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Bone-Marrow Derived Stem Cell Injections for Wound Healing and Tissue Rejuvenation: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines

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Context and Policy Issues

Orthopedic and trauma conditions occur in a variety of sites in the body, but most frequently in hip, foot and ankle, knee, leg, spine, and any joints. These conditions are debilitating and affect quality of life significantly; therefore effective treatment options are necessary.

Mesenchymal stem cells (MSCs) are known for their osteoinductive, osteoconductive, and osteogenic potential, and can differentiate into a number of cell types[1] In recent years, an increasing number of preclinical studies have shown the effectiveness of MSC-derived cell therapy.[2] However, the success in preclinical research has not translated into clinical practices.[3] The sources of MSCs and methods of administration can also vary greatly.

Bone marrow is a common source of MSCs and therefore bone marrow aspirates are frequently used, and are purified and enriched to increase the number of stem cells. Autologous bone marrow derived stem cells (BMDSC) are cultured ex vivo and then implanted back into the patient's body using a variety of methods, including bone grafts or scaffolds of materials containing BMDSCs, or injections. Injection-based methods are increasingly being used in clinical studies.[4] However, findings from these studies show significant variations with regard to the effectiveness of BMDSC treatment, as well as the type of conditions in which BMDSC injection is in use.

The objective of this report is to evaluate the clinical effectiveness, cost effectiveness, and evidence-based guidelines for the use of BMDSC injection for patients with any orthopedic or trauma conditions.

Research Questions

1. What is the clinical effectiveness of bone marrow-derived stem cell (BMDSC) injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?
2. What is the cost-effectiveness of BMDSC injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?
3. What are the evidence-based guidelines regarding the use of BMDSC injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?

Key Findings

Overall, there were an insufficient number of high quality studies that specifically looked at the effectiveness of BMDSC injection in various trauma, injury, or other orthopedic conditions. Among the four relevant systematic reviews identified, two reported improved clinical, functional and safety outcomes in patients with knee osteoarthritis (OA) by measuring knee and joint functions, quality of life, cartilage growth, pain and other subjective parameters as well as any adverse events (AE). Two other systematic reviews showed that among patients with osteonecrosis of the femoral head (ONFH), BMDSC injection can lead to a reduction in pain and other clinical symptoms, osteonecrosis volume, progression of disease and other radiological outcomes, and the need for total hip replacement (THR). However, two of the included systematic reviews lacked methodological rigor and adequate reporting. In addition, the inclusion of several non-comparative studies and heterogeneous mode of BMDSC implantation, outcomes

assessed, and methodologies of the component studies are important considerations.

Two high-quality randomized clinical trials showed that following injection of BMDSC, patients with a range of knee injuries had a significant improvement in their clinical and radiological outcomes. In addition, cell therapy was not associated with any serious AEs and no or few mild to moderate AEs as reported from these studies, in addition to a phase I safety trial.

The guideline included in this report concluded that there is insufficient high quality evidence that injection of cultured BMDSC is effective in the remedy of delayed union or nonunion of long bone fractures. In addition, owing to the differences in BMDSC harvesting and culturing as well as measurement of relevant outcomes across studies, the authors recommended against its use in clinical practice.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and May 1, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (of any age) requiring treatment for wound healing or tissue rejuvenation (e.g., due to injury, trauma, or other orthopedic conditions)
Intervention	Bone marrow-derived stem cell (BMDSC) injections
Comparator	Q1 and Q2: Standard of care; Exercise and/or physiotherapy; Cortisone injections; Non-steroidal anti-inflammatory drugs (NSAIDS); Q3: No comparator required
Outcomes	Q1: Clinical benefit (e.g., wound healing, functional outcomes, pain, quality of life); Harms (e.g., re-injury rates, infection, injection-related harms, neurological outcomes) Q2: Cost-effectiveness outcomes (e.g., cost per quality adjusted life year or health benefit gained) Q3: Evidence-based guideline recommendations regarding the use of BMDSC injections (including HCP training requirements, indications, administration etc.)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, they were older reports of a series of studies conducted by the same group of authors for which updates were available, or were published prior to 2007. In addition, meta-analyses were excluded if they pooled results from studies that used both injection and non-injection based BMDSC delivery.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR,[5] randomized studies were critically appraised using the Downs and Black checklist,[6] and guidelines were assessed with the AGREE II instrument.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 360 citations were identified in the literature search. Following screening of titles and abstracts, 321 citations were excluded and 39 potentially relevant reports from the electronic search were retrieved for full-text review. An additional 17 potentially relevant publications were retrieved from the grey literature search or hand searching. Of these potentially relevant articles, 48 publications were excluded for various reasons, while eight publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

In total, four systematic reviews without meta-analyses,[2,8-10] three clinical trials - two randomized, controlled[11,12] and one phase I safety trial,[13] and one guideline[14] – meeting the inclusion criteria were identified.

A detailed summary of study characteristics is given in Appendix 2.

Study Design

The systematic review by Filardo et al.[2] included 18 clinical trials and several preclinical studies published from 2002 to 2012, four of which used injection-based bone marrow concentrate (BMC) or cultured BMDSC treatment for cartilage regeneration. Three small studies (no more than six patients each) that used BMDSC were case series and case reports and the trial using BMC was a comparative study. Hernigou et al.[8] conducted a systematic review on the different aspects of cytotherapy in osteonecrosis since its inception 30 years ago, in which they briefly discussed results from one case series, two prospective, randomized, double-blind trials, one meta-analysis and one narrative literature review, all published after 2004. Peeters et al.[9] conducted a systematic review to describe the safety of BMDSC in cartilage repair and OA treatment, in which six studies used BMDSC injection as intervention. These studies were made up of three prospective cohort studies, one pilot study, one clinical trial, and one case series. Another systematic review by Piuzzi et al.[10] reported on BMDSC-based cell therapy in patients with osteonecrosis of femoral head (ONFH). A total of 11 studies

were included, of which seven RCTs and one retrospective cohort study used an injection-based delivery method of BMDSC.

Three clinical trials were not captured in the systematic reviews and are included in this report. Wong et al.[11] conducted a prospective, randomized controlled study in which patients were treated with cultured BMDSC with hyaluronic acid (HA) for OA of the knee and its clinical effectiveness was compared with HA injection. Vangsness et al.[12] reported a randomized, double-blind, controlled study in which patients were either treated with 2 doses of cultured BMDSC injection or sodium hyaluronate. Finally, Emadedin et al.[13] conducted a phase I safety trial on patients with bone nonunion to test whether administration of cultured BMDSC injection results in any adverse events or not.

