Mesenchymal Stromal Cell Therapies

A Comprehensive Scientific Review

Safety, Efficacy, Manufacturing, Regulatory Landscape & Policy Considerations

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Executive Summary

A. Scope and Purpose

This report constitutes an independent scientific review of the global evidence base for mesenchymal stromal cell (MSC) therapies, prepared at the request of the Ministry of Health and Medical Services of the Republic of Fiji. The review synthesises the current state of knowledge across MSC biology, mechanisms of action, safety, clinical efficacy across all major therapeutic indications, regulatory status in multiple jurisdictions, manufacturing and quality requirements, the emerging research pipeline, and the potential role of MSC-based treatments in longevity and wellness applications. It evaluates the global regulatory landscape — encompassing frameworks in the European Union, Japan, the Republic of Korea, Australia, India, China, Canada, and the United States — and assesses the alignment of MSC therapeutic applications with the non-communicable disease burden characteristic of Pacific Island nations. All recommendations are framed at the policy and pathway level to support evidence-based decision-making by the Ministry regarding whether and how to enable access to MSC-based therapies for the population of Fiji.

B. Key Findings Summary

1. Safety

- **A systematic review and meta-analysis encompassing 55 randomised controlled trials and over 2,000 patients who received systemically administered MSCs found no significant increase in the risk of infection, thrombo-embolic events, malignancy, or ectopic tissue formation.** The only adverse event significantly elevated in MSC-treated patients was transient fever. Notably, the risk of death was significantly lower in the MSC-treated group compared to controls (Thompson et al., 2020, as cited in Zhuang et al., 2021, *J Biomed Sci*. DOI: 10.1186/s12929-021-00725-7; Česnik & Švajger, 2024, *Front Cell Dev Biol*. DOI: 10.3389/fcell.2024.1400347. PMID: 39129786).
- **Pooled safety data from over 5,000 patients confirm that serious adverse event rates in MSC-treated cohorts are comparable to placebo in controlled trials.** Acute infusion reactions — principally transient fever, headache, and flushing — occur in approximately 10–30% of intravenous administrations and are typically mild and self-limiting. No malignant transformation events have been reported in clinical trials to date (Thompson et al., 2020, as cited in Česnik & Švajger, 2024, *Front Cell Dev Biol*. PMID: 39129786).
- **MSC infusion has been associated with dose-dependent coagulation abnormalities.** MSCs express tissue factor, and high-dose intravenous infusion has been linked to thrombotic and microvascular complications in isolated cases. Anticoagulant co-administration during infusion is recommended as a precautionary measure (Zhao et al., 2026, *Stem Cell Rev Rep*. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448).
- **Long-term follow-up data remain limited.** Most trials report safety over 12–24 months. An a priori plan to monitor safety — including immediate allergic reactions, local complications, vascular obstructions, systemic infections, and malignancy — should be outlined in every clinical study design (Zhuang et al., 2021, *J Biomed Sci*. DOI: 10.1186/s12929-021-00725-7).

2. Efficacy

- **Steroid-refractory acute graft-versus-host disease (SR-aGvHD) represents the most clinically validated MSC indication.** The pivotal remestemcel-L trial demonstrated a 70% overall response rate at Day 28 in paediatric SR-aGvHD, with overall survival rates of 63% at one year, 51% at two years, and 49% at four years. This product received FDA approval in December 2024 using a historical control comparison design (Zhao et al., 2026, *Stem Cell Rev Rep*. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448; Olsen et al., 2018, *Front Med*. DOI: 10.3389/fmed.2018.00178. PMID: 29977893).
- **Crohn's disease-associated perianal fistulae were the subject of a Phase III randomised, double-blind, controlled trial** in which a single intralesional injection of allogeneic adipose-derived MSCs achieved significantly higher remission rates in 107 treated patients compared to 105 placebo recipients (Guerrouahen et al., 2019, *Stem Cells Int*. DOI: 10.1155/2019/7219297. PMID: 31467564). The product received EMA marketing authorisation in March 2018 (EMEA/H/C/004258), though it was subsequently withdrawn in December 2024 following failure of the ADMIRE-CD II confirmatory trial (EMA, Alofisel EPAR).
- **Osteoarthritis (OA) is the most studied MSC indication by trial count**, with 67 registered clinical trials. Multiple Phase I/II studies demonstrate significant improvements in WOMAC pain and function scores following intra-articular MSC injection, with evidence of cartilage volume preservation on MRI. One product has received marketing authorisation in the Republic of Korea for knee cartilage defects (Margiana et al., 2022, *Stem Cell Res Ther*. DOI: 10.1186/s13287-022-03054-0. PMID: 35902958; Markov et al., 2021, *Stem Cell Res Ther*. DOI: 10.1186/s13287-021-02265-1. PMID: 33736695).
- **Ischaemic stroke has been investigated in multiple Phase I/II trials.** The first prospective randomised study by Bang et al. (2005) demonstrated safety and feasibility of autologous MSC transplantation in 30 patients with cerebral infarcts, with functional recovery benefits observed at one-year follow-up. A subsequent meta-analysis confirmed that MSC therapy in the brain is safe and improves primary clinical endpoints (Zhou et al., 2022, *Stem Cell Res Ther*. DOI: 10.1186/s13287-022-02876-2. PMID: 35551643; Lalu et al., 2020, *Transl Stroke Res*. DOI: 10.1007/s12975-019-00736-5).

3. Regulatory Status

- **At least 12 MSC-based products have received marketing authorisation from national regulatory agencies worldwide**, spanning seven countries across four continents. The Republic of Korea hosts the highest density of approved MSC products (five products), followed by Japan (two products) (Zhao et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448; Jossen et al., 2018, *Appl Microbiol Biotechnol*. DOI: 10.1007/s00253-018-8912-x. PMID: 29564526).
- **The most recent approvals include remestemcel-L for paediatric SR-aGvHD by the United States FDA (December 2024)** and Ammitel-L (human umbilical cord MSCs) for steroid-refractory acute GvHD by China's NMPA (2025), representing continued global regulatory momentum for the MSC asset class (Zhao et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448).
- **In the European Union, MSCs are classified as Advanced Therapy Medicinal Products (ATMPs)** under Regulation (EC) No 1394/2007, specifically as somatic-cell therapy medicinal products. All ATMPs require centralised marketing authorisation through the EMA's Committee for Advanced Therapies (CAT) (EMA, Advanced Therapy Medicinal Products: Overview, 2017).
- **Conditional and time-limited approval pathways** have been utilised in Japan (PMDA conditional approval) and the Republic of Korea (MFDS framework), enabling earlier patient access while post-marketing data are collected. This regulatory model is particularly relevant for nations considering phased introduction of MSC therapies.

4. Clinical Trials

- **Over 1,200 MSC clinical trials were registered on ClinicalTrials.gov as of 2020**, with the number continuing to rise. By 2018, 837 registered trials were documented, with 102 added in 2017 alone. Approximately 27% of trials are Phase I, 48% are Phase II, and 25% are Phase III, indicating a maturing pipeline approaching commercialisation (Olsen et al., 2018, *Front Med*. DOI: 10.3389/fmed.2018.00178. PMID: 29977893; Zhuang et al., 2021, *J Biomed Sci*. DOI: 10.1186/s12929-021-00725-7).

- **The most common indications by trial count are**: osteoarthritis (67 trials), Crohn's disease (25), COVID-19 (23), GvHD (23), type 2 diabetes (18), acute respiratory distress syndrome (17), ischaemic stroke (14), liver cirrhosis (13), and spinal cord injury (11) (MSC Clinical Trial Intelligence database).
- **Geographic distribution is weighted towards China, the Republic of Korea, and the United States**, with emerging trial activity in Europe, India, the Middle East, and Australia. Trials registered on the ANZCTR include MSC studies for COPD, COVID-19 pneumonia, and chronic lung allograft dysfunction in Australia (ANZCTR registry data). No MSC clinical trials are currently registered in Pacific Island nations.

5. Manufacturing

- **MSC manufacturing requires compliance with current Good Manufacturing Practice (cGMP) standards.** Critical Quality Attributes (CQAs) include identity markers ($CD73^+/CD90^+/CD105^+$; $CD34^-/CD45^-$ by flow cytometry, >95% positive), viability (>70–80% by trypan blue or automated nucleocounter), sterility (no growth at 14 days per USP <71>), mycoplasma negativity (PCR/culture), endotoxin levels (<5 EU/kg body weight), and indication-specific potency (Jayaraman et al., 2021, *Front Cell Dev Biol*. DOI: 10.3389/fcell.2021.648472. PMID: 33928083; Giovannelli et al., 2023, *Bioact Mater*. DOI: 10.1016/j.bioactmat.2023.06.013. PMID: 37456581).
- **Potency assay development remains the single greatest manufacturing challenge.** The International Society for Cellular Therapy (ISCT) recommends a matrix assay approach incorporating functional bioassays (e.g., mixed lymphocyte reaction measuring T-cell proliferation inhibition), quantitative RNA analysis, flow cytometry of functionally relevant surface markers, and protein-based secretome assays. Despite over 75,000 publications on MSCs, few companies have succeeded in commercialising MSC products, in part due to the heterogeneity of the cell population and the difficulty of standardising potency (Hansen et al., 2022, *Front Immunol*. DOI: 10.3389/fimmu.2022.1085312. PMID: 36578497; Galipeau et al., 2016, *Cytotherapy*. PMID: 26424220).
- **Transition from fetal bovine serum (FBS) to human platelet lysate (hPL) or chemically defined, xeno-free media** is an ongoing industry trend driven by regulatory preference and safety considerations. Closed-system processing reduces contamination risk by >90% and confers regulatory advantages for GMP compliance (Jayaraman et al., 2021, *Front Cell Dev Biol*. PMID: 33928083).

6. Relevance to Pacific Island Nations

- **Fiji's leading causes of death are diabetes mellitus** (age-standardised mortality rate 186.4 per 100,000 population), **ischaemic heart disease** (173.2 per 100,000), and **stroke** (78.2 per 100,000). Non-communicable diseases account for 67.3% of all deaths. The probability of premature mortality from NCDs (cardiovascular disease, cancer, diabetes, or chronic respiratory disease) between ages 30 and 70 is 38.8% (WHO, Fiji Country Profile, data.who.int/countries/242).
- **Globally, 830 million people live with diabetes**, with prevalence rising most rapidly in low- and middle-income countries. Diabetes-related foot ulcers and lower-limb amputations represent a significant burden that MSC-based wound therapies may address. More than half (59%) of adults aged 30 and over living with diabetes were not receiving treatment in 2022 (WHO, Diabetes Fact Sheet, 2024).
- **MSC indications with the strongest alignment to Fiji's disease burden include**: diabetic wound healing and chronic ulcer management; osteoarthritis (given high obesity prevalence); cardiovascular repair following myocardial infarction; and stroke recovery. Preclinical and early clinical evidence for MSC-based wound healing is robust, with autologous bone-marrow MSCs demonstrating accelerated wound closure in chronic cutaneous ulcerations, diabetic foot ulcers, and pressure ulcers (Hu et al., 2018, *Stem Cells Int*. DOI: 10.1155/2018/6901983. PMID: 29887893; Ahangar et al., 2020, *Int J Mol Sci*. DOI: 10.3390/ijms21197038. PMID: 32987830).
- **No MSC clinical trials are currently registered in Pacific Island nations**, representing both a gap in regional evidence generation and an opportunity for Fiji to participate in the global clinical development programme.

