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Box Hill Stem Cell Centre Pty Ltd ABN 35 160 608 337
Trading as Melbourne Stem Cell Centre

To whom it may concern,

RE : *Regulation of Autologous Stem Cell Therapies – Discussion Paper for Consultation*

I write this submission with reference to my role as both a clinician, clinical researcher and Clinical Director of Melbourne Stem Cell Centre. I graduated medicine at Melbourne University and hold a Bachelor of Medical Science. I am a fellow of the Australasian College of Sports Physicians with my primary area of clinical work being within the area of chronic and degenerative musculoskeletal conditions such as osteoarthritis and tendinopathy. I have published extensively within the area of biological therapies in internationally regarded medical journals. I welcome the opportunity to provide input in regards to a response to the TGA Discussion Paper on the regulation of autologous cell therapies.

Melbourne Stem Cell Centre (MSCC) is a private research founded clinic focused on advancement of cellular medical therapies through ethical and scientifically reputable processes.

MSCC is currently undertaking two of the largest internationally registered randomised controlled trials in the area of knee osteoarthritis and isolated knee cartilage lesions. These trials have prospective Human Research Ethics Committee approval via Monash University and Latrobe University respectively. These trials are funded by both MSCC and Magellan Stem Cells.

Further, it is the aim of MSCC to ensure that all patients are treated within either funded or self funded internationally registered and HREC approved trials/protocols with a commitment to formal recording and publication of outcomes and side effects. We have two further self funded ethics approved projects which are registered and another 9 projects currently in the process of ethics application.

We have a clear understanding of the importance of research. Importantly these research projects of international significance are being conducted under the Therapeutic Goods (Excluded Goods) Order No. 1. The ability to complete this research is dependent upon the current legislation being maintained.

MSCC and its clinicians are aware of their responsibilities under the Excluded Goods Order which requires autologous therapies to be used under the formal `supervision of a medical practitioner who is caring for that patient'. As per this requirement, clinicians at MSCC take absolute responsibility for the harvesting, processing and use of autologous cell based therapies. Any processing done by suitability accredited laboratory staff is done under direct supervision of the clinician and only when it has been thoroughly shown and documented that techniques used meet the required level of safety.

Further to this, clinicians recognize the responsibilities under clinician regulatory bodies (ie. AHPRA, Medical Board of Australia and Specialty Colleges) to maintain professional standards of practice as per the Health Practitioner Regulation National Law Act.[1] Clinicians are required to practice within their area of expertise/specialization and to follow the principles of evidence based medicine. This remains a cornerstone of ethical practice and should be

[1] *http://www.legislation.act.gov.au/a/db_39269/current/pdf/db_39269.pdf*

suitably enforced and regulated by the appropriate aforementioned clinician regulatory bodies.

Discussion Paper Review

The discussion paper raises a number of areas of concern relating to the use of autologous stem cells.

1. *Safety of therapies – either direct safety impacts or safety issues incidental to therapy.*

Concerns relating to the use of autologous stem cell therapies - particularly regarding safety - are dependent upon the type of therapy/product, production methods, method of delivery, condition being treated and suitable selection of patients.

It cannot be assumed that all cell therapies (when included within a broad umbrella title of `stem cell therapies') carry the same level of safety particularly due to enormous differences in the actual autologous product.

Importantly the treating clinician has primary responsibility in their duty of care to the patient to use and administer therapies with a proven level of safety. The current legislation also requires the clinician to also take primary responsibility for the `product'.

Under current requirements a clinician must be able to effectively show the proven level of safety of production, evidence of safety in the chosen method of delivery (i.e. intra-articular versus intravenous) and appropriate selection of patients. A clinician who fails to meet these standards of safety and thus fails to meet required standards of clinical care should face appropriate disciplinary actions from the regulatory body (ie. AHPRA/Medical Board of Australia).

I believe that due to the variability of possible stem cell therapies and their individual safety profile the current legislation is suitably worded/structured to place responsibility of safety on the treating clinician.

2. *Lack of evidence to support the efficacy of the product*

Evidence in regards to efficacy of cell based therapies – much like safety – is dependent upon type of stem cell therapy used and the condition being treated. Importantly in the area of osteoarthritis there exists excellent recent Level II and Phase II evidence of both safety and efficacy when using intra-articular autologous isolated mesenchymal stem cell preparations (Saw et al 2013[2], Jo et al 2014[3]).

