REGENERATIVE MEDICINE OF RAYNHAM LLC
PATIENT CLINICAL EVIDENCE SERIES

Wharton's Jelly & Umbilical-Cord-Derived Interventions

Clinical Evidence Review: Safety, Randomized Evidence, Meta-Analyses, Applicability & Limitations

Evidence Review | Current through September 2026

EXECUTIVE EVIDENCE SUMMARY

Human clinical evidence exists. Published research includes randomized controlled trials, systematic reviews and meta-analyses of umbilical-cord-derived mesenchymal stromal cell (UC-MSC) interventions for knee osteoarthritis.

The published short-term safety signal is generally favorable. Serious treatment-related complications have been uncommon or absent in the studies summarized here; reported reactions have most often been transient pain, swelling or effusion.

Efficacy findings are promising but mixed. Some meta-analyses and trials report improvements in pain and function, while other high-quality evidence shows smaller or non-significant differences versus comparators.

Applicability matters. Much of the higher-level evidence involves culture-expanded UC/WJ-derived MSCs. These interventions are not automatically equivalent to processed Wharton's Jelly tissue allografts.

EVIDENCE HIERARCHY USED IN THIS REVIEW

1 Safety	2 Systematic Reviews & Meta-Analyses	3 Randomized Human Trials	4 Tissue-Allograft Evidence
What adverse events have been reported?	What does pooled evidence show?	What have controlled trials found?	What most closely resembles tissue use?

This document is an educational evidence summary. It is not proof that any specific commercial product is safe or effective and does not replace individualized evaluation or informed consent.

1. Safety Profile in Published Human Research

Safety should be considered separately from efficacy. Across the human literature summarized below, serious treatment-related complications have generally been uncommon, while local post-injection reactions such as pain, swelling and effusion are reported more often. Longer-term and product-specific surveillance remains important.

SAFETY SYSTEMATIC REVIEW

Complications of Stem Cell-Based Injections for Knee Osteoarthritis: A Systematic Review

Riggle C, et al. HSS Journal. 2024. PMID 39564419.

Design	48 human studies; 1,924 patients receiving multiple stem-cell-based knee OA preparations, including umbilical/placental-derived interventions.
Findings	Overall transient adverse-event rate was 12.3%, most commonly swelling and injection-site pain. No infection, fat embolism or other medical complications were reported in the included studies.
Limitation	Heterogeneous preparations and study designs; not specific to one WJ product. Umbilical-cord-derived interventions had more transient local reactions than several other sources.
Applicability	Strong broad safety context; not product-specific.

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UC-MSC META-ANALYSIS

Regenerative Therapy in Osteoarthritis Using Umbilical Cord-Origin Mesenchymal Stem Cells

Lohrasbi E, et al. Stem Cells International. 2025. PMID 41378180.

Design	Systematic review/meta-analysis of 8 studies totaling 688 participants.
Findings	No serious treatment-related adverse events were reported; adverse events were described as mild, transient and manageable.
Limitation	Cell-based UC-MSC evidence; study heterogeneity and dose differences remain.
Applicability	Important UC-specific pooled safety evidence; indirect for processed WJ tissue allograft.

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WJ-SPECIFIC SYSTEMATIC REVIEW

Treatment of Knee Osteoarthritis and Chondral Injury with Umbilical Cord/Wharton's Jelly-Derived MSCs

Ishak-Samrin M, et al. J Funct Biomater. 2025;16(3):84. PMID 40137363.

Design	Six clinical studies; 97 patients and 134 knees; follow-up 3-48 months.
Findings	No serious adverse effects were reported. Reported events included pain/effusion; functional outcomes improved in several measures while radiologic outcomes were mixed.
Limitation	Small and heterogeneous evidence base; primarily WJ/UC-derived MSC interventions.
Applicability	WJ-specific human safety synthesis, but not proof of safety for every tissue-allograft product.

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SAFETY INTERPRETATION

Published human research supports a generally favorable short-term safety signal. A more precise statement than 'proven safe' is that serious treatment-related adverse events have been uncommon or absent in the studies summarized here, while transient local reactions are reported. Long-term and product-specific safety are not fully established.

2. Highest-Level Evidence: Systematic Reviews & Meta-Analyses

These publications are placed before individual trials because they synthesize multiple human studies. They also directly address a common misconception: randomized and pooled human evidence does exist for UC-MSC interventions in knee osteoarthritis.

SYSTEMATIC REVIEW + META-ANALYSIS

Effects of Umbilical Cord Mesenchymal Stem Cells in the Treatment of Knee Osteoarthritis

Xiao Z, et al. Medicine (Baltimore). 2024;103(46):e40490. PMID 39560593.

