Stem Cell Therapy for Musculoskeletal Conditions

Final Evidence Report

February 17, 2020

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February 17, 2020

This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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ABBREVIATIONS

AD: adipose
AD-MSCs: adipose derived mesenchymal stem/stromal cells
AE: adverse events
BM: bone marrow
BMAC: bone marrow aspirate concentrate
BMC: bone marrow concentrate
BM-MNCs: bone marrow mononuclear cells
BM-MSCs: bone marrow derived mesenchymal stem/stromal cells
CI: confidence interval
COI: conflict of interest
F/U: follow-up
HA: hyaluronic acid
haMPC: human autologous adipose-derived mesenchymal progenitor cells
K-L: Kellgren=Lawrence
KOA: knee osteoarthritis
MCID: minimal clinically important difference
MD: mean difference
MNC: mononuclear cells
MPCs: mesenchymal progenitor cells
MSCs: mesenchymal stem/stromal cells
NR: not reported
NSAID: non-steroid anti-inflammatory drug
OA: osteoarthritis
PASS: patient acceptable symptom state
PL: platelet lysate
PRP: platelet rich plasma
PT: physical therapy
RCT: randomized controlled trial
ROB: risk of bias
SAE: severe adverse events
SD: standard deviation
SE: standard error
SVF: stromal vascular fraction

Executive Summary

Introduction

Musculoskeletal conditions are common and can lead to chronic pain, disability and reduced quality of life. As life expectancy increases and the elderly population expands in the United States (US), so too will the prevalence and societal and economic burden of musculoskeletal conditions. Many musculoskeletal tissues have a limited capacity for endogenous repair and for many orthopedic conditions, effective non-surgical treatment options are limited. Given the public health burden and costs related to the management of such conditions, exploration of effective, safe and cost-effective management options is important. Thus, there has been much interest in and research on the use of cell-based therapy, including the use of stem cells, to stimulate repair and regeneration of tissues for such conditions. Additionally, the number of businesses performing internet marketing of cell-based therapies as "stem cell" therapies in the U.S. and Canada has rapidly expanded, particularly in orthopedics.[68,69] In the U.S., a variety of physicians and nonphysician clinicians with various types of training may provide cell-based therapies that are marketed as "stem cell" therapies.[21]

Stem cells are the basis of all tissues and organs in the body, possessing the ability to give rise to multiple cells of the same kind. Stem cell therapy, as described in this report, is the use of pluripotent or multipotent stem cells to treat a disease or condition. The terminology related to "stem-cell therapy" is imprecise, inconsistent, and has led to substantial confusion in the medical and lay literature. Some of the therapies offered in various settings as "stem cell therapy" may not contain stem cells. The terms "stem cell" and "mesenchymal stem cell" have been used very broadly and often inaccurately to describe many cell-based treatments.[68] Stem cell types are often described as embryonic stem cells (obtained at the earliest developmental stages), tissue-specific (also referred to as adult or somatic stem cells) and recently, induced pluripotent stem cells which are engineered from specialized cells. Tissue-specific (adult, somatic) stem cell preparations have been most frequently described for treatment of musculoskeletal conditions of interest for this HTA. Non-hematopoietic stem cells from tissues and organs have been collectively referred to as "mesenchymal stem cells" (MSC) in most lay and medical literature with bone marrow and adipose tissue cited most frequently as sources for musculoskeletal applications. MSCs are considered multipotent. Because adult stem cells are rare in mature tissues and a variety of other cell types are included in the sampling process, identification, isolation and growth of adult stem cells in laboratory settings is required.[16,56,70] The characteristics of MSCs and how they differentiate depend on the source within the body as well as how they are isolated, processed and cultured.

The U.S. Food and Drug Administration (FDA) regulates tissues and human cells intended for implantation, infusion or transplantation via the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271 but the guidance for Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) is complex.[38,71] The only stem cell-based products approved by the FDA for use in the U.S. consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood; approval is limited to the treatment of conditions of the hematopoietic system. The following are not considered HCT/Ps and FDA approval is not needed: minimally manipulated autologous cell preparations bone marrow concentrate, adipose stromal or stromal

vascular fraction, placental tissue fragments and platelet-rich plasma. Use of such products must follow good tissue practice regulations to assure that they do not contain communicable disease agents, are not contaminated and do not become contaminated. Clinicians must register their use. Culture-expanded connective tissue cells, i.e. MSCs, muscle-derived cells, adipose-derived cells and cartilage-derived cells for orthopedic applications are not FDA-approved. Use requires participation in prospective FDA-approved clinical trials. Additional information is found in the full report.

In general, the range of clinical conditions or diseases for which stem cells have proven to be effective is very small. Many stem-cell-based treatments are new and considered experimental. Hematopoietic stem cell transplantation (from bone marrow) has been successfully used to treat patients with leukemia, lymphoma and some inherited blood disorders. Although the safety of stem cells derived from peripheral blood or bone marrow for hematopoietic reconstitution is reasonably well established, this safety may not carry over to other applications. The mechanisms related to potential therapeutic effects and harms in humans are poorly understood and are active areas of research. Short-term and long-term harms or adverse events have not been well studied and the risk of using stem cell therapy for musculoskeletal conditions is largely unknown. The FDA has expressed concern regarding the use of unapproved stem cell therapies based on lack of evidence on the benefits and harms for such products.[42,72]

While there have been a large number of pre-clinical studies related to musculoskeletal applications of stem cell therapy, such therapy is still in the relatively early stages of development; the evidence of effectiveness and safety from methodologically rigorous clinical studies appears to be sparse and its value or safety has not been established. The focus of this review is on the evaluation of the safety and efficacy of Stem Cell Therapy (SCT) as a biological treatment for specific musculoskeletal conditions (e.g. cartilage defects, osteoarthritis or related joint conditions or joint pain, muscle, ligament, or tendon conditions, pain due to degenerative disc disease).

Policy context/Reason for selection

Stem cell therapy for musculoskeletal or orthopedic conditions is an outpatient procedure that begins with collection of stem cells from a patient (autologous) or from another person (allogeneic). The cells may be cultured or concentrated and then injected into the affected area. The topic is proposed based on concerns related to the safety, efficacy and value for stem cell injections for musculoskeletal pain.

Objectives:

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of autologous or allogenic stem cell therapy in adults for treating specific musculoskeletal conditions in an outpatient setting. The differential effectiveness and safety of stem cell therapies for subpopulations will be evaluated, as will the cost effectiveness.

Key questions:
In patients with musculoskeletal conditions (e.g. cartilage defects, osteoarthritis or related joint conditions or joint pain, muscle, ligament, or tendon conditions, pain due to degenerative disc disease)

1. What is the evidence of the short- and long-term efficacy and effectiveness of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo/sham?
2. What is the evidence regarding short- and long-term harms and complications of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo?
3. Is there evidence of differential efficacy, effectiveness, or safety of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo?
4. What is the evidence of cost-effectiveness of autologous or allogenic stem cell therapy compared with other treatment options?

Inclusion and exclusion criteria are summarized below and are detailed in the full report. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

Population: Adult patients with any of the following conditions: cartilage defects, osteoarthritis or related joint conditions, muscle, ligament, or tendon conditions, pain due to degenerative disc disease, or joint pain.

Interventions: Autologous or allogenic stem cells.

Comparators: Common conventional non-operative treatment(s) (e.g. PT, intra-articular steroid injections, medications (NSAIDS, analgesics), activity modification), surveillance, placebo/sham, or surgery.
Outcomes:

- Primary clinical outcomes
  - Function (validated measures)
  - Pain (validated measures)
  - Objectively measured medication use
  - Return to normal activities (sports, work, or activity)
  - Adverse events/harms
- Secondary or indirect (intermediate) outcomes
  - Time to recovery
  - Quality of life
  - Patient satisfaction
  - Recurrence
  - Secondary procedures (e.g., surgery)
- Economic outcomes
  - Long term and short-term comparative cost-effectiveness measures

Studies: The focus will be on high quality (low risk of bias) comparative studies (e.g., randomized controlled trials (RCTs), comparative cohort studies with concurrent controls). High quality systematic reviews of RCTs, RCTs, and high quality, prospective non-randomized comparative studies will be considered for Key Questions (KQ) 1 and 2. Case series will be consider for KQ2 (safety) if designed specifically to evaluate harms/adverse events; case series may be considered in the absence of comparative studies for KQ1. Only RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest will be considered for KQ3. Full, comparative, formal economic studies (i.e., cost-effectiveness, cost-utility, cost minimization, and cost-benefit studies) will be sought for KQ5.

Methods

A detailed description of methods, including inclusion/exclusion criteria, is contained in the full report.

Draft key questions and scope were set *a priori* and were available for public comment as was the draft report. No public comments were received. The draft report was peer reviewed.

Data Sources, Search Strategy and Study inclusion

A formal, structured systematic search of the peer-reviewed literature across multiple databases from inception to September 12, 2019 was conducted to identify relevant peer reviewed literature as well as pertinent clinical guidelines and previously performed assessments. Reference lists of relevant studies and the bibliographies of systematic reviews were also searched; in addition, citations from peer-reviewed journals listed by Regenexx® stem-cell clinics were also evaluated against the inclusion/exclusion criteria.[2] The search process is detailed in the main report and Appendix B. All records and publications selected for full text review were screened by two independent reviewers; conflicts were resolved by discussion. Conference abstracts, non-English-language articles, duplicate publications that did not report different data or follow-up times, white papers, narrative reviews, preliminary reports, and incomplete economic evaluations were excluded. Detailed inclusion/exclusion criteria are described in the full report. A list of articles excluded at full text along with the reason for exclusion is available in Appendix C. Figure 2 in the full report outlines the results for the inclusion/exclusion process.

Data Extraction

Reviewers extracted the details of study design, study period, setting, country, sample size, inclusion and exclusion criteria, study population characteristics, follow-up time, study funding and conflicts of interest, stem cell therapy characteristics (e.g. cell type, cell source, cell preparation, cell expansion (if any), autologous/allogenic, cell concentration, cell delivery, number of injections) study outcomes, and adverse events. Abstracted data were reviewed for accuracy by at least one other reviewer. Detailed study and patient characteristics and results are available in Appendix F.

Quality Assessment: Risk of Bias and Overall Strength of Evidence (SOE)

Included studies reporting on primary outcomes of interest were critically appraised independently by two reviewers evaluating the methodological quality, based on criteria and methods established in the

Cochrane Handbook for Systematic Reviews of Interventions,[29] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[1] Methods of assessing study quality are detailed in the full report and in Appendix D. An overall Strength of Evidence (SOE) combined the appraisal of study limitations with consideration of the number of studies and the consistency across them, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. The SOE for all primary health outcomes was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ).[6,25-27] The SOE was based on the highest quality evidence available from comparative studies for a given outcome. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- **Risk of bias**: the extent to which the included studies have protection against bias
- **Consistency:** the degree to which the included studies report results that is similar in terms of effect sizes, range and variability. Consistency for single studies is listed as unknown.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head to head).
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication or reporting bias:** considered when there is concern of selective publishing or selective reporting. This is difficult to assess particularly for nonrandomized studies.

Bodies of evidence consisting of RCTs are initially considered as High SOE and nonrandomized studies as Low SOE as such studies typically are at higher risk of bias due to lack of randomization and inability of investigators to control for critical confounding factors. There are situations where studies (particularly observational studies) could be upgraded if the study had large magnitude of effect or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias were considered to be unknown in all studies and this domain was eliminated from the SOE tables. The final SOE was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- **High** – Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- **Moderate** – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable, but some doubt remains.
- **Low** – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- **Insufficient** – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable efficiencies precluding judgment.

SOE was assessed for the primary outcomes only; details of other outcomes are provided in the full report. For efficacy and effectiveness, only results from comparative studies were assessed for SOE; if data from RCTs was available, comparative cohort studies were not included in SOE determination. For safety, all study types were included in determination of SOE to provide an overall view of

complications. Evidence for effectiveness outcomes consisting of case series alone was considered insufficient evidence.

Analysis

Evidence was summarized qualitatively and quantitatively. For dichotomous outcomes, crude risk ratios (RR) and 95% confidence intervals (CI) were calculated. Unless causality could be reasonably assumed for an association, RDs were not calculated. For continuous variables, differences in mean follow-up scores between treatments were analyzed to determine mean differences as an affect size. Meta-analyses were conducted using STATA 14.0 (StataCorp, College Station Texas) and Profile Likelihood estimates were reported when available[18] to account for additional uncertainty when small numbers of studies with small sample sizes are pooled. In the case of non-convergence with Profile Likelihood methods, the DerSimonian and Laird estimates were reported. Sensitivity analyses based on study quality or to understand the impact of studies on heterogeneity were conducted when sufficient data were available.

Results

Key Questions 1 and 2 (No studies that met inclusion criteria which addressed Key Questions 3 and 4 were identified).

A total of 51 studies (across 56 publications) were identified that met inclusion criteria and addressed Key Questions 1 and 2: 14 RCTs (16 publications)[13,19,20,23,32,36,37,39,40,44,58,60,61,67,73,74]; 3 cohorts[8,22,34]; 5 registries (all from Centeno et al.)[10-12,14,15]; and 29 case series (32 publications).[3-5,7-15,17,19,20,22-24,28,30-37,39-41,44-55,57-67,73-75]

The overall quality of the available evidence base for this review was considered poor with evidence for most conditions from case series or poor-quality registry studies. RCTs identified were predominately moderately high risk of bias. The majority of evidence identified was for stem cell therapy for knee OA. Studies generally did not follow proposed standards for reporting of clinical stem cell studies.[16,43] In particular, insufficient detail regarding cell processing, purification, cellular composition of injected materials, immunophenotype (e.g. for MCS specifically, tested in vitro), viability, stem-cell specific concentrations and other information were rarely reported in studies of non-cultured/non-expanded (minimally manipulated) cells and poorly reported in most studies of culture-expanded cells. In general, description of methods in most studies was likely insufficient to permit study replication. Although studies of minimally manipulated samples report using MSCs, the extent to which injected materials contained such cells or in what concentration is unclear.

Conclusions regarding the efficacy and effectiveness of stem cell therapy (SCT) are challenging for a variety of reasons including heterogeneity across trials in patient populations, stem cell sources and preparations, inadequate characterization of injectate cellular composition and stem cell concentration (particularly in studies of minimally manipulated cells from autologous sources), use of adjunctive biological components (e.g. PRP), pre- and post-injection treatments, and control conditions. Sample sizes in most included studies were small and studies may not have had sufficient power to detect differences between treatment groups. Reporting of co-interventions (e.g. NSAID use), post-treatment rehabilitation protocols (e.g. physical therapy) and other factors which might impact outcomes was variable and overall was insufficient. These factors may contribute to variability in results across

included comparative studies. It is unclear to what extent reported improvements in pain in some studies may be attributable to placebo response. Lastly, length of follow-up across studies rarely extended beyond 12 months limiting the ability to determine the long-term impact of SCT on function and pain or reduced need for subsequent surgery. Studies rarely evaluated the need for subsequent treatment, which may point to a concern of publication bias.

For safety, the overall quality of evidence was poor as the majority of data were from poor-quality RCTs and case series, registry studies or comparative cohorts considered to be at high risk of bias. Adverse events were poorly specified and poorly reported across included studies leading to concerns regarding possible reporting bias. Evaluation of and conclusions related to adverse events for the injection of stem cell preparations for musculoskeletal indications are challenging for many reasons. First, adverse events were variably defined, adjudicated and reported across included studies, precluding pooling. Authors generally did not describe whether patients could experience more than one event. Many studies did not describe potential treatment-specific (i.e. injectate-related) AEs that would be evaluated *a priori*, raising the question of reporting bias. Second, it may be unclear whether some AEs are secondary to the injection procedure itself, the components of the injectate (stem cell preparation and/or added components) or both. Third, it is unclear what the potential for long-term risks of AEs specific to "stem cells" may be. Most studies had follow-up of ≤ 12 months, which would likely preclude determination of neoplasia or other long-term consequences specific to stem cells. The majority of studies across indications are case series, which are considered at high risk of bias and preclude comparison with other logical treatment options. Lastly the samples sizes of the majority of included studies were too small to identify any but extremely common events. Details of reported adverse events are found in the full report and data abstraction.

Clinical experts prioritized the following as the most important AEs to consider for the conditions included in this report. Most could occur with injection of any substance or with the injected materials. Authors of included studies generally did not report on most of these events specifically.

- Neurologic events or nerve damage
- Allergic reaction
- Fat embolism
- Sepsis, septic arthritis
- Infection
- Joint effusion (not expected with procedure may be due to materials injected).

Donor site infection and bleeding requiring medical intervention were considered the most important AEs for harvesting of autologous cells but were rarely report across included studies.

While the safety of stem cells derived from peripheral blood or bone marrow for hematopoietic reconstitution is reasonably well established, it is still unclear from the included studies whether or not safety may carry over to applications included in this report.

Summary of Results

Given current FDA regulations related to stem cells, studies were stratified based on whether cells were culture-expanded or not and whether autologous or allogenic sources were used.

The majority of evidence identified for stem cell therapy was for knee osteoarthritis (OA) (12 RCTs); one RCT was identified for degenerative disc disease (DDD) and one for tendinopathy (Achilles tendinopathy). These three conditions are summarized below. For the following conditions, all evidence was considered insufficient as the only available data was from case series (primarily) and poor-quality comparative cohorts (of note, the single arm registry studies are all from the same registry by Centeno et. al)[10-15]; see full report for results:

- **Hip OA** (2 case series, 1 single arm registry)
- **Hip and/or Knee OA** (1 case series)
- **Shoulder OA** (1 case series, 1 single arm registry)
- **Anterior Cruciate Ligament Tear** (1 single arm registry)
- **Partial Rotator Cuff Tear** (1 cohort, 1 single arm registry)

Knee Osteoarthritis

Key Question 1 (Efficacy/Effectiveness)

Overall 14 studies (12 RCTs [across 14 publications][13,19,20,23,32,36,37,39,40,58,60,61,67,74] and two comparative cohort studies[8,22]) evaluating stem cell therapy for the treatment of knee osteoarthritis (OA) that met inclusion criteria were identified and provided data on efficacy or effectiveness. For knee OA, data from comparative cohorts were not included in SOE determination given the availability of RCT data; results from these studies are not included here but can be found in the full report.

Autologous, non-culture-expanded stem cells

Five small RCTs (6 publications)[13,23,58,60,61,67] evaluated the use of autologous, non-culture-expanded stem cell therapy for knee OA; four used bone marrow aspirate concentrate (BMC)[13,23,58,60,61] and one used adipose (AD)-derived stromal vascular fraction (SVF).[67] Comparators included placebo (2 trials)[60,61,67], hyaluronic acid (HA) (2 trials)[23,58] and exercise therapy (1 trial).[13]

- There was generally no improvement in function (across multiple measures) with various stem cell interventions compared with HA or exercise, regardless of stem cell source at any time frame across the five small, poor quality RCTs; however, evidence was insufficient to draw firm conclusions.
- No improvement in pain at 3, 6 or 12 months was seen following stem cell interventions compared with HA, placebo or exercise across four small, primarily poor quality RCTs (SOE Low).

Autologous, culture-expanded stem cells

Five small RCTs (6 publications)[19,20,36,37,39,40] evaluated the use of autologous, culture-expanded stem cell therapy for knee OA; three trials used adipose-derived mesenchymal stem cells (MSCs)[20,39] or

mesenchymal progenitor cells (MPCs; Rejoin®)[40] and two used bone-marrow (BM)-derived MSCs.[19,36,37] Comparators included placebo (2 trials),[19,39] HA (2 trials)[36,37,40] and conservative care (e.g., simple analgesics, exercise) (1 trial).[20]

- No differences in function according to pooled estimates for the WOMAC total (5 trials), physical function (4 trials), and stiffness scales (4 trials) were seen at 3, 6 or 12 months following autologous, culture-expanded stem cell injection compared with HA, placebo or conservative care (SOE Low for WOMAC total at 3, 6 and 12 months and for WOMAC physical function and stiffness at 3 and 6 months; SOE insufficient for the latter two measures at 12 months). Removal of one outlier trial from the pooled estimates for WOMAC total score at 3 and 6 months and WOMAC function score at 3 months may suggest improvement in function favoring stem cells. However, results should be interpreted cautiously given the small number of trials with small sample sizes and heterogeneity in populations and methods across trials. Longer-term data (48 months) for the WOMAC total from one small trial at moderately high risk of bias was insufficient to draw firm conclusions.
- No improvement in VAS pain scores between groups was seen across trials at 3 months, but at 6 and 12 months less pain was reported by patients who received autologous, culture-expanded stem cell injection compared with control treatments (SOE low for all timepoints); longer-term data (48 months) from one small trial at moderately high risk of bias was insufficient to draw firm conclusions. No improvement in WOMAC pain scores were seen across trials at any timepoint with SCT versus controls (SOE Low for 3 and 6 months, insufficient for 12 months); removal of one outlier trail from the 6 month pooled estimate may suggest improvement.
- The FDA does not currently approve the use of culture expanded stem cells.

Allogenic, culture-expanded stem cells

Two small RCTs evaluated the use of allogenic, culture-expanded stem cell therapy, specifically placenta-derived MSCs (vs. placebo)[32] and BM-MSCs (vs. HA),[74] for knee OA.

- There is insufficient evidence to draw firm conclusions regarding the efficacy of allogenic, culture-expanded SCT for treatment of knee OA.
    - Evidence from one small RCT (at moderately high risk of bias) showed no significant difference in functional improvement with SCT versus HA.
    - Across two RCTs, no difference between groups (SCT vs. HA) in pain improvement was seen at 3 or 6 months and at 12 months for one trial.
    - Very small sample sizes, study limitations and lack of precision were methodological shortcomings across these trials.

Key Question 2 (Safety)

Autologous, non-culture-expanded stem cells

In addition to all five RCTs, one cohort study (BM-MSCs),[22] 1 single arm registry (BMC with and without lipoaspirate)[12] and 14 case series (mix of bone marrow-derived, adipose-derived, and peripheral blood-

derived stem cells)[3,4,9,24,30,31,33,45,53-55,62,66,75] that met inclusion criteria reported safety outcomes following non-culture-expanded stem cell therapy for knee OA.

- While the number of serious AEs reported (to include death) appears to be low across four RCTs, three case series, and one registry, the evidence is insufficient to draw firm conclusions; the longest follow-up period was 12 months.
- Non-serious pain and/or swelling and effusion at the injection site were common across the RCTs and case series (to include the registry study); pain and/or swelling were the most common AEs reported in the registry study (SOE Low).
- Results should be interpreted cautiously given study limitations and small sample sizes.

Autologous, culture-expanded stem cells

In addition to all five RCTs, five case series (6 publications) (mix of bone marrow-derived MSCs and adipose-derived stromal vascular fraction)[5,7,46,47,64,65] that met inclusion criteria reported safety outcomes following culture-expanded stem cell therapy for knee OA.

- While the number of serious AEs reported (to include death) appears to be low across four RCTs and three case series, evidence is insufficient to draw firm conclusions; the longest follow-up period was 48 months in one RCT.
- Non-serious treatment-related adverse events were common following culture-expanded SCT. Across three RCTs, the vast majority of SCT recipients experienced one or more treatment-related AE (range, 67% to 100%) compared to 8% to 24% of patients in the control groups (placebo, conservative care) (SOE Low). Knee joint pain was reported in 45% and 50% of SCT patients in two RCTs (compared with 0% to 10% for controls) and ranged from 23% to 60% across 4 case series (SOE Low). Almost all events were reported to be mild and transient.
- Results should be interpreted cautiously given study limitations and small sample sizes.

Allogenic, culture-expanded stem cells

Only the two included RCTs reported safety outcomes following allogenic, culture-expanded stem cell therapy for knee OA.

- There is insufficient evidence to draw firm conclusions regarding the safety of allogenic, culture-expanded SCT for treatment of Knee OA.
    - No serious AEs were reported in one small RCT at moderately high risk of bias.
    - Across both RCTs, injection site pain, effusion and/or swelling were common with SCT (40% to 53%), however evidence compared with an active comparator (HA), is limited to one small trial at moderately high risk of bias.

Degenerative Disc Disease (DDD)

Key Questions 1 (Efficacy/Effectiveness) and 2 (Safety)

Only one comparative study, a small RCT,[44] evaluating allogenic, culture-expanded bone marrow aspirate-derived MSC (vs. sham injection), for the treatment of DDD that met inclusion criteria was identified.

- There is insufficient evidence to draw firm conclusions regarding the efficacy and effectiveness of autologous or allogenic SCT for treatment of chronic LBP due to DDD.
    - Data for autologous sources are from small case series and are at high risk of bias.
    - Only one small RCT was identified which compared allogenic culture-expanded MSCs from bone marrow aspirate with a sham treatment. While no differences between treatment groups was seen for function, pain, or quality of life through 12 months, evidence was considered insufficient due to the small sample size, moderately high risk of bias and uncertainty regarding the consistency of results from a single trial.
- There is insufficient evidence to draw conclusions regarding the safety of autologous or allogenic stem cell therapy for treatment of chronic LBP due to DDD.
    - Harms and serious adverse events were sparsely reported and not well described across studies
    - Sample sizes precluded detection of rare events

Tendinopathy

Key Questions 1 (Efficacy/Effectiveness) and 2 (Safety)

One small RCT[73] in patients with chronic non-insertional Achilles tendinopathy comparing autologous non-culture-expanded adipose-derived stromal vascular fraction (AD-SVF) versus platelet rich plasma (PRP) that met inclusion criteria was identified. In addition, one small case-series[63] of BMC plus PRP in patients with previously untreated elbow tendinopathy that provided data for safety was identified.

- There is insufficient evidence to draw firm conclusions regarding the effectiveness or safety of autologous non-expanded stem cells for treatment of tendinopathy.
    - No difference in function was seen between treatment groups in the RCT of Achilles tendinopathy over 1 to 6 months; improvement in pain with AD-SVF injection compared with PRP was seen up to 1 month only.
    - Harms and serious adverse events were sparsely reported and not well described across studies; sample sizes precluded detection of rare events

Strength of Evidence Summary for Key Question 1: Efficacy Results for Autologous, Non-Culture-Expanded Stem Cell Therapy for Knee Osteoarthritis

Outcome	Time	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
Function outcomes					
KOOS ADL (0-100, higher score = better function)	3, 6 mos.	1 RCT (N=30 at 3 mos.; N=28 at 6 mos.) Ruane 2019	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision:Yes[4] (-1)	MD in change scores: 3 mos.: 2.9 (–9.3, 15.0) 6 mos.: 3.2 (–9.6, 16.0) Conclusion: No difference between groups; sample sizes were small and CIs were wide.	⊕◯◯◯ INSUFFICIENT
	12 mos.	2 RCTs (N=83) Goncars 2017 Ruane 2019	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision:Yes[4] (-2)	Pooled MD in change scores: 3.8 (–3.8, 11.4); I^2=0% Conclusion: No difference between groups; sample size was small and CI was wide. Individually, no difference between groups was seen in either trial and CIs were wide.	⊕◯◯◯ INSUFFICIENT
KOOS Sport (0-100, higher score = better function)	3, 6 mos.	1 RCT (N=30 at 3 mos.; N=28 at 6 mos.) Ruane 2019	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision:Yes[4] (-1)	MD in change scores: 3 mos.: –0.6 (–20.6, 19.4) 6 mos.: 3.3 (–18.1, 24.6) Conclusion: No difference between groups; sample sizes were small and CIs were wide.	⊕◯◯◯ INSUFFICIENT
	12 mos.	2 RCTs (N=83) Goncars 2017 Ruane 2019	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision:Yes[4] (-2)	Pooled MD in change scores: 13.0 (0.9, 25.2); I^2=0% Conclusion: Greater improvement in function with stem cells vs. HA; however, sample size was small and CI was wide and approached zero. Individually, no difference between groups was seen in either trial and CIs were wide.	⊕◯◯◯ INSUFFICIENT
KOOS Symptoms (0-100, higher score = better symptomology)	3, 6 mos.	1 RCT (N=30 at 3 mos.; N=28 at 6 mos.) Ruane 2019	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2]	MD in change scores: 3 mos.: 3.5 (–8.4, 15.4) 6 mos.: 1.9 (–10.0, 13.7) Conclusion: No difference between groups; sample	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
			Serious Imprecision:Yes[4] (-1)	sizes were small and CIs were wide.	
	12 mos.	2 RCTs (N=83) Goncars 2017 Ruane 2019	Serious Risk of Bias: Yes[1] (-1) Serious inconsistency: Yes[2] (-1) Serious Imprecision:Yes[4] (-1)	Pooled MD in change scores: 0.69 (–16.3, 17.7); I^2=83% Conclusion: No difference between groups; sample size was small, CI was wide, and there was substantial heterogeneity in the pooled analysis. Individually, neither trial found a statistical difference between groups however, the point estimates went in opposite directions.	⊕◯◯◯ INSUFFICIENT
KSS Function and Knee scores	3 mos.	1 RCT (N=46 for KSS function; N=45 for KSS Knee) Centeno 2018	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision:Yes[4] (-1)	KSS Function (mean change): 7.5 vs. 2.3, p=0.17 KSS Knee (mean change): 12 vs. 0.6, p<0.001 Conclusion: Greater improvement in function following stem cell therapy versus exercise plus usual care for the KSS Knee score but not the KSS Function score.	⊕◯◯◯ INSUFFICIENT
	12 mos.	1 RCT (N=56) Goncars 2017	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision:Yes[4] (-1)	KSS Function (mean change): 38.3 vs. 17.5, p=NS KSS Knee (mean change): 25.4 vs. 10.7, p=NS Conclusion: No difference between groups for either outcome; a measure of variability was not provided.	⊕◯◯◯ INSUFFICIENT
Pain Outcomes					
KOOS Pain and VAS Pain† (0-100, lower score = less pain)	3 mos.	4 RCTs (N=182)‡ Centeno 2018 Goncars 2017 Ruane 2019	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision:Yes[4] (-1)	Pooled MD in change scores: –3.7 (–7.9, 0.7); I^2=0% Conclusion: No difference between groups; CI is wide. Results should be interpreted cautiously given	⊕⊕◯◯ Low

Outcome	Time	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
		Shapiro 2017/2018 (50 knees)‡		the small number of trials with small sample sizes.	
	6, 12 mos.	3 RCTs (N=134)‡ Goncars 2017 Ruane 2019 Shapiro 2017/2018 (50 knees)‡	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision:Yes[4] (-1)	Pooled MD in change scores: 6 months: –5.7 (–17.4, 5.3); I^2=85% 12 months: –6.5 (–20.4, 6.8); I^2=87% Conclusion: No difference between groups in pooled analyses at 6 and 12 months; CIs were wide and there was substantial heterogeneity. Individually only one trial (Goncars 2017) reached statistical significance favoring stem cells (at 6 and 12 months). Results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ Low

ADLs = activities of daily living; CI = confidence interval; KSS = Knee Society Clinical Rating System; KOOS: Knee injury and Osteoarthritis Outcome Score; MD = mean difference; mos. = months; NS = not statistically significant; RCT = randomized controlled trial; SoE = strength of evidence; VAS = visual analog scale.

*Stem cell type vs. control group for included RCTs:

Centeno 2018: Bone marrow concentrate (BMC) (+ platelet rich plasma [PRP] and platelet lysate [PL]) vs. Home Exercise (i.e., functional strengthening, resistance training, monitor alignment for core, pelvis and entire lower extremity, balance/neuromuscular training, aerobic activity based on what the patient had available [e.g., walk, stationary bike, etc.] and manual therapy and mobility as needed). Patients in the BMC group received post-treatment injections of PRP, hydrocortisone, and doxycycline and were given prescribed a therapeutic exercises consisting of deep water emersion walking or jogging followed by stationary bike, and then elliptical, as well as core training, non-resistance hip and knee strengthening as pain allowed.

Goncars 2017: Bone marrow derived mononuclear cells (BM-MNCs) vs. Hyaluronic Acid (HA)

Ruane 2019: Bone marrow concentrate (BMC) (+ platelet rich plasma [PRP]) vs. Hyaluronic Acid (HA; Gel-One® Hyaluronate)

Shapiro 2017/2018: Bone marrow concentrate (BMC) (+ platelet poor plasma [PPP]) vs. Placebo (saline)

Tucker 2019: Adipose-derived stromal vascular fracture (AD-SVF) vs. Placebo (saline)

†Centeno 2018 and Shapiro 2017/2018 reported pain according to the VAS pain scale and Goncars 2017 and Ruane 2019 reported pain according to the KOOS pain scale; results were pooled across these two pain measures.

‡The trial by Shapiro et al. enrolled patients with bilateral knee OA; results are given out of 50 knees (in 25 patients).

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency

of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Question 1: Efficacy Results for Autologous, Culture-Expanded Stem Cell Therapy for Knee Osteoarthritis

Outcome	Time	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
Function outcomes					
"Success": WOMAC total (0-96)	6, 12 mos.	2 RCTs (N=81) Freitag 2019 (N=29) Lu 2019 (N=52)	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) (differing cut-offs for success) Serious Imprecision: Yes[4] (-1)	**WOMAC total [Lu 2019]** ***20% improvement***: • 6 mos.: 58% (15/26) vs. 42% (11/26); RR 1.4 (0.8, 2.4) • 12 mos.: 54% (14/26) vs. 50% (13/26); RR 1.1 (0.6, 1.8) ***50% improvement***: • 6 mos.: 23% (6/26) vs. 8% (2/26); RR 3.0 (0.7, 13.5) • 12 mos.: 35% (9/26) vs. 4% (1/26); RR 9.0 (1.2, 66.1) ***70% improvement:*** • 6 mos.: 12% (3/26) vs. 0% (0/26), p=0.07 • 12 mos.: 19% (5/26) vs. 4% (1/26); RR 5.0 (0.6, 39.9) **WOMAC total – MCID 8 points [Freitag 2019]** • 12 mos.: 95% (18/19) vs. 20% (2/10); RR 4.7 (1.4, 16.4) Conclusion: Results varied depending on the cut-off used for "success".	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
"Success": WOMAC physical function (0-68)	3, 6 mos.	1 RCT (N=43) Emadedin 2018	Serious Risk of Bias:Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes[4] (-1)	**WOMAC function – MCID 9.3 points** • 3 mos: 58% (11/19) vs. 42% (10/24); RR 1.4 (0.8, 2.6) • 6 mos: 74% (14/19) vs. 54% (13/24); RR 1.4 (0.9, 2.1) **WOMAC function – PASS (cut-off not defined)** • 3 mos: 26% (5/19) vs. 4% (1/24); RR 6.3 (0.8, 49.6) • 6 mos: 37% (7/19) vs. 13% (3/24); RR 2.9 (0.9, 9.9) Conclusion: No difference between groups (BM-MSCs vs. placebo) reached statistical significance. Small sample sizes likely played a factor in the findings.	⊕◯◯◯ INSUFFICIENT
"Success": KOOS ADL, Sport, Symptoms subscales (all 0-100)	12 mos.	1 RCT (N=29) Freitag 2019	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes[4] (-1)	**KOOS Subscales – MCID 8 points** • **ADLs**: 84% (16/19) vs. 30% (3/10); RR 2.8 (1.1, 7.4) • **Sport**: 89% (17/19) vs. 30% (3/10); RR 3.0 (1.1, 7.8) • **Symptoms**: 68% (13/19) vs. 30% (3/10); RR 2.3 (0.8, 6.2) Conclusion: More patients who received AD-MSCs compared with conservative care met the criteria for "success" according to the KOOS ADL and Sport, but not the Symptoms, scales.	⊕◯◯◯ INSUFFICIENT
WOMAC total (0-96, lower score = better function)	3 mos.	4 RCTs (N=124) Emadedin 2018 Freitag 2019 Lamo-Espinosa 2016/2018 Lee 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	**Pooled MD (All):** –7.9 (–20.7, 4.3), I^2=92% **Pooled MD (Excluding outlier,‡ n=94):** –14.4 (–19.7, –9.2), I^2=0% **MD (Lee 2019, n=24; Lower RoB):** –15.0 (–25.3, –4.7) Conclusion: No difference between groups based on the overall pooled estimate; removal of one outlier trial may suggest improvement in function at 3 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes and	⊕⊕◯◯ LOW

Outcome	Time	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
				heterogeneity in populations and methods across trials.	
	6 mos.	5 RCTs (N=173) Emadedin 2018 Freitag 2019 Lamo-Espinosa 2016/2018 Lee 2019 Lu 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	**Pooled MD (All):** –6.2 (–20.3, 6.2), I^2=89% **Pooled MD (Excluding outlier,‡ n=143):** –11.3 (–20.0, –4.8), I^2=38% **Pooled MD (Lee 2019 and Lu 2019, n=71; Lower RoB):** –10.1 (–24.4, 4.2), I^2=77% Conclusion: No difference between groups based on the overall pooled estimate; removal of one outlier trial may suggest improvement in function in 6 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes and heterogeneity in populations and methods across trials.	⊕⊕◯◯ LOW
	12 mos.	3 RCTs (N=106) Freitag 2019 Lamo-Espinosa 2016/2018 Lu 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	**Pooled MD (All):** –8.2 (–28.8, 12.4), I^2=96% **Pooled MD (Excluding outlier,‡ n=76):** –15.3 (–36.1, 5.5), I^2=92% **MD (Lu 2019, n=47; Lower RoB):** –4.2 (–14.2, 5.7) Conclusion: No difference between groups at 12 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	48 mos.	1 RCT (N=25) Lamo-Espinosa 2016/2018	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes[4] (-2)	**MD:** –10.3 (–15.4, –5.1) Conclusion: Insufficient evidence from one small, moderately high risk of bias RCT.	⊕◯◯◯ INSUFFICIENT
WOMAC physical function (0-68, lower score = better function)	3 mos.	3 RCTs (N=95) Emadedin 2018 Lamo-Espinosa 2016/2018	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1)	**Pooled MD (All):** –4.1 (–14.7, 6.6), I^2=90% **Pooled MD (Excluding outlier,‡ n=65):** –9.0 (–13.7, –4.4), I^2=0% **MD (Lee 2019, n=24; Lower RoB):** –9.0 (–14.3, –3.8)	⊕⊕◯◯ LOW

Outcome	Time	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
		Lee 2019	Serious Imprecision: Yes[4] (-1)	Conclusion: No difference between groups based on the overall pooled estimate; removal of one outlier trial may suggest improvement in function at 3 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes and heterogeneity in populations and methods across trials.	
	6 mos.	4 RCTs (N=144) Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019 Lu 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	**Pooled MD (All):** –3.6 (–14.8, 7.6), I^2=84% **Pooled MD (Excluding outlier,‡ n=114):** –8.9 (–18.7, 1.7), I^2=47% **Pooled MD (Lee 2019 and Lu 2019, n=71; Lower RoB):** –6.9 (–19.9, 6.0), I^2=64% Conclusion: No difference between groups at 6 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	12 mos.	2 RCTs (N=77) Lamo-Espinosa 2016/2018 Lu 2019	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-2)	**Pooled MD (All):** 1.4 (–5.5, 8.2), I^2=55% **MD (Lu 2019, n=47; lower RoB):** –2.5 (–9.9, 4.8) Conclusion: No difference between groups based on the overall pooled estimate. Evidence from two small RCTs was insufficient to draw firm conclusions.	⊕◯◯◯ INSUFFICIENT
WOMAC stiffness (0-8, lower score = better function)	3 mos.	3 RCTs (N=95) Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-1)	**Pooled MD (All):** –0.4 (–1.5, 0.4), I^2=0% **MD (Lee 2019, n=24; Lower RoB):** –1.0 (–2.5, 0.5) Conclusion: No difference between groups. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	6 mos.	4 RCTs (N=144)	Serious Risk of Bias: Yes[1] (-1)	**Pooled MD (All):** 0.1 (–1.5, 1.5), I^2=76% **Pooled MD (Lee 2019 and Lu 2019, n=71; Lower RoB):**	⊕⊕◯◯ LOW

Outcome	Time	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
		Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019 Lu 2019	Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	–0.9 (–2.5, 0.6), I^2=50% Conclusion: No difference between groups. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	
	12 mos.	2 RCTs (N=77) Lamo-Espinosa 2016/2018 Lu 2019	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-2)	**Pooled MD (All):** –0.1 (–0.4, 0.3), I^2=0% **MD (Lu 2019, n=47; lower RoB):** –0.5 (–1.5, 0.5) Conclusion: No difference between groups based on the overall pooled estimate. Evidence from two small RCTs was insufficient to draw firm conclusions.	⊕◯◯◯ INSUFFICIENT
Pain outcomes					
"Success": WOMAC pain (scale unclear)**; NRS pain** (0-10)**; KOOS pain** (0-100)	3, 6 mos.	2 RCTs Emadedin 2018 (N=43) Freitag 2019 (N=29)	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	Emadedin: **WOMAC pain – MCID 9.7 points** • 3 mos.: 47% (9/19) vs. 38% (9/24); RR 1.3 (0.6, 2.5) • 6 mos.: 37% (7/19) vs. 29% (7/24); RR 1.3 (0.5, 3.0) **WOMAC pain – PASS (cut-off not provided)** • 3 mos.: 21% (4/19) vs. 29% (7/24); RR 0.7 (0.2, 2.1) • 6 mos.: 16% (3/19) vs. 25% (6/24); RR 0.6 (0.2, 2.2) Freitag: **NRS pain – MCID 1 point** • 12 mos.: 95% (18/19) vs. 40% (4/10); RR 2.4 (1.1, 5.1) **KOOS pain – MCID 8 points** • 12 mos.: 84% (16/19) vs. 10% (1/10); RR 8.4 (1.3, 54.6) Conclusions: Inconsistent results across trials and thresholds.	⊕◯◯◯ INSUFFICIENT
Mean difference in VAS pain (0-10, lower score = less pain)	3 mos.	4 RCTs (N=124) Emadedin 2018 Freitag 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1)	**Pooled MD (All):** –1.0 (–2.6, 0.6), I^2=84% Conclusion: No difference between groups. However, results should be interpreted cautiously given the	⊕⊕◯◯ LOW

Outcome	Time	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
		Lamo-Espinosa 2016/2018 Lee 2019	Serious Imprecision: Yes[4] (-1)	small number of trials with small sample sizes.	
	6 mos.	5 RCTs (N=173) Emadedin 2018 Freitag 2019 Lamo-Espinosa 2016/2018 Lee 2019 Lu 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	**Pooled MD (All trials):** –1.9 (–2.6, –1.3), I^2=0% **Pooled MD (Lee 2019 and Lu 2019, n=71; Lower RoB):** –1.6 (–2.5, –0.7), I^2=0% Conclusion: Less pain following SCT compared with controls at 6 mos. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	12 mos.	3 RCTs (N=106) Freitag 2019 Lamo-Espinosa 2016/2018 Lu 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	**Pooled MD (All):** –2.3 (–3.8, –1.0), I^2=76% Conclusion: Less pain following SCT compared with controls at 12 mos. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	48 mos.	1 RCT (N=25) Lamo-Espinosa 2016/2018	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes[4] (-1)	**MD:** –4.5 (–5.4, –3.6) Conclusion: Insufficient evidence from one small, moderately high risk of bias RCT.	⊕◯◯◯ INSUFFICIENT
Mean Difference in WOMAC pain (0-20, lower score = less pain)	3 mos.	3 RCTs (N=95) Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	**Pooled MD (All):** –1.7 (–4.5, 1.0), I^2=90% **Pooled MD (Excluding outlier,‡ n=65):** –2.7 (–5.1, –0.4), I^2=80% Conclusion: No difference between groups based on the overall pooled estimate; removal of one outlier trial may suggest improvement in pain at 3 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes and heterogeneity in populations and methods across trials.	⊕⊕◯◯ LOW

Outcome	Time	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
	6 mos.	4 RCTs (N=144) Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019 Lu 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	**Pooled MD (All):** –1.5 (–4.3, 1.0), I^2=83% **Pooled MD (Excluding outlier,‡ n=114):** –2.4 (–4.4, –0.4), I^2=65% **Pooled MD (Lee 2019 and Lu 2019, n=71; Lower RoB):** –2.8 (–6.9, 1.4), I^2=82% Conclusion: No difference between groups based on the overall pooled estimate; removal of one outlier trial may suggest improvement in pain at 6 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes and heterogeneity in populations and methods across trials.	⊕⊕◯◯ LOW
	12 mos.	2 RCTs (N=77) Lamo-Espinosa 2016/2018 Lu 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-1)	**Pooled MD (All):** 0.01 (–2.1, 2.1), I^2=66% Conclusion: No difference between groups. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕◯◯◯ INSUFFICIENT

ADLs = activities of daily living; CI = confidence interval; KOOS: Knee injury and Osteoarthritis Outcome Score; MCID = minimal clinically important difference; MD = mean difference; mos. = months; NRS = numerical rating scale; PASS = patient acceptable symptom state; RCT = randomized controlled trial; RR = risk ratio; SoE = strength of evidence; VAS = visual analog scale; WOMAC = Western Ontario and McMasters University Osteoarthritis Index.

*Stem cell type vs. control group for included RCTs:

Emadedin 2018: Bone marrow-derived mesenchymal stem cells (BM-MSCs) vs. Placebo (saline)

Freitag 2019: Adipose-derived mesenchymal stem cells (AD-MSCs) [2 groups, 1 and 2 injections] vs. Conservative Care (i.e., simple analgesics, weight management, and exercise)

Lamo-Espinosa 2018: Bone marrow-derived mesenchymal stem cells (BM-MSCs) [2 groups, high and low dose] + Hyaluronic Acid (HA) vs. HA alone

Lee 2019: Adipose-derived mesenchymal stem cells (AD-MSCs) vs. Placebo (saline)

Lu 2019: Adipose-derived mesenchymal progenitor cells (AD-MPC; Rejoin®) vs. Hyaluronic Acid (HA)

†Risk ratios (95% confidence intervals) and pooled mean differences were calculated by AAI.

‡Lamo-Espinosa 2018. This trial tended to favor the control group (HA) while the other trials all tended to favor stem cells. The reason why is unclear although the following may have played a factor: patients in this trial received an injection of HA along with the BM-MSCs while no other injectate were used in conjunction with the stem cells in the other trials; this trial included a higher proportion of patients with grade IV OA (stem cells, 55% vs. HA, 40%) compared with the other trials (range across all patients, 0% to 16%).

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).

2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Question 1: Efficacy Results for Allogenic, Culture-Expanded Stem Cell Therapy for Knee Osteoarthritis

Outcome*	Time	Studies N (Treatments)	Serious Risk of Bias Serious Inconsistency Serious Indirectness Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
Function: WOMAC total; Lequesne (0-100; lower score = better function)	3, 6, 12 mos.	1 RCT (N=30) Vega 2015 BM-MSCs vs. HA	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious imprecision: Yes[4] (-1)	MD (95% CI): **WOMAC total** • 3 months: –8.0 (–24.0, 8.0) • 6 months: –12.0 (–23.6, –0.4) • 12 months: –13.0 (–29.0, 3.0) **Lequesne** • 3 months: –4.0 (–15.6, 7.6) • 6 months: –15.0 (–26.6, –3.4) • 12 months: –12.0 (–23.9, –0.1) Conclusion: No differences between groups at 3 months but by 6 months, better function with BM-MSCs vs. HA; at 12 months, only the difference on the Lequesne was statistically significant favoring stem cells. Sample size was small and CIs were wide.	⊕◯◯◯ INSUFFICIENT
WOMAC pain (0-100; lower score = less pain)				MD (95% CI): • 3 months: –10.0 (–23.1, 3.1) • 6 months: –11.0 (–24.1, 2.1) • 12 months: –14.0 (–28.8, 0.8) Conclusion: No difference between groups in WOMAC pain scores at any time point.	
VAS pain (0-100; lower score = less pain)	2-3 mos.	2 RCTs (N=50) Khalifeh Soltani 2019 (PL-MSCs vs. placebo) Vega 2015 (BM-MSCs vs. HA)	Serious Risk of Bias: Yes[1] (-1) Serious imprecision: Yes[4] (-2)	Pooled MD (95% CI): –10.0 (–26.4, 6.4); I^2=13% Conclusion: No difference between stem cells vs. controls in VAS pain scores through 3 months. Individually, neither trial found a significant difference between groups.	⊕◯◯◯ INSUFFICIENT
	6 mos.	2 RCTs (N=50) Khalifeh Soltani 2019	Serious Risk of Bias: Yes[1] (-1) Serious inconsistency: Yes[2] (-1)	Pooled MD (95% CI): 0.72 (–34.5, 36.0); I^2=91% • BM-MSCs vs. HA: MD –18.0 (–36.1, 0.1)	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies N (Treatments)	Serious Risk of Bias Serious Inconsistency Serious Indirectness Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
		(PL-MSCs vs. placebo) Vega 2015 (BM-MSCs vs. HA)	Serious imprecision: Yes[4] (-1)	• PL-MSCs vs. placebo: MD 18.0 (6.8, 29.2) <u>Conclusion</u>: No difference between stem cells vs. controls in VAS pain scores at 6 months according to the pooled analysis; however, the confidence interval was wide and there was substantial heterogeneity. One trial found no statistical difference between groups (BM-MSCs vs. HA) while the other found that placebo resulted in less pain at 6 months compared with PL-MSCs; again confidence intervals were wide.	
	12 mos.	1 RCT (N=30) Vega 2015 BM-MSCs vs. HA	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious imprecision: Yes[4] (-1)	MD (95% CI): –18.0 (–37.6, 1.6) <u>Conclusion</u>: No difference between groups in VAS pain scores at 12 months.	⊕◯◯◯ INSUFFICIENT

BM-MSC = bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; MD = mean difference; PL-MSC = placenta-derived mesenchymal stem cells; RCT = randomized controlled trial; SAE = serious adverse events; SCT = stem cell therapy; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Question 2: Safety Results for Autologous, Non-Culture-Expanded Stem Cell Therapy for Knee OA

Outcome	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
All-cause mortality	**2 RCTs (N=60)** Ruane 2019 Tucker 2019 1 Registry Centeno 2014 (patients NR; authors report % based on 840 total procedures)	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-2) RCTS (unknown for registry study)	There were no deaths due to any cause over 12 months as reported by 2 RCTs. Death was reported in 0.2% (n =2) of 840 procedures, 3.5% of 57 total AEs in the registry study **Conclusion**: Study limitations and small samples for comparative studies preclude formulation of firm conclusions.	⊕◯◯◯ INSUFFICIENT
Serious Adverse Events (SAEs)	**4 RCTs (N=121 and 50 knees)** Centeno 2018 Ruane 2019 Shapiro 2017/2018 (50 knees in 25 patients) Tucker 2019 **3 Case series (N=115)** Goncars 2019 Oliver 2015 Yokota 2017 **1 Registry:** Centeno 2014 (patients NR; authors report % based on 840 total procedures; AEs from patient surveys)	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-2) RCTS (unknown for registry study)	No patient experienced a SAE as reported by 4 RCTs and 3 case series over follow-up periods up to 12 months and 6 months, respectively. Registry study: Severe AEs in 5.3% (3 events) of total AEs (n=57) were considered serious; SAEs occurred in 0.4% of 840 procedures. Authors report that none were due to the procedure or the injectate (i.e., stem cells + other biologics). **Conclusion**: SAE definition varied across studies as did reported adjudication. These factors combined with study limitations and small sample sizes preclude formulation of firm conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
Neurologic, neoplasm, allergic reaction, cardiac, bleeding/hematoma	**1 Registry** Centeno 2014 (patients NR; authors report % based on procedures; AEs from patient surveys)	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown Precision: Unknown	Two of each event were reported; frequency was 0.2% for each (out of 840 procedures) or 3.5% for each (of 57 total AEs) **Conclusion**: While the risk of such events appears to be low, study limitations and unknown consistency across comparable studies preclude formulation of firm conclusions.	⊕◯◯◯ INSUFFICIENT
Pain and/or swelling at injection site	**3 RCTs (N=143)** Centeno 2018) Goncars 2017 Tucker 2019 **7 case series (N=170 and 75 knees)** *Pain (N=145)*: Kim 2014 Oliver 2015 *Swelling (N=115, 75 knees)*: Adriani Kim 2014 Oliver 2015 Shaw 2018 *Pain and Swelling (N=55)*: Yokota 2017 Ahmad 2017 Goncars 2019 **1 Registry** Centeno 2014 (patients NR; authors report %	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-1) RCTS, case series (unknown for registry study)	**Pain or swelling (2 RCTs):** 62% (16/26) and 4% (1/26) swelling with grinding pain vs. NR for exercise (Centeno); "common" (Goncars, N=56) **Pain (2 case series):** 41% (31/75 knees) to 82% (57/70 patients) **Swelling (1 RCT, 4 case series):** 4% (1/26) vs. 0% (0/13) for placebo in one RCT (Tucker); 17% (5/30, 2 required aspiration), 59% (41/70), 90% (69/75 knees) across 3 case series; "common" reported in one case series. **Pain and swelling (3 case series, 1 registry):** described as "common" (2 series) or "majority" (1 series); 4.3% (out of 840 procedure), 63.2% of 57 AEs reported (1 registry).	⊕⊕◯◯ LOW

Outcome	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
	based on procedures; AEs from patient surveys)		**Conclusion**: Evidence from RCTs and case series suggest that pain and/or swelling at the injection site are common. These were the most common AEs in the registry study. Results should be interpreted cautiously given study limitations and small sample sizes.	
Effusion **Effusion requiring aspiration**	**2 RCTs (N=48; 50 knees)** Shapiro 2017/2018 (N=50 knees in 25 patients) Centeno 2018 (N=48)	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-1)	**Effusion (Shapiro)** • 1 wk.: 60% (15/25 knees) vs. 24% (6/25 knees); RR 2.5 (1.2–5.4) • 6 mos.: 12% (3/25 knees) vs. 8% (2/25 knees); RR 1.5 (0.3–8.2) • 12 mos.: 8% (2/25 knees) vs. 4% (1/25 knees); RR 2.0 (0.2–20.7) **Effusion requiring aspiration (Centeno)** (timing unclear, 24 mo. f/u): 4% (1/26) vs. NR for exercise **Conclusion**: Joint effusion may be somewhat common however, sample sizes are small.	⊕⊕◯◯ LOW
Definitely and possibly injectate related AEs and procedure-related AEs	**1 Registry** Centeno 2014 (patients NR; authors report % based on 840 procedures, total of 57 AEs; AEs from patient surveys)	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown Precision: Unknown	**Definitely injectate related :** 0.5% out of 840 procedures; 7.0% out of 57 total AEs **Possibly injectate related:** 2.9% out of 840 procedures; 42.1% out of 57 total AEs **Definitely procedure related :** 1.1% out of 840 procedures; 15.8% out of 57 total AEs	⊕◯◯◯ INSUFFICIENT

Outcome	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
			Possibly procedure related: 3.5% out of 840 procedures; 50.9% out of 57 total AEs: **Conclusion:** A large proportion of total AEs appear to be definitely or possibly linked to the injectate (detail not provided). It is assumed that patients may experience >1 AE	
Infection (non-serious)	**1 RCT (N=39)** Tucker 2019 **6 case series (N=111)** Adriani 2017 Ahmad 2017 Bui 2014 Hudetz 2017† Hudetz 2019† Yokota 2017	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-2)	In the RCT, two patients (8%; 2/26), one in each AD-SVF group (high and low dose), had signs of a possible infection at 3 days post-injection compared with no placebo patient (0%; 1/13) No cases of infection were reported across 6 case series of primarily AD-derived stem cells. **Conclusion**: The total number of patients experiencing infection was low; however study sample sizes are small.	⊕◯◯◯ INSUFFICIENT

ASC = adipose-derived stem cells (not otherwise specified); AD = adipose; AD-SVF = adipose derived stromal vascular fraction; AE = adverse events; BMC = bone marrow concentrate (from aspirate); BM-MNCs = bone marrow-derived mononuclear cells; BM-MSCs = bone marrow-derived mesenchymal stem cells HA = hyaluronic acid; mo. = months; MSC = mesenchymal stem cell; NR = not reported; PBSC = peripheral blood stem cells (not otherwise specified); PL = platelet lysate; PRP = platelet rich plasma; RCT = randomized controlled trial; SAE = serious adverse events; wks. = weeks.