The evidence-based guideline by the Department of Labor and Employment in the State of Colorado included meta-analyses and RCTs identified through a search using specific keywords.[14]

Country of Origin

The systematic reviews included in this report were conducted by authors from Germany, Italy,[2] France,[8] Netherlands,[9] and the USA.[10] The two randomized trials were conducted in Singapore[11] and the USA,[12] and the safety trial was conducted in Iran.[13] The evidence-based guideline was conducted in the USA.[14]

Patient Population

The four systematic reviews included patients with various orthopedic conditions in the lower limb, including cartilage defects (chondral defects to articular osteoarthritis degeneration), OA,[2,9] and ONFH.[8,10]

The randomized trial by Wong et al.[11] was conducted in 56 patients with unicompartmental OA of the knee and genu varum who underwent arthroscopy, microfracture and subsequent high tibial osteotomy (HTO). Vangsness et al.[12] conducted a randomized, double-blind, controlled trial in 55 patients who underwent meniscectomy for OA of the knee as determined by their respective surgeons in seven centres. The phase I safety trial by Emadedin et al.[13] was performed in 5 patients with long bone nonunion.

In the guideline by the Department of Labor and Employment in the State of Colorado, studies involving patients with a number of knee, foot and ankle, hip and leg injuries were included.[14]

Interventions and Comparators

The relevant studies included in the systematic review by Filardo et al.[2] and Peeters et al.[9] included various doses of cultured BMDSC and BMC injection. The source of cells was the iliac crest. Treatments received by the control group were not mentioned in these reviews; however, a number of adjuvant therapies were given to patients in addition to BMDSC injection, including serum, platelet lysate, HA, fibrin glue, or collagen. Hernigou et al.[8] did not specify the source of BMDSCs or treatments received by the control group. Piuzzi et al.[10] reviewed studies that used cultured BMDSC injection with or without core decompression (CD) and compared with those who only received CD.

In the clinical trial by Wong et al.,[11] autologous bone marrow cells were harvested from the iliac crest and subsequently purified, enriched and

cultured. Each patient received the same volume (mean cell number $1.46\pm0.29X10^7$) of a single injection of cultured BMDSC injection along with 3 separate doses of hyaluronic acid (HA) whereas the control group received HA injections only. The trial conducted by Vangsness et al.,[12] on the other hand, used bone marrow aspirate derived adult human mesenchymal stem cells from unrelated individuals with unmatched human leukocyte antigen (HLA) cultured *ex vivo* and injected into the target site. Two different doses ($50X10^6$ and $150X10^6$) of cultured BMDSC solution were used as treatment, whereas the control group received sodium hyaluronate/hyaluronan) vehicle control. The trial conducted by Emadedin et al.[13] performed bone marrow aspiration from the iliac crest, and then mononuclear cells (MNCs) were isolated, purified, cultured and injected into patients at a dose of $20\text{-}50\times10^6$ cells per patient.

The guideline provided recommendations based on the available evidence and expert consensus on different treatment options for the indications related to lower extremity injury practiced in the USA, including the use of BMDSC.[14]

Outcomes

The main outcomes reported in the included studies for symptoms in the knee, hip, and elbow can be broadly categorized into clinical, functional and radiological outcomes.

The clinical outcomes included various subjective patient reported outcomes that assessed a range of indices such as pain, movement, activity, motion, stiffness, condition of the injured site, and functional state. Tegner and Lysholm knee scores,[11,12] International Knee Documentation Committee (IKDC) scores,[11] Visual Analogue Scale (VAS),[8,10,12] Lequesne index, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score,[8,10], Harris Hip Score (HHS) and the System of Merle d'Aubigne and Postel.[10] were the clinical outcomes measured in the included studies. In addition, improvement in pain, joint functions, walking ability, and quality of life[2,8] were assessed independently rather than part of a scoring system in some studies.

Radiological outcomes included in the relevant studies were meniscus regeneration by MRI,[2,8,12] disease progression into collapse of the femoral head and conversion to Total Hip Replacement (THR),[8,10] Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring system,[11] lesion size.[10]

The safety profile of BMDSC injection treatment was assessed using a number of parameters that were categorized based on severity (serious, not serious), relatedness (definitely, probably, possibly related) or causative factor (procedure-related, stem cell injection-related).

Death, neoplasms, infections, pulmonary embolisms, and anaphylactic shock.[9,13] vital signs and ectopic tissue formation[12] were considered serious adverse events (SAE). A shift in clinical hematology, blood chemistry and urine values, including deviation of immune cell markers for T cells, natural killer cells, and B cells from baseline values were measured. Examination of the physical condition of the knee joints such as redness, swelling, deformities, abnormal tissue presentation, and/or skin changes were measured in one study.[12] Other AEs included arthralgia, joint swelling, joint stiffness, injection-site joint pain, joint effusion, headache, and peripheral edema.[12]

Summary of Critical Appraisal

Additional details regarding the critical appraisal of included studies are provided in Appendix 3.

Systematic Reviews

Overall, none of the included systematic reviews had done meta-analyses or pooling of the results. Therefore, statistical heterogeneity between studies and publication bias could not be assessed. The studies used various doses and preparations of BMDSC with or without conventional therapies, a range of outcomes to detect mostly knee and hip injuries, patients with varying baseline characteristics, and different follow-up lengths; making it difficult to qualitatively assess between study heterogeneity. The methodological quality and reporting also varied, with at least two reviews conducted poorly.

While Filardo et al.[2] clearly reported the study question, literature search strategy and characteristics of the component studies, it had several limitations. There was no evidence that the screening and data extraction was done by at least two independent reviewers. Selection was limited to studies published in English and within a 10 year timeframe, and there was no evidence of searching the grey literature. In addition, there were no clear inclusion and exclusion criteria reported, and the included studies were not tested for methodological rigor. Finally, the results were described in text without much information about the component studies.

The review by Hernigou et al.,[8] while self-identifying as a systematic review, lacked most features of this design and instead reported on various aspects of stem cell-based therapy. The aim of the study was broad, and there were no information on how studies were identified, screened and selected, whether two independent reviewers were involved in the process, and assessment of methodological quality of each study. The publication also contained very little information on the population, intervention, comparators and outcomes (PICO) of the component studies.

The systematic review by Peeters et al.[9] had a clear research question and outcome. The screening was done using clearly described keywords and in four databases. In addition, studies published in any time period and in five languages were considered. However, search in grey literature was not reported. Inclusion and exclusion criteria were clearly defined, the selection of articles and subsequent assessment of methodological quality was done by two independent reviewers, and disagreement was resolved by consensus.

Piuzzi et al.[10] conducted a two- part systematic review on the use of cell-based therapies in ONFH, and Part I was relevant to this report. The research question and outcomes were clearly described. Four major databases were searched for relevant literature, and more than one reviewer performed the screening and study selection process independently using clearly defied inclusion and exclusion criteria. The references of component studies were also searched and the PICO of each individual study was described. However, the search was limited to literature published in English and between 1990 and 2016, however, this timeframe would capture most relevant studies conducted using BMDSC technology. Several key pieces of information were missing, including how disagreement was resolved between the reviewers if any, and assessment of methodological quality of the component studies.

Clinical trials

Overall, the studies conducted by Wong et al.[11] and Vangsness et al.[12] were conducted well, while the phase I safety trial by Emadedin et al.[13] had a limited sample size (n = 5).

