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Regeneus Response to TGA discussion paper: Regulation of Autologous Stem Cell therapies March 2015

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Introduction and Background

Regeneus welcomes the opportunity to address the issues raised in the TGA's discussion paper on the regulation of autologous stem cell therapies issued on 6 January 2015.

We believe it is timely to review the operation of the autologous cells and tissues exemption as captured under the Therapeutic Goods (Excluded Goods) Order No.1 of 2011 **(Excluded Goods Order)** that was introduced in the Biologicals Regulatory Framework in May 2011. We are confident that this process will allow for a greater diversity of stakeholder interests to be considered which should improve the quality of debate about the role and regulation of autologous cell therapy in Australia.

Regeneus is an ASX-listed regenerative medicine company that develops and commercialises autologous and allogeneic "off-the-shelf" cell-based therapies for addressing unmet medical needs in the human and animal health markets with a focus on musculoskeletal disease, oncology and dermatology conditions.

Since 2011, Regeneus has provided an in-hospital cell processing and handling service to sports medicine and orthopaedic specialists wishing to use a patient's own adipose stem cells for the treatment of musculoskeletal conditions, primarily osteoarthritis. Our service relationship with medical specialists has been established and operates with careful regard to the Excluded Goods Order and guidelines issued by the TGA.

Our primary focus is on research and development of adipose-derived cell therapies for musculoskeletal conditions, particularly osteoarthritis. We engage with medical musculoskeletal specialists and conduct extensive reviews on current data and literature to assist us in refining and improving our cell therapy service. We also attend relevant cell conferences and are affiliated with other research units. We have engaged with the TGA about our service offering within the context of the Excluded Goods Order and have been open with our clinical data and adverse event reporting.

In our view, the TGA was forward thinking when it introduced the Excluded Goods Order as it has provided a regulatory framework that matches the low level of risk with autologous stem cell grafts as part of medical practice. There is a substantial and growing body of clinical data that supports the safe and often effective treatment of diseases using autologous stem cells. The Excluded Goods Order was not limited by the requirements of homologous use and minimal manipulation of the autologous cells.

This flexible framework has enabled the continued innovation in medical practice that has been driven by increasing patient interest in stem cell therapy, rapid advances in technology and extensive clinical data about therapeutic uses of stem cells. Our clinical experience and data and the scientific literature clearly supports the policy underpinning the Excluded Goods Order. There is no evidence to suggest that the introduction of homologous use and minimal manipulation requirements will reduce any safety risks of autologous stem cell transplants.

By placing the registered medical practitioner at the centre of responsibility for the autologous cell transfer procedure, the TGA can draw upon other checks and balances against any inappropriate practises. Professional performance and advertising are governed by the Australian Health Practitioners Regulation Agency and advertising is also regulated by the competition and consumer legislation.

While we acknowledge that the long term future of cell therapy is most likely to be allogeneic "off-the-shelf" cell therapy approved through the clinical trial process, there will always be a role for autologous stem cell procedures as part of medical practice and a driver of medical

innovation. We consider that it is important that there remains a regulatory pathway for Australian patients, properly advised and cared for by their medical specialist, to be able to use their own regenerative stem cells for an individual one-off therapy without the need for expensive and time consuming efficacy trials or having to travel overseas.

Regeneus considers that **Option 1** is the only option available to the medical community which will enable autologous cell therapies to continue to be available in Australia. All other options (Options 2-5) will mean that autologous cell therapies will not be able to meet the regulatory requirements as most are more than minimally manipulated and are largely for non-homologous use, or costs will be driven out of reach of patients. We outline that safety and efficacy data is available on these therapies both from the literature and from our own internal registry database of over 550 patients treated. There is a wide safety margin for these types of therapies, and thus safety is not a justifiable reason to stop availability of stem cell treatments.

We would like to propose approval of **Option 1** with some additional measures to reduce risk to patients, doctors and the community.

Our service offering to medical specialists is referred to as HiQCell.

Summary of Key issues

- This submission supports the continued use of autologous stem cell therapies under **Option 1** with some additional restrictions of only allowing treatments to be performed by a medical specialist, and mandatory adverse event reporting.
- **Option 1** is a proven acceptable method of providing autologous stem cell therapies to patients in Australia and is well regulated by other groups and agencies apart from the TGA including AHPRA (Australian Health Practitioner Regulation Agency), and the ACCC (Australian Competition and Consumer Commission).
- Safety of mesenchymal stem cell therapy is well documented in the literature with a meta-analysis in over 1000 patients (Lalu et al 2012). Very few side effects are seen, especially compared to conventional therapies. We also have safety data to show that this therapy is safe in >550 patients in over 1200 joints treated.
- Efficacy has also been demonstrated in the literature and in our extensive registry data. Refer to 'Responses to Concerns' for a summary of the data.
- As a comparison to this therapy, there are numerous surgical procedures that have limited proven efficacy but continue to be widely used in the surgical community.
- Inclusion of homologous use and minimal manipulation requirements in Options 2-5 will almost immediately mean that this type of therapy will no longer be available in Australia for the foreseeable future.
- Options 2-5 will ultimately drive cell therapy off shore and Australia will no longer be considered a leader in innovative autologous cell-based medicines. Patient rights groups see the use of autologous cell therapies as a basic right and will not support options that limit their availability especially when there are no documented safety concerns with these therapies.

Regeneus preferred option:

Regeneus' preferred option is **Option 1** but with additional requirements:

- Procedure must be under the direction of a medical specialist who *specialises in the disease being treated*.
- Adverse Event reporting to the TGA
- Safety data maintained on file for all treatments which can be accessed by regulators on request
- No direct patient advertising
- Consider only allowing procedures in accredited hospitals or day care facilities to allow for increased medical oversight

Justification for Option 1 with additional requirements

- Increases safety awareness and reporting – safety is paramount but the data and our experience suggests the safety profile is benign.
- We maintain safety and efficacy data in an ethics approved patient registry.
- The specialist requirement (of the treated disease) would allow for balanced and experienced advice of the risks and benefits of all available options to the patient
- Only medical specialists can administer the autologous stem cell therapy for musculoskeletal conditions in **high quality medical facilities.**
- By only using reputable clinics and hospitals there is medical oversight by the treating medical specialist as well as by medical staff.
- We propose that stem cell therapies remain available in Australia under tighter regulation.
- **Option 1** won't drive people offshore – it keeps the therapy available in Australia whilst being able to improve standards, safety and conditions.
- This is currently a consumer driven market and is in demand. This option allows the therapy to remain available while mitigating any potential issues such as consumer backlash and seeking treatment overseas.