*Autologous stem cell type vs. control group for included studies:

- **Centeno 2018 (RCT)**: BMC (+ PRP and PL) vs. Home Exercise (i.e., functional strengthening, resistance training, monitor alignment for core, pelvis and entire lower extremity, balance/neuromuscular training, aerobic activity based on what the patient had available [e.g., walk, stationary bike, etc.] and manual therapy and mobility as needed). Patients in the BMC group received post-treatment injections of PRP, hydrocortisone, and doxycycline and were given prescribed a therapeutic exercises consisting of deep water emersion walking or jogging followed by stationary bike, and then elliptical, as well as core training, non-resistance hip and knee strengthening as pain allowed.
- **Goncars 2017 (RCT)**: BM-MNCs vs. HA
- **Ruane 2019 (RCT)**: BMC (+ PRP) vs. HA (Gel-One® Hyaluronate)

- **Shapiro 2017/2018 (RCT)**: BMC (+ PPP) vs. Placebo (saline)
- **Tucker 2019 (RCT)**: AD-SVF vs. Placebo (saline)
- **Adriani 2017 (case series)**: ASC (percutaneous lipoaspirate injection)
- **Ahmad 2017 (case series)**: PBSC (peripheral blood injection)
- **Goncars 2019 (case series)**: BM-MNCs
- **Kim 2014 (case series):** BM-MSCs
- **Oliver 2015 (case series):** BMC
- **Shaw 2018 (case series):** BMC
- **Centeno 2014 (registry):** BMC (+ PRP and PL) with or without lipoaspirate.

†Hudetz 2017 and 2019 have substantial overlap in populations.

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Question 2: Safety Results for Autologous, Culture-Expanded Stem Cell Therapy for Knee Osteoarthritis

Outcome	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
All-cause mortality	1 RCT (N=52) **Lu 2019**	Consistency: Unknown[2] Serious Imprecision: Yes[4] (-2)	No deaths occurred in either group (AD-MPC vs. HA) over 12 months.	⊕◯◯◯ INSUFFICIENT
Serious Treatment-Related Adverse Events (SAEs)	**4 RCTs (N=136)** Freitag 2019 Lee 2019 Lamo-Espinosa 2016/2018, Lu 2019 **Case Series (N= 72)** Bansal 2017 Orozco 2013/2014 Soler 2015	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-2)	**RCTS** 0% (0/26) with **AD-MPC** vs. 4% (1/26) with **HA** over 12 months; knee infection resulting in withdrawal [1 RCT, Lu 2019]. No serious AEs reported across the remaining 3 RCTs (N=84) over 6-12 months. "Severe" AE (pain and swelling impacting ADLs for 4 weeks): 10% (2/20) following AD-MSC injection vs. NR (for UC) [1 RCT, Freitag] **Case Series:** No serious AEs reported across 3 small series **Conclusion:** Samples sizes may have been inadequate to identify serious AEs uncommon or rare events; evidence is insufficient to draw firm conclusions.	⊕◯◯◯ INSUFFICIENT
Any treatment related AE	**3 RCTs (N=101)** Emadedin 2018 Lee 2019 Freitag 2019	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-1)	**SCT vs. Placebo (N=71; 6 mos.)** 100% (22/22) vs. 24% (6/25), RR 4.2 (2.1–8.4) [Emadedin; BM-MSCs] 67% (8/12) vs. 8% (1/12); RR 8.0 (1.2–54.5) [Lee; AD-MSCs] **AD-MSCs vs. usual care (N=20, 12 mos.) [Freitag]†** 1 injection: 80% (8/10) vs. NR	⊕⊕◯◯ LOW

Outcome	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
			2 injections (baseline): 90% (9/10) vs. NR 2 injections (6 months): 100% (10/10) vs. NR **Conclusion:** Across studies the vast majority of SCT recipients experienced one or more treatment related AEs; they were reported as not serious and time-limited	
Joint Pain; pain in injected joint	**2 RCTs (N=54)** Lee 2019 Lamo-Espinosa 2016/2018 **4 Case Series (N=90)** Soler 2016 Soler 2015 Orozco 2013/2014 Al-Jajar 2017	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-1)	**RCTs** **AD-MSC vs. placebo (Lee, 6 mos.)** 50% (6/12) vs. 0% (0/12) **BM-MSC vs. HA (Lamo-Espinosa, 12 mos.)** 45% (9/20) vs. 10% (1/10); RR 4.5 (0.7, 30.7) [combined doses; all required anti-inflammatory treatment] Low dose 30% (3/10) [RR 3.0, 95% CI 0.4, 24.2; vs. HA] vs. High dose 60% (6/10) [RR 6.0, 95% CI 0.9, 41.2 vs. HA] **Case Series** Mild: 53% (8/15); Moderate: 7% (1/15) through 48 mos. [Soler 2016] Range (across all 4 series): 23% (3/13) to 50% (25/50), 12 to 48 mos. **Conclusion:** Joint pain is common with SCT.	⊕⊕◯◯ LOW
Effusion	**1 RCT (N=24)** Lee 2019 **Case series (N=22)**	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-2)	**RCT:** **AD-MSCs vs. placebo (6 mos.):** 17% (2/12) vs. 8% (1/12); RR 2.0 (0.2–19.2)	⊕◯◯◯ INSUFFICIENT

Outcome	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
	Bansal 2017 Orozco 2013/2014		**Case series (12 to 24 mos.):** Range: 10% (1/10) to 25% (3/12) **Conclusion:** Joint effusion may be common; small sample sizes are noted.	
Musculoskeletal and connective tissue disorder (treatment-related	**1 RCT (N=47)** Emadedin 2018	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes[4] (-1)	**BM-MSCs vs. Placebo (6 mos.):** **Any**: 82% (18/22) vs. 20% (5/25); RR 4.1 (1.8–9.2) **Grade 1**: 0% (0/22) vs. 4% (1/25) **Grade 2**: 77% (17/22) vs. 8% (2/25); RR 9.7 (2.5–37.2) **Grade 3**: 5% (1/22) vs. 8% (2/25); RR 0.6 (0.1–5.8) **Conclusion**: Musculoskeletal and connective tissue problems (not further specified) were common; however evidence is confined to one small RCT.	⊕◯◯◯ INSUFFICIENT
Infection (treatment-related)	**2 RCTs (N=99)** Emadedin 2018 Lu 2019 **Case series (N=20)** Roato 2019	Serious Risk of Bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-1)	**BM-MSCs vs. Placebo, 6 months (1 RCT, Emadedin)**: 5% (1/22) vs. 0% (0/25); grade 3 **AD-MPC vs. HA, 12 months (1 RCT, Lu 2019)** 0% (0/26) vs. 4% (1/26) No infections were reported in one case series. **Conclusion:** One infection occurred in each treatment group across two trials; in the SCT group it was a Grade 3 infection. Overall evidence is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome	Studies N (Treatments)*	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
Joint Swelling	2 case series (N=35) Soler 2016 Roato 2019	Serious Risk of Bias: Yes[1] (-1) Serious Inconsistency: Yes[2] (-1) Serious Imprecision: Yes[4] (-2)	Mild: 7% (1/15), Moderate: 0% (0/15) (Soler) Occurred in "most" patients (Roato) **Conclusion:** There is insufficient information from two small case series to draw conclusions.	⊕◯◯◯ INSUFFICIENT

ASC = adipose-derived stem cells (not otherwise specified); AD-MPCs = adipose-derived mesenchymal progenitor cells AD-MSCs = adipose-derived mesenchymal stem cells; AD-SVF = adipose derived stromal vascular fraction; AE = adverse events; BMC = bone marrow concentrate (from aspirate); BM-MNCs = bone marrow-derived mononuclear cells; BM-MSCs = bone marrow-derived mesenchymal stem cells; HA = hyaluronic acid; mo. = months; MSC = mesenchymal stem cell; NR = not reported; PBSC = peripheral blood stem cells (not otherwise specified); PL = platelet lysate; PRP = platelet rich plasma; RCT = randomized controlled trial; SAE = serious adverse events; wks. = weeks.

*Autologous stem cell type vs. control group for included studies:

- **Emadedin 2018 (RCT)**: BM-MSCs vs. Placebo (saline)
- **Freitag 2019 (RCT)**: AD-MSCs (2 groups, 1 and 2 injections) vs. Conservative Care (i.e., simple analgesics, weight management, and exercise)
- **Lamo-Espinosa 2018 (RCT)**: BM-MSCs (2 groups, high and low dose) + HA vs. HA alone
- **Lee 2019 (RCT)**: AD-MSCs vs. Placebo (saline)
- **Lu 2019 (RCT)**: AD-MPC (Rejoin®) vs. (HA)
- **Al-Jajar 2017 (case series)**: BM-MSCs
- **Bansal 2017 (case series)**: AD-SVF
- **Orozco 2013/2014 (case series)**: BM-MSCs
- **Roato 2019 (case series)**: Concentrated ASCs
- **Soler 2015 (case series)**: BM-MNCs
- **Soler 2016 (case series)**: BM-MNCs

†The trial by Freitag et al. included two intervention groups; one group received a single injection of AD-MSCs and the second group received two injections, the second of which was given at 6 months. Adverse events were reported for the latter group after only one injection (baseline) and then after the second injection (6 months). The authors report that ther second injection was associated with a modest increase in reported moderate AEs in comparison to the initial injection.

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Question 2: Safety Results for Allogenic, Culture-Expanded Stem Cell Therapy for Knee Osteoarthritis

Outcome	Studies N (Treatments)	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
Serious Treatment-Related Adverse Events (SAEs)	**1 RCT (N=30)** Vega 2015 BM-MSC vs. HA	Serious risk of bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes[4] (-2)	No SAEs were reported over 12 months. **Conclusion**: Evidence is insufficient from one small trial at moderately high RoB to draw conclusions regarding SAEs.	⊕◯◯◯ INSUFFICIENT
Pain, effusion and/or swelling at injection site (non-serious, transient, controlled with NSAID)	**2 RCTs (N=50)** Khalifeh Soltani 2019 (N=20, PL-MSC) Vega 2015 (N=30, BM-MSC)	Serious risk of bias: Yes[1] (-1) Serious Imprecision: Yes[4] (-2)	**SCT vs. placebo (Khalifeh Soltani, 6 mos.)** 40% (4/10) vs. 0% (0/10); **SCT vs. HA (Vega, 12 mos.)** 53% (8/15) vs. 60% (9/15), RR 0.9 (0.5–1.7); **Conclusion**: Injection site pain, effusion and/or swelling were common with SCT, however evidence compared with an active comparator, is limited to one small trial precluding firm conclusions regarding the relative frequency of these AEs.	⊕◯◯◯ INSUFFICIENT

AE = adverse events; BM-MSC = bone marrow-derived mesenchymal stem cells; HA = hyaluronic acid; mos. = months; NSAID = non-steroidal anti-inflammatory drug; PL-MSC = placenta-derived mesenchymal stem cells; SAE = serious adverse events; SCT = stem cell therapy.

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Questions 1 and 2: Efficacy and Safety Results of Stem Cell Therapy for Nonradicular Low Back Pain due to DDD

Outcome	Studies N (Treatments)	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
KQ 1. Efficacy: Allogenic, culture-expanded cells				
Function (Mean ODI, 0- 100 scale)	**1 RCT (N=24)** Noriega 2017 MSC vs. Sham	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes[4] (-1)	**MD (95%CI)** 3 month: 9 (-23.9, 6.0) 6 month: -10 (-28.7, 8.7) 12 month: -12 (-32.7, 8.7) **Conclusion**: No differences in function between allogenic MSC and sham at 3, 6 or 12 months; findings may in part be due to small sample size	⊕◯◯◯ INSUFFICIENT
Mean Pain (Mean VAS, 0-100 scale)		Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes[4] (-1)	**MD (95%CI)** 3 month: -3 (27.2, 21.2) 6 month: -11 (-35.5, 13.5) 12 Month: 0 (-27.3, 27.3) **Conclusion:** No difference in mean pain between allogenic MSC and sham at 3, 6 or 12 months; findings may in part be due to small sample size	⊕◯◯◯ INSUFFICIENT
KQ 2. Safety: Allogenic, culture-expanded cells				
Harms, Adverse events	**1 RCT (N=24)** Noriega 2017 MSC vs. Sham	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes[4] (-2)	No major adverse events identified (types unspecified); fewer allogenic MSC recipients required NSAIDS (25% vs 66.6%) versus sham and 8.3% of both groups received opioids. **Conclusion:** Evidence is based one small RCT which is underpowered to detect rare adverse events; firm conclusions regarding safety, particularly long-term or related to rare events are not possible.	⊕◯◯◯ INSUFFICIENT
KQ 2. Safety: Autologous Cell Sources (case series only available)				
Harms, Adverse events	**5 case series** **Non-culture-expanded (N=51)** Pettine 2015 Comella 2017 Haufe 2006 **Culture-expanded (N=20)** Orozco 2011 Kumar 2017	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes[4] (-1)	**Non-expanded/not cultured cells** • No serious adverse events (treatment related or otherwise, 2 series) **Expanded/cultured cells** • No serious treatment related events (2 series) **Conclusion:** Evidence for safety is sparse and poorly reported; studies underpowered to detect adverse events; firm conclusions regarding safety, particularly long-term or related to rare events are not possible.	⊕◯◯◯ INSUFFICIENT

DDD = degenerative disc disease; IVD = intervertebral disc; MSC = mesenchymal stem cell; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial.

Reasons for downgrade:
1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Questions 1 and 2: Efficacy and Safety Results of Autologous Non-Culture-Expanded Stem Cell Therapy for Achilles and Elbow Tendinopathy

Outcome	Studies N (Treatments)	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
KQ 1. Efficacy				
Function: VISA-A (0-100 [best]) **AOFAS** (0-100 [best])	**1 RCT (N=44)** Usuelli 2018 Achilles tendinopathy	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Serious Imprecision: Yes (-1)[4]	*SVF vs. PRP* **VISA-A (mean)*** 2 weeks: 43 vs. 43, NS 1 month: 59 vs. 47, NS 2 months: 66 vs. 59, NS 4 months: 70 vs. 65, NS 6 months: 71 vs. 71, NS **AOFAS (means)*** 2 weeks: 80 vs. 67, p<0.05 1 month: 80 vs. 72, NS 2 months: 85 vs. 79, NS 4 months: 80 vs. 80 NS 6 months: 87 vs. 87, NS **Conclusion**: No differences between SVF and PRP were seen except at 2 weeks for AOFAS. Evidence from this single small trial was considered insufficient to form firm conclusions.	⊕◯◯◯ INSUFFICIENT
Pain (mean VAS, 0-10 [worst]**)**		Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Yes (-1)[4]	*SVF vs. PRP* **VAS (mean)*** 2 weeks: 2.5 vs. 4.4, p<0.0.5 1 month: 2.0 vs. 3.8, p<0.0.5 2 months: 1.8 vs. 2.5, NS 4 months: 2.0 vs. 3.0, NS 6 months: 1.8 vs. 1.8, NS **Conclusion:** Improvement in pain seen with SVF vs. PRP up to 1 month post intervention did not persist. Evidence from this single small trial was considered insufficient to form firm conclusions.	⊕◯◯◯ INSUFFICIENT
KQ 2. Safety				
Harms, Adverse Events	**1 RCT (N=44)** SVF vs. PRP Usuelli 2018 Achilles tendinopathy	Serious Risk of Bias: Yes[1] (-1) Consistency: Unknown[2] Yes (-2)[4]	**SVF vs. PRP** No adverse events observed in either SVF or PRP groups up to 6 months 25% (5/21) of SVF patients complained of hematoma and cutaneous discomfort at the adipose tissue harvest site **BMC**	⊕◯◯◯ INSUFFICIENT

Outcome	Studies N (Treatments)	Reason for Downgrade	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
	1 prospective case series (N=30) BMC Singh 2014 Elbow tendinopathy		No adverse events observed **Conclusion:** Evidence for safety is sparse and poorly reported. Evidence from the trial and case series was considered insufficient to form firm conclusions.	

AOFAS = American Orthopedic Foot and Ankle Society Ankle-Hindfoot Score; BMC = bone marrow concentrate (from bone marrow aspirate); CS = case series; NR = not reported; NS = not statistically significant; PRP = platelet rich plasma; RCT = randomized controlled trial; SD = standard deviation; SVF = stromal vascular fraction; VAS = visual analogue scale; VISA-A = Victoria Institute of Sport Assessment – Achilles

*****Data are all estimated from figures; p-values are for the MD between the two groups. No SDs were provided by the authors, thus the MD cannot be calculated

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

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1 Appraisal

1.1 Background and Rationale

Musculoskeletal conditions are common and can lead to chronic pain, disability and reduced quality of life. As life expectancy continues to rise and the elderly population expands in the United States (US), so too will the prevalence and societal and economic burden of musculoskeletal conditions. Many musculoskeletal tissues have a limited capacity for endogenous repair and for many orthopedic conditions, effective non-surgical treatment options are limited. Given the public health burden and costs related to the management of such conditions, exploration of effective, safe and cost-effective management options is important. Thus, there has been much interest in and research on the use of cell-based therapy, including the use of stem cells, to stimulate repair and regeneration of tissues for such conditions. Additionally, the number of businesses performing internet marketing of cell-based therapies as "stem cell" therapies in the U.S. and Canada has rapidly expanded, particularly in orthopedics.[120,121]

In general, the range of clinical conditions or diseases for which stem cells have proven to be effective is very small. Many stem-cell-based treatments are new and considered experimental. Hematopoietic stem cell transplantation (from bone marrow) has been successfully used to treat patients with leukemia, lymphoma and some inherited blood disorders. Although the safety of stem cells derived from peripheral blood or bone marrow for hematopoietic reconstitution is reasonably well established, this safety may not carry over to other applications. Short-term and long-term harms or adverse events have not been well studied and the risk of using stem cell therapy for musculoskeletal conditions is largely unknown.

While there have been a large number of pre-clinical studies related to musculoskeletal applications of stem cell therapy, such therapy is still in the relatively early stages of development; the evidence of effectiveness and safety from methodologically rigorous clinical studies appears to be sparse and its value has not been established. The FDA has expressed concern regarding the use of unapproved and unproven stem cell therapies based on lack of evidence on the benefits and harms for such products.[68,124] The focus of this review is on the evaluation of the safety and efficacy of Stem Cell Therapy (SCT) as a biological treatment for specific musculoskeletal conditions (e.g. cartilage defects, osteoarthritis or related joint conditions or joint pain, muscle, ligament, or tendon conditions, pain due to degenerative disc disease).

Policy Context

Stem cell therapy for musculoskeletal or orthopedic conditions is an outpatient procedure that begins with collection of stem cells from a patient (autologous) or from another person (allogenic). The cells may be cultured or concentrated and then injected into the affected area. The topic is proposed based on concerns related to the safety, efficacy and value of stem cell injections for musculoskeletal pain.

Objectives

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of autologous or allogenic stem cell therapy in adults for treating specific musculoskeletal conditions in an outpatient setting. The differential effectiveness and safety of stem cell therapies for subpopulations will be evaluated, as will the cost effectiveness.

1.2 Key Questions

In patients with musculoskeletal conditions (e.g. cartilage defects, osteoarthritis or related joint conditions or joint pain, muscle, ligament, or tendon conditions, pain due to degenerative disc disease)

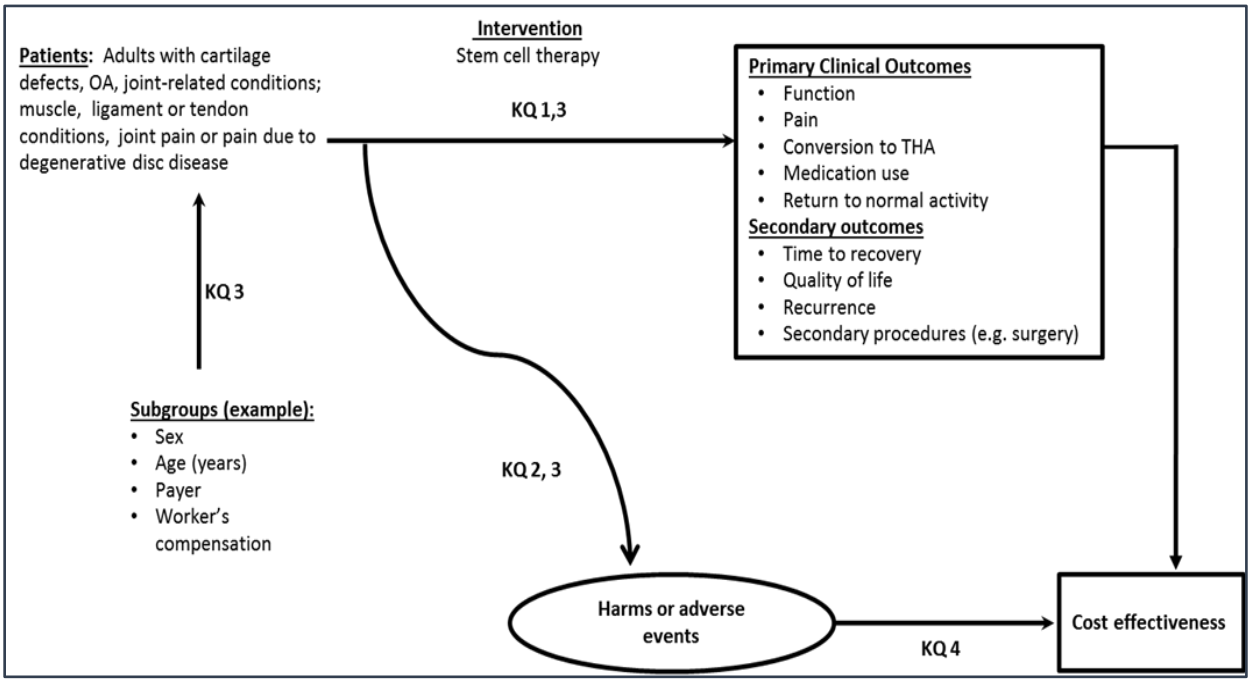
1. What is the evidence of the short- and long-term efficacy and effectiveness of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo/sham?
2. What is the evidence regarding short- and long-term harms and complications of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo?
3. Is there evidence of differential efficacy, effectiveness, or safety of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo?
4. What is the evidence of cost-effectiveness of autologous or allogenic stem cell therapy compared with other treatment options?

Inclusion and exclusion criteria are summarized below and are detailed in the full report.

- **Population**: Adult patients with any of the following conditions: cartilage defects, osteoarthritis or related joint conditions, muscle, ligament, or tendon conditions, pain due to degenerative disc disease, or joint pain.
- **Interventions**: Autologous or allogenic stem cells.
- **Comparators**: Common conventional non-operative treatment(s) (e.g. PT, intra-articular steroid injections, medications (NSAIDS, analgesics), activity modification), surveillance, placebo/sham, or surgery.
- **Outcomes**:
    - Primary clinical outcomes
        - Function (validated measures)
        - Pain (validated measures)
        - Objectively measured medication use
        - Return to normal activities (sports, work, or activity)
        - Adverse events/harms
    - Secondary or indirect (intermediate) outcomes
        - Time to recovery
        - Quality of life
        - Patient satisfaction
        - Recurrence

        - Secondary procedures (e.g., surgery)
    - Economic outcomes
        - Long term and short-term comparative cost-effectiveness measures
- **Studies**: The focus will be on high quality (low risk of bias) comparative studies (e.g., randomized controlled trials (RCTs), comparative cohort studies with concurrent controls). High quality systematic reviews of RCTs, RCTs, and high quality, prospective non-randomized comparative studies will be considered for Key Questions (KQ) 1 and 2. Case series will be consider for KQ2 (safety) if designed specifically to evaluate harms/adverse events; case series may be considered in the absence of comparative studies for KQ1. Only RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest will be considered for KQ3. Full, comparative, formal economic studies (i.e., cost-effectiveness, cost-utility, cost minimization, and cost-benefit studies) will be sought for K5; studies using modeling may be used to determine cost-effectiveness.

Figure 1. Analytic Framework



1.3 Outcomes Assessed

The primary outcomes of interest for this report are listed below.

- Function
- Pain
- Medication use
- Return to normal activity, sports, work

Strength of evidence was assessed for the primary clinical outcomes only.

Table 1. Outcome measures reported on in included studies

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID	Included studies reporting this outcome
Function Outcomes						
Knee						
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)	Patient	The WOMAC has a multi-dimensional scale comprising 24 items grouped into three dimensions: pain (5 items), stiffness (2 items), and physical function (17 items). The test is scored on a Likert scale, and the final scores are standardized to a 0-100 scale.	WOMAC-general: 0-100 -Pain (0-20) -Function (0-68) -Stiffness (0-8)	Higher scores = worse health status	MCID (at 6 months) for patients undergoing TKA[31]: WOMAC-pain: 22.87 WOMAC-function: -19.01 WOMAC-stiffness: 14.53 MCID for patients with knee OA treated with NSAIDS: WOMAC-pain: NR WOMAC-function[117]: -9.1 (95% CI -10.5 to -7.5) points WOMAC-stiffness: NR MCID for patients with hip OA treated with NSAIDS: WOMAC-pain: NR WOMAC-function[117]: -7.9 (95% CI -8.8 to -5.0) points	Hip OA Mardones 2017 Knee OA Vega 2015 Lamo-Espinosa 2016, 2018 Lu 2019 Matas 2019 Emadedin 2018 Lee 2019 Freitag 2019 Garay-Mendoza 2018 Mixed OA Rodriguez-Fontan 2018

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID	Included studies reporting this outcome
					WOMAC-stiffness: NR PASS for patients with knee OA treated with NSAIDS: WOMAC-pain: NR WOMAC-function[118]: 31.0 (95% CI 29.4 to 32.9) points WOMAC-stiffness: NR PASS for patients with hip OA treated with NSAIDS: WOMAC-pain: NR WOMAC-function[118]: 34.4 (95% CI 31.9 to 37.3) points WOMAC-stiffness: NR	
International Knee Documentation Committee scale (IKDC)	Patient	The IKDC measures knee-specific symptoms, daily function and ability to perform sports activity	0-100	Higher scores = increased function	Patients with focal cartilage defects treated surgically[38]: 6.3 points at 6 months and 16.7 points at 12 months post-treatment Patients with various knee pathologies undergoing surgery: 11.5 points[52]	ACL Centeno 2018
Knee Osteoarthritis Outcome Score (KOOS)	Clinician	42 item questions with 5 subscale scores for pain (36 points), symptoms	0-100	Higher scores = increased function & less symptoms	Research is ongoing to establish the MCID for the KOOS in	Knee OA Ruane 2019 Goncars 2017

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID	Included studies reporting this outcome
		(28 points), ADLs (68 points), sports and recreation (20 points), QOL (16 points). Scores normalized to 100 for each subscale and each subscale scored separately. An aggregate score is not calculated.			many different contexts. Though, an MCID of 8-10 has been suggested to be appropriate.[66,98]	Khalifeh Soltani 2019 Lee 2019 Freitag 2019
Knee Society Score (KSS)	Patient and Clinician	This measure consists of two parts: a knee score that rates only the knee joint itself (ROM, including stability, and pain) and a functional score that rates the patient's ability to walk and climb stairs. Each score is reported separately.	0-100	Higher scores = increased function	Patients with Knee OA undergoing TKA[63]: Function score: Range, 6.1 (95 % CI 5.1 to 7.1) to 6.4 (95 % CI 4.4 to 8.4) Knee score: Range, 5.3 (95 % CI 4.3 to 6.3) to 5.9 (95 % CI 3.9 to 7.8)	Knee OA Goncars 2017 Centeno 2018
Modified Lequesne algofunctional indices	Patient	11 items with 3 subscales; Pain (8 points), Walking Distance (8 points), ADL (8 points) The Lequesne OA index is scored as the sum of all questions ranging from 0 to 24.	0-100	Higher scores = greater disability and worse pain	No MCID identified in patients with knee OA or a similar patient population	Knee OA Vega 2015
Lower extremity activity scale (LEAS)	Patient	The LEAS is a self-administered evaluation of activity on an 18-point scale	1-18	Lowest score = confined to bed Highest score = vigorous physical activity	No MCID identified for patients with Knee OA or a similar patient population	Knee OA Centeno 2018
Lower extremity functional scale (LEFS)	Patient	20 items. The introductory statement of the questionnaire states: "Today, do you or	0-80	Higher scores = increased function†	Patients with any lower-extremity musculoskeletal condition being	ACL Centeno 2018

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID	Included studies reporting this outcome
		would you have any difficulty at all with:" followed by a listing of the functional items. Items are rated on a 5-point scale, from 0 (extreme difficulty/ unable to perform activity) to 4 (no difficulty).			treated with PT‡: 9 points[13]	
Hip						
Harris Hip Score (HHS)	Patient	The mHHS score gives a maximum of 100 points. Pain receives 44 points, function 47 points, range of motion 5 points, and deformity 4 points. Function is subdivided into activities of daily living (14 points) and gait (33 points).	0-100	Higher scores = increased function	For patients undergoing hip joint replacement surgery[43]: 4.9 points	Hip OA Mardones 2017
Oxford Hip Score (OHS)	Patient	12-item survey that assesses pain, and function of the hip in relation to daily activities including walking, dressing, climbing the stairs, and sleeping. Each item has five possible responses.	12-60 OR 0-48	Higher scores = increased function	For patients undergoing hip joint replacement surgery: 5.22 points[10]	Hip OA Centeno 2014
Vail Hip Score (VHS)	NR	10 questions relating to pain and function for patients undergoing hip arthroscopic procedures. Developed by Dr's M Philippon MD and Karen Briggs PhD.	NR	NR	No MCID identified for patients with Hip OA or a similar patient population	Hip OA Mardones 2017

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID	Included studies reporting this outcome
Upper extremities						
American Shoulder and Elbow Surgeons score (ASES)	Patient & Clinician	The patient-reported form is divided into 3 sections: pain (6 items), instability (2 items), and ADL (10 items for both sides each). The clinician-reported section has 4 parts (each for left and right): range of motion (5 items, each passive and active), signs (11 items), strength (5 items), and instability (8 items + 1 open question). Binary (yes/no) answers for pain and instability, visual analog scales (VAS) for pain and instability (where 0 = best and 10 = worst), and 4-point ordinal Likert scale for function (where 0 = unable to do, 1 = very difficult, 2 = somewhat difficult, and 3 = not difficult).	0-100	Higher scores = increased function	Patients with shoulder dysfunction treated with PT[71]: 6.4 points Patients with shoulder tendinitis or rotator cuff tear treated with PT[115]: 12 to 16.9 points	Rotator Cuff Tear Kim 2018
Disabilities of the arm, shoulder, and hand (DASH)	Patient	DASH: 30 items (total score): 6 items about symptoms (3 about pain, 1 for tingling/numbness, 1 for weakness, 1 for stiffness) and 24 about function (21 about physical function, 3 about social/role function).	0-100	Higher scores = greater disability	DASH in patients with musculoskeletal upper extremity problems treated with PT[103]: 10.2 points	Rotator Cuff Tear / Shoulder OA Centeno 2015

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID	Included studies reporting this outcome
		QuickDASH: 11 items (3 for symptoms, 8 for function)				
Patient-Rated Tennis Elbow Evaluation (PRTEE)	Patient	15 items rated by visual numeric scale and scored as a mean of all 15 items. There can be a pain subscale (5 items) and function subscale (10 items).	0-100	Higher scores = decreased function and increased pain)	In patients with elbow tendinopathy[89]: - Clinical significance defined as "a little better": 7 points (22% of baseline score) Clinical significance defined as "much better" or "completely recovered": 11 points (37% of baseline)	Elbow tendinopathy Usuelli 2018
Achilles						
Victoria Institute of Sport Assessment - Achilles (VISA-A)	Patient	8 questions that cover three domains of pain (questions 1–3), function (questions 4–6), and activity (questions 7 and 8.) Questions one to seven are scored out of 10, and question 8 carries a maximum of 30. Scores are summed to give a total out of 100. For question 8, participants must answer only part A, B, or C. If the participant has pain when undertaking sport, he or she automatically loses at least 10, and possibly 20, points	0-100	Higher scores = less symptoms	Patients undergoing treatment for insertional Achilles tendinopathy: 6.5 points[69]; 15 points	Achilles Tendinopathy Usuelli 2018
American Orthopedic Foot and Ankle Society Ankle-	Patient & Clinician	Nine questions that cover three categories: Pain (40 points), function (50	0-100	Higher scores = increased function	No MCID identified in patients with Achilles tendinopathy.	Achilles Tendinopathy Usuelli 2018

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID	Included studies reporting this outcome
Hindfoot Score (AOFAS)		points) and alignment (10 points). These are all scored together for a total of 100 points.		Score 100-91: excellent Score 90-81: good Score 80-71: fair Score <70: poor	In patients undergoing hallux valgus surgery[27]: 8.9 points	
Spine						
Oswestry Disability Scale (ODI)	Patient	Questionnaire examines perceived level of disability in 10 everyday activities of daily living. The 6 statements are scored from 0 to 5 and the final score is calculated as a percentage of the total points possible.	0%-100%	Higher scores = greater disability 0% to 20%: minimal disability 21%-40%: moderate disability 41%-60%: severe disability 61%-80%: crippled 81%-100%: bed bound	In patients with low back pain (various pathologies)[25,53,72]: Range, 9.5 to 12.9 points	Degenerative Disc Disease Kumar 2017 Orozco 2011 Pettine 2015 Comella 2017
QOL Outcomes						
Short Form Health Survey (SF-36)	Patient	The SF-36 is a measure of health status. It consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The eight sections include: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning,	0-100	Higher scores = increased QOL	For patients with low back pain[28]: SF-12-MCS: 3.77 SF-12-PCS: 3.29 MCID (at 6 months) for patients undergoing TKA[31]: ~10 points	Knee OA Lu 2019 DDD Orozco 2011 Achilles tendinopathy Usuelli 2018

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID	Included studies reporting this outcome
		emotional role functioning, social role functioning, and mental health.				
Short Form Health Survey (SF-12)	Patient	A shorter version of the SF-36 Health Survey that uses 12 questions to measure functional health and well-being from the patient's point of view. Consists of two component scores; mental and physical.	0-100	Higher scores = increased QOL	No MCIDs identified for this outcome in specified patient populations	Knee OA Vega 2015 Centeno 2018 DDD Noriega 2017 Comella 2017
Pain Outcomes						
Pain Visual Analog Scale (VAS-pain) / Numeric pain scale (NPS) / Numeric Pain Rating Scale (NPRS)	Patient	Patients are asked to indicate on a scale line (typically either 10 or 100 cm in length) where they rate their pain level.	0-10 OR 0-100	Higher scores = increased pain	MCID for patients with knee OA treated with NSAIDS[117]: -19.9 (95% CI -21.6 to -17.9) points MCID for patients with hip OA treated with NSAIDS[117]: -15.3 (95% CI -17.8 to -12.5) points PASS for patients with knee OA treated with NSAIDS[118]: 32.3 (95% CI 30.1 to 34.7) points PASS for patients with hip OA treated with NSAIDs[118]: 35.0 (95% CI 32.8 to 37.4) points	Knee OA Vega 2015 Lamo-Espinosa 2016, 2018 Lu 2019 Emadedin 2018 Khalifeh Soltani 2019 Lee 2019 Centeno 2018 Bhattacharya 2011 Garay-Mendoza 2018 Ruane 2019 Freitag 2019 DDD Pettine 2015, 2016, 2017 Comella 2017 Haufe 2006 Kumar 2017 Orozco 2011 Noriega 2017 Achilles Tendinopathy Usuelli 2018 ACL

Outcome measure	Assessed By	Components	Score range	Interpretation	MCID	Included studies reporting this outcome
						Centeno 2018

ACL = anterior cruciate ligament; CI = confidence interval; DDD = degenerative disc disease; MCID = minimal clinically important difference; NSAIDs: non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PASS = patient acceptable symptom state; QOL = quality of life; ROM = range of motion; SF-12 MCS/PCS = Short Form-12 Mental Component Score/Physical Component Score; SF-36 = Short Form-36

* The original (i.e. non-modified) Lequesne algofunctional indices scale is from 0-24.

† Typically for the LEFS, a higher score indicates greater disability, but for the studies included in this report they have reversed the scale.

‡ Defined as any condition of the joints, muscles, or other soft tissues of the lower extremity.

1.4 Washington State Utilization Data

2 Background

2.1 Epidemiology and Burden of Disease

Musculoskeletal conditions are common and can lead to chronic pain, disability and reduced quality of life. As life expectancy continues to rise and the elderly population expands in the United States (US), so too will the prevalence and societal and economic burden of musculoskeletal conditions. In 2015, more than half of US adults—124 million Americans over the age of 18—reported having a musculoskeletal medical condition, exceeding that of the next two most common health conditions, namely circulatory and respiratory conditions. The most common musculoskeletal conditions leading to disability are back or neck pain and arthritis/chronic joint pain. According to the Centers for Disease Control and Prevention National Health Interview Survey, 38 in 1000 adults in the work force reported they were unable to work at all due to a musculoskeletal condition, with an additional 21 in 1000 reporting they could only do limited work. In the US between 2009 and 2011, musculoskeletal conditions were associated with 574 million physician visits, 379 million visits to non-physician health providers, 390 million home health care visits, about 21 million hospital admissions, and 2.1 billion prescribed medications, which all surmounted to an estimated economic impact of musculoskeletal conditions of $796.3 billion.[128] Given the public health burden and costs related to management musculoskeletal conditions, exploration of effective, safe and cost-effective management options is important. The use of stem cells for management of such conditions has been an area of active research. Additionally, the number of businesses performing internet marketing of cell-based therapies as “stem cell” therapies in the U.S. and Canada has rapidly expanded, particularly in orthopedics.[120,121] In the U.S., a variety of physicians and nonphysician clinicians with various types of training may provide cell-based therapies that are marketed as “stem cell” therapies.[33]

While there have been a large number of pre-clinical studies related to musculoskeletal applications of stem cell therapy, such therapy is still in the relatively early stages of development; the evidence of effectiveness and safety from methodologically rigorous clinical studies appears to be sparse and its value has not been established. The focus of this review is on the evaluation of the safety and efficacy of Stem Cell Therapy (SCT) as a biological treatment for specific musculoskeletal conditions.

2.2 Conditions of Interest

In general, the range of clinical conditions or diseases for which stem cells have proven to be effective is very small. Many stem-cell-based treatments are new and considered experimental. Hematopoietic stem cell transplantation (from bone marrow) has been successfully used to treat patients with leukemia, lymphoma and some inherited blood disorders. Grafting of tissues derived from or maintained by stem cells has also been used to treat some bone, skin and corneal conditions.

Many musculoskeletal tissues have a limited capacity for endogenous repair and for many orthopedic conditions effective non-surgical treatment options are limited. Thus, there has been much interest in and research on the use of cell-based therapy, including the use of stem cells, to stimulate repair and regeneration of tissues for such conditions.

The focus of this Health Technology Assessment (HTA) is on application of stem cell therapies to specific musculoskeletal conditions including, cartilage defects, osteoarthritis or related joint conditions or joint

pain, muscle, ligament, or tendon conditions, pain due to degenerative disc disease.

2.3 Intervention: Stem Cell Therapy

Stem cells are the basis of all tissues and organs in the body, possessing the ability to give rise to multiple cells of the same kind. Stem cell therapy, as described in this report, is the use of pluripotent or multipotent stem cells to treat a disease or condition. The terminology related to "stem-cell therapy" is imprecise, inconsistent, and has led to substantial confusion in the medical and lay literature. Some of the therapies offered in various settings as "stem cell therapy" may not contain stem cells. The terms "stem cell" and "mesenchymal stem cell" have been used very broadly and often inaccurately to describe many cell-based treatments.[120,121] The National Institute of Health (NIH) defines stem cells as "different from other kinds of cells in the body.[122] All stem cells have three general properties: they are capable of dividing and renewing themselves for long periods of time, they are *unspecialized*, and they can give rise to specialized cell types".

Stem cell types are often described as embryonic stem cells (obtained at the earliest developmental stages), tissue-specific (also referred to as adult or somatic stem cells) and recently, induced pluripotent stem cells which are engineered from specialized cells. Embryonic stem-cells are unspecialized, are able to generate any type of cell and are referred to as pluripotent, thus meeting the NIH definition.[51,91] Under the right conditions, they can be replicated and cultured in this undifferentiated state. Induced pluripotent cells are a topic of ongoing research. Their production involves the engineering or "reprograming" of adult cells to behave like pluripotent embryonic stem cells. In contrast, tissue-specific (adult, somatic) stem cells have already differentiated into specialized cells that have the potential to produce some or all of the mature cell types contained in a specific organ or tissue. These are termed multipotent and are often found deep within tissues of organs that continuously replenish themselves (Table 2). Stem cell sources may be autologous or allogenic; the biological activity may differ between these two general sources.

Tissue-specific (adult, somatic) stem cell preparations have been most commonly described for treatment of musculoskeletal conditions of interest for this HTA and will be the focus of this HTA. Peripheral blood, umbilical cord blood and bone marrow are sources of one type of tissue-specific stem cells called hematopoietic stem cells which give rise to all types of blood cells. Hematopoietic stem cell (blood stem cell) transplants have been used for treatment of certain cancers and blood and immune system disorders. Their inability to proliferate and differentiate in vitro presents a challenge for using them beyond replacement of blood and immune cells.

Non-hematopoietic stem cells from tissues and organs have been collectively referred to as "mesenchymal stem cells" (MSC) in most lay and medical literature. They were first identified in bone marrow (called bone marrow stromal cells) and demonstrated an ability to make bone, cartilage and fat cells. These cells are considered multipotent adult stem cells that have potential to differentiate into various musculoskeletal tissues. MSCs have since been grown from other tissues such as adipose tissue[50], the amnion, Wharton's jelly and the umbilical cord as well as muscle, synovial membrane, tendons and peripheral blood.[92] MSCs are most commonly harvested via bone marrow aspirate (BMA) for orthopedic applications described in peer-reviewed medical literature. BMA may be "concentrated" (BMAC or BMC) using centrifugation to concentrate progenitor cells, stem cells, platelets and growth factors; BMAC is frequently used for musculoskeletal applications. Cells are most frequently harvested from the iliac crest. This procedure may result in donor site morbidity to include pain, infection and bleeding. Adipose tissue is another common source of MCSs for musculoskeletal applications. There is

lack of consensus regarding optimal anatomic location for cell harvesting, processing, delivery, timing or concentration for BMAC or adipose tissue preparations.[100,102] Age, patient co-morbidities, medications, nutritional status and sex may impact the number of viable cells and their ability to differentiate; the bioactivity is of MSCs variable[122]. MSC preparations are used as a stand-alone therapy in the form of an injection (which may include a carrier substance) or in combination with scaffolds.[127] Injectable stem cell carriers that provide a favorable cell micro-environment may be used and include PRP, platelet concentrate, HA and a variety of hydrogel systems.[97]

Because adult stem cells are rare in mature tissues and a variety of other cell types are included in the sampling process, identification, isolation and growth of adult stem cells in laboratory settings is required; methods for expanding and culturing stem cells in sufficient numbers for transplantation are not well developed.[122] There are only a small number of actual stem cells in organs and tissues and their ability to divide is limited; thus they must be cultured and manipulated to produce sufficient quantities for potential treatment. The characteristics of MSCs and how they differentiate depend on the source within the body as well as how they are isolated, processed and cultured.[23,95,122]

While a variety of cells have been categorized as MSCs, in the literature there is lack of consistency in reporting specific cell characteristics and markers for accurate categorization, what source may be best for a specific application, procedures for culturing them and what "dose" of cells may be optimal for any given application. In addition, there is not a full understanding of whether the cells are actually "stem cells" or of the mechanisms involved in the differentiation into desired tissue type or any specific range of tissue types.[23,73]

The accuracy and use of the term "mesenchymal stem cell" has been questioned.[111] MSCs are isolated from the connective tissue surrounding organs and other tissues called stroma, prompting some scientists to suggest that "mesenchymal *stromal* cells" may be more accurate. The International Society for Cell Therapy (ISCT) has defined mesenchymal *stromal* cells as multipotent progenitor cells derived from non-hematopoietic tissues (e.g. bone marrow, fat, synovium) that are plastic adherent, express certain cell markers but not others and are capable of differentiating into bone, cartilage and fat forming cells.[15,29] Such cells may modulate immune and inflammatory responses and may support and stimulate cells to enhance repair processes.[15,16] The term "stem cell" has been broadly used to include minimally manipulated cell preparation as well as tissue-derived culture-expanded cells.[23] Cells meeting the ISCT criteria must be cultured in the laboratory; cultured cells are not currently FDA-approved for use in the U.S. Some experts suggest that the term "stem cell" be reserved for laboratory-purified, culture-expanded cells[15]. A 2018 American Academy of Orthopedic Surgeons (AAOS)/NIH U-13 consensus document recognizes that stem cells have unique properties that are not met by minimally manipulated mixed cell preparations.[23] They suggest that the term "cell therapy" be used for minimally manipulated cell products. Currently there are not established guidelines or standard protocols for how to isolate stem cells, concentrate them and process them or on the number to inject. Processes for procuring and expanding autologous and allogenic MCS may be proprietary.[95]

In addition to lack of consistency in terminology related to stem cells in general and mesenchymal cells in particular, there is substantial inconsistency across the literature relative to reporting of preparation, processing, cell marker characteristics, culture conditions, composition, stem cell concentration, dose, purity, and delivery of bone marrow aspirate products or other MSC sources.[88] Minimum reporting standards for clinical studies of cell-based therapies to include details related to these and other factors have recently been proposed.[23,73] An outline check list of the proposed standards based on the 2018

AAOS/NIH U-13 conference[23] and related 2017 AAOS/ AOSSM consensus document[73] are found in Appendix D.

