Mesenchymal Stromal Cell-Derived Exosomes and Extracellular Vesicles Across Therapeutic Indications

A Structured Review of Published Preclinical and Early-Phase Clinical Study Designs, Administration Parameters, and Reported Outcomes

Indications reviewed: Intervertebral disc degeneration and spinal cord injury; traumatic (acquired) brain injury; chronic obstructive pulmonary disease and chronic lung disease; knee osteoarthritis; and selected additional indications (chronic wound, graft-versus-host disease, COVID-19/ARDS).

Scientific Literature Review — Working Draft for Peer Review

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Important Notice and Disclaimers

Read before proceeding.

This document is a scientific literature review prepared for research and educational purposes only. It summarizes what independent investigators have published. It is not medical advice, not a treatment protocol, not a clinical guideline, and not a recommendation to use any product for any purpose.

As of the date of this review, the U.S. Food and Drug Administration has not approved any exosome or mesenchymal stromal cell-derived extracellular vesicle product for any therapeutic indication. Exosomes intended to treat, diagnose, cure, mitigate, or prevent disease in humans are regulated as drugs and biological products under the Federal Food, Drug, and Cosmetic Act and Section 351 of the Public Health Service Act. In the United States they may lawfully be administered to humans only under an active Investigational New Drug (IND) application or an approved Biologics License Application (BLA).

Nothing in this document should be read as a claim that any exosome or extracellular vesicle product is safe or effective for any use. All efficacy and safety statements are attributed to the cited authors and reflect their published reports, which have not been independently verified or confirmed by any regulatory authority and are subject to the methodological limitations discussed herein.

The complete Legal, Regulatory, and Scientific Disclaimers section appears at the end of this document and forms part of this review. By reading further, the reader acknowledges the investigational status of the subject matter and the non-promotional, educational purpose of this document.

Contents

Abstract

Mesenchymal stromal cell (MSC)-derived exosomes and extracellular vesicles (EVs) are nanoscale, cell-secreted particles under active investigation as cell-free candidates for tissue repair and immune modulation. This review compiles the published designs, administration parameters, and author-reported outcomes of studies spanning five indication areas: spine (intervertebral disc degeneration, spinal cord injury, spinal fusion), traumatic brain injury (TBI), chronic obstructive pulmonary disease (COPD) and related chronic lung disease, knee osteoarthritis (OA), and selected additional indications (chronic wound, graft-versus-host disease, and COVID-19/acute respiratory distress syndrome).

Across all five areas the evidence base is dominated by in vitro work and small-animal models, with a smaller number of large-animal studies and early-phase human trials that are principally designed to assess safety and tolerability rather than to establish efficacy. A central methodological finding of this review is that administered dose is reported inconsistently across the literature. Preclinical studies most often express dose as total EV protein mass (commonly in the tens to low hundreds of micrograms), whereas the human inhalation and intra-articular studies that do report particle counts span several orders of magnitude, from roughly 2 x 10^8 to 5 x 10^11 particles per administration. Because particle count as measured by nanoparticle tracking analysis does not distinguish bioactive vesicles from co-isolated non-vesicular particles and is not a validated potency metric, cross-study dose comparison is limited. This review reports each study's dose as published and does not propose, endorse, or standardize any dose. A frequently cited reference figure of 20 billion (2 x 10^10) particles per milliliter is discussed only as an illustrative unit for orienting the reader to the particle-count scale and is expressly not a recommended dose.

The review concludes that the field is scientifically active and mechanistically coherent in preclinical models but remains early in clinical translation, with no FDA-approved product in any indication and a pressing need for harmonized characterization, potency assays, and dose reporting consistent with the International Society for Extracellular Vesicles (ISEV) MISEV frameworks.

