Background

Sydney Sportsmed Specialists (SSS) are comprised of a group of specialist Sport and Exercise Medicine Physicians (SEM Physicians), as well as Orthopaedic Surgeons. A number of the group, including SEM Physicians Drs Diana Robinson, Ameer Ibrahim and Donald Kuah and Orthopaedic Surgeon Dr Peter Walker have been involved in performing autologous cell therapies for musculoskeletal conditions for several years. Most importantly, the medical specialists at SSS have built an expertise in sport and exercise medicine over a long period of time, and have held many and varied positions in this field, including professional and National sporting bodies, government boards, panels and advisory committees and in the education and promotion of sports medicine. Attached are the relevant curriculum vitaes of Drs Robinson, Ibrahim and Kuah. SEM Physicians provide medical services, assessment and treatment to patients of all ages and sporting levels, as well as to non-athletic and workplace injury population. We are committed to providing excellence in injury management and where appropriate, a multi- disciplinary team approach is employed to optimise patient outcomes. Our centre has a long history of providing accurate diagnosis, rapid and appropriate investigations and evidence-based treatment programs, and hence has established a local, national and international reputation as a centre of excellence. We pride ourselves on our holistic approach to all patient presentations. Stem cell therapy is a small part of each of our individual practices.

As a practice and individually, we continually assess new information and evidence in the peer reviewed medical literature for both medical and surgical options to treat injured athletes and patients. Prior to offering cell therapy to our patients, we extensively researched the use of autologous stem cell therapy in osteoarthritis, tendinopathies and chondral defects. We spent considerable time with cell biology scientists who were researching the mechanisms of action of these cells and thus developed a deep understanding of the possible benefits, complications and related issues of this treatment. We also pride ourselves in continuing to keep up to date with the relevant literature surrounding stem cell treatment and adjust our practices based on clinical findings reported in peer reviewed journals, by others. This has also involved reviewing research into the safe and effective handling and storage of the cell suspensions where necessary. We have been intimately involved in the development of protocols with regard to cell processing and treatment, and tissue storage, along with rehabilitation and monitoring of patients using cell therapy.

Dr's Robinson, Ibrahim and Kuah have also been involved in collaborative stem cell investigations including human ethics approved research into areas such as;

- in vitro cell secretions,
- serum and urinary biomarker levels in patients pre and post treatment,
- an ongoing stem cell Registry involving over 500 patients, along with
- research into other cellular therapies such as PRP
- Dr Kuah has also been involved in a University of Queensland study on osteoarthritis symptoms (the NORSE study).

SEM physicians are *medical specialists* in a field which includes the treatment and management of musculoskeletal disorders such as osteoarthritis, tendinopathies and chondral defects. We offer a range of treatments for these conditions, such as advice regarding the modification of activity, weight loss, exercise rehabilitation programs, pharmaceutical options, platelet rich plasma injections and hyaluronic acid injections where appropriate. A treatment option includes autologous cell therapy using HiQCell. Traditional treatment offerings for osteoarthritis are limited to mostly drug therapies which treat the symptoms and but do not affect disease progression, or to joint replacement, once the disease has progressed. Morbidity of the patient

following joint arthroplasty is high. Other surgical options such as arthroscopic debridement have been convincingly proven to be ineffective.

Autologous cell therapy should be considered a serious treatment option and offers an intermediate solution to control symptoms, improve quality of life, reduce reliance on medications, improve patient activity levels and delay joint replacement. Arguably, this treatment option offers much more than the current pharmacological treatment of osteoarthritis/tendinopathy, by providing anti-inflammatory effects and by possibly modifying disease progression via the biological action of the cells' secretions (see OSCARS study at RNSH, Sydney; manuscript submitted for publication currently), improving health and encouraging repair of cartilage.

We consider ourselves specialists who are transplanting tissue or cells into other parts of the body. This can be compared to a surgeon who transplants veins or arteries into diseased areas, uses skin grafts and bone grafts, or who transplants gut tissue into the bladder. These procedures are not considered homologous use, are within standard medical practice and are not regulated by the TGA. We see autologous cell transplantation in much the same way.

