



**Submission to the Therapeutic Goods Administration's
Public Consultation – *Regulation of autologous stem cell
therapies***

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Executive Summary

We strongly believe that there is an urgent need for more stringent oversight of autologous cell-based interventions, to protect the Australian public and overseas visitors from provision of unproven, costly, and potentially hazardous cell therapies, and to bring Australia into alignment with other jurisdictions and recommendations of leading international learned scientific and research organisations.

The development of novel autologous-based therapeutics remains in its infancy.

It should not be assumed that, just because the cells are obtained from the patient undergoing treatment, that there is no risk associated with these procedures.

We believe that that the current blanket exclusion enables provision of unproven and potential unfounded autologous therapies that pose risks to the health of Australians and overseas visitors due to questions regarding:

- safety of product;
- lack of long-term follow-up and ongoing care;
- patient deviation from conventional 'best practice' medical care.

As highlighted by the International Society for Stem Cell Research (ISSCR), it should be considered unethical to market unproven stem cell-based interventions – even when the patient's own cells are used.

It is essential that Australian regulations be amended to recognise that regulatory oversight should be governed by how cells are manufactured and how they are used, even if the patient's own tissue is the source of the preparation.

We believe the Therapeutic Goods Administration (TGA) is the appropriate Australian body to ensure that such products are safe and fit for their intended purpose.

We believe Option 5 outlined in the TGA Discussion Paper would be an appropriate long-term regulatory remedy for the current lack of oversight and argue that implementation of a Ministerial Order could immediately address our concerns.

We reject the claim that greater regulatory oversight will inhibit medical innovation or delay the introduction of promising new treatments into clinical trial.

We need, and must insist on, a strong evidence base as we translate stem cell research to clinical application.

Immediate action is required to curb the growth of exploitative unproven and unfounded practices in Australia.

Overview

We welcome the opportunity to contribute to the TGA 2015 public consultation on the regulation of autologous stem cell therapies.

For many years we have been concerned about the provision of unproven autologous 'stem cell' interventions by Australian practitioners and/or clinics^{1,2}. Such practices raise many of the same concerns levelled at unregulated providers overseas:

- direct to consumer marketing;
- lack of evidence of safety;
- promoting success based on patient testimonials rather than objective scientific evidence;
- single treatments promoted for multiple, unrelated diseases;
- scientific rationale not offered or available;
- lack of patient follow-up; results of treatment not available in peer-reviewed journals, and
- significant fees per treatment (many thousands dollars with no reimbursement).

We strongly believe that there is an urgent need for more stringent oversight of autologous cell-based interventions, to protect the Australian public and overseas visitors from provision of unproven, costly, and potentially hazardous cell therapies, and to bring Australia into alignment with other jurisdictions and recommendations of leading international learned scientific and research organisations. The current regulatory framework – in particular the blanket exemption of all autologous cell therapies from TGA oversight – has proved to be an unsatisfactory instrument to influence the development of safe and effective new cell-based therapeutics in this country. Rather than encourage responsible translation through the appropriate route of preclinical research and clinical trials, the last four years has seen an exponential growth in clinics and individual doctors providing unproven and unfounded autologous interventions^{2,3,4}.

Australian clinics and individual practitioners offer a wide range of autologous cell therapy interventions, often for a considerable fee. Such interventions range from the use of adipose-derived stromal vascular fraction⁵ (SVF) administered via intra-articular injection for various musculoskeletal conditions; to intravenous (IV) delivery of a variety of cellular products. These include resuspended SVF; cultured mesenchymal stromal cells (MSCs), and cells from blood and skin that have been so extensively manipulated that they are claimed to be reprogrammed to a multi-potent state². In addition to the treatment of musculoskeletal conditions, patients with Multiple Sclerosis, retinal neuropathy, Parkinson's disease, infertility, chronic fatigue syndrome, motor neurone disease and many other conditions are being offered unproven cell therapies. None of the available treatment regimes are considered 'standard medical practice' and many are not supported by even the lowest level of medical evidence. Very few have been subject to peer-review. Most if not all interventions are being offered outside the context of a clinical trial by a growing number of practitioners, many of whom appear to have limited expertise in the

¹ Pera & Munsie (2012) Submission to the NHMRC Public Consultation – Stem Cell Treatments [<http://www.stemcellsaustralia.edu.au/AboutUs/Document-Library.aspx> (accessed 27 February 2015)]

² Munsie & Pera (2014) Regulatory loophole enables unproven autologous cell therapies to thrive in Australia. *Stem Cells Dev* 23 (Suppl 1):34-8.

³ McLean et al (2014) The emergence and popularization of autologous somatic cellular therapies in Australia: therapeutic innovation or regulatory failure? *J Law Med* 22(1):65-89.

⁴ McLean et al (2015) Untested, unproven and unethical: the promotion and provision of autologous stem cell therapies in Australia. *Stem Cell Res Ther* 6(1):12.

⁵ **SVF** is a heterogeneous mixture of cells derived from adipose tissue or liposuction aspirates following collagenase digestion or other mechanical disruption and centrifugation. Pelleted cells include stromal cells, vascular endothelial, leucocytes and erythrocytes with adipocytes assumed to be separated and discarded in the supernatant during preparation.

condition they are treating. In many cases, there is not even preclinical evidence regarding the efficacy or safety of the products in the indications for which they are provided. Under the current regulatory framework, there is no requirement that providers adhere to Good Manufacturing Practice in the preparation of the cells used in therapy.

It should not be assumed that, just because the cells are obtained from the patient undergoing treatment, that there is no risk associated with these procedures, a point illustrated by rare but nonetheless not insignificant number of reports and published studies of low frequency serious adverse events following autologous cell therapy.