Design	Meta-analysis of 3 randomized controlled studies.
Findings	UC-MSC treatment significantly favored controls for WOMAC (MD -25.85; 95% CI -41.50 to -10.20; P=.001) and Lysholm score (MD +18.33; 95% CI 12.89-23.77; P<.00001).
Limitation	Only three RCTs were available; small evidence base and cell-based interventions.
Applicability	Direct evidence that randomized human UC-MSC trials exist; indirect for processed WJ tissue allograft.

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SYSTEMATIC REVIEW + META-ANALYSIS

Regenerative Therapy in Osteoarthritis Using Umbilical Cord-Origin Mesenchymal Stem Cells

Lohrasbi E, et al. Stem Cells International. 2025. PMID 41378180.

Design	8 studies; 688 participants.
Findings	Overall VAS reductions at 6 and 12 months were not statistically significant; WOMAC improved significantly at 6 months. Dose subgroup findings favored lower/medium doses. No serious treatment-related adverse events were reported.
Limitation	Heterogeneity, variable dosing and mixed efficacy findings.
Applicability	Useful balanced pooled evidence: favorable findings are present, but not all outcomes are statistically significant.

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SYSTEMATIC REVIEW

Umbilical Cord-Derived Stem Cells for the Treatment of Knee Osteoarthritis

Systematic review. Orthop J Sports Med. 2022. PMID 35859650.

Design	7 studies; 385 patients; mean follow-up 23.4 months.
Findings	Weighted WOMAC, ICRS, IKDC and VAS measures improved from pre- to post-treatment; no severe adverse reactions were recorded.
Limitation	Included evidence levels 1-4 and was not restricted to randomized comparisons; authors called for additional high-quality randomized studies.
Applicability	Useful UC-derived human evidence synthesis; indirect for a specific processed WJ allograft.

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WHAT THIS LEVEL OF EVIDENCE ESTABLISHES

It is inaccurate to characterize the field as having **no human evidence, no randomized trials, or no meta-analytic evidence**. It is equally important not to overstate these publications as proof that every Wharton's Jelly tissue product is effective.

3. Randomized Controlled Human Evidence

Randomized trials provide stronger protection against bias than uncontrolled observational studies. Their findings are not uniformly positive, which is precisely why they are important in a balanced clinical evidence review.

RANDOMIZED PHASE I/II

Umbilical Cord-Derived Mesenchymal Stromal Cells for Knee Osteoarthritis

Matas J, et al. Stem Cells Transl Med. 2019;8(3):215-224. PMID 30592390.

Design	26 patients: hyaluronic acid, single 20-million-cell UC-MSC dose, or repeated 20-million-cell UC-MSC dosing.
Findings	No severe adverse events were reported. Repeated dosing produced better pain/function outcomes than HA at 12 months; MRI outcomes did not differ.
Limitation	Small sample; culture-expanded UC-MSCs rather than processed WJ tissue allograft.
Applicability	Randomized human evidence for UC-MSC therapy, not direct proof for tissue allograft.

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MULTICENTER RANDOMIZED TRIAL

Cell-Based Versus Corticosteroid Injections for Knee Pain in Osteoarthritis

Mautner K, et al. Nature Medicine. 2023;29:3120-3126. PMID 37919438.

Design	480 patients randomized among bone marrow concentrate, adipose SVF, allogeneic umbilical-cord-tissue-derived MSCs, and corticosteroid groups.
Findings	No procedure-related serious adverse events were reported. At one year, none of the orthobiologic groups was superior to corticosteroid for the primary pain outcomes; no significant MRI OA-score change was demonstrated.
Limitation	Multiple biologic preparations; the UC intervention was cell-based.
Applicability	High-value balanced evidence. It demonstrates both randomized UC-derived human research and the limits of efficacy claims.

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PHASE I HUMAN SAFETY

Repeated Intra-Articular Injections of Umbilical Cord-Derived MSCs for Knee Osteoarthritis

Phase I single-arm study. PMID 37312112.

Design	14 patients received repeated UC-MSC injections; safety was the primary outcome.
Findings	5 of 14 experienced transient adverse reactions that resolved spontaneously; no serious adverse events were reported. Pain/function measures improved during follow-up.
Limitation	Small, single-arm study; cannot establish comparative efficacy.
Applicability	Supports human safety characterization of repeated UC-MSC dosing; indirect for processed tissue allograft.

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WHY INCLUDE A NEUTRAL RCT?

