remestencel-L (Prochymal®), which was approved in Canada and New Zealand for the treatment of graft v. host disease, a complication of HSC transplantation.<sup>[1]</sup>

The stem cell controversies of the past two decades originated from the use of ESCs for medical research. Given that a fertilised embryo is destroyed in order to derive these cells, albeit in the laboratory setting with donated embryos, such research was deemed unacceptable by many and understandably has resulted in a quagmire of ethical debates.<sup>[2]</sup> More recently, however, the use of unproven stem cell therapies and the subsequent emergence of a 'stem cell tourism' industry have provided a concerning source of controversy.<sup>[3]</sup> In such cases, vulnerable patients are enticed to travel abroad to dubious stem cell clinics and are subjected to unproven stem cell therapies at

their own expense. Given the unique properties of MSCs and the ease with which they can be prepared from fat tissue, they have become the most attractive product on offer at a large number of suspicious stem cell clinics around the world. The most concerning aspect of this is the extensive list of diseases that these clinics claim to treat. Although over 100 indications are being treated in the clinical trial setting, none have been able to demonstrate sufficient benefit (with the exception of the previously mentioned Prochymal® preparation).

In December 2014, the Food and Drug Administration (FDA) – the American regulatory authority – released two draft guidance documents, describing their view on the preparation of MSCs from fat and their use in patients. In essence, these draft guidelines state that MSCs are to be regarded as biological drugs in future, meaning that the provider and/or manufacturer will have to prove benefit in the clinical trial setting before it will be reviewed and considered for marketing approval by the FDA. Once this becomes official, no clinic in the USA will be able to offer unproven MSC products legally. Since there is no approved MSC therapy in the US market, any clinic preparing MSCs for treatment purposes will stand the risk of having to engage legally with the FDA, for which the outcome will in all likelihood be in favour of the latter. It is anticipated that regulatory authorities in other major markets will follow suit, particularly the European Union.

### Stem cell therapy as biological medicine

In South Africa (SA) MSC therapy is similarly categorised as a biological medicine in terms of the Medicine Control Council's (MCC) Guidelines for the Registration of Medicines where the active ingredient or key excipients have been derived from living organisms or tissues, or manufactured using a biological process.<sup>[4]</sup> Biological medicines are therefore largely differentiated from other medicines through the methods used to manufacture them and include 'medicines prepared from substrates such as: (1) microbial cultures (fermentation); (2) plant or animal cell cultures (including those resulting from recombinant DNA or hybridoma techniques); (3) extraction from biological tissues; and (4) propagation of live agents in embryos or animals.'<sup>[5]</sup> Considering its production methods stem cell therapy qualifies as biological medicine and falls within the ambit of the Medicines and Related Substances Control Act (MRSCA).<sup>[6]</sup>

The classification of stem cell therapy as biological medicine with regard to autologous stem cell therapy, where a patient's own stem cells are administered back to the same patient after having been processed, cultured, mixed with other therapeutic substances, stored or even cryopreserved, was challenged in the USA in the Regenexx-case.<sup>[7]</sup> In this case the FDA claimed that the autologous stem cell based substance produced using the Regenexx procedure qualifies as a 'biological product' that falls within the regulatory ambit of the FDA and subsequently ordered its developers, Regenerative Sciences, to stop offering their unapproved biological drug product. However, foreign to SA regulations, the FDA regulations mandate the FDA to only regulate so-called 'one-on-many' public health risks as opposed to 'one-on-one' doctor-patient medical care risks. The developers of Regenexx argued that their product, based on its 'one-on-one' doctor-patient medical care risk, did not fall under the regulation of the FDA and accordingly did not require any approval from the FDA. The important fact is that the court found that 'the biological characteristics of the cells changed during the process' causing the cells to be more than 'minimally manipulated' resulting in a biological medicinal product. In SA, autologous stem cell products similar to

Regenexx also qualify as biological medicine, as described above and will be regulated by the MRSCA.<sup>[5]</sup>