It is essential that Australian regulations be amended to recognise that regulatory oversight should be governed by how cells are manufactured and how they are used, even if the patient's own tissue is the source of the preparation. Extensive *ex vivo* manipulation of cells, and their administration to heterotopic sites, carries inherent risk to the patient irrespective of whether the cells are autologous or allogeneic origin. We believe the TGA is the appropriate Australian body to ensure that such products are safe and fit for their intended purpose. It is salutary that four of the five options outlined in the TGA Discussion Paper concede the need to more effectively regulate products produced using techniques that involve more than minimal manipulation⁶ and where the intended use is no longer homologous⁷.

We argue that Option 5 would be an appropriate regulatory remedy for the current lack of oversight. We are concerned that the Discussion Paper implies that any change to the current legislation will entail lengthy and cumbersome review processes. The current regulatory vacuum should be addressed urgently, and it is our conviction that amendment of 4(q) the Therapeutic Goods (Excluded Goods) Order No.1 of 2011 by Ministerial Order would be an effective and immediate means to address this current regulatory deficit. This could be achieved by inserting wording to the effect that the current exclusion would remain only where the autologous cells or tissues are utilised in specific recognised medical interventions (reflecting those listed in Appendix 1 of the Discussion Paper). All other use of autologous cells and tissues would then be regulated under the Act.

We believe urgent action is required to address a disturbing new development wherein overseas companies appear to be moving to Australia to take advantage of our more lenient regulatory environment. These companies appear to be offering remedies that rely on extensively manipulated cells that would be considered to carry the highest level of risk under the Biologicals Framework. Without immediate action Australians, overseas patients seeking treatment in Australia, and indeed the reputation of Australian biotechnology and healthcare sector, will be placed at significant risk.

Modification of the Excluded Goods Order as outlined would immediately curb the growth of exploitative unproven and unfounded practices in Australia.

We reject the claim that such action will inhibit medical innovation or delay the introduction of promising new treatments into clinical trial. It is arguable of course that the existing mechanisms for testing new cell therapies could be streamlined considerably, and indeed this is an area that is receiving increasing attention internationally. However, we are not aware of any instance in any jurisdiction in which the proposed solution to this problem entails abandoning clinical trials or regulatory oversight altogether. We are aware of arguments, put forward locally by a coalition of cell therapy providers, that some sort of self-regulatory framework would

⁶ **TGA definition of Minimal manipulation:** A process involving any of the following actions: (a) centrifugation; (b) trimming, cutting or milling; (c) flushing or washing; (d) refrigeration; (e) freezing; (f) freeze drying (of structural tissues only); (g) the use of additives such as cryopreservatives, anticoagulants, antimicrobial agents; (h) irradiation for the purpose of bioburden reduction; (i) any other action that is similar to an action mentioned in paragraph (a), (b), (c), (d), (e), (f), (g) or (h).

⁷ **TGA definition of Homologous use:** The repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with a biological that performs the same basic function in the recipient as in the donor.

suffice to control autologous cell therapies. We oppose this model, because of the inherent conflict of interest built into it. It is possible that a scheme of voluntary regulation with true independent oversight and mandatory inspections and reporting of outcomes, similar to that which operated in the early days of in vitro fertilisation in the United Kingdom, might be appropriate for autologous cell therapies involving minimal manipulation and homologous use.

In this submission we address the specific questions raised in the TGA Discussion Paper and provide an analysis of each of the five regulatory options canvassed. We argue that a Ministerial Order could immediately address our concerns yet not interfere with medical innovation and advancing the use of stem cell science for therapeutic benefit.

Who we are

Martin Pera is Professor of Stem Cell Sciences at The University of Melbourne, the Florey Institute of Neuroscience and Mental Health, and the Walter and Eliza Hall Institute for Medical Research. He serves as Program Leader for Stem Cells Australia, the Australian Research Council Special Research Initiative in Stem Cell Science. His research interests include the cell biology of human pluripotent stem cells, early human development, and germ cell tumours. Pera was among a small number of researchers who pioneered the isolation and characterisation of pluripotent stem cells from human germ cell tumours of the testis, work that provided an important framework for the development of human embryonic stem cells. His laboratory at Monash University was the second in the world to isolate embryonic stem cells from the human blastocyst, and the first to describe their differentiation into somatic cells in vitro. He has provided extensive advice to state, national and international regulatory authorities on the scientific background to human embryonic stem cell research.

Megan Munsie is a stem cell scientist who combines her extensive technical expertise in stem cell science with an interest and understanding of the complex ethical, social and regulatory issues associated with stem cells in research and in the clinic. Munsie is a member of a multi-disciplinary ARC funded research team that is exploring community expectation in relation to stem cell science, and in particular attitudes to unproven stem cell treatments offered abroad and in Australia. She is Head of the Education, Ethics, Law & Community Awareness Unit at Stem Cells Australia; Chair of an ISSCR taskforce on public education; and Chair of the Australasian Society for Stem Cell Research's Policy, Ethics and Translation sub-committee.

Response to specific questions raised in the discussion paper

1. *What are the public health risks of 'autologous stem cells' in your view?*

There are three key risks for patients pursuing unproven and potential unfounded autologous therapies: safety of product; lack of long-term follow-up and ongoing care; and deviation from conventional care.

The development of novel autologous-based therapeutics remains in its infancy. It cannot be automatically assumed that cells or tissues taken from the patient for treatment of the same patient pose little or no **risks to the health of that patient**. Both allogeneic and autologous products carry risks to the health of a patient depending on how the cells are prepared and the intended use of the cells.

Ex vivo manipulation of cells, which may entail the use of a range of reagents or devices of ill-defined quality or provenance, can inadvertently introduce toxins or pathogens into a preparation, or alter the cell's epigenetic or genetic status in a fashion that might adversely affect its function or cause oncogenic transformation. The fact that a sample is sourced from the patient does not eliminate these risks.