Because this review is intended to withstand scrutiny. The large Nature Medicine trial did **not** show superiority over corticosteroid for its primary pain endpoints. Including it prevents the evidence presentation from becoming selective marketing.

4. Evidence Most Directly Relevant to Umbilical-Cord / Wharton's Jelly Tissue Allograft

Much of the highest-level literature evaluates culture-expanded UC/WJ-derived MSCs. The studies below are separated because their interventions more closely resemble the use of umbilical-cord or Wharton's Jelly tissue allograft. They are also lower-level evidence and should be interpreted accordingly.

PROSPECTIVE HUMAN STUDY

Homologous Use of Allogeneic Umbilical Cord Tissue to Reduce Knee Pain and Improve Knee Function

Timmons RB, Sugaya K, Bane LD. Life (Basel). 2022;12(2):260. PMID 35207547.

Design	30 consenting human knee-pain subjects received cryopreserved umbilical cord tissue and were followed for 24 weeks.
Findings	Mean resting and activity VAS scores improved significantly; WOMAC and medication-use outcomes also improved during follow-up.
Limitation	Single-site study without a randomized control group; product-specific characteristics limit generalization.
Applicability	More directly relevant to tissue use than culture-expanded UC-MSC trials, but lower-level evidence.

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OBSERVATIONAL TISSUE-ALLOGRAFT STUDY

Evaluation of Cryopreserved Human Umbilical Cord Tissue Allografts in Knee Osteoarthritis

Davis JM, Sheinkop MB, Barrett TC. Physiologia. 2022;2(3):109-120. DOI 10.3390/physiologia2030010.

Design	55 patients, age 56-93, received a single Wharton's Jelly tissue allograft application under ultrasound guidance; 90-day follow-up.
Findings	NPRS and WOMAC pain, stiffness and function measures improved significantly. No adverse events or adverse reactions were reported.
Limitation	Uncontrolled observational design, short follow-up, and author affiliations with a tissue company; results require confirmation in independent randomized trials.
Applicability	Directly relevant by intervention category, but substantially lower evidentiary strength than an RCT or meta-analysis.

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CLINICAL REVIEW

Allogenic Umbilical Cord Tissue for Treatment of Knee Osteoarthritis

Review article. PMID 35921598.

Design	Review of available clinical-grade umbilical-cord tissue formulations and registered clinical trials.
Findings	Summarized preliminary human findings suggesting pain/function improvement and emphasized the need for appropriately powered higher-level investigations.
Limitation	Review of limited preliminary tissue evidence rather than a definitive efficacy trial.
Applicability	Useful bridge between direct tissue-allograft evidence and the broader UC-MSC literature.

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WHY THIS SECTION MATTERS

The most defensible interpretation is not to treat all 'umbilical cord' studies as interchangeable. **Higher-level UC-MSC evidence and lower-level tissue-allograft evidence answer related but different questions.**

5. What the Evidence Does — and Does Not — Establish

A credible evidence review should make its boundaries explicit. The following distinctions are central to interpreting the literature.

SUPPORTED BY THE PUBLISHED LITERATURE	NOT ESTABLISHED BY THE CURRENT LITERATURE
• Human clinical evidence exists. • Randomized controlled trials exist for UC-derived MSC interventions. • Systematic reviews and meta-analyses exist. • Several studies report improvements in pain and function. • Published short-term safety findings are generally favorable, with serious treatment-related events uncommon or absent in many reports.	• Every Wharton's Jelly product is equivalent. • UC-MSC trials prove effectiveness of processed WJ tissue allografts. • Consistent cartilage regeneration or disease modification has been demonstrated. • Long-term and product-specific safety is fully established. • Every patient will improve.

Independent high-level perspective

COCHRANE LIVING SYSTEMATIC REVIEW

Stem Cell Injections for Osteoarthritis of the Knee

Cochrane Review. 2025. PMID 40169165.

Design	25 randomized trials; 1,341 participants across multiple stem-cell sources and comparators.
Findings	Compared with placebo and based on low-certainty evidence, stem-cell injections may slightly improve pain and function. Serious adverse events were infrequently reported.
Limitation	Cochrane judged safety evidence uncertain because serious events were rare and evidence was imprecise; structural progression remained uncertain.
Applicability	Broad MSC evidence rather than WJ-specific evidence. Included here as an important independent counterweight.