C. Evidence Strength Assessment

Indication	Evidence Level	Basis of Assessment
Steroid-refractory acute GvHD	Strong	Phase III pivotal trial (70% ORR at Day 28); multiple regulatory approvals (FDA, PMDA, Health Canada, Medsafe NZ, NMPA); >500 patients in controlled studies; four-year survival data available
Osteoarthritis (knee)	Moderate	One approved product (Republic of Korea); 67 registered trials; consistent WOMAC improvements in Phase I/II; Phase III data emerging; MRI evidence of cartilage preservation
Crohn's disease / perianal fistulae	Moderate	Phase III RCT positive (ADMIRE-CD); EMA approval granted (2018) then withdrawn (2024) after confirmatory trial failure; mechanism validated; 25 registered trials
Spinal cord injury	Emerging	One conditionally approved product (Japan, PMDA); Phase I/II data show safety and modest neurological improvement; 11 registered trials; limited sample sizes
Ischaemic stroke	Emerging	Phase I/II trials confirm safety and feasibility; Phase II randomised data suggest functional recovery benefit; meta-analysis supports safety; 14+ registered trials; no Phase III completed
Acute respiratory distress syndrome	Emerging	17 registered trials (accelerated during COVID-19 pandemic); Phase I/II safety established; efficacy signals inconsistent across studies
Diabetic wounds / chronic ulcers	Emerging	Robust preclinical evidence; early clinical case series (n < 50) show accelerated wound closure; no Phase III data; high relevance to Pacific Island disease burden
Cardiac repair (post-MI)	Emerging	One approved product (Republic of Korea); Phase I/II trials show modest ejection fraction improvement; heterogeneous results; 10+ registered trials for heart failure
Chronic low back pain	Emerging	Phase III trial data pending; Regenerative Medicine Advanced Therapy (RMAT) designation granted by FDA for one programme
Liver disease / cirrhosis	Emerging	13+ registered trials; Phase I/II safety established; improvements in Child-Pugh scores reported; efficacy data preliminary
Amyotrophic lateral sclerosis	Emerging	One conditionally approved product (Republic of Korea); Phase I/II data show safety and potential slowing of disease progression
Longevity / wellness	Preclinical	No controlled clinical trial evidence for anti-ageing indications; marketed in unregulated settings without scientific validation; ISSCR guidelines caution against unproven interventions

D. Regulatory Status Snapshot: Approved MSC Products Worldwide

Product	Indication	Cell Source	Regulatory Body	Approval Year	Country
Queencell	Subcutaneous tissue defect	Autologous adipose-derived mixture	MFDS	2010	Republic of Korea
Cellgram-AMI	Acute myocardial infarction (ejection fraction improvement)	Autologous BM-MSC	MFDS	2011	Republic of Korea
Cartistem	Knee osteoarthritis (cartilage defects)	Allogeneic UC-MSC	MFDS	2012	Republic of Korea
Cupistem	Crohn's fistula	Autologous AD-MSC	MFDS	2012	Republic of Korea

Product	Indication	Cell Source	Regulatory Body	Approval Year	Country
Prochymal	Paediatric acute GvHD	Allogeneic BM-MSC	Health Canada; Medsafe (NZ)	2012	Canada; New Zealand
Neuronata-R	ALS (conditional)	Autologous BM-MSC	MFDS	2014	Republic of Korea
Temcell HS	Acute and refractory GvHD	Allogeneic BM-MSC	PMDA	2015	Japan
Stempeucel	Critical limb ischaemia	Allogeneic BM-MSC	DCGI	2016	India
Alofisel (darvadstrocel)†	Complex perianal fistulae (Crohn's disease)	Allogeneic AD-MSC	EMA	2018	European Union
Stemirac	Spinal cord injury (conditional)	Autologous BM-MSC	PMDA	2018	Japan
Remestemcel-L	Paediatric SR-aGvHD	Allogeneic BM-MSC	FDA	2024	United States
Ammitel-L	Steroid-refractory acute GvHD	Allogeneic hUC-MSC	NMPA	2025	China

†Marketing authorisation withdrawn December 2024 following failure of the ADMIRE-CD II confirmatory trial.

Sources: Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448; Jossen et al., 2018, Appl Microbiol Biotechnol. DOI: 10.1007/s00253-018-8912-x. PMID: 29564526; EMA, Alofisel EPAR, EMEA/H/C/004258.

E. Recommendation Framework

The evidence reviewed in this report supports a phased, partnership-led approach for any nation considering structured introduction of MSC-based therapies. The framework presented here reflects the maturation of the international cell therapy supply chain: reliable allogeneic MSC products manufactured under cGMP can today be procured from FDA-registered, EMA-aligned, and PMDA-aligned contract manufacturers, with validated cold-chain logistics extending to Pacific Island destinations. The pragmatic question for Fiji is therefore not whether to defer access until a domestic manufacturing capability is built, but how to enter the field through structured partnerships while installing a credible regulatory and quality framework concurrently. **Phase 1 (Regulatory Foundation and Partnership Formation, Years 1–2)** should focus on establishing a national regulatory pathway for advanced therapy medicinal products through a reference-agency reliance model recognising approvals by established regulators such as the Therapeutic Goods Administration (TGA, Australia), the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency (PMDA, Japan), or the Ministry of Food and Drug Safety (MFDS, Republic of Korea); concurrently, formal supply and technical partnerships should be established with cGMP-compliant cell therapy contract manufacturers in source markets aligned with Fiji's regulatory reference selection. **Phase 2 (Controlled Clinical Access, Years 2–4)** would enable access to MSC therapies with the strongest evidence base — initially steroid-refractory GvHD, osteoarthritis, and indications aligned with Fiji's non-communicable disease burden — through importation of approved products under a structured access scheme, with mandatory pharmacovigilance and outcome reporting aligned with the International Society for Stem Cell Research (ISSCR) Guidelines for Stem Cell Research and Clinical Translation (ISSCR, 2025). The conditional and time-limited approval pathways utilised in Japan and the Republic of Korea provide instructive precedent for enabling earlier patient access while post-marketing data are collected. **Phase 3 (Capacity Building and Regional Leadership, Years 3–7)** would involve investment in clinical workforce training, expansion of indications based on Phase 2 outcomes, and positioning of Fiji as a regional access hub for Pacific Island neighbours, with continued reliance on established international cGMP manufacturing supply rather than domestic build-out. Throughout all phases, the Ministry should ensure that any MSC-based interventions offered to patients hold marketing authorisation from a stringent regulatory authority, are manufactured to cGMP standards, and are subject to rigorous post-market surveillance. Detailed recommendations, including specific regulatory pathway options, infrastructure requirements, workforce development strategies, and cost-benefit considerations, are presented in Chapter 12 of this report.

Chapter 1: Introduction to Mesenchymal Stromal Cells

1.1 Definition and Nomenclature

1.1.1 Historical Context

The cells now broadly referred to as mesenchymal stromal cells (MSCs) were first identified in the 1960s by Alexander Friedenstein, who described a population of clonogenic, fibroblast-like cells within bone marrow capable of osteogenic differentiation upon transplantation (Friedenstein AJ et al., 1966, *J Embryol Exp Morphol*. PMID: 5336210). In subsequent work, Friedenstein and colleagues characterised these cells as a minor subpopulation of marrow-derived, plastic-adherent cells with osteogenic and haematopoietic-supportive potential, establishing the term "colony-forming unit-fibroblast" (CFU-F) to describe the clonogenic precursor population (Friedenstein AJ et al., 1970, *Cell Tissue Kinet*. PMID: 5523063; Friedenstein AJ et al., 1974, *Transplantation*. PMID: 4150881). In the 1990s, Caplan coined the term "mesenchymal stem cells" on the basis of the multilineage differentiation potential of these cells (Caplan AI, 1991, *J Orthop Res*. PMID: 1870029), and Pittenger and colleagues provided the landmark demonstration that adult human bone marrow–derived MSCs could differentiate into osteoblasts, adipocytes, and chondrocytes under defined in vitro conditions (Pittenger MF et al., 1999, *Science*. PMID: 10102814).

1.1.2 ISCT Minimal Criteria (2006)

To address the lack of a universally accepted definition, the International Society for Cellular Therapy (ISCT) published a position statement in 2006 establishing minimal criteria for defining multipotent mesenchymal stromal cells. These criteria comprise three pillars (Dominici M et al., 2006, *Cytotherapy*, 8(4): 315–317. DOI: 10.1080/14653240600855905):

1. **Plastic adherence**: Cells must adhere to plastic under standard tissue culture conditions.
2. **Surface marker profile**: ≥95% of the cell population must express CD105, CD73, and CD90; ≤2% must express CD45, CD34, CD14 (or CD11b), CD79α (or CD19), and HLA-DR.
3. **Trilineage differentiation**: Cells must demonstrate the capacity to differentiate into osteoblasts, adipocytes, and chondroblasts under standardised in vitro differentiating conditions.

These criteria remain the most widely cited identity standard for MSCs in both research and clinical manufacturing (Lechanteur C et al., 2016, *J Transl Med*. DOI: 10.1186/s12967-016-0892-y. PMID: 27207011; Hu MS et al., 2018, *Stem Cells Int*. DOI: 10.1155/2018/6901983. PMID: 29887893). Subsequent refinements have been proposed, including the addition of functional potency assays — notably, the ISCT working proposal on immunological characterisation recommended that MSCs be induced to express indoleamine 2,3-dioxygenase (IDO) upon interferon-γ (IFN-γ) stimulation and demonstrate suppression of T-cell proliferation in co-culture (Krampera M et al., 2013, *Cytotherapy*, 15(9): 1054–1061; Chen X et al., 2022, *Cell Prolif*. DOI: 10.1111/cpr.13141. PMID: 34936710). Tumorigenicity testing using immunodeficient animal models and comprehensive microbiological screening have also been incorporated into more recent quality standards (Chen X et al., 2022, *Cell Prolif*. DOI: 10.1111/cpr.13141. PMID: 34936710).

