

STEMMING THE TIDE OF UNPROVEN AUTOLOGOUS STEM CELL THERAPIES IN AUSTRALIA

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I INTRODUCTION

There is an increasingly alarming number of for-profit private clinics offering unproven stem cell medical treatments to vulnerable patients all over the world including Australia. There were accounts of unsubstantiated claims of cures and adverse events. Previously, these untested stem cell treatments were available primarily in developing countries with less regulation or weak enforcement.¹ However, since 2011, Australia too has stem cell businesses offering autologous stem cell treatments (that is, stem cells from the patient's own body, not donated cells), and they have grown to more than 70.² This country has among the world's highest concentration of stem cell clinics,³ with websites advertising medical procedures (such as for the treatment of sports injuries, stroke, osteoarthritis, and so forth) as well as anti-ageing therapies (such as facial rejuvenation).⁴ While there are various forms of regulation to govern stem cell therapies such as the traditional law and professional guidelines, they are ineffective and failing to protect vulnerable patients. In October 2017, the Therapeutic Goods Administration ('TGA') announced that there are proposed amendments to the *Therapeutic Goods Regulations 1990* (Cth) to introduce regulatory requirements around the autologous human cell and tissue therapies including stem cells in 2018.⁵ It is anticipated that the proposed changes are likely to close the regulatory gap and thus this long-awaited control is welcomed.

II THE SCIENCE: INVESTIGATIONAL TREATMENTS

Stem cell research is considered a holy grail for the medical treatment of different kinds of diseases and conditions. As master cells, stem cells have the capacity for self-renewal and to differentiate into multiple types of cell.⁶ However, much more work is necessary in order to translate the research into safe and effective treatments.

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¹ See Sarapop Kiatpongsan and Douglas Sipp, 'Monitoring and Regulating Offshore Stem Cell Clinics' (2009) 323 *Science* 1564.

² Megan Munsie, Cameron Stewart and Ian Kerridge, 'Finally, Unproven Stem Cell Clinic Practices Might be Curtailed', *The Conversation* (online), 27 October 2017 <<https://theconversation.com/finally-unproven-stem-cell-clinic-practices-might-be-curtailed-86388>>; see also Megan Munsie et al, 'Open for Business: A Comparative Study of Websites Selling Autologous Stem Cells in Australia and Japan' (2017) 12 *Regenerative Medicine* 777.

³ Israel Berger et al, 'Global Distribution of Businesses Marketing Stem Cell-Based Interventions' (2016) 19 *Cell Stem Cell* 158, 158.

⁴ Munsie et al, above n 2.

⁵ Therapeutic Goods Administration, *Regulation of Autologous Cell and Tissue Products* (24 October 2017) Australian Government Department of Health <<https://www.tga.gov.au/media-release/regulation-autologous-cell-and-tissue-products>>. The proposed amendments do not become law until they have the Governor General's approval. Examples of autologous cell and tissue products are skin grafts, bone grafts, blood and blood components (plasma, serum, platelets) and stem cells.

⁶ National Institutes of Health *Stem Cell Information* <https://stemcells.nih.gov/info.htm>.

Many medical breakthroughs are the result of years of rigorous studies run by universities, research establishments and companies.^{7 8} Before receiving the formal approval from the regulatory agencies to be applied to treat humans, stem cell therapies must be thoroughly assessed. It requires a lengthy and labourious course that proceeds from basic research to clinical research and ultimately clinical trials.⁹ The range of illnesses and conditions for which there are established stem cell-based therapies is minuscule at present. The only proven, safe and effective stem cell treatment is haematopoietic stem cell transplantation ('HSCT') transplantation (for decades, doctors have been extracting stem cells from bone marrow to treat blood disorders, for instance, leukaemia). Other stem cell therapies are experimental and unproven; these have not been tested in Phase 3 efficacy clinical trials.¹⁰

Research on stem cells is still at early stages. Promising medicines are first developed in the laboratory and then translated into products for medical use. They require rigorous review and testing to ensure they are safe and effective. Despite limited evidence for their safety or efficacy, some private clinics leapfrogged this crucial step and advertised stem-cell-based medical procedures on the internet.¹¹ While stem cell research holds the promise for the treatment of a broad range of illnesses, there is still much work necessary to translate this research into safe and effective therapies. In the early stages, these treatments may not be effective; and worse, they may even cause adverse effects. Accordingly, it is critical for patients, and their caregivers, to know what to look out for and consider before making a firm decision whether to opt for a stem cell therapy.

