Table of Contents

General Discussion 2
Introduction 2
Safety 3
Efficacy 3
Public Health Risks 4
Costs 5
Executive summary 6
Recommendations 6
Answers to Discussion Questions 8
What are the public health risks of 'autologous stem cells' in your view? 8
What is the evidence for these risks? 8
What identified risks should have the highest priority for resolving? 10
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. 12
How do you think each option addresses the risks you identified in the earlier question? 13
Are there additional issues with the regulation of autologous stem cells that any changes should consider and/or address? 14
Discussion question for Option 1 15
Discussion question for Option 2 15

General Discussion

Introduction

This document is prepared by Kevin Boundy. I license a bone marrow derived stem cell procedure for the treatment of musculoskeletal problems from Regenexx in the United States. I will be confining most of my comments to the discussion of the use of bone marrow derived stem cells for musculoskeletal problems.

Safety

I believe that at present I am using bone marrow derived stem cells homologously. All of the stem cells are autologous and only used to treat a single patient for a single indication in a single course of treatment. The stem cells are derived from bone marrow. Bone marrow has been used by orthopaedic surgeons when performing the Steadman Technique (microfracture) to repair damaged articular cartilage for some years.

I believe the use of bone marrow derived stem cells has been proven to be safe. There are very few recorded incidences of side effects in the literature, and the American Cancer Society reports that hundreds of thousands of people have been treated with bone marrow transplants (by infusion) with no side effects.

Numerous safety studies have been published and a meta-analysis[1] of the safety studies has been done showing that stem cells are indeed safe. The meta analysis was based on a review of papers examining the safety of cultured stem cells, which, according to the TGA's discussion paper, are associated with higher risk then non-cultured stem cells. The meta-analysis singled out Chris Centeno's paper in particular as being robust and thorough in it's recording methods. Chris Centeno is the founder of Regenexx. I follow the Regenexx protocols for reporting adverse effects to the parent company. Any adverse events are then followed up with further investigation.

Efficacy

The efficacy of bone marrow derived stem cells in a culture-expanded form has been shown in a systemic review[2]. Although no placebo controlled trials of significance have been performed, this is the same with most surgical procedures. The meta-analysis of experimental groups leaves no doubt that, in appropriate numbers, stem cells can lead to an improvement in cartilage cover in an arthritic or otherwise damaged joint.

Apart from the benefits of improving cartilage cover with high doses of stem cells[3],

---

[1] **Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: a systematic literature review**

Peeters, C.M.M. et al.

Osteoarthritis and Cartilage, Volume 21, Issue 10, 1465 - 1473

[2] **Stem cell therapy for human cartilage defects: a systematic review**

Pastides, P. et al.

Osteoarthritis and Cartilage, Volume 21, Issue 5, 646 - 654

[3] **Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial.**

even in lower doses there are strong anti-inflammatory (immuno-modulatory) effects that reduce the number and type of chemicals that lead to cartilage damage and formation of osteophytes.

Much has been made of the bi-modal immunological effects of stem cells in the discussion paper from the TGA, as if it were a potentially dangerous and unwanted side effect. When I asked for a reference list so I could review these articles the TGA would not release it. The refusal of the TGA to release the original articles on which their statements were based has made it impossible for me to talk to this point in more detail. It would appear, however, that this and many of the other side effects mentioned in the discussion paper are not related to the musculoskeletal use of stem cells.

Public Health Risks

Public health risks fall into three broad categories.

Firstly, there is a risk to the individual that they are receiving a product that may be dangerous to them. This has been discussed above under safety. The two main risks to the individual patient are that the tissue samples are not handled in accordance with TGA guidelines on GMP, or that the procedure will not make any difference to their condition.

Regenexx insists that all of its licensees follow standard operating procedures that meet or exceed the standards outlined in the TGA's guide to GMP. Only one patient's tissues are processed at any one time, and strict sterile techniques are followed. Bone marrow is harvested in an operating theatre and processed in a biological safety cabinet. All transportation between the OT and the laboratory is performed in sterile bags that are clearly labeled with the patient's identification.

