ROYAL AUSTRALASIAN
COLLEGE OF SURGEONS

Stem cell therapy in Surgery

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Contents

Abbreviations

ANZCTR	Australian New Zealand Clinical Trials Registry
ASC	Adipose-derived stem cells
BMSC	Bone marrow-derived stem cells
CHF	Congestive heart failure
CIDP	Chronic inflammatory demyelinating polyneuropathy
CIHR	Canadian Institutes of Health Research
DDD	Degenerative disc disease
ESC	Embryonic stem cells
EU	European Union
FDA	Food and Drug Administration, USA
HART	Human assisted reproductive technology
hESC	Human embryonic stem cells
HSC	Haematopoietic stem cells
IHD	Ischemic heart disease
iPSC	Induced pluripotent stem cells
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
MSC	Mesenchymal stem cells
NHMRC	National Health and Medical Research Council, Australia
NIH	National Institutes of Health, USA
NSW	New South Wales, Australia
PSC	Pluripotent stem cells
QLD	Queensland, Australia
RCT	Randomised controlled trial
TGA	Therapeutic Goods Administration, Australia

USA	United States of America
VIC	Victoria, Australia
WA	Western Australia

Executive summary

This review identifies the existing evidence for the current use of stem cells within surgical specialities, stem cell treatment centres in Australia and New Zealand, and the range of treatments they provide. Legislation governing stem cell treatments in Australia and other relevant overseas jurisdictions is also covered.

The scientific literature identified through PubMed and Embase searches and filtered to three categories based on maturity of evidence base for each stem cell treatment. The categories are:

- Category A – This reflects that multiple randomised controlled trials (RCTs) are available, and their outcomes suggest superior or non-inferior safety and efficacy of the stem cell treatment for a given disease or condition compared with standard treatment. Their safety and efficacy is likely assessed by systematic reviews.
- Category B – This reflects that comparative studies with inconclusive safety or efficacy outcomes of the stem cell treatment for a given disease or condition compared with standard treatment are available. Their safety or efficacy is currently unproven or uncertain.
- Category C – This reflects that no comparative evidence on safety and efficacy of the stem cell treatment compared with standard therapy is available. These treatments are still in the process of evaluation through early, animal or pre-clinical trials.

The secondary research questions were addressed by conducting targeted grey literature searches in Google and in websites of key regulatory bodies in Australia and other international jurisdictions.

Key findings:

- In total, this review identified 69 systematic reviews and 10 additional comparative studies regarding stem cell treatments in surgery, and stem cells were used in the management of over 100 diseases and medical conditions within surgical specialities.
- Overall, the use of stem cells for certain indications in Cardiothoracic Surgery (ischaemic heart disease (IHD) and congestive heart failure (CHF)) seems safe and effective.
- Although there are a number of studies published in other areas, particularly for Orthopaedic Surgery and Plastic and Reconstructive Surgery, there is no consistent, good quality evidence to show the clinical utility of stem cell treatment for any indications other than those cardiovascular indications.
- There are many elements of variability across published trials. The variable domains include:
  - Source of stem cells
  - Method of harvesting and potential adverse events at the donor site
  - Method of isolation at the clinic or laboratory
  - Methods of cell manipulation and expansion
  - Cryopreservation and cell storage
  - Cell density/dose used
  - Intended use or indication
  - Method of application, including use of matrix or other device.
- The lack of standardisation between published stem cell trials and other research studies in terms of isolation, manipulation and expansion protocols makes comparison between studies difficult.

- The review identified 34 ongoing local clinical trials in Australia and New Zealand across the range of surgical specialties (Table 16).
- A number of centres were identified which offer stem cell treatment in Australia (16 clinics) and New Zealand (seven clinics). The treatments are used across a range of indications across all surgical specialties. As for the published research, there is large variability in the methods used, and ambiguity as to the options, methods of delivery and therapies offered. None of the indications provided in the private clinics had proven evidence for safety and effectiveness.
- Regulatory issues for the oversight of stem cell treatments remain a problem both locally and internationally. Due to the complexity of the cells themselves and the variety of ways in which they can be used and manipulated, stem cells do not fit within current frameworks for biological products or medicines. As a result, this has led to unproven therapies being provided to patients, which could possibly lead to adverse events and death.
- It is uncertain whether the stem cell procedures are provided in appropriately accredited surgical facilities, and all cell manipulations are undertaken in accredited laboratories, where there are exacting quality control standards that are independently verified.
- An upcoming Therapeutic Goods Administration (TGA) review is highly anticipated and should provide much needed clarity around the use of stem cells in Australia. It is likely that significant cooperation between regulatory agencies, governments, researchers, practitioners and industry will be required to improve the oversight.
- In surgery, many questions remain regarding the use of stem cells. Although there is a great deal of potential, there are still uncertainties in terms of safety and effectiveness. Important questions include:
    - What is the best source of stem cells?
    - How should stem cells be manipulated and expanded?
    - For each indication, what is the appropriate density or dose of stem cells?
    - For each indication, what is the mechanism of action *in vivo* and how do stem cells impact local tissue and biological processes?
    - Are there negative consequences in the long-term?

Background

Stem cells are characterised by their ability to both differentiate and proliferate.[1] In theory, they are capable of developing into any cell type, and are essential in maintaining tissue and organ health. These characteristics make stem cells a potential treatment to assist organ and tissue repair after invasive procedures such as surgery.

Human stem cells are categorised in many ways. Based on their potency or ability to differentiate, stem cells are defined by two main groups, they are;

- Multipotent stem cells (also called adult tissue-specific or somatic stem cells; and,
- Pluripotent stem cells (PSC).

Multipotent stem cells are limited in their potential to differentiate and are restricted to one of the germ layers (endoderm, mesoderm, or ectoderm) or adult cell lineages such as skin, muscle, brain, heart, eye, lung, pancreas, liver, intestine and bone marrow.[2] In contrast, PSC have the potential to grow into any type of cell in the body. Examples of PSC are embryonic stem cells (ESC)[3]; however, their use in clinical and research settings is still the subject of significant and ongoing ethical debate.

Adult stem cells have been the cell of choice when developing stem cell treatments. Treatments have utilised two main tissue origins, these being the haematopoietic and mesenchyme tissues. Adult bone marrow, peripheral blood and umbilical cord blood are sources of haematopoietic stem cells (HSC). Bone marrow stroma, adipose tissue, umbilical cord blood and the placenta are sources of mesenchymal stem cell (MSC).[4] Irrespective of stem cell type or tissue origin, stem cell treatment is based either on recipient-derived cells (autologous) or from a separate donor (allogeneic).

For therapies based on HSC, the cells are either collected from the peripheral blood after mobilisation from the bone marrow using growth factors, or less commonly directly from the bone marrow.[5] In contrast, MSC-based treatment protocols rely on the isolation of stems cell in the laboratory following the harvesting of the source tissue. However, due to the low numbers of stem cells in adult tissues, there is usually a need to expand their numbers to achieve cell numbers suitable for therapeutic use.

Stem cells are a recognised therapy for a limited number of conditions. For example, bone marrow transplantation for treatment of blood, metabolic and autoimmune diseases, and for cancers have been used for decades.[6] However, the application of stem cell treatment is broadening despite many aspects of stem cell treatment remaining unclear. Uncertain components include the matching of cell source and type to specific diseases /conditions, the need to expand stem cells following harvesting and the impact of laboratory processing on stem cell function as well as the cell density required to affect tissue repair.

Despite uncertainties around stem cells, many surgical specialities are turning to stem cell treatments to improve therapeutic outcomes. This trend raises the question as to whether there is sufficient evidence to support their use.

Project scope and research questions

For this report, our objective was to map the current evidence for the use of stem cell treatment in surgery across nine surgical specialities. The report does not review the safety and effectiveness of stem cell treatments but seeks to identify volume and maturity of the available evidence for stem cell use in surgery. The review aims to identify stem cell treatment centres in Australia and New Zealand, and the range of treatments they provide. It will also cover the legislation governing stem cell treatments in Australia, New Zealand and other relevant overseas jurisdictions.

The research questions of this review are:

Primary question

1. Based on a systematic literature review of stem cell treatments, for which surgical services and indications is there clinical evidence on the effectiveness of these treatments?

Secondary questions

2. Based on targeted searches, which stem cell treatments are provided in Australia and New Zealand?
3. What is the legislation governing use of stem cell treatment in Australia, New Zealand and other relevant jurisdictions?

Methods

Literature searches were performed in Embase and PubMed databases to address the primary research question. MeSH terms and keywords were used for identifying relevant literature, listed in Table 4, Appendix A. The database searches were restricted to English language, human studies published over the last ten years. Google Scholar was searched to identify any supporting evidence. Using specifically designed search filters provided in Table 5, separate searches were undertaken for systematic reviews and meta-analyses, and for comparative studies. The search filters developed were composed using existing strategies from the Canadian Agency for Drugs and Technologies in Health and the Scottish Intercollegiate Guidelines Network.[168, 169]

To answer the secondary research questions, targeted grey literature searches were performed using the Google search engine. This included 22 websites of key regulatory bodies in Australia, New Zealand and other international jurisdictions. A list of domains searched is provided in Table 6, Appendix A. Websites of major Australian and New Zealand news agencies were searched to identify news articles related to local treatment centres and any reported safety concerns of their practice. The Australian New Zealand Clinical Trials Registry (ANZCTR) was searched to identify local ongoing clinical trials.

References were screened against the primary research question. The full-texts of all relevant articles were retrieved and reviewed. All key articles identified following full-text review are included in this report.

In addressing the primary research question, a staggered selection methodology was applied across both search strategies. First, systematic reviews that addressed stem cell use for a specific disease or condition were identified. Some reviews broadly assessed treatment options for a disease, where

stem cell treatment was also identified. These references and their conclusions have been summarised without reference to primary studies included in their evidence base and available in Appendix B. Following this search, the library containing RCTs and comparative studies was screened for studies that identified stem cell treatments and indications not previously identified in systematic reviews. Comparative studies that are not included in systematic reviews for a specific stem cell treatment were considered key studies and extracted in the relevant summary table (Table 7 to Table 15).

For the purpose of this review, the stem cell treatments are categorised into three groups; Category A, Category B and Category C, based on evidence available and stage of development of the stem cell treatment for a specific disease or condition.

Category A – This reflects that multiple RCTs are available, and their outcomes suggest superior or non-inferior safety and efficacy of the stem cell treatment for a given disease or condition compared with standard treatment. Their safety and efficacy is likely to be assessed by systematic reviews.

Category B – This reflects that comparative studies with inconclusive safety or efficacy outcomes of the stem cell treatment for a given disease or condition compared with standard treatment are available. Their safety or efficacy is currently unproven or uncertain.

Category C – This reflects that no comparative evidence on safety and efficacy of the stem cell treatment compared with standard therapy is available. These treatments are still in the process of evaluation through animal, pre-clinical or observational trials.

Results

Use of stem cells within surgical specialities

The results of the literature searches are shown in the PRISMA diagram in Figure 1, Appendix A. The complete evidence base for stem cell use in surgery consisted of 69 systematic reviews. These reviews were supplemented with 10 comparative studies of stem cell treatments not identified by the systematic reviews. Documented in Appendix B are the detailed evidence base summaries and the classification by category, for stem cell treatments pertaining to the nine surgical specialties. In addition, to the published evidence, 34 clinical trials that are ongoing and registered with ANZCTR were identified; they are listed in Table 16, Appendix C.

The identified evidence base illustrates the diversity of the proposed applications for stem cell treatments, with their use indicated in the management of over 100 diseases and medical conditions within surgical specialities. To describe the maturity of the evidence base within the nine surgical specialities the included studies were mapped against the three classifications as defined in the methods (Table 1).

Category A evidence was only available for Cardiothoracic Surgery. Seven of the 11 systematic reviews assessed 23 RCTs involving 1,255 participants who received stem cell treatments for conditions of IHD and CHF. These evidence syntheses provide a view of between trial consistency in outcomes, and indicate that for those indications the use of stem cells seems safe and effective.

In contrast, five surgical specialities had category B evidence as the highest evidence category, these included General Surgery, Neurosurgery, Orthopaedic Surgery, Urology and Vascular Surgery. With the exception of Vascular Surgery, the evidence on stem cell treatment was supplemented by individual reports of comparative studies. Based on the characteristic of category B the evidence is considered equivocal and the use of stem cell treatments unproven.

For the three remaining specialties (Otolaryngology Head and Neck Surgery, Paediatric Surgery and Plastic and Reconstructive Surgery), the evidence base was limited to category C. This indicates that there is little or no comparative evidence, and the use of stem cells is considered experimental.

Continuing research was identified in the ANZCTR for five of the surgical specialities these being Cardiothoracic Surgery, General Surgery, Neurosurgery, Orthopaedic Surgery and Urology. Close to 70 per cent of the ongoing clinical trials in the ANZCTR are assessing stem cell treatments for orthopaedics. This volume of research is reflected in the published evidence with Orthopaedic Surgery contributing 21 systematic reviews and two comparative studies. Collectively this indicates greater research interest in stem cell treatments by surgeons in this craft group. In contrast, it appears the speciality of Otolaryngology Head and Neck Surgery is least impacted by stem cell treatments and researched for its potential.

Table 1 Evidence for the use of stem cells within surgical specialities

Speciality	Availability of evidence			Ongoing clinical trials: ANZCTR[1]
	Category A	Category B	Category C	
Cardiothoracic Surgery	7 reviews	1 review[2]	3 reviews	1
General Surgery	-	3 reviews[3], 2 comparative studies	6 reviews[3], 1 comparative study	3
Neurosurgery	-	2 reviews, 1 comparative study	2 reviews	1
Orthopaedic Surgery	-	16 reviews, 2 comparative studies	5 reviews	15
Otolaryngology Head and Neck Surgery	-	-	2 reviews	-
Paediatric Surgery	-	-	5 reviews, 2 comparative studies	-
Plastic and Reconstructive Surgery	-	-	9 reviews, 1 comparative study	-
Urology	-	2 reviews, 1 comparative study	5 reviews	2
Vascular Surgery	-	2 reviews[2]	-	-

1 Australian New Zealand Clinical Trials Registry (www.anzctr.org.au, accessed 01/08/2016)

2 Systematic review identified stem cell treatments relevant to multiple specialities.

3 Systematic review identified stem cell treatments relevant to multiple evidence categories.

Category A: reflects that multiple RCTs are available, and their outcomes suggest superior or non-inferior safety and efficacy of the stem cell treatment for a given disease or condition compared with standard treatment. Their safety and efficacy is likely to be assessed by systematic reviews.

Category B reflects that comparative studies with inconclusive safety or efficacy outcomes of the stem cell treatment for a given disease or condition compared with standard treatment are available. Their safety or efficacy is currently unproven or uncertain.

Category C reflects that no comparative evidence on safety and efficacy of the stem cell treatment compared with standard therapy is available. These treatments are still in the process of evaluation through animal, pre-clinical or observational trials.

[1]Australian New Zealand Clinical Trials Registry (www.anzctr.org.au, accessed 01/08/2016)

There are many elements of variability and heterogeneity across published trials. The variable domains include:

- Source of stem cells
- Method of harvesting and potential adverse events at the donor site
- Method of isolation at the clinic or laboratory
- Methods of cell manipulation and expansion
- Cryopreservation and cell storage
- Cell density/dose used
- Intended use or indication
- Method of application, including use of matrix or other device

The lack of standardisation between published stem cell trials and research in terms of isolation, manipulation and expansion protocols makes comparison between studies difficult.

Stem cell treatments provided in Australia and New Zealand

For many years, patients who were interested in stem cell treatments travelled overseas in what is termed 'stem cell tourism' to receive their therapy.[87] However, in recent years there have been a growing number of health practitioners and clinics offering these treatments in Australia and New Zealand, with a recent suggestion that as many as 60 clinics in Australia are offering stem cell treatment for various diseases and conditions.[88] Some of these clinics and healthcare providers advertise their services online; however, most appear not to.

Based on targeted Google searches, a number of stem cell treatment clinics with online presence were identified. Searches of news agency websites identified news articles related to local treatment centres. A list of Australian treatment centres is provided in Table 2 and New Zealand centres provided in Table 3. These lists are not intended to be exhaustive. There is ambiguity on certain websites regarding the stem cell treatment options they provide, whether all the promoted treatment options are actually available to patients and if they are provided by the same clinic or by another provider.

A number of issues related to the stem cell treatments are noted:

- Stem cell treatments for degenerative bone diseases (e.g. osteoarthritis degenerative disc disease (DDD), tendinopathies), sports injuries (bone, joint, tendon and cartilage injuries) and chronic pain (joint or back pain) were commonly treated within Australian and New Zealand stem cell treatment centres. Cosmetic and anti-ageing procedures also involved stem cell treatments. In comparison, fewer centres offered stem cell treatments for Parkinson's disease, multiple sclerosis, autism, Alzheimer's disease, dementia or urological conditions (Table 2 and Table 3).
- Where reported, the most common source of stem cells was adipose-derived stem cells (ASC) harvested following abdominal liposuction. BMSC treatments are offered by some clinics for osteoarthritis and tendinopathies, although normally these conditions are treated using ASC by most centres.
- In general, treatment centres process stem cells within a few hours (same day processing). Two centres in Australia, one in Western Australia (WA) and the other in New South Wales (NSW), and one centre in New Zealand offer two schedules of cell processing; same day or five-week cell processing.[89-91]
- Macquarie Stem Cells Centre (NSW) provides the biggest variety of stem cell treatments in Australia.[92] One centre in New Zealand, Regenerative Medicine NZ Stem Cell Treatment Centre (Whangarei), promotes stem cell treatments for a broad range of autoimmune, urological and neurological conditions (Table 3).[93]
- Usually patients who seek stem cell treatment for a medical condition are not referred to that treatment by the specialist who treated their condition. Instead, patients are self-directed after reading an advertisement or article about the stem cell treatment.[94]
- Stem cell treatments are likely to be provided by medical practitioners who are not specialists of the disease they treat with stem cells. For example, in Australia, cosmetic surgeons treat degenerative bone diseases such as osteoarthritis with autologous stem cell injections.[94]

- Previous treatment recipient testimonials are used to support benefits of a treatment (anecdotal evidence) while no robust scientific evidence is provided to support safety or efficacy.[94] The Australian Health Practitioner Regulation Agency Code of Conduct for clinicians does not allow using patient's testimonials to promote treatments; however, some clinicians are breaching these guidelines.
- None of the treatments offered within Australian and New Zealand are associated with strong safety and effectiveness data based on evidence this report has identified.
- Some of these treatments are being offered as an experimental treatment, with the recipient patients not a part of a registered clinical trial.[94]
- The same treatment in terms of stem cell source, processing technique, duration and dose is offered for a variety of conditions with different pathogenesis and within varied body systems.[94, 95]
- These treatments are expensive, costing from $9,000 to $60,000 per treatment, and patients are often encouraged to consider multiple treatments. The cost is not reimbursed by Australian or New Zealand governments (e.g. MBS in Australia), or by private health insurance.[96]
- From the information provided, it is not clear where the stem cell treatment procedures are being undertaken. This may be in an accredited facility, or in an office-based environment which in certain instances is not regulated. In a similar manner, the location of cell processing is often not clear, but should always be undertaken in an appropriately accredited laboratory.[96]