III DIRECT-TO-CONSUMER ('DTC') ADVERTISING AND RISKS/HARMS OF UNPROVEN STEM CELL TREATMENTS

Vulnerable and desperate sick people are at significant risk of becoming patients without the safeguards of a clinical trial that will ensure stringent oversight and transparency. There is no cogent evidence that these therapies will be effective. Moreover, there are possible risks that could develop after receiving the stem cell treatments including allergic reactions, infection, cancer, rejection of cells by the patient's immune system and other complications that could even be fatal.¹² Some patients are willing to pay a high price to pursue these treatments. Rather than relying on scientific evidence, they tend to be influenced by anecdotal evidence and testimonials from other patients. There are some providers that use the doctor and

⁷ Heather Main, Megan Munsie and Michael D O'Connor, 'Managing the Potential and Pitfalls During Clinical Translation of Emerging Stem Cell Therapies' (2014) 3 *Clinical and Translational Medicine* <<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4049443/>>.

⁸ International Society for Stem Cell Research, 'Patient Handbook on Stem Cell Therapies: Appendix I of the Guidelines for the Clinical Translation of Stem Cells' (3 December 2008) <<http://www.isscr.org/docs/default-source/patient-handbook/isscrpatienthandbook.pdf>>.

⁹ *Ibid.*

¹⁰ *Ibid.*

¹¹ StemCells Australia, *Unproven Stem Cell Treatments* <<http://www.stemcellsaustralia.edu.au/About-Stem-Cells/For-Patients/Unproven-stem-cell-treatments.aspx>>.

¹² Alison K McLean, Cameron Stewart and Ian Kerridge, 'Untested, unproven, and unethical: the promotion and provision of autologous stem cell therapies in Australia' (2015) 6(33) *Stem Cell Research and Therapy* 1.

patient narratives on websites, television (such as appearances/interviews) and radio.¹³ Some of them even tapped into the endorsements of celebrities and sportspeople.

Private clinics or companies proffering these services advertise the procedures on websites, YouTube and blogs. Research led by Timothy Caulfield analysed various websites that promote stem cell treatments.¹⁴ The team evaluated whether the statements provided on the sites were validated by established medical literature. The study found that a number of clinics underestimated the possible harm and hyped the results of the treatments they offered.¹⁵ It noted that the advertisements made on a multitude of internet sites were effortlessly available to patients and their caregivers. Disturbingly, subsequent research reported that those unscrupulous practices still continue.¹⁶

In a recent study of websites offering autologous stem cells services, it was found that there were sites promoting 88 point-of-sale clinics in Australia.¹⁷ It found that the stem cell interventions were mostly for orthopaedic conditions, cosmetic and anti-ageing. Adipose fat-derived stem cells derived from liposuction was commonly used. According to this study, these providers employ marketing ‘tokens of legitimacy’ to advertise their services to make them appear consistent with ethical and evidentiary standards of science to confer credibility to their business. These ‘tokens of legitimacy’ include website information that claims to possess expertise, membership of professional organisations and ethical approval.