Experience with thousands of patients in America means that all patients who express an interest in a Regenexx stem cell procedure can be given an indication of the likelihood of success on a rating of good through fair to poor. My own experience means that patients who demonstrate certain characteristics such as loss of joint ROM or significant osteophytic disease on x-ray or MRI are advised they are not suitable candidates for the procedure. Having specialist training in Sports and Exercise Medicine I am able to give all patients a range of treatment options if they are not yet or no longer candidates for a stem cell procedure.

Understanding who will and who will not benefit from the treatment helps keep the public health risk of performing an ineffective treatment to a minimum.

Secondly, there are risks to the community if treatments provided lead to an increased risk in the community of further disease.

Stem cell therapy only requires a day stay in hospital. This reduces the patient's exposure to hospital-acquired pathogens. It also frees up beds that might have been occupied by patients having major procedures such as knee replacements.

The regenerative nature of the treatment compared to arthroscopic chondroplasty or meniscectomy means that there is less likelihood the patient will be readmitted for further surgery in the near future.

Thirdly there are the health risks from associated disease states, or co-morbidities.

Being sedentary, or un-fit, is a major contributor to death of Americans today[4]. Severe degenerative joint disease is often associated with an increasingly sedentary lifestyle and hence the development or worsening of cardiovascular disease, hypertension, and type II diabetes. Keeping people on a public hospital waiting list until a hospital can accommodate the theatre time and bed space for major surgery puts the patient at risk of worsening of these co-morbidities.

Costs

Lastly, much has been made of the "high cost" of these procedures. This is a classic case of detractors seizing on a snippet of information to malign something with which they do not agree.

Although patients are quoted about $9000 for a stem cell procedure this quote includes the total cost of the procedure, the hospital stay, the anaesthetist's fees, and aftercare.

The private hospital where I work charges $1400 for the use of the operating theatre (and $700 for the day stay bed) for the bone marrow draw. This is rated as a "band 4" procedure. Patients are charged less if they have an arthroscopy. This seems odd considering a bone marrow draw only requires a trocar, some heparin, and some 30cc syringes. An arthroscopy can require trays of sterilized equipment, cameras and TV screens, and irrigation fluids. It also generates liters of contaminated waste.

The surgeons in my area routinely charge $2000 for the arthroscopy and $400 for the assistant (even though basic arthroscopies do not attract a rebate for assistants). This fee is to cover their time and expertise in the OT. They are not required to fund and maintain their own laboratory. Any tissue sampling, handling, or processing is done by a pathology company for a further fee. Anaesthetic fees are comparable for both procedures.

Regenexx procedures are probably more labor intensive than many other stem cell providers. Apart from guided injections to the affected joint both pre and post treatment to maximize the therapeutic effect of the stem cells, in the operating theatre the stem cells are always injected as close to the affected area of the joint as

[4] Conference presentation by Dr K Kahn, editor BMJ, at ACSP National conference Feb 2015

possible using ultrasound or image intensifier guidance. When image intensifier is used this generates further costs.

There are further costs associated with licensing (which maintains a high standard of patient safety and treatment homogeneity), and the provision of pharmaceuticals from compounding pharmacies.

After everything is taken into account there is little difference between the doctor's fees for a stem cell procedure and an arthroscopy.

The total direct cost of a knee replacement in the PUBLIC system is $20,000[5] and rising. It is higher in the private system. The indirect costs of osteoarthritis to the community equate to 150% of the direct costs[6].

Executive summary

The use of stem cells to treat the pain associated with joint injuries is both safe and efficacious. Even in low doses the stem cells perform an immunomodulatory activity that reduces the pain and ongoing chemical destructive changes that lead to progression of degenerative disease. Effectively this improves patient comfort, and usually functional ability, and stops the progression of the disease for at least three, and probably five years (based on Regenexx registry data).