Furthermore when the intended function of the cells, tissues and/or their derivatives is different the biological function that they held in the tissue from which they were harvested - non-homologous use - it cannot be assumed that the cells or their derivatives will behave in a predictable fashion. Introduction of cells into heterotopic sites can dramatically affect their behaviour and that of the surrounding tissue in ways that are difficult to predict. Automatic exclusion from regulatory oversight should only be considered where the cells are minimally manipulated and are intended for homologous use.

It should be noted that the Excluded Goods Order is not limited to adipose or bone marrow derived MSCs for which there is a considerable body of clinical data. There is evidence that other types of cell therapy (for which there is much less clinical data) are being offered to Australian patients under the exemption⁸. From details on their website, a Brisbane-based company is offering treatment allegedly using pluripotent stem cells converted from patient's peripheral blood cells for a myriad of conditions in a "closed system environment" without the "requirement or use of any animal components, expansion and/or genetic engineering of any cells"⁹. If this treatment is what it claims to be, it would fall under TGA Level 4 risk classification were it not for the fact that it involves the use of autologous cells. Indeed as there is no requirement to disclose details about the protocols used, nor any need to characterise the material being delivered to the patient to any standards, it is completely unclear what this product contains. We are also aware of two other groups whose promotional material imply that they are also offering or seeking to offer treatments involving highly manipulated autologous cells¹⁰.

A survey of ongoing or recent clinical trials of autologous cell therapy (clinicaltrials.gov) revealed that autologous cells are undergoing assessment in humans for a wide range of conditions: haematopoietic stem cells for Crohn's Disease and Type 1 diabetes; intracardiac injection of hematopoietic stem cells; bone marrow mononuclear fraction, or cardiac stem cells for myocardial infarction or pediatric cardiomyopathy; intrathecal injection of bone marrow cells (mononuclear fraction) for stroke, spinal cord injury, or cerebral palsy; umbilical cord cell infusion for hearing loss in children; intrapancreatic infusion of stem cells (unspecified) for Type 2 diabetes; intraurethral injection of *ex vivo* expanded muscle cells for urinary incontinence; neural stem cells for spinal cord injury; olfactory ensheathing cells into brain or spinal cord for stroke or spinal cord injury; retinal pigment epithelium derived from induced pluripotent stem cells for macular degeneration. The scientific rationale and preclinical data behind these studies ranges from poor or almost non-existent to excellent, but they all have several things in common. They all involve autologous cells, they all involve unproven and generally controversial interventions, and they all carry considerable risks to the patient. Under the Excluded Goods Order, any clinic could offer these treatments to patients for profit outside of a trial setting with no requirement for regulatory oversight whatsoever.

The current Excluded Goods Order broadly exempts all autologous cell and tissue therapies from meeting the requirements set-out under the Biologicals Framework. Such a broad exclusion is out of step with the risk-based regulatory approaches in other jurisdictions where only autologous products that have "not been manipulated extensively or combined with other articles, are intended for homologous use in functionally compatible tissues, and/or are harvested and transplanted as part of the same surgical procedure" are excluded from regulatory oversight of the centralised government agency that controls the marketing of drugs, medical devices, and

⁸ Munsie & Pera (2014) Regulatory loophole enables unproven autologous cell therapies to thrive in Australia. *Stem Cells Dev* 23 (Suppl 1):34-8.

⁹ Autologous Stem Cell Technology [<http://ascotech.com.au/index.html-technology>](Accessed 27 February)].

¹⁰ Ophiuchus Technologies [<http://www.ophiuchustechnologies.com/products-indications/>] (Accessed 27 February)] and Scellife [<http://www.scellife.com.au/Doctors>](Accessed 27 February)].

biologicals within that jurisdiction¹¹. Furthermore, recent developments in the USA leans towards a far more stringent requirement than currently in place in Australia. In 2014 the US Court of Appeals for the District of Columbia Circuit upheld the right of the US Food and Drug Administration (FDA) to regulate the manufacture of this ex vivo expanded autologous MSCs – derived from bone marrow or synovial fluid – as a product rather than a medical procedure¹². To further address this issue, the FDA recently issued a draft guidance statement that recommends that interventions utilising adipose derived tissue, including SVF, should be regulated as a drug where their production involved more than minimal manipulation and/or non-homologous use¹³.

An additional consideration is the **lack of substantive long-term follow-up** offered by many of the Australian operations. As there is currently no mandated premarket testing for safety and efficacy, nor any requirement for post market surveillance, long-term follow-up of the patients following treatment is haphazard, with adverse events under reported or not reported at all. Because many of the clinics also encourage a ‘fly-in and fly-out’ service, direct consultation with medical staff and full assessment may not be possible. We note that even the published literature on MSC or adipose derived stem cells contains very little information on long-term risks, including tumourigenesis. This is indeed an unknown factor at present that will require careful ongoing assessment, particularly if the adverse event is both somewhat infrequent but also very serious (e.g, tumour formation).

There is also a risk that the current regulatory framework encourages a **deviation from conventional ‘best practice’ medical care**. Even for those conditions where there is no curative treatment available, these expensive, unproven and in many situations completely unfounded interventions are encouraging patients to depart from established care plans placing them at unnecessary financial and emotional risks. This risk is compounded by direct-to-consumer advertising via websites stating that therapies “appear 100% safe” and “improve your quality of life”¹⁴. There is no requirement for a referral to these clinics or practitioners and treatment maybe provided without any knowledge of other treating medical specialists.