In all three studies, the objective, patients' inclusion and exclusion criteria, intervention and outcomes of interest as well as major findings and any AEs were clearly described. The outcomes in the study by Wong et al.[11] were measured in a valid and reliable manner, whereas MRI-based measurement used by Vangsness et al.[12] produced inconsistent results attributed to differences in study sites, visits and edge-detection evaluation. Emadedin et al.[13] examined AEs presenting following surgery and lacked sufficient details on how these outcomes were measured. For the two randomized trials,[11,12] the treatment allocation process was blinded to the patients and the person or facilities administering it. In both instances, the personnel responsible for assessing the main outcomes were blinded to the participants' treatment status, except in Wong et al.[11] where it was not reported if the non-MRI based outcomes were assessed blindly or not. Since the patients received autologous BMDSCs by Wong et al.[11] they could not be blinded due to pain and wound at the site of aspiration. However, Vangsness et al.[12] used a double-blind design where the injection containing allogenic BMDSC was administered by the physician using a cellophane wrapped syringe, thereby maintaining the double-blind status of both the physician and patient. The safety trial by Emadedin et al.[13] was not randomized and therefore these measures were not taken. Both randomized trials had adequate power to detect a meaningful difference for the outcome of interest, however sample size was not calculated for the third trial. Both randomized trials used appropriate statistical tests to analyze the outcomes. There were five dropouts in the Vangsness et al.[12] study; however, it was unclear whether any measures were taken to account for this other than excluding those observations from analyses. No losses to follow-up were reported in the other studies. Finally, principle confounders and baseline characteristics were provided in all studies, and they were either similar in different groups or differences were taken into account in the analyses. An exception to this was differences in the distribution of OA among the 3 groups in the Vangsness et al.[12] study, and it is unclear whether these differences had an impact on the results.

The major limitation common to all three trials is related to external validity. None of the trials provided information to assess whether the patients included in the studies were representative of the general population and whether they were recruited at the same time. In addition, it is unclear if the treatment facility, physicians and study personnel involved in the study were representative of the treatment the general population would receive.

Guideline

The relevant guideline by the Department of Labor and Employment in the State of Colorado[14] consisted of high quality evidence and had demonstrated strong methodological rigor. The overall objective of the guideline, health question and target population were clearly described. The literature search strategy was thorough, with clearly defined search terms and exclusion criteria. The guideline limited the included evidence to meta-analyses and RCTs. Grey literature searching was not conducted. From the guideline, it appears individuals from relevant professional groups and workers were not consulted during the preparation of the report. The evidence was graded into

"some evidence," "good evidence," and "strong evidence" according to the General Guidelines Principles in each of the Division Medical Treatment Guidelines. The recommendations were based on the availability of evidence for a given indication and intervention and there were explicit links between the evidence and specific recommendations. Clarity of presentation and was ensured throughout the guideline; however, the authors did not disclose whether there was any conflict of interest within the members of the guideline development group and between the editorial body and funders. In addition, some elements of applicability were addressed in the guideline, such as recommendations on putting different treatment options into practice for specific indications, and benefits and challenges associated with each treatment option. However, the resources required for implementing the recommendations as well as monitoring and auditing criteria were not discussed.

Summary of Findings

What is the clinical effectiveness of bone marrow-derived stem cell (BMDSC) injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?

A detailed summary of key findings and author's conclusion is given in Appendix 5.

The systematic review by Filardo et al.[2] described one comparative and three non-comparative studies in which injection of BMDSC resulted in an improvement in cartilage thickness and volume as well as functional improvement in pain, subjective parameters, and quality of life. However, no details on specific measures of association were given. In addition, case series, case reports and one comparative study were included in the review, thereby making the conclusions more exploratory.

Hernigou et al.[8] reported that among early stage ONFH patients, BMDSC injection results in a decrease in necrosis volume (26 cm^3 to 12 cm^3 on average), progression into advanced stage (as determined by stage 1–2 osteonecrosis and need for THR), reduced pain and joint symptoms, alone or compared to core decompression. Peeters et al.[9] reviewed safety related outcomes and reported that BMDSC treatment in patients with OA is safe to administer, after concluding that no SAEs in the component studies were related to stem-cell therapy, instead two instances of probable and possible infection and pulmonary embolism, respectively and two unrelated tumours were reported to be due to the procedure. Seven AEs reported in the component studies involved pain and swelling, all of which were resolved easily.

Piuzzi et al.[10] reported that among patients with ONFH, treatment with autologous BMDSCs was associated with similar or better patient reported outcomes (VAS, WOMAC score, Lequesne index, and HHS). MRI results showed that 24.5% of the cell-therapy group had radiographic progression of ONFH lesion as opposed to 40% in the control group. Total hip arthroplasty (THA) conversion rate was lower in the cell-therapy group (16%) compared to the control group (21%) although this difference was not always significant. Similar to the systematic review by Peeters et al.,[9] few minor AEs were reported in either group (2.4% in the control group and 2.9% in the cell-therapy group), no major AEs were reported, and the frequency of AEs did not significantly differ between the groups. Pain and hematoma at the site of

surgery were the most common complaint, and a small number of cases of infection were reported.

In the randomized trial by Wong et al.[11] both the BMDSC cell-treated group and the HA-treated control group had an improvement in clinical outcomes, but the improvement in the BMDSC cell-treated group was significantly better, as shown by an added improvement of 7.65 (95% confidence interval [CI]: 3.04 to 12.26, P=0.001) for IKDC, 7.61 (95% CI: 1.44 to 13.79, P=0.016) for Lysholm scores, and 0.64 (95% CI: 0.10 to 1.19, P=0.021) for Tegner scores. There was a mean difference of 19.6 (95% CI: 10.5 to 28.6, P=0.001) in adjusted MOCART score between the two groups. In addition, 32% of cell-treated patients had a complete cartilage coverage and 36% had >50% coverage of the lesion, which was significantly better than the control group (0% and 14%). Of the cell-treated patients, 61% showed significantly better integration of regenerated cartilage whereas 86% control patients had visible signs of incomplete integration. Finally, no SAEs were reported in the study. The randomized trial by Vangsness et al.[12] showed no SAEs related to any of the comparing treatments, and the reported AEs did not result in discontinuation. While 95% patients reported a total of 427 AEs, most were mild or moderate in nature and involved musculoskeletal, connective tissue, general, and administration-site disorders. There were also no trends in blood and urine analyses results, vital signs and ectopic tissue formation before and after injection. In terms of clinical efficacy, a >15% increase in meniscus volume from baseline was seen among 24% and 6% of the two cell treatment groups as compared to controls at the end of the 2 year follow-up period. VAS score decreased significantly for all 3 groups (P<0.001); however the average relative improvement in VAS score after 2 years were 27.3 mm and 24.1mm for the two cell treatment groups compared to the control, respectively. The Lysholm knee score also improved significantly in all three groups.

The phase I safety trial by Emadedin et al.[13] reported no AEs in any of the five included patients and 3 out of 5 showed signs of healing an bone union. However, the authors provided very little detail on the AEs measured and description of results.

What is the cost-effectiveness of BMDSC injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?

No relevant evidence regarding the cost-effectiveness of BMDSC injections for wound healing or tissue rejuvenation was identified; therefore, no summary can be provided.