The safety of cultured stem cells has been demonstrated many times in both clinical trials and large registries when used to treat musculoskeletal problems. Even when used to treat malignancies in irradiated and immune compromised individuals' bone marrow injections into hundreds of thousands of patients have not resulted in a significant number of serious side effects.

Recommendations

The use of bone marrow derived stem cells to treat musculoskeletal conditions fills a small niche. People recommending these procedures should understand what other treatment options are available. As this is an evolving field of medicine, although it is relatively safe, it is important that practitioners understand the importance of reporting any adverse event properly. A central registry for reporting these events is an excellent idea. Enshrining it in legislation runs the risk of doctors who make an error in their paperwork being classed as criminals.

I believe the administration of bone marrow derived stem cells should be restricted to medical practitioners with specific training in the nature and extent of joint diseases and who are used to recording and reporting the findings. It would be my recommendation that there is no need to further regulate the use of stem cell treatments for musculoskeletal procedures, but the practitioners performing the procedures to treat such conditions should have a specialist qualification in Orthopaedics, Rheumatology, or Sports and Exercise Medicine or equivalent further

[5] http://www.health.nsw.gov.au/Hospitals/Going_To_hospital/Pages/Cost-of-Care.aspx
[6] http://www.deloitteaccesseconomics.com.au/uploads/File/Painful%20Realities%20-%20The%20economic%20impact%20of%20arthritis%20in%20Australia%20in%202007.pdf

training or experience

The greatest risks associated with the use of non-expanded stem cells come from tissue handling. Regenexx has a full suite of standard operating procedures that agree with the TGA's code of GMP. To further regulate all stem cells as if they were a single product would be do nothing to improve on this standard and would overly complicate applications for safe and proven uses of stem cells as they become more widely available.

Answers to Discussion Questions

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

There are no public health risks of **autologous, bone marrow** derived stem cells. Bone Marrow transplants have been used since the late 1960's. The American Cancer Society wrote in 2013 in a document entitled

Stem Cell Transplant (Peripheral Blood, Bone Marrow, and Cord Blood Transplants)

That in relation to infusion of stem cells

> "Infusion side effects are rare and usually mild. The preserving agent used when freezing the cells (called dimethylsulfoxide or DMSO) causes many of the side effects. …
> "Patients who have transplants from cells that were not frozen do not have this problem because the cells are not mixed with the preserving agent.
> "Other short-term or immediate side effects of the stem cell infusion might include:
> Fever or chills
> Shortness of breath
> Hives
> Tightness in the chest
> Low blood pressure
> Coughing
> Chest pain
> Less urine output
> Feeling weak
> "Again, side effects are rare and usually mild. If they do happen, they are treated as needed. The stem cell infusion must always be completed."

It should be noted that these infusions are given intravenously and despite the "hundreds of thousands of people treated" none of the side effects listed in section 2 of the discussion paper appear in the American Cancer Society paper.

There are dangers associate with peripheral aspects of the treatment, such as the risk of infection if the tissue is not handled and processed in accordance with GMP, but anyone who has spoken with the TGA is aware that they must follow GMP, including appropriate labelling, documentation, and the use of a BSC when processing patient materials. These peripheral processes are already covered by TGA regulation and apply to all providers of biological products.

What is the evidence for these risks?

Although attachment 2 outlines possible risks of stem cell treatment the references have not been released. The evidence may be in these articles, but often such articles are misquoted to put a chosen slant on the "evidence". For example, the NHMRC claims in a document entitled…

Stem Cell Treatments – A Quick Guide for Medical Practitioners

That…

> "Participation in unproven stem cell treatments may pose serious risk to the health and well-being of patients. Serious adverse events have been reported as a result of stem cell treatments, including the development of **tumours** [4,5] **and abnormal bone growth**[6] as a result of stem cell injections". (my highlighting)

Reference 4 is a case study, Amarigli N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthl R, Trakhtenbrot, L. et al. **Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient**. PLOS Medicine 2009;6:221-331.