It should also be noted that many of those providing the treatment might lack speciality training for the conditions in which they are offering the interventions. For example, general practitioners and/or self-described ‘stem cell’ specialists offering to treat patients with motor neurone disease or multiple sclerosis whose care would usually be expected to be overseen by an accredited neurologist.

In considering access to unproven therapies, some have raised the issue of the patients right to choose. Right to choose implies there is a rational basis for making an informed choice and giving consent. With many autologous cell therapies, there is no such basis for informed choice. When there is no sound information on whether or not the treatments might work and no evidence on potential dangers, when there is indeed no process in place to assess safety or efficacy, when it is often not even clear what the treatment actually entails, and when the sole information available is testimonials or misleading claims and advertising, then there is no basis for rational choice on the part of the patient.

Regulators have a responsibility to protect the public from any medical treatment that is unfounded, potentially dangerous, and exploitative.

¹¹ Lysaght et al (2013) Oversight for clinical uses of autologous adult stem cells: lessons from international regulations. *Cell Stem Cell* 13(6):647-651.

¹² United States v. Regenerative Sciences and LLC (2014). [<http://www.gpo.gov/fdsys/pkg/USCOURTS-dcd-1-10-cv-01327>] (12-5254 (D.C. Cir. 2014) (Accessed 27 February)).

¹³ Food and Drug Administration (2014), Minimal manipulation of human cells, tissues and cellular and tissue-based products: Draft guidance [<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm427692.htm>] (Accessed 27 February).

¹⁴ McLean et al (2014) The emergence and popularization of autologous somatic cellular therapies in Australia: therapeutic innovation or regulatory failure? *J Law Med* 22(1):65-89.

When we consider the question of a patient's right to try unproven treatments, it is also important to recognize that costs associated with access to unproven treatments are not only born by the patient. If a patient receives an unproven stem cell treatment, and there are medical complications, or the patient defers or forgoes access to conventional treatments that would have had genuine benefits, then our health care system has to deal with the consequences. This entails expenditure on the part of a health care system where costs are of increasing concern.

Since 2011, Stem Cells Australia has responded to over 1,300 public enquiries from patients or their loved ones seeking information about stem cell research. Whilst enquiries were initially restricted to overseas providers, we have seen a growing number discuss treatments they have been offered in Australia for conditions for which stem cell therapies remain unproven and unfounded¹⁵. For example, we spoke to a patient who was considering discontinuing painful conventional care for retinal neuropathy at a metropolitan specialty clinic for IV adipose-derived SVF treatment by a cosmetic surgeon – potentially compromising her long-term medical care.

2. What is the evidence for these risks?

Establishing a true assessment of the risks posed by autologous cell therapies currently available in Australia is challenging given the lack of information publically available on how the cells are prepared prior to administration and an almost complete lack of information on follow-up. It can certainly not be assumed just because the patient's own cells are used that this mitigates against risk and that as is often stated on website advertising autologous interventions that they are "100% safe"¹⁶.

It must also be acknowledged that the cells being used in Australia are not restricted to MSCs, but rather an ill-defined conglomeration of cell types ranging from suspended liposuction-derived SVF; to aliquots of cultured MSCs which may or may not be characterised; to cells from blood and skin that appear to have been so extensively manipulated that they are claimed to be reprogrammed to a multi-potent state. Often these products are implied to be 'stem cells' when marketed to the potential patients, but have little in the way of recognised characterisation details provided to justify such claims, even if the dose being administered is what is considered to be a clinically effective level. Supporting pre-clinical data demonstrating safety and efficacy using the same manufacturing approach also appears to be absent. Rather, Australian providers are extrapolating from published findings often with scant links to product similarity.

Further compounding the challenge of identifying risks is the fact that the cells appear to be administered in a variety of ways. While most Australian providers restrict application to intra-articular injection for musculoskeletal conditions, when treating other conditions cells are administered via IV routes no matter the cell type, or the purity of preparation. As noted in Attachment 2 of the TGA Discussion Paper, pulmonary embolism and infarction are theoretical risks of IV administration – although this should not be couched in terms that imply only for MSCs (as may be interpreted from Attachment 2) but indeed linked to any bolus cellular preparation introduced via this route.

There are also risks associated with collection of the cells and/or tissue that appear to be dismissed in marketing material. Liposuction in itself can present the patient with complications such as bleeding, infection and possibly disfigurement.

¹⁵ Munsie & Pera (2014) Regulatory loophole enables unproven autologous cell therapies to thrive in Australia. *Stem Cells Dev* 23 (Suppl 1):34-8.

¹⁶ Munsie & Hyun (2014) A question of ethics: Selling autologous stem cell therapies flaunts professional standards. *Stem Cell Research* 13:647-653.

While tumourigenicity is a recognised risk associated with pluripotent stem cells – both embryonic stem cells and induced pluripotent stem cells – it cannot be assumed that all autologous cell therapy carries no risk in regard to inappropriate/aberrant cellular growth. An important consideration here is the degree of manipulation that the cells have been exposed to - not currently a consideration Australian regulations and a potentially substantive public health issue. Exposure to toxins or adventitious agents, epigenetic changes, and reactivation of latent viral infection are all potential risks, as is tumourigenicity. Ex vivo expansion of human MSCs is associated with development of mutations in the cells, including lesions in genes associated with cancer¹⁷. It is particularly concerning that we have now identified three overseas companies that have websites promoting treatments in Australia - involving transformed or reprogramed patient cells as therapy they are or plan to offer in here - with no apparent unease about tumourigenicity or any obvious safeguards in place.