For purposes of this HTA, studies that report use of active pluripotent or multipotent stem cells will were included. Studies of more differentiated cell types such as tenocytes, chondrocytes, fibroblasts, etc., are excluded. Studies of dehydrated and/or cryopreserved cells (e.g. amniotic membrane or fluid) are also excluded as they do not contain concentrations of live stem cells. Similarly studies of solely of platelet-rich plasma (PRP) as a cell-based therapy were excluded; it was the focus of a previous report.[44]

Table 2. Overview of stem cells

	Cell potency	Cell source	Cell differentiation examples	Comments
High Potency	**Totipotent Stem Cell**: Having the ability to give rise to all the cell types of the body plus all of the cell types that make up the extraembryonic tissues such as the placenta	• Zygote formed at egg fertilization	• All cell types	
	Pluripotent Stem Cell:* Having the ability to give rise to all of the various cell types of the body (mesoderm, endoderm, or ectoderm tissue).	• Embryonic stem cells; Primitive (*undifferentiated*) cells derived from a 5 day pre-implantation embryo	• Mesoderm: forming bone, cartilage, most of the circulatory system, muscles, connective tissue, and more. • Endoderm: forming the gastrointestinal and respiratory tracts, endocrine glands, liver, and pancreas. • Ectoderm: giving rise to the skin and nervous system.	Capable of dividing without differentiating for a prolonged period in culture. Pluripotent cells cannot make extra-embryonic tissues such as the amnion, chorion, and other components of the placenta.
	Multipotent Stem Cell: cells have *differentiated into specialized cells* but have the ability to develop into more than one cell type of the body, but less potential than a pluripotent or totipotent cell;	• Amniotic fluid • Umbilical cord blood • Placental tissue • Bone marrow • Circulating blood and lymph • Adipose tissue • Heart tissue • Neural tissue	• Skin, cartilage, cardiac tissue, nerves, muscle, bones (non-hematopoietic) • All types of blood cells • All types of blood cells • Blood cells (hematopoietic) • Bone, cartilage, fat (non-hematopoietic) • Hematopoietic cells • Bone, cartilage, fat, others(non-hematopoietic) • Coronary vessels and heart muscles (cardiomyocytes) (non-hematopoietic) • Neurons and Glia of the nervous system (non-hematopoietic)	**Mesenchymal Stromal Cells, (Mesenchymal Stem Cells)**:† non-blood, tissue-specific (adult or somatic) stem cells; may come from a variety of sources; **bone marrow and adipose tissue** are frequently used in musculoskeletal applications; MSCs comprise a small fraction of cells contained in a sample; they can be cultured increase the number and to give rise to various connective tissue types such as bone, cartilage and fat; the mechanism of differentiation in the human body is unclear.
Low Potency	**Unipotent Cells**: Can only differentiate to one lineage	• Muscle cells • Blood cells • Epithelial cells	• Muscle cells • Blood cells • Skin cells, fibroblasts	Not technically be "stem" cells; they can only reproduce the same cell type

*****Induced Pluripotent Stem Cell: Somatic (adult) cells reprogrammed to enter an embryonic stem cell–like state by being forced to express factors important for maintaining the "stemness" of embryonic stem cells; these are investigational.

†The terms mesenchymal stem cell, mesenchymal stromal cell, mesenchymal multipotent cells are broadly used in the literature and may be inaccurately applied see text for details and FDA regulatory information

2.4 Proposed Benefits of Stem Cell Therapy

Stem cell's ability to "self-renew" (i.e. give rise to multiple cells of the same kind) for long periods of time and to differentiate into mature cells with specific functions are part of normal physiologic processes for replacing injured tissues and cells. These properties of stem cells make them attractive, promising approaches for treating a variety of medical conditions. Some have referred to the use of stem-cell therapies as part of "regenerative medicine". Musculoskeletal tissues that have a limited capacity for endogenous repair include vertebral discs, cartilage, tendons, ligaments and muscle. For many orthopedic conditions, effective non-surgical treatment options are limited. Thus, there has been much interest in the use of cell-based therapy to stimulate repair and regeneration for such conditions. Tissue engineering and use of cell-based therapy have been active areas of research for the treatment of musculoskeletal conditions.

2.5 Harms and Adverse Events of Stem Cell Therapy

Stem cell therapies have the potential to create unique and serious risks depending on the processes for obtaining, manipulating and re-inserting them into a person, whether from autologous or allogenic sources. Although the safety of stem cells derived from peripheral blood or bone marrow for hematopoietic reconstitution is reasonably well established, this safety may not carry over to other applications. Stem cell biology is quite complex and beyond the scope of this review. The mechanisms related to potential therapeutic effects and harms in humans are poorly understood and are active areas of research. For adult stem cells (e.g. MSCs), cell to cell contact coupled with secretion of a wide array of biologically active substances (e.g. grown factors and cytokines) may be responsible for therapeutic effects but may also impact multiple biologic mechanisms and cell types[47] and MCS responses may differ based on the local host environment.[54] The potential for adverse events is influenced by multiple patient factors (e.g. comorbidities, medications, age, disease process, etc.). Potential safety concerns in addition to the potential failure of cells to work as expected include administration site reactions or infection, abnormal immune reactions, undesirable bone formation, ability of cells to migrate from placement sites and differentiate into inappropriate cell types or excessive multiplication and tumor growth. A 2018 review identified 35 cases of acute or chronic complications or death based on CARE case reporting guidelines[34] following SCT provided in stem cell clinics, using various cell sources for a variety of conditions.[9] Authors suggest that complications from SCT applied outside of regulatory guidelines are underreported. A December 2018 CDC report described 12 culture-confirmed infections requiring initial hospital stays ranging from 4 to 58 days in 12 patients who had received SCT using umbilical cord blood-derived stem cell products which are not FDA approved.[83] Eight of the cases were in patients receiving intra-articular injections. Although documented cancer cases have not been identified in the U.S. related to musculoskeletal applications, some recent research suggests that MSCs may contribute pathogenesis.[62,93] Cases of neoplasia have been reported in persons receiving SCT in other countries.[9] Short-term and long-term harms or adverse events have not been well studied and the risk of using MSC therapy for musculoskeletal conditions is largely unknown.

2.6 Food and Drug Administration (FDA) Regulation

The U.S. Food and Drug Administration (FDA) regulates tissues and human cells intended for implantation, infusion or transplantation via the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. The regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) is described as a three-tiered, risk-based approach which

includes consideration of whether the cell source is from structural tissue (e.g. adipose, cartilage) or cells/nonstructural tissues as well as the processing, degree of manipulation and whether the HCT/P is intended for homologous use.[61,123]

- The only stem cell-based products approved by the FDA for use in the U.S. consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood; approval is limited to the treatment of conditions of the hematopoietic system.
- The following are *not* considered HCT/Ps: Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow). Examples of minimally manipulated autologous cell preparations for which FDA approval is not needed include bone marrow concentrate, adipose stromal or stromal vascular fraction, placental tissue fragments and platelet-rich plasma. Use of such products must follow good tissue practice regulations to assure that they do not contain communicable disease agents, are not contaminated and do not become contaminated. Clinicians must register their use.
- Culture-expanded connective tissue cells, i.e. MSCs, muscle-derived cells, adipose-derived cells and cartilage-derived cells for orthopedic applications are *not* FDA-approved. Use requires participation in prospective FDA-approved clinical trials.
- Demineralized bone matrix (DBM) is generally considered minimally processed tissue and does not require FDA approval, however, whether allograft bone products containing viable stem cells, including but not limited to DBM with stem cells would be considered minimally manipulated it not clear. A product which is dependent upon the metabolic activity of living cells for its primary function would not meet the FDA regulation part 1271.10. A product not meeting the criteria for this part would be considered a biologic product and demonstration of its safety and efficacy for the intended use would be required via a New Drug Application (NDA) or Biologics License Application (BLA).

The FDA has expressed concern regarding the use of unapproved and unproven stem cell therapies based on lack of evidence on the benefits and harms and has issued general warnings about them with advice to consumers considering procedures advertised as stem cell therapies.[68,124] Although use of minimally manipulated autologous cell preparations do not require FDA approval, concerns regarding misrepresentation of such products as “stem cell” therapies have been raised by professional organizations and others as the unique characteristics of stem cells are not considered to have been met by minimally manipulated cell-based therapies that are widely marketed in the U.S.[15,51,95]

2.7 Comparator Treatments

Conventional treatments for musculoskeletal conditions vary by etiology and may include conservative non-operative management, minimally invasive injections, or surgical repair (the current standard therapy for many musculoskeletal diseases). Conservative non-operative management of musculoskeletal conditions may include physical therapy, exercise, weight reduction, and/or pharmacological management. These treatments may improve symptom burden and facilitated natural, innate healing processes but are not usually curative. Patients may also elect to receive injections of corticosteroids, hyaluronic acid, or other biologics, such as platelet rich plasma. However, the efficacy of these injections in treating musculoskeletal conditions remains uncertain and ultimately many patients

may require surgery. For example, patients with advanced stage OA may require a total knee replacement and patients with full thickness rotator cuff tears may undergo arthroscopic repair. Autologous grafts, cadaveric allografts and synthetic grafts are often used to facilitate surgical repair and healing, however, may not be feasible in all patients. Graft site availability, morbidity related to harvesting and patient-related factors (e.g. comorbid conditions, medications) may limit use of these grafting options. Thus, there is a need for effective ways of managing musculoskeletal conditions and stem cell therapy may have the potential to help.

2.8 Clinical Guidelines, Consensus Statements, Appropriateness Criteria

The ECRI Guideline Trust (based on the former National Guideline Clearing House), PubMed, Google, Google Scholar, professional orthopedic societies, references in other publications, and the websites of the International Society for Stem Cell Research, Regenexx®, and the International Society for Cell and Gene Therapy, were searched for evidence-based clinical guidelines related to the use of stem cells for treating musculoskeletal conditions. One evidence-based clinical guideline from the American Society of Interventional Pain Physicians addressing the use of stem cell therapy in patients with low back pain was identified via the ECRI Guidelines Trust. A position statement from the Australasian College of Sports Physicians concerning the place of mesenchymal stem/stromal cell therapies in sports and exercise medicine was also identified. The International Society for Stem Cell Research (ISSCR) provides recommendations regarding the use of stem cells for treating OA, but the strength of their recommendation was not assessed.

A consensus document on optimizing use of biological therapies in orthopedics that resulted from a 2018 AAOS conference was identified; it provides recommendations for improving accountability for reporting and clinical use of cell therapies and future research. The ISSCR guideline also provides recommendations for stem cell research and clinical translation. The identified documents are summarized in Table 3 below. It should be noted that evidence used to form these guidelines and consensus statements was not exclusively focused on stem cell therapy in the outpatient setting.

Table 3. Summary of Guidelines and Consensus Statements

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
American Society of Interventional Pain Physicians (ASIP) 2019 *Responsible, Safe, and Effective Use of Biologics in the Management of Low Back Pain: ASIPP Guidelines*	Lumbar Disc Injections of Mesenchymal Stem Cells 1 RCT, 4 case series, 4 comparative cohorts, 1 single arm meta-analysis, 2 SRs	Informed Consent A consent form should be discussed with the patient and signed by both the provider and the patient. Office Set-up The environment in which a stem cell injection occurs must be a highly aseptic environment with comprehensive controls of both raw materials and handlers. The physicians performing the procedures need to be properly trained and comfortable in performing the interventional techniques. They must be ready and available to handle any resulting complications at all times and be available on-call for emergencies that may ensue from the procedure. Contraindications • Hematologic blood dyscrasias • Platelet dysfunction • Septicemia or fever • Cutaneous infections in the area to be injected • Anemia (hemoglobin less than 10 g/dl) • Malignancy, particularly with hematologic or bony involvement • Allergy to bovine products if bovine thrombus is to be used • Severe psychiatric impairment or unrealistic expectation For an autologous therapy procedure, cell harvesting from the patient will be aimed at collecting healthy cells whenever this is possible. This is an especially important consideration for patients with inherited diseases. Pre-injection Management of Patient 1. The patient candidacy requirements, as emphasized above, are met. Imaging modalities must also demonstrate the pathology, and can include MRI, computed tomography (CT) scan, ultrasound, or x ray as appropriate for viewing a specific pathology. 2. The patient should avoid the use of any corticosteroids two or three weeks before the procedure. Also, NSAIDs are avoided within one week of the procedure; any necessary anticoagulation precautions should be taken before the procedure as recommended by consensus guidelines from ASIPP and American Society of Regional Anesthesia and Pain Medicine.	Level III

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
		3. Before and during the procedure, anti-anxiety medications and mild sedation may be required for certain patients. However, deep sedation should be avoided ensuring that the patients are arousable and alert at all times. <u>Pre-injection management of biologic materials</u> 1. To be clinically effective, it is agreed that platelet concentration in an injectate should be at least 2.5 times greater than the baseline plasma concentration. 2. The biologics follow the FDA recommended "minimal manipulation" and "homologous use" draft guidelines in clinical practice. 3. Cell viability is comparable between fresh extraction, 24 hours, and 72 hours, though proliferation may be enhanced at 24 hours. It is recommended to use the cells within 24 hours of thawing from a frozen medium if so used. 4. The tri-lineage capabilities, differentiation, and viability of MSCs are not affected by the gauge of the needle used to extract them, although it has been found that a 19-gauge needle reduced the incidence of apoptosis. 5. A 2 mL syringe is recommended to avoid over inflation. The majority of available studies are also performed with this value. <u>Intra-injection management</u> 1. Cell material, patient, joint location and effected side should be verified before injection. 2. Materials should be injected under direct visualization with image guidance such as with ultrasound, fluoroscopic, CT, MRI or arthroscopic/endoscopic guidance. <u>Post-injection management</u> 1. Patients should be instructed to rest and partially immobilize the injected body part for a few days to 2 weeks. 2. The patient should avoid anti- inflammatory medications for at least a few weeks postoperatively, as the therapy is grounded in the benefit of the patient's inflammatory cascade. The risks and benefits for Aspirin should be reviewed in conjunction with the patient and the clinician prescribing it. 3. Post-operative instructions should be verbally discussed with the patient and the person driving the patient home. Red flags and appropriate pain control measures should also be reviewed. A written copy of the instructions should be given to the patient or the patient's driver prior to discharge.	

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
		4. Close follow-up should be scheduled every 2-4 weeks post-procedure. Follow-ups can extend to 1 or 2 times per year once there has been a demonstration of significant subjective and objective report of improvement in pain and function and is based on the discretion of the clinic thereafter. <u>Continued Therapy</u> 1. Repeat injections may be required, depending on the patient's response. 2. Frequent repeat imaging is not recommended unless there has been a change in patient symptoms or pathology. However, obtaining an x-ray to determine improvement in a joint space or as an indirect assessment of cartilage interval while treating osteoarthritis or obtaining an MRI scan to identify changes in soft tissue structures including articular cartilage, may be considered necessary. <u>Antithrombotic Therapy</u> Antithrombotic therapy should be halted (even temporarily) <u>Adverse Reactions and Complications</u> Risks may include, but are not limited to, infection, tissue rejection and changes in the characteristics of the cells in the product that may alter how they respond. Generalized rest and restraining from the use of NSAID medications are important to optimize therapy. A final concern for the use of biologic therapies is the induction of neoplasms from undifferentiated cells in high volume. A multicenter analysis of over 2,300 patients treated with MSCs (bone marrow and adipose included) for musculoskeletal conditions demonstrated that after nine years, only seven patients developed a neoplasm. This is lower than the rate of neoplasm development in the general population, MSC therapy is therefore not considered causative. The review also noted that the majority of postoperative complications were very few, but included pain post-procedure (3.9%), and pain due to continued degeneration of the joint (3.8%).	
International Society for Stem Cell Research (ISSCR) 2019	1 SR, 2 RCTs, 1 comparative cohort	The effects and effectiveness of cell therapies for the treatment of OA in humans remains unproven and as such cannot be recommended at the present time.	NR

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
Current State of Cell-based Therapies for Osteoarthritis			
Australasian College of Sports Physicians (ACSP) 2016 *ACSP—Position Statement: The Place of Mesenchymal Stem/Stromal Cell Therapies in Sport and Exercise Medicine*	<u>Osteoarthritis</u> 1 SR, 5 RCTs, 2 comparative cohorts, 21 case series <u>Tendinopathy</u> 1 SR, 4 case series <u>Muscle Injury</u> No evidence identified	1. Mesenchymal stem cell (MSC) therapies are still under investigation. 2. Research evidence to date suggests MSCs may be safe in the treatment of OA and tendinopathies so that it is reasonable to proceed to further robust clinical trials with rigorous long-term follow-up. 3. There is limited evidence that suggests that non-expanded MSC therapies do not work. Further research is required to determine the safety and efficacy of expanded MSCs with and without biological scaffolds/growth factors. 4. There is currently insufficient evidence from high-quality clinical trials to recommend the clinical use of MSC therapies for joint or tendon regeneration. 5. The ACSP encourages the establishment of research studies to determine the safety and efficacy of MSCs for the treatment of musculoskeletal conditions. • Clinical research trials must be registered with an appropriate clinical research trial registry. • Any research trial must be subjected to peer review and receive human research ethics committee approval. • Any and all research findings will be shared within the scientific and medical community including adverse outcomes. 6. The ACSP believes that any use of MSCs for musculoskeletal conditions must fit within either of the following pathways: • As part of a rigorous clinical research trial. • As an individualized innovative therapy. It is expected that only small numbers of patients would go through this pathway. 7. The use of MSCs must only be undertaken within the expectations of the relevant medical regulatory organizations. 8. Australasian College of Sports Physicians members must inform all patients receiving MSC therapy that: • They are part of a research trial or are receiving innovative therapy. • Mesenchymal stem cells are experimental and have not yet been proven to be safe or effective for clinical use. • The long-term harms from the use of MSCs have not been determined. • Identifiable personal patient or participant information and treatment will be entered to a database and accessed by researchers. • They may be contacted at a later date for research purposes. • Ethical approval will be sought before accessing patient data.	NR

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
		• Any conflicts of interest held by the researcher or clinician providing innovative therapy will be declared. • The full cost of the procedure, including a full breakdown will be provided to the patient. Costs involved in MSC interventions used within research will not be passed onto participants. • Informed consent to the procedure will be obtained in writing.	
Research and clinical translation			
International Society for Stem Cell Research (ISSCR) 2016 *Guidelines for Stem Cell Research and Clinical Translation*	Expert Consensus	<u>Sourcing Stem Cells</u> • In the case of donation of cells for allogeneic use, the donor should give written and legally valid informed consent that covers, where applicable, terms for potential research and therapeutic uses, return of incidental findings, potential for commercial application, and other issues. • Donors should be screened for infectious diseases and other risk factors, as is done for blood and solid organ donation, and for genetic diseases as appropriate. • Components of animal origin used in the culture or preservation of cells should be replaced with human or chemically defined components whenever possible. • Criteria for release of cells for use in humans must be designed to minimize risk from culture-acquired abnormalities. Final product as well as in-process testing may be necessary for product release and should be specified during the review process. • Funding bodies, industry, and regulators should work to establish public repositories and databases of clinically useful lines that contains adequate information to determine the lines' utility for a particular disease therapy. <u>Manufacturing of Stem Cells</u> • All reagents and processes should be subject to quality control systems and standard operating procedures to ensure the quality of the reagents and consistency of protocols used in manufacturing. For extensively manipulated stem cells intended for clinical application, GMP procedures should be followed. • The degree of oversight and review of cell processing and manufacturing protocols should be proportionate to the risk induced by manipulation of the cells, their source and intended use, the nature of the clinical trial, and the number of research subjects who will be exposed to them. <u>Standards for Clinical Conduct</u>	NR

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
		• Risks should be identified and minimized, unknown risks acknowledged, and potential benefits to subjects and society estimated. Studies must anticipate a favorable balance of risks and benefits. • When testing interventions in human subjects that lack capacity to provide valid informed consent, risks from study procedures should be limited to no greater than minor increase over minimal risk unless the risks associated with the intervention are exceeded by the prospect of therapeutic benefit. • A stem cell-based intervention must aim at ultimately being clinically competitive with or superior to existing therapies or meet a unique therapeutic demand. Being clinically competitive necessitates having reasonable evidence that the nature of existing treatments poses some type of burden related to it that would likely be overcome should the stem cell-based intervention prove to be safe and effective. • Individuals who participate in clinical stem cell research should be recruited from populations that are in a position to benefit from the results of this research. Groups or individuals must not be excluded from the opportunity to participate in clinical stem cell research without rational justification. Unless scientifically inappropriate, trials should strive to include women as well as men and members of racial and/or ethnic minorities. • Clinical research should compare new stem cell-based interventions against the best therapeutic approaches that are currently or could be made reasonably available to the local population. • Where there are no proven effective treatments for a medical condition and stem cell-based interventions involve invasive delivery, it may be appropriate to test them against placebo or sham comparators, assuming early experience has demonstrated feasibility and safety of the particular intervention. <u>Stem Cell-Based Medical Innovation</u> • Clinician-scientists may provide unproven stem cell-based interventions to at most a very small number of patients outside the context of a formal clinical trial and according to the highly restrictive provisions outlined in this section. <u>Clinical Application of Stem Cells</u> • The introduction of novel products into routine clinical use should be dependent on the demonstration of an acceptable balance of risk and clinical benefit appropriate to the medical condition and patient population for which new treatments are designed.	

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
		• Developers, manufacturers, providers, and regulators of stem cell-based interventions should continue to systematically collect and report data on safety, efficacy, and utility after they enter clinical use. • Registries of specific patient populations can provide valuable data on safety and outcomes of stem cell-based interventions within defined populations but should not substitute for stringent evaluation through clinical trials prior to introduction into standard care. • Off-label uses of stem cell-based interventions should be employed with particular care, given uncertainties associated with stem cell-based interventions. <u>Access and Economics</u> • Stem cell-based interventions should be developed with an eye towards delivering economic value to patients, payers, and healthcare systems. • Developers, funders, providers, and payers should work to ensure that cost of treatment does not prevent patients from accessing stem cell-based interventions for life-threatening or seriously debilitating medical conditions.	
Consensus document on accountability and future direction			
American Academy of Orthopaedic Surgeons (AAOS) 2018 *Optimizing Clinical Use of Biologics in Orthopaedic Surgery: Consensus Recommendations From the 2018 AAOS/NIH U-13 Conference*	8 level I, 12 level II, 3 level III, 10 level IV studies, and 19 level V (expert opinion) publications	A collaborative symposium was convened to create a consensus framework for improving, and accelerating clinical evaluation, use and optimization of biologic therapies for musculoskeletal conditions in response to public demand for such therapies and concerns regarding misinformation on unproven "biologic" treatments. Authors state that misrepresentation of uncharacterized and unproven minimally manipulated products as stem cells may erode public trust and compromise development of legitimate cell therapies. **Recommendations to improve accountability**: 1. Define Terminology to Clearly Distinguish Uncharacterized Minimally Manipulated Autologous Cell Products from Rigorously Characterized, Culture-expanded and Purified Stem Cell and Progenitor Cell Populations. • The term "stem cell" has been overused to include minimally manipulated cell preparations in addition to tissue-derived, culture –expanded cell preparations. • "Cell therapy" should be used for minimally manipulated cell products and tissue-derived culture-expanded cells	NR

Guideline	Evidence Base	Recommendation/Consensus	Rating/Strength of Recommendation
		• The untested and uncharacterized nature of these treatments should be understood by providers, communicated within the profession and to patients and the public 2. Standardize Reporting Requirements. • There is substantial variability in progenitor and MSC populations isolated from a donor and variability due to preparation, age, sex, source, harvest and processing; standards are needed for characterization of products. • Minimum Information for studies reporting Biologics (MIBO) check lists should be used to guide study design and reporting. • Regarding MSC, ISCT standard can be used to indicate whether cells meet published standard 3. Establish Registries for Postmarket Monitoring and Quality Assessments of Biologic Therapies. **Recommendations to accelerate discovery, development and delivery of 21st Century cures** 4. Designate Osteoarthritis (OA) as a Serious Medical Condition. 5. Clarify, by Disease State, a Consensus Approach for Biological Markers of Interest and Clinical Trial Design. 6. Establish the Framework for a Multicenter Knee OA Clinical Trial Consortium. 7. Explore Accelerated Pathways for FDA Approval of New Drug Applications for Biologics to Treat Musculoskeletal Conditions General Recommendation: Patient demand and clinical need along with the international experience support exploration of new pathways developed through the 21st Century Cures Act to accelerate clinical evaluation of the use of autogenous cell sources and culture-expanded cell-based therapies to treat musculoskeletal conditions.	

CT = computed tomography; FDA = Food and Drug Administration; GMP = Good Manufacturing Procedures; MIBO = Minimum Information for studies reporting Biologics; MRI = magnetic resonance imaging; MSC = mesenchymal stem cell; NR = not reported; NSAIDs = nonsteroidal anti-inflammatory drugs; OA = osteoarthritis; RCT = randomized controlled trial; SR = systematic review

2.9 Previous Systematic Reviews & Health Technology Assessments

Systematic reviews (SRs) and health technology assessments (HTAs) were found by searching PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the ECRI Guideline Trust from database inception to September 12, 2019. Reference lists of relevant studies and the bibliographies of SRs were hand searched. See Appendix B for search terms and full search strategy.

No previous HTAs were identified regarding the comparative effectiveness, safety, and/or economic value of SCT for the treatment of musculoskeletal pain and/or conditions in the outpatient setting. Several SRs evaluating the effectiveness and/or safety of SCT were identified and are summarized below (Table 4). Due to the high number of SRs identified, only reviews published within the previous two years (2019, 2018) and reviews that included high quality evidence (i.e. RCTs) have been summarized below. The focus has been placed on SRs of knee osteoarthritis (OA) and degenerative disc disease (DDD), as these are the two conditions for which there is the greatest body of evidence available. Studies contained in these reviews that met inclusion criteria for this HTA were included. None of the identified SRs provided quantitative synthesis.

Table 4. Summary of selected previous systematic reviews of outpatient stem cell therapy for musculoskeletal pain

Author (year)	Purpose	Treatments Evaluated	Network Meta-analysis or Indirect Analysis?	Search Dates	Evidence Base Available	Primary Conclusions
Knee Osteoarthritis						
Delanois 2019	To evaluate PRP, BMSCs, ADSCs, and amniotic MSCs for treatment of knee OA*	• BMAC vs. saline • BM-MSC vs. HA • BM-MSC + HA vs. placebo • ADSC vs. placebo • Cryopreserved amnion suspension allograft† • Human umbilical cord blood derived MSCs	No	March 1 2013 to March 31 2018	• BMSC: 4 RCTs • ADSC: 1 RCT • Amniotic MSCs: 1 small case series, 1 small dose ranging study	**General Conclusions** - There remains a paucity of high-level evidence to either justify the expense of or warrant the use of PRP, BMSCs, ADSCs, and AMSCs in the management of knee OA. - Of the studies reporting positive results, major limitations included varying study protocols, inconsistent formulations, and number of intra-articular infiltrations, as well as short follow-up periods. **BMSC** - 3 studies showed efficacy, 1 study showed no differences. BMSC may be effective in improving cartilage damage, pain, and function. - Relatively small sample sizes, and no level II, III, or IV studies available to provide further evidence. - Evidence suggests benefits are short lived and need repeat administration. **ADSC** - VAS scores improved from baseline at all times points through 12 months of follow-up (P≤0.05 for all) - Percentage of patients with ≥30% increase improvement from baseline: 88%

Author (year)	Purpose	Treatments Evaluated	Network Meta-analysis or Indirect Analysis?	Search Dates	Evidence Base Available	Primary Conclusions
						- Patients experienced improvement in WOMAC pain (P≤0.014) and stiffness (P≤0.05) for all follow-up times. Significant improvement in WOMAC stiffness subscale scores at 3, 6, and 12 months (P≤0.05). **Amniotic MSCs** - 1 study demonstrated an increase in KOOS, IKDC, and SANE from baseline to 12-month follow-up; 1 study demonstrated an increase in VAS and IKDC from baseline to 6 months - Both studies were limited by small sample size and lack of randomization or a control group.
Di Matteo 2019	To assess the clinical applications of "minimally" manipulated MSCs, either as BMAC or SVF, in the treatment of knee osteoarthritis.	• BMAC alone • BMAC + PRP • BMAC + adipose tissue • Adipose tissue alone • SVF alone [Comparators included various concentrations of cells, differing number of injections, TKA, placebo, HA, PeCaBoo delivery system, and surgery]	No	1998 to October 10 2018	23 studies • BMAC: 10 studies‡ (2 RCTs, 2 retrospective comparative cohorts, 6 case series) • SVF: 13 studies§ (2 RCTs, 3 prospective comparative cohorts, 8 case series)	**General Conclusions** - The available literature concerning the use of BMAC and SVF for knee OA is characterized by a lack of sound methodologies. With only a paucity of RCTs the authors determined that solid conclusions on the real therapeutic potential of SCT compared with others cannot be made. - However, BMAC and SVF have been shown to be safe and to have some short-term beneficial effect on the treatment of knee OA **BMAC** - The average Coleman methodology score was 37.4 out of 100, thus

Author (year)	Purpose	Treatments Evaluated	Network Meta-analysis or Indirect Analysis?	Search Dates	Evidence Base Available	Primary Conclusions
						showing overall poor methodology in the available literature. - Significant improvement in pain and function in almost all case series. - No superiority over standard treatments identified. - No difference reported between BMAC + adipose vs. BMAC alone. - Higher BMAC concentration and multiple injections associated with better outcome. **SVF** - The average Coleman methodology score was 47 out of 100, which is still insufficient to define the available evidence as "methodologically" robust. - Proportion of studies reporting serious adverse events: 0% (0/13 studies) - Proportion of included studies reporting significant improvement in range of movement, pain, and articular function during daily activities**: 100% (13/13 studies)
Lopa 2019	To provide the reader with the tools necessary to interpret the data, deriving from the available clinical studies concerning the intraarticular injection of MSCs, in the form of either expanded cells or progenitor cell	• BMSC alone • HA + BMSC vs. HA • HA + BMSC vs. placebo • BMAC alone • BMAC + PRP vs. BMAC + adipose graft + PRP • BMAC + PRP + PL • BMAC + PRP	No	NR	27 studies • BMSC: 11 studies (3 RCT, 6 prospective cohort, 2 case series) • BMAC: 5 studies (1 RCT, 1 prospective cohort, 2 retrospective cohort, 1 retrospective case series)	**General conclusions** - Although substantial data have been published to date mostly accompanied by satisfactory results, the complexity of MSC metabolism and related therapeutic effects as well as the weakness of most of the studies do not allow withdrawing definitive conclusions about the superiority of one tissue

Author (year)	Purpose	Treatments Evaluated	Network Meta-analysis or Indirect Analysis?	Search Dates	Evidence Base Available	Primary Conclusions
	concentrates, for the treatment of knee OA.	• BMAC + PRP vs. placebo • ASC alone • SVF + PRP + dexamethasone • SVF + PRP • SVF + HA + PRP • SVF alone • SVF + PRP • Adipose tissue alone • Amniotic fluid cells [Comparators also included various concentrations of cells and differing number of injections]			• ASC: 4 studies (1 RCT, 1 proof of concept clinical trial, 2 prospective cohort) • SVF: 6 studies (3 case series, 3 prospective cohort) • ASA: 1 case series	source over another, as well as about the best cell dose and the long-term durability of the effects of these procedures. - Only 14% of the included studies presented a control group and more than one-third of them reported the results on less than ten patients. **BMSC** - Proportion of studies reporting decrease in pain: 73% (8/11) - Proportion of studies reporting increase in knee function: 73% (8/11) - Proportion of studies reporting increase in walking distance: 18% (2/11) **BMAC** - Proportion of studies reporting decrease in pain: 100% (5/5) - Proportion of studies reporting increase in knee function: 60% (3/5) - Proportion of studies reporting high patient satisfaction: 20% (1/5) **ASC** - Proportion of studies reporting decrease in pain: 75% (3/4) - Proportion of studies reporting increase in knee function: 75% (3/4)

Author (year)	Purpose	Treatments Evaluated	Network Meta-analysis or Indirect Analysis?	Search Dates	Evidence Base Available	Primary Conclusions
						SVF - Proportion of studies reporting decrease in pain: 100% (6/6) - Proportion of studies reporting increase in knee function: 100% (6/6) - Proportion of studies reporting increase in walking distance: 17% (1/6) **Amniotic fluid cells** - One small study (N=6) demonstrated significant improvements in pain and function from baseline.
Degenerative Disc Disease						
Meisel 2019	To review, critically appraise, and synthesize evidence on use of cell therapy for intervertebral disk repair.	• MSC vs. placebo • Allogenic chondrocytes alone • Autologous BMA MSCs alone • Autologous adipose-derived MSCs alone • hematopoietic stem cells alone • Autologous chondrocytes alone (all patients received sequestrectomy as part of treatment)		Through October 31 2018 (PubMed/MEDLINE), and through April 13 2018 (EMBASE and ClinicalTrials.gov)	8 studies (2 RCT, 5 case series, 1 prospective cohort)	**General Conclusions** - The overall strength of evidence for efficacy and safety of cell therapy for lumbar IVD repair was very low primarily due to substantial risk of bias, small sample sizes and lack of a comparator intervention. Methodologically sound studies comparing cell therapies to other treatments are needed. - Proportion of studies reporting need for subsequent surgery: 37.5% (3/8) **Allogenic cells** (1 RCT, 1 case series) - No differences between MSC vs. placebo (1 RCT, n=12 vs. n=12) for function based on ODI compared to baseline (12 months, p=0.2431)

Author (year)	Purpose	Treatments Evaluated	Network Meta-analysis or Indirect Analysis?	Search Dates	Evidence Base Available	Primary Conclusions
						or pain based on VAS compared to baseline (12 months, P=1.0000). - Improvements reported in use of allogenic chondrocytes (1 case series, n=15) for function based on ODI compared to baseline (P<0.0001) and pain based on NPRS compared to baseline (P=0.0025) - No serious adverse events identified in either the RCT or case series. **Autologous cells** (5 case series) - Proportion of studies reporting improved function based on mean ODI scores compared with baseline: 60% (3/5) - Proportion of studies reporting improved pain based on VAS or NPRS scores: 60% (3/5) - Proportion of studies reporting need for subsequent surgery: 60% (3/5) - No serious adverse events reported in the 4-case series reporting on such events. - 1 treatment event was reported as serious and requiring further surgery (1 RCT, n=24)

ADSCs: adipose-derived mesenchymal stem cells; AMSCs: amnion-derived mesenchymal stem cells; ASCs: adipose tissue stem cells; BMAC: bone marrow aspirate concentrate BMSC: bone marrow-derived mesenchymal stem cells; HA: hyaluronic acid; ODI: Oswestry disability index; PL: platelet lysate; PRPs: platelet-rich plasma injections; SVF: stromal vascular fractions; TKA: total knee arthroplasty; VAS: visual analog score; WOMAC: Western Ontario and McMaster Universities arthritis index.

* Although this SR reported on the evidence for PRP injections, since PRP is not an intervention of interest for this HTA, the data for PRP has not been included in this table.

† For the purposes of this HTA, cryopreserved amnion suspension allografts are an excluded intervention. It is unclear if tissues contain any true stem cells after undergoing cryopreservation. However, the study has been included here for completeness.

‡ 1 of these studies assesses SCT as an adjunct to surgery. These types of studies are not included in this HTA.
§ 6 of these studies assess SCT as an adjunct to surgery. These types of studies are not included in this HTA.
** Measured via WOMAC, IKDC, KOOS, Lysholm score, Tegner activity scale, and VAS pain scale.

2.10Medicare and Representative Private Insurer Coverage Policies

For the purposes of this report we obtained and summarized payer policies from two bellwether payers and any relevant information on National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) from the Centers for Medicare and Medicaid Services (CMS). Coverage decisions are summarized briefly below (Table 5). It should be noted that evidence used to form these policies was not specific to the use stem cell therapy in the outpatient setting.

- **Centers for Medicare and Medicaid Services (CMS) National Coverage Determination**
  There is no national coverage determination.
- **Aetna (2019)**

  Aetna considers the use of mesenchymal stem cell therapy (e.g., AlloStem, Osteocel, Osteocel Plus, Ovation, Regenexx, and Trinity Evolution), progenitor cells, and bone marrow aspirate experimental and investigational for all orthopedic applications, with the exception of bone cysts (unicameral/simple), for which Aetna considers bone marrow injections to be medically necessary to treatment.
- **Anthem (2019)**

  Anthem considers mesenchymal stem cell therapy investigational and not medically necessary for the treatment of joint and ligament disorders caused by injury or degeneration as well as autoimmune, inflammatory and degenerative diseases.
- **Premera Blue Cross (2019)**

  Premera Blue Cross considers mesenchymal stem cell therapy to be investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.
- **Wellmark Inc. (BCBS of Iowa and South Dakota) (2019)**

  Mesenchymal stem cell therapy from bone marrow, adipose tissue, peripheral blood or synovial tissue alone or in combination with platelet-derived products (e.g. platelet-rich plasma, lysate) is considered investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.

Table 5. Overview of CMS and Payer Policies

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
CMS NCD	N/A	There is no national coverage determination.	N/A
Aetna (2019)	16 studies/articles	The use of mesenchymal stem cell therapy (e.g., AlloStem, Osteocel, Osteocel Plus, Ovation, Regenexx, and Trinity Evolution) and/or the use of progenitor cells experimental and investigational for all orthopedic applications including repair or regeneration of musculoskeletal tissue, osteochondritis dissecans, spinal fusion, and bone nonunion is considered experimental. The use of bone marrow aspirate is considered experimental and investigational for all other orthopedic applications including nonunion fracture, repair or regeneration of musculoskeletal tissue, osteoarthritis, and as an adjunct to spinal fusion.	There is insufficient evidence to support its use for these indications, especially its safety and long-term outcomes.
Anthem (2019)	4 SRs, 3 RCTs, 1 comparative cohort, 3 case series	Anthem considers mesenchymal stem cell therapy investigational and not medically necessary for the treatment of joint and ligament disorders caused by injury or degeneration as well as autoimmune, inflammatory and degenerative diseases.	Although preclinical studies, case series, and small, RCTs suggest that mesenchymal stem cell therapy may improve regeneration of bone or tissue in orthopedic indications, the lack of validated, comparable scoring, robust sample sizes and long-term follow-up data, preclude definitive conclusions regarding the net health benefit of mesenchymal stem cell therapy. Furthermore, there are known risks related to the various methods utilized to harvest MSCs from the bone marrow, including pain and hemorrhage.
Premera Blue Cross (2019)	NR	Mesenchymal stem cell therapy is considered investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.	This evidence includes small randomized and nonrandomized comparative trials with insufficient data to evaluate health outcomes. Also, expanded MSCs for orthopedic applications are not U.S. FDA–approved (concentrated autologous MSCs do not require agency approval). Overall, there is a lack of evidence that clinical outcomes are improved. The evidence is

Payer (year)	Evidence Base Available	Policy	Rationale/Comments
			insufficient to determine the effects of the technology on health outcomes.
Wellmark Inc. (2019)	7 RCTs, 3 case series, 3 SRs	Mesenchymal stem cell (MSC) therapy from bone marrow, adipose tissue, peripheral blood or synovial tissue alone or in combination with platelet-derived products (e.g. PRP, PL) is considered investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue. MSC therapy may include, but are not limited to the following: • Regenexx™ • Regenexx™ Stem Cell Same Day Procedure • Regenexx™ Super Concentrated PRP • BMAC • MSC Therapy	The lack of validated, comparable scoring, robust sample sizes and long-term follow-up data, preclude definitive conclusions regarding the net health benefit of MSC therapy. While the results of early trials have been promising a number of questions remain. The available data has not yet established that MSCs when infused or transplanted into an area can: 1) truly regenerate by incorporating themselves into the native tissue, surviving and differentiating; or 2) promote the preservation of injured tissue and tissue remodeling. In addition, the optimal source of MSCs has not been clearly identified. Further studies are needed to determine the mechanism of action, duration of efficacy, optimal frequency of treatment and regenerative potential. The evidence is insufficient to determine the effects on net health outcomes.

BMAC =Bone marrow aspirate concentrate; CMS = Centers for Medicare and Medicaid; FDA = Food and Drug Administration; MSC = mesenchymal stem cell; N/A = not applicable; NCD = National Coverage Determination; PL = platelet lysate; PRP = Platelet Rich Plasma; RCT = randomized controlled trial; SR = systematic review.

3 The Evidence

3.1 Methods of the Systematic Literature Review

Objectives

The aim of this report is to systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of autologous or allogenic stem cell therapy in adults for treating musculoskeletal conditions in an outpatient setting. The differential effectiveness and safety of stem cell therapies for subpopulations will be evaluated, as will the cost effectiveness.

Key Questions

In patients with musculoskeletal conditions (e.g. cartilage defects, osteoarthritis or related joint conditions or joint pain, muscle, ligament, or tendon conditions, pain due to degenerative disc disease).

1. In patients with musculoskeletal conditions (e.g. cartilage defects, osteoarthritis or related joint conditions or joint pain, muscle, ligament, or tendon conditions, pain due to degenerative disc disease) What is the evidence of the short- and long-term efficacy and effectiveness of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo/sham?
2. What is the evidence regarding short- and long-term harms and complications of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo?
3. Is there evidence of differential efficacy, effectiveness, or safety of autologous or allogenic stem cell therapy compared with common conventional treatment options, surgery or no treatment/placebo?
4. What is the evidence of cost-effectiveness of autologous or allogenic stem cell therapy compared with other treatment options?

Inclusion/Exclusion Criteria

The complete inclusion and exclusion criteria, defined *a priori,* can be found in Table 6 below. Briefly, included studies met the following requirements with respect to participants, intervention, comparators, outcomes, and study design:

- **Population**: Adult patients with any of the following conditions: cartilage defects, osteoarthritis or related joint conditions, muscle, ligament, or tendon conditions, pain due to degenerative disc disease, or joint pain.
- **Interventions**: Autologous or allogenic stem cells.
- **Comparators**: Common conventional non-operative treatment(s) (e.g. PT, intra-articular steroid injections, medications (NSAIDS, analgesics), activity modification), surveillance, placebo/sham, or surgery.

- **Outcomes**:
    - Primary clinical outcomes
        - Function (validated measures)
        - Pain (validated measures)
        - Objectively measured medication use
        - Return to normal activities (sports, work, or activity)
        - Adverse events/harms
    - Secondary or indirect (intermediate) outcomes
        - Time to recovery
        - Quality of life
        - Patient satisfaction
        - Recurrence
        - Secondary procedures (e.g., surgery)
    - Economic outcomes
        - Long term and short-term comparative cost-effectiveness measures
- **Studies**:
  The focus will be on high quality (low risk of bias) comparative studies (e.g., randomized controlled trials (RCTs), comparative cohort studies with concurrent controls). High quality systematic reviews of RCTs, RCTs, and high quality, prospective non-randomized comparative studies will be considered for Key Questions (KQ) 1 and 2. Case series will be consider for KQ2 (safety) if designed specifically to evaluate harms/adverse events; case series may be considered in the absence of comparative studies for KQ1. Only RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest will be considered for KQ3. Full, comparative, formal economic studies (i.e., cost-effectiveness, cost-utility, cost minimization, and cost-benefit studies) will be sought for K5; studies using modeling may be used to determine cost-effectiveness.

Table 6. Summary of Inclusion and Exclusion Criteria

Study Component	Inclusion	Exclusion
Population	Adult patients with any of the following conditions: • Cartilage defects, osteoarthritis or related joint conditions • Muscle, ligament, or tendon conditions • Pain due to degenerative disc disease • Joint pain	• Persons <18 years of age • Studies in which <80% of patients have a condition of interest • Cutaneous wounds • Neurosurgery • Ophthalmological conditions • Cosmetic conditions • Maxillofacial surgery • Urological conditions • Cardiothoracic conditions • Dental conditions, TMJ • Neuropathic pain • Bone fractures, nonunion • Osteogenesis Imperfecta or other congenital abnormalities

Study Component	Inclusion	Exclusion
		• Femoral head osteonecrosis, avascular necrosis • Radicular back pain • Spinal fusion
Intervention	Autologous or allogenic stem cell therapy	• SCT used in conjunction with surgery (e.g., ACL reconstruction, high tibial osteotomy for cartilage defects/OA) • Other biologics (PRP, growth factor injections, etc.)
Comparator	• Common conventional non-operative treatment(s) (e.g. PT, intra-articular steroid injections, medications (NSAIDS, analgesics), activity modification, etc.) or surveillance • Placebo/sham • Surgery	
Outcomes	***Primary Outcomes*** • Function (validated measures) • Pain (validated measures) • Objectively measured medication use • Return to normal activities (sports, work, or activity) • Adverse events/harms ***Secondary or intermediate outcomes*** • Time to recovery • Quality of life • Patient satisfaction • Recurrence • Secondary procedures (e.g., surgery)	• Non-clinical outcomes • Radiographic feature such as disc height
Study Design	Focus on studies with the least potential for bias. **<u>Key Questions 1-2:</u>** • High quality systematic reviews of randomized controlled trials (RCTs) will be considered • RCTs • High quality, prospective non-randomized comparative studies • Case series will be considered for KQ2 (safety) if designed specifically to evaluate harms/adverse events; case series may be considered in the absence of comparative studies for KQ1 **<u>Key Question 3:</u>** • RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest. **<u>Key Question 4:</u>** • Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	• Indirect comparisons • Comparisons of different cell types, concentrations, preparations or procedures (except for safety) • Incomplete economic evaluations such as costing studies • Studies with fewer than 10 patients per treatment group; case series of <10 patients • Case reports

Study Component	Inclusion	Exclusion
Setting	• Outpatient setting, office setting	
Publication	• Studies published in English in peer reviewed journals or publicly available FDA reports	• Abstracts, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Preliminary reports when results are published in later versions • Patient testimonials

ACL = anterior cruciate ligament; FDA = Food and Drug Administration; KQ = Key Question; NSAIDs = non-steroidal anti-inflammatory drugs; PT = physical therapy; RCTs = randomized controlled trials; OA = osteoarthritis; PRP = platelet-rich plasma; TMJ = temporomandibular joint disorder; SCT = stem cell therapy.

Data Sources and Search Strategy

We searched electronic databases from database inception to September 12, 2019 to identify publications assessing the use of SCT for the treatment of musculoskeletal conditions in an outpatient setting. A formal, structured systematic search of the peer-reviewed literature was performed across a number of databases including PubMed and EMBASE (see Appendix B for full search strategy) to identify relevant peer reviewed literature as well as other sources (ClinicalTrials.gov, ECRI Guidelines Trust, Google Scholar) to identify pertinent clinical guidelines and previously performed assessments. We also hand searched the reference lists of relevant studies and the bibliographies of systematic reviews. Citations from peer-reviewed journals listed by Regenexx® stem-cell clinics were also evaluated against the inclusion/exclusion criteria.[2]

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of the comprehensive electronic search and bibliography review. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals independently. Those articles that met a set of a priori retrieval criteria were included for full-text review. We excluded conference abstracts, non-English-language articles, duplicate publications that did not report different data or follow-up times, white papers, narrative reviews, preliminary reports, and incomplete economic evaluations. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the review and selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Discrepancies were resolved through discussion and if necessary adjudicated by a third investigator.

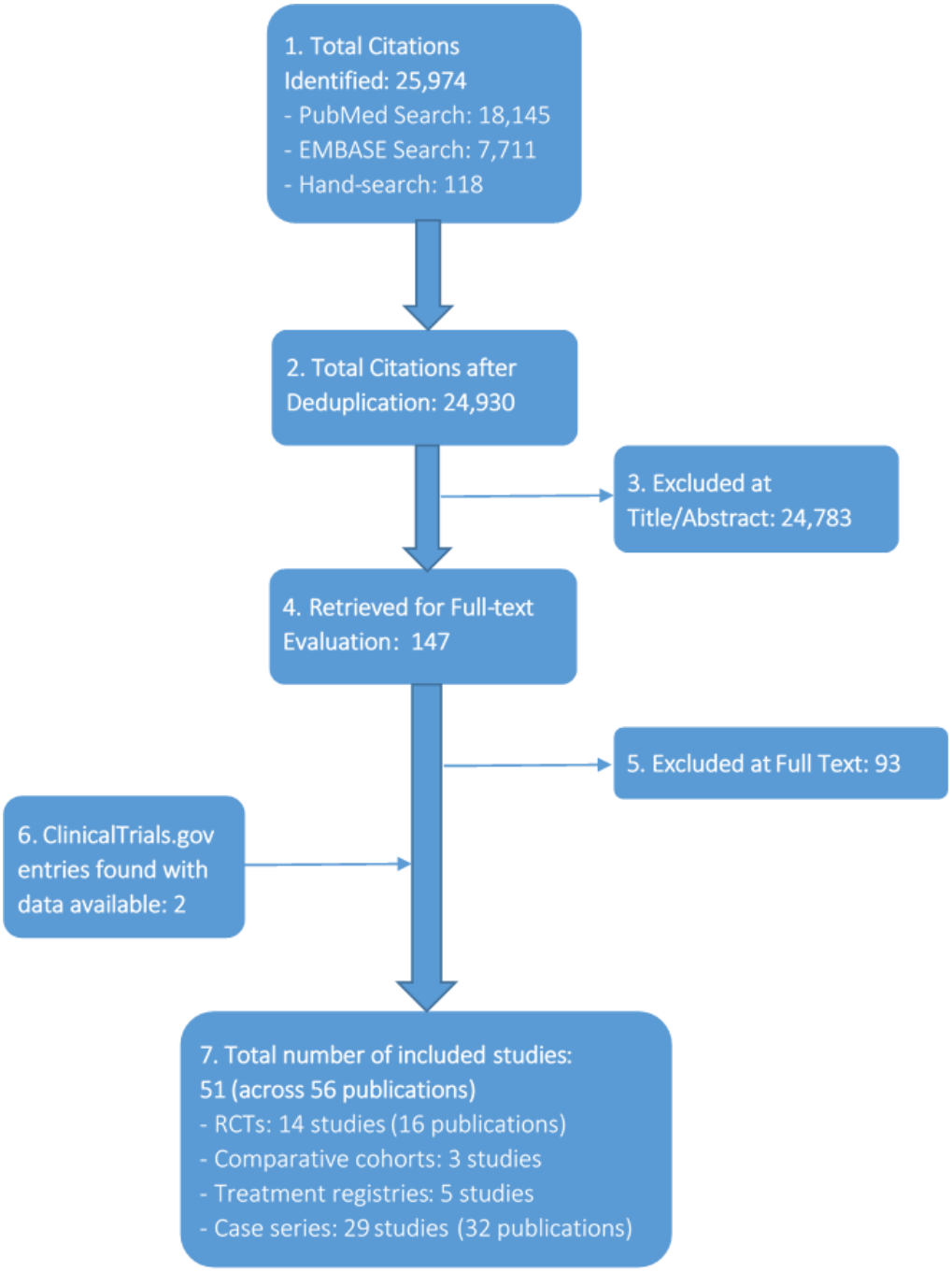
Studies of placental tissue allograft and amniotic fluid were excluded if processing, preservation, and sterilization (e.g. dehydration, cryopreservation, etc.) resulted in no living, active MSCs.[70] Placental allograft contents include growth factors, cytokines, extracellular matrix proteins and other specialty

proteins which are thought to be responsible for the any observed beneficial effects.[42,70,130] Similarly studies of fibroblasts, juvenile chondrocytes, tenocytes or "tenocyte-like" cells were excluded as these types of cells represent a further stage of cell differentiation beyond the stem-cell stage. Studies evaluating use of stem cells as an adjunct to surgery were also excluded. Although not currently FDA approved, studies of cultured/expanded cells were included in this report under the premise that such studies may eventually be used as an evidence base for approval and there are ongoing U.S.-based studies of culture-expanded cells (Appendix G). If there were an adequate number of comparative studies for primary effectiveness outcomes, case series were only included for harms/safety data. In the absence of comparative studies, only limited reporting of case series focusing on primary outcomes (function, pain) was done; data abstraction of case series is available in the appendices.

A list of articles excluded at full text, along with the reason for exclusion is available in Appendix C.

Figure 2 below depicts the flow of studies reviewed for this report.

Figure 2. CONSORT diagram: flow of studies



RCT = randomized controlled trials.

Data Extraction

Reviewers extracted the following data from the clinical studies: study design, study period, setting, country, sample size, inclusion and exclusion criteria, study population characteristics, follow-up time, study funding and conflicts of interest, stem cell therapy characteristics (e.g. cell type, cell source, cell preparation, cell expansion (if any), autologous/allogenic, cell concentration, cell delivery, number of injections) study outcomes, and adverse events. For economic studies, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. Data abstraction was reviewed for accuracy by at least one other investigator. Detailed study and patient characteristics and results are available in Appendix F.