Donor derived stem cells are not used in Australia for musculoskeletal treatments so this article is not relevant to the Australian discussion.

Reference 5 is another case study, Thirabanjasak D, Tantiwongse K, Thorner, PS. **Angiomyeloproliferative lesions following autologous stem cell therapy**. CJASN 2010;21:1218–1222

In this case a woman with renal failure secondary to SLE had stem cells extracted from the circulation after mobilisation with G-CSF. These cells were then injected "blind" (without ultrasound guidance) in the region of her kidneys. The treatment did not help her kidney function and she presented 9 months later while on dialysis with heamaturia and flank pain. The article continues…

> "Ultrasound and magnetic resonance imaging studies showed a 4.0-cm enhancing mass in the left renal pelvis, with smaller lesions in the left kidney, the liver, and right adrenal gland. … The clinical impression was urothelial cell carcinoma with metastatic spread to the right adrenal and liver. The patient underwent a left nephrectomy 11 months after stem cell therapy."

Later in the article the authors state that subsequent histopathology of the lesions showed them to be benign, so although there was a tumour, it was a benign tumour. Moreover…

> "The patient continued on hemodialysis over the next year but gradually deteriorated and died of sepsis after infection of the arteriovenous shunt."

In other words, the patient died from a complication of the established medical treatment of her renal failure, not from any complication of the stem cell treatment, remembering that the masses in the liver and adrenal gland were left in place.

The last reference, number 6, comes from Scientific American.

It would be hard to imagine anyone being able to build a case *for* using a treatment modality based on 2 case studies and an article from a popular magazine, but the NHMRC, with all the resources at its disposal is trying to use such flimsy evidence to build a case against.

Despite the inference in the discussion document that "Because these treatments can be used in some circumstances without evidence, there is no incentive to undertake research of the kind designed to determine efficacy (including clinical trials)" a glance at the Australia New Zealand Clinical Trials Registry found 3 trials listed for musculoskeletal uses of stem cells.

1.Trial ID: ACTRN12614001044617 Start date 31/01/2015

A Randomised, Stratified, Placebo-Controlled, Observer Double-Blind Multicentre Proof of Concept Study of the Safety and Efficacy of Autologous Stromal Vascular Fraction (SVF) With or Without Platelet Rich Plasma (PRP) and Hyaluronic Acid (HA) in Patients with Osteoarthritis of the Knee.

2.Trial ID: ACTRN12614000814673 Start date 07/08/2014

The effectiveness of autologous adipose derived mesenchymal stem cells versus accepted conservative management as treatment for symptomatic knee osteoarthritis on pain, function and cartilage volume in osteoarthritis patients.

3. Trial ID: ACTRN12614000812695 Start date 15/08/2014

The effect of mesenchymal stem cell injections following arthroscopic microfracture versus microfracture alone on cartilage healing in patients with an isolated knee cartilage defect.

The American trial site lists numerous clinical trials for a number of conditions. Any group that can conclusively prove that their treatment improves patient outcomes would have a hugely successful treatment, both medically and commercially.

What identified risks should have the highest priority for resolving?

There are no identified risks unique to the therapeutic use of autologous stem cells for musculoskeletal problems.

The main risk with Autologous Stem Cells is the risk of a handling error, and the handling of biological is already regulated by the TGA. There have been no reports of any complications that could not have been equally attributed to other factors (such as stroke occurring in **both** the treatment and placebo group, in a study with catheterisation of the heart in a group of anticoagulated patients).