Table 2 Examples of stem cell treatments provided in Australia

Disease or condition treated with stem cells	Clinic	Source of stem cell	Stem cell processing
Osteoarthritis	Macquarie Stem Cells (NSW)[92, 97, 98]	ASC	Same day
	Stem Cell Solutions (QLD)[99]	ASC, BMSC	Same day
	Sydney Stem Cell Centre (NSW)[90]	ASC	Same day
	Dr Robert Simons Spine & Joint Regenerative Medicine (WA)[89]	ASC	Two schedules; Same day, or first injection in approx. 5 weeks, follow-up injection in 3-6 months
	Melbourne Stem Cell Centre (VIC)[100]	NR	'Low dose'
	Brisbane Regeneration (QLD)[101]	NR	NR
	Nepean Specialist Sports Medicine (NSW)[102]	MSC	Same day
	Adult Stem Cell Foundation (NSW, VIC, QLD, SA, WA)[103]	NR	Same day
	Lakeside Sports Medicine Centre (VIC)[104]	NR	Same day
	Norwood Day Surgery (SA)[94, 105]	ASC	Same day
	ASC Treatment (QLD)[106]	MSC	Same day
Rheumatoid arthritis and scleroderma	Macquarie Stem Cells (NSW)[92]	ASC	Same day
	MasterDerm (QLD)[94, 107]	ASC	Same day
Pain, back pain and joint pain (chronic)	Metro Pain Group (VIC)[108]	MSC	NR
	Melbourne Stem Cell Centre (VIC)[100]	NR	'High dose'
	Brisbane Regeneration (QLD)[101]	NR	NR
	Nepean Specialist Sports Medicine (NSW)[102]	MSC	Same day
	Adult Stem Cell Foundation (NSW, QLD, SA,)[103]	NR	Same day
	Macquarie Stem Cells (NSW)[92]	ASC	Same day
	MasterDerm (QLD)[94, 107]	ASC	Same day
	ASC Treatment (QLD)[106]	MSC	Same day
Sport injuries	Orthocell Ltd (WA)[109]	NR	NR
	Dr Robert Simons Spine & Joint Regenerative Medicine (WA)[89]	ASC	Two schedules; Same day treatment, or First injection in approx. 5 weeks, follow-up injection in 3-6 months
	Nepean Specialist Sports Medicine (NSW)[102]	MSC	Same day
	Adult Stem Cell Foundation (VIC, WA)[103]	NR	Same day
	Lakeside Sports Medicine Centre (VIC)[104]	NR	Same day
	ASC Treatment (QLD)[106]	MSC	Same day
	ASCRO (QLD)[110]	NR	NR
Tendon injuries and tendinopathies	Sydney Stem Cell Centre (NSW)[90]	NR	First injection in approx. 5 weeks, follow-up injection in 3-6 months
	St Vincent SportsMed (NSW)[111]	NR	NR
	Orthocell Ltd (WA)[109]	ASC	Same day

Disease or condition treated with stem cells	Clinic	Source of stem cell	Stem cell processing
	Dr Robert Simons Spine & Joint Regenerative Medicine (WA)[89]	BMSC	NR
	Macquarie Stem Cells (NSW)[92]	ASC	Same day
	ASC Treatment (QLD)[106]	MSC	Same day
Cartilage injuries	Sydney Stem Cell Centre (NSW)[90]	Autologous Chondrocyte	Approx. 5 weeks
	Dr Robert Simons Spine & Joint Regenerative Medicine (WA)[89]	BMSC	NR
	Adult Stem Cell Foundation (VIC, WA)[103]	NR	Same day
	ASC Treatment (QLD)[106]	MSC	Same day
Multiple sclerosis	MasterDerm (QLD)[94, 107]	NR	NR
	ASCRO (QLD)[110]	NR	NR
Spinal cord injuries	ASCRO (QLD)[110]	NR	NR
Parkinson's disease	MasterDerm (QLD)[94, 107]	ASC	Same day
	ASCRO (QLD)	NR	NR
Cerebral palsy	ASCRO (QLD)	NR	NR
Hair loss	Adult Stem Cell Foundation (SA)[103]	NR	NR
	MasterDerm (QLD)[94, 107]	ASC	Same day
	ASCRO (QLD)[110]	NR	NR
Diabetes	Me Clinics (VIC, NSW)[112]	NR	NR
Migraines	Macquarie Stem Cells (NSW)[92]	ASC	Same day
Anti-ageing	MasterDerm (QLD)[107]	ASC	Same day
	ASC Treatment (QLD)[106]	MSC	Same day
Erectile dysfunction	MasterDerm (QLD)[94, 107]	ASC	Same day
	ASCRO (QLD)[110]	NR	NR
Autism[113]	Macquarie Stem Cells (NSW)[98]	NR	NR
	MasterDerm (QLD) [94]	NR	NR
Alzheimer's disease / dementia	MasterDerm (QLD)[94]	ASC	Same day
Deafness and hearing disorders	MasterDerm (QLD)[94]	NR	NR
Lymphoma, myeloma or leukaemia	Brisbane Clinic for Lymphoma, Myeloma and Leukaemia (QLD)[114]	BMSC	NR
Critical limb ischemia	ASCRO (QLD)[110]	NR	NR
Stroke	ASCRO (QLD)[110]	NR	NR
Diabetes	ASCRO (QLD)[110]	NR	NR

ASC=Adipose-derived stem cells; BMSC=Bone marrow-derived stem cells; NR=Not reported; NSW=New South Wales; MSC=Mesenchymal stem cells; QLD=Queensland; SA=South Australia; VIC=Victoria; WA=Western Australia.

Table 3 Examples of stem cell treatments provided in New Zealand

Disease or condition treated with stem cells	Clinic	Source of stem cell	Stem cell processing
Degenerative orthopaedic diseases	Regenerative Medicine NZ Stem Cell Treatment Centre (Whangarei)[93]	ASC	NR
Osteoarthritis	Stem Cell NZ (Wellington, Nelson)[115]	NR	NR
	Queenstown Regenerative Medicine (Queenstown)[91]	ASC	6 weeks
	New Zealand Stem Cell Clinic (Auckland, Christchurch)[116]	ASC	Same day
Pain, back pain and joint pain (chronic)	Stem Cell NZ (Wellington, Nelson)[115]	NR	NR
Sports injuries	Stem Cell NZ (Wellington, Nelson)[115]	NR	NR
	New Zealand Stem Cell Clinic (Auckland, Christchurch)[116]	ASC	Same day
Tendon injuries and tendinopathies	Stem Cell NZ (Wellington, Nelson)[115]	NR	NR
Spinocerebellar ataxia	NR (Christchurch and Auckland)[117]	ASC	NR
Cosmetic surgery / anti-aging	NR (Christchurch and Auckland)[117]	ASC	NR
	Dr Robert Beulink Medical Cosmetic & Vein Clinic (Christchurch)[118]	ASC	NR
	Skin & Vein Clinic (Whangarei)[119]	NR	NR
	Clinic42 (Auckland)[120]	NR	NR
Auto-immune diseases*	Regenerative Medicine NZ Stem Cell Treatment Centre (Whangarei)[93]	ASC	NR
	New Zealand Stem Cell Clinic (Auckland, Christchurch)[116]	ASC	Same day
Neurological conditions†	Regenerative Medicine NZ Stem Cell Treatment Centre (Whangarei)[93]	ASC	NR
Multiple sclerosis	New Zealand Stem Cell Clinic (Auckland, Christchurch)[116]	ASC	Same day
Autism	New Zealand Stem Cell Clinic (Auckland, Christchurch)[116]	ASC	Same day
Urology‡	Regenerative Medicine NZ Stem Cell Treatment Centre (Whangarei)[93]	ASC	NR
Diabetes mellitus	Regenerative Medicine NZ Stem Cell Treatment Centre (Whangarei)[93]	ASC	NR
	New Zealand Stem Cell Clinic (Auckland, Christchurch)[116]	ASC	Same day

ASC=Adipose-derived stem cells; NR=Not reported.
* Lichen sclerosis, COPD, cardiomyopathy, Crohn's disease, inclusion body myositis, rheumatoid arthritis, scleroderma, chronic inflammatory demyelinating polyneuropathy, sarcoidosis, polymyositis, Takayasu's arteritis, lichen planus.
†Amyotrophic lateral sclerosis, multiple sclerosis, peripheral neuropathy, Parkinsonism, "Potts disease" muscular dystrophy, stroke recovery and regeneration, cerebral palsy, early dementia and Alzheimer's disease.
‡ Interstitial cystitis, Peyronies disease, erectile dysfunction and male incontinence.

Legislation governing the use of stem cell treatments

Summary of the international regulatory environment for stem cells

Internationally, the regulation of stem cells is complex. Issues differ according to the source of the tissue (e.g. adult or embryo), manipulation of the cells *in vitro*, intended use and combination with other materials or health technologies.

ESC come from embryos that develop from eggs that have been fertilised *in vitro*; research with and use of human ESC (hESC) is more controversial than those involving adult stem cells.[121]

- Because of the complexity and diversity of stem cell products and treatments, they present complex regulatory challenges. It is likely that existing frameworks such as drug development models will need to be adapted to meet the unique challenges that stem cell treatments present.
- Regulation of stem cell treatments has been contentious in many jurisdictions, including in terms of delineating between the use of these cells as either tissue for transplant or products for cell therapy. However, most regulatory bodies uphold the position that stem cell treatments are medicinal products when they are subject to "more than minimal manipulation of any cell type destined for clinical application or where the intended use of the cells is different to their normal function in the body. Any use of such cell-based medicines is subject to authorisation and controls, including their manufacture."[122]
- Unclear regulatory requirements may present barriers to research, or in contrast opportunities to exploit unproven treatments for profit. Enforcement of regulation has proven to be challenging in many jurisdictions.
- It is clear that regulatory bodies are moving towards clearer and more explicit guidance around regulation of stem cell products.
- Well-defined compassionate use programmes as used for 'medical practice' or 'same surgical procedure' exemptions, allow patients access to treatments that are not yet licensed. There is often some ambiguity around the scope of the exemption that can allow exploitation by commercial operators.
- Legislation governing research on stem cells varies across jurisdictions.

Regulation of stem cell research and stem cell-based treatments within Australia, New Zealand, USA, Canada and the European Union (EU) is described below.

Australia

Within Australia, the TGA is responsible for the regulation of all medical products, including human cells and tissues, which includes certain stem cell treatments. The Australian Regulatory Guidelines for Biologicals outline the legal arrangements in Australia for the supply and use of human cell and tissue-based therapeutic goods.[123] Certain stem cell treatments which require processing, such as HSC transplant for disorders of the blood and immune system, fall under the oversight of, and are approved by, the TGA.[124] However, many autologous stem cell treatments are not regulated by the TGA. These treatments would be considered "medical practice" and are excluded from regulation under the Therapeutic Goods (Excluded Goods) Order No. 1 of 2011.[124] The definition of excluded treatments is "human cells that are collected, processed and returned to the same patient, in a single course of treatment while under the clinical care and supervision of a registered medical

practitioner." However, all other stem cell therapeutic products of human origin not covered by this exclusion would be regulated as biologicals by the TGA under the Australian Regulatory Guidelines for Biologicals.[187, 188]

The TGA notes that an increased number of autologous stem cell treatments are proliferating within Australia and that these products are of unproven safety and efficacy and are often provided to patients at a high cost. Given this situation the TGA is undertaking a review of current oversight, and is considering whether the current regulatory model needs to change.[125]

Research involving stem cells in Australia

Within Australia both public and private funding of stem cell research occurs;[126] however, the use of ESC in research was subject of a conscience vote in 2002 that led to some harmonisation of state and territory legislation regarding research on human embryos. Within Australia relevant legislation includes *the Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Bill 2006.* [127] This bill allows for research on excess *in vitro* fertilisation embryos and somatic cell nuclear transfer; however, it prohibits cloning for reproductive purposes. WA, however, still prohibits somatic cell nuclear transfer.[126, 128]

Various aspects of research involving stem cells are subject to Commonwealth, state and territory legislation, and guidelines and standards issued by the Australian Health Ethics Committee, which is a Principal Committee of the National Health and Medical Research Council (NHMRC). In particular the use of human stem cell lines in research must comply with relevant NHMRC guidelines and must be approved by a Human Research Ethics Committee acting in compliance with the National Statement.[131] Bodies such as the Advisory Committee on Biologicals and the Gene and Related Therapies Research Advisory Panel are available to provide expertise to local Human Research Ethics Committees in reviewing these proposals.[129, 130] Human embryos can only be used for research purposes in Australia if authorised by a licence issued by the NHMRC Embryo Research Licensing Committee.[131]

New Zealand

The New Zealand Government is currently working on a new and comprehensive regulatory regime to regulate therapeutic products in New Zealand, which will replace the Medicines Act 1981, and its Regulations. Medsafe (the New Zealand Medicines and Medical Devices Safety Authority) is the body responsible for regulation of medicines and medical devices in New Zealand. Certain stem cell products, including Prochymal,[132] have been approved in New Zealand by Medsafe. Prochymal is an allogeneic MSC treatment, manufactured by Osiris Therapeutics Inc, intended for the treatment of acute graft versus host disease in children who have failed all previous treatments following bone marrow transplantation. However, it is not clear how autologous stem cells are regulated in New Zealand. Clinics providing autologous stem cell treatments claim that these procedures fall under the category of physician's practice of medicine, under which the physician and patient are free to consider their chosen course of treatment.[133] This involves minimal manipulation of the patient's own cells.

Research involving stem cells in New Zealand

Two committees are particularly relevant to the conduct of research involving ESC: the Advisory Committee on Assisted Reproductive Technologies and the Ethics Committee on Assisted Reproductive Technology.[134, 135] These committees were established under the Human Assisted Reproductive Technology (HART) Act 2004. The Advisory Committee on Assisted Reproductive Procedures Technologies is tasked with providing information and advice to the Minister relating the use of gametes and human embryos in human reproductive research. The Ethics Committee on Assisted Reproductive Technology considers applications for research involving stem cells using the Guidelines for Research on Gametes and Non-viable Embryos, and the Guidelines for Using Cells from Established Human Embryonic Stem Cell Lines for Research.[135, 136] The HART Act provides that embryos of less than 14 days gestation may in principle be used in human reproductive research, subject to comprehensive ethical oversight and approval by the Minister of Health. Furthermore, it appears that research on embryos is only permissible on donated non-viable embryos.[135, 136]

It is not clear how national funding of stem cell research in New Zealand is regulated. A report from 2006 stated that "currently, no hESC research is being conducted in New Zealand."[134, 137] This may have changed substantially since then.

USA

The Food and Drug Administration (FDA) Center for Biologics Evaluation and Research regulates human cells, tissues, and cellular and tissue-based products intended for implantation, transplantation, infusion or transfer into a human recipient, including HSC. A number of separate FDA processes are relevant to stem cells. Under the authority of Section 361 of the Public Health Service Act, the FDA has established regulations for all human cells, tissues, and cellular and tissue-based products to prevent the transmission of communicable diseases. Also, Section 351 is relevant to Therapeutic Biological Products, which include products containing cells which, similarly to drugs, are used for the treatment, prevention or cure of disease in humans.[138]

The FDA has approved certain stem cell-based products for use. Currently this is limited to cord blood-derived hematopoietic progenitor cells (blood forming stem cells) for certain indications. However, the FDA's role and authority on restricting stem cell-based products in the USA has been contested because that cripples medical innovation.[139, 140] However, it is clear that stem cell treatments are being delivered by clinics across the USA without FDA approval.

A recently published article identified 351 businesses that use direct-to-consumer marketing of stem cell interventions in the USA. The article also identified 570 clinics that were offering these services. The authors state that many of the businesses "market autologous cell-based interventions, with an estimated one in five advertising allogeneic stem cell interventions sourced from amniotic material (17%), placental tissue (3.4%), and umbilical cords (0.6%). Some clinics market both autologous and allogeneic stem cells."[141]

The FDA has released new draft guidance on how to meet regulations that pertain to stem cells that, at the time of writing, is at the comment phase. The authority of the FDA has been supported by court decisions, as in the case of USA vs. Regenerative Sciences Inc. which upheld the position that a patient's stem cells for therapeutic use fall under the aegis of the FDA.[142] In 2012 and 2013 the FDA took action against a number of stem cell clinics and it continues to issue warning letters to clinics around the country asserting that marketed products fall under FDA regulations and advising that

providers must hold a valid biologic licence or be in receipt of an investigational new drug application.[143]

Research involving stem cells in the USA

The National Institute for Health directly funds stem cell research in the USA. In terms of the use of ESC, there are both social and ethical issues that affect the research agenda in the USA. Historically the USA has imposed restrictions on embryonic stem cell research; [121] however, in recent years this has been altered and federal funding of such research has been permitted. In terms of federal funding, the National Institute for Health sets out guidelines for determining under what circumstances research using hESCs could be eligible for such funding.[144] Embryonic stem cell research in the USA is also subject to state laws, and some states have passed legislation permitting research on hESCs whilst others have imposed restrictions on, or prohibit entirely, such research.

Canada

Health Canada's Biologics and Genetic Therapies Directorate is the relevant regulatory body for stem cells of all types in Canada; the Authority of Health Canada is derived from the Food and Drugs Act and pertinent regulations.[145] Health Canada, in 2012 issued marketing approval for Prochymal,[146] a MSC therapy, manufactured by Osiris Therapeutics Inc.. This approval is described as the first stem cell product approved by regulatory authorities in the world.[147]

Despite this, there remains concern that regulatory requirements around clinical trials and use of stem cell treatments in Canada are currently difficult to understand and interpret, and may inhibit developments in the field.[148] There have been reports of Canadian citizens accessing stem cell treatments from the USA based clinics because such treatments are unavailable within Canada; however, it should be noted that these treatments are not necessarily approved by the FDA either.

Research involving stem cells in Canada

The policy directing stem cell research in Canada is the "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans", compiled by Canada's three central science-funding agencies—the Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada.[149] The CIHR's Stem Cell Oversight Committee has produced research guidelines specifically for ESC: "Human Pluripotent Stem Cell Research: Guidelines for CIHR-Funded Research; the Guidelines",[150] which have been incorporated into the Tri-Council Policy Statement. The Guidelines apply both to the derivation of ESC from embryos, and to research carried out on established ESC lines.[145, 150] The Stem Cell Oversight Committee will consider research on ESC upon the proviso that:

- The embryos used must originally have been created for reproductive purposes
- The persons for whom the embryos were created must provide free and informed consent for the unrestricted research use of any embryos created, which are no longer required for reproductive purposes
- The ova, sperm, nor embryo must not have been obtained through commercial transactions.[151]

European Union

Within the EU stem cell treatments are regulated by the European Medicines Agency's Committee for Advanced Therapies (CAT).[122, 152] Legislation which facilitates this regulation was introduced by the European parliament in 2007; this legislation is the Advanced Therapy Medicinal Products Legislation.[153] The Committee for Advanced Therapies (EU) makes scientific recommendations regarding whether a medicine can be classed as an advanced therapy medicinal product and their recommendations facilitate the movement of such products within the EU.[152] In 2015, Holocar®, a product containing eye stem cells was the first advanced therapy medicinal product to be granted conditional marketing authorisation.[154]

However, as with other jurisdictions there have been instances of regulatory loopholes being used for commercial use of stem cell treatments, which have led to a number of adverse events and death.[155]

Research involving stem cells in the EU

Funding for research involving stem cells in the EU is provided for, although it was the subject of some controversy in the lead up to the decision about funding from 2014-2020. The European Commission has continued funding of stem cell research as part of Horizon 2020: The EU Framework Programme for Research and Innovation. EU funds can be used for research in member states which allow stem cell research; however, funds are not available for research that actively destroys embryos.[156, 157] Within the EU some countries have in place their own legislation regarding research on ESC, and several countries prohibit or severely restrict the use of ESC.

Within the United Kingdom embryonic stem cell research is actively undertaken, for example through the UK Stem Cell Foundation and through facilities such as the Cambridge University Stem Cell Institute, a strategic partnership between the Welcome Trust and the Medical Research Council.[158, 159] All research requires approval from an independent Research Ethics Committee. ECS research is allowed but requires a licence from the Human Fertilisation and Embryology Authority. The purposes for which research on human embryos is allowed is outlined in the Human Fertilisation and Embryology Act (1990) and the subsequent Human Fertilisation and Embryology (Research Purposes) Regulations 2001.[160]

Discussion

The objective of this report was to review the existing evidence relevant to stem cell treatment within surgical specialities. As such, the search strategy was not designed to capture evidence of stem cell use within other clinical specialities. However, based on search results which were not considered for this report, it is clear that stem cells are used across a range of other fields including oncology,[161, 162] autoimmunology,[27, 163] dentistry,[164] ophthalmology[165, 166] and sports medicine.[167] These treatments are beyond the scope of this report and have not been elaborated further.