[2] *Saw KY, et al. Articular cartilage regeneration with autologous peripheral blood stem cells versus hyaluroninc acid: a randomised controlled trial. Arthroscopy 2013; 29(4): 684-694.*

[3] *Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof of concept clinical trial. Stem Cells 2014; 32 (5): 1254-1266.*

As a specialist in the area of musculoskeletal conditions including osteoarthritis I am comfortable that if an equivalent preparation is used, and similar protocols undertaken then use of autologous mesenchymal stem cells meets the National Health and Medical Research Council requirement of evidence based practice.

An inability of a clinician to show this accepted level of evidence would put that clinician in direct conflict in regards to their obligations of `duty of care' and again should mean disciplinary action to be undertaken by the appropriate regulatory authority (AHPRA).

3. *Large sums of money being charged for unproven treatments*

I agree with concern regarding unjustifiable expense of unproven therapies (though my primary concern is the practice of unproven therapies). However, in areas of proven efficacy - using protocols/techniques/therapies with qualified scientific outcome data – the expense to treat a patient is justifiably prohibitively high. We are running two internally funded Randomised Controlled Trials on stem cell therapy for degenerative knee conditions at a cost of over $10000 per enrolled participant. These costs are easily appreciable when considering costs of developing a suitably accredited laboratory and procedural clinic and expense of expert qualified staff and additional costs of medical consumables.

4. *Lack of mechanisms for reporting of adverse effects of the products*

Currently there exists no enforceable reporting of adverse effects of stem cell procedures. Much like efficacy, adverse effects will be dependent upon the exact type of therapy and also protocols used by (i.e. administration method, cell number, number of injections etc). Adverse effects will not be consistant across all these variables of therapeutic production and application.

Unfortunately forced reporting of adverse events is not common practice within medicine. As a clinician working in the area of a developing field such as cellular therapy I firmly believe it is a responsibility of the clinician to document adverse events and publish this data on a recognized scientific platform (i.e. journal). Good examples of adverse event recording that have been independently and successfully implemented exist – i.e. the Australian Orthopaedic Association National Joint Replacement Registry.

5. *Inappropriate advertising of the products*

The Australian Health Practitioner Regulation Agency has clearly defined `Guidelines for Advertising Regulated Health Services'. These guidelines have been created in accordance with the accepted and legally enforceable Health Practitioner Regulation National Law and are aimed to protect the public.

Anyone advertising regulated health services (i.e. a registered medical practice) must ensure that their advertisement complies with the National Law. Breach of these advertising requirements is a recognised criminal offence and a court may impose a suitable penalty. Further, a breach of these requirements may also constitute professional misconduct which will mean appropriate disciplinary action be undertaken by regulatory bodies such as the Medical Board of Australia/AHPRA.

As the aforementioned legally enforceable requirements regarding advertising are thorough and well recognised I do not believe at any further changes are necessary.

The TGA Discussion Paper further highlights areas to be a focus of discussion and in which an opinion is requested :

Discussion Questions :

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

I believe that the public health risks posed by autologous stem cells exist only when a treating clinician fails to show an appropriate and accepted level of `duty of care'. The current legislation requires the clinician to take complete responsibility of both the preparation and administration of the stem cell therapy. Separate regulatory requirements enforced by AHPRA and the Medical Board of Australia requiring that a clinician practice in an ethically and both safe and efficacious manner should (if enforced appropriately) mean the appropriate use and development of cellular therapies within clinical medicine.

- *What is the evidence of these public health risks?*

If current regulations encompassing clinical practice were enforced I do not believe that within these requirement a level of `public risk 'would exist. However, I believe their exists examples within Australia of autologous cell therapies (I use the term `cell therapies' and not `stem cell therapies' as these therapies whilst reported to be stem cell therapies may not purely be stem cell based – i.e. stromal vascular fraction) where required levels of efficacy and safety cannot be shown, nor can the clinician appreciably argue that they are practising within their area of expertise. These circumstances should be - and importantly can be – prosecuted by the appropriate regulatory body.

- *What identified risks should have the highest priority for resolving?*

The Australian Health Practitioner Regulation Agency in partnership with the Medical Board of Australia and various specialist colleges have an obligation to appropriately regulate/enforce a level of care such that the public can trust that their clinician will need to meet the highest of ethical standards. Rather than any area needing `priority' it is the already accepted standards of care which should be maintained.