What are the evidence-based guidelines regarding the use of BMDSC injections for wound healing or tissue rejuvenation in orthopedic and trauma patients?

The Lower Extremity Injury Medical Treatment Guidelines by the Department of Labor and Employment in the State of Colorado[14] assessed the use of different treatment methods for a range of orthopedic conditions, in which BMDSC injection was not reported to be a successful and recommended treatment option. Of the 15 indications in which bone marrow was used, one condition, ONFH, was shown to be improved by BMDSC injection. The authors concluded that cultured BMDSC can markedly reduce the progression of early stage ONFH, but due to the heterogeneity in techniques and study methodologies, the practice of BMDSC injection is not recommended, particularly in the US where stem cell culture is prohibited.

Limitations

A number of limitations were present in the included studies. The systematic reviews that were included were poorly done or lacked the objective of solely including results from studies with BMDSC injection. Therefore, only the findings from relevant component studies were reported and it was impossible to include a meta-analysis to obtain a pooled effect estimate. Results from the component studies were described narratively, and included varying interventions and outcomes; therefore drawing a firm conclusion was difficult. Two systematic reviews[2,9] were done without the involvement of a second reviewer and may therefore lead to bias. The RCTs were of high-quality and provided good evidence on the effectiveness and safety of BMDSC injection on a number of orthopedic conditions. However, the external validity of these studies is limited, as the sources of patients were not disclosed. The guideline included 184 high quality studies, but lacked an external reviewer and information regarding independence of the editorial board and the authors. Finally, there was no evidence regarding the cost-effectiveness of BMDSC injections for wound healing or tissue regeneration.

Conclusions and Implications for Decision or Policy Making

This report provided an overview of the clinical results with regard to the use of BMDSC injection in patients with various orthopedic conditions. The original studies included in the systematic review and clinical trials mostly included patients with knee injury and ONFH. Therefore, it is yet to be determined how BMDSC treatment fares in other orthopedic conditions. Furthermore, current use of BMDSC treatment is done among patients who previously underwent some other interventions depending on the conditions, and BMDSC treatment is sometimes provided as an adjuvant to other conventional therapies. Evidence of BMDSC as a primary mode of treatment is lacking. In patients with knee and hip conditions, successful reduction in clinical symptoms, disease progression and improvement in functional symptoms were observed. In addition, the relative safety of this method was reported in all the relevant studies. However, due to the variable patient and study characteristics, and BMDSC harvesting and culturing conditions, BMDSC injection is more common in preclinical studies than in clinical practice.[2] This was reflected in the included guideline[14] in which authors reported insufficient evidence of the effectiveness of BMDSC in treating orthopedic conditions and advised against its use.

In conclusion, due to the lack of sufficient high quality evidence for BMDSC injection in orthopedic and trauma conditions, the use of this treatment method is not prevalent and requires further high quality studies.

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14. Lower extremity injury medical treatment guidelines [Internet]. Denver (CO): State of Colorado, Department of Labor and Employment; 2016. [cited 2017 May 18]. Available from: https://www.colorado.gov/pacific/sites/default/files/Rule_17_Exhibit_6_Lower_Extremity_Guideline.pdf

15. Kim YS, Lee M, Koh YG. Additional mesenchymal stem cell injection improves the outcomes of marrow stimulation combined with supramalleolar osteotomy in varus ankle osteoarthritis: short-term clinical results with second-look arthroscopic evaluation. J Exp Orthop [Internet]. 2016 Dec;3(1):12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4875581

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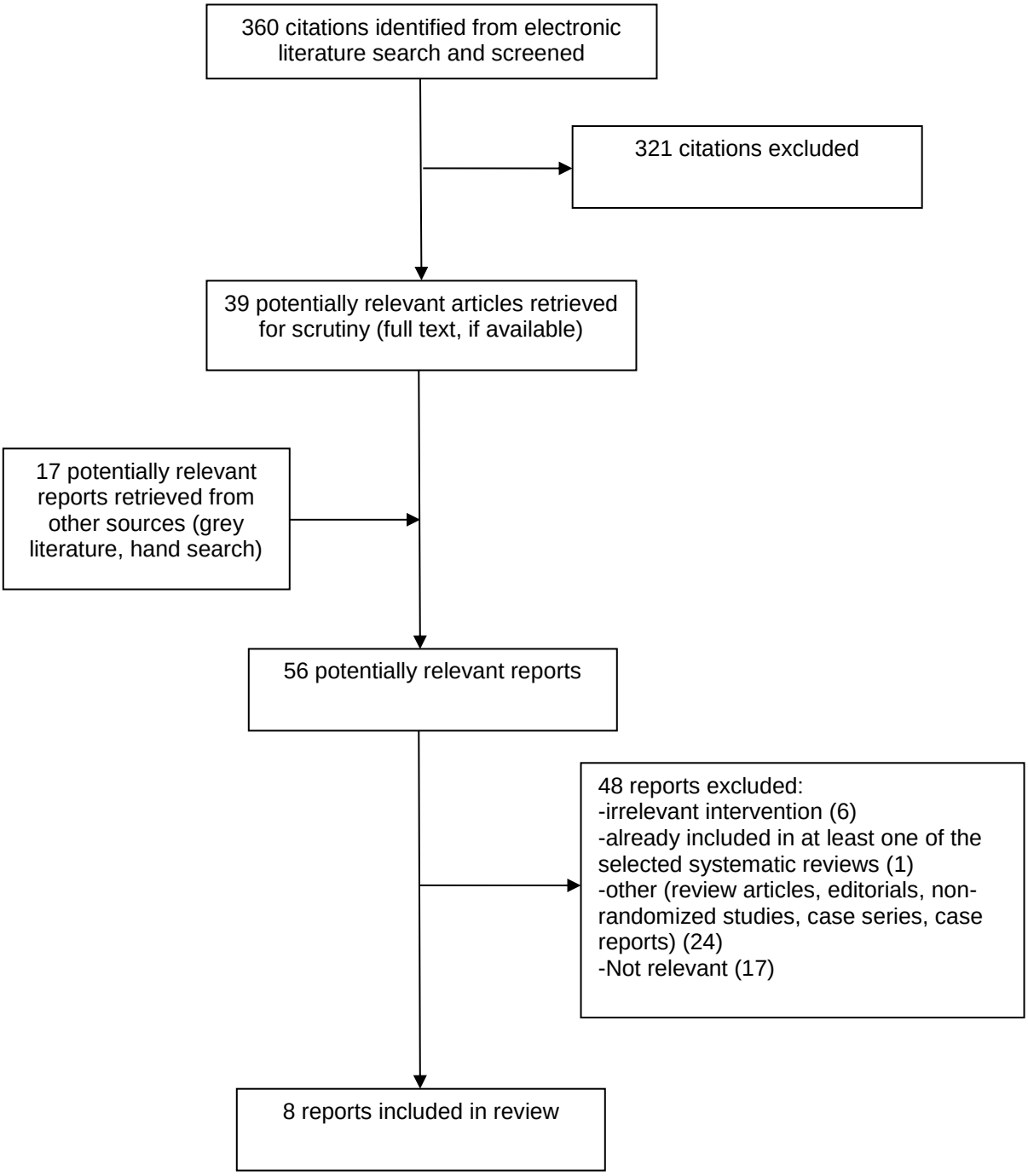
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year	Types and numbers of primary studies included	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Filardo et al. 2013[2]	18 Clinical trials on cartilage regeneration, 3/11 used BMDSC injection, 0 randomized, 2 case series, 1 case report 1/5 used BMC injection, 1 comparative study	Patients with a range of cartilage defect from focal chondral defects to articular OA degeneration. Three Studies using BMDSC included 6, 4 and 1 patients Study using BMC had 50 patients	Injection of Cultured BMDSC or BMC+ debridement (different dose)	No comparator in 3 studies using BMDSC; Debridement in study involving BMC	Cartilage defect regeneration by clinical symptoms (e.g. pain), cartilage growth, functional outcomes (e.g. walk, motion), quality of life. Follow-up varied from 24 weeks-12 months
Hernigou et al. 2016[8]	1 retrospective case-series; 2 Prospective, double-blind, controlled trial; 1 meta-analysis; 1 narrative literature review (496 citations)	Patients with avascular ON or ONFH	BMC injection CD and autologous BMC injection CD+ autologous bone marrow implantation CD+ autologous BMA containing MSCs	Not reported or CD alone	Clinical symptoms (VAS, Lequesne index, WOMAC score) and disease progression (ARCO stage 1/2 to 3); Radiologic outcomes: Volume of the necrotic lesion, conversion to THR; Any AE; Follow-up 8-18 years
Peeters et al. 2013[9]	8 studies, 6 used cultures BMDSC injection, 3 prospective cohort studies, 1 clinical trial and 1 pilot study, 1 case series	Patients treated with culture-expanded BMDSCs in joints for cartilage repair and OA, 470 subjects, 844 intra-articular procedures, 789 injections	Autologous BMDSC (doses vary) supplemented with platelet lysate or plasma, autologous serum, albumin	Not reported	Possibly procedure-related, stem cell product-related, or unrelated SAE (death, neoplasms, infections, pulmonary embolisms, anaphylactic shock and haematological neoplasms) or AE; Follow-up 21 months