Justification against options 2-5

- Options 2-5 will increase regulatory overheads thus causing the treatment to be too expensive and out of reach to the average patient. This will also be inhibitory to practitioner uptake. Overheads will include the passed on cost of listing as a biological, additional clinical trial work and changing of procedures.
- Including homologous use and minimal manipulation requirements will force stem cell therapy into Option 5. Consideration must be given to redefining these terms in light of the latest scientific and clinical data.
- Options 2 to 5 will slow innovation and deny patient's the right to use their own stem cells as a one-off treatment option. This does not appear to be in line with discussion on medicines and medical devices regarding provision of innovative therapies in Australia.

Responses to concerns and criteria on page 7 of the discussion paper

Regeneus would like to comment on the concerns that have been expressed to the TGA and in public forums:

1. Safety of the products – either direct safety impacts or safety issues incidental to the therapy
2. Lack of evidence to support the efficacy of the products
3. The large sums of money being charged for unproven treatments
4. Lack of mechanisms for reporting of adverse effects of the products
5. Inappropriate advertising of the products

1. Safety of the products – either direct safety impacts or safety issues incidental to the therapy

In a recent literature review (Feb 2015) completed by Regeneus, a total of 30 individual journal articles detailing safety data on the systemic or percutaneous administration of adipose or bone marrow derived autologous cells to 2,149 patients were identified. Of the studies recorded, at least 73% were conducted using greater than minimally manipulated autologous stem cells for non-homologous purposes. Of the 2,149 patients treated a total of 12 events were recorded. Nine of these events were not considered safety issues by the authors. Three (3) events were recorded as related to the injection of MSCs – pain at the injection site and a DMSO allergy (Lee *et al.* 2012a; Duijvestein *et al.* 2010). The most recent reviews state that substantial evidence now exists that preparations of autologous mesenchymal stem cells do not have adverse immune effects (see Hare et al., 2009; Kebriaei et al., 2009; Vangsness et al., 2014). Intraarticular injection is also not associated with migration out of the joint and a systemic outcome (see Horie et al, 2009). For a full discussion on safety from these journal articles see **Appendix 1** of this document.

Ethics Approved Joint Registry

Medical practitioners using HiQCell invite patients (with consent) to participate in the joint registry. The results of the joint registry are made public on the website.

To date there are >550 patients registered with data up to 2 years. There have been low numbers of adverse events reported. Of all HiQCell treated patients only 17 adverse events (3%) were reported of which 3 were rated as severe (requiring hospitalisation - 1 for collapse/fainting episode, 2 for pain). Adverse events were considered to be, probably related (n=9), possibly related (n=2), not related (n=2), and 4 events were not categorised.

Patients are carefully selected, treated in high quality facilities with medical oversight and are monitored post treatment, many on an ongoing basis through the registry.

The data has consistently shown the following:

1. HiQCell administration is safe
2. There is a significant reduction in pain in all age groups and grades of osteoarthritis
3. There is a significant improvement in knee function
4. Improvements are seen in sleep quality
5. Significant reduction in the amount of pain medication required
6. Improvement in quality of life

See the **Appendix 2** for the latest registry update

Clinical Trials

Regeneus has completed 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 known as the **OSCARS - Osteoarthritis Stem Cell Advanced Research Study** (ACTRN12611001046998).
The objective of the OSCARS study was to determine the efficacy and safety of using autologous adipose-derived cells to reduce pain symptoms in knee osteoarthritis patients.

Design: Knee osteoarthritis patients with Osteoarthritis Research Society International (OARSI) joint space Grade 1 or 2 were included in this phase II randomized double-blind, placebo-controlled trial.

Results: The safety of HiQCell treated patients was similar to placebo, and upper respiratory tract infection was the most common adverse event. One cell suspension tested positive for *Staphylococcus caprae* and the patient was treated with no residual effects.

The primary outcome measures were change in pain scale, using the Intermittent and Constant Osteoarthritis Pain (ICOAP) index at 1, 3 and 6 months post injection and the percentage of patients achieving OMERACT-OARSI responder criteria. Both treatment and placebo groups experienced a significant decrease in ICOAP total pain score from baseline. Significant pain reductions in placebo groups are common in osteoarthritis trials.

In secondary outcome biomarkers there was no significant difference between the treatment and placebo groups in the urinary concentrations of C-terminal crosslinking telopeptide of type II collagen (CTX-II), which is a biomarker of cartilage degradation and osteoarthritis progression. However exploratory analysis of longitudinal within group changes revealed that CTX-II remained stable in the treatment group but increased in the placebo group by 31% from baseline to 6 months ($p=0.033$). In addition, post-hoc ANCOVA analysis of serum biomarkers revealed that four cytokines, MIF ($p<0.0001$), IL-1Ra ($p=0.003$), IP-10 ($p=0.02$) and IL 13 ($p=0.02$) were significantly different between the groups.

In addition a study recently accepted for publishing in "Cell Transplantation" (Michalek *et al* 2015) looked at both the safety and clinical efficacy of the use of autologous mesenchymal stem cells (MSCs) in the treatment of osteoarthritis. The study was of a large cohort of patients over an extended period of time (average 17.2 months).

The case control study of 1128 patients, with 1856 treated joints, demonstrated that autologous adipose-derived SVF therapy was safe with no serious side effects, systemic infections or cancer associated with the SVF therapy reported within the follow-up period of up to 4.5 years. Of these 1128 patients, 63% reported an improvement of at least 75% in patient reported outcome scores 12 months after SVF therapy. Magnetic resonance imaging of a cohort of patients showed encouraging effects of SVF therapy on cartilage integrity and subchondral bone edema

2. Lack of evidence to support the efficacy of the products

The same review of the literature has found 36 papers reporting on efficacy of autologous stem cell therapies for musculoskeletal indications.

All studies (36 articles) reported significant improvement or no change, using autologous stem cell therapies for a variety of musculoskeletal, autoimmune or other diseases. The administration

of MSCs resulted in significant changes in patients, including healing of bone, tendon or cartilage injuries, reduction in pain and lameness, improved histological and clinical scores and improved quality of life. These findings suggest that greater than minimally manipulated autologous stem cells used for non-homologous therapies are not only safe, but highly beneficial in a wide variety of clinical settings.

Further details on this literature review are found in **Appendix 3** of this document.

3. *The large sums of money being charged for unproven treatments*

The cost of the stem cell offering we are associated with is all-inclusive and does not have hidden extras. Other comparable surgeries may appear to be less costly but when additional costs for the hospital, anaesthetist and pathology are included the costs add up. Patients are made very aware by their treating specialist of the full costs up front with HiQCell. Like many new technologies, the costs of the procedures have reduced as competition has entered the market.

There is also little to no refund from Medicare and no rebate from Private Health Insurance with HiQCell. The cost is therefore not passed on to tax payers. Inclusion in the Medicare register has been looked into but has met with complex regulation.