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

Importantly current legislation allows the appropriate translation of scientific research to the area of clinical development. This is best illustrated in the way the current legislation allows our clinic to conduct multiple world-leading ethics-committee approved trials on the use of mesenchymal stem cells in the treatment of degenerative cartilage conditions.

The public health benefits are potentially enormous in consideration of osteoarthritis. It is estimated that at least 3.85 million people are affected with arthritis across the Australian community, at a cost to our economy of greater than $23.9 billion each year (Peat et al. 2001[4]; Gupta et al. 2005[5]). Conservative estimates suggest a 58% rise in the incidence of symptomatic OA by 2032. Worldwide, osteoarthritis is considered to be the fourth leading cause of disability (Fransen et al. 2011[6]).

All practice of novel treatments should be undertaken within a registered and human research ethics committee trial – thus meeting requirements of adequate follow up, outcome and adverse event recording. Practising novel and unproven therapies outside of this would possibly constitute unethical practice and would mean the clinician was acting in direct conflict to the accepted `code of conduct' as defined by the Medical Board of Australia and thus would be answerable to the appropriate regulatory authority.

The current legislation encourages clinicians to undertake the appropriate and required level of research if they are to explore new and novel therapies ethically.

The review paper also asks for further discussion regarding each of the 5 potential options suggested within the paper :

- *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.*

Option 1.

Risks :

- the risk of maintaining the `status quo' is that there will be persistant confusion with both regulatory bodies and the medical profession as to who is responsible for regulation.

Benefit :

- the above risk is appropriately nullified by the suggestion of the TGA to use the legislative instrument under subsection 7AA(1) of the Act which would specify that autologous cells are not covered by the Act. Therefore rather than operating under an `exemption', clinicians would have to be able to show to relevant regulatory bodies (i.e. AHPRA) that their use of stem cell therapies meets appropriate standards of accepted practice. While this remains the case under current legislation it is less clear.

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[4] *Peat, G., McCarney, R., et al. (2001). "Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care." Ann Rheum Dis 60(2): 91-97.*

[5] *Gupta, S., Hawker, GA., et al. (2005). "The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition." Rheumatology (Oxford) 44(12): 1531-1537.*

[6] *Fransen, M., Bridgett, L., March, L., et al. "The epidemiology of osteoarthritis in Asia", Int J Rheum Dis; 14(2): 113-121.*

- It is important to realise that any use of instruments during the process of stem cell therapy will continue to need to meet TGA requirements.

Costs :

- this would not place any further cost on our clinic. Importantly it would allow us to continue current studies which our clinic has made a commitment (>$1,000,000) to undertake and complete.

Options 2 - 4

Risks :

- Options 2 – 4 carry the same risk in that they encourage the continued practice of therapies with little or no proof of efficacy or safety. It is important to recognise that Level II systematic review has concluded that isolated mesenchymal stem cells are relatively safe. Further, in the area of osteoarthritis the use of certain protocols of isolated mesenchymal stem cells has been shown to be efficacious. The process of isolation and characterisation of the cells confirming a `pure' stem cell therapy means `greater than minimal manipulation' as defined by the TGA.
- Cells based therapies classified as `minimal manipulation' - as per the TGA definition - are a mix of cells and there is little or no evidence of safety or efficacy.
- As expressed – these options would encourage poor clinical practices and should not be adopted.

Costs :

- If options 2,3, or 4 were adopted we would no longer be able to complete our current ethics approved trials as they are being conducted under the `exemption'. The trials are expected to take 3 years to complete at a financial commitment of >$1,000,000.
- Trials in which enrolment and treatment has already commenced over the last 6months would need to be ceased. A process of new trial submission would need to be undertaken and this may take >12months.
- Osteoarthritis is a degenerative and non-curable condition. Under the TGA exemption the course of stem cell therapy for osteoarthritis in our clinic is often documented as 5 years. Use of Option 2,3, or 4 would effectively prevent patients being treated within our clinic from having their complete course of treatment.

Option 5

Risks :

- Option 5 would require that cell based therapies undergoing one or more action of minimal manipulation would be classified as Class 2 or greater Biologicals. This would mean TGA would need to be satisfied in regards to quality, safety and efficacy.

- Due to enormous variabilities in processing methods, routes of administration, therapeutic protocols, patient selection, disease selection and management it would mean each individual practice and therefore individual practice based cell therapy processing method, treatment protocol etc would need to be independently assessed by the TGA for the above standards.