Quality Assessment: Overall Strength of Evidence (SOE), Risk of Bias, and QHES evaluation

The method used by Aggregate Analytics, Inc. (AAI) for assessing the quality of evidence of individual studies as well as the overall strength of evidence (SOE) for each primary outcome from comparative studies are based on criteria and methods established in the Cochrane Handbook for Systematic Reviews of Interventions,[46]precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group[7,39-41] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[1] Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al. in conjunction with consideration of epidemiologic principles that may impact findings.[75] Systematic reviews included as primary evidence were assessed using the AMSTAR 2 tool.[108,109] Based on these quality criteria, each comparative study chosen for inclusion for a Key Question was given a risk of bias (RoB) (or QHES) rating; details of each rating are available in Appendix E.

Standardized, pre-defined guidelines were used to determine the RoB (or QHES) rating for each study included in this assessment. Criteria are detailed in Appendix D. Risk of bias was assessed independently by two reviewers for RCTs, comparative cohort studies and registry studies. Discrepancies between reviewers were resolved by discussion and/or inclusion of a third reviewer. For comparative cohort studies, loss to follow-up (including differential loss to follow-up) and control for potential confounding are generally the primary sources of bias. For registry studies, validation of the completeness and quality of data, accounting for loss to follow-up and control for confound are some of the primary potential sources of bias evaluated. Risk of bias was not assessed for case series (single arm studies); all case series were considered to be at high risk of bias.

The SOE for all *primary* health outcomes was assessed by two researchers following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation)[7,40,41] as outlined by the Agency for Healthcare Research and Quality (AHRQ).[1]The SOE was based on the highest quality evidence available from comparative studies for a given outcome. Discrepancies in SOE determination were resolved by discussion. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- **Risk of bias**: the extent to which the included studies have protection against bias
- **Consistency:** the degree to which the included studies report results that are similar in terms of effect sizes, range and variability. SOE was downgraded for unknown consistency if evidence

was only available for a single study or if the methods or procedures across studies were substantially heterogeneous.
- **Directness**: describes whether the evidence is directly related to patient health outcomes or comparisons of interventions are direct (head to head).
- **Precision:** describes the level of certainty surrounding the effect estimates.
- **Publication or reporting bias:** considered when there is concern of selective publishing or selective reporting. This is difficult to assess particularly for nonrandomized studies.

When assessing the SOE for studies performing subgroup analysis, we also considered whether the subgroup analysis was preplanned *(a priori)* and whether a test for homogeneity or interaction was done.

Bodies of evidence consisting of RCTs are initially considered as High SOE. In general, the GRADE and AHRQ methodologies initially consider nonrandomized studies as Low SOE as such studies typically are at higher risk of bias due to lack of randomization and inability of investigators to control for critical confounding factors.

The SOE could be downgraded based on the limitations described above. There are also situations where studies (particularly observational studies) could be upgraded if the study had large magnitude of effect (strength of association) or if a dose-response relationship is identified and there are no downgrades for the primary domains listed above and confounding is not a concern. Publication and reporting bias are difficult to assess, particularly with fewer than 10 RCTs and for observational studies.[11,104] Publication bias was unknown in all studies and thus this domain was eliminated from the strength of evidence tables. The final SOE was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:
- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable, but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported from economic studies was not assessed.

Primary outcomes for this report were function (validated patient- and clinician-reported measures), pain (validated measures), objectively evaluated medication use, return to normal activities (sports, work, etc.) and adverse events/harms. SOE was assessed for these primary outcomes only. The results

and SOE focus on the highest quality of evidence available. Where RCTs or higher quality evidence were available, these were used to assess the overall strength of evidence. In the absence of RCTs, the highest quality comparative observational studies were used to assess overall SOE. Evidence for effectiveness outcomes consisting of case series alone was considered insufficient as conclusions regarding comparative effectiveness are not possible in the absence of a comparison with alternative treatments in groups of patients from the same underlying patient populations. For safety, evidence from RCTs, comparative surgery cohorts and case series were all considered in the determination of SOE.

Analysis

Evidence was summarized qualitatively and quantitatively. In the absence of adjusted effect size estimates, for dichotomous outcomes, crude risk ratios (RR) and 95% confidence intervals (CI) were calculated using either STATA[114] or Rothman Episheet,[3] particularly for harms, if differences between treatments appeared to approach statistical significance for primary outcomes/harms only. For instances with fewer than five observations per cell, exact methods were employed. These effect estimates cannot control for confounding. Where effect estimates that were adjusted for confounding were reported by study authors, they were preferred and reported. Unless causality could be reasonably assumed for an association, RDs were not calculated. Risk differences were not calculated for observational studies as causality cannot be inferred. Meta-analyses were conducted as appropriate in order to summarize data from multiple studies and to obtain more precise and accurate estimates. For continuous variables, differences in mean follow-up scores between treatments were analyzed to determine mean differences as an affect size. We report mean differences in follow-up scores where available[1]; if no baseline data were reported and only change scores were reported, we reported differences in change scores. Methods for calculating the standard deviations and for imputing missing standard deviations followed the recommendations given in The Cochrane Handbook 7.7. Meta-analyses were conducted using STATA 14.0 (StataCorp, College Station Texas) and Profile Likelihood estimates were reported when available[26] to account for additional uncertainty when small numbers of studies with small sample sizes are pooled. In the case of non-convergence with Profile Likelihood methods, the DerSimonian and Laird estimates were reported. Sensitivity analyses based on study quality or to understand the impact of studies on heterogeneity were conducted when sufficient data were available. Statistical heterogeneity was evaluated based on the I^2 statistic with values ≥50% suggestive of substantial heterogeneity. We considered potential sources of clinical heterogeneity as well.

4 Results

4.1 Number of Studies Retained & Overall Quality of Studies

Overall number of studies retained for this review

A total of 51 studies (across 56 publications)[4-6,8,12,14,17-22,24,30,32,35-37,45,48,49,55-60,64,65,67,74,76-78,80,82,84-87,90,94,96,99,101,105-107,110,112,113,116,119,125,126,129] met inclusion criteria and form the basis for this review; 29 studies (across 33 publications)[12,17,18,20,21,24,30,32,35,36,45,55,57-60,64,65,67,74,80,84-86,96,99,101,105,106,110,119,125,126] addressed efficacy or effectiveness and 48 studies (across 53 publications)[4-6,8,14,17-22,24,30,32,35-37,48,49,55-60,64,65,74,76-78,80,82,84-87,90,94,96,99,101,105-107,112,113,116,119,125,126,129] addressed safety. No studies assessing differential efficacy or cost effectiveness of stem cell therapy were identified.

The evidence base consisted of 14 RCTs (across 16 publications)[20,30,32,36,55,59,60,64,65,74,99,105,106,119,125,126], three comparative cohorts[12,35,57], five registry studies[17-19,21,22], and 29 case series (across 32 publications).[4-6,8,12,14,17-22,24,30,32,35-37,45,48,49,55-60,64,65,67,74,76-78,80,82,84-87,90,94,96,99,101,105-107,110,112,113,116,119,125,126,129] The majority of the evidence available was in knee osteoarthritis (OA) (34 studies across 37 publications), including 12 RCTs (across 14 publications),[20,30,32,36,55,59,60,64,65,99,105,106,119,126] two comparative cohorts,[12,35] one registry study[19] and 19 case series (across 20 publications).[4-6,8,14,37,48,49,56,76-78,87,90,94,107,112,113,116,129] The condition with the second largest evidence base available was degenerative disc disease (DDD), which included one RCT[74] and five case series (across 7 publications).[24,45,58,80,84-86] The final included RCT was in Achilles tendinopathy; it was the only included study for this condition. Most of the studies (35 studies across 38 publications) assessed autologous nonculture-expanded stem cell therapy, including six RCTs (across 7 publications),[20,36,99,105,106,119,125] two comparative cohorts,[35,57] five registry studies (all from the same registry and author group)[17-19,21,22] and 22 case series (across 24 publications).[4,5,14,24,37,45,48,49,56,76,82,84-87,90,94,96,101,107,110,116,129]

Table 7. Number of studies for each comparison for included conditions.

	Number of studies/study design		
Condition/ stem cell classification	**KQ1 (Efficacy/Effectiveness)**	**KQ2 (Safety)**	**Total**
Knee OA			
Autologous nonculture-expanded	5 RCTs (6 publications)[20,36,99,105,106,119], 1 cohort[35]	5 RCTs (6 publications)[20,36,99,105,106,119], 1 cohort[35], 1 registry[19], 14 case series[4,5,14,37,48,49,56,76,87,90,94,107,116,129]	20 studies (21 publications): 5 RCTs (6 publications)[20,36,99,105,106,119], 1 cohort[35], 1 registry[19], 14 case series[4,5,14,37,48,49,56,76,87,90,94,107,116,129]
Autologous culture-expanded	5 RCTs (6 publications)[30,32,59,60,64,65]	5 RCTs (6 publications)[30,32,59,60,64,65], 5 case series (6 publications)[6,8,77,78,112,113]	11 studies (13 publications): 5 RCTs (6 publications)[30,32,59,60,64,65], 5 case series (6 publications)[6,8,77,78,112,113]
Allogenic culture-expanded	2 RCTs[55,126], 1 cohort[12]	2 RCTs[55,126]	3 studies: 2 RCTs[55,126], 1 cohort[12]

	Number of studies/study design		
Condition/ stem cell classification	**KQ1 (Efficacy/Effectiveness)**	**KQ2 (Safety)**	**Total**
TOTAL	12 RCTs (14 publications)[20,30,32,36,55,59,60,64,65,99,105,106,119,126], 2 cohorts[12,35]	12 RCTs (14 publications)[20,30,32,36,55,59,60,64,65,99,105,106,119,126], 1 cohort[35], 1 registry[19], 19 case series (20 publications)	**34 studies (37 publications): 12 RCTs (14 publications)[20,30,32,36,55,59,60,64,65,99,105,106,119,126], 2 cohorts[12,35], 1 registry[19], 19 case series (20 publications)[4-6,8,14,37,48,49,56,76-78,87,90,94,107,112,113,116,129]**
Hip OA			
Autologous nonculture-expanded	1 registry[17], 1 case series[101]	1 registry study[17]	1 registry[17], 1 case series[101]
Autologous culture-expanded	1 case series[67]		1 case series[67]
TOTAL	1 registry[17], 2 case series[67,101]	1 registry[17]	**3 studies: 1 registry[17], 2 case series[67,101]**
Hip and/or Knee OA (combined population)			
Autologous nonculture-expanded	1 case series[96]	1 case series[96]	**1 case series[96]**
Shoulder OA			
Autologous nonculture-expanded	1 registry[21], 1 case series[101]		**1 registry[21], 1 case series[101]**
Degenerative Disc Disease			
Autologous nonculture-expanded	3 case series (5 publications)[24,45,84-86]	2 case series (4 publications)[24,84-86]	3 case series (5 publications)[24,45,84-86]
Autologous culture-expanded	2 case series[58,80]	2 case series[58,80]	2 case series[58,80]
Allogenic culture-expanded	1 RCT[74]	1 RCT[74]	1 RCT[74]
TOTAL	1 RCT[74], 5 case series (7 publications)[24,45,58,80,84-86]	1 RCT[74], 4 case series (6 publications)[24,58,80,84-86]	**1 RCT[74], 5 case series (7 publications)[24,45,58,80,84-86]**
Tendinopathy			
Autologous nonculture-expanded	1 RCT[125], 1 case series[110]	1 RCT[125]	**1 RCT[125], 1 case series[110]**

	Number of studies/study design		
Condition/ stem cell classification	**KQ1 (Efficacy/Effectiveness)**	**KQ2 (Safety)**	**Total**
ACL tear			
Autologous nonculture-expanded	1 registry[18]	1 registry[18]	**1 registry[18]**
Partial Rotator Cuff Tear			
Autologous nonculture-expanded	1 cohort[57], 1 registry[21]	1 cohort[57]	**1 cohort[57], 1 registry[21]**
Mixed Populations			
Autologous nonculture-expanded	N/A	2 registries[21,22], 3 case series[82,96,101]	**2 registries[21,22], 3 case series[82,96,101]**
Autologous culture-expanded	N/A	1 regsitry[22]	**1 regsitry[22]**
TOTAL	N/A	2 registries[21,22], 3 case series[82,96,101]	**2 registries[21,22], 3 case series[82,96,101]**
Grand Total	29 studies (33 publications): 14 RCTs (16 publications)[20,30,32,36,55,59,60,64,65,74,99,105,106,119,125,126] 3 cohorts[12,35,57] 3 registries[17,18,21] 9 case series (11 publications)[24,45,58,67,80,84-86,96,101,110]	48 studies (53 publications): 14 RCTs (16 publications)[20,30,32,36,55,59,60,64,65,74,99,105,106,119,125,126] 2 cohorts[35,57] 5 registries[17-19,21,22] 27 case series (30 publications)[4-6,8,14,24,37,48,49,56,58,76-78,80,82,84-87,90,94,96,101,107,112,113,116,129]	**51 studies (56 publications):** **14 RCTs (16 publications)[20,30,32,36,55,59,60,64,65,74,99,105,106,119,125,126]** **3 cohorts[12,35,57]** **5 registries[17-19,21,22]** **29 case series (32 publications) [4-6,8,12,14,17-22,24,30,32,35-37,45,48,49,55-60,64,65,67,74,76-78,80,82,84-87,90,94,96,99,101,105-107,110,112,113,116,119,125,126,129]**

ACL = anterior cruciate ligament; KQ = Key Question; N/A = not applicable; OA = osteoarthritis; RCT = randomized controlled trial

4.2 Key Question 1: Efficacy and effectiveness

Knee Osteoarthritis

Key points

Autologous, non-culture-expanded stem cells

- Five small, primarily poor quality RCTs evaluated the use of autologous, non-culture-expanded stem cell therapy for knee OA. Four trial used BMC and one used AD-SVF; comparators included placebo (2 trials), hyaluronic acid (HA) (2 trials) and exercise therapy (1 trial).
- There was generally no improvement in function (across multiple measures) with various stem cell interventions compared with HA or exercise, regardless of stem cell source at any time frame across the five small RCTs; however, evidence was insufficient to draw firm conclusions
- No improvement in pain at 3, 6 or 12 months was seen following stem cell interventions compared with HA, placebo or exercise across four RCTs (SOE Low).

Autologous, culture-expanded stem cells

- Five small, primarily poor quality RCTs evaluated the use of autologous, culture-expanded stem cell therapy for knee OA. Three trials used AD-MSCs or AD-mesenchymal progenitor cells (MPCs; Rejoin®) and two used BM-MSCs; comparators included placebo (2 trials), HA (2 trials) and conservative care (e.g., simple analgesics, exercise) (1 trial).
- No differences in function according to pooled estimates for the WOMAC total (5 trials), physical function (4 trials), and stiffness scales (4 trials) were seen at 3, 6 or 12 months following autologous, culture-expanded stem cell injection compared with HA, placebo or conservative care (SOE Low for WOMAC total at 3, 6 and 12 months and for WOMAC physical function and stiffness at 3 and 6 months; SOE insufficient for the latter two measures at 12 months). Removal of one outlier trial from the pooled estimates for WOMAC total score at 3 and 6 months and WOMAC function score at 3 months may suggest improvement in function favoring stem cells. However, results should be interpreted cautiously given the small number of trials with small sample sizes and heterogeneity in populations and methods across trials. Longer-term data (48 months) for the WOMAC total from one small trial at moderately high risk of bias was insufficient to draw firm conclusions.
- No improvement in VAS pain scores between groups was seen across trials at 3 months, but at 6 and 12 months less pain was reported by patients who received autologous, culture-expanded stem cell injection compared with control treatments (SOE low for all timepoints); longer-term data (48 months) from one small trial at moderately high risk of bias was insufficient to draw firm conclusions. No improvement in WOMAC pain scores were seen across trials at any timepoint with SCT versus controls (SOE Low for 3 and 6 months, insufficient for 12 months); removal of one outlier trail from the 6-month pooled estimate may suggest improvement.

- The FDA does not currently approve the use of culture expanded stem cells.

Allogenic, culture-expanded stem cells

- Two small RCTs evaluated the use of allogenic, culture-expanded stem cell therapy, specifically placenta-derived MSCs (vs. placebo) and BM-MSCs (vs. HA), for knee OA.
- There is insufficient evidence to draw firm conclusions regarding the efficacy of allogenic, culture-expanded SCT for treatment of knee OA.
    - Evidence from one small RCT (at moderately high risk of bias) showed no significant difference in functional improvement with SCT versus HA.
    - Across two RCTs, no difference between groups (SCT vs. HA) in pain improvement was seen at 3 or 6 months and at 12 months for one trial.
    - Very small sample sizes, study limitations and lack of precision were methodological shortcomings across these trials.

Detailed analysis

Twelve RCTs (across 14 publications)[20,30,32,36,55,59,60,64,65,99,105,106,119,126] evaluating SCT for the treatment of knee OA that met inclusion criteria were identified; 10 (across 12 publications) evaluated autologous stem cells (5 non-culture expanded and 5 culture-expanded)[20,30,32,36,59,60,64,65,99,105,106,119] and two evaluated allogenic stem cells.[55,126]

In addition, two comparative cohort studies, one evaluating autologous non-culture-expanded[35] and the other allogenic[12] stem cells, and 20 case series (across 21 publications), including one longitudinal analysis of registry data (considered a case series for our purposes),[19] that reported on adverse events following various autologous stem cell therapies for the treatment of knee OA that met inclusion criteria were identified.[4-6,8,14,19,37,48,49,56,76-78,87,90,94,107,112,113,116,129] For details related to the case series, see Appendix F.

Autologous, non-culture-expanded stem cells

Five small trials (across 6 publications) that evaluated autologous, non-culture-expanded stem cells for knee osteoarthritis which met inclusion criteria were identified (Table 8).[20,36,99,105,106,119] Four trials used bone-marrow (BM)-derived cells, all from bone marrow aspirate (BMA) from the iliac crest.[20,36,99,105,106] Specifically, three of these trials used bone marrow aspirate concentrate (BMC) which contained various cell types including mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), platelets, red and white blood cells and macrophages while the fourth trial used isolated mononuclear cells (plasma factors, platelets, and red blood cells were removed).[36] The BMC was supplemented with platelet-rich plasma (PRP),[99] PRP and plasma lysate,[20] or platelet-poor plasma (PPP)[105,106] in one trial each; in the fourth trial, no other additional biological agents were added to the mononuclear cells.[36] The fifth trial used adipose (AD)-derived (from the abdomen or inner thigh) stem cells, specifically nucleated stromal vascular fraction (SVF) cells, without the addition of other biological agents; patients in this trial were randomized to a low dose or a high dose SVF group.[119] Across all trials, the types and total number of cells injected varied widely (Table 8); only three trials confirmed that cell type and concentrations were

determined by flow cytometric analysis.[20,36,105,106] Comparators included placebo (2 trials)[105,106,119] hyaluronic acid (HA) (2 trials)[36,99] and exercise therapy (i.e., functional strengthening, resistance training, monitor alignment for core, pelvis and lower extremity, balance/neuromuscular training, and aerobic activity) in one trial.[20] All injections (intervention or control) were done under ultrasound (primarily) or fluoroscopic guidance and with the exception of the HA group in one trial which received 3 total injections 1 week apart,[36] all patients received a single injection. Anesthetic was used during all injections in the trial evaluating AD-SVF[119] and in the HA group in one trial of BMC[99]; the remaining trials either did not use anesthetic or did not report it. The trial by Centeno et al.[20] also gave the intervention group a pre-treatment injection of hyperosmolar dextrose and a post-treatment injection of PRP, PL (both from an additional blood draw), hydrocortisone and doxycycline 2-4 days prior to and after the BMC injection, respectively. Post-treatment rehabilitation consisted of 4 weeks of braces while weight bearing and standard physiotherapy rehabilitation in one trial[20], activity modification in another trial,[36] and use of crutches (i.e. non-weight bearing) for two weeks in a third trial.[119] One trial did not report post-treatment protocol specifics[99] and another stated that no specific post-treatment protocol was put in place (other than discouraged use of pain medication).[105,106]

Across four trials, the sample sizes ranged from 32 to 56; the fifth trial included 25 patients with bilateral knee OA and randomized each knee to a treatment group for a total of 50 knees treated.[105,106] Mean patient ages ranged from 55 to 60 years across the trials and the proportion of males varied from 22% to 60% across four trials (one trial did not report this variable); comorbidities were not reported (Table 8). Only three trials indicated symptom duration which appeared to be longstanding. The majority of patients had Kellgren-Lawrence (KL) grade II to III OA; no patients had grade IV OA. With the exception of one trial which did not report concomitant medication usage, NSAIDs or other analgesic pain medication and steroid use was either not allowed or discouraged. Across most trials, the inclusion criteria placed limits on how recently patients could have had surgery or previous injections prior to enrollment. The trial by Centeno et al.[20] allowed patients in the exercise group to cross-over and receive a BMC injection after 3 months. All patients in the exercise group chose to crossover at that time and the two treatment groups were combined to evaluate longer-term efficacy (through 24 months); thus, only the 3-month efficacy outcomes which provided comparative data were relevant for this report. Two of the five trials provided preliminary data via clinicaltrials.gov which were used for this report but do not yet have full-length published articles.[99,119] Four trials were conducted in the United States[20,99,105,106,119] and one trial in Latvia.[36] One trial was funded privately (Center for Regenerative Medicine, Mayo Clinic)[105,106], one by industry (Regenexx, LLC and the Centeno-Schultz Clinic),[20] and one by a non-profit healthcare system.[99] Two trials[36,119] did not reported their source of funding.

All five trials were considered to be at moderately high risk of bias. Trial limitations included lack of or failure to adequately report the following: allocation concealment (all 5 trials), randomization sequence generation (3 trials), blind assessment of outcomes (3 trials), and controlling for possible confounders (3 trials [not applicable to the trial that randomized knees rather than patients]). In addition, in the trial by Centeno et al. 2018, it is unclear whether the principle of intention-to-treat was followed and loss-to-follow-up was unable to be determined with the information provided. For details related to risk of bias determination for these trials, see Appendix E.

In addition, one prospective nonrandomized comparative cohort[35] (N=61) compared a single injection of autologous non-cultured/non-expanded BM-MSCs versus acetaminophen. Prior to the BM aspiration, patients in the stem cell group received 600 µg per day of granulocyte colony stimulating factor for 3

consecutive days. Flow cytometry was performed for CD45+, CD34+, and viability determination. The mean number of BM total nucleated cells was $302.02x10^7$ (range, $155x10^7$ to $469.23x10^7$) and the mean number of BM mononuclear cells was $67.33x10^7$ (range, $31.52x10^7$ to $114.02x10^7$). Cells were delivered via an intra-articular injection after local anesthesia with 3 mL of 1% xylocaine. Patients allocated to the acetaminophen group took 500 mg oral acetaminophen every 8 hours for 6 months. In the stem cell and acetaminophen groups, respectively, mean age was 55.7 and 59.3 years, females made up 77% and 71% of the patient population, and mean BMI was 29.5 and 31.6 kg/m^2. The study was conducted in Mexico and the source of funding was not reported. This study is considered to be at high risk of bias due to lack of blinded outcome assessment and lack of controlling for possible confounding factors. For details related to risk of bias determination for this study, see Appendix E.

Table 8. Patient and procedure characteristics of RCTs evaluating autologous non-culture-expanded stem cells for knee OA

	Shapiro 2017/2018 (N=50 knees in 25 patients)		Centeno 2018 (N=48)		Ruane 2019 (N=32)		Goncars 2017 (N=56)		Tucker 2019 (N=39)		
	BMC (n=25 knees)	Placebo (n=25 knees)	BMC (n=26)	Exercise (n=22)	BMC (n=17)	Gel-One® Hyaluronate (n=15)	BM-MNC (n=28)	HA (n=28)	Low-dose SVF (n=13)	High-dose SVF (n=13)	Placebo (n=13)
Patient demographics											
Males, %	28%		NR	NR	53%	67%	54%	36%	31%	54%	46%
Mean age, years	Median, 60		54	57	58	59	53	59	60.5	59.5	57.1
Mean BMI, kg/m2	27		26	26	29.2	29.2	NR	NR	All: <35		
Caucasian, %	80%		NR	NR	NR	NR	NR	NR	100%	100%	92%
Mean Sx duration, months	NR ("long-standing")		NR	NR	NR	NR	≥6	≥6	≥63 months		
K-L OA grade	I: 8% II: 44% III: 48%	I: 8% II: 64% III: 28%	II: 42% III: 58%	II: 45% III: 55%	I: 29% II: 35% III: 35%	I: 13% II: 53% III: 33%	II: 32% III: 68%	II: 25% III: 75%	II: 31% III: 69%	II: 31% III: 69%	II: 31% III: 69%
Co-morbidities	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Concomitant meds	Pain medication use discouraged†		NR		No NSAIDs or oral steroids 2 wks prior to treatment		NSAID use ≤1 week during observation period		None allowed 7 days prior to any visit; no ASA/NSAIDs/fish oil supplements, other pain medication, thrombolytic, anti-platelet medication, or Xeralta®. Oral steroids not allowed.		
Previous injections	None w/in prior 3 months		NR		None w/in prior 6 months		None w/in prior 2 months		Potentially, but none w/in prior 3 months‡		
Previous surgery	75% of knees§	25% of knees§	None w/in prior 6 months		65% (None w/in prior 12 months)	47% (None w/in prior 12 months)	NR		None w/in prior 6 months		
Procedural characteristics											
Patient blinded to treatment received	Yes		No		No		No		Yes		

	Shapiro 2017/2018 (N=50 knees in 25 patients)		Centeno 2018 (N=48)		Ruane 2019 (N=32)		Goncars 2017 (N=56)		Tucker 2019 (N=39)		
	BMC (n=25 knees)	Placebo (n=25 knees)	BMC (n=26)	Exercise (n=22)	BMC (n=17)	Gel-One® Hyaluronate (n=15)	BM-MNC (n=28)	HA (n=28)	Low-dose SVF (n=13)	High-dose SVF (n=13)	Placebo (n=13)
Stem cell source (volume aspirated)	BMA (26 ml), 3 iliac crest sites	NA	BMA (60-90 ml), 6 iliac crest sites	NA	BMA (60 ml), iliac crest	NA	BMA (45 ml), iliac crest	NA	Adipose tissue (~125 ml), abdomen or inner thigh		NA
Cell type(s) reported	BMC containing MSCs, platelets, HSCs, and red and white blood cells	NA	BMC containing MSCs, platelets, HSCs, and macrophages	NA	BMC (cell types NR)	NA	Mononuclear cells	NA	Nucleated SVF cells		NA
Stem cell count, mean ± SD (range)**	Median total HSCs and MSC: 4,620,000 (174,000 to 130,200,000) and 34,400 (435 to 1,449,000)	NA	Total nucleated cell count: 622 ± 235 million	NA	NR	NA	Total mono-nuclear cells: 38.64 ± 33.7 x 106 (8.3 x 106 to 158.8 x 106)	NA	15 x 106 (12.5 x 106 to 17.2 x 106)	30 x 106 (27.5 x 106 to 32.5 x 106)	NA
Local anesthetic used	NR		NR	NA	None	Vapocoolant spray	None	None	Lidocaine	Lidocaine	Lidocaine
Other injectate (w/ stem cells)	PPP (10 mL)	None	PRP (12.5% by volume) and PL (12.5% by volume)	NA	PRP (4-5 ml)	None	0.9% NaCl	None	None	None	NA
Total volume of injectate	15 ml (5 ml stem cells + 10 ml PPP)	15 ml saline	5 to 7 ml	NA	~9-10 ml (5-6 mL of BMC + 4-5 ml PRP)	3 ml	NR	NR	4 ml	4 ml	4 ml Lactated Ringer's
Imaging guidance	Ultrasound	Ultrasound	Fluoroscopy w/ contrast	NA	Ultrasound	Ultrasound	None	None	Ultrasound	Ultrasound	Ultrasound
No. of injections	1	1	1	NA	1	1	1	3 (1 wk. apart)	1	1	1

	Shapiro 2017/2018 (N=50 knees in 25 patients)		Centeno 2018 (N=48)		Ruane 2019 (N=32)		Goncars 2017 (N=56)		Tucker 2019 (N=39)		
	BMC (n=25 knees)	Placebo (n=25 knees)	BMC (n=26)	Exercise (n=22)	BMC (n=17)	Gel-One® Hyaluronate (n=15)	BM-MNC (n=28)	HA (n=28)	Low-dose SVF (n=13)	High-dose SVF (n=13)	Placebo (n=13)
Pre-treatment injection	None	None	Hyperosmolar dextrose (2-4 days prior)††	NA	None	None	None	None	None	None	None
Post-treatment injection	None	None	PRP, PL, hydrocortisone and doxycycline via US-guidance 2-4 days after	NA	None	None	None	None	None	None	None
Cross-over (timing)	NA		All 22 patients in the exercise group crossed over to the SCT group at 3 months		NA		NA		NA		
Post-treatment care	None; pain medication use discouraged		Weight-bearing w/ brace for 4 wks; activity modification; ROM and therapeutic exercises/PT‡‡ for 2 mos. then gradual return to full activity	NA	NR		Activity modification; short-term analgesic; maintained previous SYSODOA drug use		Crutches/non-weight bearing 2 wks; encouraged to bend and flex knee		
Country	USA		USA		USA		Latvia		USA		
Funding	Private		Industry		Not-for-profit healthcare system		NR		NR		
Risk of bias	Moderately High		Moderately High		Moderately High		Moderately High		Moderately High		

ASA=aspirin; BMC=bone marrow concentrate; BMI=body mass index; BM-MNC=bone marrow mononuclear cells; HA=hyaluronic acid; HSCs=hematopoietic stem cells; K-L=Kellgren-Lawrence; ml=milliliters; MSCs=mesenchymal stem/stromal cells; NA=not applicable; No.=number; NR=not reported; NSAIDs=non-steroidal anti-inflammatory drugs; OA=osteoarthritis; PL=platelets lysate; PPP=platelets poor plasma; PRP=platelets rich plasma; PT=physical therapy; RCT=randomized control trial; SCT=stem cell therapy; SD=standard deviation; SVF=stromal vascular fraction; SYSODOA=symptomatic slow acting drugs for osteoarthritis; US=ultrasound; USA=United States of America; w/=with; wks.=weeks

*Patients were treated bilaterally and randomized by knee.

†At the 3- and 6-month time points, 24% and

36% of patients, respectively, were using over the counter pain medications

‡To be included in the study, patients must have failed a minimum of at least two conservative therapies, including oral pain medications, physical therapy, corticosteroid injection of the knee, or viscosupplementation injection of the knee.
§One patient had undergone prior bilateral knee surgery.
**Stem cell count based on flow cytometry, immunological markers etc.
††2-5 cc of 12.5% dextrose and 0.125% ropivacaine in normal saline); Prolotherapy
‡‡Therapeutic exercises = deep water emersion walking or jogging; stationary bike; elliptical; core training; strengthening

Autologous, culture-expanded stem cells

Five small trials (across 6 publications) that evaluated autologous, culture-expanded stem cells for knee osteoarthritis which met inclusion criteria were identified (Table 9).[30,32,59,60,64,65] Three trials used adipose (AD)-derived MSCs[32,64] or MPCs (Rejoin®)[65] and two used bone-marrow (BM)-derived MSCs.[30,59,60] Two of these trials randomized patients to two different treatment groups; in one, patients received either a low dose or a high dose of BM-MSC[59,60] and in the second, patients received either a single injection of AD-MSCs or two injections total (a second injection at 6 months).[32] Stem cell therapy was compared with placebo in two trials,[30,64] hyaluronic acid (HA) in two trials[59,60,65] and conservative care (i.e., simple analgesics, weight management, and exercise) in one trial.[32] In one trial, patients in the treatment groups also received an HA injection at the same time as their stem cell injection.[60] Across all trials, the types and total number of cells injected varied widely (Table 9). Three studies reported performing flow cytometry analysis and one reported testing cultures for cell number, viability, and purity, but did not report how this was done; the fifth trial[65] did not report methods regarding cell analysis. A single injection was given to all patients in three trials[30,59,60,64] and in a fourth trial, patients received two stem cell injections at week 0 and 3 week (plus 2 placebo injections at weeks 1 and 2) versus four HA injections over four consecutive weeks.[65] In the fifth trial, patients randomized to the second intervention group received a second stem cell injection at 6 months.[32] In three trials, injections (intervention or control) were done under ultrasound (2 trials) or radiographic guidance (1 trials); the remaining two trials either did not use image guidance or did not report whether or not it was done.[32,65]. Only one trial mentioned using local anesthetic (2 ml of 1% lidocaine) during the stem cell injection.[60] Four of the trials did not mention a specific post-treatment protocol. One simply advised patients to rest for 24 hours.[65] In the fifth trial, patients were provided with post-injection analgesia as needed and were advised to remain non-weight bearing with the use of crutches for 4 weeks; education regarding range of motion and quadriceps activation exercises was also provided.[32]

Across the five trials (N range, 24 to 52), mean patient ages ranged from 52 to 66 years and the proportion of males varied from 12% to 63% across the trials (Table 9). The majority of patients had Kellgren-Lawrence (KL) grade II or III OA (across 4 trials); one trial included a higher proportion of patients with grade IV OA (stem cells, 55% vs. HA, 40%) compared with the other trials (range across all patients, 0% to 16%).[59,60] Only one trial reported on concomitant medication usage; acetaminophen at a dose of 4,000 mg or less was permitted, all other pain medication was not.[64] Across most trials, the inclusion criteria placed limits on how recently patients could have had surgery or previous injections prior to enrollment. One trial each was conducted in Spain, Iran, China, South Korea, and Australia. Three trials[32,64,65] were industry funded, one government funded[59,60], and one funded by a non-profit organization[30]. Two trials[64,65] were considered to be at moderately low risk of bias and three trials were considered to be at moderately high risk of bias. [30,32,59,60] The latter trials did not control for possible confounding factors; in addition, criteria for intention-to-treat, blinded assessment, and differential loss-to-follow-up were either not met or not adequately reported. For details related to risk of bias determination for these trials, see Appendix E.

Table 9. Patient and procedure characteristics of RCTs evaluating autologous culture-expanded stem cells for knee OA

	Lamo-Espinosa 2018 (N=30)			Emadedin 2018 (N=47)		Lu 2019 (N=52)		Lee 2019 (N=24)		Freitag 2019 (N=30)		
	Low dose BM-MSCs (n=10)	High dose BM-MSCs (n=10)	HA (n=10)	BM-MSCs (n=19)	Placebo (n=24)	*Rejoin*® (n=26)	HA (n=26)	Adipose-derived MSCs (n=12)	Placebo (n=12)	MSCs (x1) (n=10)	MSCs (x2) (n=10)	Usual care (n=10)
Patient demographics												
Males, %	40%	80%	70%	63.2%	62.5%	12%	12%	25%	25%	70%	40%	50%
Mean age, years	65.9	57.8	60.3	51.7	54.7	55	60	62.2	63.2	54.6	54.7	51.6
Mean BMI, kg/m2	Median, 27.1	Median, 28.5	Median, 29.6	30.2	31.5	24.3	24.3	25.3	25.4	31.6	30.4	25.2
K-L OA grade	II: 10% III: 20% IV: 70%	II: 30% III: 30% IV: 40%	II: 40% III: 20% IV: 40%	II: 10.5% III: 68.4% IV: 21.1%	II: 4.2% III: 83.3% IV: 12.5%	I: 4% II: 35% III: 62%	I: 8% II: 31% III: 62%	II: 50% III: 50% IV: 0%	II: 41.7% III: 50% IV: 8.3%	NR	NR	NR
Caucasian, %	NR											
Mean Sx duration, months	NR											
Co-morbidities	NR											
Concomitant meds	NR	NR	NR	NR	NR	NR	NR	Acetaminophen ≤ 4,000 mg†		NR	NR	NR
Previous injections	None w/in prior 6 months			NR		None w/in prior 2 months		None w/in prior 2 months		None w/in the prior 6 months		
Previous surgery	None w/in prior 6 months			NR		NR		NR		None w/in prior 6 months‡		
Procedural characteristics												
Patient blinded to treatment	Yes			Yes		Yes		Yes		No		
Stem cell source (volume aspirated)	Bone marrow (100 ml), iliac crest		NA	Bone marrow (50 ml), iliac crest	NA	Abdominal adipose tissue (NR)	NA	Abdominal adipose tissue (20 ml)	NA	Abdominal adipose tissue (60 ml)		NA
Cell type(s) reported	MSCs		NA	MSCs	NA	haMPCs	NA	MSCs	NA	MSCs		NA

	Lamo-Espinosa 2018 (N=30)			Emadedin 2018 (N=47)		Lu 2019 (N=52)		Lee 2019 (N=24)		Freitag 2019 (N=30)		
	Low dose BM-MSCs (n=10)	High dose BM-MSCs (n=10)	HA (n=10)	BM-MSCs (n=19)	Placebo (n=24)	*Rejoin*® (n=26)	HA (n=26)	Adipose-derived MSCs (n=12)	Placebo (n=12)	MSCs (x1) (n=10)	MSCs (x2) (n=10)	Usual care (n=10)
Total concentration of stem cells, mean ± SD (range)*	$10x10^6$	$100x10^6$	NA	$40x10^6$	NA	$5x10^7$	NA	$1x10^{10}$	NA	103.9 million ± 7.7	Injection 1: 95.1 million ± 11.1 Injection 2: 102.6 million ± 8.3	NA
Local anesthetic used	NR			NR		NR		NR		1% lidocaine (2 ml)		NA
Other injectate (w/ stem cells)	1 HA injection	1 HA injection	None	saline + 2% human serum albumin		None		Saline (NaCl 9 mg/ml)		Sterile isotonic (0.9%) normal saline		NA
Total volume of injectate	5.5 ml (1.5 ml BM-MSCs;4 ml HA	7 ml (3 ml BM-MSCs;4 ml HA	4 ml HA	5 ml		2.5 ml		3 ml		3 ml		NA
Imaging guidance	None			Radiographic		NR		Ultrasound		Ultrasound		
No. of injections	1	1	1	1	1	2 [2 haMPC injections at 0 and 3 wks; 2 sham injections at 1 and 2 wks]	4 [1/wk for 4 consecutive wks]	1	1	1	2 (second injection 6 mos.)	0
Pre- or post-treatment injection	None											
Cross-over (timing)	None											

	Lamo-Espinosa 2018 (N=30)			Emadedin 2018 (N=47)		Lu 2019 (N=52)		Lee 2019 (N=24)		Freitag 2019 (N=30)		
	Low dose BM-MSCs (n=10)	High dose BM-MSCs (n=10)	HA (n=10)	BM-MSCs (n=19)	Placebo (n=24)	*Rejoin*® (n=26)	HA (n=26)	Adipose-derived MSCs (n=12)	Placebo (n=12)	MSCs (x1) (n=10)	MSCs (x2) (n=10)	Usual care (n=10)
Post-treatment care	NR			NR		Rest for 24 hours following each injection		No specific physical limitation was recommended		Analgesia PRN; crutches/non-weight bearing 4 wks§; ROM and exercise education		NA
Country	Spain			Iran		China		South Korea		Australia		
Funding	Government			Non-profit organization		Industry + government		Industry		Industry		
Risk of bias	Moderately High			Moderately High		Moderately Low		Moderately Low		Moderately High		

BM=bone marrow; BMC=bone marrow concentrate; BMI=body mass index; BM-MNC=bone marrow mononuclear cells; HA=hyaluronic acid; K-L=Kellgren-Lawrence; mg=milligrams; ml=milliliters; MSCs=mesenchymal stem/stromal cells; NA=not applicable; No.=number; NR=not reported; OA=osteoarthritis; PRN=as needed; RCT=randomized control trial; ROM=range of motion; SD=standard deviation; wks=weeks

* Stem cell count based on flow cytometry, immunological markers etc.

†Medication other than acetaminophen was not permitted, and any medication that patients took were recorded. If taking an osteoarthritis medication, the drug was discontinued for 2 weeks as a wash-out period.

‡No previous meniscectomy/significant partial meniscectomy or other knee related surgery

§Participants in the 2 injection group were not required to be on-weight bearing after the second injection at 6 months.

Allogenic, culture-expanded stem cells

Two small trials (N=20 and 30) of allogenic culture-expanded stem cells for the treatment of knee OA that met inclusion criteria were identified (

Table 10). Mean patient age was the same in both trials (57 years) and females comprised the majority of the populations (90% and 63%). In both of the trials, the majority of patients had Kellgren Lawrence grade II/III OA (90% and 80%); the remaining patients had grade IV OA. Neither of the trials reported race/ethnicity, symptom duration, or comorbidities.

One trial[55] compared intra-articular injections of placenta-derived (PL-) MSCs versus a placebo (saline), and the other trial[126] compared intra-articular injections of BM-MSCs from three healthy donors versus HA (

Table 10). In both trials, patients were excluded if they had received any injections 3 months prior to study enrollment. One study excluded patients who had previously undergone knee surgery, while the other did not. In one trial[126], patients were injected with a mean of 40,000,000 stem cells, and in the other trial[55], the mean number of stem cells injected ranged from 50,000,000 to 60,000,000. Both studies performed flow cytometric analysis. Neither trial reported if the injections were done under image guidance (i.e. ultrasound or fluoroscopy). Only one trial reported on post-treatment care; patients were allowed immediate return to their activities of daily living, however, heavy lifting and prolonged walking were restricted for 1-week. One trial was conducted in Iran under private funding; the other in Spain with government funding. One trial[55] was considered to be at moderately low risk of bias; it was unclear is allocation concealment was properly performed and the authors failed to control for possible confounding factors. The other trial[126] was considered to be at high risk of bias since it was unclear whether the following criteria were met: blinded assessment, adequate follow-up rates, and controlling for confounding.

In addition, one nonrandomized comparative cohort[12] (N=52) compared a single injection of allogenic progenitor cells isolated from amniotic fluid with a single intraarticular long-acting steroid injection of triamcinolone acetonide. Prior to both injections, patients' knees were aspirated. It is unclear from the study if the cells were culture expanded; the mean number of injected of cells was not reported and the study did not indicate if flow cytometric analysis was performed. In the stem cell and steroid groups, respectively, mean age was 49 and 51 years and males made up 46% and 54% of the patient population. Sixty-nine percent (36/52) of all patients were treated bilaterally; if patients had bilateral treatment, they received the same treatment in each knee. This was a government-funded study conducted in India and is considered to be at high risk of bias given that is unclear if the following criteria were met: blinded assessment and controlling for confounding.

Table 10. Patient and procedure characteristics of RCTs evaluating allogenic culture-expanded stem cells for knee OA

	Khalifeh Soltani 2019 (N=20)		Vega 2015 (N=30)	
	Placenta-derived MSCs (n=10)	Placebo (n=10)	BM- MSCs (n=15)	HA injection (Durolane®) (n=15)
Patient demographics				
Males, %	10%	10%	40%	33%
Mean age, years	57.5	55.8	57	57
Mean BMI, kg/m2	29.6	28.9	NR	NR
K-L OA grade	II/III: 90% IV: 10%*		II: 40% III: 40% IV: 20%	II: 47% III: 33% IV: 20%
Caucasian, %	NR			
Mean Sx duration	NR			
Comorbidities	NR			
Concomitant meds	NR			
Previous injections	None w/in last 3 months		Corticosteroids: 7%; HA: 27% ;PRP: 20% (none w/in previous 3 months)	Corticosteroids: 20%; HA: 33%; PRP: 13% (none w/in previous 3 months)
Previous surgery	No (history of knee surgery was an exclusion criteria)		Medial (53%) or lateral (13%) meniscus or ACL (7%) surgery	Medial (33%) or lateral (13%) meniscus or quadriceps re-tensioning (7%) surgery
Procedural characteristics				
Patient blinded to treatment received	Yes		Yes	
Stem cell source (volume)	Donor placenta (3-4 grams)	NA	Bone marrow (iliac crest); 3 healthy donors	NA
Cell type(s) reported	MSCs	NA	MSCs	NA
Stem cell expansion?	Yes	NA	Yes	NA
Stem cell count, mean ± SD (range)†	$0.5\text{-}0.6x10^8$	NA	$40x10^6$ cells/knee from a $5x10^6$ cell/mL suspension	NA
Local anesthetic used	NR	NR	No (for donors only)	NR
Total volume of injectate	10 mL	10 mL	NR	60 mg in 3 mL
Other injectate (w/ stem cells)	None			
Imaging guidance	NR			
No. of injections	1 injection			
Pre- or post-treatment injection	None			
Cross-over (timing)	None			
Post-treatment care	Immediate return to ADLs; heavy lifting and prolonged walking restricted for 1-wk.		NR	
Country	Iran		Spain	
Funding	Private		Government	
Risk of bias	Moderately Low		Moderately High	

MSCs = mesenchymal stem/stromal cells; BM = bone marrow; HA = hyaluronic acid; NR = not reported; BMI = Body Mass Index; K-L – Kellgren Lawrence; OA = osteoarthritis; PRP = platelet rich plasma; ACL = anterior cruciate ligament; SD = standard deviation; mg = milligrams; ml = milters

* There was no statistically significant difference between the groups

† Stem cell count based on flow cytometry, immunological markers etc.

Results

4.2.1.1 Autologous, non-culture-expanded stem cells

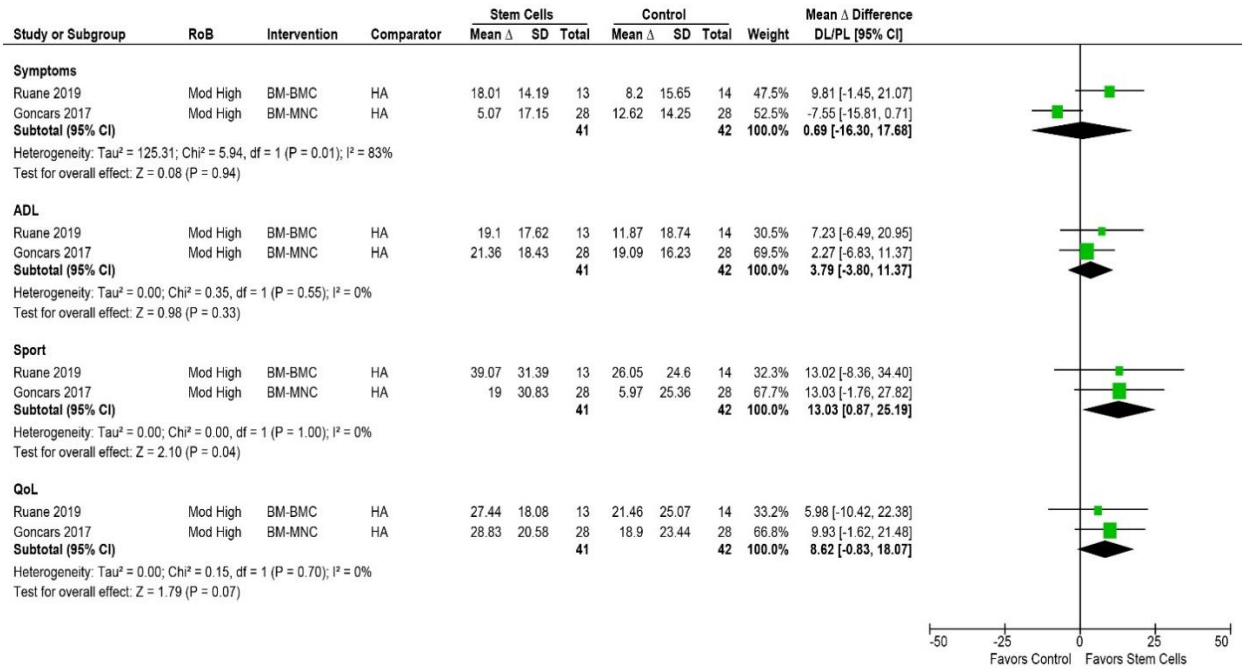
Randomized controlled trials

Primary Outcomes

Function

A variety of functional measures were reported at various time points up to 12 months across four of the trials comparing non-cultured, bone marrow- (primarily) or adipose-derived stem cells versus control treatments (HA, placebo or exercise plus usual care), Figure 3 and Table 11.[20,36,99,119] Only the 12 month data for the KOOS ADL, Sport and Symptom scales were amenable to pooling. Patients who received stem cell therapy (BM-MNC or BMAC) versus HA injection showed greater improvement in function according to the KOOS Sport scale (2 trials [N=83]; pooled MD in change scores 13.0 on a 0-100 scale, 95% CI 0.9 to 25.2; I^2=0%), although the confidence interval was wide and approached zero; no differences between the groups were seen at 12 months for any of the other KOOS scales (Figure 3).[36,99] With the exception of the Knee Society Clinical Rating System (KSS) Knee score (mean change, 12 vs. 0.6, p<0.001) and the Lower Extremity Activity Scale (LEAS) (mean change, 0.8 vs. –1.1, p=0.002) at 3 months in one trial[20] and the WOMAC (median % change, 52% [low dose SVF] and 84% [high dose SVF] vs. 25% [placebo]; p=0.02 and 0.04, respectively) at 6 months in another trial,[119] no differences were seen between groups for any other measure at any other time point (Table 11).

Figure 3. Autologous, non-culture-expanded stem cells for knee OA: mean change from baseline to 12 months on the KOOS subscales from RCTs



Δ = change (i.e., mean change scores)
ADL = activity of daily living; BM-BMC: bone marrow concentrate; BM-MNC: bone marrow-derived mononuclear cells; CI = confidence interval; HA = hyaluronic acid; KOOS = Knee injury and Osteoarthritis Outcome Score; Mod High = moderately high; OA = osteoarthritis; QoL = quality of life; RoB = risk of bias; SD = standard deviation.