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year	Types and numbers of primary studies included	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
					(mean)
Piuzzi et al. 2017[10]	11 studies, 10 used bone marrow cells, 8 used injection – based delivery; 7 RCTS, 1 retrospective cohort study	Patients treated for ONFH, 616 subjects	Autologous BMMNC, BMC, bone marrow buffy coat, cultured BMDSC (doses vary)	CD alone, or in combination with unprocessed bone marrow, autologous bone graft, or curettage	Clinical outcomes: Merle d'Aubigne and Postel, Patient-reported outcomes: WOMAC, pain (VAS), HHS, Lequesne index; Radiological outcomes: ARCO stage, lesion size; Revision rate/THA, complications; Mean follow up 37 months

AE= Adverse events; BMC= Bone marrow concentrate; BMA=Bone marrow aspirate; BMDSC= Bone marrow-derived stem cell; BMMNC= Bone marrow derived mononuclear cell; CD= Core decompression; HHS= Harris Hip Score; OA= osteoarthritis; ONFH= Osteonecrosis of the femoral head; RCT = randomized controlled trial; SAE= Serious adverse events; THR= Total hip replacement; THA= Total hip arthroplasty; VAS= Visual analogue scale; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index

Table 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Wong et al. 2013 Singapore[11]	Prospective, randomized, controlled trial; Follow-up: 6 weekly intervals, then followed by 6 months, 1 year and 2 years interval	Inclusion: Patients <55 years with medial-compartment OA and genu varum, normal lateral joint space, no fixed flexion deformity of the knee, and no collateral ligament instability; n=56 total, 28 cell treatment-group and 28 control Exclusion: Having >2^{o} joint line congruity angle, malalignment	Single Intra-articular injection of cultured BMDSCs with 3 separate doses of HA 3 weeks post-surgery (Arthroscopy, microfracture and HTO) All patients received same volume of MSC (mean cell no 1.46±0.29X10^{7})	3 separate doses of HA following surgery (Arthroscopy, microfracture and HTO)	Primary outcome: IKDC score Secondary outcome: Tegner and Lysholm clinical scores and MOCART score

Table 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
		of the knee, a fixed flexion deformity, or age>55 years			
Vangsness et al. 2014, USA[12]	Phase I/II, randomized, double-blind, controlled trial; Follow-up: Upto 2 years in intervals of 6 weeks, 6 months, 1 year, 2 years	Inclusion: Patients 18-60 (mean 46) years undergoing partial medial meniscectomy based on MRI and surgeon's evaluation; n=60 initially assigned at a 1:1:1 ratio randomly, 8 discontinued, 55 treated Exclusion: No indwelling devices or conditions interfering with MRI	Single intra-articular allogeneic BMDSC injection 7-10 days post-surgery Group A: $50X10^6$ cells (n=18) Group B: $150X10^6$ cells (n=18)	Sodium hyaluronate (HA/ hyaluronan) vehicle control (n=19)	Safety: Clinical laboratory and urine tests, vital signs, and standard physical examination, MRI: meniscus regeneration, overall condition of the knee joint, and clinical outcomes: VAS and Lysholm knee scale
Emadedin et al., 2017, Iran[13]	Prospective, phase I safety trial; Follow-up: up to 12 months	Inclusion: Patients (age 18-65 yr) with lower limb long bone nonunion, diaphyseal; n=5 Exclusion: Active infection or Inadequate fixation of nonunion, positive viral tests, pregnancy, lactating, chronic, uncontrolled diseases	Autologous cultured BMDSC injection, each patient received $20\text{-}50\times10^6$ cells	No comparators	All AE: Local (limited to the nonunion site) or Systemic (unrelated to the nonunion site), serious (death, neoplasms, infections, pulmonary embolisms, and anaphylactic shock) or non-serious, related or non-related

AE= Adverse events; HA= Hyaluronic acid; HTO= High tibial osteotomy; IKDC= International Knee Documentation Committee; MOCART= Magnetic Resonance Observation of Cartilage Repair Tissue; VAS= Visual analogue scale

Table 4: Characteristics of Included Guidelines

Objectives			Methodology		
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Guideline Validation**
Lower Extremity Injury Medical Treatment Guidelines- by the State of Colorado, Department of Labor and Employment, Division of Workers' Compensation[14]					
Intended users: Healthcare providers, patient, family, employer, insurer, policy makers, and the community **Target population:** Workers injured with lower extremity injury qualified under Colorado Workers' Compensation Act	Bone marrow derived stem cell injection	Varies, depending on the indication	Systematic reviews and RCTs	Evidence graded as some, good and strong evidence	Not stated

RCT = randomized controlled trial

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Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR tool[5]