This high-level review is therefore not an assessment of the safety and efficacy of stem cells in surgery, but should be considered an epidemiological investigation into studies published within this field. For an explicit review of the safety and effectiveness of the use of stem cell treatments for any defined surgical indication, separate individual systematic reviews would be required.

Due to the broadness of the primary research question this report has relied on high-level evidence; systematic reviews, meta-analyses and RCTs, to identify the available evidence for stem cell treatments. The search strategy excluded other types of studies and, as such, the treatments identified in this report are not expected to be an exhaustive list of stem cell treatments within surgery.

Due to pragmatic issues of summarising a large volume of evidence, the evidence-base was filtered to three categories. Because the individual studies were not analysed in terms of the quality of the study design, reporting, or the magnitude of effect of safety and effectiveness, these categories are used to suggest the overall maturity of the available evidence as primarily identified by existing systematic reviews. Further work would be needed to establish the safety and effectiveness of any individual intervention.

The literature results shows stem cells are used in the management of over 100 diseases and medical conditions within surgical specialities. Out of these, only intramyocardial transplantation of autologous BMSC for IHD and CHF appears to have supporting evidence from multiple RCTs and meta-analysis by quality systematic reviews including a Cochrane review. All other uses of stem cells are unproven.

The largest volume of evidence is for orthopaedic use; however, the evidence base for all orthopaedic indications remains unproven or investigational. Even across RCTs for orthopaedic indications, there is heterogeneity across the methods used. There is overlap of certain indications, particularly across the specialties of Orthopaedic Surgery, and Plastic and Reconstructive Surgery. Certain themes and novel uses of stem cells are relevant across specialties, particularly in the field of tissue and organ bioengineering, although uses currently are limited to laboratory trials.

Across the published evidence-base, there was large variability across a number of domains. Cell-based therapies vary depending on the origin of the stem cells, their manipulation and their intended use. In terms of the sources of stem cells, this report identified that (autologous) ASC and BMSC are commonly used for treatments. ASC is most commonly collected from liposuction from abdomen adipose tissue.[170] Bone marrow is harvested from the posterior iliac crest.[171] However, the stem cells density and dose for each treatment varies across the published trials so the ideal dose for each treatment is unknown.[94]

It is clear that many aspects of the stem cell treatments are yet to be determined. This leads to a wide diversity of potential therapies. In the identified studies, this variability was seen both across the surgical specialties, and within individual indications.

To add further complexity, the definition and categorisation of stem cells is still being defined. These can be based upon the source of the stem cell, or stem cell markers. There is no defined set of stem cell markers for MSC.[2]

The lack of standardisation between published stem cell trials and research in terms of isolation, manipulation and expansion protocols makes comparison between studies difficult. Further structured research into stem cells will be invaluable in confirming their role in future therapies. Institutions such as Stem Cells Australia will assist in this area. This is a multidisciplinary approach between a number of Australian universities in a seven year Australian Government Australian Research Council Special Research Initiative.[172] Further research should abide by the International Society for Stem Cell Research "Guidelines for the Clinical Translation of Stem Cells".[173]

Despite the limitations of current published research, many stem cell treatments are being made available to patients in Australia and New Zealand.

Sixteen Australian and seven New Zealand stem cell clinics were identified with an online presence, although it has been suggested as many as 60 clinics may be offering stem cell treatments within Australia.[88] Many other clinics and stem cell treatment providers seem not to be advertising their services online. Although Ireland, Singapore, Cayman Islands and Bahamas have more clinics per capita than Australia, Australia has a greater number of stem cell clinics per capita than the USA. As a result Australia is becoming a popular destination for foreigners as well as for locals who are interested in stem cell treatments.[174]

The content of the websites vary greatly from clinic to clinic. This includes both ambiguities regarding the specific services that are offered, and varied detail in terms of how each service is provided. Often different diseases are treated with the same type of stem cells and procedure; alternatively, similar conditions are treated with different sources of stem cells and methods. Many clinics encourage prospective patients to contact them directly to confirm which services are available.

Where reported and as with published research, there appears to be a large amount of variability in the methods used to provide the therapies. This is particularly the case for stem cell isolation and manipulation. In general, stem cells are processed at the clinic on the day of the treatment. Some clinics offer multi-day stem cell preparation including harvesting, isolation and expansion. Certain clinics offer both options for the same indication, with no explanation as to any patient benefit. Onsite processing carries risk of infection. As recommended by the National Stem Cell Foundation of Australia and Stem Cells Australia:

"Any manipulation of cells, even if they come from you, carries risk of infection and other complications. They should be prepared in an accredited laboratory, where there are exacting quality control standards independently verified, or using a device that has been approved by regulators such as the TGA (page 12)".[96]

Patients with severe diseases and conditions, especially when previous treatment options have provided little benefit, may consider unproven stem cell treatments. The NHMRC provides clear information to patients regarding stem cell treatments, which includes which stem cell treatments are proven and highlights information pertinent to participating in a clinical trial.[175] Ambiguity and misleading information regarding claims of efficacy provided by treatment centres make stem cell treatments a more attractive option for vulnerable patients. Often patients decide to proceed with these treatments without seeking clarification or a second opinion. Patient testimonials are used to support claims of benefit and to market services to potential customers.

The risks of stem cell therapy, and concerns regarding how well patients are informed prior to consent to stem cell therapy were recently shown in the findings of a NSW coroner. In July 2016, the NSW deputy coroner found that a 75-year-old woman died from uncontrolled blood loss following a liposuction procedure to source ASC. This intervention to treat Alzheimer's Disease was considered experimental. The coroner found that the cosmetic surgeon's performance was poor and resulted in the woman's death. In his report, the coroner commented that the treatment 'has some of the troubling hallmarks of "quack" medicine: desperate patients, pseudo-science and large amounts of money being charged for unproven therapies'. The coroner recommended that the TGA and the NSW Ministry of Health "consider how best to manage and regulate the provision of "experimental" or "innovative" medical or surgical procedures that have not yet been approved following clinical trials or other recognised peer-reviewed evaluation processes."[176, 177]

The proliferation of unproven stem cell treatments over recent years has placed a focus on regulatory agencies to provide clear direction. In terms of regulation, stem cells provide difficulties for all jurisdictions due to the novel manner of this therapy and the fact that stem cells do not fit into current frameworks used for either biological products or medicines. These problems have led to the exploitation of loopholes, and the provision of services without clear regulatory oversight or other guidance. Most countries have clear limits on the use of embryonic stem cells. In Australia, the use of a patient's own cells where these are not manipulated are not restricted. An existing review by the TGA is expected shortly, and will provide much anticipated clarity on existing practices.

With increasing co-operation between regulatory agencies, governments, researchers, practitioners and industry, improvements should be seen. However, this may take some time to come to fruition.

The position statements regarding stem cell treatments from various professional organisations such as the Association of Reproductive Health Professionals,[178] Australian Academy of Science,[179] Australian Rheumatology Association,[180] Australian College of Sports and Exercise Physicians,[181] Australia and New Zealand Spinal Cord Injury Network,[182] Motor Neurone Disease Australia,[183] Murdoch Children's Research Institute (for stem cell use in cerebral palsy),[184] Multiple Sclerosis Research Australia[185] and the Royal Australasian College of Physicians (for stem cell use in cerebral palsy)[186] were identified. In general, they raise concerns about patient safety, absence of unequivocal evidence regarding safety or efficacy of these treatments, and lack of knowledge in terms of many aspects of stem cells and their function.

This report identifies a number of concerns in the regulation of stem cell research and treatment practices in Australia. The following is recommended to protect patients from potential harm from receiving unproven stem cell treatments.

- The safety and efficacy of most stem cell treatments remains uncertain or unproven at the present time. Further research, specifically good quality RCTs are encouraged.
- When scientific evidence for safety and efficacy of stem treatment is lacking it is unethical for health professionals to market such treatments to patients. Such treatments should be disallowed.
- Evidence-based information detailing all the potential adverse events and regarding the effectiveness should be made available to patients and their families so they can make an informed decision. Such resources should be updated regularly based on changes to scientific knowledge, and be provided by the practicing clinician, specialty society, or by the government.
- Stem cell procedures should be in an appropriately accredited surgical facility, and all cell manipulations should be undertaken in an accredited laboratory, where there are exacting quality control standards which are independently verified.[96]
- There is no centralised system to report, record or monitor adverse events of stem cell treatments. A system of surveillance regulated by the Department of Health is encouraged.
- Clarity from relevant authorities on how to structure regulatory frameworks relating to stem cell research and therapy is essential. Due to the complex nature of stem cells and stem cell therapies, this may take a concerted effort and interaction between regulatory agencies, governments, research institutes and companies.
- Due to the wide variability in the methods of stem cell therapies, further research is essential to more clearly understand the characteristics and function of stem cells, including long-term effects of stem cell therapy.
- Increase NHMRC funding for stem cell research to maintain an equal share of private and state sponsored stem cell research.

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Appendix A Search strategies

Table 4 Search terms and strategy used for database searches (PubMed)

(stem cells [MeSH] OR mesenchymal stromal cells [MeSH] OR mesenchymal stem cell transplantation [MeSH] OR mesenchymal cell* OR stem cell*) AND (Specialties, Surgical [MeSH] OR surger* OR surgeon* OR neurosurg* OR orthopaedic* OR otolaryngology* OR reconstructi*)

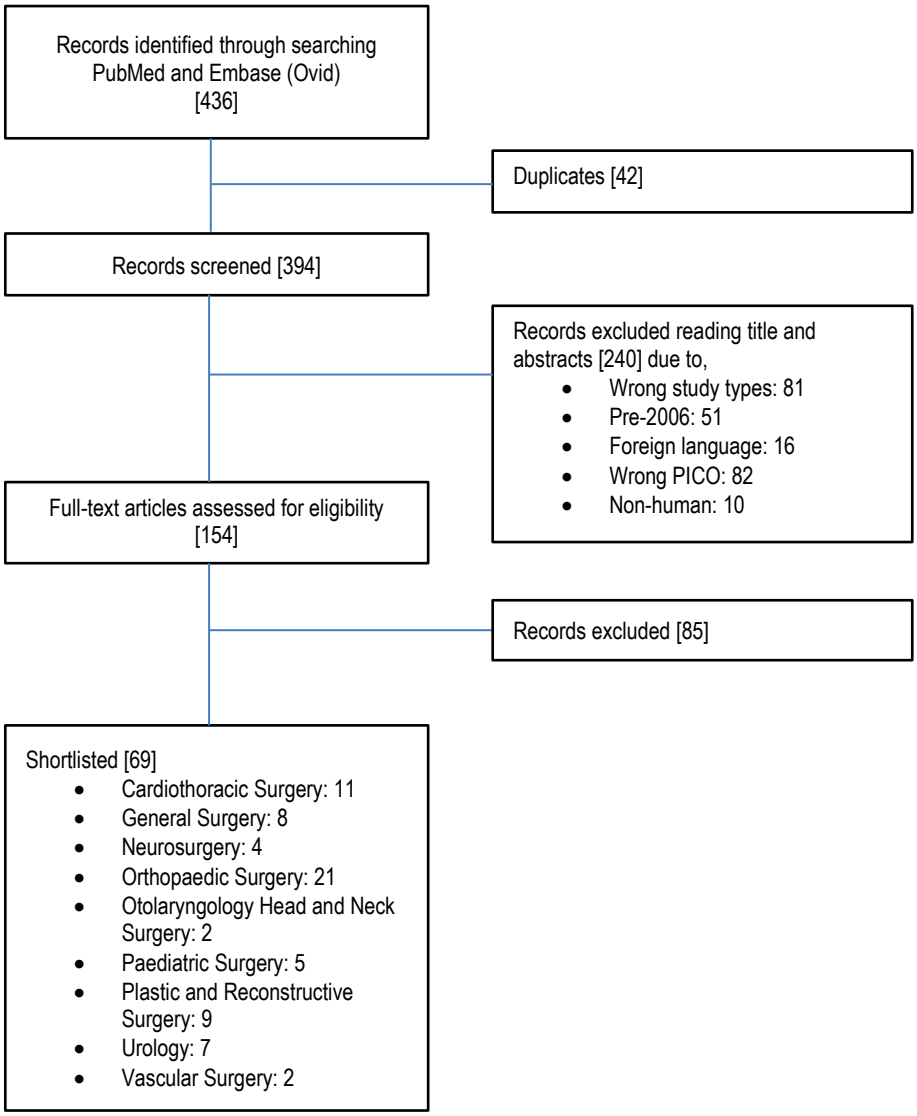
Limits: Searched within titles and abstracts, Human studies, English language, last ten years; Study types: systematic reviews, meta-analyses and comparative studies, including randomised controlled trials.

Table 5 Search filters to capture systematic reviews, meta-analyses and health technology assessments (PubMed)

systematic[sb] OR Review Literature as Topic [mh] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR technology assessment*[tiab] OR technology overview*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab]) AND comparison*[tiab]) OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Scopus[tiab] OR Embase[tiab] OR Cinahl[tiab] OR Medline[tiab] OR Pubmed[tiab] OR DARE[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[ta] OR "health technology assessment winchester, england"[ta] OR "Evid Rep Technol Assess (Full Rep)"[ta] OR "Evid Rep Technol Assess (Summ)"[ta] OR "Int J Technol Assess Health Care"[ta] OR "GMS Health Technol Assess"[ta] OR "Health Technol Assess (Rockv)"[ta] OR "Health Technol Assess Rep"[ta] OR jbi database system rev implement rep [ta]) NOT (comment OR letter OR editorial) NOT (animals[mh] NOT humans[mh])

Note: This is an updated CADTH database search filter.[168]

Figure 1 Search results summary of systematic reviews (PubMed and Embase)



Note: One systematic review (Slater et al. 2016) accounted for both Cardiothoracic Surgery and Vascular Surgery.

Table 6 Websites searched for grey literature

Regulatory body	URL
Association of Reproductive Health Professionals	http://www.arhp.org/
Australian Academy of Science	https://www.science.org.au/
Australian and New Zealand Spinal Cord Injury Network	http://www.spinalnetwork.org.au/
Australasian College of Sports and Exercise Physicians	https://www.acsep.org.au
Australian Rheumatology Association	http://www.rheumatology.org.au/
Australian Orthopaedic Association	https://www.aoa.org.au/
Australian Society of Otolaryngology Head and Neck Surgery	http://www.asohns.org.au/
Centre for Stem Cell Research	https://www.adelaide.edu.au/stemcell/
General Surgeons Australia	http://www.generalsurgeons.com.au/
Motor Neurone Disease Australia	https://www.mndaust.asn.au/
Multiple Sclerosis Research Australia	http://www.msra.org.au/
Murdoch Childrens Research Institute	https://www.mcri.edu.au/
New Zealand Society of Otolaryngology, Head and Neck Surgery	http://www.orl.org.nz/
New Zealand Association of General Surgeons	http://www.nzags.co.nz/
Neurological Society of Australasia	https://www.nsa.org.au/
New Zealand Association of Plastic Surgeons	http://www.plasticsurgery.org.nz
New Zealand Orthopaedic Association	http://www.nzoa.org.nz/
Royal Australasian College of Physicians	https://www.racp.edu.au/
Royal Australasian College of Surgeons	http://www.surgeons.org/
Stem Cells Australia	http://www.stemcellsaustralia.edu.au/
Therapeutic Goods Administration	https://www.tga.gov.au
Urological Society of Australia and New Zealand	http://www.usanz.org.au/

Appendix B Use of stem cell treatments within surgical specialities

Cardiothoracic Surgery

The search identified 11 systematic reviews assessing the safety and efficacy of stem cell treatments in cardiac diseases, lung diseases and injuries, and the potential role of stem cells in thoracic tissue- and organ-engineering.[7-17]

A summary of key studies relevant to Cardiothoracic Surgery is provided in Table 7. A separate study published by Slater et al. (2016) which assessed the potential of stem cells in the management of myocardial infarction and limb ischaemia is summarised under Vascular Surgery (Table 15).

Category A treatments

Seven systematic reviews including one Cochrane review evaluated the safety and efficacy of intramyocardial transplantation of autologous bone marrow-derived stem cells (BMSC) in the management of IHD and CHF.[7-10, 13, 15, 16] The reviews collectively included 23 RCTs involving 1,255 participants and found the treatment to be safe and effective. BMSC injection or transfusion into coronary vasculature during coronary artery bypass grafting improved cardiac functional parameters significantly with an increased left ventricular ejection fraction with a non-significant reduction in left ventricular end systolic volume. Abbasi et al. (2011) found stem cell treatment following myocardial infarction provides short-term benefits, although the long-term outcomes are uncertain.[7] The reviews did not provide details of the conditions, concentrations or processes used during autologous cell transplantation. There is a significant level of variability between each RCT in terms of how the cells were isolated, processed, and dosage of cells used for the treatment.[10]

Category B treatments

No studies were identified regarding an intervention, which could be placed in this category.

Category C treatments

Stem cell treatments for lung injury and acute respiratory distress syndrome are yet to undergo human trials. A systematic review on the use of endothelial progenitor cells to enhance angiogenesis and vascular repair in lung diseases identified the potential for the treatment based on animal and pre-clinical trials.[12]

To date, the only optimal therapeutic solution for end-stage organ failure is allogeneic organ transplantation. The shortage of donor organs and the need for immunosuppressive medication are major drawbacks in allogeneic transplantation, which could be resolved by bio-engineered tissues and organs using stem cells.[11] Rippel et al. (2012) conducted a systematic review on tissue-engineered heart valves created by MSC, fibroblasts, myofibroblasts and umbilical blood stem cells in an *in vitro* environment and identified the potential of the technology. However, the authors conclude that there is significant work required before conducting human trials.[14]

Ongoing local clinical trials

No local clinical trials were identified for Cardiothoracic Surgery. However, a multinational clinical trial evaluating the safety and efficacy of intracoronary selected CD 133+ BSC in cardiac recovery after acute myocardial infarction and left ventricular dysfunction was registered in ANZCTR (ID ACTRN12609001045202, CHUM, Quebec, Canada) and is currently recruiting participants (Table 16).

Table 7 Evidence profile of stem cell therapy usage in Cardiothoracic Surgery

Systematic review	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Management of IHD and heart failure				
Ali-Hassan-Sayegh et al. 2015	Intramyocardial transplantation of stem cells in CABG	Bone marrow	To enhance postoperative cardiac function	It improves cardiac functional parameters, significantly increasing LVEF with a non-significant reduction in LVESV. This therapeutic method has no life-threatening complications.
Qin et al. 2015	Transplantation of stem cell with CABG in the treatment of IHD	Bone marrow	To improve cardiac function	It provides a significant improvement in LVEF and the attenuation of left ventricular remodelling.
Fisher et al. 2014	Adult stem cells treatment in IHD and chronic heart failure	Bone marrow (autologous)	To improve cardiac function	There is moderate quality evidence that BMSC treatment improves LVEF. We found some evidence for a potential beneficial clinical effect in terms of mortality and performance status in the long term (after at least one year) in people who suffer from chronic IHD and heart failure, although the quality of evidence was low.
Tian et al. 2014	Intramyocardial transplantation of stem cells for IHD	Bone marrow (autologous)	To enhance cardiac function parameters, such as LVEF, LVESV and LVEDV	It contributes to improvement in left ventricular dysfunction and reduction in left ventricular volume.
Donndorf et al. 2011	Intramyocardial transplantation of stem cells in CABG	Bone marrow	To improve left ventricular function	It is associated with improvements of functional parameters in patients with chronic IHD. Procedure seems to be safe.
Abbasi et al. 2011	Intracoronary stem cell injection after myocardial infarction	Bone marrow	To improve cardiac function	It offered short-term benefits over the best medical treatment, but the long-term benefits are still a matter of debate.
Wen et al. 2011	Intracoronary stem cell therapy for IHD	Bone marrow (autologous)	To improve cardiac function	It associated with moderate but significant improvements over regular therapy in cardiac functional parameters.
Management of lung injury and acute respiratory distress syndrome				
Mao et al. 2013	Stem cells for treatment of acute lung injury and acute respiratory distress syndrome	Endothelial progenitor cells	To enhance angiogenesis of damaged vessels	It has a therapeutic potential for vascular regeneration and may emerge as novel strategy in managing acute lung injury and acute respiratory distress syndrome.
Tissue-engineered thoracic tissues and organs				
Rippel et al. 2012	Tissue-engineered heart valve	MSC, fibroblasts, myofibroblasts, and umbilical blood stem cells (*in Vitro*)	To avoid mechanic valves in heart valve replacement	Although there is still a long way to go, tissue-engineered heart valves have the capability to revolutionise cardiac surgery of the future.
Lim et al. 2013	Tissue-engineering of thoracic tissues and organs	Hematopoietic and MSC	Thoracic tissue and organs	Use of tissue-engineering technologies to develop tissues and organs for clinical transplant appears to be the next promising alternative. Biological scaffolds fulfil all essential requirements of an ideal matrix for cell seeding and subsequent in vivo application. However, major improvements are still needed.