Only medical specialists, in high quality medical facilities using highly trained technicians, offer HiQCell.

Patients are also back to work quickly which is a cost saving both to the patient and to government.

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

We already have adverse event reporting systems in place and fully support these events being reported to the TGA if requested. To date, no safety trends or signals have been identified.

5. *Inappropriate advertising of the products*

We would support no direct patient advertising.

Responses to discussion questions

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

There are a number of potential risks of using autologous stem cells. These include:

- Potential medical risks
    - Site of collection (swelling/pain/infection etc.)
    - Site of injection (swelling/pain/infection etc.)

The incidence of these reactions is low and can be mitigated by only allowing therapies by specialists in high quality facilities.

- Potential Practitioner risks

    - Inappropriate representation: Can be mitigated by consumer law, or by banning advertising to the public
    - Inappropriate delivery of services: Can be mitigated by using only medical specialists, and experts in their field

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

Potential Medical Risks

The public health risks of autologous stem cell therapy is low as reported in a number of literature reviews. Lalu et al (2012) reported that in over 1000 patients receiving mostly autologous intravascular stem cells for a variety of diseases including cardiomyopathy, myocardial infarction, Crohn's disease and ischaemic stroke, there were no associations with adverse events including infusional toxicity and malignancy. A small number of patients had transient fever associated with administration. In another review of autologous intra-articular stem cell therapy (Peeters et al 2013) in 3039 patients, 22 had possible procedure related adverse events. These included pain and dehydration following bone marrow aspiration (BMA) and increased pain and swelling at the site of joint injection. One pulmonary embolism was possibly related and one infection from BMA resolved with antibiotics. Both reports represent very low incidences of adverse events associated with autologous stem cell treatment.

A further more extensive review of the safety literature for autologous stem cell therapy is found in **Appendix 1**.

These data are complemented by our own registry data as indicated previously.

The TGA discussion document (p33) notes that "no direct and significant safety issues pertaining to therapeutic use of mesenchymal and/or adipose derived stromal cells were identified based on published data for multiple indications, using multiple delivery routes and up to seven years of follow-up evaluations".

This compares to the risks of comparable therapies e.g. knee replacement. Belmont et al (2014) in a review of >15,000 unilateral knee replacements reports that the thirty-day mortality rate was 0.18%, and 5.6% for the patients who experienced complications. Predictive factors impacting the development of postoperative complications included an American Society of Anaesthelologists classification of ≥3, increased operative time, increased age, and greater body mass.

Barlow et al (2014) reports that approximately 17% of people are dissatisfied after a total knee arthroplasty (TKA). This is consistent with Bourne et al (2010) who reviewed over 1700 cases and confirmed that approximately one in five (19%) primary TKA patients were not satisfied with the outcome. Satisfaction with pain relief varied from 72–86% and with function from 70–84% for specific activities of daily living. The strongest predictors of patient dissatisfaction after primary TKA were expectations not met, a low 1-year Western Ontario and McMaster Osteoarthritis Index (WOMAC) score, preoperative pain at rest and a postoperative complication requiring hospital readmission.

Herein, patients facing knee replacements are offered an accepted procedure, which is invasive, may cause death, has a large number of complications, and a variable outcome.

Potential Practitioner Risks

Inappropriate representation:

Business and medical practitioners are already prohibited from engaging in misleading or deceptive conduct during trade or commerce. This is covered by the ACCC. AHPRA also has guidelines for advertising health related services. As such, a person or business must not advertise a regulated health service in a way that is false, misleading or deceptive; uses testimonials or purported testimonials about the service or business; or creates an unreasonable expectation of beneficial treatment.

From the discussion paper (p12), it is clear that "Although the TGA has been made aware of concerns in relation to this advertising, as of early September 2014, the TGA, the Health Care Complaints Commission and the Australian Competition and Consumer Commission have received very few direct complaints from consumers of autologous stem cells.

Nevertheless, we would support a "no direct patient advertising" inclusion in the regulation.

Inappropriate delivery of services:

There are already multiple avenues available for health consumers to make a notification or complaint to either the federal AHPRA, or the relevant State bodies (such as the HCCC (NSW Health Care Complaints Commission), or the Medical Council of Australia regarding medical practitioners. AHPRA, on behalf of the national boards, manages investigations into professional conduct and performance of health professionals)

Most relevant to this area is s 141 of the National Law. Health practitioners must report to APHRA any "notifiable conduct". This may include where the practitioner has "placed the public at risk of harm because the practitioner has practiced the profession in a way that constitutes a significant departure form accepted standards".

It is also accepted that health professionals have a duty of care to their patients. A breach of this, may lead to a civil action in medical negligence. The terminology is that he or she acted in a manner that was widely accepted in Australia by peer professional opinion as competent professional practice. However given that the alternative treatments (e.g. total knee replacement) have associated mortality rates, and high dissatisfaction rates, and the growing rate of evidence for stem cell therapy including level I (Vangsness et al 2014) and level II (Saw et al 2013), it would appear that to not give the patient the option of stem cell therapy may breach that duty of care.

Some practices who are not experts in treating the condition in question may be unable to provide information concerning both the objective risks (normally provided to the patient) of the treatment and the subjective risks (based upon their individual circumstances). Therefore, we see increased risk if the treatments are not carried out by appropriately qualified persons.

The ISSCR's (International Society for Stem Cell Research) view is that innovative therapies should be:

- Supported by persons with clinical and administrative leadership
- Carried out by appropriately qualified personnel
- Performed in patients who give voluntary informed consent
- Monitored with an action plan for adverse events,
- Undertaken with a commitment from scientists to disseminate their findings to contribute to advancements in the field.

We support this point of view.

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

    - Use of medical specialists specialising in the indication being treated.
    - Implementation of adverse event reporting to the TGA
    - Ensuring safety data is kept on file for access if required by the TGA
    - Treatment must be in a high quality hospital

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

Keep the process, patients, companies, IP, scientists and medical staff in Australia – prevent off shore treatment in less regulated countries.

Allow the development of this therapy in Australia that is in line with previous TGA discussion paper on medical devices and medicines regarding improved access to innovative therapies.

This is a treatment gap for many indications – alternative to drug therapy, alternative to joint replacements and joint reconstructions that are surgeries with high morbidities.

Patient rights to access treatment.

Discussion questions for each of the potential 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.***

In summary **Option 1** (with some additional requirements as listed above) is the preferred option, as Options 2 to 5 will rule out most current therapies on the basis of minimal manipulation and homologous use.

Option 1

This is the only option that allows stem cell therapy to be available in the immediate future in Australia.