1.1.3 The Nomenclature Debate

The nomenclature surrounding MSCs has been a persistent source of scientific and regulatory confusion. Three principal terms compete in the literature:

- **Mesenchymal stem cells**: The original term popularised by Caplan (1991), implying indefinite self-renewal and broad differentiation capacity akin to haematopoietic stem cells.
- **Mesenchymal stromal cells**: Adopted by the ISCT in 2005–2006 to reflect the stromal residence and supportive function of these cells, and to acknowledge that rigorous evidence for in vivo self-renewal is lacking (Horwitz EM et al., 2005, *Cytotherapy*, 7(5): 393–395. DOI: 10.1080/14653240500319234. PMID: 16236628).
- **Medicinal signaling cells**: Proposed by Caplan in 2010 and elaborated in 2017, arguing that the primary therapeutic mechanism of MSCs is the secretion of bioactive molecules rather than tissue replacement, and that the term should reflect this paracrine function (Caplan AI, 2010, *Tissue Eng Part A*, 16(8): 2415–2417. DOI: 10.1089/ten.tea.2010.0216; Caplan AI, 2017, *Stem Cells Transl Med*, 6(6): 1445–1451. DOI: 10.1002/sctm.17-0051).

The current official position of the ISCT Mesenchymal Stromal Cell Committee, published in 2019, is that the acronym "MSC" should remain in use, but that the tissue source of origin must always be specified (e.g., BM-MSC, UC-MSC, AT-MSC) to reduce ambiguity (Viswanathan S et al., 2019, *Cytotherapy*, 21(10): 1019–1024. DOI: 10.1016/j.jcyt.2019.08.002. PMID: 31526643). Some investigators have argued for complete abolition of the MSC acronym altogether (Sipp D et al., 2018; Soliman H et al., 2021), though this position has not gained consensus (Česnik AB & Švajger U, 2024, *Front Cell Dev Biol*. DOI: 10.3389/fcell.2024.1400347. PMID: 39129786).

1.1.4 Regulatory Implications of Nomenclature

The nomenclature question is not merely academic. Regulatory classification of MSC-based products depends in part on whether the cells are characterised as a "stem cell" product (implying differentiation-based mechanism) or a "stromal/signaling cell" product (implying paracrine mechanism). This distinction affects the regulatory pathway applied — for example, whether a product is classified as a somatic cell therapy, a tissue-engineered product, or an advanced therapy medicinal product (ATMP) under frameworks such as the European Union's ATMP Regulation (EC) No 1394/2007. For Fiji's regulatory deliberations, clarity on nomenclature is essential to ensure that any future regulatory framework accurately reflects the biological mechanism of action and aligns with international standards.

1.2 Tissue Sources

MSCs can be isolated from a wide variety of human tissues. Although they share the core ISCT-defined characteristics, MSCs from different sources exhibit distinct phenotypic and functional properties that influence their suitability for specific clinical applications (Česnik AB & Švajger U, 2024, *Front Cell Dev Biol*. DOI: 10.3389/fcell.2024.1400347. PMID: 39129786). Comparative single-cell RNA sequencing has revealed that transcriptomic differences between tissue sources exceed those between individual donors, indicating a tissue-type-dependent pattern of MSC subpopulations (Medrano-Trochez C et al., 2021, as cited in Česnik AB & Švajger U, 2024). The most extensively studied and clinically utilised sources are bone marrow, adipose tissue, and umbilical cord/Wharton's jelly, with dental pulp and placenta/amniotic fluid representing emerging alternatives.

1.2.1 Bone Marrow–Derived MSCs (BM-MSCs)

Isolation method: BM-MSCs are obtained via bone marrow aspiration, typically from the iliac crest, followed by density gradient centrifugation (e.g., Ficoll) and selection by plastic adherence (Ullah I et al., 2015, *Biosci Rep*. DOI: 10.1042/BSR20150025. PMID: 25797907).

Yield and expansion: MSCs constitute a very small fraction of bone marrow mononuclear cells — typically 0.001–0.01% (Camilleri ET et al., 2016, *Stem Cell Res Ther*. DOI: 10.1186/s13287-016-0370-8. PMID: 27515308). Extensive ex vivo expansion is therefore required to achieve therapeutic cell doses. Clinical-scale banking experience has demonstrated that 1 to 45 therapeutic doses can be produced from a single bone marrow sample within three passages (Lechanteur C et al., 2016, *J Transl Med*. DOI: 10.1186/s12967-016-0892-y. PMID: 27207011).

Advantages: BM-MSCs are the most extensively characterised source and are considered the reference standard against which MSCs from other tissues are compared (Ullah I et al., 2015, *Biosci Rep*. PMID: 25797907). They have the longest track record in clinical trials and have demonstrated superior chondrogenic differentiation compared with some other sources (Bernardo M et al., 2007, *Connect Tissue Res*, 48: 132–140, as cited in Markov A et al., 2021, *Stem Cell Res Ther*. DOI: 10.1186/s13287-021-02265-1. PMID: 33736695).

Disadvantages: The aspiration procedure is invasive and can cause pain, bleeding, or infection (Markov A et al., 2021, *Stem Cell Res Ther*. PMID: 33736695). BM-MSC yield, proliferative capacity, and differentiation potential decline with donor age (Česnik AB & Švajger U, 2024, *Front Cell Dev Biol*. PMID: 39129786).

1.2.2 Adipose Tissue–Derived MSCs (AT-MSCs / ASCs)

Isolation method: AT-MSCs are isolated from subcutaneous adipose tissue obtained via liposuction or surgical excision, followed by enzymatic digestion (typically with collagenase) to obtain the stromal vascular fraction, from which MSCs are selected by plastic adherence (Ullah I et al., 2015, *Biosci Rep*. PMID: 25797907).

Yield and expansion: Adipose tissue is a substantially richer source of MSCs than bone marrow. Approximately 1–10% of the stromal vascular fraction comprises MSCs (Camilleri ET et al., 2016, *Stem Cell Res Ther*. PMID: 27515308). Under local anaesthesia, the volume of adipose tissue that can be harvested provides approximately 1 × 10^6 MSCs, compared with approximately 2.4 × 10^4 from an equivalent bone marrow harvest — a roughly 40-fold difference in initial yield (Pendleton C et al., 2013, *PLoS One*. DOI: 10.1371/journal.pone.0058198. PMID: 23554877).

Advantages: Minimally invasive harvesting from an abundant tissue source; higher initial cell yield; faster proliferation rate retained through multiple passages; strong anti-inflammatory and immunomodulatory properties (Zhao X et al., 2026, *Stem Cell Rev Rep*. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448; Pendleton C et al., 2013, *PLoS One*. PMID: 23554877).

Disadvantages: Donor-related heterogeneity remains a significant challenge (Zhao X et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448). Adipogenic differentiation bias may limit utility in certain applications. Secretome profiles show subtle differences from BM-MSCs (Konala VBR et al., 2020, *In Vitro Cell Dev Biol Anim*, 56: 1–12, as cited in Markov A et al., 2021).

1.2.3 Umbilical Cord and Wharton's Jelly–Derived MSCs (UC-MSCs / WJ-MSCs)

Isolation method: UC-MSCs can be isolated from multiple compartments of the umbilical cord, including Wharton's jelly (the gelatinous connective tissue), cord blood, the perivascular region, and the cord lining. Wharton's jelly MSCs are typically obtained by enzymatic digestion or explant culture of cord tissue (Ullah I et al., 2015, *Biosci Rep*. PMID: 25797907).

Yield and expansion: UC-MSCs and WJ-MSCs exhibit high proliferative potential and can be expanded for longer periods in vitro while maintaining greater genomic stability compared with adult-derived MSCs (Zhao X et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448). They demonstrate superior in vitro proliferation capacity compared with BM-MSCs (Koch TG et al., 2007, *BMC Biotechnol*. DOI: 10.1186/1472-6750-7-26. PMID: 17537254).

Advantages: Non-invasive, ethically uncontroversial collection from tissue normally discarded after birth, avoiding donor risk (Zhao X et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448). UC-MSCs express reduced HLA class I and secrete tolerogenic mediators, conferring low immunogenicity and supporting allogeneic use (Zhao X et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448). They promote immune tolerance by releasing chemokines that recruit suppressor cells, thereby reducing T-cell activation and inflammatory cytokine secretion (Zhao X et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448). These features make UC-MSCs particularly attractive for off-the-shelf allogeneic therapy.

Disadvantages: Reports of complications such as disseminated intravascular coagulation at high doses emphasise the need for standardised administration protocols (Zhao X et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448). Isolation from cryopreserved cord blood is technically challenging, and MSC isolation should ideally be performed from fresh cord blood prior to long-term cryopreservation (Koch TG et al., 2007, *BMC Biotechnol*. PMID: 17537254).

1.2.4 Dental Pulp–Derived MSCs (DP-MSCs)

Isolation method: DP-MSCs are isolated from the dental pulp of extracted teeth (deciduous or permanent) via enzymatic digestion (Ullah I et al., 2015, *Biosci Rep*. PMID: 25797907).

Advantages: DP-MSCs possess the capacity to differentiate into multiple cell types and have been used in preclinical research for periodontal disease, tooth reconstruction, dental pulp regeneration, and regeneration of neuronal and skeletal tissue (Česnik AB & Švajger U, 2024, *Front Cell Dev Biol*. PMID: 39129786). They can be obtained from surgical remnants, minimising donor morbidity.

Disadvantages: Limited tissue volume available per donor; clinical application remains predominantly in preclinical stages; less extensively characterised than BM-MSCs, AT-MSCs, or UC-MSCs.

1.2.5 Placenta and Amniotic Fluid–Derived MSCs

Isolation method: MSCs can be isolated from multiple placental compartments (chorionic villi, decidua, amniotic membrane) and from amniotic fluid, using enzymatic digestion or explant culture methods (Maacha S et al., 2020, *Stem Cells Int*. DOI: 10.1155/2020/4356359. PMID: 32215017).

Advantages: Like UC-MSCs, placental MSCs are obtained from tissue that is normally discarded, raising no ethical concerns. They can be isolated from perinatal tissues such as cord blood, placenta, amniotic fluid, and amniotic membrane (Maacha S et al., 2020, *Stem Cells Int*. PMID: 32215017). Placenta-derived MSC spheroids have been shown to secrete high levels of PGE2, HGF, and leukemia inhibitory factor (LIF), which suppress pro-inflammatory M1 macrophages and induce M2 macrophage phenotypes.

Disadvantages: Heterogeneity depending on the specific placental compartment; less standardised isolation protocols compared with BM-MSC or AT-MSC sources.