1. Introduction and Scope

Extracellular vesicles are membrane-bound particles released by essentially all cell types. The subset commonly termed exosomes originates from the endosomal system and typically measures approximately 30 to 150 nanometers in diameter. Vesicles secreted by mesenchymal stromal cells carry proteins, lipids, and RNA species and have been studied as mediators of the paracrine effects historically attributed to MSC therapy. Interest in MSC-derived EVs as a cell-free modality reflects several theoretical handling advantages discussed in the source literature, including the absence of live replicating cells and the potential for defined manufacturing, though these theoretical advantages remain to be confirmed in controlled clinical settings.

This document reviews published studies across the indications the reader specified: spine, traumatic (acquired) brain injury, COPD, knee osteoarthritis, and additional high-activity indications. For each area the review reports study type, cell source, administration route, dose as published, endpoints, author-reported outcomes, and author-stated limitations. The review deliberately reports rather than adjudicates: outcome statements are attributed to the cited authors, and this document draws no independent conclusion of clinical benefit for any indication.

1.1 Objectives

- Summarize the design and administration parameters of representative published MSC-EV/exosome studies by indication.
- Report dose exactly as expressed by the source authors, and make explicit where particle-count dosing is or is not used.
- Characterize the maturity of the evidence base (preclinical versus clinical) in each area.
- Situate the literature within current regulatory status and EV characterization standards.

1.2 What this document is not

- It does not recommend, and must not be used to justify, the administration of any exosome or EV product to any patient outside an authorized clinical trial.
- It does not define a clinical dose, route, schedule, or protocol for human use.
- It does not assert that any product is safe or effective.
- It does not promote any specific commercial product, provider, or clinic.

2. Regulatory Status and Framework

Understanding the regulatory posture is essential context for interpreting this literature, because it defines the lawful setting in which the reviewed interventions may be studied in humans.

2.1 No approved products; FDA safety notification

In December 2019 the FDA issued a Public Safety Notification on Exosome Products, informing the public of multiple reports of serious adverse events in patients in Nebraska treated with unapproved products marketed as containing exosomes; the reports were surfaced with the Centers for Disease Control and Prevention and the Nebraska Department of Health and Human Services. The notification states that there are currently no FDA-approved exosome products and that, as a general matter, exosomes used to treat diseases and conditions in humans are regulated as drugs and biological products under the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act and are subject to premarket review and approval requirements.

The FDA reaffirmed in its Consumer Alert on Regenerative Medicine Products (page content current as of April 2024) that exosome products intended to treat diseases or

conditions in humans require FDA approval and that there are currently no FDA-approved exosome products. That position has been reiterated through subsequent enforcement actions.

2.2 Why exosomes are regulated as 351 biologics

Human cells, tissues, and cellular and tissue-based products (HCT/Ps) are governed by 21 CFR Part 1271. A product may be regulated solely under Section 361 of the PHS Act (without premarket approval) only if it meets all four criteria of 21 CFR 1271.10(a), including minimal manipulation (1271.10(a)(1)) and homologous use (1271.10(a)(2)). The FDA's consistent position, articulated in warning letters, is that exosomes isolated from cultured, expanded cells constitute more than minimal manipulation of the source tissue, and that therapeutic marketing claims establish non-homologous use. Products failing any 1271.10(a) criterion are regulated as drugs under the FD&C Act and as biological products under Section 351(a) of the PHS Act, requiring an IND for investigational use and an approved BLA for marketing. The interpretive framework is set out in the FDA/CBER-CDER guidance on Minimal Manipulation and Homologous Use (July 2020).

2.3 Enforcement

The FDA has issued multiple warning letters characterizing marketed exosome products as unapproved new drugs under Section 505(a) of the FD&C Act and unlicensed biological products under Section 351(a)(1) of the PHS Act, and directing recipients to the 2019 exosome safety notification. Representative public examples include letters to New Life Medical Services, LLC (2025), Platinum Biologics, LLC (2025), and Invitrx Therapeutics, Inc. (2022). Readers are referred to the FDA Warning Letters database for the authoritative, current list.