Risks

The TGA Option 1 as it stands does not:

- Limit the treatment to medical specialists
- Address safety or reporting concerns
- Address the other concerns raised

Benefits

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

Costs

No additional costs to implement.

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?***

It could be argued that this crosses the line into medical practice. Other existing and accepted autologous transplants are not regulated.

Options 2-4

Options 2-4 do not take into account that this therapy will require non-homologous use and more than minimal manipulation (as the definition currently stands). Therefore option 5 becomes the only option. This level of regulation would not appear to be justified due to the low risk nature of the therapy under medical specialist control.

Risks

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

Benefits

TGA has more oversight in terms of reporting and product compliance (options 3 and 4).

Costs

Additional costs will be required to meet regulations and listing on a register as required.

Practitioners and businesses will lose all related business until they become regulated.

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?***

The real question here is not about homologous use or minimal manipulation, but rather one of safety – when safety should be assumed, and when safety should be regulated.

Homologous use, albeit still in the US/EU regulations is an out of date term. Its history was that homologous use and minimal manipulation would be seen as a proxy for safety. Herein, it would allow bone marrow transplants and bone/skin grafts.

If the definition remains the same, stem cell therapy will always be classed as non homologous and more than minimally manipulated. Consideration must be given to redefining the terms in light of current methods of stem cell processing and the both the extensive knowledge of practitioners and what is documented in the literature.

Option 5

Risks

Due to the minimal manipulation and homologous use requirement, most therapies will be unavailable in Australia until such time as practitioners can meet regulations. It is highly unlikely that any party will go to the time and expense of meeting these requirements.

This option would mean the largest time lag between regulation implementation and compliance.

High costs will be inhibitory to uptake and provision of services.

Slows progress and development in this area.

Is not inline with better and quicker access to innovative products and services raised by the recent TGA discussion paper on medicines and medical devices.

Benefits

Greatest level of oversight by the TGA.

Costs

Listing as a class 2, 3 or 4 biological.

Practitioners and businesses will lose all related business until they become regulated.

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

Consider not including minimal manipulation or homologous use to allow therapy to continue with some additional control and safety reporting requirements.

As mentioned above, these terms were put together when it was thought that there were some safety issues with mesenchymal stem cells (MSCs) and their main method of action was through differentiation. Today we know that the main method of action of MSCs is through their pararcrine effects, so the concept of minimal manipulation, and homologous use is out of date.

To change the law the "minister does not need to be **satisfied** that the goods do not harm the health, or are not likely to harm the health, of the public. Rather they need to **have regard to** the likelihood of harm to members of the public should the goods not be regulated under that risk might otherwise be mitigated". As mentioned previously, and in the discussion paper itself, there is an extremely low likelihood of harm to the public from the information that is currently available.

Allowing the therapy to continue has also spawned an industry in it's own right. Although there may be some teething issues as stakeholders become used to the idea of a regenerative medicine, and there may be some improvements from a regulatory sense, the latest projections indicate that the size of the regenerative medicine market will be ~$35billion by 2019[1].

Other countries are adjusting their regulations to be at the leading innovative edge of regenerative medicine. Japan seems to be leading the race with recent changes to their law allowing, allogeneic cell therapies with proven safety and "probable efficacy", onto the market

[1] http://finance.yahoo.com/news/regenerative-medicine-market-catapult-over-173000382.html

with reimbursement, while they continue to study efficacy. In the UK, the House of Lords, through their Science and Technology Committee (2013)[2] noted, "We make recommendations to the Government that, if acted upon, would facilitate the translation of scientific knowledge into clinical practice and encourage its commercial exploitation."

Australians by their nature are not likely to be silent on this. We have already seen the signs where patients do not believe that they are getting a fair go, and that they are being denied innovative treatment options. The July 2014 edition of the SBS program Insight on stem cell therapies had a number of very vocal patients who went offshore seeking cell-based treatments that were not allowed or available in Australia. This then spawned a number of other segments on the TV exposing the growing medical options overseas that are not available here.

Appendices

Appendix 1: Safety review of the literature for all autologous stem cell therapies in patients

Appendix 2: Latest Registry Report

Appendix 3: Efficacy review of the literature for all autologous stem cell therapies in patients

Appendix 4: References

[2] Science and Technology Committee. (2013). Regenerative medicine Report - House of Lords, 1–112. http://www.publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/23.pdf

Appendix 1

Safety Literature Review of Autologous Mesenchymal Stem Cells Used in Therapeutic Settings

GLOSSARY

ADMSC – adipose-derived mesenchymal stem cell

ALT- Alanine transaminase

BMMSC – Bone marrow mesenchymal stem cell

COMP - cartilage oligomeric matrix protein

CSA-1 – cross-sectional area

DMSO – Dimethyl sulfoxide

FPS – Fibre pattern score

GAG - glycosaminoglycan

GFP – green fluorescent protein

GvHD – Graft vs Host Disease

HGF – Hepatocyte growth factor

HSC – Haematopoietic stem cell transplant

OA - osteoarthritis

PGE2- prostaglandin E2

PRP – platelet rich plasma

PVF – peak vertical force

SDFT – superficial digital flexor tendon

T1D/T2D – type I/type II diabetes

TLS – Type lesion echo score

TNFα – Tumour necrosis factor α

VEGF – vascular endothelial growth factor

VI – vertical impulse

SAFETY

A total of 30 individual journal articles detailing safety data on the systemic or percutaneous administration of adipose or bone marrow derived autologous cells to 2149 patients were identified (See Table 1).

Systemic Route							
Cell type	**No. patients treated**	**Indication**	**No cells/infusion (upper and lower limit)**	**(Number) Event**	**Homologous?**	**Minimal manipulation?**	**References**
ADMSC autologous, expanded, fresh	12	Multiple sclerosis (administered with allogeneic MSCs) Autoimmune: hearing loss, multiple sclerosis, polymyotitis, atopic dermatitis, rheumatoid arthritis	2.5×10^7 7.5×10^7	No	No No	Unknown No	Riordan *et al.* 2009 Ra *et al.* 2011
BMMSC autologous, expanded, fresh	23	Toxicity test Diabetes	5×10^7	No	No No	No Unknown	Lazarus *et al.* 1995 Fotino *et al.* 2010
BMMSC autologous, non-expanded, fresh	123	GvHD HSC engraftment Ischemic heart disease	2×10^6	No	No No No	Unknown No Unknown	Dicke *et al.* 1975 Koc *et al.* 2000 Seth *et al.* 2010