In Australia, a 75-year-old patient, Mrs Sheila Drysdale, died as a consequence of hypovolaemic shock following blood loss caused by liposuction stem cell procedure used to extract stem cells to treat her severe dementia condition. Her husband, Mr Kenneth Drysdale, was desperate to help Sheila and he heard a radio advertisement. The treatment was conducted by a cosmetic physician at a private facility. This case highlights crucial issues such as the vulnerability of very sick patients and their carers, the ethics of the medical professionals, the lack of science backing the medical procedure and whether informed consent was provided. The NSW State Coroner concluded that the autologous intervention was unproven and unjustified and called for stricter regulatory measures.¹⁸ It stated:

While all medical and surgical procedures necessarily start off experimentally, there is a world of difference between rigorously and ethically conducted clinical trials that are reviewed at every stage by qualified peers and this procedure which, in relation to treatment of dementia at least, has some of the troubling hallmarks of ‘quack’

¹³ Alison K McLean, Cameron Stewart and Ian Kerridge, ‘The Emergence and Popularisation of Autologous Somatic Cellular Therapies in Australia: Therapeutic Innovation or Regulatory Failure?’ (2014) 22 *Journal of Law and Medicine* 65, 72.

¹⁴ Darren Lau et al, ‘Stem Cell Clinics Online: The Direct-to-Consumer Portrayal of Stem Cell Medicine’ (2008) 3 *Cell Stem Cell* 591.

¹⁵ Ibid 594.

¹⁶ Ubaka Ogbogu, Christen Rachul and Timothy Caulfield, ‘Reassessing Direct-to-Consumer Portrayals of Unproven Stem Cell Therapies: Is it getting better?’ (2013) 8 *Future Medicine* 361.

¹⁷ Munsie et al, above n 2.

¹⁸ Coroners Court New South Wales, ‘Inquest into the Death of Sheila Drysdale’ (Coronial Inquest 2013/383970, 15 July 2016).

medicine: desperate patients, pseudo-science and large amounts of money being charged for unproven therapies.¹⁹

There are other harms as well. Doctor-patient relationships may be affected. There is a financial difficulty as stem cell-based therapies are usually costly (estimated to be tens of thousands of dollars at the minimum).²⁰ Extremely ill and desperate patients are prepared to pay a high price for these treatments. The medical procedures may also involve repeat treatments. If anything goes wrong, there may be emergency care costs. Undergoing unproven stem cell treatment may interfere with proven therapies, and it could disqualify the patient from future participation in clinical trials. The provision of such so-called ‘therapy’ is scientifically and clinically unacceptable as well as unethical. Collectively, these different forms of harms could cause general distrust by society of this promising stem cell field.

IV REGULATORY FAILURE

In Australia, the regulations to govern stem cell therapies include the *Therapeutic Goods Act 1989* (Cth) and the ‘traditional laws’ such as the law of contract, tort law and consumer law. Moreover, there are various professional guidelines, codes of practice and policies. Unfortunately, these different forms of regulation collectively have not been effective which may explain the proliferation of the clinics offering autologous stem cell therapies in Australia. In this section, I will explore why these forms of regulations are failing.

The national drugs regulator in Australia, the Therapeutic Goods Administration (‘TGA’), is responsible for regulating the safety and efficacy of medicines, medical devices as well as the manufacturing and advertising of therapeutic goods. The TGA was established to protect the health of the Australian society through the effective regulation of therapeutic products. It performs the responsibilities through the application of the *Therapeutic Goods Act 1989* (Cth). The TGA actively monitors the quality, safety and performance of therapeutic goods to ensure continuous compliance with its regulatory requirements. It takes appropriate enforcement action where noncompliance is identified. When taking action on a compliance matter, the range of tools includes providing encouragement/ guidance, issuing warnings, suspensions, cancellations and prosecution.

Some autologous cells are subject to the TGA’s oversight and thus require the formal approval from TGA before being supplied. The TGA can deny access to applicants who cannot demonstrate compliance with the regulation.²¹ However, in 2011, the TGA introduced an exemption for some types of biologicals, including autologous therapies.²² An autologous treatment means that cells are removed from and applied to the same person, that is, both donor and recipient are the same people. After removal from the patient, the cells are then treated, processed or purified. As the cells are

¹⁹ Ibid 12 [40].

²⁰ McLean, Stewart and Kerridge, above n 12.

²¹ Therapeutic Goods Administration, *Regulation Compliance Framework* (27 June 2013) Australian Government Department of Health <<https://www.tga.gov.au/regulatory-compliance-framework>>.