ASC=Adipose-derived stem cells; CABG=Coronary artery bypass grafting; IHD=Ischemic heart disease; MSC=Mesenchymal stem cells; LVEDV=Left ventricular end-diastolic volume; LVEF=Left ventricular ejection fraction; LVESV=Left ventricular end-systolic volume.

General Surgery

Eight systematic reviews were identified on stem cell treatments for a range of diseases including hepatic diseases, lymphoedema, pre-anal fistula, pelvic organ prolapse, radiation proctitis and in the management of burn and postsurgical scars.[18-25] Three comparative trials reported on the potential of stem cells in the management of vitiligo, systemic sclerosis and Crohn's disease (Table 8).[26-28]

Category A treatments

None of the stem cell treatments used within the practice of General Surgery were supported by quality RCTs for their safety and efficacy.

Category B treatments

Hepatic administration of autologous HSC has shown feasibility and safety based on nine published trials reviewed by Stutchfield and colleagues (2010).[22] Stem cells were isolated from granulocyte-colony stimulating factor (G-CSF) mobilised peripheral blood or bone marrow from the iliac crest, and then injected to the portal vein or hepatic artery to enhance liver regeneration in chronic liver disease after portal vein embolism. The review identified the possibility of using induced pluripotent stem cells (iPSC), BMSC or adult stem cells in hepatocyte differentiation and enhancing functionality. The authors suggest further research specifically on the use of ESC for hepatic engraftment and hepatocyte differentiation. However, as noted in earlier sections of this report, there are regulatory and ethical challenges in conducting clinical trials using embryonic tissues (pp. 18-22).

A review on use of MSC including ASC for lymphoedema treatment identified a decrease in lymphoedema and an increased lymphangiogenesis when treated with stem cells.[23] An included clinical trial in this review, Maldonado et al. (2011), compared the efficacy of autologous stem cells in the treatment of lymphoedema secondary to mastectomy and axillary lymphadenectomy with traditional decongestive treatment with compression sleeves. Patients were treated with stem cells collected from GCSF-mobilised bone marrow isolated through centrifugation and delivered intra-muscularly.[29] The study concluded that stem cell injection could be an effective treatment potentially reducing arm volume and associated co-morbidities of pain and decreased sensitivity.

Although no systematic reviews were identified, two comparative studies assessed stem cell use for the treatment of Crohn's disease and vitiligo. Transplantation of cultured autologous melanocytes in the treatment of vitiligo seems promising.[28] In contrast, an RCT conducted across 11 European hospitals which compared HSC and conventional therapy for patients with refractory Crohn's disease not amenable to surgery did not support use of stem cell treatments in these patients.[26] More robust research is needed to conclude efficacy of stem cell treatments for these diseases.

Category C treatments

A systematic review identified the potential of intradermal injections of human MSC into skin in preventing scars from wounds and surgical incisions, based on animal trials.[21] Based on a phase II trial, autologous ASC (20 million cells) obtained from lipoaspiration together with fibrin glue seems a promising treatment option for inflamed perianal fistulas achieving fistula closure.[19, 20, 25] Pre-clinical evidence suggests that the use of autologous muscle-derived stem cells, fibroblasts, or MSC seeded

on biocompatible, degradable, and potentially growth-promoting scaffolds could be an alternative to surgical reconstruction of native tissue or the use of conventional implants in treating pelvic organ prolapse.[18] Also, based on animal studies, autologous MSC treatment has shown improvement in radiation induced fibrosis and inflammation; therefore, may have a role in the treatment of severe proctitis that is refractory to nonsurgical interventions.[24] HSC transplantation for systematic sclerosis has shown promising results based on *in vitro* trials.[27]

Human trials are necessary to assess the viability of these treatments.

Ongoing local clinical trials

Three clinical trials, two based at the St Vincent's Hospital (ACTRN12613000339752, ACTRN12611000826943) and one at the Westmead Hospital (ACTRN12612000800820), are registered on the ANZCTR assessing safety and efficacy of HSC transplantation in the management of autoimmune diseases including systematic sclerosis (Table 16).

Table 8 Evidence profile of stem cell therapy usage in General Surgery

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Systematic reviews				
Hepatic disease				
Stutchfield et al. 2010	NR	BMSC from iliac crest / MSC	To enhance hepatic regeneration in acute and chronic hepatic disease	Limited clinical evidence shows MSC isolation problematic potential for increased hepatic fibrosis.
	NR	Hematopoietic stem cell from mobilised peripheral blood or bone marrow from iliac crest	For matrix remodelling, vascular remodelling, immunomodulation, and facilitation of resident hepatocyte differentiation	Therapeutic potential demonstrated that further cautious clinical investigation required.
	NR	ESC (isolated from the inner cell mass of blastocyst stage of embryos), adult stem cells or progenitor with ESC	For hepatic engraftment and hepatocyte differentiation and function	Risk of malignancy with ESC. Clinical trials currently unrealistic.
Lymphoedema				
Toyserkani et al. 2015	NR	ASC	Treatment of lymphoedema	It has shown great potential. Present studies are, however, subject to bias and more preclinical studies and large-scale high quality clinical trials are needed.
Postsurgical scars				
Liu et al. 2011	Intradermal Injections of stem cells	MSC	To prevent or minimise the development of postsurgical scars	Although much remains to be understood about the exact effects of MSC, they appear to have significant potential in the enhancement of cutaneous healing.
Peri-anal fistulas				
Cadeddu et al. 2015	Injection of stem cells with fibrin glue	ASC	In the surgical management of peri-anal fistulas	A significant advantage in healing rate is shown, with no serious adverse effects. Although promising, these results need confirmation by a phase III clinical trial that aims to provide a definitive assessment of the efficacy of ASCs for complex perianal fistulas.
Gecse et al. 2014	Injection of stem cells with fibrin glue	ASC or BMSC (autologous)	For treatment of perianal fistulising Crohn's disease	Although these initial results on stem cell based therapy seem promising, results of further randomised, placebo controlled, ongoing trials on Crohn's fistulas are needed.
Gottgens et al. 2011	Injection of stem cells with or without fibrin glue	Stem cells (autologous)	Treatment of high cryptoglandular perianal fistulas	No significant differences were seen in recurrence rates between ASC injection into the fistula (n=64) group vs. ASC injection combined with Fibrin Glue injection (n=60).
Pelvic organ prolapse				
Boennelycke et al. 2013	NR	MSC and ASC (autologous)	Pelvic organ prolapse repair	Yet to be found and tested in preclinical studies.
Radiation proctitis				
Bansal et al. 2016	NR	MSC from bone marrow	For treatment of radiation proctitis	Yet to be found and tested in preclinical studies.

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Comparative studies				
Vitiligo				
Zhang et al. 2014	NR	Melanocytes (autologous)	For treatment of vitiligo	Cultured autologous melanocyte transplantation is an effective treatment for stable vitiligo.
Systemic sclerosis				
Tyndall and Furst 2007	NR	Peripheral blood-derived hematopoietic stem cell (autologous)	For treatment of scleroderma	Hematopoietic stem cell transplantation is currently being tested in prospective randomized controlled trials and appears to 'reset' autoimmunity in systemic sclerosis.
Crohn's disease				
Hawkey et al. 2015	NR	Hematopoietic stem cell	For treatment of refractory Crohn's disease	Findings do not support the widespread use of hematopoietic stem cell treatment for patients with refractory Crohn disease.

ASC=Adipose-derived stem cells; BMSC=Bone marrow-derived stem cells; ESC=Embryonic stem cells; MSC=Mesenchymal stem cells; NR=Not reported.

Neurosurgery

Four systematic reviews noted the use of stem cell treatments in cerebral palsy, facial nerve regeneration, spinal cord injury and neuromuscular disorders.[30-33] A comparative study assessed effectiveness of stem cells for traumatic brain injury (Table 9).[34]

Category A treatments

None of the stem cell treatments used within the practice of Neurosurgery were supported by quality RCTs for their safety and efficacy.

Category B treatments

A systematic review assessed the safety and efficacy of olfactory ensheathing, neural, neural progenitors, and allogeneic umbilical cord blood stem cells in the management of cerebral palsy reported a small statistically significant effect from stem cells on short term motor skills. The review also noted that umbilical cord stem cells are most effective comparably to other types of stem cells. The transplantation procedures varied across the five controlled trials ranging from central nervous system neurosurgical transplantation to intravenous infusion, which increased heterogeneity across the included five controlled trials.[31]

There is promising data for stem cell treatment for spinal and brain injury. A review on treatment options for spinal cord injury identifies the potential of bone marrow transplantation into the injured spinal cord within two weeks of injury in improving motor and sensory function. These patients also received intravenous injections of granulocyte-macrophage colony-stimulating factor with stem cell treatment. The review also identifies pre-clinical research on use of peripheral blood stem cells, human ESC and transplantation of human foetal spinal cord, transplantation of olfactory ensheathing glia and olfactory bulb, Schwann cell as treatment of spinal cord injury.[33] A comparative study which investigated the effects of umbilical cord MSC transplantation in patients with sequelae of traumatic brain injury noted improved neurological function and self-care in patients.[34]

Category C treatments

ESC, foetal stem cells and adult stem cells may have potential in facial nerve repair and regeneration based on eight animal trials. The review by Euler De Souza Lucena and colleagues did not identify any human trials in this area.[32] Similarly, autologous HSC treatment has shown some benefits in the management of chronic inflammatory demyelinating polyneuropathy, based on initial clinical trials.[30]

Further research, including sufficiently powered multi-centre RCTs are required to define the role of stem cell therapies used in Neurosurgery.

Ongoing local clinical trials

A single arm study is underway in the Royal Melbourne Hospital (Victoria (VIC)) to evaluate the safety of neural stem cells in treating patients with Parkinson's disease (NCT02452723) (Table 16).

Table 9 Evidence profile of stem cell therapy usage in Neurosurgery

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Systematic review				
Cerebral palsy				
Novak et al. 2016	NR	Olfactory ensheathing, neural, neural progenitors, and allogeneic umbilical cord blood stem cells	To improve motor and cognitive function of people with cerebral palsy	Stem cells are emerging as a scientifically plausible treatment and possible cure for cerebral palsy, but are not yet proven.
Facial nerve regeneration				
Euler et al. 2014	NR	Bone marrow MSC, ASC, dental pulp cells, and neural stem cells	For facial nerve regeneration	Stem cells derived from different sources presents promising results related to facial nerve regeneration and produces effective functional results (based on animal trials).
Spinal cord injury				
Tator 2006	Intraarterial injection of stem cells	Bone marrow transplants, PBSC and human ESC	For treatment of spinal cord injury	Poor quality human studies make scientific evaluation impossible. Only preclinical (animal) trials have been conducted.
Neuromuscular disorders				
Finsterer and Zarrouk-Mahjoub 2016	NR	Hematopoetic stem cells (autologous)	For treatment of muscle weakness in neuromuscular disorders, including CIDP	It has been shown to partially resolve gastrointestinal, muscular and cerebral manifestations of the neuromuscular diseases.
Comparative studies				
Brain injury				
Wang et al. 2013	NR	Umbilical cord mesenchymal stem cell	To improve neurological function in patients with sequelae of traumatic brain injury.	Further research, including a multi-centre and large sample size prospective randomised clinical trial, will be required to define definitively the role of umbilical cord mesenchymal stem cell transplantation on sequelae of traumatic brain injury.

ASC=Adipose-derived stem cells; CIDP=Chronic inflammatory demyelinating polyneuropathy; MSC=Mesenchymal stem cells; NR=Not reported; PBSC=Peripheral blood stem cells.

Orthopaedic Surgery

A larger pool of reviews, 21 of the 69 reviews, addressed stem cell treatments within the discipline of Orthopaedic Surgery. Degenerative orthopaedic pathologies, spinal injury, fusion surgery, shoulder and knee injury have had the focus of stem cell therapy. Mandibular distraction osteogenesis and fracture healing have also involved stem cells.[35-55] Two comparative studies have investigated the use of stem cells in the management of tibial shaft fractures and in tibial osteotomy.[56, 57]

Table 10 provides a summary of key studies. Some of the systematic reviews summarised under Plastic and Reconstructive Surgery may also be relevant for this section.

Category A treatments

None of the stem cell treatments used within the practice of Orthopaedic Surgery were supported by quality RCTs for their safety and efficacy.

Category B treatments

Five reviews assessed the safety and efficacy of stem cell treatments in the management of degenerative orthopaedic diseases; osteoarthritis, DDD and tendonopathies and in the management of osteonecrosis.[35, 36, 41, 46, 51] The reviews collectively included 11 RCTs which addressed the safety and efficacy of a degenerative pathology. Bone marrow-derived autologous MSC were used in the treatment. Bone marrow was collected by lumbar puncture and then stem cells were isolated by culturing them in *in vitro* environments 20-30 days prior to intra-articular injection at the diseased site.[46] However, some of the included studies harvested stem cells at the operating theatre on the same day before being injected. Due to heterogeneity and possible cofounds across treatment methods the reviews stress the need for further research to conclude treatment efficacy.

The effect of intra-articular injection of marrow-derived, synovium-derived, adipose-derived, and meniscus-derived MSC in meniscus repair were reported in four reviews. The reviews collectively identified three comparative studies including one RCT of 55 patients, who each received 50 million allogeneic MSC, with promising results.[42, 44, 50, 53] Bone marrow-derived MSC are also used for stimulating cartilage regeneration in the management of cartilage defects. Six reviews were identified, of which the latest included nine comparative studies, consisting of three randomised trials in their evidence base.[52] Cultured bone marrow-derived MSC in conjunction with microfracture and medial opening-wedge high tibial osteotomy and local application of recombinant human fibroblast growth factor 2 for tibial shaft fractures appear to be effective based on the two additional RCTs our search identified.[56, 57] However, the review concluded that more robust RCTs are required to draw conclusions about these treatments.

MSC and growth factors for non-unions or delayed fracture healing seems effective based on 11 non-randomised clinical trials, a review reported.[55] More research is indicated as this treatment is still in the early stages of development.

Category C treatments

Research on stem cell therapy for anterior cruciate ligament reconstruction, rotator cuff repair in the management of shoulder disorders, in spinal fusion surgery and mandibular distraction osteogenesis are yet to undergo clinical trials.[37, 38, 40, 43, 48]

Ongoing local clinical trials

Fifteen local clinical trials about stem cell treatments were identified in the area of degenerative bone diseases and tendinopathy (Table 16). Five trials are ongoing at the Melbourne Stem Cell Centre (VIC), two at the Global Orthopaedic Technology Pty Ltd (New South Wales (NSW)), and one each at the Wakefield orthopaedic clinic (South Australia), The Australian Catholic University and University of Melbourne (VIC), Sir Charles Gairdner Hospital (Western Australia (WA)), Royal North Shore Hospital (NSW), Regeneus Ltd (NSW), Stryker Australia (NSW), MMRI (Queensland (QLD)) and at the Melbourne Shoulder and Elbow Centre (VIC).

Table 10 Evidence profile of stem cell therapy usage in Orthopaedic Surgery

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Systematic review				
Fracture healing				
Sinclair et al. 2016	Stem cells with and growth factors	MSC	To promote healing in non-unions and delayed fracture	It shows promising results, as there are synergistic effects observed when combined together with growth factors. However, more research is indicated as these methods are still in the early stages of development.
Degenerative orthopaedic pathologies (e.g. osteoarthritis, DDD, tendinopathies)				
Atesok et al. 2015	Intraarticular injection of autologous or allogenic stem cells	MSC	To treat degenerative orthopaedic pathologies such as osteoarthritis, DDD, and tendinopathies, in elderly	Use of stem cells in elderly patients are still under development, and high-level RCTs with long-term outcomes are lacking.
Oehme et al. 2015	Transplantation of MSC and intervertebral disc chondrocytes	MSC	For treatment of lumbar DDD	It is likely that stem cell therapies will become a treatment option for some patients with disc disease in the near future. Percutaneous stem cell mediated disc regeneration may bridge the gap between the two current alternatives for patients with low back pain, inadequate pain management and invasive surgery.
Li et al. 2014	NR	Bone marrow-derived MSC	For treatment of osteonecrosis of the femoral head	It may provide a better therapeutic effect than core decompression.
Ahmad et al. 2012	NR	MSC	Tendon repair and regeneration	The current evidence shows that stem cells can have a positive effect on tendon healing. This is most likely because stem cells have regeneration potential, producing tissue that is similar to the preinjury state, but the results can be variable. Initial clinical trials are promising.
Andres et al. 2008	Stem cells with growth factors	MSC	For treatment of tendinopathy	Preliminary work is promising, but further study is required in these fields.
Spinal fusion surgery				
Skovrlj et al. 2014	Application of allogenic bone grafts containing live stem cells (cellular bone matrices)	MSC	For spinal fusion surgery	Although it appears to be safe for use as bone graft substitutes, their efficacy in spinal fusion surgery remains highly inconclusive. Large, nonindustrial sponsored studies evaluating the efficacy are required.
Management of cartilage defects				
Xu et al. 2015	NR	MSC	For cartilage regeneration in the management of cartilage defects	There were no significant differences after stem cell treatment compared with other treatments. However, assessment of clinical symptoms and cartilage morphology showed significant improvement after stem cell treatment.

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Counsel et al. 2015	NR	MSC	To promote regeneration of hyaline cartilage in the treatment of joint disorders.	Stem cell-based therapies appear safe and effective for joint disorders in large animal preclinical models. Evidence for use in humans, particularly, comparison with more established treatments such as autologous chondrocyte implantation and microfracture, is limited.
Gopal et al. 2014	NR	Bone marrow-derived MSC	For treatment of cartilage defects	Published studies do suggest that stem cells could provide superior cartilage repair. However, due to limited number of reports, more robust studies might be required before a definitive conclusion can be drawn.
Peeters et al. 2013	Application of cultured stem cells	Bone marrow-derived MSC (autologous)	To heal cartilage or joint pathology	It appears to be safe. We believe that with continuous caution for potential side effects, it is reasonable to continue with the development of articular stem cell therapies.
Perera et al. 2012	NR	MSC	To treat articular cartilage defects in the knee	This treatment is promising. Unfortunately, there is a lack of studies investigating the use of MSC in this area.
Nakamura et al. 2009	NR	MSC	To treat articular cartilage defects of the knee	Future RCTs will be required to evaluate the significance of stem cell therapies targeting chondral lesions.
Rotator Cuff Repair				
Beitzel et al. 2013	NR	MSC	To improve healing at the repair site after rotator cuff repair (shoulder disorders)	The current literature regarding therapeutic use of stem cells in shoulder surgery is limited. Although in vivo animal studies have shown some promising approaches to enhance tendon-to-bone healing, the use of MSC for shoulder surgery should still be regarded as an experimental technique.
Maffulli et al. 2012	NR	MSC	In rotator cuff repair	No level I or II studies were found on the use of scaffolds and stem cells for rotator cuff repair.
Knee injury repair and reconstruction				
Yu et al. 2015	NR	MSC (marrow-derived, synovium-derived, adipose-derived, and meniscus-derived)	For meniscus repair	MSC possess an intrinsic therapeutic potential that can directly and indirectly contribute to meniscus healing. Unfortunately, current research has only superficially examined this and extensive work is required to identify the best MSC source and optimise the application of these cells.
Moran et al. 2015	Intra-articular injection of stem cells	MSC	To enhance outcomes of meniscus repair and replacement	There appears to be significant potential for biological augmentation and tissue-engineering strategies. However, there are still relatively few clinical studies being reported in this regard.
Fu et al. 2014	NR	MSC	To improve healing in anterior cruciate ligament	Only animal studies identified.