Patient selection is critical when considering autologous cell therapy. Not every patient is suitable candidate and we would estimate that we would only treat 1 out of every 10 patients that present requesting advice about Hi Q cell treatment. . Patients are thoroughly assessed and a management plan is designed based on suitable treatment options for their age, health status and stage of disease. Various possibilities of treatment are discussed including current usual care and more novel treatment options such as cell therapy and platelet rich plasma injections. All patients are given a thorough explanation of all treatment options, including real and theoretical risks, realistic outcome scenarios, and, in the case of cell therapy, the experimental nature of the treatment. Patients are given reading material which outlines the possible benefits and side effects of the treatment.

We believe patients have a right to access quality, safe cell treatments through the current Option 1 regulatory framework. It is an advantage for patients to be able to access these treatments in high quality facilities in Australia, rather than going overseas where quality and safety cannot be assured. In addition, the costs to patients seeking treatment overseas are often significantly higher.

Given that there are a variety of interested parties in the stem cell debate, all with vested interests, and that there has been negative press regarding stem cell usage due to questionable practices by some parties, we are currently involved in drafting an Industry Code of Conduct for practitioners involved in this area of medicine.

We are experienced stem cell practitioners. In our first three years (May 2011-May 2014) we treated over 550 patients and more than 1200 joints with HiQCell. We have been involved in the collection of information from 500 of these patients through a human ethics approved, independently audited Registry, to aid further understanding about the outcomes, benefits and safety of stem cell treatment (named the ***HiQ cell Registry***). The HiQCell registry is a world leader providing detailed and long term results of treatment, safety data and information on any adverse effects that has been independently audited. Results are available for longer than two years in some patients to this date.

Ongoing education of General Practitioners, Physiotherapists and other allied health professionals is important. We have spent considerable energy informing these groups about the responsible and appropriate use of autologous cell therapy. In doing so, we have developed a referral base for these treatments, and as such are one of the most experienced groups of medical practitioners in Australia.

Summary

SEM Specialist Physicians have concerns that over regulation of autologous stem cell therapies will mean that this treatment option is no longer available in Australia to our patients unless as a practice we comply with meeting extensive and expensive regulatory requirements. Our

submission will only address the use of cell therapy in musculoskeletal conditions, and specifically, via the local injection of these autologous cells into joint or tendons. (as opposed to systemic use such as intravenous therapies).We have addressed some of the relevant concerns made by the TGA regarding these therapies. We would like the following points to be considered as part of our response :

- Having treated and recorded results in > 550 patients we consider this treatment to be safe and efficacious.
- The price reflects use of skilled medical professionals in high quality facilities with strong quality assurance oversight. There is full financial disclosure and the lack of rebates from Medicare or private health funds is made known to each patient.
- We would support a change in regulation to ensure that treatment must be provided by a medical specialist in the disease being treated.
- We would support an addition to regulations to ensure that any autologous cell therapy procedures are performed at an accredited hospital or day surgery facility where there is oversight by a Medical Advisory Committee (MAC) and other independent staff.
- As there are subtle differences in the various autologous cell therapy products offered for musculoskeletal conditions, we would support that there be a minimum period of monitoring and reporting through a centrally and independently managed registry.
- We would support mandatory flow cytometry testing and recording of data relating to the cells injected so that the number, type and viability of cells injected is documented, with a set minimum standard of instrumentation.
- We would encourage mandatory reporting of adverse events to the TGA
- The homologous use and minimal manipulation requirements of options 2-5 will result in us no longer being able to offer autologous cell therapy due to the use of enzymatic digestion methods.

Preferred outcome summary:

Option 1 with ***increased levels of regulation*** would be the preferred option.

- Mandatory adverse event reporting
- Treatment restricted to a medical specialist that specialises in the disease being treated.

Also Consider:

- It should be mandatory to enter data into an ethics approved registry for a minimum time period to monitor the efficacy, safety and adverse events.
- A requirement that the therapy must be completed in an accredited hospital facility or day surgery where there is secondary oversight by trained medical staff and the hospital Medical Advisory Committee.
- Flow cytometry testing and documentation of numbers, type and viability of injected cells.

Addressing TGA concerns

The TGA has indicated the following concerns as a driver for change. We would like to address these concerns.

