



FEP Medical Policy Manual

FEP 8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)

Effective Policy Date: April 1, 2021

Related Policies:

Original Policy Date: December 2011

2.01.26 - Prolotherapy
2.01.98 - Orthopedic Applications of Platelet-Rich Plasma
7.01.48 - Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)

Description

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Mesenchymal stem cells (MSCs) have the capability to differentiate into a variety of tissue types, including various musculoskeletal tissues. Potential uses of MSCs for orthopedic applications include treatment of damaged bone, cartilage, ligaments, tendons, and intervertebral discs.

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OBJECTIVE

The objective of this evidence review is to evaluate whether the use of mesenchymal stem cells in conjunction with interventions for orthopedic conditions improves the net health outcome.

POLICY STATEMENT

Mesenchymal stem cell therapy is considered **investigational** for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.

Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix with stem cells, are considered **investigational** for all orthopedic applications.

Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered **investigational** for all orthopedic applications.

POLICY GUIDELINES

This policy does not address unprocessed allograft bone.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Stem cell injections are currently performed at select centers in the United States. Therefore, requests for it may be made for an out-of-network facility.

FDA REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, Title 21, parts 1270 and 1271. MSCs are included in these regulations.

The regulatory status of the stem cell or stem cell-containing products addressed in this review is summarized below.

Concentrated autologous MSCs do not require approval by the FDA. No products using engineered or expanded MSCs have been approved by the FDA for orthopedic applications.

The following products are examples of commercialized demineralized bone matrix (DBM) products. They are marketed as containing viable stem cells. In some instances, manufacturers have received communications and inquiries from the FDA related to the appropriateness of their marketing products that are dependent on living cells for their function. The following descriptions are from the product literature.

- AlloStem (AlloSource) is a partially demineralized allograft bone seeded with adipose-derived MSCs.
- Map3 (RTI Surgical) contains cortical cancellous bone chips, DBM, and cryopreserved multipotent adult progenitor cells (MAPC).
- Osteocel Plus (NuVasive) is a DBM combined with viable MSCs isolated from allogeneic bone marrow.
- Trinity Evolution Matrix™ (Orthofix) is a DBM combined with viable MSCs isolated from allogeneic bone marrow.
- Other products contain DBM alone and are designed to be mixed with bone marrow aspirate:

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- o Fusion Flex™ (Wright Medical) is a dehydrated moldable DBM scaffold (strips and cubes) that will absorb autologous bone marrow aspirate;
- o Ignite (Wright Medical) is an injectable graft with DBM that can be combined with autologous bone marrow aspirate.

A number of DBM combination products have been cleared for marketing by the FDA through the 510(k) process. FDA product code: MQV.

Table 1 provides a representative sample of these products; some of which are specifically labeled for mixing with bone marrow aspirate.

Table 1. Demineralized Bone Matrix Products Cleared by FDA

Product	Matrix Type	Mix With Autologous MSCs	Manufacturer or Sponsor	Date Cleared	510(k) No.
Vitoss Bioactive Foam Bone Graft Substitute	Type I bovine collagen	X	Stryker	Nov 2008	K083033
NanOss BVF-E	Nanocrystalline hydroxyapatite		Pioneer Surgical	Aug 2008	K081558
OrthoBlast II Demineralized bone matrix putty and paste	Human cancellous bone chips		SeaSpine	Sep 2007	K070751
CopiOs Bone Void Filler (sponge and powder disc)	Type I bovine dermal collagen	X	Kensey Nash	May 2007	K071237
DBX Demineralized bone matrix putty, paste and mix	Processed human bone and sodium hyaluronate	X	Musculoskeletal Transplant Foundation	Dec 2006	K053218
Integra MOZAIK™ Osteoconductive Scaffold-Putty	Human cancellous bone	X	IsoTis OrthoBiologics	Dec 2006	K062353
Formagraft™ Collagen Bone Graft Matrix	Bovine fibrillary collagen	X	R and L Medical	May 2005	K050789
DynaGraft II Gel and Putty	Processed human bone particles		IsoTis Orthobiologics	Mar 2005	K040419

FDA: U.S. Food and Drug Administration; MSCs: mesenchymal stem cells.