Table 11. Autologous, non-culture-expanded stem cells for knee OA: function outcomes from RCTs not reported in the meta-analyses

Outcome Measure	Author *Stem cell type vs. control*	Time point	Stem Cells mean change ± SD or median % change (IQR)	Control mean change ± SD or median % change (IQR)	MD in change scores (95% CI)
KOOS Symptoms	**Ruane 2019** *BMC vs. HA*	Baseline	66.5 ± 16.0 (n=17)	68.8 ± 15.7 (n=15)	------
		3 months	14.0 ± 19.0 (n=15)	10.5 ± 13.8 (n=15)	3.5 (–8.4 to 15.4)
		6 months	14.3 ± 18.2 (n=14)	12.4 ± 13.3 (n=14)	1.9 (–10.0 to 13.7)
KOOS ADL		Baseline	68.6 ± 18.0 (n=17)	70.1 ± 18.3 (n=15)	------
		3 months	15.4 ± 20.2 (n=15)	12.5 ± 12.8 (n=15)	2.9 (–9.3 to 15.0)
		6 months	18.1 ± 17.4 (n=14)	14.9 ± 17.1 (n=14)	3.2 (–9.6 to 16.0)
KOOS Sport		Baseline	31.5 ± 23.6 (n=17)	39.7 ± 21.6 (n=15)	------
		3 months	29.5 ± 32.5 (n=15)	30.1 ± 22.5 (n=15)	–0.6 (–20.6 to 19.4)
		6 months	34.9 ± 28.6 (n=14)	31.6 ± 29.0 (n=14)	3.3 (–18.1 to 24.6)
KOOS Total	**Goncars 2017** *BM-MNC vs. HA*	Baseline	NR	NR	------
		12 months	18.3 ± NR (n=28)	12.6 ± NR (n=28)	NR; p=NS
KSS Function	**Centeno 2018** *BMC vs. Exercise*	Baseline	NR	NR	------
		3 months	7.5 ± NR (n=24)	2.3 ± NR (n=22)	NR; p=0.17
	Goncars 2017 *BM-MNC vs. HA*	Baseline	NR	NR	------
		12 months	38.3 ± NR (n=28)	17.5 ± NR (n=28)	NR; p=NS
KSS Knee Score	**Centeno 2018** *BMC vs. Exercise*	Baseline	NR	NR	------
		3 months	12 ± NR (n=23)	0.6 ± NR (n=22)	NR; p<0.001
	Goncars 2017 *BM-MNC vs. HA*	Baseline	NR	NR	------
		12 months	25.4 ± NR (n=28)	10.7 ± NR (n=28)	NR; p=NS
LEAS	**Centeno 2018** *BMC vs. Exercise*	Baseline	NR	NR	------
		3 months	0.8 ± NR (n=24)	-1.1 ± NR (n=21)	NR; p=0.002
WOMAC, % change	**Tucker 2019** *Low dose SVF vs. High dose SVF vs. Placebo*	Baseline	NR	NR	------
		6 months	Low: 52% (29% to 88%) (n=13) High: 84% (19% to 91%) (n=13)	25% (–25% to 58%) (n=13)	Low vs. placebo; p=0.023 High dose vs. placebo: p=0.043

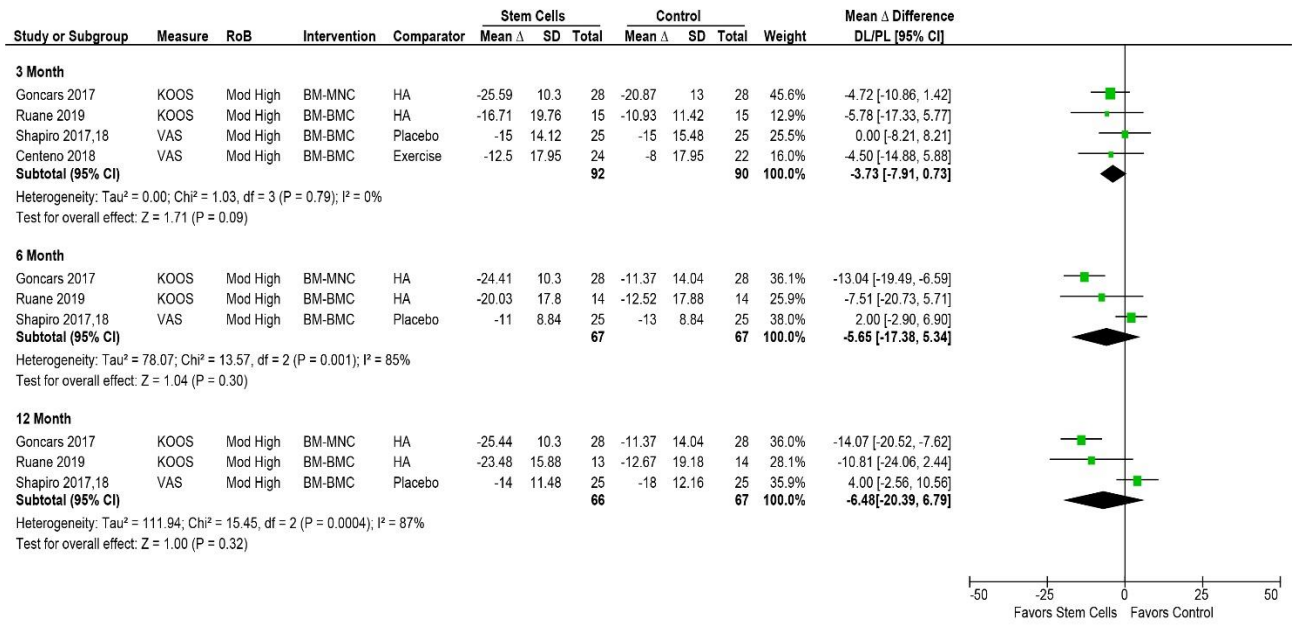
ADL=activities of daily living; BMC=bone marrow concentrate; BM-MNC=bone marrow mononuclear cells; CI=confidence interval; HA=hyaluronic acid; IQR=interquartile range; KOOS=Knee injury and Osteoarthritis Outcome Score; LEAS=Lower Extremity Activity Scale; MD=mean difference; NR=not reported; SD=standard deviation; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

Pain

Four trials reported pain according to either the VAS pain[20,105,106] or the KOOS pain[36,99] scale; pooled analyses at 3 months (4 trials, N=182)[20,36,99,105,106] and at 6 months and 12 months (3 trials each, N=133)[36,99,105,106] showed no differences in pain improvement between the stem cell and the control groups (Figure 4). Individually, greater pain improvement following stem cell therapy (BMC or BM-derived mononuclear cells) versus HA injection was reported by two trials: at 6 and 12 months as measured by the KOOS pain scale (0-100) in one trial (mean difference in change scores: –13.0 [95% CI –19.5 to –6.6] and [–14.1, 95% CI –20.5 to –7.6], respectively) (Figure 4)[36] and at 12 months as measured

by the NRS pain scale in the second (MD in change scores –15.7 on a 0-100 scale, 95% CI –29.0 to –2.4),[99] Table 12. No other differences between groups in pain improvement were noted (Table 12).

Figure 4. Autologous, non-culture-expanded stem cells for knee OA: mean change in pain scores from baseline to follow-up from RCTs*



Δ = change (i.e., mean change scores)
BM-BMC: bone marrow concentrate; BM-MNC: bone marrow-derived mononuclear cells; CI = confidence interval; HA = hyaluronic acid; KOOS = Knee injury and Osteoarthritis Outcome Score; Mod High = moderately high; OA = osteoarthritis; RoB = risk of bias; SD = standard deviation; VAS = visual analog scale.
*The trial by Shapiro et al. enrolled patients with bilateral knee OA; results are given out of 50 knees (in 25 patients).

Table 12. Autologous, non-culture-expanded stem cells for knee OA: pain outcomes from RCTs not reported in the meta-analyses

Outcome Measure	Author *Stem cell type vs. control*	Time point	Stem Cells mean change ± SD or median change (range)	Control mean change ± SD or median change (range)	MD in change scores (95% CI)
NRS pain	**Ruane 2019** *BMC vs. HA*	Baseline	45.9 ± 18.4 (n=17)	42.0 ± 17.0 (n=15)	-----
		3 months	–19.2 ± 26.7 (n=15)	–18.7 ± 17.7 (n=15)	–0.5 (–16.7 to 15.7)
		6 months	–24.5 ± 14.0 (n=14)	–17.7 ± 15.4 (n=14)	–6.8 (–17.4 to 3.8)
		12 months	–31.3 ± 16.5 (n=13)	– 15.6 ± 20.4 (n=14)	–15.7 (–29.0 to –2.4)
ICOAP total pain*	**Shapiro 2017/2018** *BMC vs. Placebo*	Baseline	32 (18 to 91) (n=25 knees)	32 (0 to 73) (n=25 knees)	-----
		3 months	–21 (–71 to 21) (n=25 knees)	–18 (–59 to 43) (n=25 knees)	NR; p=0.24
		6 months	–14 (–77 to 34) (n=25 knees)	–11 (–64 to 39) (n=25 knees)	NR; p=0.54
		12 months	−18 (−84 to 23) (n=25 knees)	−18 (−73 to 11) (n=25 knees)	NR; p=0.68

BMC=bone marrow concentrate; CI=confidence interval; HA=hyaluronic acid; ICOAP=Intermittent and constant pain score; MD=mean difference; NR=not reported; NRS=numerical rating scale; SD=standard deviation

*Similarly, no differences between groups at any time point when the ICOAP constant pain score and the intermittent pain score were considered separately. (see Appendix F)

Secondary Outcomes

Quality of Life

Two trials reported health-related quality of life (QoL) using the KOOS QoL, the Patient Reported Outcome Measurement Information System (PROMIS), and the SF-12 Physical (PCS) and Mental Component Score (MCS) scales with no differences in mean change from baseline across all measures and time points between patients who received stem cell therapy versus HA or exercise (plus usual care),[20,99] Figure 3 and

Table 13.

Table 13. Autologous non-culture-expanded stem cells for knee OA: quality of life outcomes from RCTs not reported in the meta-analyses

Outcome Measure	Author *Stem cell type vs. control*	Time point	Stem Cells mean change ± SD or 95% CI	Control mean change ± SD or 95% CI	MD in change scores (95% CI)
PROMIS physical health	**Ruane 2019** *BMC vs. HA*	Baseline	44.62 ± 7.61 (n=17)	48.23 ± 7.99 (n=15)	
		3 months	4.62 (0.84 to 8.41) (n=15)	0.59 (–3.76 to 4.94) (n=15)	4.03 (–1.74 to 9.80)
		6 months	6.76 (3.63 to 9.89) (n=14)	3.50 (0.16 to 6.83) (n=14)	3.26 (–1.32 to 7.84)
		12 months	4.77 (1.99 to 7.54) (n=13)	3.26 (–0.36 to 6.88) (n=14)	1.51 (–3.05 to 6.07)
PROMIS mental health		Baseline	51.88 ± 5.02 (n=17)	51.90 ± 9.36 (n=15)	
		3 months	–2.18 (-3.87 to -0.48) (n=15)	–0.65 (–5.13 to 5.83) n=15)	–1.53 (–7.43 to 4.37)
		6 months	–0.01 (–3.25 to 3.23) (n=14)	2.24 (–0.54 to 5.03) (n=14)	–2.25 (–6.53 to 2.03)
		12 months	0.07 (–2.64 to 2.77) (n=13)	3.01 (–0.40 to 6.42) (n=14)	–2.94 (–7.30 to 1.42)
KOOS QoL		Baseline	36.2 ± 18.5 (n=17)	38.5 ± 15.9 (n=15)	------
		3 months	21.0 ± 23.7 (n=15)	21.3 ± 20.1 (n=15)	–0.3 (–16.0 to 15.5)
		6 months	25.0 ± 20.0 (n=14)	24.2 ± 25.2 (n=14)	0.8 (–16.0 to 17.6)
SF-12 PCS	**Centeno 2018** *BMC vs. Exercise*	3 months	4.9 ± NR (n=24)	2.4 ± NR (n=22)	NR; p=0.27
SF-12 MCS		3 months	–2.4 ± NR (n=24)	–1.5 ± NR (n=22)	NR; p=0.68

BMC=bone marrow concentrate; CI=confidence interval; HA=hyaluronic acid; KOOS=Knee injury and Osteoarthritis Outcome Score; MCS=mental component score; MD=mean difference; NR=not reported; PCS=physical component score; PROMIS=Patient-Reported Outcomes Measurement Information System; QOL=quality of life; SD=standard deviation; SF-12=short form 12 item health related quality of life questionnaire

Medication use

Only one trial reported change in medication usage post-injection therapy; however, the authors did not provide data by treatment group (BMC vs. placebo).[106] Prior to enrollment, 100% of patients reported using over-the-counter or prescription pain medications, which decreased to 24% and 36% at the 3- and 6-month follow-up visits, respectively.

Secondary procedures

Four trials reported information related to additional surgeries or other procedures received by patients after study enrollment.[20,99,105,119] The trial by Centeno et al.[20] reported that three patients underwent a total knee arthroplasty (TKA) at 3, 6, and 18 months and that seven patients sought additional treatment outside the study protocol (e.g., HA injections) at 3 (1 patient), 6 (3 patients), 12 (2 patients) and 24 (1 patient) months after which point they were all withdrawn from the trial. It is unclear to which treatment group these patients were initially randomized; however, all exercise therapy patients crossed over to receive a BMC injection at 3 months so the majority of these patients had received a BMC injection at some point. In addition, 17 patients with recurrent knee pain after the BMC injection were given PRP treatments; a total of 19 additional PRP injections (15 patients received 1 injection and 2 patients received 2 injections) were given at 3 (n=4), 6 (n=3), 12 (n=10), 18 (n=1), and 24 (n=1) months.[20] A second trial[119] reported that one patient (8%; 1/13) who had received a high-dose of AD-SVF (vs. no patient in the low-dose [n=13] or placebo groups [n=13]) withdrew from the trial to have a TKA; the timing and specific reasons were not reported. In the third trial,[99] two patients randomized to BMC (12%; 2/17) vs. one randomized to HA (7%; 1/15) pursued additional treatment (not further specified) and were considered lost-to follow-up. The fourth trial reported that no patients required a surgery or additional injections during the follow-up period.[105]

Nonrandomized comparative cohort studies

One comparative cohort study at high risk of bias was identified that compared autologous BM-MSCs versus acetaminophen. At 1 and 6 months, follow-up scores for all reported measures of function and pain were significantly better in patients who underwent stem cell therapy (Table 14).

Table 14. Autologous non-culture-expanded stem cells for knee OA: primary outcomes reported by the comparative cohort study

Author Study design *Stem cell type vs. control*	Outcome*; Timing	Stem Cells mean ± SD	Control mean ± SD	p-value
Garay-Mendoza 2018 Prospective comparative cohort study Autologous BM-MSC (n=26) vs. acetaminophen (n=25)	**WOMAC total (0-100)**			
	Baseline	62.61 ± 18.55	69.93 ± 17.89	0.12
	1 month	88.58 ± 17.12	69.92 ± 14.87	<0.0001
	6 months	91.73 ± 9.45	72.96 ± 15.04	<0.0001
	WOMAC physical function (0-100)			
	Baseline	NR	NR	NR
	1 month	87.62 ± 17.61	73.34 ± 16.22	0.003
	6 months	91.48 ± 9.79	72.29 ± 14.84	<0.001
	WOMAC stiffness (0-100)			
	Baseline	NR	NR	NR
	1 month	88.88 ± 20.31	67.59 ± 23.57	0.001
	6 months	92.30 ± 11.22	70.00 ± 21.65	<0.001
	WOMAC pain (0-100)			
	Baseline	NR	NR	NR
	1 month	88.70 ± 17.24	70.35 ± 17.37	<0.001
	6 months	92.30 ± 9.40	68.80 ± 18.44	<0.001
	VAS pain (0-10)			
	Baseline	5.27 ± 2.20	4.32 ± 2.35	0.10
	1 month	1.62 ± 2.04	4.24 ± 2.72	<0.0001
	6 months	0.92 ± 1.29	4.64 ± 2.43	<0.0001

NR = not reported; VAS = visual analog scale; WOMAC = Western Ontario and McMaster's University Osteoarthritis Index.
*With the exception of VAS pain, higher values indicate better function or pain.

4.2.1.2 Autologous, culture-expanded stem cells

Primary Outcomes

Function

Function "Success"

Three trials reported the proportion of patients who met a predefined cut-off for clinically important improvement in function[30,32,65]; the outcomes and/or the cut-off used varied (

Table 15). Across two of the trials[30,65] no statistical differences were seen between groups with the exception of 50% improvement in WOMAC total score at 12 months in one trial, which was achieved by more patients who received stem cell therapy (adipose-derived MPCs) versus HA injection: 35% vs. 4%;

RR 9.0, 95% CI 1.2 to 66.1; however the confidence interval was extremely wide, likely due to the small sample size.[65] In the third trial, more patients who received stem cell therapy (adipose-derived MSCs) compared with conservative care (simple analgesia, weight management, and exercise) achieved a MCID of 8 points on three of the four measures evaluated: WOMAC total (95% vs. 20%; RR 4.7, 95% CI 1.4 to 16.4), KOOS ADL (84% vs. 30%; RR 2.8, 95% CI 1.1 to 7.4), and KOOS Sport (89% vs. 30%; RR 3.0, 95% CI 1.1 to 7.8) scales; KOOS Symptoms did not differ between groups (

Table 15).

Table 15. Autologous, culture-expanded stem cells for knee OA: Function "Success" from RCTs

Author *Stem cell type vs. control*	Outcome	Time	Intervention	Control	RR (95% CI)*
Lu 2019 *AD-MPC (Rejoin) vs. HA*	WOMAC total, 20% improvement	6 months	58% (15/26)	42% (11/26)	RR 1.4 (0.8, 2.4)
		12 months	54% (14/26)	50% (13/26)	RR 1.1 (0.6, 1.8)
	WOMAC total, 50% improvement	6 months	23% (6/26)	8% (2/26)	RR 3.0 (0.7, 13.5)
		12 months	35% (9/26)	4% (1/26)	**RR 9.0 (1.2, 66.1)**
	WOMAC total, 70% improvement	6 months	12% (3/26)	0% (0/26)	P=0.07
		12 months	19% (5/26)	4% (1/26)	RR 5.0 (0.6, 39.9)
Emadedin 2018 *BM-MSC vs. Placebo*	WOMAC function, MCID 9.3 pts	3 months	57.9% (11/19)	41.7% (10/24)	RR 1.4 (0.8, 2.6)
		6 months	73.7% (14/19)	54.2% (13/24)	RR 1.4 (0.9, 2.1)
	WOMAC function, PASS‡	3 months	26.3% (5/19)	4.2% (1/24)	RR 6.3 (0.8, 49.6)†
		6 months	36.8% (7/19)	12.5% (3/24)	RR 2.9 (0.9, 9.9)
Freitag 2019 *AD-MSC§ vs. Conservative*	WOMAC total, MCID 8 pts	12 months	95% (18/19)	20% (2/10)	**RR 4.7 (1.4, 16.4)**
	KOOS Symptoms, MCID 8 pts	12 months	68% (13/19)	30% (3/10)	RR 2.3 (0.8, 6.2)
	KOOS ADL, MCID 8 pts	12 months	84% (16/19)	30% (3/10)	**RR 2.8 (1.1, 7.4)**
	KOOS Sport, MCID 8 pts	12 months	89% (17/19)	30% (3/10)	**RR 3.0 (1.1, 7.8)**

ADL=activities of daily living; AD-MPC=Adipose-derived mesenchymal progenitor cells; AD-MSCs=adipose-derived mesenchymal; stem/stromal cells; BM-MSCs=bone marrow-derived mesenchymal stem/stromal cells; CI=confidence interval; HA=hyaluronic acid; KOOS=Knee injury and Osteoarthritis Outcome Score; MCID=minimal clinically important difference; PASS=patient acceptable symptom state; RR=risk ratio; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

*Calculated by AAI

†Authors' p-value 0.02; Fishers exact 1 sided: 0.05

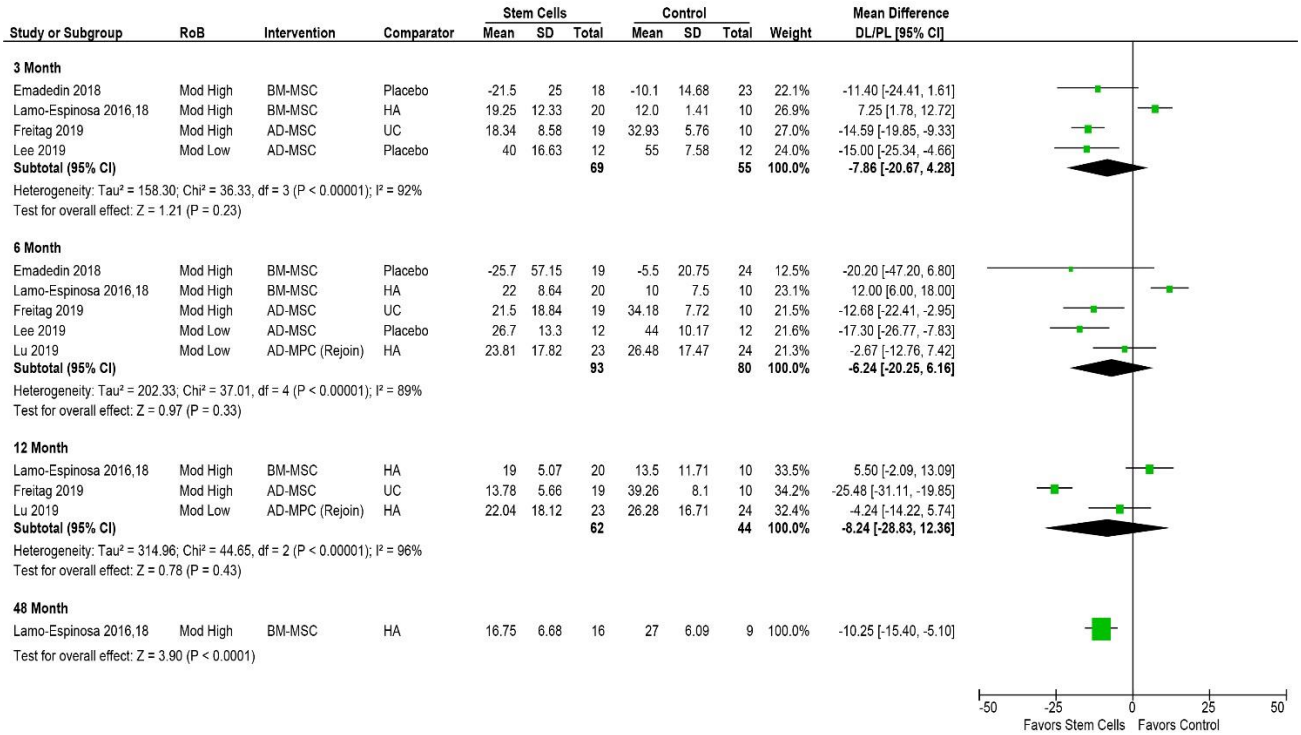
‡PASS cut-off not reported by authors.

§2 groups, 1 injection vs. 2 injections; no difference between treatment groups for any measures

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Total

All five trials evaluated function using the WOMAC total score (scale 0-96) at follow-up[30,32,59,60,64,65]; no statistical differences between groups were seen at 3, 6, or 12 months for the pooled analyses (Figure 5); in all cases, the confidence intervals were wide and statistical heterogeneity was substantial. The exclusion of one outlier trial[59,60] reduced statistical heterogeneity and resulted in somewhat larger effect sizes (though wide confidence intervals) which favored stem cells at 3 months (3 trials [N=94], pooled MD −14.4, 95% CI −19.7 to −9.2, I^2=0%)[30,32,64] and 6 months (4 trials [N=143], pooled MD −11.3, 95% CI −20.0 to −4.8, I^2=38%)[30,32,64,65]; at 12 months, there remained no difference between groups across 2 trials (N=76) (pooled MD −15.3, 95% CI −36.1 to 5.5, I^2=92%)[32,65] but there was substantial statistical heterogeneity (Appendix I). When considering only the two trials at lower risk of bias, a significant difference favoring AD-MSCs versus placebo (i.e., saline) was seen at 3 months (MD −15.0, 95% CI −25.3 to −4.6) which persisted to 6 months (MD −17.3, 95% CI −26.8 to −7.8) in one trial[64] while the other trial reported no difference between AD-MSC and HA injections at 6 months (MD −2.7, 95% CI −12.8 to 7.4) or 12 months (MD −4.2, 95% CI −14.2 to 5.7),[65] Figure 5. When the 6 month data for these two trials were pooled, no differences between groups were seen (N=71; pooled MD −10.1, 95% CI −24.4 to 4.2, I^2=77%).[64,65] Additionally, longer-term outcomes were reported by one small trial (N=25) considered to be moderately high risk of bias; at 48 months, a statistically significant difference favoring BM-MSC vs. HA was reported: −10.3 (95% CI −15.4 to −5.1) (Figure 5).[59,60]

Figure 5. Autologous, culture-expanded stem cells for knee OA: WOMAC total follow-up scores from RCTs

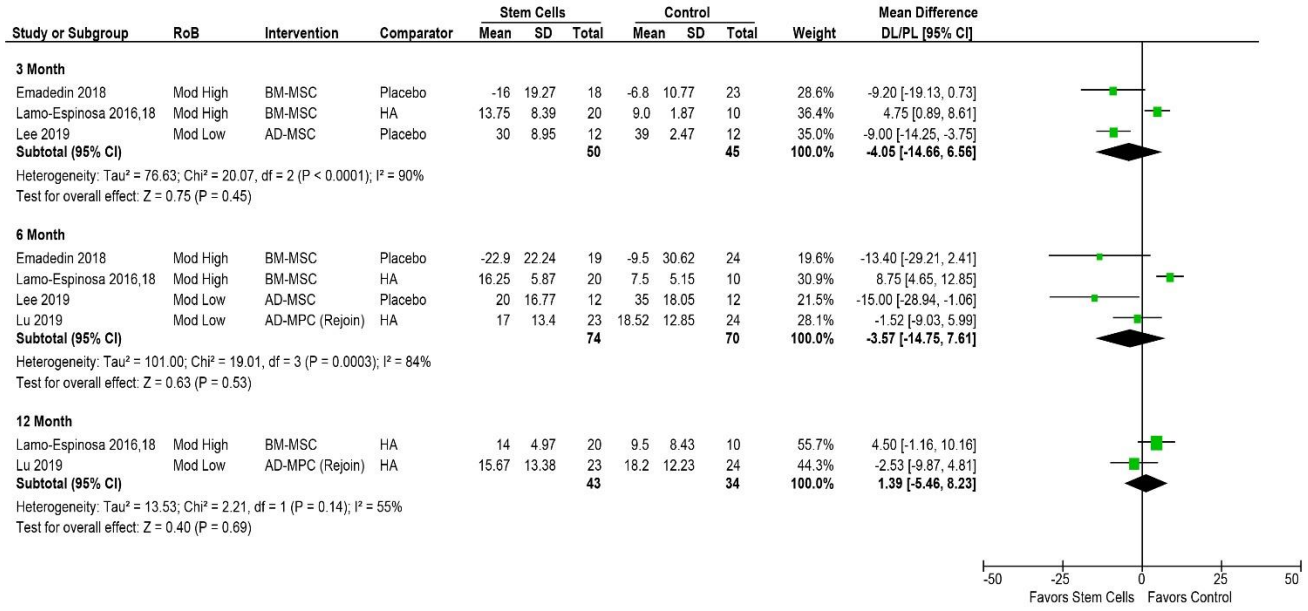


AD-MSC: adipose-derived mesenchymal stem cells; AD-MPC: adipose-derived mesenchymal progenitor cells; BM-MSC: bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; Mod = moderately; OA = osteoarthritis; RoB = risk of bias; SD = standard deviation; UC = usual care (i.e., conservative care); WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

WOMAC physical function and stiffness subscales

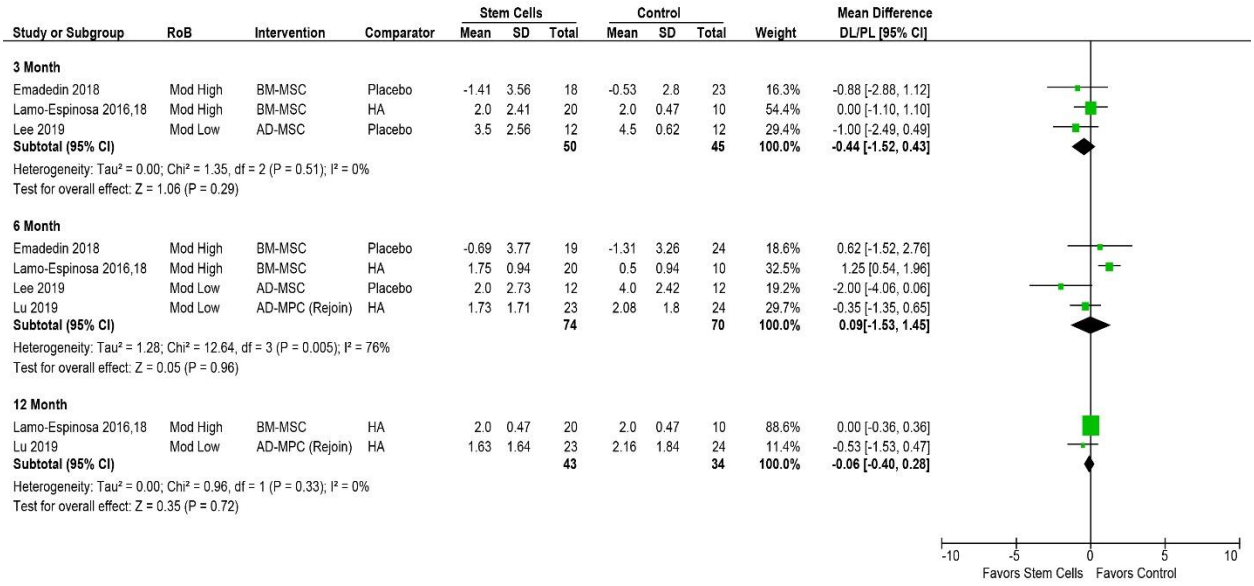
The WOMAC physical function (scale 0-68) and stiffness (scale 0-8) subscales were reported by four trials[30,59,60,64,65] and again there were no statistical differences between groups in follow-up scores at any time point (3, 6, or 12 months) for the pooled analyses (Figure 6 and Figure 7). With the exception of WOMAC function at 3 months, which showed improvement favoring stem cells versus placebo (2 trials [N=65], pooled MD −9.0, 95% CI −13.7 to −4.4, I^2=0),[30,64] the exclusion of one outlier trial[60] did not change the conclusions (Appendix I). Similarly, no differences between groups were seen when just the two trials (N=71) at lower risk of bias comparing AD-MSC versus placebo or HA were considered: WOMAC physical function (pooled MD −6.9, 95% CI −19.9 to 6.0, I^2=64%) and WOMAC stiffness (pooled MD −0.92, 95% CI −2.5 to 0.6, I^2=50%) at 6 months[64,65]; individually, only one trial found a statistically significant difference between groups which favored stem cells compared with placebo on the WOMAC function subscale at 6 months (−15.0 on a 0-68 scale, 95% CI −28.9 to −1.1).[64]

Figure 6. Autologous, culture-expanded stem cells for knee OA: WOMAC physical function follow-up scores from RCTs



AD-MSC: adipose-derived mesenchymal stem cells; AD-MPC: adipose-derived mesenchymal progenitor cells; BM-MSC: bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; Mod = moderately; OA = osteoarthritis; RoB = risk of bias; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 7. Autologous, culture-expanded stem cells for knee OA: WOMAC stiffness follow-up scores from RCTs



AD-MSC: adipose-derived mesenchymal stem cells; AD-MPC: adipose-derived mesenchymal progenitor cells; BM-MSC: bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; Mod = moderately; OA = osteoarthritis; RoB = risk of bias; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Knee Injury and Osteoarthritis Outcome Score (KOOS)

Two trials reported function according to the KOOS activities of daily living (ADL), Sport and Symptom scales at 3 and 6 months ().32,64 For the pooled analyses, only the differences at 6 months were statistically significant and favored AD-MSC versus placebo or usual care (analgesics, weight management, exercise) for all KOOS scales. In the trial at lower risk of bias64, only the differences at 6 months for the KOOS ADL and Symptoms scales were statistically significant favoring AD-MSCs but the CI was wide and approached zero. In addition, one of the trials (considered moderately high risk of bias)32 reported 12-month outcomes and found that AD-MSC resulted in improved function compared with usual care on all three KOOS scales (Table 16).

Table 16. Autologous, culture-expanded stem cells for knee OA: meta-analyses of KOOS function and pain subscales across two RCTs

	Author*	Stem cells Mean ± SD	Control Mean ± SD	MD (95% CI)	Pooled MD (95% CI)†
Function: KOOS ADL (0-100; higher score = better function)					
Baseline	Freitag 2019	56.3 ± 18.6 (n=20)	59.4 ± 13.6 (n=10)	-------	-------
	Lee 2019	51 ± NR (n=12)	55 ± NR (n=12)	-------	
3 months	Freitag 2019	81.3 ± 8.7 (n=19)	67.1 ± 6.2 (n=10)	14.2 (8.7 to 19.6)	**9.4 (−0.5 to 19.4); I^2=78%**
	Lee 2019	60 ± 10.6 (n=12)	56 ± 8.2 (n=12)	4.0 (−3.6 to 11.6)	
6 months	Freitag 2019	78.2 ± 19.2 (n=19)	65.5 ± 9.1 (n=10)	12.7 (2.4 to 23.0)	**11.9 (4.5 to 19.2); I^2=0%**
	Lee 2019	70 ± 14.09 (n=12)	59 ± 12 (n=12)	11.0 (0.5 to 21.5)	
12 months	Freitag 2019	86.6 ± 5.7 (n=19)	60.7 ± 8.5 (n=10)	25.9 (20.0 to 31.7)	-------
Function: KOOS Sport (0-100; higher score = better function)					
Baseline	Freitag 2019	28.5 ± 20.2 (n=20)	26.0 ± 20.4 (n=10)	-------	-------
	Lee 2019	18 ± NR (n=12)	27 ± NR (n=12)	-------	
3 months	Freitag 2019	51.6 ± 13.8 (n=19)	27.5 ± 13.9 (n=10)	24.1 (13.5 to 34.7)	**15.7 (−2.0 to 33.4); I^2=75%**
	Lee 2019	32 ± 17.1 (n=12)	26 ± 18.3 (n=12)	6.0 (−8.2 to 20.2)	
6 months	Freitag 2019	58.2 ± 18.1 (n=19)	31 ± 18.9 (n=10)	27.2 (12.9 to 41.4)	**21.5 (8.7 to 34.2); I^2=26%**
	Lee 2019	43 ± 17.1 (n=12)	29 ± 24.8 (n=12)	14 (−3.1 to 31.1)	
12 months	Freitag 2019	68.9 ± 11.2 (n=19)	31.5 ± 20.9 (n=10)	37.4 (23.5 to 51.3)	-------
Function: KOOS Symptoms (0-100; higher score = better symptomology)					
Baseline	Freitag 2019	60.1 ± 20.0 (n=20)	46.1 ± 11.0 (n=10)	-------	-------
	Lee 2019	53 ± NR (n=12)	53 ± NR (n=12)	-------	
3 months	Freitag 2019	74.9 ± 9.3 (n=19)	48.1 ± 8.3 (n=10)	26.8 (20.2 to 33.4)	**19.6 (−0.8 to 36.1); I^2=91%**
	Lee 2019	60.0 ± 11.2 (n=12)	52 ± 10.9 (n=12)	8.0 (−0.9 to 16.9)	
6 months	Freitag 2019	74.5 ± 17.0 (n=19)	45.3 ± 8.2 (n=10)	27.2 (18.0 to 36.3)	**19.9 (5.0 to 34.7); I^2=77%**
	Lee 2019	70 ± 15.6 (n=12)	58 ± 10.8 (n=12)	12.0 (1.2 to 22.8)	
12 months	Freitag 2019	80.4 ± 8.7 (n=19)	47.9 ± 8.6 (n=10)	32.5 (25.8 to 39.1)	-------
Pain: KOOS Pain (0-100; higher score = less pain)					
Baseline	Freitag 2019	52.6 ± 14.4 (n=20)	52.8 ± 10.8 (n=10)	-------	-------
	Lee 2019	49 ± NR (n=12)	51 ± NR (n=12)	-------	
3 months	Freitag 2019	75.4 ± 11.3 (n=19)	54.9 ± 4.7 (n=10)	20.5 (14.7 to 26.3)	**17.4 (10.2 to 24.6); I^2=51%**

	Author*	Stem cells Mean ± SD	Control Mean ± SD	MD (95% CI)	Pooled MD (95% CI)†
	Lee 2019	59 ± 13.7 (n=12)	46 ± 6.2 (n=12)	13.0 (4.5 to 21.5)	
6 months	Freitag 2019	71.2 ± 19.3 (n=19)	55.3 ± 7.2 (n=10)	15.9 (6.1 to 25.6)	**14.4 (7.6 to 21.3); I^2=0%**
	Lee 2019	69 ± 15.9 (n=12)	56 ± 6.2 (n=12)	13.0 (3.4 to 22.6)	
12 months	Freitag 2019	78.9 ± 7.0 (n=19)	48.9 ± 8.0 (n=10)	30.0 (24.1 to 35.9)	-------

ADL = activities of daily living; CI = confidence interval; KOOS = Knee Injury and Osteoarthritis Outcome Score; MD = mean difference; NR = not reported; SD = standard deviation.
*The trial by Freitag et al. included two intervention groups – single injection of AD-MSCs and 2 injections of AD-MSCs; given that outcomes were similar between these two intervention groups they were combined into one intervention group for the purposes of analysis. See the Appendix for details related to the separate treatment groups.
†Meta-analyses/pooled data calculated by AAI.

Pain

Pain "Success"

Two trials reported the proportion of patients who met a predefined cut-off for improvement in pain (Table 17).[30,32] One trial found no differences between groups at 3 and 6 months as measured by the WOMAC pain scale[30] while the second trial found that more stem cell patients, versus those treated conservatively, met the MCID for pain improvement according to the NRS (1 point) and the KOOS pain scale (8 points)[32]: 95% vs. 40% (RR 2.4, 95% CI 1.1 to 5.1) and 84% vs. 10% (RR 8.4, 95% CI 1.3 to 54.6), respectively, but the confidence interval was extremely wide for the latter.

Table 17. Autologous, culture-expanded stem cells for knee OA: Pain "Success" from RCTs

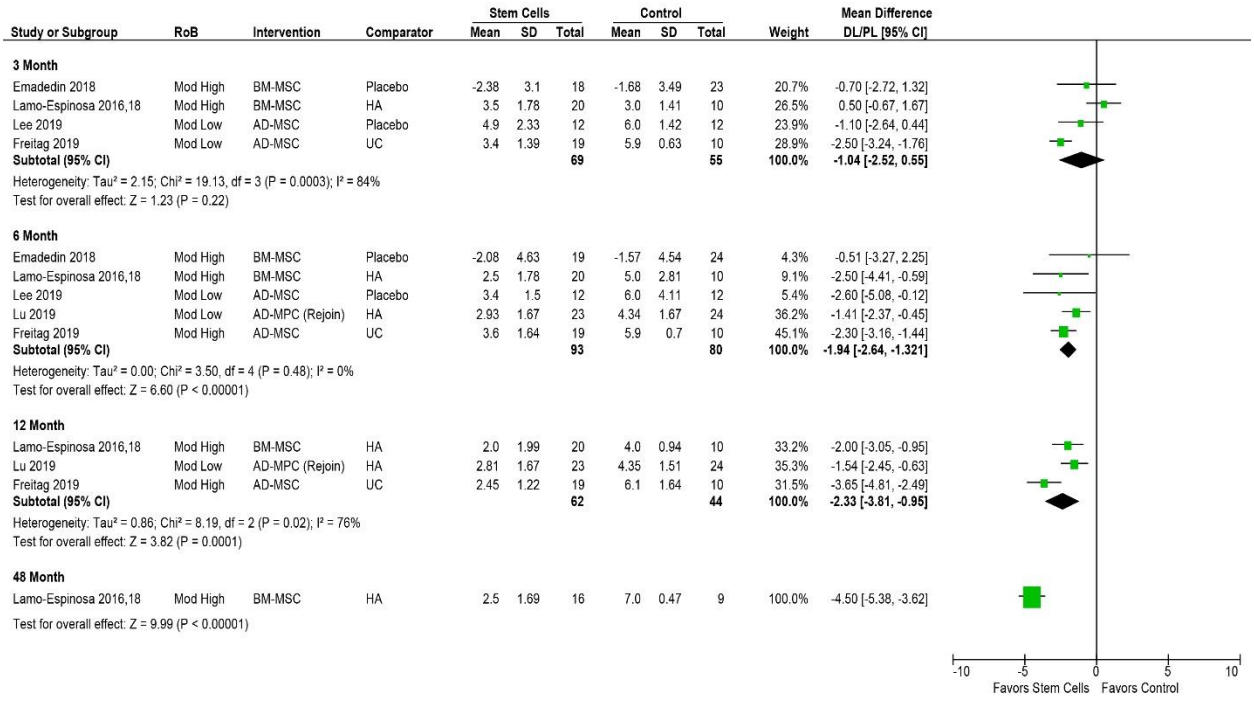
Author; *Stem cell type vs. control*	Outcome	Time	Intervention	Control	RR (95% CI)
Emadedin 2018 *BM-MSC vs. Placebo*	WOMAC pain MCID 9.7 pts	3 months	47% (9/19)	37.5% (9/24)	RR 1.3 (0.6, 2.5)
		6 months	36.8% (7/19)	29.2% (7/24)	RR 1.3 (0.5, 3.0)
	WOMAC pain, PASS*	3 months	21.1% (4/19)	29.2% (7/24)	RR 0.7 (0.2, 2.1)
		6 months	15.8% (3/19)	25% (6/24)	RR 0.6 (0.2, 2.2)
Freitag 2019 *AD-MSC vs. Conservative*	NRS pain MCID 1 pt	12 months	95% (18/19)	40% (4/10)	**RR 2.4 (1.1, 5.1)**
	KOOS pain MCID 8 pts	12 months	84% (16/19)	10% (1/10)	**RR 8.4 (1.3, 54.6)**

AD-MSCs=adipose-derived mesenchymal; stem/stromal cells; BM-MSCs=bone marrow-derived mesenchymal stem/stromal cells; CI=confidence interval; MCID=minimal clinically important difference; NRS = numeric rating scale; PASS=patient acceptable symptom state; RR=risk ratio; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index
*PASS cut-off not reported by authors.
†2 groups, 1 injection vs. 2 injections, no difference between treatments groups for either measure.

Visual Analog Scale (VAS) for Pain

All five trials evaluated pain using VAS scores (scale 0-10) at follow-up. The pooled estimate at 3 months (across 4 trials; N=124)[30,32,59,60,64] showed no statistical difference between groups; however less pain was reported by patients who received stem cells versus control treatments (placebo, HA, usual care) at 6 months (5 trials [N=173], pooled MD −1.9, 95% CI −2.5 to −1.4, I^2=0%)[30,32,59,60,64,65] and 12 months (3 trials [N=106], pooled MD −2.4, 95% CI −3.6 to −1.2, I^2=76%),[32,59,60,65] Figure 8. When the just the two trials at lower risk of bias were considered, there was no difference between groups in pain scores at 3 months according to one trial but less pain with stem cell therapy at 6 months (both trials) and 12 months (1 trial). Only one small trial (N=24), considered to be moderately high risk of bias, reported longer-term outcomes and found a statistically significant difference favoring BM-MSC vs. HA at 48 months: −4.5, 95% CI −5.4 to −3.6.[59,60]

Figure 8. Autologous, culture-expanded stem cells for knee OA: VAS pain follow-up scores from RCTs



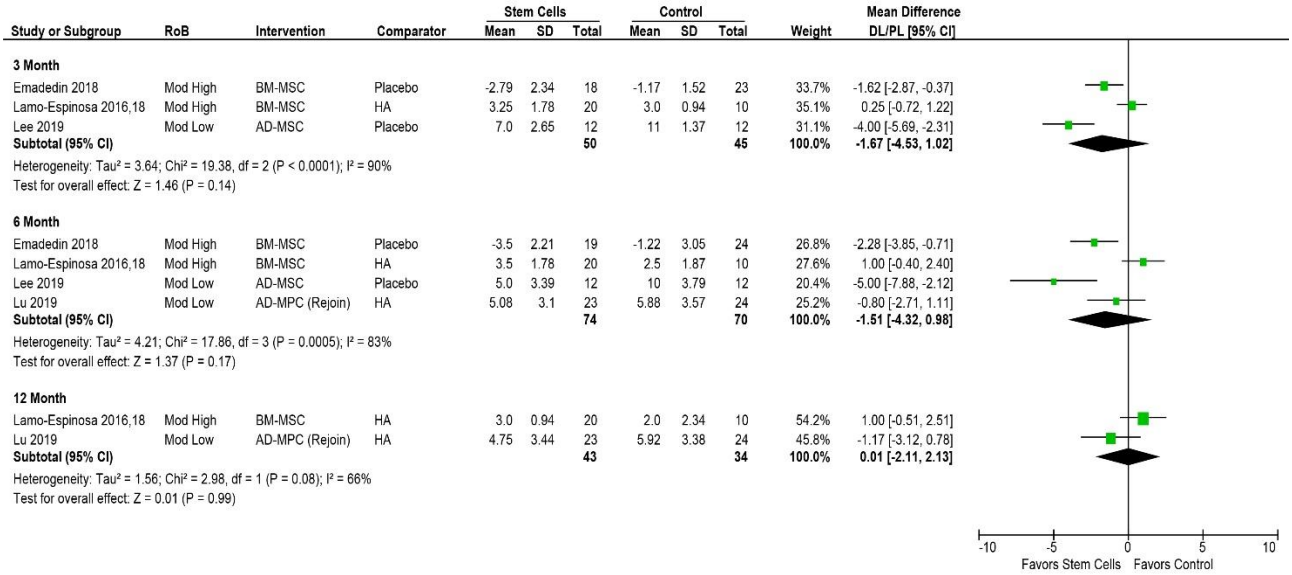
AD-MSC: adipose-derived mesenchymal stem cells; AD-MPC: adipose-derived mesenchymal progenitor cells; BM-MSC: bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; Mod = moderately; OA = osteoarthritis; RoB = risk of bias; SD = standard deviation; UC = usual care (i.e., conservative care); VAS = visual analog scale.

WOMAC Pain Subscale

The WOMAC pain subscale (scale 0-20) was reported by four trials with no statistical differences between groups in follow-up scores at any time point (3, 6, or 12 months) for the pooled analyses (Figure 9).[30,59,60,64,65] The exclusion of one outlier trial resulted in statistically significant differences between groups at 3 months (2 trials [N=65], pooled MD −2.7, 95% CI −5.1 to −0.4, I^2=80)[30,64] and 6 months (3 trials [N=114], pooled MD −2.4, 95% CI −4.4 to −0.4, I^2=65)[30,64,65] favoring stem cells (Appendix I). When considering only the two trials at lower risk of bias, a significant difference favoring AD-MSCs

versus placebo (i.e., saline) was seen at 3 months (MD −4.0, 95% CI −5.7 to −2.3) which persisted to 6 months (MD −5.0, 95% CI −7.9 to −2.1) in one trial (N=24)[64] while the other trial reported no difference between AD-MSC and HA injections at 6 months (MD −0.8, 95% CI −2.7 to 1.1) or 12 months (MD −1.2, 95% CI −3.1 to 0.8).[65] When these two trials were pooled at 6 months (N=71), no difference between groups in WOMAC pain scores was seen (pooled MD −2.8, 95% CI −6.9 to 1.4, I^2=82).

Figure 9. Autologous, culture-expanded stem cells for knee OA: WOMAC pain follow-up scores from RCTs



AD-MSC: adipose-derived mesenchymal stem cells; AD-MPC: adipose-derived mesenchymal progenitor cells; BM-MSC: bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; Mod = moderately; OA = osteoarthritis; RoB = risk of bias; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

KOOS Pain Scale

Two trials reported pain according to the KOOS Pain scale at 3 and 6 months and found that patients who received stem cell therapy (AD-MSCs) reported less pain compared with those in the placebo or UC groups at both time points in the pooled analyses (Table 16).

).[32,64] In addition, one of the trials (considered moderately high risk of bias) reported similar results at 12-months.[32]

Secondary Outcomes

Quality of Life

A total of three RCTs reported quality of life (QoL) outcomes.[32,64,65] Two trials reported QoL according to the KOOS QoL scale (

Table 18). In the pooled analyses, no difference between groups was seen at 3 months but by 6 months patients who received stem cell therapy (AD-MSCs) reported better QoL compared with those in the placebo or UC groups.[32,64] Individually, the trial at lower risk of bias did not find a statistical difference between groups at either timepoint.[64] Only one of the trials (considered moderately high risk of bias) reported longer term results and found better KOOS QoL reported by those who received stem cell therapy, compared with controls, at 12 months.[32] A third trial[65] found greater improvement in QoL according to the SF-36 among patients who received AD-MPC versus HA (

Table 18).

Table 18. Autologous, culture-expanded stem cells for knee OA: Quality of life outcomes from RCTs

	Author/RCT*	Stem cells Mean ± SD	Control Mean ± SD	MD (95% CI)	Pooled MD (95% CI)†
KOOS QoL (0-100, higher score = better QoL)					
Baseline	Freitag 2019	24.4 ± 16.8 (n=20)	30.1 ± 15.9 (n=10)	-------	-------
	Lee 2019	25 ± NR (n=12)	35 ± NR (n=12)	-------	
3 months	Freitag 2019	48.1 ± 14.7 (n=19)	29.9 ± 9.2 (n=10)	18.2 (9.5 to 26.9)	**9.4 (–8.4 to 27.3); I^2=84%**
	Lee 2019	41 ± 15.4 (n=12)	41 ± 12.2 (n=12)	0.0 (−11.1 to 11.1)	
6 months	Freitag 2019	54.2 ± 15.2 (n=19)	31.9 ± 12.5 (n=10)	22.3 (11.9 to 32.6)	**16.6 (4.6 to 28.6); I^2=56%**
	Lee 2019	50 ± 14 (n=12)	40 ± 16.4 (n=12)	10 (−2.2 to 22.2)	
12 months	Freitag 2019	59.1 ± 10.9 (n=19)	33.9 ± 12 (n=10)	25.2 (16.3 to 34.0)	-------
SF-36 (0-100, lower score = better QoL)‡					
Baseline	Lu 2019	81.4 ± 17.2 (n=26)	87.0 ± 16.7 (n=26)	-------	-------
6 months		73.0 ± 14.2 (n=23)	83.7 ± 16.5 (n=24)	−10.6 (−19.7 to −1.6)	-------
12 months		72.0 ± 12.8 (n=23)	83.2 ± 15.6 (n=24)	−11.2 (−19.6 to −2.8)	-------

CI = confidence interval; KOOS = Knee Injury and Osteoarthritis Outcome Score; MD = mean difference; OA = osteoarthritis; QoL = quality of life; RCTs = randomized control trials; SD = standard deviation; SF-36 = Short-Form-36 questionnaire.
*Stem cell type vs. control group for included RCTs:
Freitag 2019: Adipose-derived mesenchymal stem cells (AD-MSCs) [2 groups, 1 and 2 injections] vs. Conservative Care (i.e., simple analgesics, weight management, and exercise)
Lee 2019: Adipose-derived mesenchymal stem cells (AD-MSCs) vs. Placebo (saline)
Lu 2019: Adipose-derived mesenchymal progenitor cells (AD-MPC; Rejoin®) vs. Hyaluronic Acid (HA)
†As calculated by AAI.

‡Lu et al report a decrease in score on the SF-36 as indicating an improvement (this is opposite of how the SF-36 is generally interpreted).

Secondary Procedures

Two trials reported information related to additional surgeries or other procedures received by patients after study enrollment. In one trial, one patient who received low-dose BM-MSCs (+ HA) (10%; 1/10) and two patients who received HA alone (20%; 2/10) underwent a total knee arthroplasty (TKA); the timing of the TKAs is unclear however only one patient (in the control group) underwent surgery after data collection was complete (total follow-up was 48 months).[59] Also in this same trial, two HA only patients (20%; 2/10) received additional PRP injections to the effected knee. The second trial reported that one patient (4%; 1/26) in the Re-Join® group (AD-MPCs) withdrew to receive a TKA.[65]

4.2.1.3 Allogenic, culture-expanded stem cells

Randomized Controlled Trials

Primary Outcomes

Function

Only one of the two trials evaluating allogenic stem cells reported on function.[126] At 3, 6 and 12 months, patients who received BM-MSCs reported better function on the WOMAC and the Lequesne measures compared with those who received HA; however, only the mean differences at 6 months (WOMAC: –12.0, 95% CI –23.6 to –0.4; Lequesne: –15.0, 95% CI –26.6 to –3.4) and at 12 months for the Lequesne (–12.0, 95% CI –23.9 to –0.1) reached statistical significance (

Table 19). The confidence intervals were wide, likely due to the small sample size.