- ***Safety of the products – either direct safety impacts or safety issues incidental to the therapy***

There have been low numbers of reported (minor) adverse events in our experience of over 550 patients and no major adverse events. Specifically there have been no infections, foreign tissue growth or malignancies in our patient group.

The process is strictly quality controlled and monitored for safety. Microbiological testing is carried out on all cell suspensions and the procedure protocol is overseen by a Professor of Microbiology.

Patients are clinically monitored post treatment, advised regarding activity levels and postoperative course, and are prescribed ongoing rehabilitation.

High number of joints treated with very low number of (minor) safety issues.

The procedure is performed in fully accredited specialist hospital facilities, with MAC oversight, by highly qualified and experienced medical specialists. Technicians, working with the medical specialists, process the cells in an on-site laboratory. Cryopreservation in a TGA licensed GMP facility is also available. Cryopreservation is used to enable multiple injections of cells over a period of months to years, in order to prolong the period of benefit for patients and thus delay the need for joint replacement.

Only suitable patients are selected through a stringent and extensive consultation process. SSS specialists have a strict protocol as to which types of patients are offered cell therapy. Patients with very advanced osteoarthritis are not offered treatment.

There have been multiple clinical studies and safety trials to demonstrate the safety of autologous stem cell therapy.

<u>The following publications address safety:</u>

[redacted]

[redacted]

[redacted]

[redacted]

The OSCARS - Osteoarthritis Stem Cell Advanced Research Study:
A randomised double blind, placebo-controlled trial of the efficacy and safety of autologous non-expanded adipose-derived stem cells in the treatment of knee Osteoarthritis
(Manuscript submitted for Publication)

- The primary objective was to determine the efficacy of using autologous stem cells to reduce pain symptoms in knee OA.
- Secondary objectives were to determine the medium-term safety of using autologous stem cells in the treatment of knee OA; to evaluate the impact of an injection of autologous stem cells on biomarkers of disease progression
- *HiQCell was shown to be safe and feasible.*
- *Patients treated with HiQCell and the placebo group experienced reduced pain*
- *The procedure was well tolerated by patients and there were no major medium-term safety concerns and no joint infections.*

- *There was a significant difference between the treatment and placebo groups in biomarker CTX-II (C-terminal crosslinking telopeptide of type II collagen) which is a measure of cartilage degradation. The treatment group biomarker levels remained stable but the placebo group levels increased by 31% at 6 months showing evidence of reduced cartilage degradation in the treatment group.*

- ***Lack of evidence to support the efficacy of the products***

SEM physicians enlist their patients (with consent) into an ethics approved Joint Registry. Reductions in pain medication, improvements in sleep patterns and significant improvements in knee function have all be observed recorded and monitored through patient visits and the Joint Registry.

In terms of pain reduction, over 70% of patients treated have obtained a positive therapeutic effect (of greater than 30% improvement) at 12 months post treatment. Importantly, those who have responded report that their level of pain reduction has improved by up to 80%. In addition, there are even greater positive effects with regard to improved sleep, reduced use of medication, and improved function using KOOS (Knee Osteoarthritis Outcome Score) measures. There is statistically significant improvement in all the five subscales used in the KOOS measures at 12 months post treatment.

Importantly there have also been numerous published clinical trials in peer reviewed journals that attempt to demonstrate efficacy. Whilst we acknowledge the level and quality of these studies vary, it is important to note that in all studies, positive effects have been reported.

A recently published study (early online publishing for Cell Transplantation) involved a muliticentre, International study from centres in the Czech Republic, USA, Lithuania, Slovakia followed 1128 patients treated with one autologous SVF injection to osteoarthritic joints for between 12.1 and 54.3 months (median 17.2 months). Patients were followed for efficacy, medication use, function and adverse effects. No infection, malignancy or other serious side effects were documented. Their results reflect a similar efficacy to our Registry data, with 91% patients experiencing a 50% score improvement at 12 months. They also note that "In the first decade of the 21st century, more than 17,000 scientific articles involving 2,724 cell therapy clinical trials were published. These results include 323,000 patients treated with more than 675,000 cell therapy units. The treatments were very safe and often very effective in the treatment of various diseases with the potential to significantly improve health worldwide," We acknowledge that there needs to be more level 1 studies to support stem cell therapy and we would like to be involved in those studies.