> **Regulatory bottom line.**
>
> There is no FDA-approved MSC-exosome or EV product for spine, TBI, COPD, knee OA, or any other indication. In the United States, human administration outside an authorized IND/BLA is unapproved. This review describes research; it does not describe an available treatment.

3. Review Methods

This is a narrative structured review, not a systematic review or meta-analysis. Studies were identified through searches of the peer-reviewed literature and trial registries and were selected to represent the range of cell sources, routes, and study designs within each indication, with a preference for verifiable primary sources. For each included study the following fields were extracted where available: authors and year; study type and model or population; MSC tissue source; EV isolation method where reported; administration route; dose as published; primary endpoints; author-reported outcomes; and author-stated limitations. Where a specific dose could not be verified from an accessible primary source, that limitation is flagged rather than estimated.

Outcome descriptions in this review are reported as stated by the source authors and are not independent findings of this document. Selection favored breadth and verifiability over exhaustiveness; omission of a study is not a judgment about its quality.

3.1 A note on dose reporting and the particle-count reference

Dose in this literature is expressed in incompatible units across studies: total EV protein mass (micrograms), particle number (by nanoparticle tracking analysis or similar), cell-equivalents of conditioned medium, and administered volume of a proprietary preparation. This review preserves each study's original unit. It does not convert between units, because no validated conversion exists and because particle number, protein mass, and biological potency are not interchangeable.

The reader referenced a figure of 20 billion exosomes per milliliter (2 x 10^10 particles/mL). In this document that figure is used only as an illustrative anchor to help orient a non-specialist reader to the order of magnitude of particle concentrations reported in the field. It is **not** a recommended concentration, **not** a dose, and **not** a figure endorsed by this review. As the study tables below show, published particle-count doses span from roughly 2 x 10^8 to 5 x 10^11 particles per administration depending on route, model, and indication, so no single per-milliliter figure can represent the field.

4. Spine: Disc Degeneration, Spinal Cord Injury, and Spinal Fusion

Published spine work is almost entirely preclinical, comprising in vitro nucleus pulposus, neuron, and osteoblast assays together with small-animal models. No randomized controlled human efficacy trial for a spine indication was identified. Most studies dose by protein mass; particle-count dosing is the exception.

Study (first author, yr)	Model / type	MSC source	Dose (as published) / route	Author-reported outcome (verbatim-attributed)
Lam et al., 2024 (Cells)	Rat posterolateral spinal fusion, in vivo	hESC-derived MSC line	100 µg EV protein in 100 µL on collagen sponge in scaffold; single implant. Not dosed by particle count.	Reported improved fusion rate (83.3% vs 27.3%) and stability with minimal ectopic bone and no adverse responses.
Morishima/ Kawabori et al., 2024 (Int J Mol Sci)	Rat clip-compression SCI, in vivo	Human amnion-derived MSC	100 µg EV protein in 1 mL PBS IV; 24 h post-injury then daily x3. Not dosed by particle count.	Reported better locomotor recovery and reduced lesion volume, attributed in part to miR-125a-3p regulation of neutrophil extracellular traps.
Sung et al., 2022 (Biomedicines)	Rat clip-compression SCI, in vivo	Human epidural adipose MSC	1 x 10^9 (low) or 5 x 10^9 (high) particles in 0.2 mL PBS IV; at injury and day 3. Particle-count dosed.	Reported dose-dependent locomotor recovery and reduced inflammation.