Percutaneous Route							
Cell type	**No. patients treated**	**Indication**	**No cells/infusion (upper and lower limit)**	**(Number) Event**	**Homologous?**	**Minimal manipulation?**	**References**
ADMSC autologous, expanded, fresh	49	Chron's disease Calvarial defect Anterior mandibular defect	3×10^6 3×10^8	(2) pain at injection site, (1) Flu like symptoms and 1 headache (Lee *et al.* 2012a) – not classified as adverse event	No No No No No	No No No No No	Garcia-Olmo *et al.* 2005 Garcia-Olmo *et al.* 2009 Mesimaki *et al.* 2009 Lee *et al.* 2012a Sandor *et al.* 2013
ADMSC autologous, non-expanded, fresh	1137	Tracheomediastinal fistula Critical limb ischemia Knee osteoarthritis Calvarial defect Breast augmentation Parry Romberg Syndrome	5×10^6 10×10^7	(4) Cyst formation (2) and microcalcifications (2), but concluded as safe (Yoshimura *et al.* 2008a)	No No Yes Yes No No	Unknown No No No Yes No	Lendeckel *et al.* 2004 Alvarez *et al.* 2008 Yoshimura *et al.* 2008a Yoshimura *et al.* 2008b Buda *et al.* 2010 Koh *et al.* 2013
BMMSC, autologous and unspecified	568	Pseudoarthritis Bone cysts Femoral head necrosis Spinal fusion Bone defects		No	No	-	Jager *et al.* 2010 (review bone treatments 1991-2010)

Percutaneous Route							
Cell type	**No. patients treated**	**Indication**	**No cells/infusion (upper and lower limit)**	**(Number) Event**	**Homologous?**	**Minimal manipulation?**	**References**
BMMSC autologous, expanded, frozen	46	Meniscal regeneration Crohn's disease Cartilage repair	1×10^6 4×10^7 (1-10 ml)	(1) DMSO allergy (Duijvestein *et al.* 2010)	No, No No No	No, No No No	Centeno *et al.* 2008a,b Duijvestein *et al.* 2010 Nejadnk *et al.* 2010
BMMSC autologous	170	Bone reconstruction Repair knee cartilage Rectovaginal fistula (Crohn's disease) Refreactory fistulating Crohn's disease Knee osteoarthritis Liver cirrhosis Multiple sclerosis Carpalmetacarpal OA	1×10^5 2×10^7	No	No No No No No No No No No No No No	No No No No No No No No No No No No	Quarto *et al.* 2001 Wakitani *et al.* 2002 Garcia-Olmo *et al.* 2003 Bonab *et al.* 2007 Pai *et al.* 2008 Davatchi *et al.* 2011 Ciccocoippo *et al.* 2011 Wakitani *et al.* 2011 Emadedin *et al.* 2012 Lee *et al.* 2012b Centeno *et al.* 2013 Orozco *et al.* 2013
BMMSC autologous, non-expanded, fresh	21	Femoral head necrosis Hip pain Chronic liver failure Chondromalacia patellae	1×10^8 (2ml)	No	No No No	Yes No No	Gangji *et al.* 2004 Centeno *et al.* 2006 Khan *et al.* 2008

Percutaneous Route							
Cell type	**No. patients treated**	**Indication**	**No cells/infusion (upper and lower limit)**	**(Number) Event**	**Homologous?**	**Minimal manipulation?**	**References**
Total number of patients				2149			
Total number of studies				37			
Total number of events				12			
Total number of injected cell related safety events				3			
Total number of non-homologous and greater than minimal manipulation injected cell related events				3			

Table 1. Human patients treated with either bone marrow or adipose derived cells. Three (3) events, from a total of 2149, were recorded as being attributable to the injection of cells in non-homologous studies with greater than minimal cell manipulation.

Of the 37 studies recorded here, at least 73% were conducted using greater than minimally manipulated autologous stem cells for non-homologous purposes. Of the 2149 patients identified, a total of 12 events were recorded. Nine of these events were not considered safety issues by the authors. Three (3) events were recorded as related to the injection of MSCs – pain at the injection site and a DMSO allergy (Lee *et al.* 2012a; Duijvestein *et al.* 2010). Not one incidence of tumour formation associated with administration to these 2 149 patients has been reported to date.

Authors of one study suggest that systemic administration may be related to a suppression of the immune response making patients susceptible to relapse in pre-existing disease. However it is of note that more recent reviews state that substantial evidence now exists that preparations of allogeneic mesenchymal stem cells do not have adverse immune effects (see Hare et al., 2009; Kebriaei et al., 2009; Vangsness et al., 2014). Regardless, issues of systemic immune suppression appear more relevant to systemic administration of MSCs than intraarticular injection. Intraarticular injection is not associated with migration out of the joint and a systemic outcome (see Horie et al, 2009).

Conclusions on the Use of Autologous Stem Cells for the Treatment of Arthritis and Tendinopathies in Humans

The majority of studies involved greater than minimally manipulated cells for non-homologous purposes, which may be considered a greater safety hazard than minimally manipulated cells in homologous therapies. As safety concerns were associated with only 0.14% of patients, it may be concluded, based on the associated literature, that the administration of autologous cells in settings outside of the "minimal manipulation, homologous use" criteria appears to be safe in humans.

Attention, however, must be paid to the possibility of treatment related effects: pain, infection, headaches, joint flaring, stiffness and inflammation, and also the possibility of systemic immune suppression. All of these conditions appear to be manageable in the setting of percutaneous therapeutic administration.

Appendix 2

The HiQCell™ Joint Registry Interim Report

Tracking Safety and Effectiveness of an Autologous Non-Expanded Adipose-Derived Stem Cell Treatment for Osteoarthritis, Tendinopathy and Other Joint Conditions

Report based on data as at 31-Oct-2014

Principal investigator:

Professor Jegan Krishnan
International Musculoskeletal Research Institute
Chair, Orthopaedic Surgery Flinders Medical Centre, Flinders University Adelaide

Aim:

To determine the long-term safety outcomes and effectiveness of HiQCell treatment.

Introduction:

HiQCell uses autologous adipose-derived mesenchymal stem cells (MSCs) for treating osteoarthritis (OA) and tendinopathy. Adipose-derived MSCs from autologous liposuction have been transplanted for cosmetic and reconstructive purposes since the mid-1980s [1]. Many studies in the literature support the safety of MSC therapies [2,3], however, there is little information on long-term effectiveness of the treatment.

Prof. Krishnan and Regeneus have developed the HiQCell Joint Registry to evaluate real world clinical outcomes of safety and effectiveness of the HiQCell treatment. This is a long-term observational study that collects clinical data and self-reported measurements of pain and functional outcomes for up to five years post-treatment.

The Registry is approved by Bellberry Human Research Ethics Committee and is registered on the Australian and New Zealand Clinical Trials Registry. Regeneus-accredited Treating Medical Practitioners (TMPs) are co-investigators on the study and include sports physicians and orthopaedic surgeons (commencing treatments in May-2011 and May-2012 respectively) trained in the diagnosis and treatment of musculoskeletal conditions.