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

As stated previously, published articles have shown reasonable efficacy and a high degree of safety with regard to the use of stem cells. Historically IVF treatments were made available to the public long before practitioners had been able to avoid the risk of multiple pregnancies (and the public health burden that placed on the patients and their community). Now the same medical community that allowed IVF programs to proceed are baulking at the introduction of commercial stem cell treatments. This appears out of step with other parts of the world, including other parts of the first world such as Japan and Europe where recognition of the relative safety but as yet unelucidated mechanism of action of stem cells has lead to an easing of restrictions around their use.

Part of the reason that proof of efficacy is lacking is because there is no agreement as to what constitutes efficacy. Detractors continually want to see proof of cartilage regrowth. They refuse to accept that a reduction in pain and improvement in quality of life indicate a beneficial effect from processes other than the regrowth of cartilage.

For years degenerative joint disease was considered to be non-inflammatory. This was based on articles comparing the concentration of inflammatory mediators in synovial fluid from knees with osteoarthritis with that from knees with rheumatoid arthritis. The original studies did not compare these with synovial fluid from a normal knee. More recent studies have shown that osteoarthritic knees have a higher concentration of inflammatory mediators, and that these mediators activate bone morphogenic proteins (BMPs), leading to osteophyte formation. Histological studies of cartilage in knees with early changes of OA show changes to the microscopic structure of cartilage with a higher number of osteoblasts in the basal layer.

Once you get away from the present assumption that overuse alone leads to damage of the cartilage and transmission of stress to the bone it becomes easier to understand why osteophytes can form even in the absence of any significant loss of cartilage, and why x-ray changes correlate so poorly with pain scores.

If one accepts the paradigm that OA is a slow inflammatory condition this helps explain the reduction in pain reported in refereed journal articles following administration of PRP (albeit only for 6 months). It also helps explain the dramatic reduction in pain some patients experience within days of having an intra-articular stem cell injection, and the general lack of success seen in patients with severe osteophyte involvement, especially around the hip, where the mechanical problems of impingement on the osteophytes are more problematic than the background presence of inflammatory mediators.

For years the “orthopaedic mechanical” view of OA has held sway, that loss of cartilage has lead to the development of OA. As a result there has been a push for stem cell providers to try to show regrowth of cartilage. When I first contacted the

TGA about restrictions on the clinical use of stem cells I was instructed that I could not tell my patients that stem cells would regrow cartilage. I was left with the impression that the present opinion of the TGA is that OA is a problem of cartilage loss and there is no proof this is addressed by stem cell administration.

In the background a large amount of work has been done showing stem cells reduce inflammatory mediators and down regulate immune mediated inflammation and macrophage activation. Ironically, in the discussion paper released by the TGA these effects were noted as being recorded in a refereed journal article but considered as if they were an unwanted and possibly dangerous side effect.

In terms of a more general public health benefit, using figures available on the Australian Government Websites it is apparent that if just 10% of the patients on the waiting list for a joint replacement had a stem cell treatment the savings in bed days alone would free up enough beds to replace Nepean Public Hospital. Given the significant mortality associated with major surgery the overall benefit to the community and reduction in health costs of such a program could be significant. Even though stem cell treatments presently available would probably need to be repeated every 5 years the often quoted cost of $9000 a treatment compares well to the present cost to the public system of $20000 for a knee replacement expected to last less than15 years in someone in their 50's.

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, maintaining the status quo, involves the risk that anyone who believes they can extract fat or bone marrow can enter the market as a stem cell practitioner. This can only be bad for patients, and the industry as a whole. A large amount of research has gone into clinical treatment protocols by the major companies in the market. They try to ensure anyone using their techniques has adequate training in all aspects of stem cell harvesting, preparation, and reimplantation. People would baulk at seeing a self taught psychiatrist or neurosurgeon. It is reasonable for the public to expect stem cell practitioners to have adequate training and support to perform the procedures they sell.

A further risk of maintaining the status quo is I would have to endure the constant ill informed taunts that stem cell practitioners are using a loophole in the TGA's regulations. Although stem cells are presently excluded by the Act, ill informed individuals continue to misinterpret this situation as if the TGA is unaware of what is going on and therefore putting patients at risk.