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CLINICAL INTERPRETATION

The most defensible overall position is: **there is a real and growing human evidence base, including RCTs and meta-analyses; short-term safety signals are generally favorable; efficacy is promising but mixed; structural regeneration remains uncertain; and results from culture-expanded UC/WJ-MSCs cannot automatically be transferred to processed tissue allografts.**

6. Regulatory Context & Outcomes Accountability

Regulatory status and clinical evidence are separate questions. FDA states that regenerative medicine therapies, including Wharton's Jelly and orthobiologics, have not been approved for the treatment of orthopedic conditions such as osteoarthritis, knee pain, hip pain, shoulder pain or back pain.

FDA: Important Patient and Consumer Information About Regenerative Medicine Therapies

Why systematic outcomes tracking matters

When evidence is still developing, structured longitudinal follow-up provides useful observational information. Regenerative Medicine of Raynham participates in an outcomes-tracking program designed to collect patient-reported information over time. Registry participation does not prove efficacy and is not a substitute for randomized controlled trials. It does provide a systematic way to follow how participating patients report pain, function and progress.

OUR EVIDENCE STANDARD

Individualized evaluation. Transparent discussion of evidence and uncertainty. Appropriate informed consent. Systematic follow-up.

Questions worth asking before any orthobiologic procedure

1. What exactly is being administered?
2. Does the research cited evaluate the same type of intervention?
3. What adverse events have been reported, and what remains unknown?
4. What evidence supports benefit — and what evidence does not?
5. Is the goal symptom improvement, structural change, or both?
6. How will my outcome be measured over time?

Patient perspective

The purpose of this review is not to direct a patient toward a procedure. It is to make the evidence easier to inspect. Patients may reasonably choose to proceed, seek another opinion, ask additional questions, or choose another form of care.

7. Selected References & Direct Links

The sources below are provided so patients and clinicians can review the original publications. Each citation is clickable.

1. Riggle C, et al. Complications of Stem Cell-Based Injections for Knee Osteoarthritis: A Systematic Review. HSS J. PMID 39564419. **[Open Source]**
2. Lohrasbi E, et al. Regenerative Therapy in Osteoarthritis Using Umbilical Cord-Origin Mesenchymal Stem Cells: Systematic Review and Meta-Analysis. PMID 41378180. **[Open Source]**
3. Ishak-Samrin M, et al. Treatment of Knee Osteoarthritis and Chondral Injury with Umbilical Cord/Wharton's Jelly-Derived MSCs. J Funct Biomater. 2025. PMID 40137363. **[Open Source]**
4. Xiao Z, et al. Effects of Umbilical Cord Mesenchymal Stem Cells in the Treatment of Knee Osteoarthritis: Systematic Review and Meta-Analysis. Medicine. 2024. PMID 39560593. **[Open Source]**
5. Umbilical Cord-Derived Stem Cells for the Treatment of Knee Osteoarthritis: A Systematic Review. Orthop J Sports Med. 2022. PMID 35859650. **[Open Source]**
6. Matas J, et al. Umbilical Cord-Derived Mesenchymal Stromal Cells for Knee Osteoarthritis. Stem Cells Transl Med. 2019. PMID 30592390. **[Open Source]**
7. Mautner K, et al. Cell-Based Versus Corticosteroid Injections for Knee Pain in Osteoarthritis. Nat Med. 2023. PMID 37919438. **[Open Source]**
8. Repeated Intra-Articular Injections of Umbilical Cord-Derived MSCs for Knee Osteoarthritis. PMID 37312112. **[Open Source]**
9. Timmons RB, Sugaya K, Bane LD. Homologous Use of Allogeneic Umbilical Cord Tissue to Reduce Knee Pain and Improve Knee Function. Life. 2022. PMID 35207547. **[Open Source]**
10. Davis JM, Sheinkop MB, Barrett TC. Evaluation of Cryopreserved Human Umbilical Cord Tissue Allografts in Knee Osteoarthritis. Physiologia. 2022;2(3):109-120. **[Open Source]**
11. Allogenic Umbilical Cord Tissue for Treatment of Knee Osteoarthritis. PMID 35921598. **[Open Source]**
12. Cochrane. Stem Cell Injections for Osteoarthritis of the Knee. 2025. PMID 40169165. **[Open Source]**
13. FDA. Important Patient and Consumer Information About Regenerative Medicine Therapies. **[Open Source]**

Disclosure & educational-use statement

This document is intended for patient education and clinical discussion. It is not a systematic review performed by Regenerative Medicine of Raynham, does not establish the safety or effectiveness of any specific commercial product, and is not a substitute for individualized medical evaluation or informed consent. Evidence and regulatory status vary by intervention. Results vary.

SEE THE EVIDENCE. UNDERSTAND THE LIMITATIONS. MAKE AN INFORMED DECISION.

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