Study Design:

This is an observational registry with unlimited patient recruitment. Unlike a randomised, controlled clinical trial, there are no inclusion or exclusion criteria so all patients undergoing HiQCell treatment are eligible for inclusion, resulting in a heterogeneous population.

Method:

- Pre-treatment consultation by a TMP is required to assess a patient's suitability for HiQCell treatment.
- Patients provide signed informed consent to participate in the HiQCell Joint Registry.
- Patients may opt to cryopreserve cells for further injections at a later date.
- Patient demographics, diagnosis and individual joint assessment data are collected pre-treatment.
- Post-operative safety data on the liposuction site and HiQCell injection site is collected 2 weeks post-treatment.
- Self-administered patient questionnaires are completed pre-treatment then at 2 weeks, 6 months and annually post-treatment to assess pain, quality of life, sleep quality, medication use, and knee function, if applicable.
- Data was analysed by both random selection of a single treated joint per patient and also by all treated joints using a linear mixed model with unstructured covariance matrix allowing for missing data at any time-point. Where appropriate, independent samples t-tests were performed to investigate treatment outcomes over time.

Results and Discussion:

As at 31-Oct-2014, a total of 395 patients are included in the HiQCell Joint Registry, representing 73% of the total number of 543 patients treated with HiQCell. A total of 1226 joints received treatment and over 900 of these joints are being tracked in the Registry. Knees represent 63% of all treated joints (figure 1).

Since this is an ongoing study not all patients are eligible to complete all follow up visits at this time. Further, data at various time-points is missing due to patients either being uncontactable; living interstate or overseas or opting out of registry participation.

There was no significant difference between analyses of randomly selected joints and all treated joints. All data presented is for randomly selected joints since this ensures both joint and patient level independence.

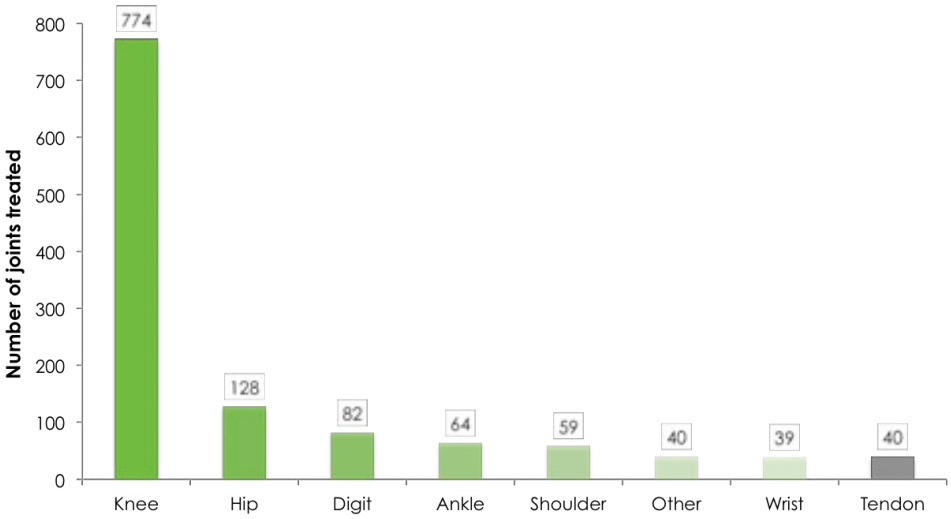

Figure1. Joints treated with HiQCell

HiQCell is safe

The 2-week post-operative safety assessment data shows that the HiQCell procedure is well tolerated by patients.

At the abdominal liposuction site, some bruising (102/191 patients, 53%), pain (103/192, 54%) or bleeding (32/193, 17%) was reported which can be expected following this type of surgical procedure.

At the HiQCell injection site some bruising (12/292 joints, 4%); pain (22/297, 7%); effusion (34/295, 12%) or tightness (24/296, 8%) was reported. These symptoms are largely consistent with joint injections and also common in OA.

From 543 patients treated with HiQCell there have been 18 adverse event reports (3.3% of all treated patients). Five (5) of these reports were serious adverse events (SAEs) (0.9% of all treated patients). Four (4) of the SAEs were considered probably related, and one possibly related, to the HiQCell procedure. Four (4) of the SAEs required hospitalisation and one was deemed medically important. All reported events completely resolved.

Significant reduction in pain

The average pain score for randomly selected treated joints significantly reduced at every post-treatment time-point: by 28% at 2 weeks; 49% at 6 months; 53% at 1 year and by 56% at 2 years post-treatment.

Analysis of mean pain change in patients who opted to have cells cryopreserved versus patients who chose to receive all their cells in one treatment indicate that there is no difference in treatment outcome between the two groups. Therefore, cryopreservation of cells may represent a viable long-term treatment option.

Responders are defined as patients who experience a 30% or greater reduction in pain score after treatment. The responder rate increased from 50% at 2 weeks to 73% at 6 months, 69% at 1 year and to 78% at 2 years post-treatment (figure 2).

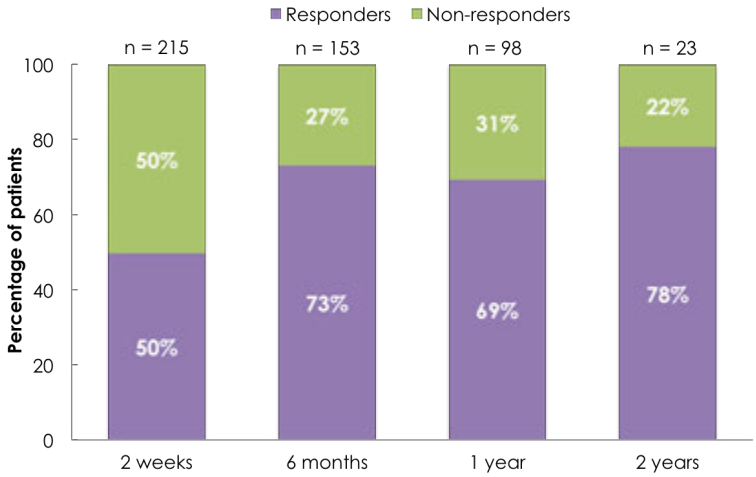

Figure 2. Responders to treatment
Responder >=30% pain reduction from pre-treatment

Responders experienced a 70% mean reduction in pain score at 2-weeks post-treatment; 71% at 6 months; 81% at 1 year and 83% at 2 years post-treatment (figure 3).