If we now turn to documented evidence in scientific and medical literature, we would acknowledge that at this stage there is little evidence of serious short to medium term adverse effects of autologous SVF or MSC therapies (including those that have included adipose extract assumed to include MSCs) administered in a clinical trial setting. Of 52 clinical trials involving over 1,500 patients receiving treatment for a range of conditions in trials conducted between 2011 and 2014, we note there was little reported systematic evidence of frequent adverse effects, though mostly the follow up was relatively short term (two years or less). While this simplistic analysis may be used by some to justify open provision of autologous cell therapies, it should be noted that many of the interventions being offered in Australia are not represented in these studies.

We would also highlight that there are a number of reports and published studies of low frequency serious adverse events following autologous cell interventions. These include:

- The 2014 announcement by Cytori Therapeutics that enrolment in their ATHENA (NCT02052427) and ATHENA II (NCT01556022) clinical trials has been placed on clinical hold due to reported adverse cerebrovascular events in three patients¹⁸. These randomized, double-blind, placebo controlled studies are evaluating use of autologous adipose-derived cells in patients with ischemic heart disease (myocardial injection). Although the events were stated by Cytori as being “related in part to the medical co-morbidities in the treated population”, it highlighted the unknown consequences of these novel cell therapy applications.
- A recent report of a spinal cord mass following injection of olfactory mucosal cell transplantation eight years after a paraplegic woman had participated in a clinical trial¹⁹. This highlights the need for long-term follow-up, in particular to monitor low frequency serious adverse effects. There is significant preclinical evidence showing the potential for malignant transformation of MSC grown in culture.
- Development of cellular masses in kidney following injection of autologous bone marrow cells in an attempt to treat lupus nephritis²⁰.
- There are several reports of serious adverse effects following administration of autologous cells intravenously, or into the heart or the central nervous system²¹.

¹⁷ Cai et al (2014) Whole genome sequencing identifies genetic variances in culture expanded human mesenchymal stem cells. *Stem Cell Reports* 3(2):277-233.

¹⁸ Cytori (2014) Press release: Cytori provides update on ATHENA trial status [<http://ir.cytori.com/investor-relations/News/news-details/2014/Cytori-Provides-Update-on-ATHENA-Trial-Status/default.aspx>] (Accessed 27 February 2015)

¹⁹ Dlouhy et al. (2014) Autograft-derived spinal cord mass following olfactory mucosal cell transplantation in a spinal cord injury patient. *J Neurosurg:Spine* 21(4):618-622.

²⁰ Thirabanjasak et al (2010) Angiomyeloproliferative lesions following autologous stem cell therapy. *J Am Soc Nephrol* 21:1218–1222.

In summary whilst at this stage there is little evidence of serious short to medium term frequent adverse effects of autologous adipose or MSC therapies administered in a clinical trial setting, there are reports of infrequent significant adverse effects of such therapies.

Importantly, our analysis of the literature showed that there is almost no high level evidence to support efficacy in most indications for which these approaches have been applied. It is of course remarkable that any intervention purported to offer real therapeutic effect of a significant magnitude in such a wide range of conditions should be completely devoid of adverse effects. The possibility remains that the actions of these cells *in vivo* are often innocuous (and largely without major benefit) because of their lack of long-term persistence in the host and the transient nature of any biological impact therein. It is of course possible that autologous therapies will prove to be safe in the long term and indeed beneficial to certain patients with certain conditions. However, we will never discover this through unregulated merchandising of these therapies without properly constituted clinical trials providing Level 1 evidence.

Under the current Australian regulatory scheme, there is no barrier to provision of autologous cell therapies that carry little or no benefit. It is hard to justify this situation even if there is only a low level of risk associated with the intervention. We note that risk/benefit analysis, rather than consideration of risk alone, is the appropriate way of assessing such therapies.

Thus, our review of the literature has done little to alleviate our concerns regarding the Excluded Goods Order. We are convinced that all autologous cell treatments – particularly those involving more than minimal manipulation of cells *ex vivo* and non-homologous use – should not be excluded but fall under the remit of the TGA.

3. What identified risks should have the highest priority for resolving?

Risk to health: It is crucial that autologous cell therapies in Australia are regulated commensurate to risks to patient health – that Australian patients and those visiting from overseas are not exposed to interventions that could further compromise their health. It is a grievous oversight that the Australian regulatory framework has enabled a *carte blanche* attitude to the development of autologous cell interventions – irrespective of the degree of manipulation or the ultimate use of the cellular material. In this regard, Australia is out of step with other leading countries and holds the real risk of being seen as a destination of choice for providers seeking to exploit regulatory weakness and establish ‘stem cell tourism’ destinations.

Risk of direct-to-consumer advertising: Despite regulations on promotion of unproven therapeutics in Australia, websites and media reporting promoting autologous treatments are common. Many of the sites make reference to the TGA exemption with the implication that these treatments are sanctioned activity. For example, promotional material for one company states that their product is the “only product certified with granted permission for administration (by a medical professional) within Australia by the Therapeutic Goods Administration”²².

4. Are there public health benefits, such as patient access to new and novel treatments, to consider?

²¹ Jung et al (2013) Familial occurrence of pulmonary embolism after intravenous, adipose tissue-derived stem cell therapy. *Yonsei Med J* 54(5):1293-6; Pytel et al (2010) Ventricular fibrillation following autologous intramyocardial cell therapy for inherited cardiomyopathy. *Cardiovasc Pathol* 19(2):e33-6; Kishk et al (2013) Possible induction of acute disseminated encephalomyelitis (ADEM)-like demyelinating illness by intrathecal mesenchymal stem cell injection. *J Clin Neurosci* 20(2):310-2.

²² Probiotech: Informational presentation [<http://probiotech.com.au/resource.html>] (Accessed 27 February 2015)]

While there is no doubt that there is an unmet need for novel treatments for a number of currently intractable conditions, and that cell-based therapeutics and regenerative medicine strategies offer great promise, such interventions should be offered outside clinical trials only when they have been shown to be safe and effective. Enthusiasm and opportunity is not sufficient justification to endorse the unregulated sale of unproven treatments in Australia.