Pain

Pooled analyses of VAS pain scores at 2 to 3 and 6 months across the two trials showed no differences between patients treated with stem cells versus HA or placebo,[55,126] (Figure 10); however, there was substantial heterogeneity in the pooled estimate at 6 months (point estimates went in opposite directions). Individually, the trial at lower risk of bias found that patients who received PL-MSCs compared with HA reported more pain on VAS at 6 months (18.0 on a 0-100 scale, 95% CI 6.8 to 29.2)[55]; conversely, in the second trial, BM-MSCs resulted in less pain on VAS at 6 months compared with placebo, however the difference did not reach statistical significance (–18.0, 95% CI –36.1 to 0.1). In the latter trial, there was also no difference between groups at 12 months according to the VAS (Figure 10) or at 3, 6 and 12 months according to the WOMAC pain subscale (

Table 19).[126] Both trials had very small sample sizes and all estimates (pooled and individual) showed marked variability (i.e., wide confidence intervals).

Secondary Outcomes

Quality of Life

No differences in SF-12 PCS or MCS scores at 3, 6 or 12 months were reported in one trial comparing patients who received BM-MSCs versus HA (

Table 19).[126]

Table 19. Allogenic, culture-expanded stem cells for knee OA: Function, pain* and quality of life outcomes reported by the RCT by Vega 2015

Outcome Measure (scale)	Time point	BM-MSC (n=15) mean ± SD	HA (n=15) mean ± SD	MD (95% CI)
WOMAC total (0-100)†	Baseline	41 ± 11.6	45 ± 11.6	
	3 months	33 ± 19.4	41 ± 23.2	–8.0 (–24.0 to 8.0)
	6 months	28 ± 15.5	40 ± 15.5	–12.0 (–23.6 to –0.4)
	12 months	28 ± 19.4	41 ± 23.2	–13.0 (–29.0 to 3.0)
Lequesne (0-100)†	Baseline	39 ± 15.5	45 ± 15.5	
	3 months	36 ± 15.5	40 ± 15.5	–4.0 (–15.6 to 7.6)
	6 months	25 ± 15.5	40 ± 15.5	–15.0 (–26.6 to –3.4)
	12 months	30 ± 11.6	42 ± 19.4	–12.0 (–23.9 to –0.1)
WOMAC pain (0–100)†	Baseline	46 ± 15.5	50 ± 15.5	
	3 months	36 ± 15.5	46 ± 19.4	–10.0 (–23.1 to 3.1)
	6 months	33 ± 15.5	44 ± 19.4	–11.0 (–24.1 to 2.1)
	12 months	30 ± 15.5	44 ± 23.2	–14.0 (–28.8 to 0.8)
SF–12 PCS (0-100)‡	Baseline	40 ± 34.9	35 ± 31.0	
	3 months	43 ± 42.6	39 ± 31.0	4.0 (–23.9 to 31.9)
	6 months	44 ± 38.7	39 ± 31.0	5.0 (–21.2 to 31.2)
	12 months	45 ± 42.6	40 ± 31.0	5.0 (–22.9 to 32.9)
SF-12 MCS (0–100)‡	Baseline	54 ± 38.7	49 ± 34.9	
	3 months	50 ± 38.7	47 ± 38.7	3.0 (–26.0 to 32.0)
	6 months	54 ± 46.5	48 ± 38.7	6.0 (–26.0 to 38.0)
	12 months	51 ± 46.5	47 ± 42.6	4.0 (–29.4 to 37.4)

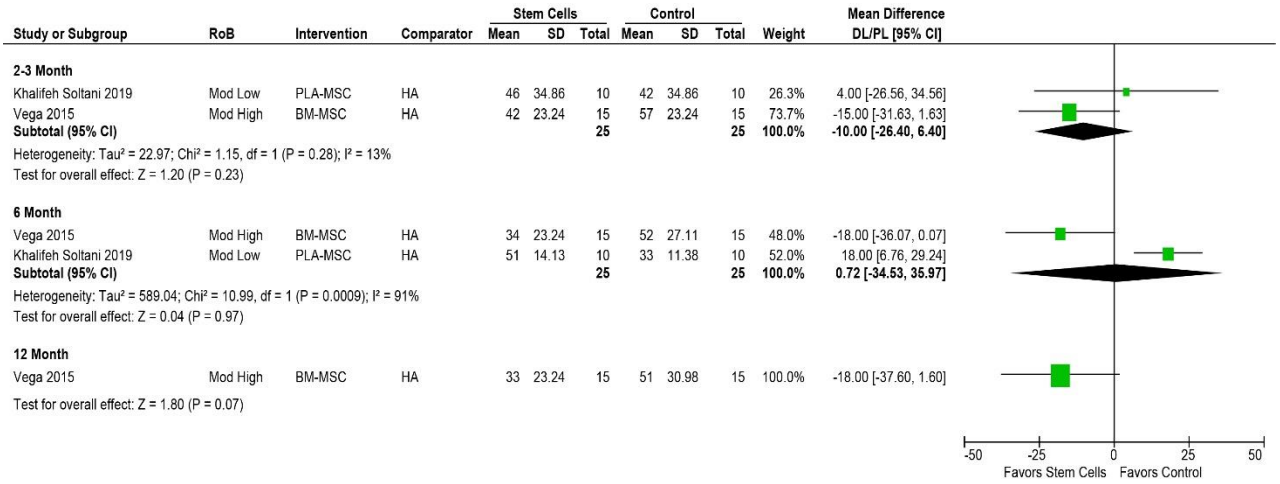
BM-MSCs=bone marrow-derived mesenchymal stem/stromal cells; CI=confidence interval; HA=hyaluronic acid; MCS=mental component score; MD=mean difference; PCS=physical component score; SF-12=short form 12 item health related quality of life questionnaire; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

*Vega 2015 also reported VAS pain which is included in the meta-analysis and therefore not reported here.

†Lower score indicates better outcome.

‡Higher score indicates better outcome.

Figure 10. Allogenic, culture-expanded stem cells for knee OA: VAS pain follow-up scores from RCTs



BM-MSC: bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; Mod = moderately; OA = osteoarthritis; PL-MSC = placenta-derived mesenchymal stem cells; RoB = risk of bias; SD = standard deviation; VAS = visual analog scale.

Nonrandomized comparative cohort studies

One comparative cohort study at high risk of bias was identified that compared amniotic fluid-derived stem cells versus triamcinolone acetonide.[12] At all time points, follow-up scores for all reported measures (function, pain, patient satisfaction) were significantly better in patients who underwent stem cell therapy (Table 20).

Table 20. Allogenic, culture-expanded stem cells: Function, pain and secondary outcomes reported by the comparative cohort study

Author	Outcome*; Timing		Stem Cells mean ± SD	Control mean ± SD	RR (95% CI) p-value
Bhattacharya 2011 Comparative cohort study Amniotic fluid (n=26) vs. triamcinolone acetonide (n=26)		**Walking distance (meters/min.)**			
	Baseline		39.8 ± 3.8	38.6 ± 4.8	NS
	3 months		58.6 ± 6.9	51 ± 4.8	<0.01
	6 months		61.4 ± 7.2	42.2 ± 4.8	<0.001
		mHAQ (0-3; lower score = better function)			
	Baseline		2.4 ± 0.3	2.2 ± 2	NS
	3 months		2.1 ± 0.12	2.3 ± 0.2	<0.01
	6 months		1.8 ± 0.31	2.2 ± 0.4	<0.001
		VAS pain (0-100; lower score = less pain)			
	Baseline		57 ± 10.2	56 ± 11.3	NS
	3 months		17 ± 3.4	21 ± 6.5	<0.01
	6 months		12 ± 4.8	32 ± 4.8	<0.001

Author	Outcome*; Timing		Stem Cells mean ± SD	Control mean ± SD	RR (95% CI) p-value
	Proportion improved†				
	3 months		80.8% ± 7.4%	46.2% ± 3.4%	<0.001
	6 months		57.7% ± 4.9%	23.1% ± 2.2%	<0.001
	12 months		50.0% ± 4.3%	15.4% ± 2.2%	<0.001
	24 months		46.2% ± 5.4%	15.4% ± 2.2%	<0.001
	Proportion satisfied with treatment, % (n/N)				
	3 months		80.8% (21/26)	46.1% (12/26)	RR 1.8 (1.1, 2.8)
	6 months		57.7% (15/26)	23.1% (6/26)	RR 2.5 (1.2, 5.4)
	12 months		50.0% (13/26)	15.4% (4/26)	RR 3.3 (1.2, 8.7)
	24 months		46.2% (12/26)	15.4% (4/26)	RR 3.0 (1.1, 8.1)

NR = not reported; mHAQ = modified Health Analysis Questionnaire; VAS = visual analog scale.
*For continuous outcomes, with the exception of walking distance, higher values indicate better function or pain.
†Subjective and objective improvement of at least seven out of nine clinical parameters (i.e. knee pain at rest; little walking is painful; definite increase in walking distance; decrease inflexibility of the joint; swelling of the joint; little power of the joint to move against gradual increasing resistance; difficulty in the initiation of the movement; stiffness of the joint and movement; range of movement is severely restricted).

Hip Osteoarthritis

Key points

- There is insufficient evidence to draw firm conclusions regarding the effectiveness of autologous stem cell therapies for treatment of hip OA based on one registry study which had no treatment comparison and one case series of non-cultured cells and one case series of cultured cells. All were considered at high risk of bias. No studies evaluating allogenic stem cell therapy for treatment of hip OA that met inclusion criteria were identified.

Detailed analysis

Three studies evaluating the use of stem cells, all from autologous sources, for the treatment of hip OA that met inclusion criteria were identified and were limited to those with no treatment comparison (i.e., case series).[17,67,101] One industry funded registry study[17] and one small case series[101] used non-culture-expanded BMC (which contains MSCs) and were conducted in the United States. An additional small case series used culture-expanded BM-MSCs[67] and was performed in Chile. Included studies are briefly summarized below. Detailed abstraction of included studies is found in Appendix F. No studies of allogenic stem cell therapies for hip OA that met the inclusion criteria were identified.

Autologous, non-culture-expanded stem cells

Two studies reported on the use of autologous, non-culture-expanded stem cells to treat hip OA.[17,101] The registry study[17] evaluated the use of BMC (which contains MSCs) augmented with PRP and platelet lysate (PL). While authors describe nucleated cell counts, no immunologic characterization of MSCs is described. An intra-articular pre-treatment injection of hypertonic dextrose was given to all patients 2 to 5 days prior to the BMC treatment as an irritant to stimulate inflammatory healing response (i.e., Prolotherapy); a pre-treatment injection was also done on "other painful extra-articular structures". Patients were followed for a mean of 4.9 months. A total of 216 hip in 196 patients (mean age 57 years; 57% male) were treated. OA grade was available for 174 patients (89%); most of these patients (68%) showed signs of moderate to severe OA (Kellgren Lawrence Grades II/III [46%] and IV [22%]) with 67% of the joints evaluated considered candidates for total hip arthroplasty; the remaining 32% had Grade I (mild) OA. The study was considered to be at high risk of bias, largely due to the lack of a comparison group (Appendix E). For the primary outcomes of interest for this report, there appeared to be substantial loss to follow-up as data were available for only 26% of patients for the OHS, 38% for the NPS and 62% for assessment of percent improvement. Furthermore, the authors do not adequately describe validation of data completeness or quality. The second study, a prospective case series, used a single injection of BMC with a follow-up injection of PRP to treat 10 patients with hip OA.[101] Patients were required to have grade III or higher OA to be included in the study. This series also included 115 other patients with other conditions and demographics, or patient characteristics were not described for the subset of patients with hip OA.

Autologous, culture-expanded stem cells

One small retrospective case series evaluated the use of culture-expanded MSCs derived from BMA.[67] Three injections were given. Patients were 50% male with a mean age of 49.7 years.

All case series are considered at high risk of bias. The overall SOE for effectiveness outcomes for which only case series are available is considered insufficient.

Results:

The only evidence for use of autologous cells comes from three studies at high risk of bias; two used BMA cells without expansion[17,101] and a third cultured cells from BMA[67]. Results should be interpreted cautiously given the high risk of bias for these studies.

4.2.1.4 Autologous, non-culture-expanded stem cells

Improvement relative to baseline for both function and pain was seen in the registry study and for pain in one case series (Table 21) for use of cells from BMA that had not been culture expanded. Both studies added PRP as part of the treatment. The registry study also added platelet lysate and patients had a pre-treatment prolotherapy injection. It is unclear to what extent effects seen are due to the added components versus MSCs and to what extent a placebo effect may be operating. Results should be interpreted cautiously given the high risk of bias for these studies.

Table 21. Summary of function and pain outcomes across case series for autologous stem cell treatment of hip osteoarthritis

Author, year Mean follow-up	Cell Origin Cell Type	Measure/Timing	Function			Pain		
			N	Mean ± SD*; % (n/N)	p-value†	N	Median (IQR); Mean ± SD*; % (n/N)	p-value†
Non-culture-expanded cells							**VAS (0-10 [worst])**	
Sampson 2016 4.9 months	BMA BMC†††‡‡	Absolute change**				10	–3.0 (–4.0 to –0.8)	NR
		% change**					–50% (–80% to –15%)	NR
Centeno 2014§ 4.9 months	BMA BMC†††‡‡		**OHS (0-48 [best])**			**NPS (0-10 [worst])**		
		Baseline	57	26.6 ± 8.8	N/A	81	4.5 ± 2.0	N/A
		Final follow-up		33.0 ± 8.7	<0.001		3.3 ± 2.3	<0.001
		% Meeting MCID‡		64% (28/44 available hips)			59% (35/59 available hips)	
Culture-expanded cells			**WOMAC-general (0-100 [worst])**			**VAS (0-10 [worst])**		
Madrones 2017 35.7 months	BMA MSCs	Baseline	10	34.5 ± 25.9	N/A	10	4.2 ± 1.6	N/A
		Final follow-up		19.2 ± 19.3	0.015		1.1 ± 0.95	0.0001
			HHS (0-100 [best])					
		Baseline	10	61.9 ± 19.2	N/A			
		Final follow-up		85.7 ± 12.3	0.003			
			VHS (scale NR)					
		Baseline	10	61.2 ± 14.2	N/A			
		Final follow-up		85.7 ± 12.3	0.021			

BMA = bone marrow aspirate; BMC = bone marrow concentrate; F/U = follow-up; HHS = Harris Hip Score; VHS = Vail Hip Score; MCID = Minimal clinically important difference; MSC = mesenchymal stem cells; N/A = Not applicable; NR = not reported; OHS = Oxford Hip Score; VAS = Visual Analogue Scale; NPS = Numeric Pain Scale; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
* If authors provided SEM, then SD was calculated by AAI and reported here.
† p-values represent Δ from baseline and are as reported by authors.
‡ MCIDs used in this study: for OHS = 4.9 points, for NPS = 2.0 points.
§ Centeno 2014 is a registry study; Data available for analysis for outcomes varied; of the 196 patients, 26% had OHS data, 38% had NPS data and of 216 hips 62% had data on percent improvement.
** Represents change from baseline to final follow-up.
††BMC contains a heterogeneous mix of white blood cells—including stem cells, progenitor cells, lymphocytes and granulocytes—and platelets.
‡‡Injection included the addition of PRP and PL for Centeno and PRP for Sampson.

4.2.1.5 Autologous, culture-expanded stem cells

Improved function and pain were reported in one small case series of culture/expanded autologous stem cells for hip OA. The small sample size and high risk of bias for this series need to be considered when interpreting results.

Hip and/or Knee Osteoarthritis (combined patient population)

Key points

- There is insufficient evidence to draw firm conclusions regarding the effectiveness of autologous non-culture-expanded stem cell therapies for treatment of hip and/or knee OA based on one case series considered to be at high risk of bias.
- No studies evaluating autologous culture-expanded or allogenic stem cell therapy for treatment of hip and/or knee OA that met inclusion criteria were identified.

Detailed analysis

Autologous, non-culture-expanded stem cells

One prospective case series[96] that evaluated the use of autologous non-culture-expanded BMC in a mixed population of patients with either hip or knee OA (data were not reported separately for these two populations) which met inclusion criteria was identified. No studies of autologous culture-expanded or allogenic stem cell use in this mixed population that met the inclusion criteria were identified. The included study is briefly summarized below. Detailed abstraction can be found in Appendix F.

The study included at total of 19 patients with 25 osteoarthritic joints (10 knees, 15 hips) treated with a single injection of non-culture-expanded BMC (containing MSCs).[96] Two patients had bilateral hip procedures, three had bilateral knee procedures, and one patient had both a hip and a knee procedure. Mean patient age was 58 years and 74% were female. Comorbidities included osteoporosis (26%), diabetes (11%), and hypothyroidism (21%). Patients were followed for a mean of 13.2 months.

All case series are considered to be at high risk of bias. The overall SOE for effectiveness outcomes for which only case series are available is considered insufficient.

Results:

4.2.1.6 Autologous, non-culture-expanded stem cells

Improvement relative to baseline for WOMAC-general was seen for the use of non-culture-expanded cells from BMC in patients being treated for hip/knee OA and 64% of patients met the specified MCID for this study of 9.15 points (Table 22). No pain outcomes were reported. At 6 months, 63.2% (12/19) of patients designated that they were satisfied with the procedure, while 38.6% (8/19) of patients reported that they experienced only mild improvement, no improvement, or a worsening of their symptoms. At 8 months post-treatment, 10.5% (2/19) of patients had undergone total hip arthroplasty.

Table 22. Summary of function and pain outcomes across 1 case series (Rodriguez-Fontan 2018) of non-culture-expanded cells for treatment of hip and/or knee osteoarthritis

	Function	
	WOMAC-general (0-48 [best])	
	Mean ± SD	p-value*
Baseline	40.8 ± 18.3	N/A
6 months	19.2 ± 18.2	N/A
6 month Δ	21.6 ± 5.1 (95% CI 11.3 to 32)	<0.001
Final follow-up†	20.6 ± 17	N/A
Final follow-up† Δ	20.2 ± 5.0 (95% CI 10.2 to 30.3)	<0.001
% Meeting MCID‡	64%	

BMA = bone marrow aspirate; MCID = minimal clinically important difference; MSCs = mesenchymal stem cells; N/A = not applicable; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index
* p-values represent Δ from baseline and are as reported by authors
† Mean follow-up was 13.2 ± 6.3 months
‡ MCID for this study was defined as 9.15 points. Ns and ns were not reported.

Shoulder Osteoarthritis

Key points

- There is insufficient evidence to draw firm conclusions regarding the effectiveness of autologous, non-culture expanded stem cell therapies for treatment of shoulder OA based on one single-arm registry study and one case series. All were considered at high risk of bias.
- No studies evaluating allogenic stem cell therapy for treatment of shoulder OA that met inclusion criteria were identified.

Detailed analysis

Studies of autologous stem cells used for treatment of shoulder OA was limited to those with no treatment comparison. One small industry-funded registry study[21] and one small case series[101] reported using non-culture-expanded autologous MSCs, from BMC. No studies of autologous culture-expanded or allogenic stem cell use for treatment of shoulder OA that met the inclusion criteria were identified.

Included studies are briefly summarized below. Detailed abstraction of included studies is found in Appendix F.

Autologous, non-culture-expanded stem cells

The included registry study[21] reported using non-culture-expanded autologous MSCs, from BMC, together with platelet rich plasma (PRP) and platelet lysate (PL). While authors describe total nucleated cell count, no immunologic characterizations of MSCs is described. An intra-articular pre-treatment injection of 3-5 mL of a 12.5% hypertonic dextrose solution (Prolotherapy) and 0.1% lidocaine or 0.25% ropivacaine was administered 2 to 5 days before the BMA/PRP/PL treatment as an irritant to stimulate inflammatory healing response. Authors report that they performed 34 procedures on patients with shoulder OA (number of patients unknown). In total, the study included 102 patients with 115 treated shoulders, 34 of which were osteoarthritic shoulder joints; demographics and patient characteristics were described separately for the subset of patients with shoulder OA. Median age was 52 years and 79% were male. Mean follow-up time could not be determined from the information provided for this subset of patients. For the primary outcomes of interest for this report, there were only data for 29% of shoulders for DASH and 41% for NPS, suggesting substantial loss to follow-up and/or data quality concerns. The study was considered to be at high risk of bias (Appendix E).

A second small case series used a single injection of BMC with follow-up injection of PRP to treat 13 patients with shoulder OA.[101] The series also included 112 other patients with other conditions and demographics or patient characteristics were not described for the subset of patients with shoulder OA. Cells were not cultured. All case series are considered to be at high risk of bias.

The overall SOE for effectiveness outcomes for which only case series are available is considered insufficient.

Results:

4.2.1.7 Autologous, non-culture-expanded stem cells

The registry study[21] reported improvement from baseline to final follow-up in both function and pain, respectively; the DASH score decreased by a mean 18.7 points at 7.1 months and the NPS by 1.6 points at 8.3 months. Whether these differences were statistically significant was not reported and could not be determined with the information provided. The case series[101] showed a statistically significant decrease in pain from baseline to final follow-up (mean, 4.9 months). (

Table 23) Both studies added PRP as part of the treatment. The registry study also added platelet lysate and patients had a pre-treatment prolotherapy injection. It is unclear to what extent effects seen are due to the added components versus MSCs and to what extent a placebo effect may be operating.

Table 23. Summary of function and pain outcomes across case series of non-culture-expanded autologous bone marrow-derived mesenchymal stem/stromal sells for treatment of shoulder osteoarthritis

	Function				Pain			
	DASH (0-100 [worst])				VAS or NPS (0-10 (worst))			
Author (year)	**N**	**Mean F/U (months)**	**Δ from baseline** Median (IQR); Mean ± SD	**p-value**	**N**	**Mean F/U (months)**	**Δ from baseline** Median (IQR); Mean ± SD	**p-value**
Centeno 2015†	10	7.1	–18.7 ± 11.2	NR	14	8.3	–1.6 ± 2.1	NR
Sampson 2016					13	4.9	–3.0 (–4.0 to –0.8)*	NR

DASH = Disabilities of the arm, shoulder, and hand; F/U = follow-up; IQR = interquartile range; NPS = numeric pain scale; NR = Not reported; SD = standard deviation; VAS – visual analogue scale

* % change from baseline in Sampson 2016 for VAS was –63% (–94% to –53%)

† Centeno 2015 is a registry study and has substantial loss to follow-up: there were only data for 29% of shoulders for DASH and 41% for NPS.

Degenerative Disc Disease

Key Points

- There is insufficient evidence to draw firm conclusions regarding the effectiveness of autologous or allogenic stem cell therapy for treatment of chronic LBP due to DDD.
    - Data for autologous sources are from five small case series and are at high risk of bias.
    - Only one small RCT was identified which compared culture expanded allogenic MSCs from BMA with a sham treatment. While no differences between treatment groups was seen for function, pain, or SF-12 MCS and PCS through 12 months, evidence was considered insufficient due to the small sample size, moderately high risk of bias and uncertainty regarding the consistency of results from a single trial.

Detailed analysis

Studies of autologous stem cell use in patients with nonradicular chronic low back pain and evidence of degenerative disc disease meeting the inclusion criteria were limited to five small case series. The total number of patients across three series[24,45,84-86] of non-culture-expanded stem cells was 51; the total across two series of culture expanded cells was 20.[58,80] No studies of non-culture-expanded allogenic cells were identified. One RCT (N=24)[74] of expanded allogenic cells versus a sham procedure was identified. Detailed abstraction of case series is found in Appendix F.

Autologous, non-culture-expanded stem cells

Two small series reported using non-culture-expanded autologous MSCs, from BMC[84-86] (N= 26, median age 40 years, 42% male) in one prospective series (across 3 publications) and from the stromal vascular fraction of adipose tissue[24] combined with PRP (N= 15, mean age 52 years, 73% male) in the other. A third small series (N=10, age 32 to 74 years, 50% male) reported use of hematopoietic cells from BMA[45]

in patients who had prior endoscopic discectomy; based on the limited information presented, it appears that cells were not expanded/cultured. Two studies did not report a funding source[45,84-86], however authors of one study were employed by a company that provided bone marrow concentration devices[84-86]; one was industry funded[24]. All studies were performed in the U.S.

Autologous, culture-expanded stem cells

Two small series of autologous culture-expanded stem cells also used different sources of cells; one series (N=10, mean age 34 years, 40% male) conducted in Spain used BMC as a source.[80] The study appears to be government funded. The other series used adipose tissue plus HA [58](N=10, mean age 44 years, 60% male) and was conducted in South Korea. The study was government funded.

Case series are considered to be at high risk of bias. The overall SOE for effectiveness outcomes for which only case series are available is considered insufficient.

Allogenic, culture-expanded stem cells

One small RCT and one small case series of different culture-expanded cell types were identified. No studies of non-culture-expanded allogenic stem cells for IVD repair/treatment of DDD were identified.

One small (N=24), government funded RCT [74] in patients with DDD comparing culture expanded allogenic BMA-derived MSCs to a sham treatment consisting of infiltration of 1% mepivacaine into paravertebral musculature was identified. BMA was obtained from 5 healthy donors who were screened for HIV and hepatitis B and C; cells from each donor were used in 1 to 3 patients. Authors report cell culture and evaluation was based on prior publications[79,81], including antigenic profiles consistent with ISCT criteria for mesenchymal cells but profiles specific to this study don't appear to be provided. Overall, patients were predominately male (71%), with a mean age of 38 (±2) years who had failed ≥6 months of conventional care (unspecified medical and physical treatment). (Table 24) Authors do not describe post-procedure treatments (e.g. physical therapy, activity restriction, etc.). The study was conducted in Spain. With regard to methodological limitations, the balance of sex and age between treatment groups could not be assessed and no other patient characteristics (e.g. pain duration, comorbidities, previous interventions, etc.) were described precluding the evaluation of potential confounding. Baseline ODI was 10 points greater in the MSC group, but neither ODI nor VAS was statistically different at baseline for the MCS versus the sham group. It is unclear whether patients were blinded (authors state that they were "blinded after assignment") and there was insufficient information about the number of screened or eligible patients randomized to determine follow-up or intention to treat analysis. The trial was considered to be at moderately high risk of bias.

Table 24. RCT (Noriega 2017) comparing allogenic bone marrow derived MSCs with sham procedure

	Noriega 2017	
	MSC (n=12)	Sham (n=12)
Patient demographics		
Males, %	71%	
Age, years; mean ± SD	38 ± 2	
Duration of pain, months; mean ± SD	NR	NR
Comorbidities	NR	NR
Other patient factors	NR	NR
Concomitant meds	NR	NR
Previous injections	NR	NR
Previous surgery	NR	NR
Procedural characteristics		
Patient blinded to treatment received	No*	No*
Stem cell source	BMA	N/A
Stem cell type (author described)	MSC	N/A
Stem cell count per disc, mean ± SD (range)†	$25x10^6$‡	N/A
Stem cell viability	>98%	N/A
Local anesthetic used	Yes	Yes
Other injectate (w/ stem cells)	Saline	NR
Imaging guidance	NR	NR
No. of injections	NR	NR
Pre-treatment injection	NR	NR
Post-treatment injection	NR	NR
Cross-over (timing)	N/A	NR
Post-treatment care	NSAID 3/12 Opioid 1/12	NSAID 8/12 Opioid 1/12
Country	Spain	
Funding	Government§	
Risk of bias	Moderately High	

* Authors state that patients and assessors were "blinded after assignment", thus patient-reported outcomes do not appear to have been blinded

† Stem cell count based on flow cytometry, immunological markers etc.

‡ Suspended in Ringers-lactate, 12.5x106 cells/mill

§ Red de Terapia Celular (RD12/0019/0036, RD12/
0019/0001 and RD16/0011/0003), Instituto de Salud Carlos III, Ministerio de Economía y Competitividad, and the Centro en Red de Medicina Regenerativa de Castilla y León is gratefully acknowledged.

Results:

4.2.1.8 Autologous, non-culture-expanded stem cells

The only evidence for use of autologous stem cells for treatment of DDD available is from case series.

Improvement from baseline on the ODI was noted in the case series that used BMA as a source of MSCs[84-86] at 3, 6 and 12 months. Patients who did not go on to have surgery (n=21) experienced an average reduction in ODI of ~57% by 12 months. Authors also report persistence of improvement through 36 months. By contrast, no improvement from baseline was seen in series using adipose tissue as an MSC source combined with PRP at 2 or 6 months.[24] Improvement in pain scores relative to baseline was reported in both case series. Neither study reported measures of estimate variability (e.g. standard deviations), precluding evaluation of estimate stability. The remaining case series reporting on use of hematopoietic cells only reported that no patient had a reduction in pain.[45] (
Table 25)

Table 25. Summary of function and pain outcomes across case series of autologous non-culture-expanded stem cells for treatment of non-radicular low back pain due to DDD or for IVD repair

F/U (months)	Author (year)	N	Stem Cell Origin, Type	Function (means)		Pain (means)	
				ODI (0-100%[worst])		VAS or NPRS (0-100 (worst))	
				Mean ± SD	p-value (Δ vs baseline)*	Mean ± SD	p-value (Δ vs baseline)*
Baseline	Pettine 2015	26	BMA, MCS	56.5±NR	N/A	79.3±NR	N/A
	Comella 2017	15	SVF (adipose), MSC	32±NR	N/A	56 ±NR	N/A
2-3 months	Pettine 2015	26	BMA	22.8±NR	p ≤0.0001	29.2±NR	p ≤ 0.0001
	Comella 2017	15	SVF (adipose), MSC	28±NR	P=0.30	42 ±NR	P=0.09
6 months	Pettine 2015	26	BMA	24.4±NR	p ≤ 0.0001	26.3±NR	p ≤ 0.0001
	Comella 2017	15	SVF (adipose), MSC	30±NR	P=0.31	36 ±NR	P= 0.01
12 months	Pettine 2015	26	BMA	25.0±NR	p ≤ 0.0001	33.2 ±NR	p ≤ 0.0001
	Haufe 2006	10	BMA, hematopoietic	NR	NR	Pain ↓ in 0%‡	N/A
				% reduction in ODI§ % Δ from baseline		% Reduction in VAS Score§ % Δ from baseline	

F/U (months)	Author (year)	N	Stem Cell Origin, Type	Function (means)		Pain (means)	
3 months	Pettine 2015	26	BMA, MSC	58.1%	N/A	64.6%	N/A
6 months				55.5%	N/A	64.2%	N/A
12 months				56.8%	N/A	58.0%	N/A

BMA = bone marrow aspirate; HA = hyaluronic acid; MSC = mesenchymal stem cells; N/A = Not applicable; NR = not reported; NS = not statistically significant; SVF = stromal vascular fraction
VAS = Visual Analogue Scale; 0-100, higher scores indicate severity of pain) NPRS = Numeric Pain Rating Scale 0-10, 0 = no pain and 10 = worst possible pain; Converted to 0-100 scale for analysis
* p-values as reported by authors
†Where standard errors (SE) were reported, values were used to estimate standard deviation (SD): SD=SE*SQRT(n)
‡ Haufe 2006 does not specify whether cells were expanded or not based on description appears to be non-cultured, not expanded. Authors only reported percentage of patients with no pain reduction.
§In patients who did not progress to surgery

In addition, two small case series reported the proportion of patients who required subsequent surgery following BMA injections. In one study that evaluated MSCs, 23% (6/26) of patients had undergone a subsequent surgery by 36 months (8% [2/26] at 12 months and 19% [5/26] at 24 months])[85,86]; in the second study, at 12 months post-injection (hematopoietic stem cells), 70% (7/10) of patients underwent a fusion procedure and one patient (10%; 1/10) required a total disc replacement.[45]

4.2.1.9 Autologous, culture-expanded stem cells

Improved function and pain relative to baseline values was seen in the case series of cultured cells derived from BMA and in the series which used adipose tissue plus HA at 3, 6 and 12 months (Table 26). The stability of the estimates is questionable, however, given the large standard deviations reported for most time frames. The series which used adipose tissue with HA reported that 6 of the 10 patients experienced a ≥50% reduction in VAS & ODI at 12 months. Small sample sizes and the high risk of bias for these studies preclude formulation of definitive conclusions.

Table 26. Summary of function and pain outcomes across case series of autologous culture-expanded cells for treatment of nonradicular low back pain due to DDD or for IVD repair

F/U (months)	Author (year)	N	Stem Cell Origin, Type, Intervention	Function (means)		Pain (means)	
				ODI (0-100%[worst])		VAS or NPRS (0-100 (worst))	
				Mean ± SD	p-value (Δ vs baseline)*	Mean ± SD	p-value (Δ vs baseline)*
Baseline	Orozco 2011	10	BMA, MSC	25.0±13.0†	N/A	68.9± 10.4†	N/A
	Kumar 2017	10	Adipose MSC + HA	42.8 ± 15.03	N/A	65±12.7	N/A
3 months	Orozco 2011	10	BMA, MSC	13.0±10.1†	p<0.05	26.5± 17.7†	p<0.001
	Kumar 2017	10	Adipose MSC + HA	31.7±14.22	p=0.01	43.0 ±16.3	p=0.02

F/U (months)	Author (year)	N	Stem Cell Origin, Type, Intervention	Function (means)		Pain (means)	
6 months	Orozco 2011	10	BMA	9.4±8.5†	p<0.01	21.6± 19.0†	p<0.001
	Kumar 2017	10	Adipose MSC + HA	21.3±7.42	p=0.002	32.0 ±14. 0	p=0.004
12 months	Orozco 2011	10	BMA, MSC	7.4±7.3†	p<0.001	20.0± 20.6†	p<0.001
	Kumar 2017	10	Adipose MSC + HA	16.8±9.77	p=0.002	29.0±16.6	p=0.002
≥50% reduction in VAS & ODI % of patients							
6 months	Kumar 2017	10	Adipose MSC + HA	70% (7/10)		N/A	
12 months		10		60% (6/10)			

BMA = bone marrow aspirate; HA = hyaluronic acid; MSC = mesenchymal stem cells; N/A = Not applicable; NR = not reported; NS = not statistically significant; SVF = stromal vascular fraction
VAS = Visual Analogue Scale; 0-100, higher scores indicate severity of pain) NPRS = Numeric Pain Rating Scale 0-10, 0 = no pain and 10 = worst possible pain; Converted to 0-100 scale for analysis
* p-values as reported by authors
†Where standard errors (SE) were reported, values were used to estimate standard deviation (SD): SD=SE*SQRT(n)

4.2.1.10 Allogenic, culture-expanded stem cells

One small RCT of culture-expanded MSCs was identified[74] for the treatment of DDD. No studies of non-culture-expanded allogenic stem cells for IVD repair/treatment of DDD were identified.

In the one RCT identified[74], there were no differences in either function based on ODI (0-100 scale) or pain (0-100 VAS) between patients who received culture-expanded MSCs and those receiving the sham treatment of infiltration of 1% mepivacaine into paravertebral musculature ad 3, 6 or 12 months based on mean differences calculated between groups. (Authors do not provide results of statistical testing on differences between groups based on medians.) (Table 27) Similarly, there were no difference between groups on the SF-12 PCS or MCS measures at any time frame (see data abstraction appendix F). The small sample size likely contributes to the large confidence intervals seen for effect estimates.

Table 27. Summary function and pain outcomes in 1 RCT (Noriega) of cultured/expanded allogenic cells for treatment of nonradicular low back pain due to DDD or IVD repair

	Function - ODI (0-100%(worse))			Pain -VAS (0-100 (worst))		
F/U (months)	MSC (n= 12) mean ± SD median (IQR)	Sham (n =12) mean ± SD median (IQR)	MD* (95% CI) P-value	MSC (n= 12) mean ± SD median (IQR)	Sham (n =12) mean ± SD median (IQR)	MD* (95% CI) P-value
0 months	34±23 26 (22-47)	24±14 22 (15-30)	10 (-6.1, 26.1) 0.2116	67±26 70 (50-90)	62±23 71 (56-77)	5 (-15.8, 25.8) 0.6228
3 months	16±20 9 (6-16)	25±15 24 (16-31)	-9 (-23.9, 6.0) 0.2255	43±30 40 (16-63)	46±27 50 (24-72)	-3 (-27.2, 21.2) 0.7992
6 months	20±24 12 (7-19)	30±20 28 (14-45)	-10 (-28.7, 8.7) 0.2795	40±29 47 (12-60)	51±29 52 (26-79)	-11 (-35.5, 13.5) 0.3629

12 months	22±24 10 (8-24)	34±25 29 (20-51)	-12 (-32.7, 8.7) 0.2431	47±36 47 (14-78)	47±28 54 (24-68)	0 (-27.3, 27.3) 1.000

CI = confidence interval; F/U = follow-up; IQR = interquartile range; MD = mean difference between treatments; MSCs = mesenchymal stem cells; ODI = Oswestry Disability Index; SD = standard deviation; VAS = Visual Analogue Scale;
* Effect sizes calculated for comparison of treatment groups based on 2 sample t-test for differences in means; authors do not provided data for statistical test of differences in medians.

Tendinopathy

Key Points:

- There is insufficient evidence to draw firm conclusions regarding the effectiveness of autologous non-expanded stem cells for treatment of tendinopathy based on data from one RCT of adipose stromal vascular fraction (SVF) versus PRP and one case series of BMAC combined with PRP for treatment of elbow tendinopathy.

Detailed analysis

Studies of autologous stem cell use for treatment of tendinopathy meeting the inclusion criteria were confined to one RCT[125] (N=44) of adipose stromal vascular fraction versus PRP for treatment of chronic non-insertional Achilles tendinopathy and one case series[110] (N=30) of BMA combined with PRP for treatment of elbow tendinopathy. Neither study employed culture-expanded cells. No studies of allogenic cells were identified.

Autologous Non-Culture-Expanded

One small RCT in patients with chronic non-insertional Achilles tendinopathy comparing non-cultured/non-expanded autologous adipose-derived MSCs from stromal vascular fraction (SVF) with PRP performed in Italy was identified. Patients with symptom duration ≥3 months and VAS of >5 were considered for inclusion; patients who had prior injection treatments were excluded. Authors do not report on funding or COI for this study. Adipose tissue was manually lipoaspirated from the abdomen in all but two patients from whom tissue was harvested form the internal thigh. Samples were processed using a proprietary system (FastKit, Italy), mechanically digested (rubbing tissues until it could pass through a 120 µm internal filter), centrifuged and then transferred to a new syringe. A volume of 4 mL for both the SVF and PRP was injected; authors do not report cell concentration or identify specific cell types in the SVF injectate based on immunologic methods. Analysis was reported only for the identification of pro-inflammatory and anti-inflammatory cytokines. More SVF patient received bilateral treatment. Patients were not allowed to tack NSAIDS the week prior to treatment and only paracetamol was permitted post-procedure. Patients were advised to use crutches for the first 24 hours following the procedure, but no specific physical therapy was prescribed; patients were allowed to progressively resume their regular activities. With regard to study quality, the method of randomization was not described, but allocation appears to have been concealed. The proportion of males and ages varied between the SVF and PRP groups (67% vs. 35% male, 47.3 year vs. 46.6 years). Authors report that radiologists and assessors were blinded to treatment allocation, but patients were not. This trial was considered to be at moderately high risk of bias,

Table 28.

Table 28. RCT (Usuelli 2018) comparing autologous non-culture-expanded AD-derived MSCs from SVF versus PRP

	Usuelli 2018	
	AD-SVF (n=21)	PRP (n=23)
Patient demographics		
Males, %	67%	35%
Age, years; mean ± SD	47.3±3.8	46.6±6.2
Duration of pain, months; mean ± SD	≥3 months	
Comorbidities	NR	NR
Other patient factors	NR	NR
Concomitant meds	NR	NR
Previous injections	Excluded	
Previous surgery	NR	NR
Procedural characteristics		
Patient blinded to treatment received	No	No
Stem cell source	adipose	NA
Stem cell type (author described)	NR	NR
Stem cell viability	NR	NR
Anesthetic used	NR	NR
Other injectate (w/ stem cells)	None	None
Imaging guidance	Yes	Yes
No. of injections	1	1
Pre-treatment injection	NR	NR
Post-treatment injection	NR	NR
Cross-over (timing)	NR	NR
Post-treatment care	None	None
Country	Italy	
Funding/COI	NR	
Risk of bias	Moderately low	

AD-SVF = adipose-derived stromal vascular fraction; COI = conflict of interest; NR = not reported; PRP = platelet-rich plasma; SD = standard deviation.

One prospective case series[110] (N=30) conducted in India evaluated the use of bone marrow mononuclear stem cells from BMAC plus PRP in patients with previously untreated elbow tendonitis was identified. Cells were not cultured or expanded. Most patients were male (60%) with a mean age of 35 years ± 6.8 years and symptom duration of 7.33 ± 2.49 weeks. Study funding and author COI were not reported. BMAC was combined with 1cc of 2% lignocaine. Use of concomitant medications was not reported. Patients were advised to rest and moderate activities post-procedure. All case series are considered at high risk of bias.

Results

4.2.1.11 Autologous, non-culture-expanded stem cells

No improvement in function was seen at any time point based on VISA-A (Victoria Institute of Sport Assessment – Achilles) scores in the one RCT in patients with Achilles tendinopathy[125] comparing SVF with PRP. A statistically significant improvement in the AOFAS (American Orthopedic Foot and Ankle Society Ankle-Hindfoot Score) favoring SVF was seen only at the 2 week post-procedure follow-up but not at any other time point up to 6 months. Improvement in VAS pain favoring SVF over PRP was seen up to 1 month post-procedure, but not beyond (Table 29). Authors also report no difference between SVF and PRP on SF-36 PCS or MCS at any time point (

Table 30 and data abstraction appendix F). Mean values for all measures were estimated from author figures; information on estimate variability (e.g. standard deviations) was not reported precluding evaluation of estimate stability and independent statistical evaluation. The impact of sample size on results is not clear.

Compared with baseline, all patients receiving BMAC experienced improved function based on the Patient Reported Tennis Elbow Evaluation (PRTEE) at each time point up to 3 months in the prospective case series.[110] Table 31) Authors do not report on pain or quality of life. The high risk of bias for case series precludes formulation of definitive conclusions.

Table 29. Summary function and pain outcomes in 1 RCT (Usuelli 2018) of non-cultured/non-expanded autologous cells for treatment of Achilles tendinopathy*

	Function						Pain		
	VISA-A (0-100 [best])			AOFAS (0-100 [best])			VAS (0-10 [worse])		
F/U (months)	SVF (n= 21; 28 tendons)	PRP (n = 23; 28 tendons)	p-value†	SVF (n= 21; 28 tendons)	PRP (n = 23; 28 tendons)	p-value†	SVF (n= 21; 28 tendons)	PRP (n = 23; 28 tendons)	p-value†
	Mean ± SD			Mean ± SD			Mean ± SD		
Baseline	41.6 ± 13.6	46.5 ± 23.6	NS	63.4 ± 20.1	63.2 ± 17.7	NS	6.5 ± 1.6	6.3 ± 1.2	NS
2 weeks.	43 ± NR	43 ± NR	NS	80 ± NR	67 ± NR	<0.05	2.5 ± NR	4.4 ± NR	<0.05
1 month	59 ± NR	47 ± NR	NS	80 ± NR	72 ± NR	NS	2.0 ± NR	3.8 ± NR	<0.05
2 months	66 ± NR	59 ± NR	NS	85 ± NR	79 ± NR	NS	1.8 ± NR	2.5 ± NR	NS
4 months	70 ± NR	65 ± NR	NS	80 ± NR	80 ± NR	NS	2.0 ± NR	3.0 ± NR	NS
6 months	71 ± NR	71 ± NR	NS	87 ± NR	87 ± NR	NS	1.8 ± NR	1.8 ± NR	NS

AOFAS = American Orthopedic Foot and Ankle Society Ankle-Hindfoot Score; NR = not reported; NS = not significant; PRP = platelet rich plasma; SD = standard deviation; SVF = stromal vascular fraction; VAS = visual analogue scale; VISA-A = Victoria Institute of Sport Assessment – Achilles

* Data are all estimated from figures.

† p-values are for the MD between the two groups. No SDs were provided by the authors, thus the MD cannot be calculated, though authors did provide p-values for the MD between the two groups, which are reported here.

Table 30. Summary of QOL outcomes in 1 RCT (Usuelli 2018) of non-cultured/non-expanded autologous cells for treatment of Achilles tendinopathy*

	QOL					
	SF-36 PCS (0-100 [best])			SF-36 MCS (0-100 [best])		
F/U (months)	SVF (n= 21; 28 tendons)	PRP (n = 23; 28 tendons)	p-value†	SVF (n= 21; 28 tendons)	PRP (n = 23; 28 tendons)	p-value†
	Mean ± SD			Mean ± SD		
Baseline	42.2 ± 5.5	38.5 ± 7.9	NS	48.7 ± 5.7	51.2 ± 8.0	NS
2 wks.	42.5 ± NR	39.5 ± NR	NS	51.5 ± NR	51 ± NR	NS
1 mo.	47.5 ± NR	46.5 ± NR	NS	52 ± NR	52 ± NR	NS
2 mos.	50.5 ± NR	46.5 ± NR	NS	52 ± NR	51.5 ± NR	NS
4 mos.	50 ± NR	47.5 ± NR	NS	49 ± NR	52.5 ± NR	NS
6 mos.	52 ± NR	51 ± NR	NS	51 ± NR	52 ± NR	NS

* Data are all estimated from figures.

† p-values are for the MD between the two groups. No SDs were provided by the authors, thus the MD cannot be calculated, though authors did provide p-values for the MD between the two groups, which are reported here.

MCS = mental component score; NR = not reported; NS = not significant; PCS = physical component score; PRP = platelet rich plasma; QOL = Quality of Life; SD = standard deviation; SVF = stromal vascular fraction; SF-36 = short form health-related quality of life survey

Table 31. Summary of function outcomes from the case series for treatment of elbow tendinopathy

Author, year	Cell Origin Cell Type	N	F/U (months)	Function	
				Mean ± SD	p-value*
Non-culture-expanded cells				**PRTEE (0-100 [worst])**	
Singh 2014	BMA MNC	30	Baseline	72.8 ± 6.97	N/A
			2 weeks	40.93 ± 5.94	<0.0001
			1.5 months	24.46 ± 4.58	<0.0001
			3 months	14.86 ± 3.48	<0.0001

BMA = bone marrow aspirate; F/U = Follow-up; MNC = mononuclear cells; MSC = mesenchymal stem cells; N/A = Not applicable; PRTEE = Patient reported tennis elbow evaluation; SD = Standard deviation
* p-values represent Δ from baseline and are as reported by authors.

Anterior Cruciate Ligament Tear

Key Points

- There is insufficient evidence to draw firm conclusions regarding the effectiveness of autologous, non-culture expanded stem cell therapy for treatment of ACL tears based on one high risk of bias registry study which had no treatment comparison.
- No studies evaluating allogenic stem cell therapy for treatment of ACL tears that met inclusion criteria were identified.

Detailed analysis

Autologous, non-culture-expanded stem cells

One small industry-funded registry study[18] of autologous non-culture-expanded BMC (containing MSCs) used for the treatment of ACL tears was identified. No studies of autologous culture-expanded or allogenic stem cell used for the treatment of ACL tears that met the inclusion criteria were identified. The included study is briefly summarized below. Detailed abstraction of included studies is found in Appendix F.

The study[18] (N=29) reported using non-culture-expanded BMC (containing MSCs) together with PRP and PL. While authors describe nucleated cell counts (mean, 690×10^6), no immunologic characterization of MSCs is described. 72% of patients received an intra-articular pre-treatment injection of 3-5ccs of hyper-molar dextrose solution (prolotherapy) two to 5 days prior to the BMA/PRP/PL treatment as an irritant to stimulate inflammatory healing response. Mean follow-up was not reported and the number of patients available at each time point varied greatly, suggesting substantial loss to follow-up and/or data quality concerns. Patients were followed for a mean 23 (SD, 10) months. The mean age was 53 years (range, 41-67) and 59% were female. 21% (6/29), 45% (13/29), and 34% (10/29) of patients had grade I, II, and III ACL tears, respectively. Mean symptom duration was 33 months (range, 6-144). The study was considered at high risk of bias (Appendix F).

The study was considered to be at high risk of bias. The overall SOE for effectiveness outcomes for which only case series are available is considered insufficient.

Results:

4.2.1.12 Autologous, non-culture-expanded stem cells

Improvement relative to baseline for functional outcomes (LEFS and IKDC) was seen at all time points (1, 3, 6, 12, 18, 24, and 36 months) for the use of non-culture-expanded cells from BMC in patients being treated for ACL tears. At patients' final follow-up (mean, 23 months), 82.6% (19/23) had met the specified MCID of 9 points for this study on the LEFS. At 6 months, 95% (18/19) of patients with available data met the specified MCID of 6.3 points for this study, and at 12 months, 100% (14/14) of patients with available data met the MCID of 16.7 points for this study on the IKDC. Mean scores for the NPS were found to be significantly different from baseline for the NPS at 6, 18, and 24 months, but not at 1, 3, 12, or 36 months. At a mean follow-up of 23 (± 10) months post-treatment, the mean M-SANE (patient perceived improvement) score was 72% (± 35%). 21.7% (5/23) of patients required ACL reconstruction surgery, four due to treatment failure and 1 due to a re-tear of the ACL. Of these patients, two had a grade 1 tear, two had grade 2 tear, and one was grade 3 tear. This study added PRP and PL as part of the treatment and patients had a pre-treatment prolotherapy injection. It is unclear to what extent effects seen are due to the added components versus MSCs and to what extent a placebo effect may be operating. Results should be interpreted cautiously given the high risk of bias for this study.

Partial Rotator Cuff Tear

Key Points

- There is insufficient evidence to draw firm conclusions regarding the effectiveness of autologous, non-culture-expanded stem cell therapies for treatment of partial rotator cuff tears based on one moderately high risk of bias comparative cohort[57] and one registry study[21] at high risk of bias.
- No studies evaluating allogenic stem cell therapy for treatment of partial rotator cuff tears that met inclusion criteria were identified.

Detailed analysis

Studies of autologous stem cells used for the treatment of partial rotator cuff tears meeting the inclusion criteria was limited to one small prospective comparative cohort[57] and one industry-funded registry study[21]; both reported using non-culture-expanded autologous MSCs, from BMC. No studies of allogenic stem cell use for treatment of rotator cuff tears that met the inclusion criteria were identified. Included studies are briefly summarized below. Detailed abstraction of included studies is found in Appendix F.

Autologous, non-culture-expanded stem cells

One small (N=24) government-funded prospective cohort[57] in patients with unilateral partial rotator cuff tears assessed the effectiveness and safety of autologous non-culture-expanded MSCs from BMC, plus PRP compared with a daily, self-regulated physical therapy (PT) program. The PT program lasted 3-months and consisted of stretching, scapular stabilization exercises, and strengthening exercises. Authors reported that all the patients in the PT group performed the rotator cuff exercises daily without omission. Patients in the BMC-PRP group were injected with 2 mL BMC and 1 mL PRP under ultrasound guidance; authors did report on the centration of MSCs contained within the injectate. Patients in the BMC-PRP group did not receive any post-procedure PT. Across the BMC-PRP and PT groups, respectively, 42% and 67% were males, mean age was 55 and 60 years, and patients had a mean symptom duration of 7.3 and 5.1 months. No patients were lost to follow-up. The study was conducted in South Korea. The study was considered to be at moderately high risk of bias (Appendix E).

The included registry study[21] reported using non-culture-expanded autologous MSCs, from BMC, together with platelet rich plasma (PRP) and platelet lysate (PL). While authors describe total nucleated cell count, no immunologic characterizations of MSCs is described. An intra-articular pre-treatment injection of 3-5 mL of a 12.5% hypertonic dextrose solution (Prolotherapy) and 0.1% lidocaine or 0.25% ropivacaine was administered 2 to 5 days before the BMA/PRP/PL treatment as an irritant to stimulate inflammatory healing response. Authors report that they performed 81 procedures on patients with partial rotator cuff tears. In total, the study included 102 patients with 115 treated shoulders, 81 of which were osteoarthritic shoulder joints; patient characteristics were described separately for the subset of patients with partial rotator cuff tears. Median age was 60 years and 65% were male. Mean follow-up time could not be determined from the information provided. For the primary outcomes of interest for this report, there were only data for 37% of shoulders available for DASH and 51% for NPS, suggesting substantial loss to follow-up and/or data quality concerns. The study was considered to be at high risk of bias (Appendix E).