In 2020, the FDA updated their guidance on "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use."²

Human cells, tissues, and cellular and tissue-based products (HCT/P) are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

- "1) The HCT/P is minimally manipulated;
- 2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

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3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

4) Either:

i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and: a) Is for autologous use; b) Is for allogeneic use in a first-degree or second-degree blood relative; or c) Is for reproductive use."

The FDA does not consider the use of stem cells for orthopedic procedures to be homologous use.

RATIONALE

Summary of Evidence

For individuals who have cartilage defects, meniscal defects, joint fusion procedures, or osteonecrosis who receive stem cell therapy, the evidence includes small randomized controlled trials (RCTs) and nonrandomized comparative trials. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Use of MSCs for orthopedic conditions is an active area of research. Despite continued research into the methods of harvesting and delivering treatment, there are uncertainties regarding the optimal source of cells and the delivery method. Studies have included mesenchymal stem cells (MSCs) from bone marrow, adipose tissue, and peripheral blood. Overall, the quality of evidence is low and there is a possibility of publication bias. The strongest evidence to date is on MSCs expanded from bone marrow, which includes several phase 1/2 RCTs. Limitations in these initial trials preclude reaching conclusions, but the results to date do support future study in phase 3 trials. Alternative methods of obtaining MSCs have been reported in a smaller number of trials and with mixed results. Additional study in a larger sample of patients with longer follow-up would be needed to evaluate the long-term efficacy and safety of these procedures. Also, expanded MSCs for orthopedic applications are not U.S. Food and Drug Administration approved (concentrated autologous MSCs do not require agency approval). Overall, there is a lack of evidence that clinical outcomes are improved. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Rheumatology and Arthritis Foundation

In 2019, guidelines from the American College of Rheumatology and Arthritis Foundation on osteoarthritis (OA) of the hand, hip, and knee gave a strong recommendation against stem cell injections in patients with knee and/or hip OA, noting the heterogeneity in preparations and lack of standardization of techniques.²⁵ No recommendation was made for hand OA, since efficacy of stem cells has not been evaluated.

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American Academy of Orthopaedic Surgeons

A 2020 guideline from American Association of Orthopaedic Surgeons on the management of glenohumeral joint OA, endorsed by several other societies, states that injectable biologics such as stem cells cannot be recommended in the treatment glenohumeral joint OA.²⁶ There was consensus from the panel that better standardization and high-quality evidence from clinical trials is needed to provide definitive evidence on the efficacy of biologics in glenohumeral OA. The strength of evidence was rated as no reliable scientific evidence to determine benefits and harms.

The 2013 guideline on treatment of osteoarthritis of the knee does not address stem cell injections.²⁶

American Association of Neurological Surgeons

In 2014, the American Association of Neurological Surgeons guidelines on fusion procedures for degenerative disease of the lumbar spine relevant to this evidence review have indicated that "The use of demineralized bone matrix (DBM) as a bone graft extender is an option for 1- and 2-level instrumented posterolateral fusions. Demineralized Bone Matrix: Grade C (poor level of evidence)."²⁷

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
September 2012	Replace policy	Updated literature search, reference number 6 added; remaining references renumbered.
September 2013	Replace policy	Policy updated with literature review. References 4, 7, 11-16 and 18 added, renumbered and removed; addition of policy statement that allograft bone containing viable stem cells is considered investigational.
June 2014	Replace policy	Policy updated with literature review; references 5, 13, and 17 added; policy statements unchanged.
October 2015	Replace policy	Policy updated with literature review; references 3, 14, 16, 18, 20, and 22 added. Investigational statement added on bone graft substitutes that must be used with autologous blood or bone marrow aspirate. Policy title change: "Orthopedic applications of stem cell therapy (including allograft and bone substitute products used with autologous bone marrow)".
March 2018	Replace policy	Policy updated with literature review through November 29, 2017; references 1, 2, 4, 12-15, 24-25 and 27-29 added/updated. Policy statements unchanged. Title changed to "Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)."
March 2019	Replace policy	Policy updated with literature review through November 29, 2017; references 14 and 24 added; references 2 and 4 updated. Policy statements unchanged.
March 2020	Replace policy	Policy updated with literature review through November 19, 2019; references added. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through December 4, 2020; references added. Policy statements unchanged.

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