Key Questions and Background

Stem Cell Therapy for Musculoskeletal Conditions

Background:
Stem cells are the basis of all tissues and organs in the body. Their ability to “self-renew” (i.e., they can 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. In general, the range of clinical conditions or diseases for which stem cells have proven to be effective is very small. 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. The use of cell-based therapy has been an active area of research for the treatment of musculoskeletal conditions.

Stem cell types are often described as embryonic stem cells (obtained at the earliest developmental stages) or tissue-specific (also referred to as adult or somatic stem cells). Tissue-specific stem cell preparations have been most commonly described related to the treatment of musculoskeletal conditions. Peripheral blood, umbilical cord blood, and bone marrow are common sources of one type of tissue-specific stem cells called hematopoietic stem cells which have been used for treatment of certain cancers and blood and immune system disorders. 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. MSCs have since been grown from other tissues such as adipose tissue, the amnion, Wharton’s jelly, and the umbilical cord as well as muscle, synovial membrane, tendons, and peripheral blood. MSCs are most commonly harvested via bone marrow aspirate for orthopedic applications described in peer-reviewed literature. Bone marrow aspirate may be “concentrated” using centrifugation to concentrate progenitor cells, stem cells, platelets, and growth factors and is referred to bone marrow aspirate concentrate (BMAC). BMAC, peripheral blood stem cells (PBSC) and minimally manipulated adipose-derived MSCs which have not been cultured or genetically modified have been most frequently used for musculoskeletal applications in outpatient settings.

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. 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.

The FDA regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) 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. 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 and clinicians must register their use.

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.

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 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?

**Scope: Summary of Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Study Component</th>
<th>Inclusion</th>
<th>Exclusion</th>
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</table>
| **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  
- 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 |
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<tr>
<th>Study Component</th>
<th>Inclusion</th>
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<tbody>
<tr>
<td>Outcomes</td>
<td>Primary Outcomes</td>
<td>Non-clinical outcomes</td>
</tr>
<tr>
<td></td>
<td>• Function (validated measures)</td>
<td>• Radiographic feature such as disc height</td>
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<tr>
<td></td>
<td>• Pain (validated measures)</td>
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<td></td>
<td>• Objectively measured medication use</td>
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<td>• Return to normal activities (sports, work, or activity)</td>
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<td>• Adverse events/harms</td>
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<td>Secondary or intermediate outcomes</td>
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<tr>
<td>Study Design</td>
<td>Focus on studies with the least potential for bias.</td>
<td>Indirect comparisons</td>
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<td>Key Questions 1-2:</td>
<td>Comparisons of different cell types, concentrations, preparations or procedures (except for safety)</td>
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<td></td>
<td>• High quality systematic reviews of randomized controlled trials (RCTs) will be considered</td>
<td>Incomplete economic evaluations such as costing studies</td>
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<td></td>
<td>• RCTs</td>
<td>Studies with fewer than 10 patients per treatment group; case series of &lt;10 patients</td>
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<td>• High quality, prospective non-randomized comparative studies</td>
<td>Case reports</td>
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<td>• 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 KQ 1</td>
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<tr>
<td>Setting</td>
<td>Outpatient setting, office setting</td>
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**Study Design**

**Key Questions 1-2:**

- 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 KQ 1

**Key Question 3:**

- RCTs which present results for both intervention and comparator such that they are stratified on patient or other characteristics of interest.

**Key Question 4:**

- Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.
### Study Component

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<th>Inclusion</th>
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<td>Studies published in English in peer reviewed journals or publically available FDA reports</td>
<td>Abstracts, editorials, letters</td>
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<td>Duplicate publications of the same study which do not report on different outcomes</td>
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<td>Single reports from multicenter trials</td>
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<td>Preliminary reports when results are published in later versions</td>
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<td>Patient testimonials</td>
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### Figure 1. Analytic framework

#### Patients
- Adults with cartilage defects, OA, joint-related conditions; muscle, ligament or tendon conditions, joint pain or pain due to degenerative disc disease

#### Intervention
- Stem cell therapy

#### Primary Clinical Outcomes
- Function
- Pain
- Conversion to THA
- Medication use
- Return to normal activity

#### Secondary outcomes
- Time to recovery
- Quality of life
- Recurrence
- Secondary procedures (e.g., surgery)

#### Harms or adverse events

#### Cost effectiveness

### Public comment and response

All comments received regarding the draft key questions have been published in a separate document.