²² *Therapeutic Goods (Excluded Goods) Order No 1 of 2011*, published in Commonwealth, *Special Gazette*, No S 91, 31 May 2011.

derived from the same patient, there is a lower chance of rejection of the cells by the patient's immune system. According to Item 4(q) of the *Therapeutic Goods (Excluded Goods) Order No 1 of 2011*,²³ autologous cells are not considered as therapeutic goods and can be supplied without the TGA's approval if some requirements are fulfilled. The conditions are as follows: first, the cells are collected from a patient who is in the clinical care and treatment of a registered medical practitioner, secondly, the cells are manufactured by the practitioner (or by a person under the medical practitioner's professional supervision), and lastly, the cells are for therapeutic application in the treatment of a single indication and in a single course of treatment by the same practitioner (or by someone under the practitioner's supervision).

The justification for introducing the exemption was that autologous stem cell treatments were considered as an extension of medical practice. The intention was to exclude straightforward procedures (such as low risk and established practices) from too much regulatory interference.²⁴ Unfortunately, this broad exception has created a regulatory loophole, and it is being exploited by private clinics as a means to proffer unproven stem cell therapies.

There is also serious concern about the complexity of the treatments provided where medical practitioners may perform high levels of manipulation of the cells which increases the risks associated with patient response and safety. The risk is characterised by how closely the intended use of the product matched the original biological function and also on how far removed the cells were from their naturally occurring condition. Moreover, there are cell handling and manufacturing risks. Thus, a greater extent of manipulation in manufacturing requires more stringent regulation such as requiring all cell manufacturing to occur only in accredited laboratories.

An aggrieved patient can resort to the 'traditional law' which includes contract law, tort law and consumer law. However, these conventional laws are costly, post hoc and reactive. Bringing a lawsuit is expensive and few plaintiffs qualify for legal aid. Moreover, in civil cases such as the tort of negligence, the burden of proof is on the plaintiff, and there are challenging evidentiary issues. There is no guarantee that the plaintiff will win the case. Thus, the traditional laws have not been effective.

Furthermore, there are various types of professional guidelines/codes of practice, also known as soft law, that provide guidance on ethical behaviour for medical practitioners. Unfortunately, these guidelines are also not effective. For instance, the Medical Board of Australia ('MBA'), a professional organisation that maintains the registration and licensure of medical practitioners, has developed standards for doctors in Australia. MBA also investigates complaints. They issued the Good Medical Practice Code of Conduct,²⁵ which provides that the information doctors publish must be factual and verifiable. Patient testimonials cannot be used to advertise their services. A doctor must not guarantee cures, exploit patients or raise unrealistic expectations for clinical outcomes.²⁶

²³ Ibid.

²⁴ Munsie et al, above n 2.

²⁵ Medical Board of Australia, 'Good Medical Practice: A Code of Conduct for Doctors in Australia' (Code of Conduct, March 2014).

²⁶ Ibid 19 [8.6.3]–[8.6.4].

The Australian Health Practitioner Regulation Agency ('AHPRA'), which is responsible for the implementation of the National Registration and Accreditation Scheme, has issued guidelines for Advertising Regulated Health Services.²⁷ The guidelines state various types of behaviour which are not compatible with those expected of the profession such as omitting crucial information, misleading patients into perceiving the doctor is more qualified than they are and advertising the benefits when there is no evidence the benefits can be obtained.²⁸

Finally, there are international guidelines, for example, the 'Guidelines for the Clinical Translation of Stem Cells' by the International Society for Stem Cell Research.²⁹ The ISSCR Guidelines provide excellent and comprehensive guidance for the future development of responsible stem cell therapies from research to clinic. By way of recommendations to investigators, review committees and research institutes, they establish the benchmark to be adopted in translational applications of stem cell science. The guidelines include requirements such as the design, reporting and scientific review of the preclinical evidence (that is, the data available before the implementation of clinical trials).³⁰