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
			reconstruction	
Liu et al. 2013	NR	MSC	For meniscus reconstruction	No clinical studies identified or included for the review.
Dave et al. 2012	NR	MSC	For articular cartilage repair, anterior cruciate ligament reconstruction or repair, augmenting meniscus repair	MSC use to promote healing following knee injury is likely to increase. There are scientific methodological concerns and ethical and legal issues regarding MSC use for treating knee injuries.
Mandibular distraction osteogenesis				
Hong et al. 2013	NR	MSC	To enhance bone consolidation in mandibular distraction osteogenesis	No clinical studies identified or included for the review.
Comparative studies				
Tibial shaft fractures				
Kawaguchi et al. 2010	NR	Human fibroblast growth factor 2	To accelerate bone union in patients with surgical osteotomy	A local application of the rhFGF-2 hydrogel accelerated healing of tibial shaft fractures with a safety profile
Tibial osteotomy				
Wong et al. 2013	Intra-articular injection of cultured stem cells with hyaluronic acid	Bone marrow-derived MSC (autologous)	For the treatment of cartilage defects which undergo high tibial osteotomy	The treatment is effective in improving clinical outcomes in patients undergoing high tibial osteotomy and microfracture for varus knees with cartilage defects.

DDD=Degenerative disc disease; MSC=Mesenchymal stem cells; NR=Not reported; RCT=Randomised controlled trials.

Otolaryngology Head and Neck Surgery

The search identified two reviews relevant to Otolaryngology Head and Neck Surgery (Table 11).[58, 59] No additional RCTs or comparative trials were identified.

Category A or B treatments

None of the stem cell treatments used within the practice of Otolaryngology Head and Neck Surgery were supported by RCTs for their safety and efficacy.

Category C treatments

A broad review of treatment options in otorhinolaryngology identified the potential use of stem cells to regenerate irreversible hearing loss in sensorineural disease.[59] Differentiation of endogenous stem cells into new cochlear hair cells, and introduction of exogenous cells into the inner ear to replace injured hair cells or neurons are currently being researched. ESC, iPSC, MSC from the bone marrow or adipose tissue, and amniotic fluid-derived stem cells are being used in animal and *in vitro* trials.

Reviews also noted the potential of stem cells in *in vitro* tissue-engineering. Trachea and laryngeal tissue were engineered using stem cells. Direct stem cell therapy to the larynx may enhance healing of the damaged tissue. [58, 59] Regeneration of tissue-engineered tracheal airway mucosa was trialled in one human study with 15 months follow-up, which showed complete epithelialisation on endoscopy.[60]

Ongoing local clinical trials

No ongoing trials were registered in the ANZCTR relevant to Otolaryngology Head and Neck Surgery. A supplementary search in Clinicaltrials.Gov did not identify ongoing trials relevant to stem cell treatment in Otolaryngology Head and Neck Surgery either.

Table 11 Evidence profile of stem cell therapy usage in Otolaryngology Head and Neck Surgery

Systematic review	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Hamilton et al. 2014	Tissue-engineering of airway mucosa	MSC and epithelial cells (autologous)	For airway regeneration during tracheal regeneration surgery	Complete epithelialisation on endoscopy (15 months), ciliated epithelia on cytology, normal perfusion scan was noted. Based on one human study only.*
Wormald et al. 2015	Regenerative surgery	ASC, ESC, iPSC, bone marrow-derived MSC, amniotic fluid-derived stem cells	To regenerate irreversible hearing loss in sensorineural disease	Results are based on animals and *in vitro* studies.

ASC=Adipose-derived stem cell; ESC=Embryonic stem cells; MSC=Mesenchymal stem cells; iPSC=induced pluripotent stem cells.
* Elliott MJ, De Coppi P, Speggiorin S, et al. Stem-cell-based, tissue-engineered tracheal replacement in a child: a 2-year follow-up study. Lancet 2012;15:380:994–1000.

Paediatric Surgery

Five systematic reviews noted the use of stem cells in the management of congenital anomalies, sickle cell disease and childhood medulloblastoma.[61-65] Two comparative studies reported their use in other areas within Paediatric Surgery (Table 12).[66, 67]

Category A or B treatments

None of the stem cell treatments used within the practice of Paediatric Surgery was supported by quality RCTs for their safety and efficacy.

Category C treatments

A Cochrane review by Oringanje and colleagues (2009) on safety and efficacy of HSC transplantation for children with sickle cell disease did not identify any RCTs but only observational studies with promising results.[63] Weih et al (2012) noted patients achieving complete remission after stem cell transplantation for inflammatory bowel disease and congenital malignancies.[65] Use of high-dose chemotherapy followed by stem cell transplantation in the management of childhood medulloblastoma have provided long-term survival in some patients, based on initial human studies based on another review.[61]

Two comparative studies noted stem cell use in management of congenital diseases and anomalies, and in autism spectrum disorders. Autistic children who received intrathecal transplantation of stem cells showed improvements of symptoms. However, neither study reported the exact source of the transplanted stem cells.[66, 67]

Stem cells may have a role in tissue-engineering proposed in the management of congenital paediatric diseases and anomalies. The use of MSC and ESC in engineering palates for cleft palate repair has undergone pre-clinical experiments.[64] MSC via tissue-engineering or direct transplantation to intestine would potentially improve the enteric function and intestinal restitution in patients with intestinal loss due to short bowel syndrome.

Significant histological and clinical improvements have also been reported in patients with coeliac disease after stem cell transplantation.[65] Tissue-engineered foetal airway reconstruction using human amniotic stem cells for laryngotracheal agenesis also seems viable but is currently in its infancy without any clinical studies.[62]

Ongoing local clinical trials

No ongoing trials are registered in ANZCTR relevant to Paediatric Surgery. A supplementary search in Clinicaltrials.Gov identified ongoing trials on stem cell treatment in children such as for Type 1 Diabetes Mellitus (NCT01121029, Mexico; NCT01350219 and NCT01219465, China), childhood haematological malignancies (NCT00145626, United States of America (USA)) and cardiomyopathy in children (NCT01219452, China).

Table 12 Evidence profile of stem cell therapy usage in Paediatric Surgery

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Systematic review				
Sickle cell disease				
Oringanje et al. 2009	Stem cell transplantation	MSC (bone marrow and blood)	To improve survival and prevent symptoms and complications associated with sickle cell disease in children	Evidence base is currently limited to observational and other less robust studies. No RCT assessing the benefit or risk of stem cell transplantations in children was found. Thus, this systematic review identifies the need for a multi-centre RCT assessing the benefits and possible risks.
Childhood medulloblastoma				
Gudrunardottir et al. 2014	HDCT followed by stem cell transplantation	NR	For childhood medulloblastoma	It seemed to provide long-term survival in some patients with recurrent medulloblastoma, primarily those who had local recurrence and had not received prior chemotherapy, or infants with local recurrence who had not received radiotherapy.
Tissue-engineering – cleft palate				
Tavakolinejad 2014	Application of stem cells to engineered palates	ESC / MSC	Correction of cleft palate in paediatric patients	Tissue-engineering may open a new window in cleft palate reconstruction. Stem cells and growth factors play key roles in this field.
Tissue engineering - short bowel				
Weih et al. 2012	Stem cell transplantation (in tissue-engineering)	MSC (bone marrow and blood)	To improve enteric function and intestinal restitution for treatment of short bowel in children	Stem cells are very promising for use in tissue-engineering. However, the long-term safety, tolerability, and efficacy of stem-cell-based treatments and their carcinogenic risk remain unclear.
Tissue-engineering - foetus				
Lange et al. 2011	NR	Human amniotic stem cells (autologous)	For foetal airway reconstruction in laryngotracheal agenesis in infants (foetal tissue-engineering)	The optimal cell source for foetal tissue-engineering remains to be determined, but a combination of decellularised scaffolds and amniotic fluid stem cells holds great promise for foetal tissue-engineering. Although this approach is still in its experimental stages, further preclinical and clinical studies are encouraged.
Comparative studies				
Autism				
Ma et al. 2015	NR	NR	For treatment of autism	NR
Congenital anomalies				
Gupta et al. 2007	Stem cells injection into the hepatic artery and the portal vein or into the hepatobiliary radicals for liver cirrhosis, or into the spinal cord and caudal space for meningomyelocele	NR (autologous)	For the treatment of congenital liver cirrhosis and meningomyelocele.	Stem cell use in liver cirrhosis and meningomyelocele has suggested beneficial results. However, long-term evaluation in randomized controlled trials is essential to draw further conclusions.

ESC=Embryonic stem cell; HDCT=High-dose chemotherapy; MSC=Mesenchymal stem cells; NR=Not reported; RCT=Randomised controlled trials.

Plastic and Reconstructive Surgery

Searches identified nine systematic reviews assessing the use of stem cells in Plastic and Reconstructive Surgery.[68-76] A comparative study noted use of stem cell treatments for bone regeneration.[77] Table 13 provides a summary of these studies. Some of the systematic reviews summarised under Orthopaedic Surgery and Paediatric Surgery are relevant for this section. For example, use of stem cells in knee construction and airway reconstruction are noted under Orthopaedic Surgery and Paediatric Surgery, respectively.[38, 62]

Category A or B treatments

None of the stem cell treatments used within the practice of Plastic and Reconstructive Surgery was supported by quality RCTs for their safety and efficacy.

Category C treatments

Autologous ASC grafting for breast reconstruction following mastectomy, breast conserving surgery or aesthetic breast augmentation seems a promising area of stem cell use. A systematic review, based on 35 clinical trials including six observational studies, 26 case series and three case reports, suggested the procedure has a low complication rate with the majority of patients and clinicians satisfied with the outcomes. [68] Another systematic review which assessed long-term cancer recurrence following ASC grafting showed no increase in breast cancer recurrence after the procedure, with an exception of one study on a subset population with recurrent intraepithelial neoplasm.[76] However, none of systematic reviews found RCT evidence published in this area or provided details of stem cell processing.

A systematic review performed to identify efficacy of ASC in subjective improvement in scars from burns did not identify any comparative evidence.[69]

A review on stem cells treatments in plastic surgery identified the use of ASC for bony and soft tissue defects and for non-healing wounds complicated by radiation and ischemia.[72, 74] Aesthetic surgery such as skin rejuvenation has also showed promising results.[73] Based on pre-clinical studies, a review identified a fat transplantation enriched with ASC as a technique to increase viability of the transplanted tissue. The procedure has the potential to be safer and effective compared with prosthetic implantation.[75]

Cells isolated from bone marrow and progenitor cells enriched in CD90- and CD14-positive cells were used for craniofacial bone regeneration. Based on data available from a single RCT, the procedure seems safe and leads to accelerated bone regeneration enabling jawbone reconstruction with oral implants.[77] A review on knee ligament tissue-engineering strategies in reconstructive surgery identified the potential of MSCs, CD34+ cells from ACL, remnant tissues, patella tendon-derived stem cells, periosteal progenitor cells, and ASC to accelerate healing and integration of the tendon graft into the bone tunnel. However, their results were derived solely from animal studies.[70] A review about MSC in oral reconstructive surgery noted 18 clinical trials using MSCs for sinus augmentation, five case reports on the repair of large bony defects, and six studies on ridge

augmentation and healing of alveolar sockets after third molar extraction, without robust RCTs or long-term follow-up.[71]

Further research with well-constructed RCTs with long-term follow-up are necessary to show the effectiveness of these treatments.

Ongoing clinical trials

No ongoing trials were registered in ANZCTR relevant to Paediatric Surgery. A supplementary search in Clinicaltrials.Gov also did not identify ongoing trials relevant to stem cell treatment in Paediatric Surgery.

Table 13 Evidence profile of stem cell therapy usage in Plastic and Reconstructive Surgery

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Systematic review				
Wound healing and scarring in burns				
Conde-Green et al. 2016	Fat grafting and adipose-derived regenerative cells	ASC	To improve wound healing and scarring in burns	At this time, there is no significant literature to suggest that fat grafting in acute burn wounds facilitates wound healing and ameliorates subsequent scarring.
Soft tissue augmentation and regeneration, and bony reconstruction				
Salibian et al. 2013	Stem cell enriched tissue injections	ASC (autologous)	In soft tissue augmentation and regeneration, bony reconstruction and non-healing wound healing	In general, it provides an effective treatment option. Further studies involving both the basic and clinical science aspects of stem cell therapies are needed.
Khojasteh et al. 2012	NR	MSC	In bone augmentation and reconstruction	Additional collaborated studies using similar homogenous designs and data analysis in advancing the science of bone reconstruction using MSCs are needed.
Aesthetic surgery				
McArdle et al. 2014	NR	MSC	In aesthetic surgery	Stem cells offer tremendous potential, but the marketplace is saturated with unsubstantiated, and sometimes fraudulent, claims that may place patients at risk.
Trojahn Kolle et al. 2012	Enrich the fat graft with ASC before transplantation	ASC	Fat transplantation in aesthetic and reconstructive surgery	No lipofilling studies in humans using a high concentration of previously expanded ASC have been carried out. ASC-enriched lipofilling theoretically has the potential for transforming lipofilling from a relatively unpredictable intervention into one in which the resorption rate, quality of tissue, and safety can be predicted, and possibly superior to prosthetic implantation.
Oral reconstructive surgery				
Jakobsen et al. 2013	Intraoperative use of adult stem cells	MSC	In oral reconstructive surgery	Most studies showed that MSC are capable of creating bone in clinical trials, but larger, well-designed RCTs with longer follow-ups are needed to show whether MSCs are to play an important role in future reconstructive surgery.
Knee reconstruction				
Hogan et al. 2015	Tissue-engineering by cell therapy	MSC, patella tendone-derived stem cells, periosteal progenitor cells, ASCs	Knee ligament reconstruction	Cell therapy has the potential to accelerate healing and integration of the tendon graft into the bone tunnel. Cell therapy for ACL reconstruction has been most studied in animal models
Breast grafting and reconstruction				
Charvet et al. 2015	Fat grafting to breasts with breast cancer recurrence	ASC	In plastic surgery for postmastectomy breast reconstruction and aesthetic breast augmentation	There is no enough good data to make a definitive claim about the oncologic safety of breast fat grafting

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Agha et al. 2015	Fat grafting for breast reconstruction after surgery for breast cancer	ASC (autologous)	For better oncological, clinical, aesthetic and functional, patient reported, process and radiological outcomes	It is a potentially useful reconstructive tool, has a relatively low complication rate, with the majority of patients and clinicians satisfied with the results. Long term clinical and radiological follow-up is required. Further research is necessary to confirm oncological ramifications.
Comparative studies				
Craniofacial bone defects				
Kaigler et al. 2013	NR	Tissue repair cells (TRCs) isolated from bone marrow	For the treatment of craniofacial bone defects	Transplantation of tissue repair cells for treatment of alveolar bone defects appears safe and accelerates bone regeneration, enabling jawbone reconstruction with oral implants.

ASC=Adipose-derived stem cells; MSC=Mesenchymal stem cells; NR=Not reported; RCT=Randomised controlled trials.

Urology

Searches identified seven systematic reviews and one RCT.[78-84,85] Table 14 provides a summary of these studies.

Category A treatments

None of the stem cell treatments used within the practice of Urology were supported by quality RCTs for their safety and efficacy.

Category B treatments

Based on seven observational studies and one RCT a systematic review suggested that transurethral injections of autologous mesoderm-derived stem cells from skeletal muscle biopsies and umbilical cord-derived stem cells for stress urinary incontinence is safe and effective in the short term. The technique of treatment varied and included different compositions of myoblasts and fibroblasts. Overall, results were promising in the treatment of urinary incontinence in children with classic bladder exstrophy.[78, 83]

Autologous MSCs are injected to reduce acute rejection in kidney recipients following kidney transplantation. Biopsies conducted to assess safety and efficacy of autologous MSC as a replacement for antibody-based induction showed the use of autologous MSCs associated with a lower incidence of acute rejection, decreased risk of opportunistic infection, and better estimated renal function at 1-year compared to the effect of antibody-based induction therapy. More RCTs would be necessary to conclude efficacy of MSC in kidney recipients.[85]

Category C treatments

A review of tissue-engineering techniques using stem cells noted their potential in the management of renal failure, kidney tissue reconstruction, in the management of Peyronie's disease and erectile dysfunction. BMSC was beneficial in protecting against renal damage and managing ischemic kidney based on animal studies. Congenital urological diseases managed using pluripotent ESC were also informed by animal trials.[83] A review on stem cell use in regenerating urological structures noted their role in differentiation of smooth muscle cells and renal cells, engineering bladder smooth muscle and extracorporeal bioartificial kidneys, in spermatogenesis, enhance recovery of leydig cell function, generation of male germ cells and restoration of urethral sphincter muscle. These results were also based on animal trials.[79] Human urethral reconstruction using bone marrow-derived MSC, ASC and urine-derived stem cells from upper urinary tract is also being trialled but are at very early stages of development.[80, 81] Yu and Estrada (2010) reviewed stem cells for bladder regeneration, repair of lower urinary tract injury and to improve erectile function also identified the potential of autologous mesoderm-derived stem cells and umbilical cord-derived stem cells, and emphasised the need for clinical trials.[84] Transplantation of spermatogenic stem cells in genitourinary cancer survivors of reproductive age may enhance fertility although current research is limited to animal models.[82]

Ongoing clinical trials

Two clinical trials relevant to Urology are registered on the ANZCTR. Researchers in the Royal Perth Hospital and Fiona Stanley Hospital (both in WA) are recruiting patients for a trial on MSC to prevent ischaemia reperfusion injury in deceased donor renal transplant recipients (ACTRN12615000678594). The Royal Brisbane & Women's Hospital (QLD) is hosting a trial on pluripotent stem cells for inheritable renal diseases (ACTRN12615000140550).

Table 14 Evidence profile of stem cell therapy usage in Urology

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Systematic review				
Treatment, repair and reconstruction for renal defects, erectile dysfunction and urinary incontinence				
Aref-adib et al. 2013	Transurethral injections	Mesoderm-derived stem cells (autologous) and umbilical cord-derived stem cells	For stress urinary incontinence	It is safe and effective in the short term. However, the quality and maturity of the data are limited. Robust data from better quality studies comparing this to current surgical techniques are needed.
Shokeir 2010	NR	Bone marrow	For treatment of renal failure	Based on animal studies / models beneficial in protecting renal damage and there is a potential for use of stem cell in the functional recovery of an ischemic kidney.
	NR	Pluripotent ESC	For construction of kidney tissue	Animal studies suggest potentiality of the construction of the whole kidney in the future.
	NR	NR	For treatment of ureter defects	NR
	NR	NR	In regenerating the bladder tissue	NR
	Transurethral ultrasonography-guided injections	Myoblasts and fibroblasts obtained from skeletal muscle biopsies (autologous)	In regenerating damaged sphincter components in the treatment of (stress) urinary incontinence	Success has been achieved in both animal models and human subjects.
	NR	NR	In treatment of complex urethral stricture	Promising, but no preclinical studies have been conducted.
	Stem cell injection therapy	NR	For treatment of erectile dysfunction	Promising, based on animal studies.
Yu & Estrada 2010	NR	ESC, embryonic germ cells, and amniotic fluid-derived stem cells	In bladder regeneration, repair of lower urinary tract injury, improve erectile function.	The future of reconstructive surgery will surely incorporate a number of these stem cell-based technologies in revolutionary ways that may improve and extend lives. However, the ultimate utility and clinical applicability of the different types of stem cells will depend on a complex synthesis of further basic research, future clinical trials, and ethical and regulatory reconcilement.
Becker & Jakse 2007	NR	MSC (derived from fat tissue, bone marrow)	For differentiation of smooth muscle cells, renal cells	Animal and in vitro studies available.
	NR	Progenitor cells derived from ESC	For tissue-engineering of bladder smooth muscle, extracorporeal bioarticficial kidney	Only animal studies available.
	NR	Adult Spermatogonial stem cells	For spermatogenesis	Only animal studies available.