Strengths	Limitations
Filardo et al., 2013[2]	
• The research question and outcome of interest was clearly defined. • Key words for literature search were provided. • Aggregated information on study characteristics was provided in a table.	• No information on performing literature screening, data extraction by at least two reviewers, and no consensus procedure to resolve disagreement. • Literature search was limited to a period of 10 years prior to this study and only restricted to the PubMed database. • Only published articles in English were considered. • No information on search in grey literature, however the references in the included literature were screened. • No information on the inclusion and exclusion criteria. • No information on the assessment of methodological qualities of individual studies. • Only narrative description of study results were given without performing a pooled/meta-analysis, therefore study results were not combined, heterogeneity not assessed statistically. • No information on assessing publication bias. • Declaration of conflict of interest provided for review authors but not for individual studies.
Hernigou et al., 2016[15]	
• The research questions and outcomes of interest were clearly defined.	• The research questions are too broad and asking different non-related questions: rationale, technique, result, mechanism, safety etc. of BMSDC therapy. • No information on literature search strategy e.g. databases screened, language and year of publication. • No information on performing literature screening, data extraction by at least two reviewers, and no consensus procedure to resolve disagreement. • No information on search in grey literature. • No information on the inclusion and exclusion criteria. • List of included and excluded articles not provided. • No information on the assessment of methodological qualities of individual studies. • Only narrative description of study results were given without performing a pooled/meta-analysis, therefore study results were not combined, heterogeneity not assessed statistically. • No information on assessing publication bias. • Declaration of Conflict of interest provided for review authors but not for individual studies.

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR tool[5]

Strengths	Limitations
Peeters et al., 2013[9]	
• The research question and outcome of interest were clearly defined. • Key words for literature search were provided. • 4 databases, PubMed, EMBASE, Web of Science and CINAHL were searched. • Literature search was not limited to a particular period. • Study published in 5 major languages other than English were included. • Clearly defined inclusion and exclusion criteria. • 2 independent reviewers screened articles for eligibility, disagreement resolved by consensus or by consulting a third reviewer. • Characteristics of the included studies (PICO) were provided in an aggregate form using a table. • Methodological quality of included studies was assessed by 2 independent reviewers using the Mcharm quality assessment scale, disagreement resolved by consensus, consultation with a third reviewer was not necessary. Methodological rigor and scientific quality was used to form conclusions and recommendations.	• Only published studies were screened, no information on searching grey literature. • List of excluded studies not provided. • Only narrative description of study results were given without performing a pooled/meta-analysis, therefore study results were not combined, heterogeneity not assessed statistically. • No information on assessing publication bias. • Declaration of Conflict of interest provided for review authors but not for individual studies.
Piuzzi et al., 2017[10]	
• The research question and outcome of interest were clearly defined. • Key words and MeSH terms for literature search were provided. • 4 databases, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed, and Medline were searched. • Clearly defined inclusion and exclusion criteria. • 2 independent reviewers screened articles for eligibility, and 3 investigators independently reviewed the shortlisted abstracts and by applying the inclusion and exclusion criteria. • Level of evidence was assigned to each include article according to the specification of Wright et al. • The references in the included literature were screened. • Characteristics of the included studies (PICO) were provided in an aggregate form using a table. In particular, stage of outcome of interest was determined using 4 different classification systems.	• Literature search in PubMed and Medline database was limited from 1990-2006, and studies published only in English were included. • Only published studies were screened, no information on searching grey literature. • List of excluded studies not provided. • No information on how disagreement was resolved between the reviewers during initial screening of articles and assessing the abstracts. • No information on the assessment of methodological qualities of individual studies. • Only narrative description of study results were given without performing a pooled/meta-analysis, therefore study results were not combined. • Heterogeneity was not assessed statistically, however, significant variation was present between studies with respect to choice of cells, method of cell processing, quantitative and qualitative characterization of the cells used, methods of cell delivery, and patient characteristics, cohorts, and the outcome measures used. • No information on assessing publication bias. • Declaration of Conflict of interest provided for review authors but not for individual studies.

Table 6: Strengths and Limitations of Randomized Controlled Trials using Down's and Black checklist[6]

Strengths	Limitations
Wong et al. 2013[11]	
• The hypothesis and aim of the study was clearly described. • The main outcomes were clearly described in the Methods section. • All the important AEs have been reported, however no information on how they were measured. • The main outcome measures were accurate (valid and reliable) as the procedure to measure those was clearly described. • Patient characteristics and inclusion/exclusion criteria were clearly described. • The main findings were clearly described. • Patients were randomized following recruitment to be in the treatment and control group in a manner which was concealed from both patients and hospitable staff member and randomization was irrevocable. • Hospital staff members were blinded to the patients' intervention group. • Assessment of patients' MRI reports was done by an author blinded to the intervention they received. However, for the other clinical outcomes, no attempt to blind the assessors was reported. • No loss to follow-up/dropout, therefore no need to take it into account in the analyses. • The interventions of interest as well as treatment received by the control group were clearly described. • The study had sufficient power to detect a clinically important effect (mean IKDC score of 1.27) for the primary outcome at 5% level of significance. • The statistical test used to assess difference in clinical scores was accurate, because adjusted mixed-effect model takes repeated measurements into account. Comparison of adjusted mean difference in MOCART score between the two groups and the individual was done using ANCOVA and Fisher's test, which were appropriate too. • Estimates of the random variability were provided for the main outcomes using confidence interval. • Actual probability values were reported. • No issue with non-compliance of the allocated treatment. • The distribution of principle confounders and baseline characteristics in each group was clearly described. • There were differences in baseline score of the outcomes of interest and age between the groups	• Unable to determine the source of patients included in the study to answer the representativeness of study participants with the general population. • Unable to determine if study subjects in both intervention groups were recruited over the same period of time. • Patients were not blinded to the intervention they would receive which might lead to patient bias, however given the nature of the surgical procedure, this would be impossible to do because of the presence of wound and pain associated with bone marrow harvesting from the iliac crest. • The study had short follow-up time; however, it is an ongoing study, with the patients being followed up for 5-10 years for long term results. • The two groups were not homogenous in terms of severity of cartilage damage as shown by larger mean lesion size in the cell-recipient group, however, better results were observed in this group. • Unable to determine if the recruited subjects were pooled from a list of subjects prepared to participate in the study and whether the second group are representative of the entire population from which they were recruited. • Unable to determine if the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients would receive.