However, these forms of soft law are not legally enforceable.³¹ As a set of guidance documents that direct ethical and responsible conduct of stem cell research and clinical applications, the guidelines do not amount to the final word.³² There is doubt expressed about the effectiveness of guidelines; Wise Young is sceptical whether they will influence a patient's decision whether to receive the medical treatment. He states that the guidelines will not prevent the clinics from providing inaccurate and misleading information.³³ Ultimately, it is the decision of the patient whether to seek an unproven stem cell treatment and as Jill Lepore explained, 'there may be "faith in science that draws" some desperate patients to any hope of a cure for illness'.³⁴

In contrast, the TGA has a number of strategies to prevent noncompliance.³⁵ It adopts a risk-management approach to compliance that is able to identify the entities which are at risk of noncompliance, whether deliberate or unintentional. Through its regulatory compliance framework, the TGA employs a combination of monitoring strategies to support its compliance program. Patients can lodge formal complaints to the TGA about misleading and illegal advertising. The TGA will publish information

²⁷ Australian Health Practitioner Regulation Agency, 'Guidelines for Advertising Regulated Health Services' (May 2014).

²⁸ Ibid 7 [6.2].

²⁹ International Society for Stem Cell Research, 'Guidelines for Stem Cell Research and Clinical Translation' (Research Guidelines, 12 May 2016) ('ISSCR Guidelines').

³⁰ Ibid.

³¹ Angela Campbell and Kathleen Cranley Glass, 'The Legal Status of Clinical and Ethics Policies, Codes, and Guidelines in Medical Practice and Research' (2001) 46 *McGill Law Journal* 473.

³² George Daley et al, 'Setting Global Standards for Stem Cell Research and Clinical Translations: The 2016 ISSCR Guidelines' (2016) 6 *Stem Cell Reports* 787, 796.

³³ Monya Baker, 'Stem Cell Society Condemns Unproven Treatments', *Reports Stem Cells* (online), 26 June 2008

<<https://www.nature.com/stemcells/2008/0806/080626/full/stemcells.2008.98.html>>.

³⁴ Harvard Stem Cell Institute, 'Stem Cell Tourism: False Hope for Real Money' (2013) 8(1) *Stem Cell Lines* 7, 8.

³⁵ Therapeutic Goods Administration, *Compliance Actions* (Australian Government Department of Health) <<https://www.tga.gov.au/compliance-actions-0>>.

about regulatory compliance decisions and actions on its website. Thus, tightening of the wording of the TGA regulation is crucial.

V THE PROPOSED NEW TGA REGULATION

Recognising that the existing control is not adequate, TGA conducted consultations in 2015³⁶ and 2016³⁷ with stakeholders to obtain their views to determine an appropriate regulatory framework to govern autologous human cell and tissue products. During the 2015 consultation, five options were proposed for the regulation; this was reduced to four choices in the 2016 consultation. The options differ according to the degree of manipulation that is permitted before the regulatory exemption no longer applies. Option 1 maintains the status quo allowing medical providers to continue marketing untested stem cell therapies to patients. Options 2, 3 and 4 prohibit the DTC marketing of autologous stem cell.

On a positive note, in October 2017, the TGA announced that proposed revisions to the biologicals regulatory framework would be implemented in 2018.³⁸ These changes are designed to set up graduated regulatory oversight of the products commensurate with the safety risks to patients. This will bring Australia into closer alignment with other jurisdictions such as the United States and the European Union.

A more substantial proportion of the autologous cell products, including stem cells, will be subject to TGA regulation. Only those cell products that are manufactured and used in an accredited hospital by a medical practitioner for a patient in the care of the same doctor are exempted from TGA's regulation. Autologous cell products that are more than minimally manipulated,³⁹ for non-homologous⁴⁰ and manufactured and used outside an accredited hospital will be fully regulated under the Biologicals Regulatory Framework. Products that are minimally manipulated and for homologous use are also regulated subject to exemptions. Access to some unapproved therapeutic goods such as through clinical trials and the special access schemes will continue to be available to patients.

The proposed amendments will prohibit direct advertising to consumers of the autologous cell products, similar to the current prohibition of the promotion of

³⁶ Therapeutic Goods Administration, 'Regulation of Autologous Stem Cell Therapies' (Discussion Paper, January 2015).