Study (first author, yr)	Model / type	MSC source	Dose (as published) / route	Author-reported outcome (verbatim-attributed)
Ekram et al., 2025 (Biomedicines)	Rat coccygeal disc puncture, in vivo	Human umbilical cord MSC	100 µg EV protein in 100 µL single intradiscal. Not dosed by particle count.	Reported improved disc height, water content, and glycosaminoglycan content, and superior retention versus cell treatment.
Xu et al., 2023 (Stem Cell Rev Rep)	NP cells + rat disc puncture	Bone marrow MSC	Intradiscal injection; exact dose not verifiable from accessible text (flagged). Not reported by particle count in accessible portion.	Reported reduced oxidative stress via the Keap1/Nrf2 axis.
Zhang et al., 2020 (J Cell Mol Med)	NP cells + mouse disc puncture	Bone marrow MSC	Intradiscal injection; exact dose not verifiable from accessible text (flagged).	Reported anti-pyroptosis effect via exosomal miR-410 suppressing NLRP3.

State of evidence (spine). Preclinical and mechanistic; no randomized controlled human efficacy trial identified. Dose is most often expressed in micrograms of protein; only Sung et al. (2022) among these used particle-count dosing. Two disc studies could not be dose-verified from accessible full text and are flagged accordingly.

5. Traumatic (Acquired) Brain Injury

The TBI evidence base is essentially all preclinical, spanning rodent models and a small number of large-animal (swine) studies. No completed TBI-specific human MSC-EV efficacy trial was identified; the nearest human registrations address stroke or are broad multi-condition registrations. Particle-count dosing appears mainly in the large-animal studies, whereas rodent studies dose by protein mass.

Study (first author, yr)	Model / type	MSC source	Dose (as published) / route	Author-reported outcome (attributed)
Williams et al., 2019 (J Neurotrauma)	Swine TBI + hemorrhagic shock	Human MSC (source not specified in abstract)	~1 x 10^13 particles/4 mL, multiple doses (5 total), systemic. Particle-count dosed.	Reported lower neurologic severity scores and faster neurologic recovery.
Williams et al., 2020 (J Trauma Acute Care Surg)	Swine severe TBI + shock	Human MSC (source not specified)	~1 x 10^12 particles in 5 mL, single dose, systemic (verify exponent vs PDF). Particle-count dosed.	Reported less brain swelling, smaller lesion, and improved blood-brain barrier integrity.
Zhang et al., 2020 (Neurorehabil Neural Repair)	Rat CCI, dose-response	Human bone marrow MSC	50, 100, or 200 µg EV protein in 0.5 mL PBS IV; window arm 100 µg. Not dosed by	Reported improved sensorimotor and cognitive function across doses; 100 µg

Study (first author, yr)	Model / type	MSC source	Dose (as published) / route	Author-reported outcome (attributed)
			particle count.	and day-1 start most effective; therapeutic window at least 7 days.
Huang et al., 2019 (Front Neurosci)	Mouse CCI, in vivo	Bone marrow MSC	30 µg EV protein, single retro-orbital dose. Not dosed by particle count.	Reported reduced lesion size and neuroinflammation via microglia/macrophage polarization.
Chen et al., 2020 (Aging)	Rat weight-drop TBI	Human adipose MSC	20 µg protein, 2.0 x 10^10 particles/mL, 20 µL single ICV. Both units reported.	Reported functional recovery and reduced neuroinflammation comparable to cell therapy.
Moss et al., 2021 (Neurochem Int)	Mouse CCI (mild), in vivo	Human adipose stem cell	10 µg per mouse, single intranasal, 48 h post-TBI. Not dosed by particle count.	Reported motor and cognitive improvement dependent on exosomal MALAT1.
Zhang ZW et al., 2022 (Open Life Sci)	Rat CCI, in vivo	Human umbilical cord MSC	100 µg protein in 0.5 mL PBS IV, single, day 1. Not dosed by particle count.	Reported improved recovery and reduced inflammation via NF-kB suppression.

State of evidence (TBI). Preclinical, consistent directionally across cell sources and routes, but without completed controlled human efficacy data. Rodent studies dose by protein mass (10 to 200 µg); the swine studies and Chen et al. (2020) report particle counts, which differ by orders of magnitude from the rodent protein-based doses and from one another.