Table 6: Strengths and Limitations of Randomized Controlled Trials using Down's and Black checklist[6]

Strengths	Limitations
and a time-effect showing improvement over time was observed and these were factored in the analyses; however, no statistical test was performed to show significance in these differences. • No evidence of "data dredging", i.e. conducting retrospective unplanned subgroup analyses.	
Vangsness et al. 2014[12]	
• The hypothesis and aim of the study was clearly described. • The main outcomes were clearly described in the Methods section. • All the important AEs have been reported. • Patient characteristics and inclusion/exclusion criteria were clearly described. • The main findings were clearly described. • Patients were randomized following recruitment to be in the 2 treatment and control group at a 1:1:1 ratio, randomization was concealed from patients by a centralized scheme and the randomization was irrevocable. • Both patients and surgeons administering the injections as well as other clinical personnel were blinded to the patients' intervention group. • Assessment of patients' meniscal volume was done by 2 independent radiologists blinded to the intervention they received. • 5 dropouts in total, their characteristics not described. • The interventions of interest as well as treatment received by the control group were clearly described. • The study had sufficient power to detect a 60% difference between the treatment groups and control for the primary outcome (>15% improvement in meniscal vol) at 5% level of significance. • The statistical tests used to analyze continuous data were accurate. Categorical data were analyzed using Mantel-Haenszel test for general association and when appropriate, using Fisher's test. Paired test was used to analyze repeated measurements within a group; all of these were appropriate tests. • Estimates of the random variability were provided for the main outcomes using confidence interval. • Actual probability values were reported. • 1 individual did not receive the allocated treatment. • The distribution of principle confounders i.e. demographic data and baseline characteristics in each group was described in the appendix, no statistically significant difference in the baseline characteristics.	• Unable to determine the source of patients included in the study to answer the representativeness of study participants with the general population. • Unable to determine if study subjects in all three intervention groups were recruited over the same period of time. • Unable to determine if the recruited subjects were pooled from a list of subjects prepared to participate in the study and whether the second group are representative of the entire population from which they were recruited. • Unable to determine if the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients would receive. • Differences in follow-up length were not reflected in the analyses, neither was the effect of dropouts. They simply stated that no imputation of missing data was done. • The main outcome measure by MRI analysis was inconsistent resulting from differences in study sites, visits and edge-detection evaluation. • Even though there were no differences in baseline characteristics among the groups, distribution of OA among the groups was different and this may affect the result.

Table 6: Strengths and Limitations of Randomized Controlled Trials using Down's and Black checklist[6]

Strengths	Limitations
• No evidence of "data dredging", i.e. conducting retrospective unplanned subgroup analyses.	
Emadedin et al. 2017[13]	
• The aim of the study was clearly described. • The main outcomes were clearly described in the Methods section. • All the important AEs have been reported. • Patient characteristics and inclusion/exclusion criteria were clearly described. • The main findings were clearly described. • No dropouts or loss to follow-up. • The intervention received by the patients was clearly described. • All individuals received the treatment. • The distribution of principle confounders i.e. demographic data and clinical characteristics in each group was described. • No evidence of "data dredging", i.e. conducting retrospective unplanned subgroup analyses.	• This was not a randomized trial, a phase I safety trial instead. • The trial was not blinded; however the aim was to test the safety of the intervention. • No sample size/power calculation was done. • No statistical test was done as no groups were being compared, rather frequency of patients with healed and bone union was reported only. • No estimate of the random variability and probability value was provided for the main outcomes as no formal test was done. • Unable to determine the source of patients included in the study to answer the representativeness of study participants with the general population. • Unable to determine if study subjects in all three intervention groups were recruited over the same period of time. • The two groups were not homogenous in terms of severity of cartilage damage as shown by larger mean lesion size in the cell-recipient group, however, better results were observed in this group. • Unable to determine if the recruited subjects were pooled from a list of subjects prepared to participate in the study and whether the second group are representative of the entire population from which they were recruited. • Unable to determine if the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients would receive.

Table 7: Strengths and Limitations of Guidelines using AGREE II [7]

Strengths	Limitations
Lower Extremity Injury Medical Treatment Guidelines[14]	
• The overall objective of the guideline is specifically described. • The clinical area covered by the guideline is clearly described. • Information regarding the target population and user is relatively easy to identify. • The literature search strategy for this guideline was clearly defined. • The recommendations are based on whether the evidence found was “some”, “good”, or “strong”, as defined in the General Guidelines Principles, • In formulating the recommendation, evidence based on health benefits, side effects and risks were considered. • The key recommendations are clearly described, and the different management options for a given condition were provided. • The guideline discussed resources and barriers to the application.	• No information on whether individuals from relevant professional groups were consulted. • No information on whether workers’ views and preferences were taken into account. • No evidence that the guideline was reviewed by an external, independent expert prior to publication. • No information on how to update the guideline. • No information on monitoring or auditing criteria. • No evidence on the independence of the editorial and funding body. • Any potential conflicts of interests between reviewers were not addressed.

Appendix 4: Main Study Findings and Author's Conclusions

Table 8: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusion
Filardo et al., 2013[2]	
3/18 included trials used BMDSC injection • Case report by Centeno et al. showed a reduction in knee cartilage lesion by an increase in cartilage and meniscus volume, and an improvement in scores measuring range of motion and pain. • Case series by Davatchi et al. reported significant improvement in subjective parameters of knee OA in 4/4 patients, but less successful for physical parameters (number of stairs to climb, walking time, and resting time) following a single intraarticular BMDSC injection. • Case series by Emadedin et al. reported in patients with knee OA, a single BMDSC injection resulted in no AEs, a decrease in pain and an improvement in joint function and walking distance in 6/6 patients, an increase in cartilage thickness and significant decrease in the size oedematous subchondral bone in 3/6 patients. **1/5 included trials used BMC injection** • A comparative trial by Varma et al. reported improvement in symptoms, hospital stay and quality of life following debridement and BMC injection in patients with mild to moderate knee OA	• While a number of clinical studies demonstrated encouraging results in the treatment of various cartilage defects by BMDSC, BMC and ADMSC using scaffold and injection-based delivery, the studies are of low-quality, have small sample size and short follow-up time. • Optimization of cell sources, delivery method, dosage, efficacy and safety using appropriate measures need further investigation. • Randomized, double-blind, controlled, multi-centre studies with long term follow-up needed for reliable clinical data. "*Knowledge on this topic is still preliminary, as shown by the prevalence of preclinical studies and the presence of low-quality clinical studies. Many aspects have to be optimized, and randomized controlled trials are needed to support the potential of this biological treatment for cartilage repair and to evaluate advantages and disadvantages with respect to the available treatments*." Page 1717
Hernigou et al. 2016[8]	
3 included studies used BMDSC/BMC injection • Hernigou et al. reported among 342 patients (534 hips) with early stage avascular ON, a combination of core decompression and autologous BMDSC injection resulted in a decrease in osteonecrosis volume from 26 cm^3 to 12 cm^3 in 371 patients, and only 94/534 cases required THR. 69/534 hips showed full resolution. • Gangji et al. reported significant improvement in pain and joint symptoms, and in disease progression. 8/11and 3/13 hips in the control and BM graft group, respectively, progressed to the fractural stage. Significant difference in time to stage 1–2 osteonecrosis progression was present between the two groups and also in the decrease in volume of necrotic lesion. The treatment was associated with minor side	• Cytotherapy is best indicated in symptomatic, pre-collapse hips, and successful outcomes in Steinberg stage III patients were obtained within 5-10 years. • Autologous BMDSC implant can effectively treat early stage ONFH condition. • Autologous BMDSC implant supplemented with CD is a better treatment than CD alone in ONFH patients.