<u>The following publications also address efficacy:</u>

[redacted]

[redacted]

- ***The large sums of money being charged for unproven treatments***

The price is reflective of a surgical procedure using medical specialists in high quality hospital settings. We also use highly trained laboratory technicians. It is important to note that the pricing in the industry in Australia is fairly comparable, and is in contrast to overseas options where patients are often charged upwards of US$20000. Our current charge is approximately $6500 for treatment of one joint. This includes the hospital and operating theatre fees, cell biologist and laboratory use, the miniliposuction procedure, quality assurance with flow cytometry and microbiology through an accredited pathology provider, licensing fees to Regeneus, injection of cells and after care/follow up. There is an extra charge of $1500 for cryopreservation of cells, initial processing and transportation and 12 months of storage.

There is no specific Medicare or private health fund rebate available to patients.

We ensure there is adequate financial disclosure to each patient with a clear explanation of what is being charged. The price includes everything including the hospital admission and at least 2 follow-up consultations. This cannot be said for many other treatments where hospital admission, pathology, surgical assistant and anaesthetic services are usually charged as extra.

These costs are not always known to the patient before committing to surgery.

Compared to similar surgeries the cost is very comparable once all of the extra items are totalled. It is not unusual for many medical procedures to have a large variation in cost, based on use of different surgeons and locations – why target stem cell therapy when this happens across the industry? For example, orthopaedic, specialist dental surgeons and neurosurgeons are well known in the industry to often charge 3-4 times the recommended AMA fee.

Finally we would like to point out the minimal time required to be taken off work to recover from this procedure. This is often a large financial gain to the patient compared to surgical options such as joint replacement surgery, where patients will often require more than 6 weeks recovery time prior to returning to regular duties.

- ***Lack of mechanisms for reporting of adverse effects of the products***

This could be addressed by including mandatory adverse event reporting as part of the regulations.

To date we have had very few minor incidents to report, such as joint pain and swelling, all of which resolved in a short period. We have established our own internal Adverse Event reporting system and monitor patients until an event is resolved. As we work in a high quality hospital setting, there is also medical oversight by the Medical Advisory Committee (MAC) to whom all adverse events are reported.

We have had very low numbers of minor events, none of which required hospital admission.

- ***Inappropriate advertising of the products***

Stem cell therapy was initially offered by SSS in 2011 but we have always avoided aggressive marketing. We have not involved ourselves in advertising in the print, radio or TV media. We have occasionally given interviews in these mediums, but have restricted the information to scientific date and results of the Registry and Oscars trial. At the end of 2014 that we launched a website explaining our treatment options and detailing the most recent results from the ethics approved, independently audited registry. Possible adverse events are addressed: www. stemcells.com.au.

We would support tighter regulations on advertising but would expect these regulations to be across the medical intervention industry and not just related to the cell therapies. Again, we are currently involved in a collaborative development of an industry code of conduct.

Preferred outcome: Option 1

SEM Specialist Physicians together recognize that the autologous stem cell market will be improved with increased regulation. It does not believe there is enough negative evidence on safety and efficacy to warrant options 2 to 5. Based on response to TGA concerns above we would like to propose a new option.

Option 1 with ***increased levels of regulation*** would be the preferred option.

- Adverse event reporting
- Treatment restricted to a medical specialist that specialises in the disease being treated

Also Consider:

- Making it mandatory to enter data into an ethics approved registry for a minimum time period to monitor the efficacy, safety and adverse events. This is particularly to cover the subtle differences between different products being offered.
- Making a requirement that the therapy must be performed in an accredited hospital facility or day surgery where there is secondary oversight by trained medical staff and the hospital Medical Advisory Committee.
- Flow cytometry testing and documentation of numbers, type and viability of injected cells.