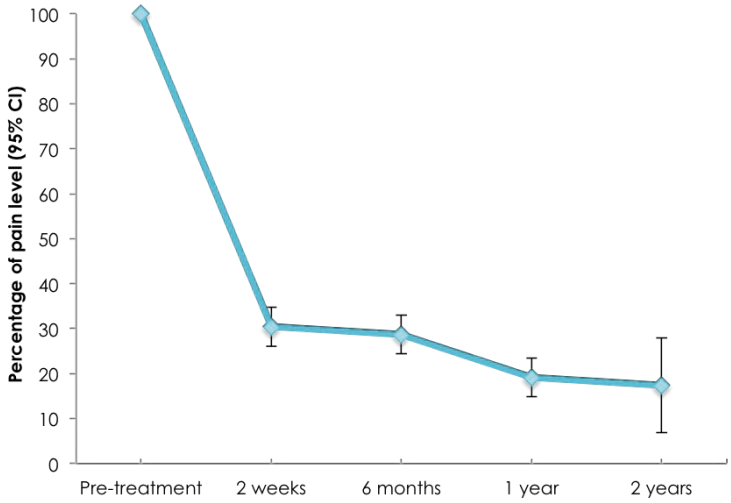

Figure 3. Percentage pain reduction for responders
Responder = 30% or more pain reduction from pre-treatment

All age groups and osteoarthritis grades showed reduced pain

Sub-group analyses were conducted to determine if gender, age or OA grade would be a predictor of HiQCell treatment clinical outcomes. All age groups (<40, 40-60 & >60), OA grades and both genders showed reduced pain from pre-treatment to all post-treatment time-points.

There was no difference in responder rate between genders or age groups, however, grades 3-4 OA had a greater proportion of responders than grades 1-2 indicating that HiQCell treatment may be most effective in the treatment of mid – late stage OA.

Significant improvement in knee function

Patients who received treatment to one or both knees completed the Knee Injury and Osteoarthritis Outcome Scale (KOOS) questionnaire comprised of five separate sub-scales: Symptoms, Pain, Activities of Daily Living (ADL), Sports and Recreational Activities (Sports/Rec) and Quality of Life (QOL). A score is obtained for each sub-scale and transformed to a 0 – 100 scale, with 0 representing extremely limited knee function and 100 representing no knee limitations.

Mean KOOS scores in all 5 sub-scales improved from pre-treatment to 6 months, 1 year and 2 years post-treatment. At 1 year post-treatment mean sub-scale scores showed significant increases with Sport/Rec and QOL scores improving by more than 20 points (figure 4).

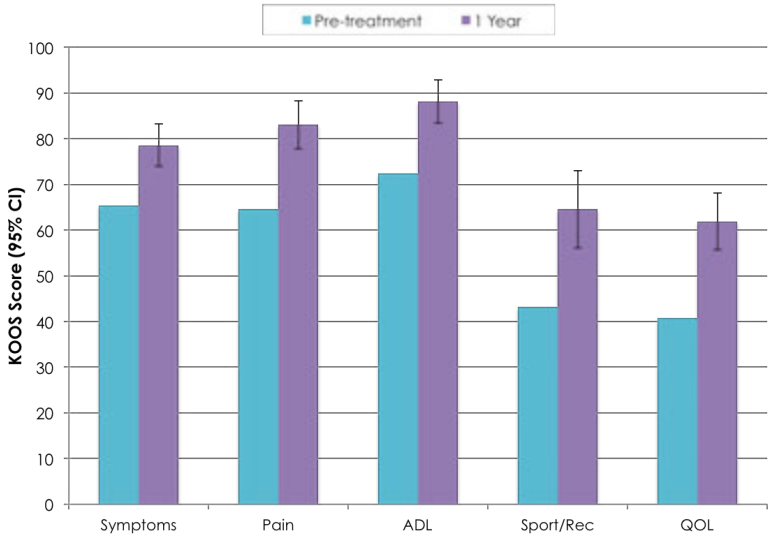

Figure 4. Mean KOOS scores pre-treatment and 1 year post-treatment
P <0.0001 for all sub-scores

Knee outcomes at 6 months and 1 year post-treatment are comparable to the KOOS scores published in studies of patients who have had a total knee replacement [4], or arthroscopy for OA with meniscal tears [5].

Sub group analyses by OA grade indicates that patients with grades 3-4 OA experienced significantly better KOOS sub-scale scores at 2-weeks and 1 year post-treatment than patients with grade 1-2 OA.

Improvement in sleep quality

At 2 weeks post-treatment 39% of patients reported improved sleep quality, increasing to 42% at 6 months and to 46% at 1 year post-treatment. All patients reported either the same or improved sleep quality at 1 year post-treatment (figure 5).

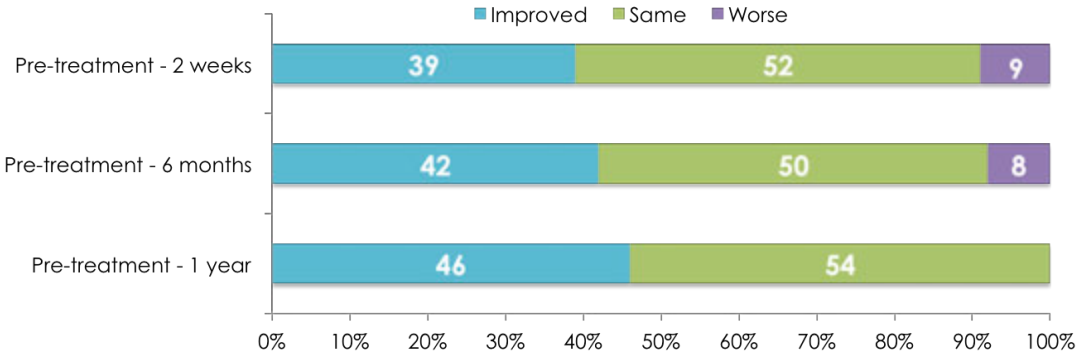

Figure 5. Sleep quality post-treatment

Significant reduction in level of medication use

Patients rated their medication level for joint pain as follows: none (no treatment), simple (e.g. Panadol), intermediate (e.g. Endone) or complex (e.g. Morphine).

Patients using no medication to treat their joint pain increased from 41% pre-treatment to 64% at 2 weeks, 65% at 6 months and 73% at 1 year post-treatment.

Improvement in quality of life

The AQoL-4D questionnaire consists of 12 questions in 4 quality of life dimensions: Independent Living, Mental Health, Relationships and Senses. A utility score between 0.00 (worst health) – 1.00 (full health) is generated from the responses provided. AQoL mean utility scores improved from 0.75 at pre-treatment to 0.81 at 6 months, 0.87 at 1 year and 0.82 at 2 years post-treatment.