Table 8: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusion
effects. • Papakostidis et al. and Hernigou et al. reported improvement in clinical and radiological results following treatment with autologous BMC enriched in MSCs in combination with CD among patients with ON by slowing the progression of disease, limit the requirement for THR, as well as reduction of painful joint symptoms and improvement in the Harris hip score.	
Peeters et al. 2013[9]	
• 4 reported SAEs: one infection, one pulmonary embolism probably and possibly, respectively, related to procedure; and two unrelated tumours. • 22 and 7 possible procedure and stem cell product-related AEs, respectively, were reported. Stem cell-related AEs: Increased pain and swelling, all mild and transient; resolved or remedied with simple therapies.	• The authors concluded that use of autologous cultured BMDSC is safe to use in joint diseases. "*In conclusion, intra-articular cell-therapy with culture-expanded MSCs appears to be safe based on 844 treatments in eight studies. Based on the reported AEs and their classification in this systematic literature review we conclude that there are no compelling arguments against proceeding with intra-articular stem cell application in human cases.*" Page 1465
Piuzzi et al. 2017[12]	
• Studies that reported PROs showed varying results depending on the outcome, Measure of pain by VAS score, Womac score and Lequesne index showed cell therapy to be better than control group, whereas assessment of HHS score showed both groups to be benefitted by their respective treatment; however the beneficial effect was greater in the cell therapy group. • 93/380 hips in the cell-therapy group showed to radiographic progression as opposed to 98/245 in the control group. • A lower proportion of patients who received cell therapy reported THA compared to the control group, 68/380 vs 52/252 hips. • Cell therapy was not associated with any significant AE with only <3% complication rate.	• Overall results favored the use of cell therapy over the control group. "*Cell-therapies for the treatment of ONFH have been reported to be safe and suggest improved clinical outcomes with lower disease progression rate. However, there was substantial heterogeneity in the included studies, and in the cell-based therapies used. Specific clinical indications and cell-therapy standardization are required because studies varied widely with respect to cell sourcing, cell characterization, adjuvant therapies, and assessment of outcomes*." Page 1698

ADMSC= Adipose tissue-derived mesenchymal stem cell; BMC= Bone marrow concentrate; CD=Core decompression; HHS=Harris Hip Score; OA= osteoarthritis; ONFH= Osteonecrosis of the femoral head; PRO=Patient reported outcome; SAE=Severe adverse event; THA/R = Total hip arthroplasty/replacement

Table 9: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusion
Wong et al. 2013[11]	
• Improved Tegner, Lysholm, IKDC and MOCART scores were observed in both groups, however the cell-recipient group had significantly better score after adjustment for age, baseline scores, and time of evaluation. • In the cell-treatment arm, an added improvement of 7.65 (95% CI: 3.04-12.26) for IKDC, 7.61 (95% CI: 1.44-13.79) for Lysholm scores, and 0.64 (95% CI: 0.10-1.19 for Tegner scores. • Age-adjusted mean difference in MOCART score was 19.6 (95% CI: 10.5-28.6) showing improved outcome in the cell-treatment arm. • Integration rate of the regenerated cartilage was also significantly higher in the treatment group (61%). • No AEs such as deep infections of implants, periprosthetic fractures, or any other SAEs were reported during the study duration.	"*Intra-articular injection of cultured MSCs is effective in improving both short-term clinical and MOCART outcomes in patients undergoing HTO and microfracture for varus knees with cartilage defects*." Page 2020 and 2027
Vangsness et al. 2014[12]	
<u>Clinical evaluation of AEs</u> • No ectopic tissue formation was reported. • No deaths or AE resulting in treatment discontinuation or study termination. • 427 AEs in total recorded among 55 (95%) patients, 272 mild, 126 moderate, and 28 severe and 1 life-threatening. • 9 SAEs in 8 patients, deemed unrelated to any of the treatment by blinded investigators. • Most common AEs were musculoskeletal and connective tissue disorders (50/55): arthralgia, joint swelling, joint stiffness, injection-site joint pain, joint effusion, headache, and peripheral edema. • No changes in immunological parameters, hematology, blood chemistry, or urine analyses following injection. • No appreciable changes in vital signs, physical examination data, or ectopic tissue formation. <u>MRI evaluation of meniscus growth</u> • Meniscal volume significantly increased (>15% from baseline) in 24% and 6% of group A and B patients, respectively, compared to 0 in the control group (p=0.029) at the end of 2 years. • 76% of the patients had no additional articular cartilage degeneration by year 1. 2 patients in each cell-treatment group and 1 patient in the	"*There was evidence of meniscus regeneration and improvement in knee pain following treatment with allogeneic human mesenchymal stem cells. These results support the study of human mesenchymal stem cells for the apparent knee-tissue regeneration and protective effects*." Page 90 "*This study investigated the single administration of stem cells at two dose levels. The data do not suggest that there was increased benefit from the higher dose. Whether providing additional injections influences the effect on pain, meniscus regeneration, or osteoarthritis remains to be evaluated*". Page 97

Table 9: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusion
control group developed articular degeneration by this period. 21% control and 6% cell-treated group patients reported subchondral sclerosis and osteophyte formation. <u>Patient-Reported Assessments</u> • Significant reduction in pain was observed among group A and B patients as measured by VAS (P<0.001). • Lysholm knee scale total scores also showed significant improvement in all groups compared to baseline throughout the follow-up period (P≤0.03), but no comparison test was done.	
Emadedin et al. 2017[13]	
• No AE in any participants. • 3/5 patients had an improvement in healing and bone union.	• Use of autologous cultured BMDSC implant is a safe treatment method for bone nonunion and can improve healing in previously unresponsive patients. Further randomized controlled trials with more patients are required to determine its efficacy.

ADMSC= Adipose tissue derived stem cell; HTO= High Tibial Osteotomy; IKDC= International Knee Documentation Committee; MOCART= Magnetic resonance observation of cartilage repair tissue; (S)AE= (Severe) Adverse events; VAS= Visual Analogue Scale

Table 10: Summary of Findings of Included Guidelines

Main Study Findings	Author's Conclusion
Lower Extremity Injury Medical Treatment Guidelines[14]	
• Only 1 randomized clinical trial in 100 ONFH patients set to assess the effectiveness of cultured BMDSC injection improved progression of disease and the need for total hip replacement in early-stage osteonecrosis of the hip in comparison with core decompression. • Other indications considered in which injection containing bone marrow cells were not recommended include- delayed union or nonunion of fractures, fracture in acetabulum, pelvis, femur, hip, tibia, and trochanter area.	"*Numerous trials are currently in process or have not been published regarding the use of stem cells from bone marrow aspirate or demineralized bone matrix. The only clear effects are on small bone deficits. They are considered to be experimental and thus are* ***not recommended*** *for delayed union or nonunion of long bone fractures.*" Page 149 "*There is some evidence from one study that, in the setting of core decompression, the use of bone marrow derived mesenchymal stem cells, taken from subtrochanteric marrow, cultured in vitro for two weeks, and implanted back into the necrotic lesion, greatly reduces the rate of progression of the disease process over the following five years. There is also some evidence that the procedure similarly reduces the need for total hip replacement. It is not known how this study related to non-cultured stem cells. Core decompression has been tried with mesenchymal stem cells and bone marrow derived cells. However, currently stem cells cannot be cultured in the United States. Due to differing techniques and study methodologies, these procedures continue to be considered experimental and are* ***not generally recommended***". Page 150