6. COPD and Chronic Lung Disease

Chronic lung work is predominantly preclinical (cigarette-smoke/LPS COPD, elastase/papain emphysema, bleomycin fibrosis). A distinguishing feature of this area is the emergence of early-phase human inhalation studies, though these address pulmonary fibrosis, acute lung injury surrogates, and COVID-19 pneumonia rather than COPD specifically. No dedicated registered human inhaled MSC-EV trial for COPD was identified. Human inhalation studies dose predominantly by particle count.

Study (first author, yr)	Model / type	MSC source	Dose (as published) / route	Author-reported outcome (attributed)
Zhou et al., 2026 (Sci Rep)	Mouse CS+LPS COPD	Umbilical cord MSC	100 µg EV protein daily IV x10. Protein-based; prep characterized but administered dose not stated as particle count.	Reported improved lung function and reduced inflammation/collagen; proposed UC-MSC-Exo/macrophage/CXCR4 axis.

Study (first author, yr)	Model / type	MSC source	Dose (as published) / route	Author-reported outcome (attributed)
Wang et al., 2025 (Cell Immunol)	Rat CS+LPS COPD, nebulized vs IV	Bone marrow MSC	Nebulized; numeric dose behind paywall (flagged as unconfirmed).	Reported improved lung function and reduced remodeling/EMT via Wnt/beta-catenin suppression.
Chen Q et al., 2022 (Regen Ther)	Rat papain emphysema	Human umbilical cord MSC	200 µg EV protein, single IV. Not dosed by particle count.	Reported reversal of emphysematous changes and reduced apoptosis.
Mansouri et al., 2019 (JCI Insight)	Mouse bleomycin fibrosis	Human bone marrow MSC	Single IV, ~8.6 x 10^8 particles (5 x 10^6 MSC-equivalents). Particle count reported; no µg dose.	Reported prevention and reversal of experimental fibrosis via monocyte modulation.
Shi et al., 2021 (J Extracell Vesicles)	Mouse lung injury + healthy-volunteer Ph 1 (NCT04313647)	Human adipose MSC	Clinical nebulized escalation 2 x 10^8 to 16 x 10^8 particles. Particle-count dosed.	Reported preclinical survival benefit; volunteers tolerated nebulization with no serious adverse events.
Chu et al., 2022 (Stem Cell Rev Rep)	COVID-19 pneumonia pilot, n=7 (ChiCTR2000030261)	Umbilical cord (Wharton's jelly)	Nebulized twice daily; ~7 x 10^7 to 7.66 x 10^8 particles/mL. Particle-count dosed.	Reported no acute allergic events and shorter hospitalization for mild cases; authors note non-robust efficacy (uncontrolled).
Zhu et al., 2022 (Stem Cell Res Ther; MEXCOVID, NCT04276987)	Severe COVID-19 Ph 2a, n=7	Human adipose MSC	Nebulized 2.0 x 10^8 particles/day x5 days. Particle-count dosed.	Reported good tolerability and variable radiographic resolution; no efficacy conclusions drawn by authors.
STTT group, 2025 (Signal Transduct Target Ther; ChiCTR2300075466)	Pulmonary fibrosis Ph 1 RCT, n=24	Human umbilical cord MSC	Nebulized 2 x 10^9 particles twice daily x7 days. Particle-count dosed.	Reported good safety over 12 months and improvement in some pulmonary function measures versus saline.

State of evidence (COPD/lung). Preclinical for COPD specifically; the human inhalation experience exists in fibrosis, ALI surrogate, and COVID-19 pneumonia and is principally safety-oriented and small. Human inhaled doses cluster at 10^8 to 10^9 particles per administration, well below the intra-articular particle numbers reported in orthopedic studies, underscoring route- and indication-dependence of dose.

7. Knee Osteoarthritis and Cartilage Repair

Knee OA has the most clinical activity of the orthopedic indications, though the human data remain early and largely uncontrolled. Preclinical work across bone marrow, embryonic, umbilical cord, and infrapatellar fat pad sources is comparatively robust. Intra-articular particle-count doses reported here are the highest in this review.