1.2.6 Comparative Summary

Feature	BM-MSC	AT-MSC	UC-MSC / WJ-MSC	DP-MSC
Harvest invasiveness	Invasive (aspiration)	Minimally invasive (liposuction)	Non-invasive (birth tissue)	Minimally invasive (extraction)
Initial cell yield	Very low (0.001–0.01%)	High (1–10% of SVF)	Moderate–High	Low (limited tissue)
Proliferative capacity	Moderate; declines with age	High; retained across passages	High; superior genomic stability	Moderate
Immunogenicity	Low (HLA-I low)	Low	Very low (reduced HLA-I)	Low
Chondrogenic potential	Superior	Moderate	Moderate	Limited data
Clinical trial experience	Most extensive	Extensive	Rapidly growing	Limited
Ethical concerns	Donor discomfort	Minimal	None	Minimal

Comparative analyses of MSCs from bone marrow, adipose tissue, and Wharton's jelly have confirmed that while all sources share fundamental MSC characteristics, they exhibit differences in immunomodulatory capacity, secretome composition, and differentiation bias (Jin HJ et al., 2013, *Int J Mol Sci*, 14: 17986–18001; Wang Q et al., 2016, *Hum Vaccin Immunother*, 12: 85–96, as cited in Markov A et al., 2021, *Stem Cell Res Ther*. PMID: 33736695). The choice of tissue source should be guided by the intended therapeutic application, manufacturing considerations, and regulatory requirements.

1.3 Mechanisms of Action

1.3.1 The Paracrine Hypothesis

A paradigm shift in the understanding of MSC therapeutics occurred with the recognition that MSCs exert their beneficial effects primarily through the secretion of bioactive molecules — the so-called paracrine mechanism — rather than through direct engraftment and differentiation into target tissues. Multiple studies have demonstrated that only a small number of transplanted MSCs engraft and differentiate in vivo, yet therapeutic effects are consistently observed (Rendra E et al., 2020, *F1000Research*. DOI: 10.12688/f1000research.21862.1. PMID: 32148780). Caplan and Correa proposed that MSCs function as site-regulated "drugstores" in vivo, secreting trophic and immunomodulatory factors in response to local microenvironmental cues (Caplan AI & Correa D, 2011, *Cell Stem Cell*, 9(1): 11–15. PMID: 21726829). This concept was further supported by Prockop, who described MSCs as "guardians of inflammation" (Prockop DJ, 2012, *Mol Ther*, 20(1): 14–20. PMID: 22008910).

The paracrine hypothesis was substantively advanced by the demonstration that intravenously administered MSCs, which become embolised in the lungs, are activated to secrete the anti-inflammatory protein TSG-6, which mediates therapeutic benefit in myocardial infarction models without requiring direct engraftment at the injury site (Lee RH et al., 2009, *Cell Stem Cell*, 5(1): 54–63. PMID: 19570514).

1.3.2 Key Secreted Factors

MSCs secrete a broad repertoire of bioactive molecules, collectively termed the secretome, which includes cytokines, chemokines, growth factors, and extracellular vesicles. The composition of the secretome is not fixed but adapts dynamically to the local milieu (Rendra E et al., 2020, *F1000Research*. PMID: 32148780). Key secreted factors and their principal functions include:

- **Vascular endothelial growth factor (VEGF)**: Pro-angiogenic; promotes neovascularisation and endothelial cell survival. VEGF and TGF-β1 secreted in conditioned medium promote angiogenesis via PI3K/Akt and MAPK pathways (Maacha S et al., 2020, *Stem Cells Int*. DOI: 10.1155/2020/4356359. PMID: 32215017).
- **Hepatocyte growth factor (HGF)**: Pro-angiogenic and anti-fibrotic; induces VEGF expression; participates in TGF-β/HGF–mediated regulation of regulatory T cells (Mishra VK et al., 2020, *Cells*. DOI: 10.3390/cells9051145. PMID: 32384763).
- **Insulin-like growth factor-1 (IGF-1)**: Pro-regenerative; promotes cell survival and proliferation. Hypoxia and serum deprivation priming increase production of VEGF, bFGF, HGF, IGF, and TGF-β (Maacha S et al., 2020, *Stem Cells Int*. PMID: 32215017).
- **Transforming growth factor-β (TGF-β)**: Immunomodulatory and anti-inflammatory; directly promotes Treg activation in concert with PGE2 (Mishra VK et al., 2020, *Cells*. PMID: 32384763).
- **Prostaglandin E2 (PGE2)**: A central mediator of MSC-mediated immunosuppression. PGE2 is constitutively secreted by MSCs and its production is dramatically enhanced by IFN-γ, TNF-α, or IL-1β stimulation. PGE2 negatively affects T-cell and NK-cell proliferation, increases the pool of regulatory T cells, stimulates macrophages to produce IL-10, and prevents monocyte differentiation into dendritic cells (Mishra VK et al., 2020, *Cells*. PMID: 32384763; Markov A et al., 2021, *Stem Cell Res Ther*. PMID: 33736695).
- **TNF-stimulated gene 6 (TSG-6)**: Anti-inflammatory; counteracts TNF-α and IL-1–mediated inflammation. TSG-6 has been identified as one of the most important mediators of MSC-mediated immunosuppression in vivo (Lee RH et al., 2009, *Cell Stem Cell*. PMID: 19570514; Egger D et al., 2018, *Bioengineering*. DOI: 10.3390/bioengineering5020048. PMID: 29921755).
- **Indoleamine 2,3-dioxygenase (IDO)**: Catalyses the breakdown of tryptophan, causing suppression of T cells. IDO is expressed by MSCs upon IFN-γ stimulation and drives M2 polarisation in macrophages and induces a tolerogenic phenotype in dendritic cells and Tregs (Samsonraj RM et al., 2017, *Stem Cells Transl Med*. DOI: 10.1002/sctm.17-0129. PMID: 29076267; Mishra VK et al., 2020, *Cells*. PMID: 32384763).

Additional immunoregulatory factors include IL-6, IL-10, HLA-G5, CCL-2, CCL-5, nitric oxide (NO), and heme oxygenase-1 (HO-1) (Mishra VK et al., 2020, *Cells*. PMID: 32384763; Samsonraj RM et al., 2017, *Stem Cells Transl Med*. PMID: 29076267).

1.3.3 Immunomodulation

The immunomodulatory capacity of MSCs is among their most therapeutically significant properties. MSCs interact with virtually all major immune cell populations, and the nature of their immunomodulatory effect is context-dependent — MSCs can adopt either pro-inflammatory or anti-inflammatory phenotypes depending on the levels of inflammatory stimulation in their microenvironment, a phenomenon termed "MSC polarisation" (Mishra VK et al., 2020, *Cells*. DOI: 10.3390/cells9051145. PMID: 32384763).

T-cell suppression: Under high levels of IFN-γ and TNF-α, MSCs produce TGF-β, HGF, IDO, PGE2, and NO, which directly inhibit T-lymphocyte activation and proliferation (Mishra VK et al., 2020, *Cells*. PMID: 32384763). MSC-to-T-cell contact induces IL-10 secretion, which attenuates T-cell proliferation, and stimulates HLA-G5 secretion, which inhibits activated T cells (Samsonraj RM et al., 2017, *Stem Cells Transl Med*. PMID: 29076267).

Regulatory T-cell (Treg) induction: MSC-derived TGF-β, HGF, and PGE2 directly promote the activation and expansion of $CD4^+CD25^+FOXP3^+$ regulatory T cells (Mishra VK et al., 2020, *Cells*. PMID: 32384763). Conditioned medium from MSCs has been shown to increase FOXP3 expression and positively adjust the Treg:Th17 balance in inflammatory arthritis models (Kay AG et al., 2017, *Sci Rep*. DOI: 10.1038/s41598-017-18144-w. PMID: 29269885).

Macrophage polarisation (M1→M2): MSCs induce the switch of monocytes and macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. This effect is mediated by PGE2, IDO, and IL-6, and results in increased IL-10 production and reduced TNF-α secretion (Mishra VK et al., 2020, *Cells*. PMID: 32384763; Egger D et al., 2018, *Bioengineering*. PMID: 29921755). M2 macrophages express CD206 and CD163 co-stimulatory molecules and enrich the microenvironment with IL-6 and IL-10 (Mishra VK et al., 2020, *Cells*. PMID: 32384763).

NK-cell modulation: MSCs inhibit NK-cell cytokine production, cytotoxicity, and proliferation through PGE2 and IDO (Mishra VK et al., 2020, *Cells*. PMID: 32384763). IFN-γ–treated MSCs are less susceptible to NK-cell–mediated lysis (Mishra VK et al., 2020, *Cells*. PMID: 32384763).

Dendritic cell regulation: PGE2 from MSCs hampers dendritic cell (DC) precursor differentiation and maturation. In the vicinity of MSC-treated microenvironments, mature DCs ($CD83^+$ with CD80 and CD86 co-stimulatory molecules) are impaired in their capacity for T-cell activation (Mishra VK et al., 2020, *Cells*. PMID: 32384763; Markov A et al., 2021, *Stem Cell Res Ther*. PMID: 33736695).

1.3.4 Anti-Inflammatory, Anti-Fibrotic, and Pro-Angiogenic Mechanisms

Beyond direct immunomodulation, MSCs exert therapeutic effects through three additional mechanistic axes:

Anti-inflammatory: MSCs secrete IL-10, galectins, IDO, PGE2, HO-1, TSG-6, CCL2, and NO, which collectively maintain tissue homeostasis and suppress inflammatory cascades (Mishra VK et al., 2020, *Cells*. PMID: 32384763). The anti-inflammatory effect is enhanced by preconditioning strategies such as hypoxia, 3D culture, or cytokine priming, which activate Akt, ERK, and p38MAPK signalling pathways (Rendra E et al., 2020, *F1000Research*. PMID: 32148780).

Anti-fibrotic: MSCs reduce fibrosis through modulation of extracellular matrix remodelling, suppression of TGF-β–driven fibrogenic pathways, and promotion of matrix metalloproteinase activity. Human bone marrow MSC-derived exosomes have been shown to alleviate liver fibrosis through the Wnt/β-catenin pathway (Rong X et al., 2019, *Stem Cell Res Ther*, 10: 98, as cited in Hoang DH et al., 2020, *Front Mol Biosci*. DOI: 10.3389/fmolb.2020.00119. PMID: 32671095).

Pro-angiogenic: MSCs release a plethora of angiogenic factors including bFGF, VEGF, TGF-β, PDGF, angiopoietin-1, placental growth factor, IL-6, HGF, and MCP-1, which stimulate angiogenesis both in vitro and in vivo (Maacha S et al., 2020, *Stem Cells Int*. DOI: 10.1155/2020/4356359. PMID: 32215017). MSC aggregate cultivation further enhances secretion of pro-angiogenic factors including bFGF and angiogenin (Egger D et al., 2018, *Bioengineering*. PMID: 29921755).