A growing number of patient groups and professional bodies recognize the need to encourage those considering treatment to appreciate the unfounded basis of many of these treatments:

- For example, in 2013 ISSCR released an additional statement reiterating the criteria under which stem cell research should be translated – even when the cells are from the patient – and calling on “medical licensing bodies, legal authorities, patient advocacy organizations, physicians, and others to exercise their influence to discourage commercial provision of unproven autologous cell-based interventions outside of clinical trials”²³.
- MND Australia recently issued a position statement warning patients and their loved ones that new treatments, especially in stem cell research, are considered experimental and that any intervention “must have been proven to be safe and to improve outcomes before it is made available outside a clinical trial”²⁴.
- The Australian Rheumatology Association also issued a position statement that there is “not enough supportive evidence to recommend stem cell therapy/Autologous Cell Base Intervention as a clinical intervention for osteoarthritis outside of a clinical trial setting”²⁵.

It should also be noted that access on compassionate grounds is available to Australian patients and their treating doctors outside the clinical trial framework. The Special Access Scheme provides the opportunity for the import and/or supply of an unapproved therapeutic good for a single patient, on a case-by-case basis under a range of circumstances such as:

- early access for terminally ill patients to almost any product, including experimental and investigational products (see Category A);
- access to products which have been withdrawn from the Australian market for commercial or other reasons;
- access to products provided initially to patients through a clinical trial while a marketing application is being considered; and
- access to products available overseas but not marketed in Australia.

In the case of Category A patients, there is no need to seek approval from the TGA for the use of an unapproved product but the practitioner is required to notify that the informed consent has been obtained and that the product will be prescribed in accordance with good medical practice²⁶. For all other patients the treating medical practitioner will need to seek the approval of a 'delegate' authorised under the *Therapeutic Goods Act 1989*. Requests can be made to either a delegated medical officer within the TGA or a delegate outside the TGA.

In addition, access is also possible via the Clinical Trial Exemption (CTX) scheme which would require information about the product provided by the sponsor, including the overseas status of the medicine, proposed Usage Guidelines, a pharmaceutical

²³ ISSCR (2013) Statement on Delivery of Unproven Autologous Cell-based Interventions to Patients [<http://www.isscr.org/home/about-us/news-press-releases/2013/2013/09/12/isscr-statement-of-delivery-of-unproven-autologous-cell-based-interventions-to-patients>](Accessed 27 February).

²⁴ MND Australia (2014) Position Statement: Alternative and Unproven therapies and people diagnosed with MND [<http://www.mndaust.asn.au/About-us/Policies-and-position-statement/National-policies-and-position-statements/Unproven-therapies-for-MND-and-the-internet.aspx>] (Accessed 27 February)

²⁵ Australian Rheumatology Association (2014) ARA Position Statement on Stem Cell Therapies [https://www.rheumatology.org.au/downloads/ARA_Position_Statement_042014.pdf] (Accessed 27 February 2015)

²⁶ TGA, Access to unapproved therapeutic goods via the Special Access Scheme; [<https://www.tga.gov.au/access-unapproved-therapeutic-goods-special-access-scheme>] (Accessed 27 February).

data sheet, a summary of the preclinical data and clinical data to be provided and reviewed by TGA²⁷.

It has been argued by one provider of autologous cell therapy that removing the exclusion order “risked stifling the development of a world-leading regenerative technology industry”, “would threaten the ability of Australian clinicians and scientists to be involved in world-leading clinical trials of autologous stem cell treatments “and “will only serve to delay and prevent the development of cell-based therapies within Australia”²⁸. We point out that it is entirely appropriate and desirable that we prevent the premature dissemination of unproven, unfounded, costly, and potentially hazardous cell based therapies in Australia. Moreover, the bulk of the autologous therapies currently offered are outside of any clinical trial context, and are lacking in any serious innovative component. There is no barrier to the conduct of proper clinical trials of cell therapy in Australia, and in our estimation, no one has put forward any convincing argument as to why experimental therapies with autologous cells should be regulated in a different fashion to allogeneic therapies.

We reject the claim that removal of the Exclusion Order will inhibit medical innovation or delay the introduction of promising new treatments into clinical trial. It is arguable of course that the existing mechanisms for testing new cell therapies could be streamlined considerably, and indeed this is an area that is receiving increasing attention internationally. However, we are not aware of any instance in any jurisdiction in which the proposed solution to this problem entails abandoning clinical trials or regulatory oversight altogether. We are aware of arguments, put forward locally by a coalition of cell therapy providers, that some sort of self-regulatory framework would suffice to control autologous cell therapies. We oppose this model, because of the inherent conflict of interest built into it. It is possible that a scheme of voluntary regulation, with true independent oversight and mandatory inspections and reporting of outcomes, similar to that which operated in the early days of *in vitro* fertilisation in the United Kingdom, might be appropriate for autologous cell therapies involving minimal manipulation and homologous use²⁹.

5. What do you see as the likely risks, benefits and costs of each option to you? If possible, please attempt to quantify these costs and benefits.

We have addressed the risk and benefit of each of the five options (Table 1). We propose that a modification to the current Excluded Goods Order by Ministerial Order should be immediately implemented to curb unproven and unfounded practices being sold in Australia.