³⁷ Therapeutic Goods Administration, 'Consultation: Regulation of Autologous Cell and Tissue Products and Proposed Consequential Changes to the Classification of Biologicals' (Discussion Paper, August 2016).

³⁸ Therapeutic Goods Authority, 'Regulation of Autologous Cell and Tissue Products' (Media Release, 24 October 2017).

³⁹ Minimal manipulation of the cells means that the cells undergo a process that does not result in the change of its biological characteristics, physiological functions or structural properties relevant to the intended use of the cells such as trimming, cutting, freezing, washing, etc. Thus, they are not substantially compromised by the processing. In contrast, cell culture, genetic modification and in vitro differentiation are considered to be more than minimal manipulation. See Therapeutic Goods Administration, 'Biologicals Regulatory Framework Proposed Changes to Start on 1 July 2018: Including Changes to Regulation of Autologous Human Cell and Tissue Products and Classification of Biologicals' (Proposal, April 2018).

⁴⁰ Homologous use of the cells means the repair or replacement of a recipient's cells with cells that perform the same basic functions in the recipient as the donor (eg, skin graft collected from one area of the body and used to replace damaged skin in another location): see *ibid.*

prescription medicines.⁴¹ In Mrs Drysdale case, Mr Drysdale heard the radio advertisement. Under the new regulation, the advertising should be generally worded and it cannot make specific reference to the autologous product. Abbreviations, acronyms and colloquial terms like stem cells cannot be used. The prohibitions are applicable to every type of media, whether conventional (television, radio, print media, posters, and so forth) or electronic (such as websites, social media, YouTube, blogs, discussion forums, or emails). Testimonials provided by patients (typically on websites) are considered as advertising. The requirements apply to doctors, media outlets, business ventures and professional organisations. When the TGA is notified about the noncompliant advertising, the advertiser will be contacted. In the first instance, the TGA will educate and assist advertisers to comply with the advertising requirements. If this path fails, it will escalate to further steps by the TGA to achieve compliance. Fines imposed for advertising breaches is up to \$840 000 for individuals and up to \$4 200 000 for corporations.

In addition, the autologous product will be subject to other stringent regulatory requirements. For instance, patients who suffer from an adverse medical event subsequent to the treatment received have to be reported to the TGA. The manufacturer and the facilities that carry out testing on the cell product must possess a TGA-issued licence or certification. The cell product has to be included in the Australian Register of Therapeutic Goods ('ARTG') where the TGA must be satisfied as to the safety, efficacy and quality of the product. The TGA has powers to recall the cell product and also suspend and cancel the inclusion of the product in the ARTG. There is also compliance with all applicable standards and compliance with matters concerning records and reporting.

Thus, under the proposed new regulation, autologous stem cell therapies will be stringently governed by the TGA. Prior to being supplied, the TGA's approval is needed and applicants who do not show compliance with the regulation will be refused access. The TGA monitors the safety, quality and performance of therapeutic goods to confirm continuous compliance with the regulatory obligations and recurses to enforcement action where noncompliance is identified.

VI CONCLUSION

The harms caused to patients could affect public confidence and even undermine the legitimacy of the nascent stem cell field. Accordingly, more regulation is favoured as this will offer legitimacy to medical practice and also it will make Australia a trusted, reputable destination for stem cell tourism. The proposed new TGA law will prohibit DTC advertisements and also require medical practitioners to report adverse medical events suffered by patients, thus affording more safeguards to vulnerable patients. However at this early stage, much remains to be seen as to how effective the proposed regulation is going to be. Detailed guidance is being drafted which will assist in the interpretations and enforcement of the law. A transition period, which may be complete at the end of 2018, will enable medical providers time to make the necessary adjustments to the new regulation such as the need to obtain a manufacturing license and/or approval of a clinical trial. Meanwhile, the TGA will consult the various stakeholders on the development of these guidance documents. Nevertheless, the

⁴¹ Ibid 7–8.

Australian government's long awaited decision to amend the law is a positive step forward, and the hope is that it will sieve out unscrupulous doctors and safeguard vulnerable patients' interests.