1.4 Exosome and Secretome Biology

1.4.1 Definition and Biogenesis of MSC-Derived Extracellular Vesicles

The MSC secretome encompasses both soluble factors (cytokines, chemokines, growth factors) and insoluble nano/microstructured extracellular vesicles (EVs) (Mocchi M et al., 2021, *Pharmaceutics*. DOI: 10.3390/pharmaceutics13081129. PMID: 34452088). EVs are broadly classified by size and biogenesis into three categories: exosomes (30–150 nm, of endosomal origin), microvesicles (100 nm–1 µm, shed from the plasma membrane), and apoptotic bodies (>1 µm) (Vizoso FJ et al., 2017, *Int J Mol Sci*. DOI: 10.3390/ijms18091852. PMID: 28841158). MSC-derived exosomes transfer functional cargoes including miRNA, mRNA, peptides, proteins, cytokines, and lipids from MSCs to recipient cells, participating in intercellular communication and contributing to tissue repair (Tsiapalis D & O'Driscoll L, 2020, *Cells*. DOI: 10.3390/cells9040991. PMID: 32316248).

1.4.2 Therapeutic Mechanisms of MSC-Derived Exosomes

MSC-derived exosomes recapitulate many of the therapeutic effects attributed to their parent cells. Key evidence includes:

- **Cardioprotection**: Exosomes secreted by MSCs reduce myocardial ischaemia/reperfusion injury by increasing ATP levels, decreasing oxidative stress, and activating the PI3K/Akt pathway to enhance myocardial viability (Lai RC et al., 2010, *Stem Cell Res*, 4(3): 214–222. PMID: 20138817; Arslan F et al., 2013, *Stem Cell Res*, 10(3): 301–312. PMID: 23399448).
- **Wound healing**: MSC exosomes induce proliferation and migration of normal and chronic wound fibroblasts and enhance angiogenesis in vitro (Shabbir A et al., 2015, *Stem Cells Dev*, 24: 1635–1647. PMID: 25867197). Comparative studies have demonstrated differential wound-healing capacity of exosomes from BM-MSCs, AT-MSCs, and UC-MSCs (Hoang DH et al., 2020, *Front Mol Biosci*. DOI: 10.3389/fmolb.2020.00119. PMID: 32671095).
- **Immunomodulation**: Exosomes from IL-1β–primed MSCs deliver miR-21 and miR-146a, which induce macrophage M2 polarisation and ameliorate sepsis in preclinical models.
- **Neuroprotection**: Exosome-mediated transfer of miR-133b from MSCs to neural cells contributes to neurite outgrowth (Xin H et al., 2012, *Stem Cells*, 30: 1556–1564, as cited in Ahangar P et al., 2020, *Int J Mol Sci*. DOI: 10.3390/ijms21197038. PMID: 32987830).

1.4.3 The Cell-Free Therapy Concept

The use of MSC-derived secretome or exosomes as cell-free therapeutics offers several potential advantages over whole-cell MSC infusion (Vizoso FJ et al., 2017, *Int J Mol Sci*. DOI: 10.3390/ijms18091852. PMID: 28841158):

1. **Safety**: Resolves concerns associated with transplantation of living, proliferative cell populations, including immune compatibility, tumorigenicity, emboli formation, and transmission of infections.
2. **Standardisation**: The secretome can be evaluated for safety, dosage, and potency in a manner analogous to conventional pharmaceutical agents.
3. **Storage**: Can be stored without potentially toxic cryopreservative agents for extended periods without loss of product potency. Freeze-dried MSC secretome formulations have been developed under GMP-compliant conditions, producing shelf-stable powder products containing preserved extracellular vesicles and proteins (Mocchi M et al., 2021, *Pharmaceutics*. DOI: 10.3390/pharmaceutics13081129. PMID: 34452088).
4. **Scalability**: Bioreactor-based production systems enable scalable manufacturing of MSC-derived EVs under serum-free and xeno-free conditions (de Almeida Fuzeta M et al., 2020, *Front Cell Dev Biol*. DOI: 10.3389/fcell.2020.553444. PMID: 33224943).

1.4.4 Current Clinical Development

MSC-derived exosome products are at an early stage of clinical development. A landmark case report demonstrated that MSC-derived exosomes could treat therapy-refractory graft-versus-host disease (Kordelas L et al., 2014, *Leukemia*, 28: 970–973. PMID: 24445866, as cited in de Almeida Fuzeta M et al., 2020). The ISEV (International Society for Extracellular Vesicles) and ISCT have jointly published position papers on defining MSC-derived small extracellular vesicles for therapeutic applications, establishing minimum characterisation requirements (Witwer KW et al., 2019, *J Extracell Vesicles*. DOI: 10.1080/20013078.2019.1609206. PMID: 31069028). Standardised protocols for secretome and exosome extraction remain an active area of development, with recent reviews emphasising the imperative of establishing unified methodologies for reliable clinical trial evaluation (Zununi Vahed S et al., 2025, as cited in knowledge base. PMID: 40058715).

1.5 Key Biological Properties for Therapy

1.5.1 Immune Privilege and Low Immunogenicity

MSCs have historically been considered "immune-privileged" cells, a property attributed to their low expression of MHC class I molecules and absence of MHC class II (HLA-DR) and co-stimulatory molecules under basal conditions (Lechanteur C et al., 2016, *J Transl Med*. PMID: 27207011). This immunological profile enables MSCs to escape lysis by cytotoxic T cells and NK cells, permitting transplantation between HLA-mismatched individuals without the need for immunosuppression (Chambers DC et al., 2017, *Stem Cells Transl Med*. DOI: 10.1002/sctm.16-0372. PMID: 28186707).

However, recent data have nuanced this view. MSCs can upregulate both HLA class I and class II upon exposure to inflammatory factors, potentially triggering host immune responses (Rendra E et al., 2020, *F1000Research*. PMID: 32148780). In allogeneic settings, MSC transplantation may provoke humoral and cellular immune responses, including the development of donor-specific antibodies, although the clinical significance of this phenomenon remains debated (Rendra E et al., 2020, *F1000Research*. PMID: 32148780; Česnik AB & Švajger U, 2024, *Front Cell Dev Biol*. PMID: 39129786). Repeated intra-articular injection of allogeneic MSCs in an equine model resulted in adverse clinical responses, suggesting potential for immune recognition upon repetitive exposures (Joswig et al., 2017, as cited in Česnik AB & Švajger U, 2024). Notably, UC-MSCs and WJ-MSCs exhibit an immunological profile characterised by further reduced HLA class I expression and secretion of tolerogenic mediators, which may confer superior immune compatibility for allogeneic applications (Zhao X et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448).

1.5.2 Homing to Injury Sites

MSCs exhibit selective tropism toward sites of tissue injury and inflammation, a property termed "homing." The chemokine receptor CXCR4 and its ligand stromal-derived factor 1-α (SDF-1α) play a central role in this process (Ullah I et al., 2015, *Biosci Rep*. PMID: 25797907; Markov A et al., 2021, *Stem Cell Res Ther*. PMID: 33736695). Inflammatory cytokines including IL-1β, TNF-α, and TGF-1β enhance MSC migration by upregulating matrix metalloproteinases (MMPs) (Ullah I et al., 2015, *Biosci Rep*. PMID: 25797907).

However, the homing efficiency of MSCs is influenced by multiple factors. When administered intravenously, MSCs are predominantly trapped in the pulmonary capillary bed and die within 24 hours, with limited migration to distal injury sites (Rendra E et al., 2020, *F1000Research*. PMID: 32148780). This observation has led to the recognition that local or intra-arterial delivery may be more effective than systemic intravenous infusion for applications requiring direct cellular presence at the target site (Ullah I et al., 2015, *Biosci Rep*. PMID: 25797907). Three-dimensional spheroid culture has been shown to upregulate CXCR4 expression, potentially enhancing homing capacity of spheroid-derived MSCs (Petrenko Y et al., 2017, *Stem Cell Res Ther*. DOI: 10.1186/s13287-017-0558-6. PMID: 28446248).

1.5.3 Passage Number Effects on Potency

The ex vivo expansion required to achieve therapeutic cell doses introduces the risk of replicative senescence, which progressively compromises MSC functionality. Key findings include:

- **Proliferative decline**: The average number of population doublings (PDs) decreases with increasing passage number. BM-MSCs can typically be expanded to 15–30 cumulative PDs before approaching senescence, with some reports of up to 50 PDs under optimised conditions (Bonab MM et al., 2006, *BMC Cell Biol.* DOI: 10.1186/1471-2121-7-14. PMID: 16529651; Yang YK et al., 2018, *Stem Cell Res Ther.* DOI: 10.1186/s13287-018-0876-3. PMID: 29751774).
- **Telomere shortening**: Mean telomere restriction fragment length decreases from approximately 9.2 kbp in early passages to 8.7 kbp by the 9th passage, consistent with replicative ageing (Bonab MM et al., 2006, *BMC Cell Biol.* PMID: 16529651).
- **Functional impairment**: Differentiation potential drops from approximately the 6th passage onward (Bonab MM et al., 2006, *BMC Cell Biol.* PMID: 16529651). Population doubling has been reported to inversely correlate with MSC potency, with early-passage cells being more potent than extensively expanded batches (Česnik AB & Švajger U, 2024, *Front Cell Dev Biol.* PMID: 39129786).
- **Morphological changes**: Late-passage MSCs display enlarged, flattened morphology characteristic of senescence, in contrast to the uniform fibroblast-like spindle shape of early cultures (Yang YK et al., 2018, *Stem Cell Res Ther.* PMID: 29751774).
- **Homing capacity**: Higher passage number decreases the engraftment efficiency of MSCs; freshly isolated MSCs demonstrate greater homing efficiency than extensively cultured cells (Ullah I et al., 2015, *Biosci Rep.* PMID: 25797907).

These observations underscore the importance of establishing passage limits and cumulative population doubling thresholds as critical quality attributes in MSC manufacturing for clinical use (Wagner W et al., 2010, *Aging*, DOI: 10.18632/aging.100136. PMID: 20453259; Turinetto V et al., 2016, *Int J Mol Sci.* DOI: 10.3390/ijms17071164. PMID: 27447618).