### Registration of biological medicine

The MRSCA prohibits the sale of any unregistered medicine which is subject to registration.<sup>[8]</sup> An official notice issued in terms of the MRSCA by the MCC specifically subjects all medicines that are biological medicine to registration with the MCC.<sup>[9]</sup> Only when the Registrar of Medicines is satisfied that medicine is safe, efficacious, of good quality and suitable for the purpose for which it is intended, complies with the prescribed requirements and that registration thereof is in the public interest will he or she approve an application for registration and issue the applicant with a certificate of registration, which after the registered medicine can be legally sold.<sup>[10]</sup>

Biological medicine will also be evaluated for safety, quality and efficacy by the Biological Medicines Committee prior to registration, in addition to the standard MCC committees.<sup>[11]</sup> In this regard the MCC will consider both national and international guidelines such as the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, which focuses on global harmonisation of safety, efficacy and quality standards resulting from Good Manufacturing Practices and properly designed and conducted clinical trials.<sup>[12]</sup>

Although selling unregistered medicine is an offence punishable with a fine and/or imprisonment not exceeding 10 years, prosecutions and convictions are extremely rare.<sup>[13]</sup>

### Consequences of unproven or fraudulent stem cell therapy

It has been recorded that money spent on stem cell tourism, including clinically unproven treatments, averages around R122 500, and that some stem cell tourists even received stem cells from animals such as sheep or rabbits.<sup>[14]</sup>

From 2002 to 2006 Biomark International, a biotechnology company in the USA, defrauded individuals suffering from amyotrophic lateral sclerosis (Lou Gehrig's disease), Parkinson's disease, muscular dystrophy, multiple sclerosis and other incurable diseases by making false representations '...that science had proven the therapeutic power of stem cells and that Biomark was simply making it available to the world.'<sup>[15]</sup> Under these pretences every patient was injected with the same type and quantity of stem cells, regardless of the disease the patient was suffering from and charged between US\$10 000 and US\$32 000, if not negotiated otherwise. In 2006 Laura Brown and Stephen Mark van Rooyen, directors of Biomark, were criminally indicted. During their hearing the court found that Biomark's website and advertisements made numerous false, misleading and inaccurate statements and that the proffered information had no scientific credibility. It further found that the stem cell treatments were illegally administered without a biologics product licence<sup>[16]</sup> and that licensing was very unlikely as pre-clinical trials in this regard only involved non-humans. None of the patients undergoing these treatments were cured and many even died during treatment.

### Undesirable practices

Joint efforts of stem cell researchers, clinicians, ethicists and regulatory officials from 13 countries culminated in the International Society for Stem Cell Research's (ISSCR) Guidelines for the Clinical Translation of Stem Cells.<sup>[17]</sup> These guidelines acknowledge the worrisome

cases where unproven stem cell therapies are marketed, resulting in stem cell tourism to countries with insufficient local regulation and oversight of host clinics. It also condemns the administration of unproven stem cell therapy or direct derivatives to patients outside of a clinical trial, especially when charged for such services. It states that countries hosting illegal therapies have a responsibility to prevent patient exploitation and urges them to close fraudulent clinics and take disciplinary action against involved clinics.

Locally, authorised institutions<sup>[18]</sup> may acquire, use and supply any blood products, including stem cells, for prescribed medical purposes, the advancement of health and therapeutic services and the production of therapeutic, diagnostic or prophylactic substances.<sup>[19]</sup> These activities are largely controlled by the Minister of Health as only he has the authority to authorise cell removal and impose conditions.<sup>[20]</sup> This process may significantly frustrate or delay translational stem cell research. Regulations, issued in terms of the National Health Act (NHA) which only requires informed consent from the stem cell donor when acquiring cells, contradicts this prescription, leaving legal uncertainty in its wake.<sup>[21]</sup>