Study	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
	NR	Adult Leydig cell progenitor cells	For recovery of leydig cell function	Only animal studies available.
	NR	ESC	For generation of male germ cells	Only animal studies available.
	NR	Progenitor cells derived from skeletal muscle	For restoration of urethral sphincter muscle	Only animal studies available.
Genitourinary cancers				
Polland & Berookhim 2016	Spermatogenic stem cell transplant	NR	In management of genitourinary cancers in patients of reproductive age	The frontier of stem cell therapy has gone from mice to monkeys, and bed side research is likely on the horizon.
Urethroplasty and urinary reconstruction				
De Kemp et al. 2015	NR	Cultured ASC, urine-derived stem cells from upper urinary tract (autologous)	Urethral reconstruction	Knowledge is expanding and is still finding its way into clinical implementation. Although experience with differentiation of stem cells towards different lineages is gaining ground, protocols with *in vitro* expansion of original tissue are better established at this moment.
Fu & Cao 2012	NR	ESC, marrow-derived MSC, ASC	In urethroplasty and urinary reconstruction	Stem cells can provide the seed cells for tissue-engineering, but much basic research is still needed before their clinical use is possible.
Comparative studies				
Kidney transplantation				
Tan et al. 2012	NR	Bone marrow-derived MSC (autologous)	To reduce acute rejection in patients with end-stage renal disease who undergo ABO-compatible, cross-match-negative kidney transplants from a living-related donor.	The treatment lowered incidence of acute rejection, decreased risk of opportunistic infection, and better estimated renal function at 1 year.

ASC=Adipose-derived stem cells; ESC=Embryonic stem cell; MSC=Mesenchymal stem cells; NR=Not reported.

Vascular Surgery

Two reviews relevant to stem cell treatments in Vascular Surgery were identified (Table 15).[17, 86] No additional RCTs were found for this specialty.

Category A treatments

The safety and efficacy of intramyocardial transplantation of autologous BMSC in the management of IHD is discussed under Cardiothoracic Surgery.

Category B treatments

Autologous cell treatments in critical limb ischaemia seem to be safe and effective based on a systematic review which assessed 45 clinical trials, including seven RCTs and 1,272 patients. Overall, cell therapy led to a low adverse event rate and low mortality compared to control patients. Treatment protocols that isolated mononuclear cells directly from bone marrow were associated with more procedure-related adverse events such as pain, whereas peripheral blood protocols had adverse events related to granulocyte-colony stimulating factor therapy such as bleeding. With regard to efficacy, cell therapy reduced amputation rates when compared to controls and improved a variety of functional and surrogate outcome measures.[86]However, a more recent review raised questions about uncertainties of stem cells in the management of limb ischemia and concluded this treatment should be considered with caution and considered experimental.[17]

Ongoing clinical trials

A multinational clinical trial evaluating the safety and efficacy of intracoronary selected CD 133+ BMSC in cardiac recovery after acute myocardial infarction and left ventricular dysfunction is registered in ANZCTR (ID ACTRN12609001045202) and is currently recruiting participants (Appendix C). No Australian centres are explicitly listed on the trial site (Table 16).

Table 15 Evidence profile of stem cell therapy usage in Vascular Surgery

Systematic review	Surgery / procedure	Source of stem cell	Intentions of use	Study conclusion
Limb ischaemia				
Slater 2016	Delivery techniques: intro-myocardial infusion, intra-coronary infusion, encapsulation, scaffold	Bone marrow-derived stem cells, MSC, cardiac stem cells, mesenchymal progenitor cells, EPC and pericytes	For treatment of myocardial infarction	Stem cell therapies (regardless of cell source - bone marrow, MSC or EPC) are a safe option for treatment of myocardial infarction.
	Intra-muscular infusion	Pericytes, MSC, endothelial progenitor cells	For treatment of limb ischaemia,	Stem cell treatment was found to be promising for treatment of limb ischaemia.
Benoit et al. 2013	Intramuscular injections of stem cells into the threatened limb	Unclear	For treatment of critical limb ischemia	Stem cell treatment was found to be promising for treatment of limb ischaemia.

EPC=Endothelial progenitor cells; MSC=Mesenchymal stem cells.

Appendix C Ongoing clinical trials registered in Australian New Zealand Clinical Trial Registry

Table 16 Ongoing clinical trials registered in Australian New Zealand Clinical Trial Registry

Trial ID, Location	Study title	Status
IHD		
ACTRN12609001045202 CHUM, Quebec (Canada)	An evaluation of the safety and efficacy of intracoronary selected CD 133+ bone marrow stem cells in cardiac recovery after acute myocardial infarct and left ventricular dysfunction: COMPARE-AMI a randomized controlled double blind clinical study	Recruiting
Neurosurgery		
NCT02452723 Dept of Neurology, The Royal Melbourne Hospital, VIC	A single arm, open-label phase 1 study to evaluate the safety and tolerability of isc-hpnsc injected into the striatum and substantia nigra of patients with Parkinson's disease	Recruiting
Degenerative disease		
ACTRN12609000932268 Wakefield orthopaedic clinic SA	A prospective, multi-centre, randomized migration study of the Anthology cementless femoral stem in patients with degenerative hip disease	Withdrawn
ACTRN12615000257561 Melbourne Stem Cell Centre VIC	The evaluation of autologous adipose derived mesenchymal stem cells in combination with arthroscopic microfracture as treatment for symptomatic hip osteoarthritis on pain, function and cartilage volume in osteoarthritis patients	Not yet recruiting
ACTRN12615000260527 Melbourne Stem Cell Centre VIC	The evaluation of autologous adipose derived mesenchymal stem cells as treatment for symptomatic hip osteoarthritis on pain, function and cartilage volume in osteoarthritis patients	Recruiting
ACTRN12611000274976 Australian Catholic University (VIC) and University of Melbourne (VIC)	Adipose-derived stem cells in patients with knee osetoarthritis: A randomised controlled trial evaluating pain, function and cartilage repair	Withdrawn
ACTRN12615000258550 Melbourne Stem Cell Centre VIC	The evaluation of autologous adipose-derived mesenchymal stem cells as treatment for symptomatic knee osteoarthritis on pain, function and cartilage volume in osteoarthritis patients	Recruiting
ACTRN12614000814673 Melbourne Stem Cell Centre VIC	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	Active, not recruiting
ACTRN12612000672853 Regeneus Ltd NSW	A Registry of Autologous Non-Expanded Adipose-Derived Stem Cells (HiQCellTM) in the Treatment of Osteoarthritis to determine prevalence of joint infections	Completed
ACTRN12611001046998 Royal North Shore Hospital NSW	A Randomised Double Blind, Placebo Controlled Study Of The Efficacy And Safety Of Autologous Non-Expanded Adipose-Derived Stem Cells In The Treatment Of Knee Osteoarthritis	Completed
ACTRN12614000812695 Melbourne Stem Cell Centre VIC	The effect of mesenchymal stem cell injections following arthroscopic microfracture versus microfracture alone on cartilage healing in patients with an isolated knee cartilage defect	Recruiting
ACTRN12615000060549 Global Orthopaedic Technology Pty Ltd NSW	Prospective clinical trial assessing subsidence and rotation after Paragon hip stem arthroplasty in patients with a primary diagnosis of non-inflammatory degenerative joint disease	Recruiting
ACTRN12614000294651	A Multi-centre, Prospective, Consecutive Series, Clinical Outcomes Study to evaluate the safety and performance of the Paragon Hip Stem and Global	Not yet recruiting

Trial ID, Location	Study title	Status
Global Orthopaedic Technology Pty Ltd NSW	Acetabular Cup prostheses combination following primary Total Hip Arthroplasty in patients with non-Inflammatory Degenerative Joint Disease	
ACTRN12611000954921 Stryker Australia NSW	A prospective, non-randomized Roentgen Stereophotogrammetric Analysis study to determine the migration pattern of the Stryker Accolade II(R) Hip Stem in patients undergoing total hip arthroplasty	Active, not recruiting
ACTRN12611000095965 Sir Charles Gairdner Hospital WA	In patients with non-inflammatory joint disease who qualify for total hip replacement (THR) surgery, does insertion of the Nanos short stem femoral component enhance clinical outcomes?	Not yet recruiting
ACTRN12613001183774 Melbourne Shoulder and Elbow Centre VIC	The effect of the Mathys Affinis Short Stem Total Shoulder Replacement on medium to long term pain and functional outcomes in patients with shoulder arthritis	Recruiting
Tendinopathy		
ACTRN12610000985088 MMRI QLD	A phase 1 study to evaluate the potential role of mesenchymal stem cells in the treatment of chronic refractory Achilles tendinopathy	Recruiting
HIV		
ACTRN12615000763549 St Vincent's Hospital NSW	An adaptive phase I/II, dose-ranging study to evaluate the safety and feasibility of busulfan conditioning prior to transplant of CD4+ T lymphocytes and CD34+ haematopoietic stem/progenitor cells (HSPCs) transduced with LVSH5/C46 (CAL-1), in adults diagnosed at primary HIV-1 infection who are established on effective combination antiretroviral therapy (ART)	Recruiting
Multiple sclerosis		
ACTRN12615000687594 Mastercell Stem Cell Centre QLD	A single group prospective study to evaluate the efficacy and safety of treatments using autologous, non-expanded adipose-derived stem cells, platelet-rich-plasma and peptides on patients with Multiple Sclerosis.	Not yet recruiting
Renal diseases		
ACTRN12615000678594 Royal Perth Hospital and Fiona Stanley Hospital WA	Mesenchymal Stem Cells to prevent ischaemia reperfusion injury in deceased donor renal transplant recipients	Recruiting
ACTRN12615000140550 RBWH QLD	Next Generation Sequencing and Induced Pluripotent Stem Cell Applications to clarify diagnosis for those with Genetic and Inheritable Forms of Renal Disease	Recruiting
Haematological malignancies		
ACTRN12614000351617 Australasian Leukaemia and Lymphoma Group VIC	Phase III Clinical Study of Allogeneic Stem Cell Transplantation with Reduced Conditioning (RICT) versus Best Standard of Care in Acute Myeloid Leukaemia (AML) in First Complete Remission	Not yet recruiting
ACTRN12614000290695 Royal Brisbane and Women's Hospital QLD	A phase I study of haploidentical haematopoietic stem cell transplantation with add-back of donor T cells transduced with inducible caspase 9 suicide gene in patients with poor risk haematological malignancies	NR
ACTRN12613000338763 St Vincent's Hospital Sydney NSW	A comparison of leukaemia free and overall survival following Haploidentical donor stem cell transplantation compared to matched unrelated donor stem cell transplantation for haematological malignancies	
ACTRN12613000337774 St Vincent's Hospital Sydney NSW	Pilot Study of partially Human Leucocyte Antigen (HLA)-mismatched stem cell infusions after chemotherapy for acute myeloid leukaemia in patients over the age of 60: an evaluation of incidence of Graft vs Host Disease and treatment related mortality	Stopped early
ACTRN12608000129381	Cotransplantation of mesenchymal stem cells with nonmyeloablative haploidentical peripheral blood stem cells without T cells deleted for high-risk	

Trial ID, Location	Study title	Status
Affiliated Hospital of Academy of Military Medicine Science (China)	acute leukaemia: to reduce the severity of graft versus host disease and relapse	
ACTRN12607000347460 Australasian Leukaemia and Lymphoma Group NSW	A Phase III Study Comparing Low Dose Cyclosporine, Methotrexate And Prednisone Versus Standard Dose Cyclosporine and Methotrexate As Graft Versus Host Disease Prophylaxis In Myeloblative Allogeneic Stem Cell Transplantation (ALLG BM10 trial) in patients with haematological malignancies. (Incorporating an Open-Label Sub-study Investigating The Use Of Valganciclovir In The Prevention Of Cytomegalovirus Infection In Hematopoietic Stem Cell Transplant Recipients in patients with haematological malignancies	Not yet recruiting
ACTRN12609000173291 Royal Melbourne Hospital VIC	A Phase II Study of the Impact of Two Different Schedules of Thymoglobulin on the Incidence of Extensive Chronic Graft Versus Host Disease (GVHD) in Undergoing Unrelated Donor or Mismatched Related Donor Stem Cell Transplantation for Haematological Malignancy	Recruiting
ACTRN12607000224426 Sydney West Area Health Service NSW	Infusion of Ad5f35pp65 stimulated donor-derived cytotoxic T lymphocytes for the prevention of cytomegalovirus reactivation following allogeneic stem cell transplantation for haematological malignancy	Not yet recruiting
Multiple Myeloma		
ACTRN12613000487718 The Children's Hospital at Westmead, NSW	High Dose Melphalan: A pilot study to evaluate pharmacokinetic-based dose determination in patients with multiple myeloma scheduled to undergo autologous stem cell transplantation	Recruiting
ACTRN12613000344796 Peter MacCallum Cancer Centre, VIC	A Phase II Study of Lenalidomide Induction, Autologous Peripheral Stem Cell Transplant and Adjuvant Vaccination with Autologous Dendritic Cells and Lenalidomide Maintenance in Multiple Myeloma	Active, not recruiting
ACTRN12609000595213 Launceston General Hospital TAS	Quality of life assessment and disease free survival and overall survival in patients with multiple myeloma after Tandem Autologous Stem Cell Transplantation (ASCT)	Completed
Auto-Immune Diseases		
ACTRN12613000339752 St Vincent's Hospital, Sydney, NSW	A Single Centre Phase II Study Of the safety and efficacy of Haematopoietic Stem Cell Transplantation For Severe Auto-Immune Diseases	Recruiting
ACTRN12612000800820 Westmead Hospital NSW	In haemopoietic stem cell transplant patients, does infusion of infection-specific T-cells combined with vaccination (compared to no vaccination) enhance immune reconstitution safely?	Not yet recruiting
ACTRN12611000826943 St Vincents Hospital NSW	A retrospective review of patients with severe Systemic Sclerosis and Rheumatoid Arthritis who have had a Haematopoietic Stem Cell Transplant as a means of immunosuppression to achieve disease remission - assessment of safety and efficacy of response	Recruiting

Registry: www.anzctr.org.au; search date 01/08/2016; Search term 'stem'; Limits: Australia and New Zealand only, intervention 'treatment: surgery', trial type 'RCT'.

Appendix D International stem cell regulatory and research funding organisations

Table 17 Summary table regarding regulatory bodies and relevant research funding bodies in Australia, Canada, The EU, The USA and New Zealand

	Regulatory bodies dealing with stem cell therapies including autologous stem cells and legislation that is relevant	Relevant research bodies dealing with centralised funding of research on hESC or other stem cell products and their guidelines or frameworks
Australia	**The Therapeutic Goods administration** Legislation The Therapeutic Goods Act, Regulations and Orders the Therapeutic Goods (Excluded Goods) Order No. 1 of 2011	Both publicly funded organisations and companies are involved in adult and embryonic stem cell research in Australia. Research must be approved by AHEC, which is a Principal Committee of the NHMRC. Also, human embryos can only be used for research if authorised by a licence issued by the NHMRC Embryo Research Licensing Committee. Relevant legislation regarding research includes: *the Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Bill 2006* which amends the *Prohibition of Cloning Act 2002* and the *Research Involving Human Embryos Act 2002.*
Canada	**Health Canada:** the Biologics and Genetic Therapies Directorate Legislation The Food and Drugs Act Safety of Human Cells, Tissues and Organs for Transplantation Regulations	Three central funding bodies: • the Canadian Institutes of Health Research (CIHR), • the National Sciences and Engineering Research Council, and • the Social Sciences and Humanities Research Council. The CIHR have guidelines for research: Canadian Institutes of Health Research (CIHR): *Human Pluripotent Stem Cell Research: Guidelines for CIHR-Funded Research; the Guidelines.*
The European Union	**The European Medicines Agency:** the Committee for Advanced Therapies Legislation REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Directive 2003/63/EC (amending Directive 2001/83/EC), which defines cell therapy products as clinical products and includes their specific requirements. Directive 2001/20/EC, which emphasizes that CTs are mandatory for such cell therapy products and describes the special requirements for approval of such trials. Directive 2004/23/EC, which establishes the standard quality, donation safety, harvesting, tests, processing, preservation, storage, and distribution of human tissues and cells.	The European Union has provided funding for scientific research through a series of "framework programs for research and technological development", after much debate the European Commission agreed to the continued funding of stem cell research as part of Horizon 2020[a]. Details are provided in Horizon 2020: *The European Union Framework Programme for Research and Innovation.*

	Regulatory bodies dealing with stem cell therapies including autologous stem cells and legislation that is relevant	Relevant research bodies dealing with centralised funding of research on hESC or other stem cell products and their guidelines or frameworks
New Zealand	**Medsafe (the New Zealand Medicines and Medical Devices Safety Authority)** Legislation The New Zealand Government is currently working on new and comprehensive regulatory regime to regulate therapeutic products in New Zealand; this will replace the Medicines Act 1981 and its Regulations.	The funding situation is unclear. *Guidelines for Research on Gametes and Non-Viable Embryos*, developed by the (former) National Ethics Committee on Assisted Human Reproduction. Also the *Guidelines for Using Cells from Established Human Embryonic Stem Cell Lines for Research* (Ministry of Health). For research using established human embryonic stem cell lines that fits the definition of human reproductive research (ie, research that uses or creates a human gamete, a human embryo, or a hybrid embryo) under the HART Act 2004, the appropriate ethics committee is the HART Act ethics committee (the Ethics Committee on Assisted Reproductive Technology).
The United States of America	**The Food and Drug Administration:** The Center for Biologics Evaluation and Research Legislation Section 361 of the Public Health Service Act IND regulations (21 CFR 312), biologics regulations (21 CFR 600) and cGMP (21 CFR 211) Good Tissue Practice (GTP).[7] CFR, Part 1271	The National Institute for Health is the funding agency that provides federal funds for research in the USA; in current times federal funding of research involving hESC is permitted. The NIH sets out eligibility requirements in the *National Institutes of Health Guidelines for Human Stem Cell Research*.

AHEC=Australian Health Ethics Committee; CAT= Committee for Advanced Therapies; CIHR= Canadian Institutes of Health Research; HART= Human Assisted Reproductive Technology; hESC= Human embryonic stem cells; NHMRC=National Health and Medical Research Council; NIH= National Institutes of Health.