Study (first author, yr)	Model / type	MSC source	Dose (as published) / route	Author-reported outcome (attributed)
Wang Y et al., 2025 (J Transl Med)	Human pilot, n=41/45 knees; dose-escalation, no control	Human umbilical cord MSC	3 x 10^11, 4 x 10^11, or 5 x 10^11 particles intra-articular every 21 days. Particle-count dosed.	Reported no safety differences over 9 months and within-group WOMAC/MRI improvement, most in the high-dose group; first clinical application of hUC-MSC exosomes in OA per authors.
Zhang S/Toh et al., 2016 (Osteoarthritis Cartilage)	Rat osteochondral defect	Human ESC-derived MSC	100 µg EV protein intra-articular weekly x12. Not dosed by particle count.	Reported ordered cartilage and subchondral bone regeneration.
Wu J et al., 2019 (Biomaterials)	Mouse DMM OA	Human infrapatellar fat pad MSC	Intra-articular; protein-based dosing (µg-scale). Not dosed by particle count.	Reported cartilage protection and improved gait via miR-100-5p/mTOR autophagy.
He L et al., 2020 (Stem Cell Res Ther)	Rat MIA OA	Rat bone marrow MSC	~40 µg/100 µL intra-articular, weekly. Not dosed by particle count.	Reported cartilage repair, matrix synthesis, and reduced OA pain.

Registered knee OA exosome trials. Examples include ExoOA-1 (NCT05060107), a Phase I intra-articular MSC-sEV safety/dose-escalation study, and NCT06431152, a Phase 1 open-label UC-MSC exosome dose-escalation pilot. Both are early-phase and safety-focused.

State of evidence (knee OA). Strong preclinical signal by author report; human data limited to small, mostly uncontrolled early-phase studies. Intra-articular particle doses (3 to 5 x 10^11) are two to three orders of magnitude above inhaled pulmonary doses, illustrating why a single reference concentration cannot generalize across indications.

8. Selected Additional Indications

To situate the reviewed indications within the broader field, three additional areas with notable human activity are summarized: chronic wound/diabetic foot ulcer, graft-versus-host disease (GvHD), and COVID-19/ARDS. These illustrate the range of routes (topical, systemic infusion) and dose conventions (volume, cell-equivalent units) in use.

Study (first author, yr)	Model / type	MSC source	Dose (as published) / route	Author-reported outcome (attributed)
Wharton's jelly DFU RCT, 2025 (Stem Cell Res Ther)	Human RCT, n=110, diabetic foot ulcer	Wharton's jelly MSC	Topical exosome gel weekly x4 + standard care; per-application EV quantity not stated in accessible source (flagged).	Reported faster complete healing (mean 6 vs 20 weeks) versus control.
Kordelas et al., 2014 (Leukemia)	Single-patient, steroid-refractory acute GvHD	Bone marrow MSC (pooled donors)	Dosed in 'units' (1 unit = EVs from 4 x 10^7 MSC/48 h); ~1.3 to 3.5 x 10^10 particles and 0.5 to 1.6 mg protein per unit; escalating IV.	Reported improvement of GvHD symptoms and good tolerability (n=1).
Lightner et al., 2023 (CHEST; ExoFlo)	Ph 2 RCT, n=102, COVID-19 respiratory failure	Bone marrow MSC EV	Placebo, 10 mL, or 15 mL IV on days 1 and 4. Dosed by volume; no particle count.	Primary/secondary endpoints not met; a post hoc subgroup mortality signal is flagged by authors for cautious interpretation.
Sengupta et al., 2020 (Stem Cells Dev; ExoFlo)	Expanded-access safety, n=24, severe COVID-19	Bone marrow MSC exosome	Single IV 15 mL. Dosed by volume.	Reported no adverse events within 72 h and clinical/laboratory improvement (uncontrolled).