The MRSCA requires that the Director-General of Health must be informed of the therapeutic efficacy and effect of any medicine as soon as practically possible after registration with the MCC, including the purpose, circumstances and manner in which such medicine should be used.<sup>[22]</sup> Any advertisements subsequent to such registration, making any claims regarding the therapeutic effects and efficacy of the medicine or use thereof for any purposes contrary to the reported effects, efficacy and purpose of use is prohibited as being false or misleading.<sup>[23]</sup>

All transactions or agreements concluded between healthcare providers and patients for the supply of healthcare goods, including biological medicine, or services in exchange for consideration, including the marketing of stem cell therapies, falls within the ambit of the Consumer Protection Act (CPA).<sup>[24]</sup>

The CPA also prohibits false or misleading marketing which includes deceptions of 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.<sup>[25]</sup> Patients may therefore not be enticed into stem cell therapy with scientifically unproven promises or false statements relating to the exact nature and possible effects of such therapy. Patients suffering from debilitating diseases are often physically and mentally handicapped as a result and unable to substantially protect their own interests. Should physical force, coercion, undue influence, pressure, duress, harassment or unfair tactics be used against these patients when marketing, supplying or negotiating the supply of any stem cell therapy, such conduct will amount to being unconscionable in terms of the CPA.<sup>[26]</sup> Practices where suppliers of stem cell therapy knowingly take advantage of illiterate, ignorant patients who are unable to understand the language of the agreement are prohibited by the CPA. Failing to correct patients' apparent misapprehension of proposed stem cell therapy, using exaggeration, innuendo or ambiguity as to material facts or failing to disclose material facts relating to stem cell therapy will also amount to a false, misleading or deceptive representation.<sup>[27]</sup> Any agreement between patients and suppliers of stem cell therapies which subjects patients to any of the aforementioned fraudulent conduct, contravenes any of the provisions of the CPA or constitutes an assumption of risk or liability

by the patient for losses suffered resulting from the gross negligence of suppliers or any persons acting for or on behalf of suppliers is strictly prohibited.<sup>[28]</sup> 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.<sup>[29]</sup> Liability resulting from stem cell therapy can accordingly not be escaped through contractual terms.

Any contravention of the aforementioned provisions, which may result in serious illness, disablement or even death of the patient, is considered to be serious enough that patients may deviate from the standard consumer complaint route and directly approach the court to restore money to the patient or compensate the patient for losses or expenses relating to harm suffered resulting from stem cell therapy transactions or agreements, including the patient's legal costs relating to such court proceedings.<sup>[30]</sup> Although the CPA does not limit the heads of damages that may be claimed upon contravention of these prohibitions, it is arguable that the patient will also be entitled to claim for general damages. The court will, among others, consider the power imbalances between the parties which is influenced by the parties' relationship to each other, their relative capacity to enter into contractual agreements, levels of education and sophistication, experience and bargaining position; whether the patient knew or ought reasonably to have known of the existence and extent of any unfair, unreasonable or unjust provisions contained in the agreement; the respective conduct of suppliers and patients; the amount for which, and circumstances under which the patient could have acquired identical or equivalent goods or services from a different supplier and whether the biological medicine was manufactured, processed or adapted to special orders of the patient.<sup>[31]</sup>

The court can also require the supplier to cease any stem cell therapy or alter any practices to avoid a repetition of the supplier's conduct in an effort to prevent further future harm to patients.<sup>[32]</sup> If the MCC is also of the opinion that it is not in the public interests that any medicine be made available to the public it may order the disposal of any undesirable medicine.<sup>[33]</sup> 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 translational research, future funding and development of this promising biological medicine.

## Patient safety

Although false and misleading advertising is punishable as a criminal offence in terms of the MRSCA,<sup>[34]</sup> these practices can also result in civil liability in terms of the implied warranty<sup>[35]</sup> and faultless liability regimen<sup>[36]</sup> provided for in the CPA.