1.5.4 Cryopreservation Effects on Function

Cryopreservation is essential for the banking of off-the-shelf MSC products, but introduces functional perturbations that must be carefully managed:

- **Viability**: Mean viability at freezing is approximately 90%, dropping to approximately 76% after thawing, with a mean decrease of 14% (Lechanteur C et al., 2016, *J Transl Med.* PMID: 27207011). Long-term cryopreservation (up to 7–8 years) can maintain post-thaw viability of 77–83% (Lechanteur C et al., 2016, *J Transl Med.* PMID: 27207011).
- **Functional impairment ("cryo stun effect")**: In the first 24 hours after thawing, cryopreservation reduces metabolic activity, increases apoptosis, and impairs immunosuppressive potency and adhesion potential (Česnik AB & Švajger U, 2024, *Front Cell Dev Biol.* PMID: 39129786). Thawed MSCs demonstrate compromised immunosuppressive function and increased susceptibility to T-cell–mediated lysis compared with fresh MSCs, with enhanced cytolysis observed in allogeneic conditions (Chinnadurai R et al., 2016, *Stem Cells*, 34: 2429–2442. PMID: 27299362).
- **Recovery**: It remains unclear how quickly MSCs recover their full therapeutic activity post-thaw, and whether the cryo stun effect is clinically relevant (Moll G et al., 2016, *Adv Biochem Eng Biotechnol.* PMID: 27837556). IFN-γ pre-licensing before cryobanking has been shown to partially restore immunosuppressive function of thawed MSCs through IDO-dependent mechanisms, though lung homing defects persist (Chinnadurai R et al., 2016, *Stem Cells.* PMID: 27299362).
- **Emerging solutions**: DMSO-free cryopreservation reagents have demonstrated improved post-thaw viability (>90% pre-freeze viability maintained after 24-hour room temperature holding) and enhanced functional recovery compared with conventional DMSO-based formulations (Lam A et al., 2026, *Front Bioeng Biotechnol.* DOI: 10.3389/fbioe.2026.1736526).

1.5.5 Dose-Dependent Effects

MSC therapeutic effects are dose-dependent, though the optimal dose varies by indication, route of administration, and tissue source. Higher cell numbers and hypoxic culture conditions influence the expression of MMPs and other factors important for migration and homing (Ullah I et al., 2015, *Biosci Rep.* PMID: 25797907). Clinical trials have employed a wide range of doses, typically from 1×10^6 to 10×10^6 cells per kilogram of body weight for intravenous administration, though standardised dose-finding studies remain limited across most indications. The relationship between dose, route of administration, and clinical outcome is an area requiring further systematic investigation to inform evidence-based dosing guidelines.

1.5.6 Summary of Key Biological Properties

The biological properties of MSCs — their multilineage differentiation capacity, paracrine signalling, immunomodulatory potency, low immunogenicity, homing behaviour, and amenability to ex vivo expansion and cryopreservation — collectively underpin their therapeutic potential across a broad range of clinical indications. However, each of these properties is subject to variability arising from tissue source, donor characteristics, manufacturing processes, and storage conditions. Understanding and controlling these variables is essential for the translation of MSC-based therapies from preclinical promise to reproducible clinical benefit. For the Republic of Fiji, where the disease burden includes conditions potentially amenable to MSC therapy — including diabetes, cardiovascular disease, chronic wounds, and osteoarthritis — a thorough appreciation of MSC biology provides the necessary foundation for informed policy decisions regarding the evaluation, regulation, and potential adoption of these therapies.

Chapter 2: Fiji Healthcare Landscape and Public Health Needs

2.1 Fiji Health System Overview

2.1.1 Population and Demographics

The Republic of Fiji is an archipelagic nation in the South Pacific comprising over 330 islands, of which approximately 110 are permanently inhabited, spanning more than 18,000 square kilometres of land across a vast maritime zone (Fiji Ministry of Health and Medical Services [MHMS], "About Us," 2024). As of 2023, Fiji's population stands at **924,145**, with a population growth rate of 0.51% and a projected increase of 8.2% to approximately 1,000,261 by 2050 (WHO, Country Data Profile: Fiji, 2023; UNDESA Population Division, World Population Prospects 2022).

The population pyramid reveals a relatively young demographic structure, with substantial cohorts in the 0–34 age range. The 2007 census placed the population at 837,271, distributed across four administrative divisions: Central (342,477), Western (319,611), Northern (135,961), and Eastern (39,313). The urban population (50.7%) slightly exceeded the rural population (49.3%), a trend that has continued to accelerate in subsequent years (MHMS Fiji, "About Us," 2024). Fiji is classified by the World Bank as an **upper-middle income country** (UMC) and falls within the **WHO Western Pacific Region** (WHO, Country Data Profile: Fiji, 2023).

2.1.2 Life Expectancy

Life expectancy at birth in Fiji was **65.5 years** [95% CI: 64.7–66.6] in 2021, representing a slight worsening of 0.32 years from 65.8 years in 2000 (WHO, Global Health Estimates, 2024). This trajectory stands in stark contrast to the global average of 71.4 years and the WHO Western Pacific regional average of 77.4 years in the same year. Female life expectancy (67.7 years) exceeds male life expectancy (63.5 years), though both have deteriorated marginally since 2000 (WHO, Global Health Estimates, 2024).

Healthy life expectancy (HALE) at birth was **57.7 years** [95% CI: 56.9–58.9] in 2021, a decline of 0.44 years from 58.1 years in 2000. This compares unfavourably with the global HALE of 61.9 years and the Western Pacific regional HALE of 68.2 years (WHO, Global Health Estimates, 2024). The gap between life expectancy and HALE (approximately 7.8 years) represents the average duration of life spent in less-than-full health, predominantly attributable to non-communicable disease (NCD) morbidity.

2.1.3 Healthcare Infrastructure

Fiji's health system is administered by the Ministry of Health and Medical Services (MHMS), which operates under four main administrative divisions and 21 sub-divisions, including Rotuma. The public health infrastructure comprises:

- **3 Divisional Hospitals** (tertiary-level referral centres in Suva, Lautoka, and Labasa)
- **18 Sub-divisional Hospitals** (secondary-level facilities)
- **Over 80 Health Centres** (primary care)
- **99 Nursing Stations** (community-level outposts, as of 2014)

(MHMS Fiji, "About Us," 2024)

The geographic dispersion of the population across a vast maritime territory poses significant challenges for health service delivery. Outer island communities frequently rely on nursing stations staffed by a single nurse, with referral to sub-divisional or divisional hospitals requiring inter-island transport that may be delayed by weather, distance, or logistical constraints. This geographic reality is a fundamental consideration for any advanced therapy programme, as cold-chain logistics, specialist administration, and post-treatment monitoring would need to accommodate island geography.

2.1.4 Health Workforce

WHO data for Fiji report the following health workforce densities:

Indicator	Value	Year
Density of dentistry personnel (per 10,000 population)	1.17	Most recent available
Density of pharmaceutical personnel (per 10,000 population)	1.03	Most recent available
Density of physicians (per 10,000 population)	~5.0	
Density of nursing and midwifery personnel (per 10,000 population)	~25	

(WHO, Country Data Profile: Fiji, 2023)

Fiji faces persistent challenges in specialist retention, with many trained physicians and specialists emigrating to Australia, New Zealand, and other higher-income countries. Specialist services in orthopaedics, nephrology, endocrinology, and cardiology are concentrated in the divisional hospitals, particularly the Colonial War Memorial Hospital in Suva, creating bottlenecks in referral pathways and limiting access for rural and outer-island populations.

2.1.5 Healthcare Expenditure

Current health expenditure as a percentage of GDP was reported at **5.38%** (2021) by the WHO Global Health Expenditure Database, though a more recent WHO country page figure indicates **10.33%** (2022), which may reflect pandemic-related spending or methodological revision (WHO, Global Health Expenditure Database, 2024; WHO, Country Page: Fiji, 2022). Even at the higher estimate, per-capita health spending remains constrained relative to the disease burden, and the health system is heavily dependent on external development assistance from partners including the Australian Government (DFAT), New Zealand (MFAT), WHO, the Secretariat of the Pacific Community (SPC), JICA, UNICEF, UNFPA, and the Global Fund (MHMS Fiji, "About Us," 2024).

2.1.6 Key Challenges

The principal structural challenges facing Fiji's health system include:

1. **Geographic dispersion**: Over 330 islands with dispersed populations requiring maritime or aerial transport for referral care.
2. **Health workforce shortages**: Emigration of trained specialists; limited sub-specialist capacity in areas relevant to advanced therapies (immunology, haematology, cell biology).
3. **Infrastructure limitations**: Absence of GMP-grade cell processing facilities, limited cold-chain capacity for biological products, and no established biobanking infrastructure.
4. **Epidemiological transition**: A dual burden of persistent communicable diseases (leptospirosis, tuberculosis incidence of 72 per 100,000 [WHO, 2023], typhoid) alongside a dominant and growing NCD burden.

5. **Climate vulnerability**: As a Small Island Developing State (SIDS), Fiji faces recurrent cyclones and flooding that disrupt health service delivery and exacerbate chronic disease management gaps.

2.2 Disease Burden — Non-Communicable Diseases

Non-communicable diseases constitute the dominant cause of mortality and morbidity in Fiji. WHO estimates that **67.3% of all deaths** in Fiji are attributable to NCDs, with an additional 3.3% from injuries and 22.4% from communicable, maternal, perinatal, and nutritional conditions (WHO, Country Data Profile: Fiji, 2023). The probability of premature mortality from NCDs (dying between ages 30 and 70 from cardiovascular disease, cancer, diabetes, or chronic respiratory disease) is **38.8%** [95% CI: 27.3%–49.6%], among the highest in the world (WHO, Country Data Profile: Fiji, 2023).

2.2.1 Diabetes Mellitus (Type 2)

Diabetes mellitus is the **leading cause of death** in Fiji among females (age-standardised mortality rate: 202.4 per 100,000) and the leading or second-leading cause overall (combined sex rate: 186.4 per 100,000) (WHO, Country Data Profile: Fiji, 2023). This positions Fiji among the countries most severely affected by diabetes globally.

The WHO reports that globally, 14% of adults aged 18 years and older were living with diabetes in 2022, an increase from 7% in 1990, with prevalence rising more rapidly in low- and middle-income countries (WHO, Diabetes Fact Sheet, 2024). Pacific Island nations, including Fiji, consistently rank among the highest-prevalence countries worldwide. The International Diabetes Federation (IDF) has estimated Fiji's age-adjusted diabetes prevalence at approximately 15–20% of the adult population.

Diabetes in Fiji drives a cascade of complications with direct relevance to MSC therapy research:

- **Diabetic foot ulcers and lower-limb amputations**: Peripheral neuropathy and vascular disease lead to chronic, non-healing wounds that frequently progress to amputation.
- **Diabetic nephropathy**: A major contributor to chronic kidney disease and end-stage renal failure.
- **Diabetic retinopathy**: A leading cause of preventable blindness.
- **Cardiovascular complications**: Diabetes is a major independent risk factor for ischaemic heart disease and stroke.

Globally, diabetes was the direct cause of 1.6 million deaths in 2021, with 47% occurring before age 70. An additional 530,000 kidney disease deaths were attributable to diabetes, and high blood glucose contributed to approximately 11% of cardiovascular deaths (WHO, Diabetes Fact Sheet, 2024; Global Burden of Disease Collaborative Network, GBD Study 2021).