No studies of allogenic stem cells for the treatment of partial rotator cuff tears were identified.

Results:

4.2.1.13 Autologous, non-culture-expanded stem cells

In the one cohort[57] identified, there was a statistically significant difference in function based on ASES (0-100 scale) and pain (VAS 0-10) between patients who received non-culture-expanded BMC-PRP and those receiving the PT program at 3 months based on mean differences calculated between groups. This difference was not seen for either outcome at 3 weeks (Table 32). Patients in the BMC-PRP group were 3.0 times as likely to decrease the frequency or dose of their medication compared to patients in the PT group, however, this calculation did not reach statistical significance (p=0.09) (Table 33). In the registry study[21], the DASH (0-100 scale) score decreased (improved) by 19.1 (± 11.2) points from baseline to final follow-up (mean, 7.1 months) and the NPS (0-10) score decreased (improved) by 2.1 (± 2.5) from baseline to final follow-up (mean, 8.3 months). Baseline data for this subgroup of patients with partial rotator cuff tears was not reported and therefore significance could not be determined.

Table 32. Summary of function and pain outcomes in 1 comparative cohort (Kim 2018) of non-culture-expanded autologous cells for treatment of rotator cuff tears

	Function				Pain			
	ASES (0-100 [best])				VAS (0-10 [worst])			
	Mean ± SD		MD (95% CI)*	p-value†	Mean ± SD		MD (95% CI)*	p-value
Follow-up	BMC + PRP (n=12)	PT (n=12)			BMC + PRP (n=12)	PT (n=12)		
Baseline	39.4 ± 13.0	45.9 ± 12	-6.5 (-17.1 to 4.1)	0.216	5.8 ± 1.9 vs.	5.7 ± 1.6	0.1 (-1.39 to 1.59)	0.890
3 weeks	54.5 ± 11.5	56.3 ± 12.3	-1.8 (-11.9 to 8.3)	0.715	2.3 ± 0.8 vs.	3.6 ± 2.3	0.08 (-2.76 to 0.16)	0.078
3 months	74.1 ± 8.5	62.2 ± 12.2	11.9 (3.0 to 20.8)	0.011	1.9 ± 0.7 vs.	3.7 ± 1.8	-1.8 (-2.96 to -0.64)	0.004

ASES = American Shoulder and Elbow Surgeons score; BMC = bone marrow concentrate; CI = confidence interval; MD = mean difference; PRP = platelet rich plasma; PT = physical therapy; SD = standard deviation; VAS = visual analogue scale
* Mean differences and 95% CIs calculated by AAI using the means and SDs provided by the authors.

Table 33. Proportion of patients changing frequency or dose of medication at 3 months in 1 comparative cohort (Kim 2018) of non-culture-expanded autologous cells for treatment of rotator cuff tears

	% (n/N)		RR (95% CI)	p-value†
	BMC + PRP (n=12)	PT (n=12)		
Decreased use	50% (6/12)	17% (2/12)	3.0 (0.75 to 12.0)	0.09
Increased Use	8% (1/12)	25% (3/12)	0.33 (0.04 to 2.8)	0.284
Remained the same	42% (5/12)	58% (7/12)	0.71 (0.31 to 1.63)	0.424

BMC = bone marrow concentrate; CI = confidence interval; PRP = platelet rich plasma; PT = physical therapy; RR = risk ratio
* Risk ratios, 95% Cis, and p-values calculated by AAI

4.3 Key Question 2: Harms and complications

Knee Osteoarthritis

Key Points

Autologous, non-culture-expanded stem cells

- In addition to all five RCTs and the one cohort study included for efficacy/effectiveness, one single-arm registry (BMC with and without lipoaspirate) and 14 case series (mix of bone marrow-derived, adipose-derived, and peripheral blood-derived stem cells) that met inclusion criteria reported safety outcomes following non-culture-expanded stem cell therapy for knee OA.

- While the number of serious AEs reported (to include death) appears to be low across four RCTs, three case series, and one registry, the evidence is insufficient to draw firm conclusions; the longest follow-up period was 12 months.
- Non-serious pain and/or swelling and effusion at the injection site were common across the RCTs and case series (to include the registry study); pain and/or swelling were the most common AEs reported in the registry study (SOE Low).
- Results should be interpreted cautiously given study limitations and small sample sizes.

Autologous, culture-expanded stem cells

- In addition to all five RCTs included for efficacy, five case series (6 publications) (mix of bone marrow-derived MSCs and adipose-derived stromal vascular fraction) that met inclusion criteria reported safety outcomes following culture-expanded stem cell therapy for knee OA.
- While the number of serious AEs reported (to include death) appears to be low across four RCTs and three case series, evidence is insufficient to draw firm conclusions; the longest follow-up period was 48 months in one RCT.
- Non-serious treatment-related adverse events were common following culture-expanded SCT. Across three RCTs, the vast majority of SCT recipients experienced one or more treatment-related AE (range, 67% to 100%) compared to 8% to 24% of patients in the control groups (placebo, conservative care) (SOE Low). Knee joint pain was reported in 45% and 50% of SCT patients in two RCTs (compared with 0% to 10% for controls) and ranged from 23% to 60% across 4 case series (SOE Low). Almost all events were reported to be mild and transient.
- Results should be interpreted cautiously given study limitations and small sample sizes.

Allogenic, culture-expanded stem cells

- Only the two included RCTs reported safety outcomes following allogenic, culture-expanded stem cell therapy for knee OA and the evidence is insufficient to draw firm conclusions regarding the safety.
    - No serious AEs were reported in one small RCT at moderately high risk of bias.
    - Across both RCTs, injection site pain, effusion and/or swelling were common with SCT (40% to 53%), however evidence compared with an active comparator (HA), is limited to one small trial at moderately high risk of bias.

Results:

All 12 RCTs (across 14 publications) included for efficacy[20,30,32,36,55,59,60,64,65,99,105,106,119,126] and one of the nonrandomized comparative cohorts included for effectiveness (of autologous non-cultured stem cells)[35] also reported safety outcomes following stem cell therapy for knee OA. In addition, a total of 18 case series (across 20 publications) that reported on adverse events and met inclusion criteria were

identified; all evaluated autologous stem cell therapy for knee OA including 13 studies of non-cultured[4,5,14,37,48,49,56,76,87,90,107,116,129] and six studies (across 7 publications) of cultured[6,8,77,78,94,112,113] stem cell therapy.

4.3.1.1 Autologous, non-culture-expanded stem cells

Randomized controlled trials

All five trials evaluating autologous, non-cultured stem cell therapy for knee OA reported on safety (Table 34). No serious treatment-related adverse events (AEs) or serious AEs were reported in either group across four trials[20,99,105,106,119] with follow-up periods up to 12 months to include all-cause mortality in two trials.[99,119] One trial reported persistent popliteal fluid accumulation (requiring aspiration) and swelling and grinding of the knee with pain that occurred in one patient each (4%, 1/26) following BMC injection.[20] Two cases (8%, 2/26; one case each in the high and low dose groups) of possible infection in the AD-SVF group at day 3 were reported in another trial, compared with none in the placebo group.[119] A variety of other non-serious and primarily expected AEs following stem therapy were reported across the trials and were somewhat more common compared with controls (placebo, HA), including pain or swelling at the injection site (3 trials)[20,36,119] and effusion (1 trial)[105,106]; most events were transient and resolved without additional intervention. Only one trial reported safety related to BM harvesting with no AEs (including pain) in its population.[36]

Table 34. Adverse events reported by RCTs evaluating autologous, non-culture-expanded stem cell therapy for knee OA.

Outcome	Author,* (Source, Cell type), time frame	Risk (n/N); RR (95% CI)
Serious treatment-related AE or serious AE	**Centeno 2018**; N=48, BMC vs. exercise, timing unclear **Ruane 2019**; N=34, BMC vs. HA, 12 months **Shapiro 2017/2018**; N=50 knees, BMC vs. placebo, 12 months **Tucker 2019**; N=39, AD-SVF vs. placebo, 12 months	None reported in any RCT
All-cause mortality	**Ruane 2019**; N=34, BMC vs. HA, 12 months **Tucker 2019**; N=39, AD-SVF vs. placebo, 12 months	None reported in either RCT
Persistent popliteal fluid accumulation requiring aspiration	**Centeno 2018**; N=48, BMC vs. exercise, timing unclear	4% (1/26) vs. NR
Swelling and grinding with pain		4% (1/26) vs. NR
Infection (non-serious)	**Tucker 2019**; N=39, AD-SVF vs. placebo, 12 months	8% (2/26) [1 case each in high and low dose groups] vs. 0% (0/13)
MRI abnormalities		No cases reported through 12 months
Pain or swelling at injection site (non-serious)	**Centeno 2018**; N=48, BMC vs. exercise, timing unclear [Pain]	62% (16/26) vs. NR
	Goncars 2017; N=56, BM-MNC vs. HA, 12 months [Pain or Swelling]	NR; "common" and transient, no additional treatment required
	Tucker 2019; N=39, AD-SVF vs. placebo, 12 months [Swelling]	4% (1/26) [occurred in high dose group; n=13] vs. 0% (0/13)
Effusion (non-serious)	**Shapiro 2017/2018**; N=50 knees, BMC vs. placebo, 12 months	1 wk: 60% (15/25 knees) vs. 24% (6/25 knees); RR 2.5 (1.2–5.4) 6 mos.: 12% (3/25 knees) vs. 8% (2/25 knees); RR 1.5 (0.3–8.2) 12 mos.: 8% (2/25 knees) vs. 4% (1/25 knees); RR 2.0 (0.2–20.7)
Warmth (non-serious)		1 case (4%) at 6 months, unclear to which group knee was randomized
Erythema; abnormal ROM (non-serious)		No cases reported at 6 or 12 months
Nausea and vomiting (non-serious)	**Ruane 2019**; N=34, BMC vs. HA, 12 months	6% (1/17) vs. 0% (0/17)
AEs from injection or BM harvesting (to include pain)	**Goncars 2017**; N=56, BM-MNC vs. HA, 12 months	No events reported for either outcome

AD-SVF = adipose stromal vascular fraction; AE = adverse event; BM = bone marrow; BMC = bone marrow concentrate; BM-MNC = bone marrow mononuclear cells; HA = hyaluronic acid; mos.= months; MRI = magnetic resonance imaging; NR = not reported; OA = osteoarthritis; RCT = randomized control trial; ROM = range of motion; RR = risk ratio; wks.= weeks.

Cohort studies

One comparative cohort study reported that patients experienced swelling, pain and stiffness during the first few days after the BM-MSC injection.[35] Bone pain was reported by twelve patients (46%; n=26) during the stimulation with granulocyte colony stimulating factor (given for 3 consecutive days before the treatment). The authors report that no other clinical complications were seen; no information on AEs in the control group (acetaminophen) was provided.

Case series

A total of 14 case series (N range, 11 to 121) evaluating autologous non-cultured stem cell therapy for the treatment of knee OA that met inclusion criteria were identified (Table 35).[4,5,14,37,48,49,56,76,87,90,94,107,116,129]; two series had a substantial overlap in patient populations.[48,49] No serious AEs were reported by three studies (total N=115) using varying stem cell therapies (AD-SVF, BM-MSC, and BM-MNC).[37,76,129] An additional six studies (total N=209) reported that no AEs or complications occurred in their patient populations; four studies evaluated AD-MSC and two BM-MSCs or MNC.[14,48,49,87,90,116] No cases of infection were reported across six studies (total N=111) of primarily adipose-derived stem cells (three studies of AD-MSCs and one study each of AD-SVF, whole fat injection, and peripheral blood stem cells).[4,5,14,48,49,129] One small study (N=13) reported no incidences of the following treatment-related AEs: fat embolism, deep venous thrombosis, sepsis due to intra-articular infection, adhesion of the knee associated with AD-SVF injection, intra-articular bleeding at the injection site or reduced knee range of motion.[129] Additionally, one study each reported no cases of neurovascular complications (following whole fat injection)[4]; tumor formation (following AD-MSC injection)[14]; and allergic skin reaction (following BMC injection).[76]

Pain and/or swelling at the injection site were commonly reported treatment-related AEs across seven studies (Table 35).[4,5,37,56,76,107,129] Across the three studies that provided data, the frequency of pain was 81% (n=70) and 41% (n=75 knees) and swelling was 59% (n=30) and 92% (n=75 knees) in two studies evaluating BMC and BM-MSC injections, respectively[4,56,76]; in the third study, the frequency of swelling was 17% (n=30) following percutaneous whole fat injection.[4] Of the five patients in the latter trial, two required aspiration to resolve the swelling. One trial in which patients received four consecutive BMC injections reported that grinding, popping, snapping and stiffness were also commonly reported AEs.[107] Four trials reported AEs associated with the harvest site. Two studies reported that pain at the harvest site (iliac spine for BMC and lower abdomen for SD-SVF) was common[107,129] while a third reported that no patient complained of pain following iliac crest puncture for BMA.[37] A forth study evaluating whole fat injections reported that three patients (10%) had a hematoma of the abdominal region, one of which was deemed an "important" complication with pain.

Table 35. Adverse events reported across case series assessing autologous, non-cultured-expanded stem cell therapy for knee OA

Outcome	Author	Mean age	Male	Stem Cell Type	Source	F/U (mos.)	% (n/N)
Severe adverse events	Yokota 2017	75	15%	SVF	AD	6	0% (0/13)
	Goncars 2019	54	50%	MNC	BM	Post-tx	0% (0/32)
	Oliver 2015*	60	31%	BMC	BM	3, 6	0% (0/70)
Any adverse event or complication	Rajput 2018	61	36%	MNC	BM	1, 3, 6, 12	0% (0/11)
	Themistocleous 2018	70	30%	MSCs	BM	mean 11	0% (0/121)
	Bui 2014	NR (adults)	NR	MSCs	AD	6	0% (0/21)
	Pintat 2017	43	53%	MSC	AD	6	0% (0/19)
	Hudetz 2017†	69	29%	MSC	AD	3,6,12	0% (0/17)
	Hudetz 2019†	NR (adults)	75%	MSC	AD	12	0% (0/20)
Pain at harvest site	Shaw 2018	68	33%	BMC	BM	3	"common"
	Yokota 2017	75	15%	SVF	AD	6	"common"
	Goncars 2019	54	50%	MNC	BM	Post-tx	0% (0/32)
Hematoma of the abdominal region (harvest site)	Adriani 2017	63	40%	ASC	AD	1 wk, 1, 3, 6, 12	10% (3/30)‡
Infection	Adriani 2017	63	40%	ASC	AD	1 wk, 1, 3, 6, 12	0% (0/30)
	Bui 2014	NR (adults)	NR	MSCs	AD	6	0% (0/21)
	Yokota 2017	75	15%	SVF	AD	6	0% (0/13)
	Hudetz 2017†	69	29%	MSC	AD	3,6,12	0% (0/17)
	Hudetz 2019†	NR (adults)	75%	MSC	AD	12	0% (0/20)
	Ahmad 2017	51	30%	PBSC	PB	12	0% (0/10)
Pain and swelling at injection site	Yokota 2017	75	15%	SVF	AD	6	"common"
	Ahmad 2017	51	30%	PBSC	PB	12	“common”
	Goncars 2019	54	50%	MNC	BM	Post-tx	“majority”
Swelling at injection site	Shaw 2018	68	33%	BMC	BM	3	"common"
	Adriani 2017	63	40%	ASC	AD	1 wk, 1, 3, 6, 12	17% (5/30)§

Outcome	Author	Mean age	Male	Stem Cell Type	Source	F/U (mos.)	% (n/N)
	Oliver 2015	60	31%	BMC	BM	3, 6	59% (41/70)
	Kim 2014	61	42%	MSC	BM	Mean 8.7	92% (69/75 knees)**
Pain at injection site	Kim 2014	61	42%	MSC	BM	Mean 8.7	41% (31/75 knees)**
	Oliver 2015	60	31%	BMC	BM	3, 6	81% (57/70)
Grinding, popping, snapping, stiffness	Shaw 2018	68	33%	BMC	BM	3	"common"
DVT; fat embolism; sepsis; intraarticular bleeding at injection sites; adhesion of the knee	Yokota 2017	75	15%	SVF	AD	6	0% (0/13) for all
Neurovascular complication	Adriani 2017	63	40%	ASC	AD	1 wk, 1, 3, 6, 12	0% (0/30)
Tumor formation	Bui 2014	NR (adults)	NR	MSCs	AD	6	0% (0/21)
Allergic skin reaction	Oliver 2015	60	31%	BMC	BM	3, 6	0% (0/70)
Fall	Shaw 2018	68	33%	BMC	BM	3	7% (1/15)

AD = adipose; BM = bone marrow; BMC = bone marrow concentrate; F/U = follow-up; MNC = mononuclear cells; mos. = months; OA = osteoarthritis; PBSC = peripheral blood stem cells; SVF = stromal vascular fraction; tx = treatment; wks. = weeks

*Authors listed neoplasm and thrombosis as possible SAEs

†Heavy cross over of patients between Hudetz 2017 and 2018

‡1 was deemed an important hematoma with pain, and the other two were deemed less important.

§Two patients required aspiration

**16% of patients in this study had their injection in combination with surgery.

††Unlikely to be treatment related.

In addition, one longitudinal analysis of registry data[19] which compared two groups of patients, those who received BMC plus PRP alone (n=616 procedures in 518 patients) versus those who received BMC plus PRP with the addition of lipoaspirate (n=224 procedures in 163 patients), for the treatment of knee OA which met inclusion criteria was identified. All patients received an injection of hypertonic dextrose solution 2 to 5 days prior to BMC injection. For further details regarding patient and study characteristics and for data comparing the two treatment groups, see Appendix F. For the purposes of this report this study was treated as a case series. Adverse events (AEs) appear to have been reported out of the total number of procedures rather than patients; it is unclear if patients could have had more than one event.

The frequency of any adverse event was 6.8% over a mean follow-up period of 17.7 months (range, 1-41 months); the majority of AEs were mild and due primarily to pain and swelling at the injection site (Table 36). Most AEs were deemed possibly related to either the procedure or the injected components; only nine and four events, respectively, were considered definitely related to treatment. Only three severe events were reported (0.4% overall; 5.3% of the 57 events); however, none were considered to be related to the study procedure or resulted in prolonged disability. Two deaths (0.2% overall) were reported, which are assumed to be included in the three "severe" outcomes reported by the authors, however it is unclear from the study and no further information is provided. Most AEs had resolved at the time of reporting (4.6% overall, 39 events; 68.4% of the 57 events) and 11 were still ongoing (1.3% overall; 19.3% of the 57 events). Of note, adverse events were assessed via postal survey and the response rate was not provided by the authors; however, the response rates for other outcomes measures ranged from 35% to 68% (effectiveness outcomes from non-RCTs of knee OA are not within the scope of this report). Given that the response rate for AEs is not reported it is unclear the impact that missing data may have on the reported frequencies of AEs.

Table 36. Adverse events following BMC and PRP with and without lipoaspirate for the treatment of knee OA from the registry study by Centeno et al. 2014

Adverse event*	No. of events	Frequency out of 840 total procedures	Frequency out of 57 total AEs
Any AE	57	6.8%	-------
Death†	2	0.2%	3.5%
Severe AE	3	0.4%	5.3%
Mild AE	40	4.8%	70.2%
Pain and Swelling	36	4.3%	63.2%
Neurologic, neoplasm, allergic reaction, cardiac, bleeding/hematoma	2 each	0.2% each	3.5% each
Skin reactions, renal	1 each	0.1% each	1.8% each
Definitely procedure-related	9	1.1%	15.8%
Definitely injectate-related	4	0.5%	7.0%
Possibly procedure-related	29	3.5%	50.9%
Possibly injectate-related	24	2.9%	42.1%

AE = adverse event; BMC = bone marrow concentrate; No. = number; OA = osteoarthritis; PRP = platelet rich plasma.
*Adverse events appear to have been reported out of the total number of procedures rather than patients; it is unclear if patients could have had more than one event.

†The authors do not indicate whether these deaths were included under "severe AEs" and do not provide further information regarding the causes of death.

4.3.1.2 Autologous, culture-expanded stem cells

Randomized controlled trials

All five trials evaluating autologous, cultured stem cell therapy for knee OA reported on safety (Table 37). Across four trials,[32,59,60,64,65] one serious AE was reported and occurred in the control group (4% [1/26]; knee infection following HA injection resulting in withdrawal from the trial).[65] All-cause mortality was reported by one trial with no deaths in either group (AD-MPC vs. HA).[65] A total of three severe, treatment-related AEs were reported after stem cell therapy across two trials. In one trial, two patients (10%; n=20) experienced pain and swelling for 4 weeks that resulted in significant impact on usual ADLs (one each in the single injection and the double injection AD-MSC groups).[32] In the second trial, one grade 3 infection was reported in a patient treated with BM-MSCs (5%; n=22) compared with no cases in the placebo group.[30]

The frequency of any treatment-related AEs was more common following stem cell therapy compared with controls as reported by three trials[30,59,60,64]; a fourth trial reported a high frequency of AEs following stem cell therapy but did not report AEs for the control group (conservative care),[32] Table 37. Two trials with 6 month follow-up reported primarily non-serious joint effusion, arthralgia, pain and/or injection site reactions (warmth, erythema) following stem cells versus placebo: 100% with BM-MSCs vs. 24% (RR 4.2, 95% CI 2.4 to 8.4)[30] and 67% with AD-MSCs vs. 8% (RR 8.0, 95% CI 1.2. to 54.5).[64] In the third trial, 45% of BM-MSC vs. 10% of HA patients experienced articular pain requiring anti-inflammatory therapy.[59,60] In the fourth trial,[32] non-serious treatment-related AEs, mostly mild discomfort and/or swelling post injection, were reported in almost all patients who received AD-MSCs; these AEs were self-limiting and controlled with analgesia and/or oral anti-inflammatory use. Of note, this trial randomized patients to two intervention groups, a single injection or two injections of AD-MSCs (second injection at 6 months); the authors report that the second injection of AD-MSCs was associated with a modest increase in reported moderate AEs compared with the initial injection (Table 37). Only the latter trial reported AEs associated with the cell harvesting procedure; mild, transient discomfort and bruising after lipo-harvest was commonly reported in the AD-MSC groups.[32]

Table 37. Adverse events reported by RCTs evaluating autologous, cultured-expanded stem cell therapy for knee OA

Outcome	Author, (Source, Cell type), time frame	Risk (n/N); RR (95% CI)
Serious treatment-related AE or serious AE	**Freitag 2019**; N=30, AD-MSC vs. UC*, 12 months **Lamo-Espinosa 2016/2018†**; N=30, BM-MSC vs. HA, 12 months **Lee 2019**; N=24, AD-MSC vs. placebo, 6 months **Lu 2019**; N=52, AD-MPC vs. HA, 12 months	0% (0/26) with AD-MPC vs. 4% (1/26) with HA [1 RCT, Lu 2019]; knee infection resulting in withdrawal from study. No serious AEs reported across the remaining 3 RCTs.
All-cause mortality	**Lu 2019**; N=52, AD-MPC vs. HA, 12 months	No deaths occurred.
Severe AE‡ (treatment-related)	**Freitag 2019**; N=30, AD-MSC vs. UC*, 12 months	10% (2/20) vs. NR; pain and swelling for 4 weeks with significant impact on ADLs; 1 patient each randomized to the single and double AD-MSC injection groups.
Treatment-related AE (any)	**Emadedin 2018**; N=47, BM-MSC vs. placebo, 6 months	100% (22/22) vs. 24% (6/25), RR 4.2 (2.1–8.4); see below for specifics
	Lee 2019; N=24, AD-MSC vs. placebo, 6 months	67% (8/12) vs. 8% (1/12); RR 8.0 (1.2–54.5); see below for specifics
	Freitag 2019; N=30, AD-MSC vs. UC*, 12 months	1 injection: 80% (8/10) vs. NR 2 injection (baseline): 90% (9/10) vs. NR 2 injection (6 months): 100% (10/10) vs. NR Mostly discomfort and/or swelling post-injection. AEs were self-limiting, requiring a period of unloading, analgesia and/or oral anti-inflammatory use.
Joint effusion (treatment-related)	**Lee 2019**; N=24, AD-MSC vs. placebo, 6 months	17% (2/12) vs. 8% (1/12); RR 2.0 (0.2–19.2)
Arthralgia (treatment-related)		50% (6/12) vs. 0% (0/12)
General disorders and administration site condition (treatment-related)	**Emadedin 2018**; N=47, BM-MSC vs. placebo, 6 months	14% (3/22) vs. 0% (0/25); all grade 2
Infections (treatment-related)		5% (1/22) vs. 0% (0/25); grade 3
Skin and subcutaneous tissue disorders (treatment-related)		0% (1/22) vs. 0% (1/25); grade 1
Musculoskeletal and connective tissue disorder (treatment-related)		Any: 82% (18/22) vs. 20% (5/25); RR 4.1 (1.8–9.2) Grade 1: 0% (0/22) vs. 4% (1/25) Grade 2: 77% (17/22) vs. 8% (2/25); RR 9.7 (2.5–37.2) Grade 3: 5% (1/22) vs. 8% (2/25); RR 0.6 (0.1–5.8)

Outcome	Author, (Source, Cell type), time frame	Risk (n/N); RR (95% CI)
Mild AE (NOS; treatment-related)	**Freitag 2019**; N=30, AD-MSC vs. UC*, 12 months	1 injection: 60% (6/10) vs. NR 2 injection (baseline): 50% (5/10) vs. NR 2 injection (6 months): 40% (4/10) vs. NR
Moderate AE (NOS; treatment-related)		1 injection: 10% (1/10) vs. NR 2 injection (baseline): 30% (3/10) vs. NR 2 injection (6 months): 60% (6/10) vs. NR
Discomfort and bruising after lipo-harvest (treatment-related)		% NR but was "commonly noted in the treatment group" (n=20); mild, resolved spontaneously
Articular pain, requiring anti-inflammatory therapy	**Lamo-Espinosa 2016/2018†**; N=30, BM-MSC vs. HA, 12 months	45% (9/20) vs. 10% (1/10); RR 4.5 (0.7, 30.7) Low dose 30% (3/10) [RR 3.0, 95% CI 0.4, 24.2; vs. HA] vs. High dose 60% (6/10) [RR 6.0, 95% CI 0.9, 41.2 vs. HA] BM-MSC
AE (any)§	**Lee 2019**; N=24, AD-MSC vs. placebo, 6 months	83% (10/12) vs. 58% (7/12); RR 1.4 (0.8–2.5)
	Lu 2019; N=52, AD-MPC vs. HA, 12 months	73% (19/26) vs. 54% (14/26), RR 1.4 (0.9–2.1); most commonly mild to moderate transient pain and swelling of injection-site joint

ADL = activities of daily living; AD-MPC = adipose-derived multiprogenitor cells; AD-MSC = adipose-derived mesenchymal stem cells; AD-SVF = adipose-derived stromal vascular fraction; AE = adverse event; BM = bone marrow; BM-MSC = bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; MRI = magnetic resonance imaging; NR = not reported; OA = osteoarthritis; UC = usual care; ROM = range of motion; RR = risk ratio.

*To include, simple analgesics, weight management and exercise

†Includes high and lose dose treatment groups

‡Authors define this differently than they do serious AEs. Serious = unexpected medical incident with requires hospitalization long-term disability life threatening or results in death

§Defined as any undesired medical incident that does not necessarily have a cause-and-effect relationship with the treatment.

Case series

A total of 6 small case series (across 7 publications) (N range, 10 to 50) evaluating autologous cultured stem cell therapy for the treatment of knee OA that met inclusion criteria were identified (Table 38).[6,8,77,78,94,112,113] No serious treatment-related or serious AEs were reported across three studies evaluating BM-MSCs or MNC and AD-SVF with follow-up periods of 12 to 24 months.[8,77,78,113] No cases of infection or thromboembolism following treatment with concentrated adipose tissue through 18 months were reported by a fourth study.[94] Two small studies reported a total of four patients with reactive synovitis causing swelling and pain; one patient (10%; 1/10) received an AD-SVF injection[8] and three (25%; 3/12) received BM-MSC injection.[77] In all cases, the events resolved with conservative management. Pain at the injection site/joint was a commonly reported treatment-related AE ranging from 23% to 50% of patients across three small studies (N=12 to 50) evaluating BM-MSCs or -MNCs.[6,77,112] Arthralgia, mostly mild, was also common following BM-MSC injection in one trial and was reported in nine patients total (60%; 9/15).[112] Mild joint swelling was reported in a small number patients across two small (n=15 and 20) trials; these same trials also reported "joint lock" which was transient and occurred in most patients in one trial[94] and only one patient (7%) in the other.[112] Only two small trials reported AEs associated with the cell harvesting procedure which included mostly mild, transient pain (27% [4/15] for BM and 10% [1/10] for AD-SVF extraction).[8,112] A number of other possibly treatment-related or otherwise unclear AEs were reported by two studies[77,112] (Table 38). In addition, these same studies reported several AEs not related to the study treatment which can be found in Appendix Table F19.

Table 38. Adverse events reported across case series assessing autologous, culture-expanded cell therapy for knee OA

Author	Mean age	Male	Stem Cell Type	Source	Cell Concentration (mean)	F/U (mos.)	% (n/N)
Treatment-related adverse events							
Serious adverse events							
Bansal 2017	58	60%	SVF	AD	1 x 10^6/ml	24	0% (0/10)
Orozco 2013/2014	49	50%	MSCs	BM	1.13 ± 0.21 x 10^9	12, 24	0% (0/12)
Soler 2015	58	60%	MNC	BM	1.13 ± 0.21x10e9	12	0% (0/50)
Pain at harvest site							
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	40.9 × 10^6 ± 0.4 × 10^6	12, 48	Mild: 20% (3/15) Moderate: 7% (1/15)
Bansal 2017	58	60%	SVF	AD	1 x 10^6/ml	24	10% (1/10)
Pain in injected joint (transient)							
Soler 2015	58	60%	MNC	BM	1.13 ± 0.21x10e9	12	50% (25/50)
Orozco 2013/2014	49	50%	MSCs	BM	1.13 ± 0.21 x 10^9	12	50% (6/12)
Al-Najar 2017	50	46%	MSCs	BM	30.5 x 10^6	48	23% (3/13)
Joint swelling							
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	40.9 × 10^6 ± 0.4 × 10^6	12, 48	Mild: 13% (2/15) Moderate: 0% (0/15)
Roato 2019	60	45%	MSCs	AD	31.220.000 ± 268.426	18	5% (1/20)
Joint lock							
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	40.9 × 10^6 ± 0.4 × 10^6	12, 48	Mild: 7% (1/15) Moderate: 0% (0/15)
Roato 2019	60	45%	MSCs	AD	31.220.000 ± 268.426	18	“Most patients”
Arthralgia							
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	40.9 × 10^6 ± 0.4 × 10^6	12, 48	Mild: 53% (8/15) Moderate: 7% (1/15)
Contusion							
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	40.9 × 10^6 ± 0.4 × 10^6	12, 48	Mild: 7% (1/15) Moderate: 0% (0/15)

Author	Mean age	Male	Stem Cell Type	Source	Cell Concentration (mean)	F/U (mos.)	% (n/N)
Synovitis / Synovial Effusion							
Bansal 2017	58	60%	SVF	AD	1 x 10^6/ml	24	10% (1/10)
Orozco 2013/2014	49	50%	MSCs	BM	1.13 ± 0.21 x 10^9	12	25% (3/12)*
Infection							
Roato 2019	60	45%	MSCs	AD	31.220.000 ± 268.426	18	0% (0/20)
Thrombo-embolism							
Roato 2019	60	45%	MSCs	AD	31.220.000 ± 268.426	18	0% (0/20)
Possibly treatment-related or otherwise unclear adverse events							
Abdominal pain							
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	$40.9 \times 10^6 \pm 0.4 \times 10^6$	12, 48	Mild: 7% (1/15) Moderate: 0% (0/15)
Dental infection							
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	$40.9 \times 10^6 \pm 0.4 \times 10^6$	12, 48	Mild: 0% (0/15) Moderate: 7% (1/15)
Upper respiratory tract infection							
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	$40.9 \times 10^6 \pm 0.4 \times 10^6$	12, 48	Mild: 7% (1/15) Moderate: 0% (0/15)
Ligament sprain							
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	$40.9 \times 10^6 \pm 0.4 \times 10^6$	12, 48	Mild: 7% (1/15) Moderate: 0% (0/15)
Muscle rupture							
Soler 2016	52 (median; range, 33-64)	40%	MSCs	BM	$40.9 \times 10^6 \pm 0.4 \times 10^6$	12, 48	Mild: 7% (1/15) Moderate: 0% (0/15)
Articular inflammation attributable to knee overloading							
Orozco 2013/2014	49	50%	MSCs	BM	1.13 ± 0.21 x 10^9	12	25% (3/12)
Ischiotibial tendonitis							
Orozco 2013/2014	49	50%	MSCs	BM	1.13 ± 0.21 x 10^9	12	8% (1/12)

Author	Mean age	Male	Stem Cell Type	Source	Cell Concentration (mean)	F/U (mos.)	% (n/N)
Low back pain							
Orozco 2013/2014	49	50%	MSCs	BM	$1.13 \pm 0.21 \times 10^9$	12	25% (3/12)
Pain in contralateral knee							
Orozco 2013/2014	49	50%	MSCs	BM	$1.13 \pm 0.21 \times 10^9$	12	8% (1/12)

AD = adipose; BM = bone marrow; F/U = follow-up; ml = milliliters; MNC = mononuclear cells; mos. = months; MSCs = mesenchymal stem/stromal cells; OA = osteoarthritis.
*Authors reported this AE to be possible treatment-related, but we have reported it here as a treatment related AE.

4.3.1.3 Allogenic, culture-expanded stem cells

Randomized controlled trials

Both trials evaluating allogenic stem cell therapy for knee OA reported on safety (Table 39). No serious adverse events were report in one trial comparing BM-MSC vs. HA over 12 months.[126] No cases of ectopic mass or internal organ impairments over 6 months of follow-up were noted in another small trial comparing PL-MSC with placebo; follow-up was likely too short to capture rare events.[55] Across both trials, non-serious, treatment-related pain, effusion and/or swelling at the injection site were common following stem cell therapy; the frequency was similar when BM-MSCs (53%) were compared with HA (60%) in one trial[126] while only patients who received PL-MSCs reported events (40% vs. 0% with placebo) in the second trial,[55] (Table 39); the AEs were transient and controlled with simple analgesics.

Table 39. Adverse events reported by RCTs evaluating allogenic, culture-expanded stem cells for knee OA.

Outcome	Author, (Source, Cell type), time frame	Risk (n/N); RR (95% CI)
Serious treatment-related AE or serious AE	**Vega 2015**; N=30, BM-MSC vs. HA, 12 months	No SAEs were reported.
Ectopic mass; internal organ impairment	**Khalifeh Soltani 2019**; N=20, PL-MSC vs. placebo, 6 months	No cases of either AE reported over 6 months.
Pain, effusion and/or swelling at injection site (non-serious)	**Khalifeh Soltani 2019**; N=20, PL-MSC vs. placebo, 6 months	40% (4/10) vs. 0% (0/10); self-limiting, resolved within 48-72 hours
	Vega 2015; N=30, BM-MSC vs. HA, 12 months	53% (8/15) vs. 60% (9/15), RR 0.9 (0.5–1.7); transient and controlled with ibuprofen

AD-SVF = adipose-derived stromal vascular fraction; AE = adverse event; BM = bone marrow; BMC = bone marrow aspirate concentrate; BM-MNC = bone marrow-derived mononuclear cells; HA = hyaluronic acid; MRI = magnetic resonance imaging; NT = not reported; OA = osteoarthritis; ROM = range of motion; RR = risk ratio.

Hip Osteoarthritis

Key Points

- There is insufficient evidence to draw firm conclusions regarding the safety of autologous stem cell therapies for treatment of hip OA based on one registry study of non-cultured cells which had no treatment comparison and one case series of cultured cells. All were considered at high risk of bias.

4.3.1.4 Autologous, non-culture-expanded stem cells

One registry study of non-culture expanded cells from BMA[17] and the one retrospective case series of culture expanded cells from BMA[67] provided limited information on harms. Both studies were previously

described in section 0 on effectiveness. No serious adverse events were observed in either study. The case series also reported that no patient experienced complications due to the harvesting procedure and provided no further information on harms[67].
The registry study reported that 6.1% (12/196) of patients experienced at least 1 AE.[17] Results are poorly reported and described in terms of numbers of events (no clear denominator was provided). Authors report that only 1 AE considered to be likely related to the procedure, 8 were possibly related, and 3 were unlikely to be related. Authors report six pain and swelling events and two skin reaction events. The denominator for reported events is unknown. Patients included in this study appear to be included in a larger safety-specific registry study[22] by the same authors. Results of this study can be found in section 0.

No studies evaluating the safety of autologous culture-expanded or allogenic stem cells for treatment of hip OA were identified.

Degenerative Disc Disease

Key Points

- There is insufficient evidence to draw conclusions regarding the safety of autologous or allogenic stem cell therapy for treatment of chronic LBP due to DDD.
    - Harms and serious adverse events were sparsely reported and not well described across studies
    - Sample sizes precluded detection of rare events

4.3.1.5 Autologous, culture-expanded and non-culture-expanded stem cells and allogenic, culture-expanded stem cells

Across included studies of stem cell therapy for chronic low back pain due to DDD or for IVD repair, adverse events and harms were sparsely reported precluding firm conclusions regarding safety. Table 40. While adverse events were not observed in the included studies, it was not clear what specific events were considered or monitored and small sample sizes would have precluded identification of rare events. Only one case series followed patients beyond 12 months; the risk of harms specific to the use of stem cells is unclear, particularly over the long term.

Table 40. Summary of reported harms and adverse events in studies of stem cell therapy for nonradicular low back pain due to DDD or for IVD repair

Outcome	Author, (Source, Cell type), time frame	Risk (n/N)
Autologous Stem Cells (Not expanded)	**Case series**	
Serious treatment-related AE or serious AE	Pettine 2015, N= 26(BMA, MSC), 36 months Comella 2017, N=15 (Adipose + PRP), 12 months	None reported in either series;
Second injection	Pettine 2015, N=26(BMA, MSC)	6 months: 7.7% (2/26)
Infection	Comella 2017, N- 15 (Adipose + PRP), 12 months	No incidence of infection
Autologous Stem Cells (Culture expanded)	**Case series**	
Serious treatment-related adverse events	Kumar 2017, N=10 (Adipose, MSCs +HA), 12 months Orozco 2011, N=10 (BMA, MSC), 12 months	None reported in either series
Allogenic (Culture expanded)	**RCT**	
Serious AE	Noriega 2017, N=24 (BMA, MSC vs. sham), 12 months	MSC (n= 12): 0% vs Sham (n =12): 0%
Pain requiring opioids		MSC (n= 12): 8.3% (1/12) vs. Sham (n =12): 8.3% (1/12)
Minor pain (NSAID use)		MSC (n= 12): 25% (1/12) vs. Sham (n =12): 66.6%(8/12)

AE = adverse event; BMA = bone marrow aspirate, HA = hyaluronic acid; MSC = mesenchymal stem cells; PRP= platelet risk plasma; NR = not reported; TDR = total disc replacement; N/A= not applicable; NSAID = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial

No studies evaluating the safety of allogenic, non-culture-expanded stem cells for treatment of degenerative disc disease were identified.

Tendinopathy

Key Points

- There is insufficient evidence to draw firm conclusions regarding the safety of autologous non-expanded stem cells for treatment of tendinopathy based on data from one RCT of adipose stromal vascular fraction (SVF) versus PRP and one case series of BMAC combined with PRP for treatment of elbow tendinopathy.

4.3.1.6 Autologous, non-culture-expanded stem cells

Reporting of adverse events was limited in the two included studies of autologous non-culture-expanded stem cell treatment for tendinopathy. Studies have been previously described in section 0.

Neither study described what specific AEs they would evaluate. The RCT[125] of SVF versus PRP for Achilles tendinopathy reported that no serious adverse events were observed in either group, however 25% (5/21) SVF recipients experienced hematoma and cutaneous discomfort at the site adipose tissue harvest site. No adverse events were observed in the case series of BMAC for elbow tendonitis[125].

No studies evaluating the safety of autologous culture-expanded or allogenic stem cells for treatment of tendinopathies were identified.

Anterior Cruciate Ligament Tear

Key Points

- There is insufficient evidence to draw firm conclusions regarding the safety of autologous, non-culture expanded stem cell therapy for treatment of ACL tears based on one high risk of bias registry study which had no treatment comparison.
- No studies evaluating allogenic stem cell therapy for treatment of ACL tears that met inclusion criteria were identified.

4.3.1.7 Autologous, non-culture-expanded stem cells

One small (N=23), previously described registry study[18] (see section 0) of non-culture-expanded autologous MSCs, from BMC for the treatment of ACL tears reported that 4.3% (1/23) of patients experienced swelling at the injection site and 4.3% (1/23) of patients experienced a vasovagal episode; both complications resolved on their own. Patients included in this study were treated between December 2011 and May 2015 and therefore some patients may also be included in a larger safety-specific registry study[22] completed by the same author group. The larger safety-specific registry study included patients with any condition who were treated between December 2005 and September 2014; results of this study can be found in section 0.

No studies evaluating the safety of autologous culture-expanded or allogenic stem cells for treatment of ACL tears were identified.

Partial Rotator Cuff Tear

Key Points

- There is insufficient evidence to draw firm conclusions regarding the safety of autologous, non-culture-expanded stem cell therapies for treatment of partial rotator cuff tears based on one moderately high risk of bias comparative cohort study.
- No studies evaluating allogenic stem cell therapy for treatment of partial rotator cuff tears that met inclusion criteria were identified.

4.3.1.8 Autologous, non-culture-expanded stem cells

One previously described prospective cohort study[57] of patients treated with autologous non-culture-expanded BMC, containing MSCs reported that there were no complications during bone marrow aspiration or injection of BMC-PRP, and no complications in the 3-month follow-up period. 25% (3/12) of patients in the PT group experienced increased pain during the exercises and 17% (2/25) of patients in the BMC-PRP group experienced pain immediately after injection. In all cases, patients' pain was transient and subsided after taking an NSAID.

No studies evaluating the safety of autologous culture-expanded or allogenic stem cells for treatment of partial rotator cuff tears were identified.

Mixed Populations

Key Points

- There is insufficient evidence to draw firm conclusions regarding the safety of autologous, non-culture-expanded stem cell therapies for treatment of various musculoskeletal conditions based on two registry studies (from the same author group) and three case series. All studies were considered to be at high risk of bias.
- There is insufficient evidence to draw firm conclusions regarding the safety of autologous, culture-expanded stem cell therapies for the treatment of various musculoskeletal conditions based on one registry study considered to be at high risk of bias.
- No studies evaluating allogenic stem cell therapy for treatment of various musculoskeletal conditions that met inclusion criteria were identified.

Detailed Analysis

One large industry-funded registry study[22] (N=2372 patients) that assessed the safety of autologous MSCs, derived from BMC for the treatment of various orthopedic conditions that met the inclusion criteria was identified. Three different treatment protocols were assessed: autologous non-culture-expanded BMC + PRP + PL (1590 patients with 1949 injections), autologous non-culture-expanded BMC + PRP + PL + fat graft (247 patients with 364 injections), and autologous cultured-expanded BMC alone (535 patients with 699 injections). As part of all three protocols, patients received an intra-articular pre-treatment injection of hyper-dextrose solution (prolotherapy) two to 5 days prior to the stem cell treatment as an irritant to stimulate inflammatory healing response. The most commonly treated location was the knee, which was treated in 55%, 95%, and 52% of patients across the three groups, respectively. 23%, 2.4%, and 23% of patients received treatment to their hip across the three treatment groups, respectively. A small number of patients in each group received treatment to their foot/ankle, spine, shoulder, hand/elbow, and/or another location. Authors do not describe what conditions patients were treated for, only treatment location.

Patients in the BMC + PRP + PL group were followed for a mean of 13.2 months; 61% were male, mean age was 55.6 years and mean BMI was 26.2 kg/m^2. Patients in the BMC + PRP + PL + fat graft group were

followed for a mean of 21.6 months; 54% were male, mean age was 60 years and mean BMI was 27.1 kg/m^2. Patients in the culture-expanded BMC group were followed for a mean of 52.8 months; 54% were male, mean age was 53 years, and mean BMI was 26.2 kg/m^2. Several studies reported on previously, also appear to include patients that are included in this study.[18,19,21] In the BMC + PRP + PL and the BMC + PRP + PL + fat graft groups, patients generally received an injection containing between 0.2 and 1.5 × 10^8 nucleated cells. In the culture-expanded BMC group, patients generally received between 0.1 and 6 × 10^7 MSCs. No immunologic characterization of MSCs is described. Authors note that injectate volumes and dose were recorded, but not controlled and were determined by the treating physician.

Four additional studies assessing the safety of autologous non-culture-expanded stem cells for the treatment of various orthopedic conditions that met inclusion criteria were identified. Of these studies, three[21,96,101] have been described previously, and the fourth is a case series[82] (N=91 patients, 100 treated joints) of autologous adipose-derived MSCs + PRP + HA + CaCl2. 81% of all procedures were completed for patients with hip or knee OA. Patients were followed for a mean of 26.6 months. Mean age was 51 years and 50% of patients were males.

All studies included in this section were considered to be at high risk of bias.

Results:

4.3.1.9 Autologous, non-culture-expanded stem cells

Based on one large registry study and four case series/single arm treatment registries, adverse events as a result of autologous non-culture expanded stem cell treatment appear to be minimal. In the larger registry, incidence of serious adverse events (SAEs) was 0.3/100 person-years and 0.91/100 person-years, in the BMC + PRP + PL and BMC + PRP + PL groups, respectively. Across both groups, adverse events deemed definitely related to either the procedure or the stem cells themselves were reported in 1.4% (26/1837) and 0.43% (8/1837) of patients, respectively. The majority of adverse events were post-procedure pain or pain attributed to degenerative joint disease for which the treatment was sought. (Table 41)

Four additional studies assessing the safety of autologous non-culture-expanded stem cells for the treatment of various orthopedic conditions that met inclusion criteria were also identified. In general, the adverse events reported across these studies were mild, with many reporting that most patients experienced pain at the injection site. No severe adverse events were reported. Patients included in one of these studies[21] also appear to be included in a larger safety-specific registry study by the same authors.[22] Adverse events reported by these studies can be found in Table 42.

Table 41. Frequency, proportion, and incidence (per 100 person-years) of adverse events in patients treated for various orthopedic conditions with non-culture-expanded stem cells from a single treatment-specific registry study (Centeno 2016)

	Autologous non-culture-expanded BMC + PRP + PL			Autologous non-culture-expanded BMC + PRP + PL + fat graft		
	%	(n/N)	Incidence	%	(n/N)	Incidence
Total:	7.20%	(114/1590)	4.87	12.2%	(30/247)	6.79
SAE:	0.40%	(7/1590)	0.3	1.6%	(4/247)	0.91
Non-serious AE:	6.70%	(107/1590)	4.66	10.6%	(26/247)	5.89
Expected?						
Yes:	1%	(16/1590)	0.77	0.8%	(2/247)	0.45
No:	6.20%	(98/1590)	4.22	11.4%	(28/247)	6.34
Procedure-related?						
Definite:	1.30%	(21/1590)	0.9	2%	(5/247)	1.13
Possible:	3.50%	(55/1590)	2.44	6.1%	(15/247)	3.4
Not related or unlikely:	2.40%	(38/1590)	1.62	4.1%	(10/247)	2.33
Stem cells related?						
Definite:	0.40%	(7/1590)	0.3	0.4%	(1/247)	0.23
Possible:	2.40%	(39/1590)	1.77	4.9%	(12/247)	2.72
Not related or unlikely:	4.30%	(68/1590)	2.9	6.9%	(17/247)	3.99
Category						
Allergic:	0.40%	(6/1590)	0.26	0%	(0/247)	0
Cardiac:	0.20%	(3/1590)	0.13	1.2%	(3/247)	0.68
Gastrointestinal:	0.10%	(1/1590)	0.04	0%	(0/247)	0
Immune:	0.20%	(3/1590)	0.13	0%	(0/247)	0
Infection:	0.10%	(1/1590)	0.04	0.4%	(1/247)	0.23
Lab work:	0.10%	(2/1590)	0.09	0%	(0/247)	0
Neoplasm:	0.10%	(1/1590)	0.04	0%	(0/247)	0
Neurologic:	0.10%	(2/1590)	0.09	0.8%	(2/247)	0.45
Other:	0.70%	(11/1590)	0.47	0.8%	(2/247)	0.45
Pain-other area:	0.40%	(6/1590)	0.26	1.2%	(3/247)	0.45
Pain-post procedure:	2.30%	(37/1590)	1.58	4.5%	(11/247)	2.49
Pain-DJD:	1.90%	(30/1590)	1.28	2.4%	(6/247)	1.36
Renal:	0%	(0/1590)	0	0.4%	(1/247)	0.23
Rheumatological:	0.10%	(1/1590)	0.04	0%	(0/247)	0
Vascular:	0.50%	(8/1590)	0.34	0.4%	(1/247)	0.23

	Autologous non-culture-expanded BMC + PRP + PL			Autologous non-culture-expanded BMC + PRP + PL + fat graft		
	%	(n/N)	Incidence	%	(n/N)	Incidence
Skin:	0.10%	(2/1590)	0.09	0%	(0/247)	0
Endocrine, Pulmonary, Bone:	0%	(0/1590)	0	0%	(0/247)	0

AE = adverse event; BMC = bone marrow concentrate; DJD = degenerative joint disease; PL = platelet lysate; PRP = platelet rich plasma. SAE = serious adverse event.