Modification of Excluded Goods Order needs to recognize that some autologous interventions that are provided as part of current medical practice (listed in Appendix 1 of the Discussion Paper) should continue to be excluded. This could be implemented by the following amendment (new text underlined and in red):

4 (q) human tissue and cells that are:

- a. collected from a patient who is under the clinical care and treatment of a medical practitioner registered under a law of a State or an internal Territory; and*
- b. manufactured by that medical practitioner, or by a person or persons under the professional supervision of that medical practitioner, for therapeutic application in the treatment of a single indication and in a single course of treatment of that*

²⁷ TGA, Access to unapproved therapeutic goods – clinical trials in Australia [<https://www.tga.gov.au/publication/access-unapproved-therapeutic-goods-clinical-trials-australia>] (Accessed 27 February).

²⁸ Rollins (2015) Stem Cell Cowboys Bring the Watchdogs Sniffing Australian Medical Association eMagazine [<https://ama.com.au/ausmed/stem-cell-cowboys-bring-watchdog-sniffing>] (Accessed 27 February).

²⁹ MacNaughton (2005) Regulation before HFEA. *Human Fertility* 8(2):61-62.

patient by the same medical practitioner, or by a person or persons under the professional supervision of the same medical practitioner; and

- c. utilised in one of the following recognised medical interventions:
- i. skin grafts inclusive of sprayed and/or cultured skin;
 - ii. skull flaps;
 - iii. vascular conduits;
 - iv. transplantation of pancreatic islet cells;
 - v. bone grafts;
 - vi. blood to seal CSF leaks and reinfused during surgery;
 - vii. cosmetic/reconstructive procedures utilising skin, bone and fat transfer.

6. How do you think each option addresses the risks you identified in the earlier question?

Only option 5 fully addresses these risks.

7. Are there additional issues with the regulation of autologous stem cells that any changes should consider and/or address?

We acknowledge that regulation of autologous cell therapies should not be solely the responsibility of the TGA and that other bodies such as AHPRA, medical boards and Australian Competition and Consumer Commission all have a role in effective management of these practices.

However, it is imperative that oversight moves to TGA. Although in principle unsafe and unsound practices currently permitted under the Excluded Goods order could be policed by AHPRA, through its notification procedures, in fact this is an unsatisfactory mechanism to tackle this problem, for the following reasons:

1. The AHPRA can only act after the fact to limit unfounded and unsafe practices. There is no scope for prevention, only for action once a specific case has become sufficiently egregious so as to come to the attention of the AHPRA.
2. The AHPRA can only deal with this problem on a case-by-case basis. There is a growing epidemic of unfounded cell therapy clinics that will rapidly deplete the AHPRA bandwidth.
3. The AHPRA have no specialist expertise in cell therapy.
4. The problem is not really a single physician based issue; rather there are corporate entities delivering and disseminating cell therapy technologies through networks of clinics via the Excluded Goods loophole.

In summary, many autologous therapies should come under the TGA Regulatory Framework for Biologicals and the TGA should bear the authority to regulate such interventions.

We also believe it is essential that homologous use of autologous lipoaspirates is carefully considered. Amendment of the Excluded Goods Order to allow direct transplantation of adipose transfer for use in cosmetic/reconstructive procedures would enable this currently accepted medical practice to continue (see suggested modification to 4(q)).

We would also like to acknowledge the effective oversight of autologous cell therapies is an issue that regulators in various jurisdictions are grappling with. Although hundreds of clinical trials are underway around the world, the vast majority of these are seeking to address issues around safety³⁰. Given the inherent characteristics of stem cells – that they engraft, are retained by the body and can

³⁰ Li et al (2013) The global landscape of stem cell clinical trials. *Regen. Med.* 9 (1): 1–13.

give rise to other more specialised cells – a cautious approach to translation of this promising science is warranted.

Since 2007, the International Society for Stem Cell Research (ISSCR) – the leading body representing the global stem cell research community – has recognised the need to provide guidance on acceptable standards for clinical translation of stem cell research, specifically voicing concern about the “potential physical, psychological, and financial harm to patients who pursue unproven stem cell-based therapies and the general lack of scientific transparency and professional accountability of those engaged in these activities”³¹.

While these guidelines recognised medical innovation - where unproven stem cell interventions may in very specific circumstance be provided during the course of patient care and outside a trial context - it is recommended that such interventions be provided to under very specific circumstance. These include limiting administration to a small numbers of seriously ill patients who would be cared for under a stringent set of oversight requirements including independent peer review of the proposed innovative stem cell procedure and its scientific rationale, institutional accountability, rigorous informed consent and careful patient monitoring, transparency, speedy adverse-event reporting, and a committed plan by clinician-scientists to move toward a formal clinical trial after experience with the intervention in a few patients. With a specific recommendation that the ISSCR “condemns the administration of unproven uses 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. Scientists and clinicians should not participate in such activities as a matter of professional ethics”³².

In response to a rise in the number of providers of autologous-based stem cell interventions being marketed around the world, in 2013 the ISSCR released an additional statement reiterating the criteria under which stem cell research should be translated – even when the cells are from the patient – and calling on “medical licensing bodies, legal authorities, patient advocacy organizations, physicians, and others to exercise their influence to discourage commercial provision of unproven autologous cell-based interventions outside of clinical trials”³³.

Autologous-based cell interventions are often couched as ‘medical practice’, with an implication of low risk as the cells are from the patient and being used for that patient. As such the increasing use of autologous-based interventions has been a challenge to regulate³⁴. However in the United States and other jurisdictions steps are being taken to curb these practices:

- The FDA recently issued a draft guidance statement recommending oversight of production of autologous interventions that involve more than minimal manipulation and/or non-homologous use³⁵ (as discussed above);
- The Chinese Ministry of Health classified stem cell treatments as Category 3 medical technologies defined as “high risk” and requiring the approval of a

³¹ Hyun et al (2008) New ISSCR guidelines underscore major principles for responsible translational stem cell research. *Cell Stem Cell* 3 (6): 607–609.