Reasons for the above option are as follows:

- We would like the therapy to remain in Australia under tighter regulation. We have a history in Australia of sending our Intellectual Property off shore. Closing off this therapy option will mean that Australia does not benefit from this IP and will lose it overseas. Companies, scientists, practitioners as well as patients will follow.
- This therapy cannot meet the homologous use and minimal manipulation requirements (under current definitions), therefore making Option 1 our only option to keep this therapy immediately available in Australia. The main issue is the definition used for "minimal manipulation" which would include enzymatic digestion using collagenase.
- Increases safety awareness and reporting – safety is key but safety issues have been shown to be of low concern. We can provide safety data and registry data – please see our response above on safety.
- Other options (2-5) are not commercially viable – the treatment will be too expensive due to regulatory overheads. High levels of paperwork and regulatory costs are inhibitory to practitioner uptake.
- Options 2 to 5 are likely to slow the development, innovation and research in this therapy. The recent discussion paper released by the TGA on medicines and medical device reforms does not appear to be in line with over regulation of stem cell therapy.

Reponses to discussion questions

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

For osteoarthritis and tendinopathy the public health risks have been shown to be very low.

This is due to:

- Therapy offered in line with medical speciality of this practice.
- Long term monitoring of patients
- Use of highly trained laboratory professionals in a quality hospital setting.
- Thorough patient screening for treatment suitability

Moreover, the public health risk will be increased if the treatment is not allowed in Australia. By keeping the option of this type of medical treatment in Australia, patients keen to avoid or delay joint replacement procedures will be able to continue to obtain it locally rather than being forced into "medical tourism". If treatment becomes unavailable then Australians may be forced overseas where they may not benefit from the same level of safety and care and where costs are likely to be higher. This therapy does not impact on Medicare/tax payers as with many other

procedures that have similar levels of evidence.

There is a theoretical public health risk which may arise from the procedure due to complications of the liposuction surgery or joint injections. Patients may need to return to hospital for further medical treatment; - however the human ethics approved registry and continuing internal (SSS) mandatory adverse effects reporting (see above) covering the treatment of >550 patients and >1200 joints has not seen any patient be admitted to hospital. We have prided ourselves on the highest levels of infection control after taking expert advice from an infectious disease physician and undertaking ongoing monitoring of our procedures. These risks are inherent in any type of medical procedure. We also attend at least 2 multidisciplinary workshops each year with scientists, technicians and doctors to discuss protocols, safety issues and relevant other concerns.

Public risk is heightened if doctors who are not trained to care for patients with musculoskeletal (MSK) conditions are allowed to continue to treat patients for their MSK complaints with cell therapy, as they have no true understanding the pathology of the disease, or the likely consequences of the different treatment options. In our opinion, doctors who have no MSK training should not be treating MSK conditions. This will ensure that there is appropriate patient selection for treatment, and is more likely to manage the issue of inappropriate treatment eg cell therapy being administered to advanced grade IV Osteoarthritis patients. Where cell therapy is administered to patients by professional, expertly trained MSK specialists who are subject to Peer Review and clear professional standards, there is likely to be less risk of "commercialisation" or blatant profiteering.

We support greater regulation to maintain these high levels of care and infection control by ensuring procedures are only carried out in accredited hospitals of day care surgery facilities.

There is currently little regulation or monitoring about the nature, numbers and viability of cells being injected. It has been reported that some doctors have been injecting suspensions of cells which have little or no viability. Clearly this is not in the public interest and poses a variety of risks. Improved regulatory structures, such as our submission discusses, involving monitoring and reporting of cell numbers and viability, measured using industry accepted minimum standard equipment would allay this risk.

The main risk is that non-medical specialists can offer this treatment for indications that they are not fully qualified to treat.

- ***What is the evidence for these risks?***

Offering and advertising autologous cell therapy for many and varied indications by cosmetic surgeons and non-medical specialists without GP referrals have become evident in the lay press and online.

Procedures are being carried out in private consulting rooms resulting in a lack of medical oversight and monitoring. Staff are almost always employees of the doctor.

Some cell processing procedures used in Australia have been found to be inadequate and that most cells injected by a particular provider were shown to be non-viable cells (ABC 7.30 report 2014).

We use a high quality hospital facility where there is independent medical oversight and mandatory reporting of events. We are both answerable to the MAC and to the referring GP and perform the procedure witnessed by other independent hospital staff. We have never used the treatment for conditions other than those that fall within our area of expertise.