Table 42. Additional case series evaluating the safety of autologous non-culture-expanded stem cells for the treatment of various orthopedic conditions

Author, year Mean follow-up N Intervention	Conditions treated	Adverse Events, % (n/N)
Centeno 2015* NR 102 patients (115 shoulders Autologous BMC + PRP + PL)	Shoulder OA: n=34 shoulders Rotator Cuff Tear: n=81 shoulders	• **Any AE**: 4.9% (5/102 patients) -**Pain**: 3% (3/102 patients) -**Cardiac event**: 1% (1/102 patients) -**Other**: 1% (1/102 patients)
Sampson 2016 4.9 months 125 patients Autologous BMC + PRP	Ankle OA: n=6 Knee OA: n=73 C-spine OA: n=5 Hip OA: n=14 Shoulder OA: n=18 Other OA: n=9	• **Any acute AE**: 0% (0/125) • **Any AE during the follow-up period**: 0% (0/87)†
Rodriguez Fontan 2018 13.2 months 19 patients (25 treated joints) Autologous BMC alone	Knee OA: n=7 (10 knees) Hip OA: n=13 (15 hips) (1 patient underwent a single hip and a single knee injection and therefore is included in both groups)	• **Major complication**: 0% (0/19 patients) • **Experienced at least 1 minor complication**: 57.9% (11/19 patients) -**Mild pain at BMC extraction site**: 15.8% (3/19 patients) -**Hip joint discomfort**: 36.8% (7/19 patients) -**Pain first 2 weeks after injection**: 26.3% (5/19patients)
Pak 2013 26.6 months 91 (100 treated joints) Autologous adipose-derived MSCs + PRP + HA + CaCl2	Knee OA: 74 procedures Hip OA: 7 procedures Hip AVN: 15 procedures Low back: 2 procedures Ankle: 2 procedures	- **Pain and swelling**: 37% (37/100 procedures) - **Tendonitis/Tenosynovitis**: 22% (22/100 procedures) - **Skin rash**: 1% (1/100 procedures) - **Infection**: 0% (0/100 procedures) - **Neurological event**: 1% (1/100 procedures) - **Tumor**: 0% (0/100 procedures)

AE = adverse event; BMC = bone marrow concentrate; HA = hyaluronic acid; MSCs = mesenchymal stem/stromal cells; PL = platelet lysate; PRP = platelet rich plasma; SAE = serious adverse event

*Patients included in this study also appear to be included in a larger safety-specific registry study by the same authors [22]

†Only 70% (87/125) of patients had follow-up data available

4.3.1.10 Autologous, culture-expanded stem cells

One large registry[22] study evaluating the safety of autologous culture-expanded bone marrow-derived MSCs for the treatment of multiple orthopedic conditions was identified. In the subgroup of patients treated with culture-expanded cells, the incidence of serious adverse events (SAEs) was 1.11/100 person-years. Adverse events deemed definitely related to either the procedure or the stem cells themselves were reported in 2.3% (12/535) and 0.4% (2/535) of patients, respectively. The majority of adverse events were post-procedure pain or pain attributed to degenerative joint disease for which the treatment was sought. (Table 43)

Table 43. Frequency, proportion, and incidence (per 100 person-years) of adverse events in patients treated for various orthopedic conditions with culture-expanded stem cells from a single treatment-specific registry study (Centeno 2016)

	Culture-expanded BM-MSCs		
	%	(n/N)	Incidence
Total:	34.2%	(181/535)	7.79
SAE:	4.7%	(25/535)	1.11
Non-serious AE:	30.2%	(160/535)	6.89
Expected?			
Yes:	4%	(21/535)	0.9
No:	30.2%	(160/535)	6.89
Procedure-related?			
Definite:	2.3%	(12/535)	0.52
Possible:	10.6%	(56/535)	2.41
Not related or unlikely:	21.4%	(113/535)	4.99
Stem cells related?			
Definite:	0.4%	(2/535)	0.09
Possible:	8.1%	(43/535)	1.85
Not related or unlikely:	25.7%	(136/535)	5.86
Category			
Allergic:	0.9%	(5/535)	0.22
Bone:	0.2%	(1/535)	0.04
Cardiac:	0.4%	(2/535)	0.09
Endocrine:	0.8%	(4/535)	0.17
Gastrointestinal:	0.4%	(2/535)	0.09
Immune:	1.1%	(6/535)	0.26
Infection:	0.8%	(4/535)	0.17

	Culture-expanded BM-MSCs		
	%	(n/N)	Incidence
Lab work:	0.9%	(5/535)	0.22
Neoplasm:	1.1%	(6/535)	0.26
Neurologic:	1.9%	(10/535)	0.43
Other:	2.6%	(14/535)	0.6
Pain-other area:	1.5%	(8/535)	0.34
Pain-post procedure:	8.5%	(45/535)	1.94
Pain-DJD:	10.2%	(54/535)	2.33
Pulmonary:	0.4%	(2/535)	0.09
Renal:	0.6%	(3/535)	0.13
Rheumatological:	0%	(0/535)	0
Skin:	0.9%	(5/535)	0.22
Vascular:	0.9%	(5/535)	0.22

AE = adverse event; BM-MSC = bone marrow-derived mesenchymal stem cells; DJD = degenerative joint disease; SAE = serious adverse event

4.4 Key Question 3: Differential efficacy, effectiveness, or harms

No studies evaluating differential efficacy or harms were identified.

4.5 Key Question 4: Cost-effectiveness

No studies evaluating cost-effectiveness were identified.

5 Strength of Evidence (SOE)

5.1 Strength of Evidence Summary: Knee OA

Strength of Evidence Summary for Key Question 1: Efficacy Results for Autologous, Non-Culture-Expanded Stem Cell Therapy for Knee Osteoarthritis

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
Function outcomes								
KOOS ADL (0-100, higher score = better function)	3, 6 mos.	1 RCT (N=30 at 3 mos.; N=28 at 6 mos.) Ruane 2019	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	MD in change scores: 3 mos.: 2.9 (–9.3, 15.0) 6 mos.: 3.2 (–9.6, 16.0) Conclusion: No difference between groups; sample sizes were small and CIs were wide.	⊕◯◯◯ INSUFFICIENT
	12 mos.	2 RCTs (N=83) Goncars 2017 Ruane 2019	Yes[1] (-1)	No	No	Yes[4] (-2)	Pooled MD in change scores: 3.8 (–3.8, 11.4); I^2=0% Conclusion: No difference between groups; sample size was small and CI was wide. Individually, no difference between groups was seen in either trial and CIs were wide.	⊕◯◯◯ INSUFFICIENT
KOOS Sport (0-100, higher score = better function)	3, 6 mos.	1 RCT (N=30 at 3 mos.; N=28 at 6 mos.) Ruane 2019	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	MD in change scores: 3 mos.: –0.6 (–20.6, 19.4) 6 mos.: 3.3 (–18.1, 24.6) Conclusion: No difference between groups; sample sizes were small and CIs were wide.	⊕◯◯◯ INSUFFICIENT
	12 mos.	2 RCTs (N=83) Goncars 2017 Ruane 2019	Yes[1] (-1)	No	No	Yes[4] (-2)	Pooled MD in change scores: 13.0 (0.9, 25.2); I^2=0%	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
							Conclusion: Greater improvement in function with stem cells vs. HA; however, sample size was small and CI was wide and approached zero. Individually, no difference between groups was seen in either trial and CIs were wide.	
KOOS Symptoms (0-100, higher score = better symptomology)	3, 6 mos.	1 RCT (N=30 at 3 mos.; N=28 at 6 mos.) Ruane 2019	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	MD in change scores: 3 mos.: 3.5 (–8.4, 15.4) 6 mos.: 1.9 (–10.0, 13.7) Conclusion: No difference between groups; sample sizes were small and CIs were wide.	⊕◯◯◯ INSUFFICIENT
	12 mos.	2 RCTs (N=83) Goncars 2017 Ruane 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	Pooled MD in change scores: 0.69 (–16.3, 17.7); I^2=83% Conclusion: No difference between groups; sample size was small, CI was wide, and there was substantial heterogeneity in the pooled analysis. Individually, neither trial found a statistical difference between groups however, the point estimates went in opposite directions.	⊕◯◯◯ INSUFFICIENT
KSS Function and Knee scores	3 mos.	1 RCT (N=46 for KSS function; N=45 for KSS Knee) Centeno 2018	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	KSS Function (mean change): 7.5 vs. 2.3, p=0.17 KSS Knee (mean change): 12 vs. 0.6, p<0.001 Conclusion: Greater improvement in function following stem cell therapy versus exercise plus usual care for the KSS Knee score but not the KSS Function score.	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
	12 mos.	1 RCT (N=56) Goncars 2017	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	KSS Function (mean change): 38.3 vs. 17.5, p=NS KSS Knee (mean change): 25.4 vs. 10.7, p=NS <u>Conclusion</u>: No difference between groups for either outcome; a measure of variability was not provided.	⊕◯◯◯ INSUFFICIENT
Pain Outcomes								
KOOS Pain and VAS Pain† (0-100, lower score = less pain)	3 mos.	4 RCTs (N=182)‡ Centeno 2018 Goncars 2017 Ruane 2019 Shapiro 2017/2018 (50 knees)‡	Yes[1] (-1)	No	No	Yes[4] (-1)	Pooled MD in change scores: –3.7 (–7.9, 0.7); I^2=0% <u>Conclusion</u>: No difference between groups; CI is wide. Results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ Low
	6, 12 mos.	3 RCTs (N=134)‡ Goncars 2017 Ruane 2019 Shapiro 2017/2018 (50 knees)‡	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	Pooled MD in change scores: 6 months: –5.7 (–17.4, 5.3); I^2=85% 12 months: –6.5 (–20.4, 6.8); I^2=87% <u>Conclusion</u>: No difference between groups in pooled analyses at 6 and 12 months; CIs were wide and there was substantial heterogeneity. Individually only one trial (Goncars 2017) reached statistical significance favoring stem cells (at 6 and 12 months). Results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ Low

ADLs = activities of daily living; CI = confidence interval; KSS = Knee Society Clinical Rating System; KOOS: Knee injury and Osteoarthritis Outcome Score; MD = mean difference; mos. = months; NS = not statistically significant; RCT = randomized controlled trial; SoE = strength of evidence; VAS = visual analog scale.

*Stem cell type vs. control group for included RCTs:
Centeno 2018: Bone marrow concentrate (BMC) (+ platelet rich plasma [PRP] and platelet lysate [PL]) vs. Home Exercise (i.e., functional strengthening, resistance training, monitor alignment for core, pelvis and entire lower extremity, balance/neuromuscular training, aerobic activity based on what the patient had available [e.g., walk, stationary bike, etc.] and manual therapy and mobility as needed). Patients in the BMC group received post-treatment injections of PRP, hydrocortisone, and doxycycline and were given prescribed a therapeutic exercises consisting of deep water emersion walking or jogging followed by stationary bike, and then elliptical, as well as core training, non-resistance hip and knee strengthening as pain allowed.
Goncars 2017: Bone marrow derived mononuclear cells (BM-MNCs) vs. Hyaluronic Acid (HA)
Ruane 2019: Bone marrow concentrate (BMC) (+ platelet rich plasma [PRP]) vs. Hyaluronic Acid (HA; Gel-One® Hyaluronate)
Shapiro 2017/2018: Bone marrow concentrate (BMC) (+ platelet poor plasma [PPP]) vs. Placebo (saline)
Tucker 2019: Adipose-derived stromal vascular fracture (AD-SVF) vs. Placebo (saline)
†Centeno 2018 and Shapiro 2017/2018 reported pain according to the VAS pain scale and Goncars 2017 and Ruane 2019 reported pain according to the KOOS pain scale; results were pooled across these two pain measures.
‡The trial by Shapiro et al. enrolled patients with bilateral knee OA; results are given out of 50 knees (in 25 patients).

Reasons for downgrade:
1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Question 1: Efficacy Results for Autologous, Culture-Expanded Stem Cell Therapy for Knee Osteoarthritis

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
Function outcomes								
"Success": WOMAC total (0-96)	6, 12 mos.	2 RCTs (N=81) Freitag 2019 (N=29) Lu 2019 (N=52)	Yes[1] (-1)	Yes[2] (-1) (differing cut-offs for success)	No	Yes[4] (-1)	**WOMAC total [Lu 2019]** ***20% improvement***: • 6 mos.: 58% (15/26) vs. 42% (11/26); RR 1.4 (0.8, 2.4) • 12 mos.: 54% (14/26) vs. 50% (13/26); RR 1.1 (0.6, 1.8) ***50% improvement***: • 6 mos.: 23% (6/26) vs. 8% (2/26); RR 3.0 (0.7, 13.5) • 12 mos.: 35% (9/26) vs. 4% (1/26); RR 9.0 (1.2, 66.1) ***70% improvement:*** • 6 mos.: 12% (3/26) vs. 0% (0/26), p=0.07 • 12 mos.: 19% (5/26) vs. 4% (1/26); RR 5.0 (0.6, 39.9) **WOMAC total – MCID 8 points [Freitag 2019]** • 12 mos.: 95% (18/19) vs. 20% (2/10); RR 4.7 (1.4, 16.4) <u>Conclusion</u>: Results varied depending on the cut-off used for "success".	⊕◯◯◯ INSUFFICIENT
"Success": WOMAC physical function (0-68)	3, 6 mos.	1 RCT (N=43) Emadedin 2018	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	**WOMAC function – MCID 9.3 points** • 3 mos: 58% (11/19) vs. 42% (10/24); RR 1.4 (0.8, 2.6) • 6 mos: 74% (14/19) vs. 54% (13/24); RR 1.4 (0.9, 2.1) **WOMAC function – PASS (cut-off not defined)**	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
							• 3 mos: 26% (5/19) vs. 4% (1/24); RR 6.3 (0.8, 49.6) • 6 mos: 37% (7/19) vs. 13% (3/24); RR 2.9 (0.9, 9.9) Conclusion: No difference between groups (BM-MSCs vs. placebo) reached statistical significance. Small sample sizes likely played a factor in the findings.	
"Success": KOOS ADL, Sport, Symptoms subscales (all 0-100)	12 mos.	1 RCT (N=29) Freitag 2019	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	**KOOS Subscales – MCID 8 points** • **ADLs**: 84% (16/19) vs. 30% (3/10); RR 2.8 (1.1, 7.4) • **Sport**: 89% (17/19) vs. 30% (3/10); RR 3.0 (1.1, 7.8) • **Symptoms**: 68% (13/19) vs. 30% (3/10); RR 2.3 (0.8, 6.2) Conclusion: More patients who received AD-MSCs compared with conservative care met the criteria for "success" according to the KOOS ADL and Sport, but not the Symptoms, scales.	⊕◯◯◯ INSUFFICIENT
WOMAC total (0-96, lower score = better function)	3 mos.	4 RCTs (N=124) Emadedin 2018 Freitag 2019 Lamo-Espinosa 2016/2018 Lee 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** –7.9 (–20.7, 4.3), I^2=92% **Pooled MD (Excluding outlier,‡ n=94):** –14.4 (–19.7, –9.2), I^2=0% **MD (Lee 2019, n=24; Lower RoB):** –15.0 (–25.3, –4.7) Conclusion: No difference between groups based on the overall pooled estimate; removal of one outlier trial may suggest improvement in function at 3 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes	⊕⊕◯◯ LOW

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
							and heterogeneity in populations and methods across trials.	
	6 mos.	5 RCTs (N=173) Emadedin 2018 Freitag 2019 Lamo-Espinosa 2016/2018 Lee 2019 Lu 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** –6.2 (–20.3, 6.2), I^2=89% **Pooled MD (Excluding outlier,‡ n=143):** –11.3 (–20.0, –4.8), I^2=38% **Pooled MD (Lee 2019 and Lu 2019, n=71; Lower RoB):** –10.1 (–24.4, 4.2), I^2=77% Conclusion: No difference between groups based on the overall pooled estimate; removal of one outlier trial may suggest improvement in function in 6 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes and heterogeneity in populations and methods across trials.	⊕⊕◯◯ LOW
	12 mos.	3 RCTs (N=106) Freitag 2019 Lamo-Espinosa 2016/2018 Lu 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** –8.2 (–28.8, 12.4), I^2=96% **Pooled MD (Excluding outlier,‡ n=76):** –15.3 (–36.1, 5.5), I^2=92% **MD (Lu 2019, n=47; Lower RoB):** –4.2 (–14.2, 5.7) Conclusion: No difference between groups at 12 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	48 mos.	1 RCT (N=25) Lamo-Espinosa 2016/2018	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-2)	**MD:** –10.3 (–15.4, –5.1)	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
							Conclusion: Insufficient evidence from one small, moderately high risk of bias RCT.	
WOMAC physical function (0-68, lower score = better function)	3 mos.	3 RCTs (N=95) Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** –4.1 (–14.7, 6.6), I^2=90% **Pooled MD (Excluding outlier,‡ n=65):** –9.0 (–13.7, –4.4), I^2=0% **MD (Lee 2019, n=24; Lower RoB):** –9.0 (–14.3, –3.8) Conclusion: No difference between groups based on the overall pooled estimate; removal of one outlier trial may suggest improvement in function at 3 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes and heterogeneity in populations and methods across trials.	⊕⊕◯◯ LOW
	6 mos.	4 RCTs (N=144) Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019 Lu 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** –3.6 (–14.8, 7.6), I^2=84% **Pooled MD (Excluding outlier,‡ n=114):** –8.9 (–18.7, 1.7), I^2=47% **Pooled MD (Lee 2019 and Lu 2019, n=71; Lower RoB):** –6.9 (–19.9, 6.0), I^2=64% Conclusion: No difference between groups at 6 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	12 mos.	2 RCTs (N=77)	Yes[1] (-1)	No	No	Yes[4] (-2)	**Pooled MD (All):** 1.4 (–5.5, 8.2), I^2=55%	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
		Lamo-Espinosa 2016/2018 Lu 2019					**MD (Lu 2019, n=47; lower RoB):** –2.5 (–9.9, 4.8) Conclusion: No difference between groups based on the overall pooled estimate. Evidence from two small RCTs was insufficient to draw firm conclusions.	
WOMAC stiffness (0-8, lower score = better function)	3 mos.	3 RCTs (N=95) Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019	Yes[1] (-1)	No	No	Yes[4] (-1)	**Pooled MD (All):** –0.4 (–1.5, 0.4), I^2=0% **MD (Lee 2019, n=24; Lower RoB):** –1.0 (–2.5, 0.5) Conclusion: No difference between groups. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	6 mos.	4 RCTs (N=144) Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019 Lu 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** 0.1 (–1.5, 1.5), I^2=76% **Pooled MD (Lee 2019 and Lu 2019, n=71; Lower RoB):** –0.9 (–2.5, 0.6), I^2=50% Conclusion: No difference between groups. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	12 mos.	2 RCTs (N=77) Lamo-Espinosa 2016/2018 Lu 2019	Yes[1] (-1)	No	No	Yes[4] (-2)	**Pooled MD (All):** –0.1 (–0.4, 0.3), I^2=0% **MD (Lu 2019, n=47; lower RoB):** –0.5 (–1.5, 0.5) Conclusion: No difference between groups based on the overall pooled estimate. Evidence from two small RCTs was insufficient to draw firm conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
Pain outcomes								
"Success": WOMAC pain (scale unclear); **NRS pain** (0-10); **KOOS pain** (0-100)	3, 6 mos.	2 RCTs Emadedin 2018 (N=43) Freitag 2019 (N=29)	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	Emadedin: **WOMAC pain – MCID 9.7 points** • 3 mos.: 47% (9/19) vs. 38% (9/24); RR 1.3 (0.6, 2.5) • 6 mos.: 37% (7/19) vs. 29% (7/24); RR 1.3 (0.5, 3.0) **WOMAC pain – PASS (cut-off not provided)** • 3 mos.: 21% (4/19) vs. 29% (7/24); RR 0.7 (0.2, 2.1) • 6 mos.: 16% (3/19) vs. 25% (6/24); RR 0.6 (0.2, 2.2) Freitag: **NRS pain – MCID 1 point** • 12 mos.: 95% (18/19) vs. 40% (4/10); RR 2.4 (1.1, 5.1) **KOOS pain – MCID 8 points** • 12 mos.: 84% (16/19) vs. 10% (1/10); RR 8.4 (1.3, 54.6) Conclusions: Inconsistent results across trials and thresholds.	⊕◯◯◯ INSUFFICIENT
Mean difference in VAS pain (0-10, lower score = less pain)	3 mos.	4 RCTs (N=124) Emadedin 2018 Freitag 2019 Lamo-Espinosa 2016/2018 Lee 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** –1.0 (–2.6, 0.6), I^2=84% Conclusion: No difference between groups. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
	6 mos.	5 RCTs (N=173) Emadedin 2018 Freitag 2019 Lamo-Espinosa 2016/2018 Lee 2019 Lu 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All trials):** –1.9 (–2.6, –1.3), I^2=0% **Pooled MD (Lee 2019 and Lu 2019, n=71; Lower RoB):** –1.6 (–2.5, –0.7), I^2=0% Conclusion: Less pain following SCT compared with controls at 6 mos. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	12 mos.	3 RCTs (N=106) Freitag 2019 Lamo-Espinosa 2016/2018 Lu 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** –2.3 (–3.8, –1.0), I^2=76% Conclusion: Less pain following SCT compared with controls at 12 mos. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕⊕◯◯ LOW
	48 mos.	1 RCT (N=25) Lamo-Espinosa 2016/2018	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	**MD:** –4.5 (–5.4, –3.6) Conclusion: Insufficient evidence from one small, moderately high risk of bias RCT.	⊕◯◯◯ INSUFFICIENT
Mean Difference in WOMAC pain (0-20, lower score = less pain)	3 mos.	3 RCTs (N=95) Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** –1.7 (–4.5, 1.0), I^2=90% **Pooled MD (Excluding outlier,‡ n=65):** –2.7 (–5.1, –0.4), I^2=80% Conclusion: No difference between groups based on the overall pooled estimate; removal of one outlier trial may suggest improvement in pain at 3 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes	⊕⊕◯◯ LOW

Outcome	Time	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI)† Findings	Quality (SoE)
							and heterogeneity in populations and methods across trials.	
	6 mos.	4 RCTs (N=144) Emadedin 2018 Lamo-Espinosa 2016/2018 Lee 2019 Lu 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** –1.5 (–4.3, 1.0), I^2=83% **Pooled MD (Excluding outlier,‡ n=114):** –2.4 (–4.4, –0.4), I^2=65% **Pooled MD (Lee 2019 and Lu 2019, n=71; Lower RoB):** –2.8 (–6.9, 1.4), I^2=82% Conclusion: No difference between groups based on the overall pooled estimate; removal of one outlier trial may suggest improvement in pain at 6 months. However, results should be interpreted cautiously given the small number of trials with small sample sizes and heterogeneity in populations and methods across trials.	⊕⊕◯◯ LOW
	12 mos.	2 RCTs (N=77) Lamo-Espinosa 2016/2018 Lu 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	**Pooled MD (All):** 0.01 (–2.1, 2.1), I^2=66% Conclusion: No difference between groups. However, results should be interpreted cautiously given the small number of trials with small sample sizes.	⊕◯◯◯ INSUFFICIENT

ADLs = activities of daily living; CI = confidence interval; KOOS: Knee injury and Osteoarthritis Outcome Score; MCID = minimal clinically important difference; MD = mean difference; mos. = months; NRS = numerical rating scale; PASS = patient acceptable symptom state; RCT = randomized controlled trial; RR = risk ratio; SoE = strength of evidence; VAS = visual analog scale; WOMAC = Western Ontario and McMasters University Osteoarthritis Index.

*Stem cell type vs. control group for included RCTs:
Emadedin 2018: Bone marrow-derived mesenchymal stem cells (BM-MSCs) vs. Placebo (saline)
Freitag 2019: Adipose-derived mesenchymal stem cells (AD-MSCs) [2 groups, 1 and 2 injections] vs. Conservative Care (i.e., simple analgesics, weight management, and exercise)
Lamo-Espinosa 2018: Bone marrow-derived mesenchymal stem cells (BM-MSCs) [2 groups, high and low dose] + Hyaluronic Acid (HA) vs. HA alone
Lee 2019: Adipose-derived mesenchymal stem cells (AD-MSCs) vs. Placebo (saline)
Lu 2019: Adipose-derived mesenchymal progenitor cells (AD-MPC; Rejoin®) vs. Hyaluronic Acid (HA)

†Risk ratios (95% confidence intervals) and pooled mean differences were calculated by AAI.
‡Lamo-Espinosa 2018. This trial tended to favor the control group (HA) while the other trials all tended to favor stem cells. The reason why is unclear although the following may have played a factor: patients in this trial received an injection of HA along with the BM-MSCs while no other injectates were used in conjunction with the stem cells in the other trials; this trial included a higher proportion of patients with grade IV OA (stem cells, 55% vs. HA, 40%) compared with the other trials (range across all patients, 0% to 16%).

Reasons for downgrade:
1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from "mild" to "substantial". If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for "mild/small" effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Question 1: Efficacy Results for Allogenic, Culture-Expanded Stem Cell Therapy for Knee Osteoarthritis

Outcome*	Time	Studies N (Treatments)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
Function: WOMAC total; Lequesne (0-100; lower score = better function)	3, 6, 12 mos.	1 RCT (N=30) Vega 2015 BM-MSCs vs. HA	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	MD (95% CI): **WOMAC total** • 3 months: –8.0 (–24.0, 8.0) • 6 months: –12.0 (–23.6, –0.4) • 12 months: –13.0 (–29.0, 3.0) **Lequesne** • 3 months: –4.0 (–15.6, 7.6) • 6 months: –15.0 (–26.6, –3.4) • 12 months: –12.0 (–23.9, –0.1) Conclusion: No differences between groups at 3 months but by 6 months, better function with BM-MSCs vs. HA; at 12 months, only the difference on the Lequesne was statistically significant favoring stem cells. Sample size was small and CIs were wide.	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies N (Treatments)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
WOMAC pain (0-100; lower score = less pain)							MD (95% CI): • 3 months: –10.0 (–23.1, 3.1) • 6 months: –11.0 (–24.1, 2.1) • 12 months: –14.0 (–28.8, 0.8) Conclusion: No difference between groups in WOMAC pain scores at any time point.	
VAS pain (0-100; lower score = less pain)	2-3 mos.	2 RCTs (N=50) Khalifeh Soltani 2019 (PL-MSCs vs. placebo) Vega 2015 (BM-MSCs vs. HA)	Yes[1] (-1)	No	No	Yes[4] (-2)	Pooled MD (95% CI): –10.0 (–26.4, 6.4); I^2=13% Conclusion: No difference between stem cells vs. controls in VAS pain scores through 3 months. Individually, neither trial found a significant difference between groups.	⊕◯◯◯ INSUFFICIENT
	6 mos.	2 RCTs (N=50) Khalifeh Soltani 2019 (PL-MSCs vs. placebo) Vega 2015 (BM-MSCs vs. HA)	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-1)	Pooled MD (95% CI): 0.72 (–34.5, 36.0); I^2=91% • BM-MSCs vs. HA: MD –18.0 (–36.1, 0.1) • PL-MSCs vs. placebo: MD 18.0 (6.8, 29.2) Conclusion: No difference between stem cells vs. controls in VAS pain scores at 6 months according to the pooled analysis; however, the confidence interval was wide and there was substantial heterogeneity. One trial found no statistical difference between groups (BM-MSCs vs. HA) while the other found that placebo resulted in less pain at 6 months compared with PL-MSCs; again, confidence intervals were wide.	⊕◯◯◯ INSUFFICIENT

Outcome*	Time	Studies N (Treatments)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
	12 mos.	1 RCT (N=30) Vega 2015 BM-MSCs vs. HA	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	MD (95% CI): –18.0 (–37.6, 1.6) Conclusion: No difference between groups in VAS pain scores at 12 months.	⊕◯◯◯ INSUFFICIENT

BM-MSC = bone marrow-derived mesenchymal stem cells; CI = confidence interval; HA = hyaluronic acid; MD = mean difference; PL-MSC = placenta-derived mesenchymal stem cells; RCT = randomized controlled trial; SAE = serious adverse events; SCT = stem cell therapy; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there is substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Question 2: Safety Results for Autologous, Culture-Expanded Stem Cell Therapy for Knee Osteoarthritis

Outcome	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
All-cause mortality	1 RCT (N=52) **Lu 2019**	No	Unknown[2]	No	Yes[4] (-2)	No deaths occurred in either group (AD-MPC vs. HA) over 12 months.	⊕◯◯◯ INSUFFICIENT
Serious Treatment-Related Adverse Events (SAEs)	**4 RCTs (N=136)** Freitag 2019 Lee 2019 Lamo-Espinosa 2016/2018, Lu 2019 **Case Series (N= 72)** Bansal 2017 Orozco 2013/2014 Soler 2015	Yes[1] (-1)	No	No	Yes[4] (-2)	**RCTS** 0% (0/26) with **AD-MPC** vs. 4% (1/26) with **HA** over 12 months; knee infection resulting in withdrawal [1 RCT, Lu 2019]. No serious AEs reported across the remaining 3 RCTs (N=84) over 6-12 months. "Severe" AE (pain and swelling impacting ADLs for 4 weeks): 10% (2/20) following AD-MSC injection vs. NR (for UC) [1 RCT, Freitag] **Case Series:** No serious AEs reported across 3 small series **Conclusion:** Samples sizes may have been inadequate to identify serious AEs uncommon or rare events; evidence is insufficient to draw firm conclusions.	⊕◯◯◯ INSUFFICIENT
Any treatment related AE	**3 RCTs (N=101)** Emadedin 2018 Lee 2019 Freitag 2019	Yes[1] (-1)	No	No	Yes[4] (-1)	**SCT vs. Placebo (N=71; 6 mos.)** 100% (22/22) vs. 24% (6/25), RR 4.2 (2.1–8.4) [Emadedin; BM-MSCs] 67% (8/12) vs. 8% (1/12); RR 8.0 (1.2–54.5) [Lee; AD-MSCs] **AD-MSCs vs. usual care (N=20, 12 mos.) [Freitag]†** 1 injection: 80% (8/10) vs. NR 2 injections (baseline): 90% (9/10) vs. NR 2 injections (6 months): 100% (10/10) vs. NR	⊕⊕◯◯ LOW

Outcome	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
						Conclusion: Across studies the vast majority of SCT recipients experienced one or more treatment related AEs; they were reported as not serious and time-limited	
Joint Pain; pain in injected joint	**2 RCTs (N=54)** Lee 2019 Lamo-Espinosa 2016/2018 **4 Case Series (N=90)** Soler 2016 Soler 2015 Orozco 2013/2014 Al-Jajar 2017	Yes[1] (-1)	No	No	Yes[4] (-1)	**RCTs** **AD-MSC vs. placebo (Lee, 6 mos.)** 50% (6/12) vs. 0% (0/12) **BM-MSC vs. HA (Lamo-Espinosa, 12 mos.)** 45% (9/20) vs. 10% (1/10); RR 4.5 (0.7, 30.7) [combined doses; all required anti-inflammatory treatment] Low dose 30% (3/10) [RR 3.0, 95% CI 0.4, 24.2; vs. HA] vs. High dose 60% (6/10) [RR 6.0, 95% CI 0.9, 41.2 vs. HA] **Case Series** Mild: 53% (8/15); Moderate: 7% (1/15) through 48 mos. [Soler 2016] Range (across all 4 series): 23% (3/13) to 50% (25/50), 12 to 48 mos. **Conclusion:** Joint pain is common with SCT.	⊕⊕◯◯ LOW
Effusion	**1 RCT (N=24)** Lee 2019 **Case series (N=22)** Bansal 2017 Orozco 2013/2014	Yes[1] (-1)	No	No	Yes[4] (-2)	**RCT:** **AD-MSCs vs. placebo (6 mos.):** 17% (2/12) vs. 8% (1/12); RR 2.0 (0.2–19.2) **Case series (12 to 24 mos.):** Range: 10% (1/10) to 25% (3/12) **Conclusion:** Joint effusion may be common; small sample sizes are noted.	⊕◯◯◯ INSUFFICIENT

Outcome	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
Musculoskeletal and connective tissue disorder (treatment-related	**1 RCT (N=47)** Emadedin 2018	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	**BM-MSCs vs. Placebo (6 mos.):** **Any**: 82% (18/22) vs. 20% (5/25); RR 4.1 (1.8–9.2) **Grade 1**: 0% (0/22) vs. 4% (1/25) **Grade 2**: 77% (17/22) vs. 8% (2/25); RR 9.7 (2.5–37.2) **Grade 3**: 5% (1/22) vs. 8% (2/25); RR 0.6 (0.1–5.8) **Conclusion**: Musculoskeletal and connective tissue problems (not further specified) were common; however, evidence is confined to one small RCT.	⊕◯◯◯ INSUFFICIENT
Infection (treatment-related)	**2 RCTs (N=99)** Emadedin 2018 Lu 2019 **Case series (N=20)** Roato 2019	Yes[1] (-1)	No	No	Yes[4] (-1)	**BM-MSCs vs. Placebo, 6 months (1 RCT, Emadedin)**: 5% (1/22) vs. 0% (0/25); grade 3 **AD-MPC vs. HA, 12 months (1 RCT, Lu 2019)** 0% (0/26) vs. 4% (1/26) No infections were reported in one case series. **Conclusion:** One infection occurred in each treatment group across two trials**;** in the SCT group it was a Grade 3 infection. Overall evidence is insufficient to draw conclusions.	⊕◯◯◯ INSUFFICIENT
Joint Swelling	2 case series (N=35) Soler 2016 Roato 2019	Yes[1] (-1)	Yes[2] (-1)	No	Yes[4] (-2)	Mild: 7% (1/15), Moderate: 0% (0/15) (Soler) Occurred in “most” patients (Roato) **Conclusion:** There is insufficient information from two small case series to draw conclusions.	⊕◯◯◯ INSUFFICIENT

ASC = adipose-derived stem cells (not otherwise specified); AD-MPCs = adipose-derived mesenchymal progenitor cells AD-MSCs = adipose-derived mesenchymal stem cells; AD-SVF = adipose derived stromal vascular fraction; AE = adverse events; BMC = bone marrow concentrate (from aspirate); BM-MNCs = bone marrow-derived mononuclear cells; BM-MSCs = bone marrow-derived mesenchymal stem cells; HA = hyaluronic acid; mo. = months; MSC = mesenchymal stem cell; NR = not reported; PBSC = peripheral blood stem cells (not otherwise specified); PL = platelet lysate; PRP = platelet rich plasma; RCT = randomized controlled trial; SAE = serious adverse events; wks. = weeks.

*Autologous stem cell type vs. control group for included studies:

- **Emadedin 2018 (RCT)**: BM-MSCs vs. Placebo (saline)
- **Freitag 2019 (RCT)**: AD-MSCs (2 groups, 1 and 2 injections) vs. Conservative Care (i.e., simple analgesics, weight management, and exercise)
- **Lamo-Espinosa 2018 (RCT)**: BM-MSCs (2 groups, high and low dose) + HA vs. HA alone
- **Lee 2019 (RCT)**: AD-MSCs vs. Placebo (saline)
- **Lu 2019 (RCT)**: AD-MPC (Rejoin®) vs. (HA)
- **Al-Jajar 2017 (case series)**: BM-MSCs
- **Bansal 2017 (case series)**: AD-SVF
- **Orozco 2013/2014 (case series)**: BM-MSCs
- **Roato 2019 (case series)**: Concentrated ASCs
- **Soler 2015 (case series)**: BM-MNCs
- **Soler 2016 (case series)**: BM-MNCs

†The trial by Freitag et al. included two intervention groups; one group received a single injection of AD-MSCs and the second group received two injections, the second of which was given at 6 months. Adverse events were reported for the latter group after only one injection (baseline) and then after the second injection (6 months). The authors report that the second injection was associated with a modest increase in reported moderate AEs in comparison to the initial injection.

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there are substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Question 2: Safety Results for Autologous, Non-Culture-Expanded Stem Cell Therapy for Knee OA

Outcome	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
All-cause mortality	**2 RCTs (N=60)** Ruane 2019 Tucker 2019 1 Registry Centeno 2014 (patients NR; authors report % based on 840 total procedures)	Yes[1] (-1)	No	No	Yes[4] (-2) RCTS (unknown for registry study)	There were no deaths due to any cause over 12 months as reported by 2 RCTs. Death was reported in 0.2% (n =2) of 840 procedures, 3.5% of 57 total AEs in the registry study **Conclusion**: Study limitations and small samples for comparative studies preclude formulation of firm conclusions.	⊕◯◯◯ INSUFFICIENT
Serious Adverse Events (SAEs)	**4 RCTs (N=121 and 50 knees)** Centeno 2018 Ruane 2019 Shapiro 2017/2018 (50 knees in 25 patients) Tucker 2019 **3 Case series (N=115)** Goncars 2019 Oliver 2015 Yokota 2017 **1 Registry:** Centeno 2014 (patients NR; authors report % based on 840 total	Yes[1] (-1)	No	No	Yes[4] (-2) RCTS (unknown for registry study)	No patient experienced a SAE as reported by 4 RCTs and 3 case series over follow-up periods up to 12 months and 6 months, respectively. Registry study: Severe AEs in 5.3% (3 events) of total AEs (n=57) were considered serious; SAEs occurred in 0.4% of 840 procedures. Authors report that none were due to the procedure or the injectate (i.e., stem cells + other biologics). **Conclusion**: SAE definition varied across studies as did reported adjudication. These factors combined with study limitations and small sample sizes preclude formulation of firm conclusions.	⊕◯◯◯ INSUFFICIENT

Outcome	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
	procedures; AEs from patient surveys)						
Neurologic, neoplasm, allergic reaction, cardiac, bleeding/hematoma	**1 Registry** Centeno 2014 (patients NR; authors report % based on procedures; AEs from patient surveys)	Yes[1] (-1)	Unknown	No	Unknown	Two of each event were reported; frequency was 0.2% for each (out of 840 procedures) or 3.5% for each (of 57 total AEs) **Conclusion**: While the risk of such events appears to be low, study limitations and unknown consistency across comparable studies preclude formulation of firm conclusions.	⊕◯◯◯ INSUFFICIENT
Pain and/or swelling at injection site	**3 RCTs (N=143)** Centeno 2018) Goncars 2017 Tucker 2019 **7 case series (N=170 and 75 knees)** *Pain (N=145)*: Kim 2014 Oliver 2015 *Swelling (N=115, 75 knees)*: Adriani Kim 2014 Oliver 2015 Shaw 2018 *Pain and Swelling (N=55)*:	Yes[1] (-1)	No	No	Yes[4] (-1) RCTS, case series (unknown for registry study)	**Pain or swelling (2 RCTs):** 62% (16/26) and 4% (1/26) swelling with grinding pain vs. NR for exercise (Centeno); "common" (Goncars, N=56) **Pain (2 case series):** 41% (31/75 knees) to 82% (57/70 patients) **Swelling (1 RCT, 4 case series):** 4% (1/26) vs. 0% (0/13) for placebo in one RCT (Tucker); 17% (5/30, 2 required aspiration), 59% (41/70), 90% (69/75 knees) across 3 case series; "common" reported in one case series. **Pain and swelling (3 case series, 1 registry):** described as "common" (2 series) or "majority" (1 series); 4.3% (out of 840 procedure), 63.2% of 57 AEs reported (1 registry).	⊕⊕◯◯ LOW

Outcome	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
	Yokota 2017 Ahmad 2017 Goncars 2019 **1 Registry** Centeno 2014 (patients NR; authors report % based on procedures; AEs from patient surveys)					**Conclusion**: Evidence from RCTs and case series suggest that pain and/or swelling at the injection site are common. These were the most common AEs in the registry study. Results should be interpreted cautiously given study limitations and small sample sizes.	
Effusion **Effusion requiring aspiration**	**2 RCTs (N=48; 50 knees)** Shapiro 2017/2018 (N=50 knees in 25 patients) Centeno 2018 (N=48)	Yes[1] (-1)	No	No	Yes[4] (-1)	**Effusion (Shapiro)** • 1 wk.: 60% (15/25 knees) vs. 24% (6/25 knees); RR 2.5 (1.2–5.4) • 6 mos.: 12% (3/25 knees) vs. 8% (2/25 knees); RR 1.5 (0.3–8.2) • 12 mos.: 8% (2/25 knees) vs. 4% (1/25 knees); RR 2.0 (0.2–20.7) **Effusion requiring aspiration (Centeno)** (timing unclear, 24 mo. f/u): 4% (1/26) vs. NR for exercise **Conclusion**: Joint effusion may be somewhat common however, sample sizes are small.	⊕⊕◯◯ LOW
Definitely and possibly injectate related AEs and procedure-related AEs	**1 Registry** Centeno 2014 (patients NR; authors report % based on 840 procedures, total	Yes[1] (-1)	Unknown	No	Unknown	**Definitely injectate related :** 0.5% out of 840 procedures; 7.0% out of 57 total AEs **Possibly injectate related:** 2.9% out of 840 procedures; 42.1% out of 57 total AEs	⊕◯◯◯ INSUFFICIENT

Outcome	Studies N (Treatments)*	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
	of 57 AEs; AEs from patient surveys)					**Definitely procedure related :** 1.1% out of 840 procedures; 15.8% out of 57 total AEs **Possibly procedure related:** 3.5% out of 840 procedures; 50.9% out of 57 total AEs: **Conclusion:** A large proportion of total AEs appear to be definitely or possibly linked to the injectate (detail not provided). It is assumed that patients may experience >1 AE	
Infection (non-serious)	**1 RCT (N=39)** Tucker 2019 **6 case series (N=111)** Adriani 2017 Ahmad 2017 Bui 2014 Hudetz 2017† Hudetz 2019† Yokota 2017	Yes[1] (-1)	No	No	Yes[4] (-2)	In the RCT, two patients (8%; 2/26), one in each AD-SVF group (high and low dose), had signs of a possible infection at 3 days post-injection compared with no placebo patient (0%; 1/13) No cases of infection were reported across 6 case series of primarily AD-derived stem cells. **Conclusion**: The total number of patients experiencing infection was low; however, study sample sizes are small.	⊕◯◯◯ INSUFFICIENT

ASC = adipose-derived stem cells (not otherwise specified); AD = adipose; AD-SVF = adipose derived stromal vascular fraction; AE = adverse events; BMC = bone marrow concentrate (from aspirate); BM-MNCs = bone marrow-derived mononuclear cells; BM-MSCs = bone marrow-derived mesenchymal stem cells HA = hyaluronic acid; mo. = months; MSC = mesenchymal stem cell; NR = not reported; PBSC = peripheral blood stem cells (not otherwise specified); PL = platelet lysate; PRP = platelet rich plasma; RCT = randomized controlled trial; SAE = serious adverse events; wks. = weeks.

*Autologous stem cell type vs. control group for included studies:

- **Centeno 2018 (RCT)**: BMC (+ PRP and PL) vs. Home Exercise (i.e., functional strengthening, resistance training, monitor alignment for core, pelvis and entire lower extremity, balance/neuromuscular training, aerobic activity based on what the patient had available [e.g., walk, stationary bike, etc.] and manual therapy and mobility as needed). Patients in the BMC group received post-treatment injections of PRP, hydrocortisone, and doxycycline and were given prescribed a therapeutic exercises consisting of deep water emersion walking or jogging followed by stationary bike, and then elliptical, as well as core training, non-resistance hip and knee strengthening as pain allowed.
- **Goncars 2017 (RCT)**: BM-MNCs vs. HA

- **Ruane 2019 (RCT)**: BMC (+ PRP) vs. HA (Gel-One® Hyaluronate)
- **Shapiro 2017/2018 (RCT)**: BMC (+ PPP) vs. Placebo (saline)
- **Tucker 2019 (RCT)**: AD-SVF vs. Placebo (saline)
- **Adriani 2017 (case series)**: ASC (percutaneous lipoaspirate injection)
- **Ahmad 2017 (case series)**: PBSC (peripheral blood injection)
- **Goncars 2019 (case series)**: BM-MNCs
- **Kim 2014 (case series):** BM-MSCs
- **Oliver 2015 (case series):** BMC
- **Shaw 2018 (case series):** BMC
- **Centeno 2014 (registry):** BMC (+ PRP and PL) with or without lipoaspirate.

†Hudetz 2017 and 2019 have substantial overlap in populations.

Reasons for downgrade:
1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there are substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

Strength of Evidence Summary for Key Question 2: Safety Results for Allogenic, Culture-Expanded Stem Cell Therapy for Knee Osteoarthritis

Outcome	Studies N (Treatments)	Serious risk of bias	Serious inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
Serious Treatment-Related Adverse Events (SAEs)	**1 RCT (N=30)** Vega 2015 BM-MSC vs. HA	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-2)	No SAEs were reported over 12 months. **Conclusion**: Evidence is insufficient from one small trial at moderately high RoB to draw conclusions regarding SAEs.	⊕◯◯◯ INSUFFICIENT
Pain, effusion and/or swelling at injection site (non-serious, transient, controlled with NSAID)	**2 RCTs (N=50)** Khalifeh Soltani 2019 (N=20, PL-MSC) Vega 2015 (N=30, BM-MSC)	Yes[1] (-1)	No	No	Yes[4] (-2)	**SCT vs. placebo (Khalifeh Soltani, 6 mos.)** 40% (4/10) vs. 0% (0/10); **SCT vs. HA (Vega, 12 mos.)** 53% (8/15) vs. 60% (9/15), RR 0.9 (0.5–1.7); **Conclusion**: Injection site pain, effusion and/or swelling were common with SCT, however evidence compared with an active comparator, is limited to one small trial precluding firm conclusions regarding the relative frequency of these AEs.	⊕◯◯◯ INSUFFICIENT

AE = adverse events; BM-MSC = bone marrow-derived mesenchymal stem cells; HA = hyaluronic acid; mos. = months; NSAID = non-steroidal anti-inflammatory drug; PL-MSC = placenta-derived mesenchymal stem cells; SAE = serious adverse events; SCT = stem cell therapy.

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there are substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

5.2 Strength of Evidence Summary: Degenerative Disc

Strength of Evidence Summary for Key Questions 1 and 2: Efficacy and Safety Results of Stem Cell Therapy for Nonradicular Low Back Pain due to DDD

Outcome	Studies N (Treatments)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
KQ 1. Efficacy: Allogenic, culture-expanded cells							
Function (Mean ODI, 0- 100 scale)	**1 RCT (N=24)** Noriega 2017 MSC vs. Sham	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	**MD (95%CI)** 3 month: 9 (–23.9, 6.0) 6 month: –10 (–28.7, 8.7) 12 month: –12 (–32.7, 8.7) **Conclusion**: No differences in function between allogenic MSC and sham at 3, 6 or 12 months; findings may in part be due to small sample size	⊕◯◯◯ INSUFFICIENT
Mean Pain (Mean VAS, 0-100 scale)		Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	**MD (95%CI)** 3 month: –3 (27.2, 21.2) 6 month: –11 –35.5, 13.5) 12 Month: 0 –27.3, 27.3) **Conclusion:** No difference in mean pain between allogenic MSC and sham at 3, 6 or 12 months; findings may in part be due to small sample size	⊕◯◯◯ INSUFFICIENT
KQ 2. Safety: Allogenic, culture-expanded cells							
Harms, Adverse events	**1 RCT (N=24)** Noriega 2017 MSC vs. Sham	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-2)	No major adverse events identified (types unspecified); fewer allogenic MSC recipients required NSAIDS (25% vs 66.6%) versus sham and 8.3% of both groups received opioids. **Conclusion:** Evidence is based one small RCT which is underpowered to detect rare adverse	⊕◯◯◯ INSUFFICIENT

Outcome	Studies N (Treatments)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
						events; firm conclusions regarding safety, particularly long-term or related to rare events are not possible.	
KQ 2. Safety: Autologous Cell Sources (case series only available)							
Harms, Adverse events	**5 case series** **Non-culture-expanded (N=51)** Pettine 2015 Comella 2017 Haufe 2006 **Culture-expanded (N=20)** Orozco 2011 Kumar 2017	Yes[1] (-1)	Unknown[2]	No	Yes[4] (-1)	**Non-expanded/not cultured cells** • No serious adverse events (treatment related or otherwise, 2 series) **Expanded/cultured cells** • No serious treatment related events (2 series) **Conclusion:** Evidence for safety is sparse and poorly reported; studies underpowered to detect adverse events; firm conclusions regarding safety, particularly long-term or related to rare events are not possible.	⊕◯◯◯ INSUFFICIENT

DDD = degenerative disc disease; IVD = intervertebral disc; MSC = mesenchymal stem cell; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial.

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there are substantial differences between study populations across studies.
3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade.

5.3 Strength of Evidence Summary: Tendinopathies

Strength of Evidence Summary for Key Questions 1 and 2: Efficacy and Safety Results of Autologous Non-Culture-Expanded Stem Cell Therapy for Achilles and Elbow Tendinopathy

Outcome	Studies N (Treatments)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
KQ 1. Efficacy							
Function: **VISA-A** (0-100 [best]) **AOFAS** (0-100 [best])	**1 RCT (N=44)** Usuelli 2018 Achilles tendinopathy	Yes[1] (-1)	Unknown[2]	No	Yes (-1)[4]	*SVF vs. PRP* **VISA-A (mean)*** 2 weeks: 43 vs. 43, NS 1 month: 59 vs. 47, NS 2 months: 66 vs. 59, NS 4 months: 70 vs. 65, NS 6 months: 71 vs. 71, NS **AOFAS (means)*** 2 weeks: 80 vs. 67, p<0.05 1 month: 80 vs. 72, NS 2 months: 85 vs. 79, NS 4 months: 80 vs. 80 NS 6 months: 87 vs. 87, NS **Conclusion**: No differences between SVF and PRP were seen except at 2 weeks for AOFAS. Evidence from this single small trial was considered insufficient to form firm conclusions.	⊕◯◯◯ INSUFFICIENT
Pain (mean VAS, 0-10 [worst]**)**		Yes[1] (-1)	Unknown[2]	No	Yes (-1)[4]	*SVF vs. PRP* **VAS (mean)*** 2 weeks: 2.5 vs. 4.4, p<0.0.5 1 month: 2.0 vs. 3.8, p<0.0.5 2 months: 1.8 vs. 2.5, NS 4 months: 2.0 vs. 3.0, NS 6 months: 1.8 vs. 1.8, NS	⊕◯◯◯ INSUFFICIENT

Outcome	Studies N (Treatments)	Serious Risk of Bias	Serious Inconsistency	Serious Indirectness	Serious Imprecision	Stem Cells vs. Controls Effect estimate (95% CI) Findings	Quality (SoE)
						Conclusion: Improvement in pain seen with SVF vs. PRP up to 1 month post intervention did not persist. Evidence from this single small trial was considered insufficient to form firm conclusions.	
KQ 2. Safety							
Harms, Adverse Events	**1 RCT (N=44)** SVF vs. PRP Usuelli 2018 Achilles tendinopathy **1 prospective case series (N=30)** BMC Singh 2014 Elbow tendinopathy	Yes[1] (-1)	Unknown[2]	No	Yes (-2)[4]	**SVF vs. PRP** No adverse events observed in either SVF or PRP groups up to 6 months 25% (5/21) of SVF patients complained of hematoma and cutaneous discomfort at the adipose tissue harvest site **BMC** No adverse events observed **Conclusion:** Evidence for safety is sparse and poorly reported. Evidence from the trial and case series was considered insufficient to form firm conclusions.	⊕◯◯◯ INSUFFICIENT

AOFAS = American Orthopedic Foot and Ankle Society Ankle-Hindfoot Score; BMC = bone marrow concentrate (from bone marrow aspirate); CS = case series; NR = not reported; NS = not statistically significant; PRP = platelet rich plasma; RCT = randomized controlled trial; SD = standard deviation; SVF = stromal vascular fraction; VAS = visual analogue scale; VISA-A = Victoria Institute of Sport Assessment – Achilles

*Data are all estimated from figures; p-values are for the MD between the two groups. No SDs were provided by the authors, thus the MD cannot be calculated

Reasons for downgrade:

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT (or cohort study) related to the outcome reported (see Appendix for details). All case series are considered to have serious risk of bias. Studies which did control for confounding via study design and/or statistical analyses (e.g. Adequate randomization and concealment, matching, multivariate regression, propensity matching) may not be downgraded for risk of bias depending other potential sources of bias (e.g. substantial loss to follow-up).
2. Inconsistency: differing estimates of effects across trials; if point estimates/effect size across trials are in the same direction, do not vary substantially or heterogeneity can be explained, results may not be downgraded for inconsistency. The consistency of single studies is unknown; evidence from single studies was not downgraded. Consistency may also be unknown if there are substantial differences between study populations across studies.

3. Indirect, intermediate or surrogate outcomes may be downgraded.
4. Imprecise effect estimate for an outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with the intervention may be downgraded; If sample size is likely too small to detect rare outcomes, evidence may be downgraded twice. If the estimate is statistically significant, it is imprecise if the CI ranges from “mild” to “substantial”. If the estimate is not statistically significant, it is imprecise if the CI crosses the threshold for “mild/small” effects. Wide (or unknown) confidence interval and/or small sample size may result in downgrade

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