References

1. National Institutes of Health. Stem cell basics. U.S. Department of Health and Human Services; 2015 [cited 2016 05/09]; Available from: http://stemcells.nih.gov/info/basics/Pages/Default.aspx.
2. Saeed H, Ahsan M, Saleem Z, Iqtedar M, et al. Mesenchymal stem cells (MSCs) as skeletal therapeutics - An update. Journal of biomedical science. 2016;23:41.
3. California Institute for Regenerative Medicine. Stem Cell Key Terms. California Institute for Regenerative Medicine; 2015 [cited 2016 05/09]; Available from: https://www.cirm.ca.gov/patients/stem-cell-key-terms.
4. Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. Cell Transplant. 2011;20(1):5-14.
5. National Institutes of Health. Stem Cell Information. U.S. Department of Health and Human Services; 2001 [cited 2016 05/09]; Available from: http://stemcells.nih.gov/info/scireport/pages/chapter5.aspx.
6. Henig I, Zuckerman T. Hematopoietic stem cell transplantation-50 years of evolution and future perspectives. Rambam Maimonides Medical Journal. 2014;5(4):e0028.
7. Abbasi M, Javan H, Alizadeh B, Afzalnia S. Can intracoronary stem cell injection permanently improve cardiac function after myocardial infarction? Interactive Cardiovascular and Thoracic Surgery. 2011;12(2):229-31.
8. Ali-Hassan-Sayegh S, Mirhosseini SJ, Lotfaliani MR, Dehghan HR, et al. Transplantation of bone marrow stem cells during cardiac surgery. Asian Cardiovascular and Thoracic Annals. 2015;23(3):363-74.
9. Donndorf P, Kundt G, Kaminski A, Yerebakan C, et al. Intramyocardial bone marrow stem cell transplantation during coronary artery bypass surgery: A meta-analysis. Journal of Thoracic and Cardiovascular Surgery. 2011;142(4):911-20.
10. Fisher SA, Brunskill SJ, Doree C, Mathur A, et al. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. The Cochrane Database of Systematic Reviews. 2014;4:CD007888.
11. Lim ML, Jungebluth P, Ajalloueian F, Friedrich LH, et al. Whole organ and tissue reconstruction in thoracic regenerative surgery. Mayo Clinic Proceedings. 2013;88(10):1151-66.
12. Mao M, Xu X, Zhang Y, Zhang B, et al. Endothelial progenitor cells: The promise of cell-based therapies for acute lung injury. Inflammation Research. 2013;62(1):3-8.
13. Qin SL, He CY, Xu JS, Lai XY, et al. Meta-analysis of coronary artery bypass graft surgery combined with stem cell transplantation in the treatment of ischemic heart diseases. Coronary Artery Disease. 2015;26(2):170-5.
14. Rippel RA, Ghanbari H, Seifalian AM. Tissue-engineered heart valve: future of cardiac surgery. World journal of surgery. 2012;36(7):1581-91.
15. Tian T, Chen B, Xiao Y, Yang K, et al. Intramyocardial autologous bone marrow cell transplantation for ischemic heart disease: A systematic review and meta-analysis of randomized controlled trials. Atherosclerosis. 2014;233(2):485-92.
16. Wen Y, Meng L, Xie J, Ouyang J. Direct autologous bone marrow-derived stem cell transplantation for ischemic heart disease: A meta-analysis. Expert Opinion on Biological Therapy. 2011;11(5):559-67.
17. Slater SC, Carrabba M, Madeddu P. Vascular stem cells-potential for clinical application. British Medical Bulletin. 2016;118(1):127-37.
18. Boennelycke M, Gras S, Lose G. Tissue engineering as a potential alternative or adjunct to surgical reconstruction in treating pelvic organ prolapse. International Urogynecology Journal. 2013;24(5):741-7.
19. Cadeddu F, Salis F, Lisi G, Ciangola I, et al. Complex anal fistula remains a challenge for colorectal surgeon. International Journal of Colorectal Disease. 2015;30(5):595-603.

20. Gottgens KW, Smeets RR, Stassen LP, Beets G, et al. Systematic review and meta-analysis of surgical interventions for high cryptoglandular perianal fistula. International Journal of Colorectal Disease. 2015;30(5):583-93.
21. Liu A, Moy RL, Ozog DM. Current methods employed in the prevention and minimization of surgical scars. Dermatologic Surgery. 2011;37(12):1740-6.
22. Stutchfield BM, Forbes SJ, Wigmore SJ. Prospects for stem cell transplantation in the treatment of hepatic disease. Liver Transplantation. 2010;16(7):827-36.
23. Toyserkani NM, Christensen ML, Sheikh SP, Sorensen JA. Stem cells show promising results for lymphoedema treatment-A literature review. Journal of Plastic Surgery and Hand Surgery. 2015;49(2):65-71.
24. Bansal N, Soni A, Kaur P, Chauhan AK, et al. Exploring the management of radiation proctitis in current clinical practice. Journal of Clinical and Diagnostic Research. 2016;10(6):XE01-XE6.
25. Gecse KB, Bemelman W, Kamm MA, Stoker J, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut. 2014;63(9):1381-92.
26. Hawkey CJ, Allez M, Clark MM, Labopin M, et al. Autologous Hematopoetic Stem Cell Transplantation for Refractory Crohn Disease: A Randomized Clinical Trial. JAMA. 2015;314(23):2524-34.
27. Tyndall A, Furst DE. Adult stem cell treatment of scleroderma. Current Opinion in Rheumatology. 2007;19(6):604-10.
28. Zhang DM, Hong WS, Fu LF, Wei XD, et al. A randomized controlled study of the effects of different modalities of narrow-band ultraviolet B therapy on the outcome of cultured autologous melanocytes transplantation in treating vitiligo. Dermatologic Surgery. 2014;40(4):420-6.
29. Maldonado GEM, Perez CAA, Covarrubias EEA, Cabriales SAM, et al. Autologous stem cells for the treatment of post-mastectomy lymphedema: A pilot study. Cytotherapy. 2011;13(10):1249-55.
30. Finsterer J, Zarrouk-Mahjoub S. Treatment of muscle weakness in neuromuscular disorders. Expert review of neurotherapeutics. 2016.
31. Novak I, Walker K, Hunt RW, Wallace EM, et al. Concise Review: Stem Cell Interventions for People With Cerebral Palsy: Systematic Review With Meta-Analysis. Stem Cells Translational Medicine. 2016.
32. Euler De Souza Lucena E, Guzen FP, Lopes De Paiva Cavalcanti JR, Galvao Barboza CA, et al. Experimental considerations concerning the use of stem cells and tissue engineering for facial nerve regeneration: A systematic review. Journal of Oral and Maxillofacial Surgery. 2014;72(5):1001-12.
33. Tator CH. Review of treatment trials in humanspinal cord injury: Issues, difficulties, and recommendations. Neurosurgery. 2006;59(5):957-82.
34. Wang S, Cheng H, Dai G, Wang X, et al. Umbilical cord mesenchymal stem cell transplantation significantly improves neurological function in patients with sequelae of traumatic brain injury. Brain Research. 2013;1532:76-84.
35. Ahmad Z, Wardale J, Brooks R, Henson F, et al. Exploring the application of stem cells in tendon repair and regeneration. Arthroscopy - Journal of Arthroscopic and Related Surgery. 2012;28(7):1018-29.
36. Andres BM, Murrell GAC. Treatment of tendinopathy: What works, what does not, and what is on the horizon. Clinical Orthopaedics and Related Research. 2008;466(7):1539-54.
37. Beitzel K, Solovyova O, Cote MP, Apostolakos J, et al. The future role of mesenchymal stem cells in the management of shoulder disorders. Arthroscopy - Journal of Arthroscopic and Related Surgery. 2013;29(10):1702-11.
38. Fu SC, Cheuk YC, Yung SH, Rolf CG, et al. Systematic review of biological modulation of healing in anterior cruciate ligament reconstruction. Orthopaedic Journal of Sports Medicine. 2014;2(3).

39. Gopal K, Amirhamed HA, Kamarul T. Advances of human bone marrow-derived mesenchymal stem cells in the treatment of cartilage defects: A systematic review. Experimental Biology and Medicine. 2014;239(6):663-9.
40. Hong P, Boyd D, Beyea SD, Bezuhly M. Enhancement of bone consolidation in mandibular distraction osteogenesis: A contemporary review of experimental studies involving adjuvant therapies. Journal of Plastic, Reconstructive and Aesthetic Surgery. 2013;66(7):883-95.
41. Li X, Xu X, Wu W. Comparison of bone marrow mesenchymal stem cells and core decompression in treatment of osteonecrosis of the femoral head: A meta-analysis. International Journal of Clinical and Experimental Pathology. 2014;7(8):5024-30.
42. Liu C, Toma IC, Mastrogiacomo M, Krettek C, et al. Meniscus reconstruction: Today's achievements and premises for the future. Archives of Orthopaedic and Trauma Surgery. 2013;133(1):95-109.
43. Maffulli N, Longo UG, Loppini M, Berton A, et al. Tissue engineering for rotator cuff repair: An evidence-based systematic review. Stem Cells International. 2012;418086.
44. Moran CJ, Busilacchi A, Lee CA, Athanasiou KA, et al. Biological augmentation and tissue engineering approaches in meniscus surgery. Arthroscopy - Journal of Arthroscopic and Related Surgery. 2015;31(5):944-55.
45. Nakamura N, Miyama T, Engebretsen L, Yoshikawa H, et al. Cell-Based Therapy in Articular Cartilage Lesions of the Knee. Arthroscopy - Journal of Arthroscopic and Related Surgery. 2009;25(5):531-52.
46. Oehme D, Goldschlager T, Ghosh P, Rosenfeld JV, et al. Cell-based therapies used to treat lumbar degenerative disc disease: A systematic review of animal studies and human clinical trials. Stem Cells International. 2015;946031.
47. Peeters CMM, Leijs MJC, Reijman M, van Osch GJVM, et al. Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: A systematic literature review. Osteoarthritis and Cartilage. 2013;21(10):1465-73.
48. Skovrlj B, Guzman JZ, Al Maaieh M, Cho SK, et al. Cellular bone matrices: Viable stem cell-containing bone graft substitutes. Spine Journal. 2014;14(11):2763-72.
49. Xu S, Liu H, Xie Y, Sang L, et al. Effect of mesenchymal stromal cells for articular cartilage degeneration treatment: A meta-analysis. Cytotherapy. 2015;17(10):1342-52.
50. Yu H, Adesida AB, Jomha NM. Meniscus repair using mesenchymal stem cells - A comprehensive review. Stem Cell Research and Therapy. 2015;6(1)86.
51. Atesok K, Fu FH, Sekiya I, Stolzing A, et al. Stem cells in degenerative orthopaedic pathologies: Effects of aging on therapeutic potential. Knee Surgery, Sports Traumatology, Arthroscopy. 2015.
52. Counsel PD, Bates D, Boyd R, Connell DA. Cell therapy in joint disorders. Sports Health. 2015;7(1):27-37.
53. Dave LY, Nyland J, McKee PB, Caborn DN. Mesenchymal stem cell therapy in the sports knee: Where are we in 2011? Sports Health. 2012;4(3):252-7.
54. Perera JR, Gikas PD, Bentley G. The present state of treatments for articular cartilage defects in the knee. Annals of the Royal College of Surgeons of England. 2012;94(6):381-7.
55. Sinclair KL, Mafi P, Mafi R, Khan W. The Use of Growth Factors and Mesenchymal Stem Cells in Orthopaedics. Current stem cell research & therapy. 2016.
56. Kawaguchi H, Oka H, Jingushi S, Izumi T, et al. A local application of recombinant human fibroblast growth factor 2 for tibial shaft fractures: A randomized, placebo-controlled trial. Journal of Bone and Mineral Research. 2010;25(12):2459-67.
57. Wong KL, Lee KBL, Tai BC, Law P, et al. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: A prospective, randomized controlled clinical trial with 2 years' follow-up. Arthroscopy - Journal of Arthroscopic and Related Surgery. 2013;29(12):2020-8.
58. Hamilton N, Bullock AJ, Macneil S, Janes SM, et al. Tissue engineering airway mucosa: A systematic review. Laryngoscope. 2014;124(4):961-8.

59. Wormald JC, Fishman JM, Juniat S, Tolley N, et al. Regenerative medicine in otorhinolaryngology. The Journal of laryngology and otology. 2015;129(8):732-9.
60. Elliott MJ, De Coppi P, Speggiorin S, Roebuck D, et al. Stem-cell-based, tissue engineered tracheal replacement in a child: a 2-year follow-up study. Lancet. 2012;380(9846):994-1000.
61. Gudrunardottir T, Lannering B, Remke M, Taylor MD, et al. Treatment developments and the unfolding of the quality of life discussion in childhood medulloblastoma: A review. Child's Nervous System. 2014;30(6):979-90.
62. Lange P, Fishman JM, Elliott MJ, De Coppi P, et al. What can regenerative medicine offer for infants with laryngotracheal agenesis? Otolaryngology--Head and Neck Surgery. 2011;145(4):544-50.
63. Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for children with sickle cell disease. Cochrane Database of Systematic Reviews. 2009;(1)CD007001.
64. Tavakolinejad S, Ebrahimzadeh Bidskan A, Ashraf H, Hamidi Alamdari D. A glance at methods for cleft palate repair. Iranian Red Crescent medical journal. 2014;16(9):e15393.
65. Weih S, Kessler M, Fonouni H, Golriz M, et al. Current practice and future perspectives in the treatment of short bowel syndrome in children - A systematic review. Langenbeck's Archives of Surgery. 2012;397(7):1043-51.
66. Gupta DK, Sharma S, Venugopal P, Kumar L, et al. Stem Cells as a Therapeutic Modality in Pediatric Malformations. Transplantation Proceedings. 2007;39(3):700-2.
67. Ma YH, Li YW, Ma L, Cao CH, et al. Anesthesia for stem cell transplantation in autistic children: A prospective, randomized, double-blind comparison of propofol and etomidate following sevoflurane inhalation. Experimental and Therapeutic Medicine. 2015;9(3):1035-9.
68. Agha RA, Fowler AJ, Herlin C, Goodacre TE, et al. Use of autologous fat grafting for breast reconstruction: A systematic review with meta-analysis of oncological outcomes. Journal of Plastic, Reconstructive & Aesthetic Surgery. 2015;68:143-61.
69. Conde-Green A, Marano AA, Lee ES, Reisler T, et al. Fat grafting and adipose-derived regenerative cells in burn wound healing and scarring: A systematic review of the literature. Plastic and Reconstructive Surgery. 2016;137(1):302-12.
70. Hogan MV, Kawakami Y, Murawski CD, Fu FH. Tissue engineering of ligaments for reconstructive surgery. Arthroscopy: Journal of Arthroscopic & Related Surgery. 2015;31(5):971-9.
71. Jakobsen C, Sorensen JA, Kassem M, Thygesen TH. Mesenchymal stem cells in oral reconstructive surgery: A systematic review of the literature. Journal of Oral Rehabilitation. 2013;40(9):693-706.
72. Khojasteh A, Behnia H, Dashti SG, Stevens M. Current trends in mesenchymal stem cell application in bone augmentation: A review of the literature. Journal of Oral and Maxillofacial Surgery. 2012;70(4):972-82.
73. McArdle A, Senarath-Yapa K, Walmsley GG, Hu M, et al. The role of stem cells in aesthetic surgery: fact or fiction? Plastic and Reconstructive Surgery. 2014;134(2):193-200.
74. Salibian AA, Widgerow AD, Abrouk M, Evans GR. Stem cells in plastic surgery: A review of current clinical and translational applications. Archives of Plastic Surgery. 2013;40(6):666-75.
75. Trojahn Kolle SF, Oliveri RS, Glovinski PV, Elberg JJ, et al. Importance of mesenchymal stem cells in autologous fat grafting: A systematic review of existing studies. Journal of Plastic Surgery and Hand Surgery. 2012;46(2):59-68.
76. Charvet HJ, Orbay H, Wong MS, Sahar DE. The oncologic safety of breast fat grafting and contradictions between basic science and clinical studies: A systematic review of the recent literature. Annals of Plastic Surgery. 2015;75(4):471-9.
77. Kaigler D, Pagni G, Park CH, Braun TM, et al. Stem cell therapy for craniofacial bone regeneration: A randomized, controlled feasibility trial. Cell Transplantation. 2013;22(5):767-77.
78. Aref-Adib M, Lamb BW, Lee HB, Akinnawo E, et al. Stem cell therapy for stress urinary incontinence: A systematic review in human subjects. Archives of Gynecology and Obstetrics. 2013;288(6):1213-21.

79. Becker C, Jakse G. Stem cells for regeneration of urological structures. European Urology. 2007;51(5):1217-28.
80. De Kemp V, De Graaf P, Fledderus JO, Bosch JLHR, et al. Tissue engineering for human urethral reconstruction: Systematic review of recent literature. PLoS ONE. 2015;10(2):e0118653.
81. Fu Q, Cao YL. Tissue engineering and stem cell application of urethroplasty: From bench to bedside. Urology. 2012;79(2):246-53.
82. Polland A, Berookhim BM. Fertility concerns in men with genitourinary malignancies: Treatment dilemmas, fertility options, and medicolegal considerations. Urologic Oncology. 2016.
83. Shokeir AA, Harraz AM, El-Din AB. Tissue engineering and stem cells: basic principles and applications in urology. International Journal of Urology. 2010;17(12):964-73.
84. Yu RN, Estrada CR. Stem cells: a review and implications for urology. Urology. 2010;75(3):664-70.
85. Tan J, Wu W, Xu X, Liao L, et al. Induction therapy with autologous mesenchymal stem cells in living-related kidney transplants: A randomized controlled trial. JAMA. 2012;307(11):1169-77.
86. Benoit E, O'Donnell TF, Patel AN. Safety and efficacy of autologous cell therapy in critical limb ischemia: A systematic review. Cell Transplant. 2013;22(3):545-62.
87. JDRF. What is... Stem cell tourism? JDRF Australia; 2010 [cited 2016 31/08]; Available from: http://blog.jdrf.org.au/2010/03/09/what-is-stem-cell-tourism/.
88. Pash C. Australian clinics are using a loophole to charge up to $60,000 for unproven stem cell therapies. Allure Media; 2016 [cited 2016 22/08]; Available from: http://www.businessinsider.com.au/rogue-australian-clinics-are-charging-up-to-60000-for-unproven-stem-cell-therapies-2016-3.
89. Dr Robert Simons Spine & Joint Regenerative Medicine. Bone Marrow Concentrate Dr Robert Simons; 2016 [cited 2016 22/08]; Available from: http://www.jointmedicine.com.au/.
90. Sydney Stem Cell Centre. Learn about Celgen® stem cell therapy. Sydney Stem Cell Centre 2016 [cited 2016 22/08]; Available from: http://www.stemcells.com.au/learn-about-celgen-stem-cell-therapy.html.
91. Queenstown Regenerative Medicine. Cellular therapy & stem cell therapy pricing. Queenstown Regenerative Medicine; 2016 [cited 2016 24/08]; Available from: http://www.queenstownrm.co.nz/cellular-therapy-pricing/.
92. Macquarie Stem Cells. Welcome to Macquarie Stem Cells 2016; Available from: http://www.macquariestemcells.com/.
93. Regenerative Medicine. What can be treated? NZ Stem Cell Treatment Centre; 2016 [cited 2016 24/08]; Available from: http://stemcell.co.nz/what-can-be-treated/.
94. ABC. Selling the stem cell promise. ABC; 2016 [cited 2016 22/08]; Available from: http://www.abc.net.au/radionational/programs/backgroundbriefing/2016-07-17/7621838.
95. Milligan L. Stem cell harvesting methods used by Sydney doctor Ralph Bright untested by clinical trials. ABC; 2014; Available from: http://www.abc.net.au/news/2014-09-16/stem-cell-methods-doctor-ralph-bright-untested-clinical-trials/5748588.
96. National Stem Cell Foundation of Australia, Stem Cells Australia. The Australian Stem Cell Handbook. National Stem Cell Foundation of Australia; 2015 [cited 2016 22/08]; Available from: http://www.stemcellfoundation.net.au/about-stem-cells/stem-cell-treatment-information/handbook.
97. Milligan L. Stem cell harvesting methods used by Sydney doctor Ralph Bright untested by clinical trials. ABC; 2014; Available from: http://www.abc.net.au/news/2014-09-16/stem-cell-methods-doctor-ralph-bright-untested-clinical-trials/5748588.
98. Skynews. Patient dies after Liposuction treatment. Skynews; 2016; Available from: http://www.skynews.com.au/news/national/nsw/2016/06/14/patient-dies-after-liposuction-treatment.html.
99. Stem Cell Solutions. Stem cell treatment Australia. Stem Cell Solutions; 2016 [cited 2016 22/08]; Available from: http://www.stemcellsolutions.com.au/stem-cell-treatments.