2.2.2 Cardiovascular Disease

Ischaemic heart disease is the **leading cause of death among males** in Fiji (age-standardised mortality rate: 222.8 per 100,000) and the second or third leading cause overall (combined rate: 173.2 per 100,000) (WHO, Country Data Profile: Fiji, 2023). Stroke ranks fourth overall (78.2–83.0 per 100,000), and hypertensive heart disease contributes an additional 15.7–17.0 per 100,000 deaths (WHO, Country Data Profile: Fiji, 2023).

The combined cardiovascular disease burden — encompassing ischaemic heart disease, stroke, and hypertensive heart disease — represents the single largest disease category in Fiji and is closely interlinked with the diabetes and obesity epidemics. Management is constrained by limited access to interventional cardiology, cardiac surgery, and specialist rehabilitation services.

2.2.3 Chronic Kidney Disease

Kidney diseases rank as the **fifth leading cause of death** in Fiji (27.7–36.3 per 100,000), driven predominantly by diabetic nephropathy and hypertensive nephrosclerosis (WHO, Country Data Profile: Fiji, 2023). Dialysis services in Fiji are limited and concentrated in urban centres, with peritoneal dialysis and haemodialysis capacity insufficient to meet demand. Renal transplantation is not routinely available domestically, and patients requiring transplant must seek care overseas, predominantly in India or Australia, at substantial personal and public cost.

2.2.4 Obesity

Fiji, in common with many Pacific Island nations, has among the highest obesity prevalence rates globally. WHO NCD Risk Factor Collaboration data indicate that adult obesity (BMI ≥ 30 kg/m²) prevalence in Fiji exceeds 30%, with overweight (BMI ≥ 25 kg/m²) prevalence exceeding 60% in some surveys. Obesity is a primary driver of type 2 diabetes, cardiovascular disease, osteoarthritis, and certain cancers, and its prevalence in Fiji has been rising steadily over recent decades. Dietary transition toward energy-dense, nutrient-poor imported foods, combined with declining physical activity, underpins this trend.

2.2.5 Cancer

Breast cancer (41.2 per 100,000 in females) and cervical cancer (22.2 per 100,000 in females) feature among the top ten causes of death in Fiji (WHO, Country Data Profile: Fiji, 2023). Cancer diagnostic and treatment services are limited, with no radiation therapy facility currently operational in Fiji. Patients requiring oncological care frequently travel to Australia, New Zealand, or India. While MSC therapies are not currently indicated for cancer treatment — and indeed, the immunomodulatory properties of MSCs raise theoretical concerns regarding tumour promotion — the cancer burden contextualises the broader NCD crisis and the need for comprehensive health system strengthening.

2.2.6 Chronic Respiratory Disease

Asthma ranks among the top ten causes of death in Fiji (19.8–25.1 per 100,000), and chronic obstructive pulmonary disease (COPD) contributes an additional 20.3–24.4 per 100,000 deaths (WHO, Country Data Profile: Fiji, 2023). While MSC therapies for respiratory conditions remain largely investigational, the burden of chronic respiratory disease adds to the overall NCD-driven demand on Fiji's health system.

Summary Table: Leading Causes of Death in Fiji

Rank	Cause of Death (Both Sexes)	Age-Standardised Mortality Rate (per 100,000)
1	Diabetes mellitus	186.4
2	Ischaemic heart disease	173.2
3	COVID-19	153.2
4	Stroke	78.2
5	Kidney diseases	32.1
6	Lower respiratory infections	23.0
7	Asthma	22.5
8	Breast cancer	20.6

Rank	Cause of Death (Both Sexes)	Age-Standardised Mortality Rate (per 100,000)
9	COPD	20.3
10	Hypertensive heart disease	15.7

Source: WHO, Country Data Profile: Fiji (data.who.int/countries/242), Global Health Estimates, extracted 2023.

2.3 Musculoskeletal and Wound Burden

2.3.1 Osteoarthritis

Osteoarthritis (OA) represents a significant and under-documented burden in Fiji. While Fiji-specific prevalence data are limited, the Global Burden of Disease Study 2019 estimated that OA affects approximately 7% of the global population, with prevalence rising sharply with age and obesity (GBD 2019 Diseases and Injuries Collaborators, *Lancet*, 2020). Given Fiji's high obesity prevalence and ageing population trajectory, OA prevalence is likely to be at or above global averages. Knee OA is the most common form and is a leading cause of disability in adults over 50 years.

OA is of particular relevance to MSC therapy assessment because intra-articular MSC injection for knee OA is among the most extensively studied MSC indications globally, with multiple Phase I/II and Phase II/III trials demonstrating safety and preliminary efficacy signals including pain reduction (VAS, WOMAC scores) and cartilage quality improvement on MRI (Goldberg et al., 2017, *J Orthop Surg Res.* DOI: 10.1186/s13018-017-0534-y; Filardo et al., 2016, *J Orthop Surg Res.* DOI: 10.1186/s13018-016-0378-x; Margiana et al., 2022, *Stem Cell Res Ther.* DOI: 10.1186/s13287-022-03054-0. PMID: 35902958).

2.3.2 Sports and Occupational Injuries

Fiji has a strong sporting culture, particularly in rugby union and rugby sevens, with high rates of musculoskeletal injuries including ligament tears, cartilage damage, and fractures. Occupational injuries in agriculture, fishing, and construction also contribute to the musculoskeletal burden. Cartilage injuries and meniscal damage in younger populations represent potential future indications for regenerative approaches, though current evidence for MSC-based cartilage repair remains at the Phase I/II stage.

2.3.3 Chronic Wounds

The intersection of diabetes, peripheral vascular disease, and obesity creates a substantial chronic wound burden in Fiji. Diabetic foot ulcers are a major clinical challenge, frequently progressing to infection, gangrene, and lower-limb amputation. WHO notes that many people with diabetes develop foot problems from nerve damage and poor blood flow, which can cause foot ulcers and may lead to amputation (WHO, Diabetes Fact Sheet, 2024).

MSC-based therapies for chronic wound healing have demonstrated promising preclinical and early clinical results. Hu et al. (2018) conducted a comprehensive review demonstrating that MSCs promote cell migration, angiogenesis, epithelialisation, and granulation tissue formation, resulting in accelerated wound closure and reduced scarring (Hu et al., 2018, *Stem Cells Int.* DOI: 10.1155/2018/6901983. PMID: 29887893). Clinical studies have shown that autologous bone marrow-derived MSCs applied to chronic non-healing wounds achieved complete healing in 90% of cases (n = 20) when delivered on collagen sponges, and randomised studies demonstrated significantly decreased wound size (72% vs. 25%) at 12 weeks compared to standard wound care (Hu et al., 2018, *Stem Cells Int.* PMID: 29887893). Adipose-derived MSCs have similarly shown efficacy in diabetic wound models, with Zhou et al. reporting improved granulation tissue coverage in 346 patients with skin wounds (Margiana et al., 2022, *Stem Cell Res Ther.* PMID: 35902958).

2.3.4 Burns

Fiji experiences a notable burden of burn injuries, particularly in rural and peri-urban settings where open-fire cooking remains common. Burn wound management is resource-intensive and frequently complicated by infection and scarring. MSC-based approaches, including MSC-conditioned medium and MSC-derived exosomes, have shown promise in preclinical burn models for accelerating re-epithelialisation and reducing scar formation (Ahangar et al., 2020, *Int J Mol Sci.* DOI: 10.3390/ijms21197038. PMID: 32987830).

2.3.5 Chronic Pain

Chronic pain associated with OA, diabetic neuropathy, musculoskeletal injuries, and post-surgical conditions represents a significant quality-of-life burden. Limited access to specialist pain management services and physiotherapy in Fiji means that many patients rely on non-steroidal anti-inflammatory drugs (NSAIDs) with attendant gastrointestinal and renal risks. MSC therapies that could address underlying tissue pathology rather than merely managing symptoms would represent a paradigm shift in chronic pain management, though such applications remain investigational.

2.4 Fiji Medicines Regulatory Authority

2.4.1 Current Regulatory Framework for Pharmaceuticals

Fiji's pharmaceutical regulation is governed by the **Fiji Pharmaceutical and Biomedical Services Centre (FPBSC)** within the Ministry of Health and Medical Services, operating under the **Medicinal Products Act 2011** (as amended). The regulatory framework covers the registration, importation, distribution, and quality assurance of conventional pharmaceutical products. Fiji maintains a National Medicines List aligned with the WHO Model List of Essential Medicines and participates in the WHO Prequalification Programme for procurement of quality-assured medicines.

The MHMS operates a **Fiji Human Health Research Ethics Review Committee** that reviews all health research proposals, including clinical trials, conducted within Fiji (MHMS Fiji, 2024). This committee provides ethical oversight but is not equivalent to a dedicated clinical trial regulatory authority.

2.4.2 Biologics and Biosimilar Regulation

Fiji's regulatory framework for biological products, including vaccines, blood products, and biosimilars, is less developed than its framework for conventional pharmaceuticals. There is no publicly available, dedicated biologics regulatory pathway comparable to the Australian Therapeutic Goods Administration (TGA) Australian Regulatory Guidelines for Biologicals (ARGB) or the European Medicines Agency (EMA) biologics framework. Vaccine regulation benefits from WHO prequalification reliance and procurement through UNICEF Supply Division and the Pan American Health Organization (PAHO) Revolving Fund mechanisms.

2.4.3 Cell Therapy and ATMP-Specific Regulation

There is currently no dedicated regulatory framework for advanced therapy medicinal products (ATMPs), including cell therapies, gene therapies, or tissue-engineered products, in Fiji. This represents a significant regulatory gap. By contrast:

- The **European Union** regulates ATMPs under Regulation (EC) No 1394/2007, with centralised evaluation by the EMA's Committee for Advanced Therapies (CAT) (EMA, "Advanced Therapy Medicinal Products: Overview," 2024).
- **Australia's TGA** classifies cell and tissue products as "biologicals" under a four-class risk-based system, with Class 2–4 products requiring inclusion on the Australian Register of Therapeutic Goods (ARTG) (TGA, "Australian Regulatory Guidelines for Biologicals," 2024).

- **Japan's PMDA** operates a conditional and time-limited approval pathway for regenerative medicine products under the Act on the Safety of Regenerative Medicine (2014).
- **South Korea's MFDS** has approved multiple MSC products (CARTISTEM, Cupistem, Cellgram) under its biologics regulatory framework.

The absence of ATMP-specific regulation in Fiji means that any MSC-based therapy would currently fall into a regulatory vacuum — neither explicitly prohibited nor explicitly authorised. This creates risks for patient safety, quality assurance, and legal liability.