³² ISSCR (2008) Guidelines for the clinical translation of stem cells. [<http://www.isscr.org/docs/default-source/clin-trans-guidelines/isscrgclinicaltrans.pdf> (Accessed 27 February)].

³³ ISSCR (2013) Statement on Delivery of Unproven Autologous Cell-based Interventions to Patients [<http://www.isscr.org/home/about-us/news-press-releases/2013/2013/09/12/isscr-statement-of-delivery-of-unproven-autologous-cell-based-interventions-to-patients>](Accessed 27 February)].

³⁴ DeFrancesco (2012) Adult stem cell therapies walk the line. *Nat Biotechnol* 30 (8): 739–741; Bianco & Sipp (2014) Regulation: Sell help not hope *Nature* 510:336-7; Lysaght et al (2013) Oversight for clinical uses of autologous adult stem cells: lessons from international regulations. *Cell Stem Cell* 13(6):647-651.

³⁵ Food and Drug Administration (2014), Minimal manipulation of human cells, tissues and cellular and tissue-based products: Draft guidance [<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm427692.htm> (Accessed 27 February)].

technical audit board before use, however concerns have been raised about the effectiveness of this policy;³⁶

- Stance taken by the Italian Ministry of Health that has seen the cessation of unproven stem cell interventions being offered;³⁷
- The Indian Council of Medical Research and the Indian Department of Biotechnology have issued guidelines that any use of stem cells in patients can only be done within the purview of an approved and monitored clinical trial with the intent to advance science and medicine³⁸.

Immediate action is required to bring Australia into alignment with other jurisdictions and recommendations of leading international learned scientific and research organisations.

8. Discussion question for Option 1 – Is there an argument that autologous stem cells are not therapeutic goods and, therefore, should remain under the current Section 7 declaration?

No, for many reasons discussed above.

9. Discussion question for Option 2 – Should autologous stem cells that are more than minimally manipulated and/or are not for homologous use continue to be excluded from regulation? Why or Why not?

No, for many reasons discussed above.

³⁶ Cyranoski (2012) China's stem cell rules go unheeded *Nature* 484:149-150.

³⁷ Margottini (2014) Final chapter in Italian stem cell controversy? *Science Insider* [<http://news.sciencemag.org/biology/2014/10/final-chapter-italian-stem-cell-controversy>]

³⁸ Dhar (2014) ICMR redefines stem cell use to curb malpractice *The Hindu* [<http://www.thehindu.com/sci-tech/health/medicine-and-research/icmr-redefines-stem-cell-use-to-curb-malpractice/article5719780.ece>] (Accessed 25 February)]

Table 1: Analysis of possible options to regulate provision of autologous cell-based interventions in Australia

Analysis	Benefit	Risk
<p>Option 1 [Status quo with Ministerial exclusion]</p>	<p>Little benefit other than removing ambiguity about TGA responsibility by clearly stating that ALL autologous cell-based therapies are excluded from Biologicals framework.</p>	<p>Imparts legitimacy to ALL autologous cell based therapies – no barrier to entry.</p> <p>Direct-to-consumer advertising unrestricted.</p> <p>Places Australian regulations apart from other key jurisdictions and may further attract overseas operators to establish clinics – creating Australia a ‘safe haven’ for unproven stem cell therapies.</p> <p>No reporting of adverse events.</p> <p>No transparency re supply/ manufacture or use of excluded goods.</p> <p>No incentive to demonstrate efficacy.</p>
<p>Option 2 [Ministerial exclusion when homologous; not more than minimal manipulated and not advertised directly to the public]</p>	<p>High risk products - cultured cells or those used for non-homologous purposes - would viewed as Biologicals under the Act.</p> <p>No advertising to public.</p>	<p>All low risk - minimal manipulation and homologous use – effectively unregulated with no requirement to report adverse event to TGA. No accountability regarding supply or manufacture of such goods. No incentive to demonstrate efficacy or to perform adequate follow-up.</p> <p>Unclear how this Exclusion would be enforced and concerned that it may be an ineffective means to curb exploitative practices.</p>
<p>Option 3 [Regulated as biological but exempt from registration and manufacturing requirements]</p>	<p>High risk products - cultured cells or those used for non-homologous purposes - would viewed as Biologicals under the Act.</p> <p>No advertising to public.</p> <p>Limited regulation of low risk products – adverse event reporting.</p>	<p>All low risk - minimal manipulation and homologous use – automatically exempt from having to meet manufacturing requirements. No incentive to demonstrate efficacy or to perform long term follow up.</p> <p>Concern about how option would be enforced. Stated TGA could require information on supply and handling to determine they were in fact exempt but how would such a determination this be triggered.</p>

Analysis	Benefit	Risk
<p>Option 4 [Regulated under that Act as Class 1 Biological]</p>	<p>High risk products - cultured cells or those used for non-homologous purposes - would viewed as Biologicals and full under the Act.</p> <p>Limited regulation of low risk products with listing on ARTG – provided self-certification that the biological is safe; meets certain standards, and requires adverse event reporting.</p>	<p>By listing on ARTG implies legitimacy to all minimal manipulated, homologous use interventions but no requirement to show efficacy prior to listing.</p> <p>Relies on self-reporting and self-regulation of manufacturing standards – a problem for the sector given the infancy and broad range of application.</p>
<p>Option 5 [Regulated as per appropriate class]</p>	<p>Would ensure that all autologous cell therapies full under the Act and would require TGA oversight and provide optimum safety and manufacturing quality.</p> <p>No advertising.</p> <p>Adverse data reported.</p> <p>Incentive for gaining good quality clinical evidence for all autologous cell interventions.</p>	<p>May restrict access to low risk products.</p> <p>Substantially raises costs for any development.</p>