Reference-figure caution (Nassar 2016).

A commonly circulated claim that Nassar et al. (2016) was a diabetic-wound EV trial appears to be a conflation. The Nassar et al. (2016) trial in Biomaterials Research studied UC-MSC EVs in chronic kidney disease, not wound healing. It should not be cited as a wound study.

9. Cross-Cutting Issue: Dose and Potency Are Not Standardized

The single most important interpretive caveat for this literature is that dose is not reported on a common scale, and the units that are used do not measure the same thing.

9.1 Particle count is not potency

Nanoparticle tracking analysis and comparable methods count all light-scattering particles within a size window. They do not distinguish true EVs from co-isolated protein aggregates or lipoproteins of similar size, and they have limited sensitivity below roughly 50 to 70 nanometers. A particle count is therefore a count of particles, not a count of bioactive exosomes, and it does not by itself define potency. There is no consensus potency assay for exosome products, and particle number and total protein do not necessarily correlate with biological activity.

9.2 Incompatible dose units across the field

As the tables above show, the reviewed studies express dose as micrograms of protein (most preclinical studies), as particle number (most human inhalation and orthopedic studies, ranging from ~2 x 10^8 to 5 x 10^11 per administration), as cell-equivalent units (Kordelas GvHD), or as administered volume of a proprietary preparation (ExoFlo). No validated conversion links these units. This is why the review reports each dose as published and does not compute a unified figure.

On the 20 billion per mL reference, restated.

20 billion particles per milliliter (2 x 10^10/mL) is used in this document only to orient the reader to the particle-count scale. It is not a recommended concentration or dose. Reported particle-count doses in the reviewed human studies range from roughly 2 x 10^8 (inhaled pulmonary) to 5 x 10^11 (intra-articular knee) per administration, and preclinical studies frequently do not use particle counts at all. Any operational dose for human use would be defined by an IND sponsor and the FDA, not by this literature.

9.3 Characterization standards (ISEV MISEV)

The ISEV MISEV2018 position statement and its MISEV2023 update define minimum reporting expectations for EV studies, including documentation of EV source and separation method, quantification metrics, and protein characterization demonstrating at least three positive EV markers (including a transmembrane/lipid-bound protein such as CD9, CD63, or CD81, and a cytosolic protein such as TSG101 or ALIX) together with at least one negative marker to demonstrate purity. Bulk measures such as particle number or total protein alone are considered insufficient without purity metrics and functional characterization. Readers should interpret every quantitative claim in this review against these frameworks; heterogeneity in isolation and characterization across the cited studies limits cross-study comparability.

10. Limitations of the Evidence Base

1. Maturity. Across all reviewed indications the evidence is dominated by in vitro and small-animal work; human studies are few, generally small, and predominantly designed to assess safety rather than efficacy.
2. Controls. Several human studies are uncontrolled or single-arm; where controlled trials exist (e.g., ExoFlo Phase 2), primary efficacy endpoints were not met and positive signals were confined to exploratory post hoc analyses.
3. Dose incomparability. Incompatible dose units and the absence of a validated potency assay prevent meaningful cross-study dose-response synthesis.
4. Characterization heterogeneity. EV isolation and characterization vary widely and do not uniformly meet MISEV expectations, limiting reproducibility.
5. Source verification. For two spine disc studies and one wound RCT, exact administered doses could not be verified from accessible primary sources and are flagged; certain particle-count exponents warrant confirmation against original PDFs.

6. Publication and reporting bias. Positive preclinical results are more likely to be published, and author-reported outcomes have not been independently adjudicated in this review.