A benefit of maintaining the status quo is that I could continue to service my patients and hopefully grow the patient base. A larger number of patients would result in a greater distribution of the fixed costs and hopefully a lowering of prices. Considering medical inflation always runs at a greater rate than general inflation this would represent an amazing scientific breakthrough.

Maintaining the status quo would theoretically cost me no more than it does now. The use of IP from Regenexx runs into tens of thousands of dollars each year, as do

staff costs. Maintenance, inspections and certification of the laboratory come at a cost. Medications ordered specifically from compounding pharmacists are expensive. Each hospital admission costs a shade under $3000, and with the Regenexx treatment program there are two outpatient injections (1 before and 1 after the procedure) and 2 sets of lab fees to cover. Then there are 2 follow up appointments for which the patient is not being charged (in line with regular practice for other surgical procedures). The process is labour intensive and highly skilled.

Options 2 and 3 would be relatively cost neutral as I already report all cases to the parent company in America for inclusion in a registry that tracks all adverse events and seeks responses to standardised health questionnaires on a regular basis after a treatment has been performed. Copying reports to another Australian body would hopefully add little extra expense to the process.

All Australian patients are referred to me through my specialist practice. Overseas patients make up less than 10% of my practice.

Option 4 would theoretically be relatively cost neutral, as Regenexx safety data is some of the more robust in the literature. Their seminal paper is

Safety and complications reporting update on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique.
Curr Stem Cell Res Ther. 2011 Dec;6(4):368-78.
Centeno CJ[1], Schultz JR, Cheever M, Freeman M, Faulkner S, Robinson B, Hanson R.

Option 5 would close the business. The burden of proof would run to numerous clinical trials run over years. Experience with orthopaedic surgeons who scoff at the technique (despite their use of the Steadman Procedure) has shown me that no matter how many studies were done the detractors would never be satisfied.

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

They do not address the problem of underqualified operators. Unfortunately this falls outside the scope of the TGA, and whatever option of 1 through 3 was applied the same operators who presently run large chains of bulk billing medical centres would be able to set up “stem cell factories” where all the procedures and ancillary staff were in place to maximise throughput. The greater the administrative burden of using stem cells the less likely it is that the treatment will be controlled by doctors and the more likely it is that it will be controlled by entrepreneurs. The only sensible option is to manage the doctors on the basis of their qualifications and experience.

The options presented all stop advertising to the public, but the reality is the public will still seek out stem cell practitioners in Australia.

As a Sports Physician I found patients sought me out and asked their GP for a referral. Strangely, many GP’s refused to refer patients because they had not heard of Sports Physicians, despite the fact that Sports and Exercise Medicine is now a registered specialty in Australia. It was the patients who had kept abreast of the emergence of the specialty, not the GP’s. The patients wanted to see a doctor who focussed on health rather than illness and they drove the referral. Many GP’s resented being told what to do and refused to refer. Even now I speak to GP’s who

have no knowledge of how to treat conditions suffered by their patients and yet who refuse to write a referral that would allow their patients to get a legitimate Medicare rebate.

All medical advertising is presently restricted in its scope by legislation. Not allowing doctors to have some communication of a factual basis outlining the services they offer will only create confusion in the market place. The TGA has stated in its discussion paper "some companies have developed business models that are designed to limit the regulatory oversight of the products they use." Stopping medical advertising to the general public will allow such companies to flourish while ethical doctors feel conflicted about what they say to their patients.

A proliferation of corporate advertisers would probably only confuse the issue in the minds of GP's who will therefore be unable to advise patients about the potential benefits and pitfalls of this emerging field of Medicine.