100. Melbourne Stem Cell Centre. Treatment. Melbourne Stem Cell Centre; 2016 [cited 2016 22/08]; Available from: http://www.melbournestemcellcentre.com/treatment/.
101. Brisbane Regeneration. Stem cell treatment Australia. Brisbane Regeneration; 2016 [cited 2016 22/08]; Available from: http://www.brisbaneregeneration.com.au/treatments/.
102. Nepean Specialist Sports Medicine. Regenexx Procedures. Nepean Specialist Sports Medicine; 2016 [cited 2016 22/08]; Available from: http://www.nssm.com.au/regenexx-procedures/.
103. Adult Stem Cell Foundation. Your location choices for treatment. Adult Stem Cell Foundation 2016 [cited 2016 22/08]; Available from: http://www.adultstemcellfoundation.org/blog/application-form-for-experimental-adult-stem-cell-therapyand-integrated-cancer-protocols/.
104. Lakeside Sports Medicine Centre. Stem cell therapy. Lakeside Sports Medicine Centre; 2016 [cited 2016 22/08]; Available from: http://lakesidesmc.com.au/specialty-services/stem-cell-therapy/.
105. Norwood Day Surgery. The Stem Cell Therapy Procedure. Norwood Day Surgery; 2016 [cited 2016 22/08]; Available from: http://stemcelladelaide.com.au/stem-cell-treatment/the-stem-cell-therapy-procedure/.
106. ASC Treatment. Applications. ASC Treatment; 2016 [cited 2016 22/09]; Available from: http://www.asctreatment.com/index.php/pages/details/77.
107. MasterDerm. Stem Cell Therapy. MasterDerm; 2016 [cited 2016 22/08]; Available from: http://www.masterderm.clinic/stem_cell%20_therapy.html.
108. Magellan Stem Cells. Associates. Magellan Stem Cells; 2016 [cited 2016 22/08]; Available from: http://www.magellanstemcells.com.au/associates/.
109. Orthocell. Patient Information. Orthocell; 2016 [cited 2016 22/08]; Available from: http://www.orthocell.com.au/jeromewaddellmecom/.
110. Autologous Stem Cell Research Organisation. Health conditions treated by ASCRO stem cell clinic. Autologous Stem Cell Research Organisation Pty Ltd; 2016 [cited 2016 22/09]; Available from: http://www.ascro.online/.
111. St Vincent's SportsMed. Sporting an injury? Our team is here to help. St. Vincent's SportsMed; 2016 [cited 2016 22/08]; Available from: http://stvincentssportsmed.com.au/.
112. Me Clinic Cosmetic Surgery. Stem cell therapy. Me clinic; 2016 [cited 2016 22/08]; Available from: http://www.meclinic.com.au/face/anti-ageing-procedures/stem-cell-therapy.html.
113. Aubusson K. GP used stem cell therapy in autism. Cirrus Media; 2014; Available from: http://www.australiandoctor.com.au/news/latest-news/gp-used-stem-cell-therapy-in-autism.
114. Brisbane Clinic for Lymphoma Myeloma and Leukaemia. Stem Cell Transplantation. Brisbane Clinic for Lymphoma Myeloma and Leukaemia 2016 [cited 2016 22/08]; Available from: http://www.myhaematologist.com.au/stemcell.html.
115. Stem Cell NZ. Cell Regeneration For Injury or Arthritic Pain Relief. Stem Cell NZ; 2016 [cited 2016 24/08]; Available from: http://www.jointpainrelief.co.nz/regeneration-services.php.
116. New Zealand Stem Cell Clinic. Adult stem cell treatment. New Zealand Stem Cell Clinic; 2016 [cited 2016 24/08]; Available from: http://stemcelltreatment.co.nz/Adult_Stem_Cell_Treatment.php.
117. Wall T. Magical thinking or miracle cure? Fairfax Media Digital; 2013 [cited 2016 22/08]; Available from: http://www.stuff.co.nz/national/health/9166215/Magical-thinking-or-miracle-cure.
118. Dr Robert Beulink Medical Cosmetic & Vein Clinic. Procedures. Dr Robert Beulink Medical Cosmetic & Vein Clinic; 2016 [cited 2016 24/08]; Available from: http://www.drbeulink.co.nz/Procedures.html.
119. Skin & Vein Clinic. Stem Cells & Regenerative Medicine. Skin & Vein Clinic; 2016 [cited 2016 24/08]; Available from: http://skinandvein.co.nz/surgical-treatments/stem-cells.
120. Aclinic42. Clinic42. Aclinic42; 2016 [cited 2016 24/08]; Available from: http://clinic42.co.nz/.
121. Reisman M, Adams KT. Stem cell therapy: A look at current research, regulations, and remaining hurdles. P & T. 2014;39(12):846-57.

122. McGregor C, Peterson, A, Munsie, M. Regulation of unproven stem cell therapies – medicinal product or medical procedure? EuroStemCell; 2015 [updated 2015 30/07; cited 2016 26/08]; Available from: http://www.eurostemcell.org/commentanalysis/regulation-unproven-stem-cell-therapies-medicinal-product-or-medical-procedure.
123. Therapeutic Goods Administration. Australian regulatory guidelines for biologicals (ARGB). 2014 [cited 2016 24/08]; Available from: https://www.tga.gov.au/publication/australian-regulatory-guidelines-biologicals-argb.
124. Therapeutic Goods Administration. Stem cell treatments and regulation - a quick guide for consumers. Australian Government; 2016 [updated 2016 06/04; cited 2016 30 /08]; Available from: https://www.tga.gov.au/community-qa/stem-cell-treatments-and-regulation-quick-guide-consumers.
125. Therapeutic Goods Administration. Submissions received: Regulation of autologous stem cell therapies. Australian Government; 2016 [updated 2015 29/04; cited 2016 30/08]; Available from: https://www.tga.gov.au/submissions-received-regulation-autologous-stem-cell-therapies.
126. Australian Law Reform Commission. Genes and Ingenuity: Gene patenting and human health (ALRC Report 99): 15. Stem Cell Technologies. Australian Gocernment; unknown [cited 2016 30 /08]; Available from: http://www.alrc.gov.au/publications/15-stem-cell-technologies/stem-cell-research-australia#_ftn21.
127. Australian Government. Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006, 172(2006).
128. Australian StemCell Centre. Ethics & Law of Stem Cell Research. Australian StemCell Centre; unknown [cited 2016 30/08]; Available from: http://www.stemcellfoundation.net.au/docs/fact-sheets/fact-sheet-6---law-and-ethics-of-stem-cell-research.pdf?sfvrsn=13.
129. Therapeutic Goods Administration. Advisory Committee on Biologicals (ACB). Therapeutic Goods Administration; 2016 [cited 2016 20/09]; Available from: https://www.tga.gov.au/committee/advisory-committee-biologicals-acb.
130. Trent RJ. Oversight and monitoring of clinical research with gene therapy in Australia. Medical journal of Australia. 2005;182(9):441-2.
131. National Health and Medical Research Council. Stem cells, cloning and related issues Australian Government; 2014 [updated 2014 20/02; cited 2016 30/08]; Available from: https://www.nhmrc.gov.au/about/nhmrc-committees/embryo-research-licensing-committee/human-embryos-and-cloning/stem-cells-clon.
132. Medsafe. Data Sheet: Prochymal 2016 [cited 2016 26/08]; Available from: http://www.medsafe.govt.nz/profs/datasheet/p/prochymalsol.pdf.
133. Regenerative Medicine. Frequently Asked Questions. NZ Stem Cell Treatment Centre; 2014 [cited 2016 26/08]; Available from: http://stemcell.co.nz/faqs/#6.
134. Ministry of Research Science and Technology. Stem cell research in New Zealand challenges and opportunities for the research sector. Futurewatch; 2006 [cited 2016 19/09]; Available from: http://tinyurl.com/zb25qb2.
135. ACART. Guidelines for Research on Gametes and Non-viable Embryos. New Zealand Ministry of Health; 2005 [updated 2013 20/12; cited 2016 26/08]; Available from: http://acart.health.govt.nz/guidelines-research-gametes-and-non-viable-embryos.
136. New Zealand Ministry of Health. Guidelines for Using Cells from Established Human Embryonic Stem Cell Lines for Research. New Zealand Ministry of Health; 2006 [cited 2016 26/08]; Available from: http://www.moh.govt.nz/notebook/nbbooks.nsf/0/7d723ee803f89c67cc2576d5006cbbcc/$FILE/guidelines-stem-cell-use.pdf.
137. Jones DG. Where does New Zealand stand on permitting research on human embryos? The New Zealand medical journal. 2014;127(1399):74-82.
138. Food and Drug Administration. Frequently asked questions about Therapeutic Biological Products. Food and Drug Administration; 2015 [cited 2016 20/09]; Available from:

http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/ucm113522.htm.
139. Drabiak-Syed K. Challenging the FDA's authority to regulate autologous adult stem cells for therapeutic use: Celltex therapeutics' partnership with RNL Bio, substantial medical risks, and the implications of United States v. Regenerative Sciences. Health matrix . 2013;23(2):493-535.
140. Freeman M, Fuerst M. Does the FDA have regulatory authority over adult autologous stem cell therapies? 21 CFR 1271 and the emperor's new clothes. Journal of Translational Medicine. 2012;10:60.
141. Turner L, Knoepfler P. Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry. Cell Stem Cell.19(2):154-7.
142. Grens K. Judges Side with FDA on Stem Cells. The Scientist; 2014 [updated 2014 06/02; cited 2016 25/08]; Available from: http://www.the-scientist.com/?articles.view/articleNo/39108/title/Judges-Side-with-FDA-on-Stem-Cells/.
143. Food and Drug Administration. Irvine Stem Cell Treatment Center 12/30/15. Food and Drug Administration; 2015 [updated 2015 30/12; cited 2016 25/08]; Available from: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm479837.htm.
144. National Institutes of Health. National Institutes of Health Guidelines for Human Stem Cell Research. National Institutes of Health; 2009 [updated 2015 12/04; cited 2016 25/08]; Available from: http://stemcells.nih.gov/policy/pages/2009guidelines.aspx.
145. Nguyen T, von Tigerstrom B, Knoppers B. Regulatory Framework for the Development of Stem Cell-Based Therapies. Stem Cell Ethics Education; 2011 [cited 2016 25/08]; Available from: http://www.stemcellethics.ca/sites/default/files/roadmap_june_2011.pdf.
146. Health Canada. Report of the Expert Advisory Panel on Prochymal 2012 [updated 2012 26/01; cited 2016 25/08]; Available from: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/sci-consult/prochymal/report-rapporteng.php.
147. Clarke T. Prochymal approval makes Canada first country to OK stem cell therapy. The Globe and Mail; 2012 [updated 2012 18/05; cited 2016 25/08].
148. von Tigerstrom B, Nguyen TM, Knoppers BM. Regulation of stem cell-based therapies in Canada: current issues and concerns. Stem cell reviews. 2012;8(3):623-8.
149. Canadian Institutes of Health Research, Natuaral Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Government of Canada; 2010 [cited 2016 20/09]; Available from: http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf.
150. Canadian Institutes of Health and Research. Terms of Reference - Stem Cell Oversight Committee. Canadian Institutes of Health and Research; 2014 [updated 2014 19/12; cited 2016 25/08]; Available from: http://www.cihr-irsc.gc.ca/e/20410.html.
151. Government of Canada. Human Biological Materials Including Materials Related to Human Reproduction. Government of Canada; 2014 [cited 2016 21/09]; Available from: http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter12-chapitre12/#toc12-1F.
152. European Medicines Agency. Stem-cell-therapy treatments. European Medicines Agency; 2013 [updated 2013 22/04; cited 2016 26/08]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/04/news_detail_001769.jsp&mid=WC0b01ac058004d5c1.
153. Witherspoon Council on Ethics and the Integrity of Science. The Stem Cell Debates: Lessons for Science and Politics -Appendix E Overview of International Human Embryonic Stem Cell Laws. The New Atlantis. 2012;34(Winter):129-46.
154. EuroStemCell. Europe approves Holoclar®, the first stem cell-based medicinal product EuroStemCell; 2015 [updated 2015 26/02; cited 2016 26/08]; Available from: http://www.eurostemcell.org/story/europe-approves-holoclar-first-stem-cell-based-medicinal-product.

155. McGregor C, Peterson, A., Munsie, M. Stem cell tourism: selling hope through unproven stem cell treatments - lessons from the X-Cell Center controversy. EuroStemCell; 2015 [updated 2015 30/04; cited 2016 26/08]; Available from: http://www.eurostemcell.org/commentanalysis/stem-cell-tourism-selling-hope-through-unproven-stem-cell-treatments-lessons-x-cell-.
156. European Commission. Horizon 2020: The EU framework Programme for Research and Innovation 2011 [cited 2016 26/08]; Available from: https://ec.europa.eu/programmes/horizon2020/en/official-documents.
157. EuroStemCell. Regulation of stem cell research in Europe. EuroStemCell; 2016 [updated unknown; cited 2016 26/08]; Available from: http://www.eurostemcell.org/stem-cell-regulations.
158. UK Stem Cell Foundation. Stem cell research. UK Stem Cell Foundation; 2016 [cited 2016 21/09]; Available from: http://www.ukscf.org/about-stem-cell-research.html.
159. Welcome Trust - Medical Research Council Cambridge Stem Cell Institute. Research. Stem Cell Institute; 2016 [cited 2016 21/09]; Available from: http://www.stemcells.cam.ac.uk/researchers/.
160. EuroStemCell. Regulation of stem cell research in the United Kingdom. EuroStemCell; 2015 [updated 2011 14/12; cited 2016 26/08]; Available from: http://www.eurostemcell.org/regulations/regulation-stem-cell-research-united-kingdom.
161. Verma S, Younus J, Haynes AE, Stys-Norman D, et al. Dose-intensive chemotherapy with growth factor or autologous bone marrow or stem-cell transplant support in first-line treatment of advanced or metastatic adult soft tissue sarcoma: a clinical practice guideline. Current oncology. 2008;15(2):80-4.
162. Kostaras X, Easaw JC. Management of recurrent medulloblastoma in adult patients: a systematic review and recommendations. Journal of neuro-oncology. 2013;115(1):1-8.
163. Granel B, Daumas A, Jouve E, Harle JR, et al. Safety, tolerability and potential efficacy of injection of autologous adipose-derived stromal vascular fraction in the fingers of patients with systemic sclerosis: an open-label phase I trial. Annals of the Rheumatic Diseases. 2015;74(12):2175-82.
164. Effinger KE, Migliorati CA, Hudson MM, McMullen KP, et al. Oral and dental late effects in survivors of childhood cancer: A Children's Oncology Group report. Supportive Care in Cancer. 2014;22(7):2009-19.
165. Ontario HQ. Limbal stem cell transplantation: an evidence-based analysis. Ontario Health Technology Assessment Series. 2008;8(7):1-58.
166. Boureaux E, Chaput B, Bannani S, Herlin C, et al. Eyelid fat grafting: Indications, operative technique and complications: A systematic review. Journal of Cranio-maxillo-facial Surgery. 2016;44(4):374-80.
167. Riboh JC, Saltzman BM, Yanke AB, Cole BJ. Human Amniotic Membrane-Derived Products in Sports Medicine: Basic Science, Early Results, and Potential Clinical Applications. American Journal of Sports Medicine. 2015.
168. Canadian Agency for Drugs and Technologies in Health. Strings Attached: CADTH's Database Search Filters. Canadian Agency for Drugs and Technologies in Health; 2016 [cited 2016 20/09]; Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#syst.
169. Scottish Intercollegiate Guidelines Network. Search filters. Scottish Intercollegiate Guidelines Network; 2016 [cited 2016 21/09]; Available from: http://www.sign.ac.uk/methodology/filters.html.
170. Gimble JM, Katz AJ, Bunnell BA. Adipose-derived stem cells for regenerative medicine. Circulation Research. 2007;100(9):1249-60.
171. Pierini M, Di Bella C, Dozza B, Frisoni T, et al. The posterior iliac crest outperforms the anterior iliac crest when obtaining mesenchymal stem cells from bone marrow. The Journal of Bone and Joint Surgery American Volume. 2013;95(12):1101-7.

172. StemCells® Australia. About us. StemCells® Australia; 2016 [cited 2016 21/09]; Available from: http://www.stemcellsaustralia.edu.au/AboutUs.aspx.
173. International Society for Stem Cell Research. Guidelines for the clinical translation os stem cells. International Society for Stem Cell Research; 2008 [cited 2016 21/09]; Available from: http://www.isscr.org/docs/guidelines/isscrglclinicaltrans.pdf.
174. Ross J. Stem cell 'tourists' flock to Australia. The Australian; 2016; Available from: http://www.theaustralian.com.au/news/health-science/stem-cell-tourists-flock-to-australia/news-story/3f36a4e22b46e5df931f75828f87df7b.
175. National Health and Medical Research Council. Stem cell treaments - frequently asked questions. National Health and Medical Research Council; 2013 [cited 2016 21/09]; Available from: https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/rm001a_stem_cell_treatments_faq_131220.pdf.
176. Arnold A. 'Hallmarks of quack medicine' in fatal stem cell treatment, Coroner finds. ABC; 2016; Available from: http://www.abc.net.au/radionational/programs/backgroundbriefing/hallmarks-of-quack-medicine-in-fatal-stem-cell-treatment/7630288.
177. Coroners Courts New South Wales. Inquest into the death of Sheila Drysdale. NSW State Coroner's Court; 2016 [cited 2016 21/09]; Available from: http://www.coroners.justice.nsw.gov.au/Documents/Findings%20Drysdale.pdf.
178. Association of Reproductive Health Professionals. Position Statements: Stem Cell Research/Cloning. Association of Reproductive Health Professionals; 2012 [cited 2016 29/08]; Available from: http://www.arhp.org/about-us/position-statements#13.
179. Australian Academy of Science. Summary of previous statements—Stem cells and human cloning. Australian Academy of Science; 2011 [cited 2016 29/08]; Available from: https://www.science.org.au/supporting-science/science-policy/position-statements/stem-cells-cloning.
180. Australian Rheumatology Association. A.R.A Position Statement on Stem Cell Therapies. Australian Rheumatology Association; 2014 [cited 2016 29/08]; Available from: https://rheumatology.org.au/downloads/ARA%20Position%20Statement%20042014.pdf.
181. Osborne H, Anderson L, Burt P, Young M, et al. Australasian College of Sports Physicians-position statement: the place of mesenchymal stem/stromal cell therapies in sport and exercise medicine. British Journal of Sports Medicine. 2015.
182. Australia and New Zealand Spinal Cord Injury Network. Stem cell interventions for spinal cord injury. NSW Government Lifetime Care & Support Authority; 2009 [cited 2016 29/08]; Available from: http://www.lifetimecare.nsw.gov.au/__data/assets/pdf_file/0006/18393/ANZSCIN_stem_cell_interventions.pdf.
183. Motor Neurone Disease Australia. Position Statement: Alternative and Unproven therapies and people diagnosed with MND Motor Neurone Disease Australia; 2014 [cited 2016 29/08]; Available from: http://www.mndaust.asn.au/Documents/Policies-and-position-statements/Unproven-therapies-for-MND-and-the-internet.aspx.
184. Murdoch Childrens Research Institure. Stem cell therapy for cerebral palsy. Centre of Research Excellence; 2016 [cited 2016 29/08]; Available from: http://www.cre-cp.org.au/wordpress/wp-content/uploads/2014/10/Stemcell-Fact-Sheet-Professionals.pdf.
185. Multiple Sclerosis Research Australia. Position Statement: Autologous Haematopoietic Stem Cell Transplant (AHSCT) for MS. Multiple Sclerosis Research Australia; 2016 [cited 2016 29/08]; Available from: http://www.msra.org.au/files/2016%20AHSCT%20Position%20Statement.pdf.
186. Royal Australasian College of Physicians, Australasian Faculty of Rehabilitation Medicine. Position Statement on the use of stem cells as a therapy for cerebral palsy. Centre of Research Excellence in Cerebral Palsy; 2014 [cited 2016 29/08]; Available from: http://www.cre-cp.org.au/wordpress/wp-content/uploads/2014/10/AFRM-Position-Statement-stem-cells-as-therapy-for-CP.pdf.

187. Therapeutic Goods Administration. Products regulated as biologicals. Therapeutic Goods Administration; 2016 [cited 2016 17/11]; Available from: https://www.tga.gov.au/products-regulated-biologicals.

188. Therapeutic Goods Administration. Australian regulatory guidelines for biologicals (ARGB). Therapeutic Goods Administration; 2016 [cited 2016 17/11]; Available from: https://www.tga.gov.au/publication/australian-regulatory-guidelines-biologicals-argb.