11. Summary Observations

MSC-derived exosomes and EVs constitute a scientifically active field with mechanistically coherent preclinical findings across spine, TBI, COPD, knee OA, and additional indications. Clinical translation remains early. No product is FDA-approved in any indication; human trials are principally early-phase and safety-oriented; and the field lacks harmonized characterization, potency assays, and dose reporting. Progress toward credible clinical evaluation will depend on standardized manufacturing and release testing, fit-for-purpose potency assays tied to mechanism of action, MISEV-consistent characterization and reporting, and adequately controlled trials conducted under appropriate regulatory authorization.

This review reports what has been published. It does not establish, and should not be read to establish, that any exosome or EV product is safe or effective for any use, nor does it define any protocol for human administration.

12. Legal, Regulatory, and Scientific Disclaimers

12.1 Investigational status

Exosome and MSC-derived extracellular vesicle products are investigational. As of the date of this document, the U.S. Food and Drug Administration has not approved any exosome product for any therapeutic indication. Exosomes intended to treat, diagnose, cure, mitigate, or prevent disease in humans are regulated as drugs and biological products under the Federal Food, Drug, and Cosmetic Act and Section 351 of the Public Health Service Act, and may lawfully be administered to humans in the United States only under an active Investigational New Drug (IND) application or, if approved, a Biologics License Application (BLA).

12.2 Research and educational purpose; not medical advice

This document is a scientific literature review prepared for research and educational purposes only. It is not intended as, and must not be relied upon as, medical advice, a treatment protocol, a clinical guideline, a recommendation, or an endorsement of any product, provider, or procedure. It does not establish a standard of care. Clinical decisions must be made by qualified, licensed professionals in the context of applicable law, an individual patient's circumstances, and, where required, an authorized IND.

12.3 No efficacy or safety claims

Nothing in this review should be interpreted as a claim that any exosome or extracellular vesicle product is safe or effective for any use. Descriptions of preclinical or clinical findings reflect the published literature and are provided for scientific context only; they have not been evaluated or confirmed by the FDA and do not support any conclusion of safety or efficacy. Reported results are subject to the methodological limitations discussed herein, including the absence of standardized potency assays and dosing metrics.

12.4 Off-label and unapproved use

Any use of exosome or MSC-derived extracellular vesicle products outside an authorized clinical trial is unapproved. This document does not encourage, promote, or facilitate the use of unapproved products, and it should not be construed as promotional labeling. The FDA has issued public safety notifications and warning letters regarding the marketing of unapproved exosome products; readers are referred to those communications and to their own regulatory counsel.

12.5 Characterization and dose caveat

Findings summarized here derive from studies with heterogeneous extracellular vesicle isolation, characterization, and reporting practices. Particle concentration (for example, by nanoparticle tracking analysis) does not by itself define dose or potency and may include non-vesicular particles. The figure of 20 billion particles per milliliter referenced in this document is an illustrative unit only and is not a recommended dose or concentration. Comparisons across studies are limited by the absence of harmonized

standards; readers should interpret quantitative claims in light of the MISEV2018 and MISEV2023 reporting frameworks of the International Society for Extracellular Vesicles.

12.6 No legal or regulatory advice; independent verification

This document does not constitute legal, regulatory, or financial advice. Regulatory status, guidance, and enforcement positions change over time and vary by jurisdiction. Statements about FDA positions reflect publicly available materials as of the date of preparation and should be independently verified against current FDA sources before any reliance. Any party contemplating research, development, or commercialization of EV products should obtain qualified regulatory and legal counsel.

12.7 Accuracy and citation

Reasonable care was taken to represent cited sources accurately, and outcome statements are attributed to their authors. Errors of transcription or interpretation are possible; readers should consult the primary sources listed in the References. Certain doses could not be verified from accessible primary sources and are flagged in the text. This document should be read in full, including all disclaimers, which form an integral part of it.

References

Primary studies are listed by indication, followed by regulatory and standards sources. Digital object identifiers (DOIs) and identifiers are provided where available. Readers should consult the primary sources directly.

Spine

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END OF DOCUMENT — This review is investigational in subject matter, non-promotional, and not medical advice. See Section 12.