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

Include a requirement for the treatments to only be offered by medical specialists trained in the area of treatment.

Increase safety or adverse event reporting requirements.

Ensure minimum standards of infection control are in place - address these points by ensuring that these procedures are carried out at an accredited hospital or day surgery.

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

Patient rights to access treatment need to be considered by not overregulating this procedure and allowing it to be available in Australia. As long as there is fully informed consent and full disclosure, patients have the right to obtain a medical treatment that may offer a benefit for their condition, even if it is new and novel.

There are obvious public health benefits to using this procedure, as long as it is safe and without major adverse effects. Our independently audited human ethics approved Registry has shown that the procedure is safe, and this is supported by numerous other research publications.(see above) Medical specialists are always looking at different conditions and developing specialised treatment options.

According to the Australian Charter of Healthcare Rights, patients have a right to safe and high quality health care. They have a right to be informed of services, treatment options and costs in a clear and open way. They have a right to be included in the decisions and choices about their care and to comment on their care and have concerns addressed. We believe that we comply with all these requirements in offering stem cell treatment. By removing the option of responsible provision of stem cell treatment for MSK conditions we believe that the TGA would be removing a viable and safe treatment option in Australia that the patient has the right to consider among a variety of treatment options. Significantly this type of treatment is a viable and accepted option in many first world countries eg Japan, Europe and Asia

Government should be promoting and funding development in this area to allow access to new and novel treatments such as stem cell therapy. Currently, the majority of government funding in stem cell therapy is directed at areas such as embryonic or cord blood stem cell where the ethical issues have not passed through public debate and are unlikely to be available in the near to medium term. Funding should be directed more towards the area of autologous cell therapies which are generally more accepted by the public and have already been shown to be safe.

By using autologous cell therapy (particularly with cryopreservation), many patients are able to delay joint replacement surgery for a number of years. Given the age of the patient at cell treatment time, this may allow the patient to avoid a revision surgery or even surgery at all, and hence save the public purse considerable money.

Response to Options

- ***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

This is the only option that allows stem cell therapy to be available in the immediate future in Australia. We would like some modification of this option with increased regulation to ensure patient's are protected from rogue operators and there is adequate centralised documentation of any safety concerns or adverse effects.

Risks

Not enough control over who can offer treatment

In current form, does not address safety or reporting concerns

Benefits

Allows the therapies to be available in Australia – does not drive patients overseas

In a clearly ageing population we need to provide an alternative to patients with osteoarthritis in middle age, in an attempt to delay joint replacement for as long as possible. We need to promote and look for alternative therapies such as stem cell treatment which has shown significant promise. These types of treatments can allow continued mobility; maintain quality of life and active participation in the workforce.

The individual needs the right to choose, with full financial disclosure from the practitioner in a high quality hospital or day surgery facility.

Costs

No additional costs

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?***

As previously mentioned this can cross the line into medical practice and therefore we would like Option 1 to be the preferred outcome.

Option 2-5

Risks

Due to the minimal manipulation and homologous use requirement, most therapies will be unavailable in Australia until such time as service providers and practitioners can meet regulations.

Option 5 will have the longest time lag to meeting regulation.

High costs and delay until treatment availability will deter many practitioners, scientists, service providers and patients all of whom may go offshore.

Benefits

TGA has more oversight – but this could be built into Option 1.

Costs

Additional costs will be required to meet regulations – this will be in addition to the already questioned cost of treatment. Cost is likely to be inhibitory to uptake of this therapy by the average patient.

We would lose all immediate work in this area until we can meet regulations. The TGA would also need to consider what appropriate practice is for those patients who already have paid to

have cells frozen and stored for future injections. Many of these patients have had an excellent therapeutic effect and may not wish to have further injections (of their stored cells) for a number of years to come.

Discussion question for Option 2-5

- ***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?***

The extraction process for the stem cells (in our case using collagenase) will always be more than minimal manipulation (under current TGA definitions) and by the nature of the therapy will not be for homologous use. Therefore, yes, autologous stem cells should still be excluded from regulation to allow these therapies to still be available in Australia in the immediate future. There is minimal evidence to show that these therapies are unsafe.