The CPA provides for the joint and individual liability of all persons involved in the chain supplying any unsafe, hazardous goods without adequate instructions or warnings pertaining to any hazard that can result from using such goods '...irrespective of whether the harm resulted from any negligence...<sup>[37]</sup> on the suppliers' part. A patient only needs to prove that the harm (death, injury, illness or pure economic loss) he wrongfully suffered resulted from unsafe or hazardous stem cell therapy, without adequate instructions or warnings pertaining to such hazards, to succeed with his claim against any person in the therapy's supply chain.

Patients are entitled to assume that suppliers of stem cell therapies have the legal right to sell and administer biological medicine.<sup>[38]</sup> This presumption entails that a patient has the right to assume that any biological medicine offered as therapy has been registered with the MCC

subsequent to clinical studies providing evidence of product safety and established proof-of-principle for the desired therapeutic effect,<sup>[39]</sup> failing which, and upon suffering harm as a result of unproven, unregistered therapy, a patient can claim for damages as discussed above.

Every patient has the right to information regarding proposed stem cell therapy in plain understandable language so that a person of average literacy skills and minimal experience as a consumer of biological medicine, could be expected to understand the content and significance of such information.<sup>[40]</sup> Considering the novelty of stem cell treatments almost everyone will be considered to have minimal experience with such therapy and with further regard to the complex and unpredictable nature thereof, healthcare practitioners will need to take extraordinary communication steps to ensure that patients adequately understand and consent to such therapies. Information relating to genetically modified ingredients or reconditioned goods, as may be the case with stem cell products, must be clearly displayed on the biological medicine's packaging or prescribed notice.<sup>[41]</sup> This, as well as the extensive guidelines offered by the ISSCR<sup>[17]</sup> will further aid patients in exercising informed decisions regarding their treatment options.

Patients can further expect goods or services to be safe, free of defects or hazard,<sup>[35,42]</sup> such as contamination, and of a quality that persons are generally entitled to expect from stem cell therapy.<sup>[43]</sup> Having regard to the novelty, unpredictability and unknown long-term results of stem cell therapy it is questionable what exactly persons are generally entitled to expect of it. What is clear is that unproven stem cell therapies, posing significant risks of personal injury, qualify as unsafe and hazardous in terms of the CPA, and patients are entitled to be protected from such dangers.

Whenever the stipulations of any other act is in conflict with those contained in the CPA, the act offering the greater protection to the consumer, being the patient, will apply.<sup>[44]</sup>

## Medical innovation

Stem cell based medical innovation interventions are unproven stem cell based interventions outside the context of a formal clinical trial. In very limited cases the ISSCR guidelines allow clinicians to attempt medically innovative stem cell based interventions on seriously ill patients, albeit under heightened levels of caution and with informed consent clearly emphasising the experimental and preliminary nature of the clinical intervention.<sup>[45]</sup> A case in point is the stem cell therapy received by Gordon Howie, a Canadian ice hockey player, after suffering a stroke in October 2014.<sup>[46]</sup> However, due to the fact that patients do not receive these treatments for consideration, these transactions will locally not fall within the ambit of the CPA and patients will no longer enjoy the faultless liability the protection affords. However the principles of therapeutic research in SA include well-informed consent and the constitutional protection of research participants' bodily and psychological integrity,<sup>[47]</sup> ethically reviewed research proposals to ensure safety monitoring and the management of any harm experienced by participants, including compensation for any research-related injuries and providing for the long-term care and observation of participants of innovative therapy such as stem cell therapy.<sup>[48]</sup>

## Conclusion

In countries which are unregulated or poorly regulated, undesirable practices, inviting stem cell tourists and patient harm resulting from unproven stem cell therapy, would thrive as patients will increasingly

move into areas that are medically untested. In SA the MRSCA, regulating the quality of biological medicine which enters the market through registration, and the CPA, providing patients with remedies when suffering harm or losses resulting from stem cell therapies, protects patients against undesirable practice and its inherent dangers to patient safety.

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