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

It has often been stated that these treatments are being offered at high cost. This is because the cost quoted to the patient includes all the costs that Medicare would cover if the patient was having e.g. an arthroscopy (despite many journal articles highlighting the damage done by supposed arthroscopic treatment of osteoarthritis) but that are not part of the proceduralist's charge. If all other proceduralists were held to the same standard people would be shocked at the ancillary costs of surgery e.g. anaesthesia, renting the operating theatre, bed costs.

With regard to stem cells much of the cost is in the technology and recovering the lab set up and maintenance costs. These are fixed costs independent of the number of patients seen. While demand is low prices will stay high.

Lastly, although this is outside the scope of the discussion paper, it is worth noting that our long held beliefs regarding the pathophysiology of osteoarthritis are now under threat. A recent paper, **Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations** (Jeremy Sokolove and Christin M. Lepus. Ther Adv Musculoskelet Dis. Apr 2013; 5(2): 77–94.), details the chemical changes that precede the structural changes of osteoarthritis. Given the known immunomodulatory effects of stem cells this means that if the right cohort is targeted then osteoarthritis could be stopped before it began, with a commensurate reduction in comorbidity and a benefit in general health of all those patients who could remain more active. The reduction in health costs generally, if this were the case, would be enormous.

Given that most patients only present when structural changes are already present, it suggests that the present medical paradigm for treating osteoarthritis is sadly lacking. If people used stem cells as a "vaccine" against arthritis then the uptake would lead to a dramatic fall in unit processing costs and greater availability of the treatment to the general public. The potential reduction in comorbidities would

represent a massive reduction in the public health burden of disease leading to significant net cost savings.

It is difficult to know why the TGA feels the need to respond to demands for this area to be more regulated. With respect to bone marrow derived stem cells hundreds of thousands of patients have received bone marrow transplants without problems. Side effects from stem cell treatments appear in case reports in tiny numbers and can often be explained away as related to the treatment method used. The risks associated with not following GMP are already regulated.

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?

Yes. Treatment of a patient with stem cells provides them with a biologically unique formulation. A patient's own stem cells are not a therapeutic good that can be traded or sold to anyone else. If the cells are not expanded then nothing has been created or manufactured.

No matter how many cells are harvested they can provide a unique benefit to patients with any level of joint disease. They are not a drug of specific dose or a device with certain sterilization requirements. If handled properly the cells come from and return to the patient in their original state.

They should also not be overregulated because there **might** be a problem, as this ignores the fact that hundreds of thousands of patients have received bone marrow transplants with no ill effect.

The handling and processing of the biological tissue is already controlled by the TGA, which is appropriate because this is where the greatest risk of the procedure lies.

Having said the above there are also advantages to having the Minister make a Determination, or in ensuring the qualifications or experience of practitioners meet certain requirements.

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?

This very much depends on the definition of homologous. In my case the use of bone marrow appears to be homologous use as a bony or cartilaginous fracture would result in the release of bone marrow into the area, which would assist with healing. This has been accepted since at least 1985 by orthopaedic surgeons who use the Steadman technique (microfracture) to repair damaged cartilage. On his web page Dr Steadman claims…

> **"**The rehabilitation program after microfracture is crucial to optimize the success of the surgical technique. The program is designed to promote the

> ideal physical environment in which the bone marrow cells can transition into the appropriate cartilage-like cell lines."

Somehow the same orthopaedic surgeons who believe that stem cell transplants do not work have no problem believing that "bone marrow cells can transition into the appropriate cartilage-like cell lines".

If it is the case that bone marrow stem cells transition into cartilage cells, then bone marrow derived stem cells for orthopaedic uses are for homologous use. If this is not the case then stopping the use of bone marrow derived stem cells to treat joint pain should be associated with the banning of microfracture with arthroscopy.

Whether or not adipose derived cells should be considered homologous falls outside the scope of my expertise, but I believe that their similarities with regard to their musculoskeletal uses outweigh any differences.

The use of stem cells for non-musculoskeletal uses falls outside my area of interest and clinical application. Having not read widely outside of my own field I would not like to comment on these issues.