- The above requirements would be incredibly prohibitive in regards to cost and time. I disagree with the TGA Discussion Paper in its assertion that this option offers the clearest incentive for gaining good quality clinical evidence. The cost would discourage private entities from investing in ethics approved research and therefore would directly prevent the clinical development of cell based therapies within Australia.

Costs :

- As per option 2-4.

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

- When used as it was intended, the Exemption is a robust tool in stipulating that the clinician takes complete responsibility and therefore has a duty of care – needing to be able to show that they are practicing in an ethical, safe and efficacious manner. As it is currently worded there is unfortunately an apparent confusion in regards to who – i.e. TGA, AHPRA, NHMRC, Medical Board of Australia, Medical Colleges and other professional bodies such as the ACCC – is responsible for areas of regulation in regards to clinical practice.

- Within the area of autologous therapy there is an accepted precedence of `self regulation' – the Australian Health Minister Council ratified the self regulation of Assisted Reproductive Therapy in 2008. An industry appointed regulatory body – whilst not having formal legal disciplinary entitlements – may be able to appropriately identify practices/clinicians that are behaving outside of an accepted `code of practice' and report these events/persons to the appropriate regulatory authority. Professor Bernard Tuch has previously written on this issue within the Medical Journal of Australia (Tuch et al 2014[7]). I am aware of the development the Australian Cell Therapy Society and this may be able to perform the required role.

Discussion question for option 1

- *Is there an argument that autologous stem cells are not a therapeutic good and therefore, should remain under the current section 7 declaration?*

- I agree that autologous stem cells are therapeutic goods but the variability in their development, protocol of use, method of delivery and difficulty in characterisation makes it implausible to regulate unless done on an individual clinic and condition basis.

[7] *Tuch BE, Wall DM. 'Self-regulation of autologous cell therapies', Med J Aust 2014; 200 (4): 196*

Therefore use of section 7AA to enable the Minster to exclude them from the act is an appropriate step.

Discussion question for Option 2

- *Should autologous stem cells that are more than minimally manipulated and/or are not homologous use continue to be excluded from regulation? Why or why not?*

As indicated above, the accepted safety data for mesenchymal stem cells and also evidence of efficacy in the treatment of osteoarthritis is for isolated mesenchymal stem cells. This means greater than minimal manipulation under current TGA definition. To continue to exclude other minimal manipulation techniques with no proven level of safety or efficacy and yet obstruct use of proven safe and efficacious therapies would be contradictory to the intention of the TGA and reasons for regulation.

Summary

I welcome the formal TGA review of the regulation of autologous cell based therapies.

Importantly I believe it needs to be recognized that the current legislation has allowed Australian clinicians and scientists to be involved in world leading clinical trials. Clinical trials that offer the exciting ability to translate laboratory and pre-clinical research to clinical management – trials which have an ability to change the way in which we practice. Appropriate, safe and significant medical advancement under the current regulation is a reality – as reflected by our two world leading randomized controlled trials on the use of stem cells in degenerative knee conditions.

The strength of the current TGA `Exemption' legislation is that it places the responsibility of therapy `production' and administration solely on the treating clinician. If the clinician is unable to show appropriate levels of safety and efficacy and that they are acting within their area of expertise/specialty then they are acting outside of the realms of `good medical practice' as described by the Medical Board of Australia's `Code of Conduct'[8]. As such they should face investigation and prosecution by the appropriate regulatory authority (i.e. AHPRA, Medical Board of Australia).

Some alternatives suggested in place of the current legislation (Options 2,3, and 4), rather than preventing poor medical practice, in fact encourage the continued use of unproven therapies (those with minimal manipulation) which have little or no evidence of both efficacy and safety. Option 5 – due to the infinite variability in production methods, characterization, treatment protocols and administration methods which will all affect safety and efficacy is arguably unachievable and will only serve to delay and prevent the development of cell based therapies within Australia.

I believe that option 1 - and the potential use of Section 7AA - more clearly defines the sole responsibility of the treating clinician and therefore the role of clinical regulatory bodies.

[8] *http://www.medicalboard.gov.au/Codes-Guidelines-Policies/Code-of-conduct.aspx*

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Clinicians will continue to need to show that they are acting in an ethical and scientifically justifiable manner and otherwise will face appropriate disciplinary actions. Appropriate clinical research (arguably an ethical requirement when working in this field) will continue to be encouraged within this framework and will see that Australia remains at the forefront of medical advancement.

Yours sincerely,

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Melbourne Stem Cell Centre