Conclusion:

Regeneus is committed to being a leader in regenerative medicine. The HiQCell Joint Registry is the first of its

kind in the follow-up of long-term clinical outcomes of patients undergoing this type of treatment using adipose-derived cell therapy. The results show that HiQCell is safe and well tolerated. There was a significant reduction in pain, significant improvement in knee functional outcomes as well as better sleep quality, reduced medication usage and improved quality of life after HiQCell treatment, which was maintained to 2 years post-treatment.

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Appendix 3

Efficacy Literature Review of Autologous Mesenchymal Stem Cells Used in Therapeutic Settings

Of these studies reporting safety results, efficacy findings were also recorded for 13 different categories of disease (See Table 2).

Indication	Efficacy results	References
Bone injury	New bone formed in defects with treatment whilst controls were partially degraded, covered with fibrous tissue or significantly less regenerated. Successful ectopic bone formation in microvascular reconstruction surgery. Significant pain reduction. In one study, bone cysts showed either no difference in bone marrow cells vs steroids. However, another showed that steroid therapy had higher recurrence rates. Another showed slow regression of the cyst and progressive healing. One study showed no bone healing on treatment with MSCs/PRP (Jager *et al.* 2010)	Mesimaki *et al.* 2009 Sandor *et al.* 2013 Jager *et al.* 2010 (review bone treatments 1991-2010) Quarto *et al.* 2001 Gangji *et al.* 2004 Lendeckel *et al.* 2004
Osteoarthritis and other joint disease	Significant reduction in pain scores. Regeneration of subchondral bone and cartilaginous tissue. Proteoglycan-rich matrix, cells homogeneously distributed throughout tissue. Positive detection of type-II collagen. Improved arthroscopic scores. An increase in meniscal cartilage volume. Improvement in quality of life of patients post-cartilage repair. One study showed improvements in pain and walking ability up to 6 months, after which scores decreased (Emadedin *et al.* 2012). Significant improvement in physical knee and MRI scores.	Buda *et al.* 2010 Jiang *et al.* 2013 Centeno *et al.* 2008a,b Nejadnk *et al.* 2010 Wakitani *et al.* 2002 Wakitani *et al.* 2011 Emadedin *et al.* 2012 Lee *et al.* 2012b Centeno *et al.* 2013 Orozco *et al.* 2013 Centeno *et al.* 2006 Koh *et al.* 2013 Davatchi *et al.* 2011
Myocardial disease	Function and clinical scores significantly improved in treatment groups. Significant improvement of quality of life. Increased capillary density and ejection fraction.	Seth *et al.* 2010
Cancer	Clonogenic MSCs were detected in venous blood up to 1 hour after infusion in 13 of 21 patients (62%). Autologous MSC infusion at the time of PBPC transplantation is feasible and safe (Koc *et al.* 2000)	Koc *et al.* 2000
Multiple Sclerosis (MS)	Improvement in cognition, reduction in spasticity of extremities & no more seizures. Intact cranial nerve function, normal motor function, intact sensory & cerebellar functions and intact mental status. Improved memory, sexual function, energy levels. Lesions observed at 6 months similar to those prior to treatment. Production of new neurons and anti-inflammatory cytokines. Expanded Disability Status Scale increased in most patients (Bonab *et al.* 2007), whilst one improved and others remained the same. Majority of patients showed no difference by MRI.	Riordan *et al.* 2009 Ra *et al.* 2011 Bonab *et al.* 2007

Indication	Efficacy results	References
Various autoimmune diseases	Autoimmune inner ear disease (AIED): improved hearing, hair cell stabilization, reduced proliferation of antigen-specific Th1/Th17 cells and induced anti-inflammatory cytokine IL-10 in splenocytes, induction of antigen-specific CD4(+) CD25(+) Foxp3(+) regulatory T-cells with the capacity to suppress autoantigen-specific cytotoxic T-cell responses Polymyositis: Ability to walk up stairs and gentle slope holding handrail Atopic Dermatitis: SCORAD (scoring atopic dermatitis) decreased in all patients Rheumatoid Arthritis: Improved standing and walking ability, off steroids, decreased pain scores	Ra *et al.* 2011
Diabetes	T1D: Preservation of beta-cell function. Insulin independence achieved by 87% in one study (in one case up to 4 years). Another study showed no effect of treatment on C-peptide levels. T2D: Reductions in non-fasting & postprandial plasma glucose, HbA1c; increase in C-peptide levels; decrease in number & dose of oral hypoglycemic drugs/insulin. Insulin independence or reduced insulin requirements demonstrated in all subjects of one study.	Fotino *et al.* 2010
Crohn's Disease	>70% fistulas healed (Garcia-Olmo *et al.* 2003, 2005, 2009; Ciccocoippo *et al.* 2011) Quality of life scores improved, with recurrence rates low In one study, 30% patients required surgery due to disease worsening – others and 30% showed clinical response (Crohn's disease activity index decrease ≥ 70; Duijvestein *et al.* 2010) Increased mucosal & circulating regulatory T cells	Garcia-Olmo *et al.* 2005 Garcia-Olmo *et al.* 2009 Duijvestein *et al.* 2010 Garcia-Olmo *et al.* 2003 Ciccocoippo *et al.* 2011
Critical limb ischemia	One study showed clinical improvement in 66.7% patients, 5 patients requiring minor amputation at follow-up (all healed completely). Significant improvement in pain scores and claudication walking distance. A number of vascular collateral networks across arteries with digital subtraction angiography.	Lee *et al.* 2012a
Tracheomediastinal fistula	Re-epithelialisation & neovascularisation, leading to successful closure of the fistula	Alvarez *et al.* 2008
Liver disease	Improvements in serum albumin, bilirubin and ALT one month after infusion of cells into hepatic artery.	Khan *et al.* 2008
Facial lipoatrophy	Lipoinjection supplemented with ADSCs to adipose grafts showed better clinical improvement than lipoinjection alone (however not significantly)	Yoshimura *et al.* 2008b
Breast augmentation	ADSCs+lipoinjection resulted in final breast volume of 100-200ml from 270ml fat injected. Minimal atrophy with all patients satisfied with soft & natural-appearing augmentation – cysts or microcalcification detected in all patients.	Yoshimura *et al.* 2008a

Table 2. Human patients treated with either bone marrow or adipose derived autologous cells. Efficacy findings reported for 13 different types of disease, showing positive outcomes.

All studies (37 articles) reported either no change or significant improvement, using autologous stem cell therapies for a variety of musculoskeletal, autoimmune or other diseases. The administration of MSCs resulted in significant changes in patients, including healing of bone, tendon or cartilage injuries, reduction in pain and lameness, improved histological and clinical scores and improved quality of life. These findings suggest that greater than minimally manipulated autologous stem cells used for non-homologous therapies are not only safe, but highly beneficial in a wide variety of clinical settings.

Appendix 4

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