2.4.4 Clinical Trial Approval Pathways

Clinical trials in Fiji require approval from the Fiji Human Health Research Ethics Review Committee and, for pharmaceutical trials, notification to or approval from the FPBSC. However, the capacity to evaluate complex biological investigational products — including assessment of chemistry, manufacturing, and controls (CMC) data, potency assays, and cell characterisation — is limited. There is no Fiji equivalent of a Clinical Trial Application (CTA) or Investigational New Drug (IND) pathway specifically designed for biological or cell-based products.

2.4.5 Import and Export of Biological Products

The importation of biological products into Fiji is subject to biosecurity and customs regulations, but specific provisions for the importation of living cell products, cryopreserved cell therapies, or tissue-engineered products are not established. Cold-chain requirements, customs clearance timelines, and biosafety classification of MSC products would need to be addressed through new regulatory instruments or through adaptation of existing biologics import provisions.

2.4.6 Reference-Agency Reliance and Regional Context

Given the resource constraints of small island developing states, a **reference-agency reliance model** represents the most pragmatic regulatory pathway for Fiji. Under this approach, Fiji would recognise regulatory decisions made by established reference agencies — most relevantly:

- **TGA (Australia)**: Geographic proximity, existing bilateral health cooperation, and the TGA's comprehensive biologicals framework make it the most natural reference agency.
- **EMA**: Provides the most developed ATMP-specific regulatory framework globally.
- **WHO Prequalification**: While not currently applicable to ATMPs, the WHO PQ programme could potentially be extended or adapted.

Neighbouring Pacific Island nations face similar regulatory gaps. Papua New Guinea, Samoa, Tonga, and Vanuatu lack ATMP-specific frameworks, and the Pacific Islands–WHO Multi-Country Cooperation Strategy 2024–2029 identifies health system strengthening and regulatory capacity building as priorities (WHO, Pacific Islands–WHO Multi-Country Cooperation Strategy 2024–2029, 2024).

2.5 Relevance of MSC Therapies to Fiji's Health Needs

The disease burden profile of Fiji aligns remarkably closely with the therapeutic indications for which MSC therapies have the most advanced clinical evidence. The following table maps Fiji's leading health challenges to the corresponding MSC evidence base:

Fiji Health Challenge	MSC Therapeutic Application	Evidence Level	Key References
Diabetes mellitus (Type 2) — leading cause of death	MSC-based beta-cell regeneration; immunomodulation in T1DM	Phase I/II	Margiana et al., 2022, *Stem Cell Res Ther.* PMID: 35902958
Diabetic foot ulcers / chronic wounds — major complication	Topical/injected MSCs for wound healing; MSC-conditioned medium	Phase I/II; multiple clinical studies	Hu et al., 2018, *Stem Cells Int.* PMID: 29887893; Ahangar et al., 2020, *Int J Mol Sci.* PMID: 32987830
Ischaemic heart disease / heart failure	Intramyocardial or intracoronary MSC injection	Phase II; multiple RCTs	Margiana et al., 2022, *Stem Cell Res Ther.* PMID: 35902958 (NCT00644410, NCT01291329, NCT03047772)
Stroke	Intravenous MSC administration	Phase I/IIa	Margiana et al., 2022, *Stem Cell Res Ther.* PMID: 35902958 (NCT01678534)
Chronic kidney disease	Intravenous MSC infusion; MSC-derived exosomes	Phase I/II; early clinical	Margiana et al., 2022, *Stem Cell Res Ther.* PMID: 35902958 (NCT02195323); Lotfy et al., 2023, *Stem Cell Res Ther*
Osteoarthritis — high prevalence due to obesity	Intra-articular MSC injection	Phase II/III; systematic reviews	Goldberg et al., 2017, *J Orthop Surg Res.* DOI: 10.1186/s13018-017-0534-y; Filardo et al., 2016, *J Orthop Surg Res.* DOI: 10.1186/s13018-016-0378-x
Burns and traumatic wounds	MSC-based wound healing	Preclinical; early clinical	Ahangar et al., 2020, *Int J Mol Sci.* PMID: 32987830

2.5.1 Potential Public Health Impact

The conditions for which MSC therapies show the most clinical promise — diabetic wound healing, osteoarthritis, and cardiovascular repair — are precisely the conditions that impose the greatest burden on Fiji's health system. Several impact scenarios merit consideration:

Diabetic wound healing: If MSC-based wound therapies could reduce the rate of lower-limb amputations by even a modest fraction, the downstream savings in surgical costs, prosthetics, rehabilitation, disability support, and lost productivity would be substantial. Each avoided amputation represents not only a quality-of-life benefit but also a reduction in long-term healthcare utilisation.

Osteoarthritis: Effective MSC-based cartilage repair or regeneration could reduce the need for total knee arthroplasty — a procedure that is currently available only in limited numbers in Fiji and frequently requires overseas referral. Intra-articular MSC injection, if validated, could be delivered in an outpatient setting at substantially lower cost than joint replacement surgery.

Cardiovascular disease: While MSC therapies for cardiac repair remain at an earlier stage of clinical development, the potential to improve outcomes in post-myocardial infarction patients or those with heart failure could address a leading cause of premature mortality.

2.5.2 Healthcare Cost Implications

Fiji's constrained health budget necessitates rigorous cost-effectiveness analysis before any advanced therapy adoption. Key cost considerations include:

- **Manufacturing and procurement costs**: MSC products require GMP-grade manufacturing, quality control testing, and cold-chain logistics, all of which add substantially to per-dose costs.
- **Infrastructure investment**: Establishing even a basic cell processing capability would require capital investment in cleanroom facilities, equipment, and trained personnel.
- **Opportunity cost**: Resources directed toward advanced therapies must be weighed against investments in primary prevention (diabetes prevention programmes, tobacco control, nutrition interventions) that may yield greater population-level health gains.

- **Medical travel reduction**: If MSC therapies could be delivered domestically for conditions currently requiring overseas referral (joint replacement, renal transplant workup), the savings in medical travel costs could partially offset therapy costs.

A phased approach — beginning with clinical trial participation or compassionate-use programmes for the most evidence-supported indications, rather than immediate large-scale adoption — would allow Fiji to accumulate local evidence while managing financial risk.

2.6 Existing Regenerative Medicine in the Pacific

2.6.1 Stem Cell Activity in Fiji

There is no established stem cell therapy programme, cell processing facility, or regenerative medicine clinical service currently operating in Fiji. The Fiji National University's College of Medicine, Nursing and Health Sciences conducts biomedical research, but no published clinical trials of MSC or other stem cell therapies originating from Fiji were identified in searches of ClinicalTrials.gov, the Australia New Zealand Clinical Trials Registry (ANZCTR), or the EU Clinical Trials Register.

The MHMS operates a Fiji Human Health Research Ethics Review Committee that could provide ethical oversight for future clinical research involving cell therapies, but the regulatory and technical infrastructure for conducting such research does not currently exist (MHMS Fiji, 2024).

2.6.2 Medical Tourism Patterns

Pacific Island patients, including Fijians, frequently travel overseas for specialist medical care not available domestically. Common destinations include:

- **India**: Cardiac surgery, renal transplantation, orthopaedic surgery, and oncology.
- **Australia and New Zealand**: Complex surgical procedures, cancer treatment, and specialist consultations, often facilitated through bilateral aid programmes.
- **Southeast Asia (Thailand, Malaysia, Singapore)**: Increasingly accessed for a range of specialist services.

Stem cell tourism — the practice of patients travelling to clinics offering unproven stem cell-based interventions — represents a growing global concern. The International Society for Stem Cell Research (ISSCR) has explicitly warned that "it is a breach of professional medical ethics and responsible scientific practices to market or provide stem cell-based interventions prior to rigorous and independent expert review of safety and efficacy and appropriate regulatory approval" (ISSCR, Guidelines for Stem Cell Research and Clinical Translation, 2021, Recommendation 3.5.1). The ISSCR further recommends that "government authorities and professional organizations should establish and strictly enforce policies and regulations governing the commercial use of stem cell-based medical interventions" (ISSCR, 2021).

The EMA and the Heads of Medicines Agencies (HMA) issued a joint statement in March 2025 warning of the risks of unregulated advanced therapies, noting reports of providers offering unregulated treatments in the EU and advising patients to verify regulatory approval status with national competent authorities before proceeding (EMA/HMA, Joint Statement on Unregulated Advanced Therapy Medicinal Products, March 2025).

There is anecdotal evidence that Pacific Island patients, including Fijians, have sought unregulated stem cell treatments in Asia and elsewhere, though systematic data on the scale of this phenomenon are not available. The absence of a domestic regulatory framework for cell therapies means that Fiji currently lacks the legal instruments to either regulate domestic provision or advise citizens seeking such treatments overseas.

2.6.3 Regional Partnerships and Opportunities

The Pacific Islands–WHO Multi-Country Cooperation Strategy 2024–2029 provides a framework for regional health cooperation, including health technology assessment and regulatory harmonisation (WHO, Pacific Islands–WHO Multi-Country Cooperation Strategy 2024–2029, 2024). Potential regional approaches to regenerative medicine could include:

- **Shared regulatory assessment**: Pacific Island nations could collectively adopt reference-agency reliance on TGA decisions for biological products, reducing the regulatory burden on individual countries.
- **Regional clinical trial networks**: Participation in Australia- or New Zealand-based MSC clinical trials through satellite sites in Fiji could provide access to investigational therapies while building local research capacity.
- **Tele-medicine and tele-consultation**: Remote specialist consultation for patient selection, treatment monitoring, and adverse event management could partially address the specialist workforce gap.
- **Academic partnerships**: Collaboration between Fiji National University and established regenerative medicine research centres in Australia (e.g., through ANZCTR-registered trials) or Japan (through PMDA-regulated regenerative medicine frameworks) could accelerate knowledge transfer.

No Pacific Island nation has yet established a dedicated regenerative medicine programme or approved an MSC-based product. Fiji, by virtue of its relatively larger population, established medical education infrastructure, and existing international health partnerships, is arguably the best-positioned Pacific Island country to serve as a regional pioneer in evaluating the applicability of MSC therapies — provided that such evaluation proceeds within a rigorous scientific and regulatory framework aligned with international standards as articulated by the ISSCR, WHO, and established reference regulatory agencies.

Chapter 3: MSC Safety Profile — Preclinical and Clinical Evidence

3.1 Preclinical Safety Data

3.1.1 Animal Model Toxicology Studies

The preclinical safety evaluation of mesenchymal stromal cell (MSC) products follows a framework broadly analogous to that used for conventional biologics, yet with adaptations necessitated by the living, heterogeneous nature of cell-based therapies. Good Laboratory Practice (GLP)-compliant studies typically encompass acute toxicity, repeat-dose toxicity, biodistribution, and tumorigenicity assessments. The International Society for Stem Cell Research (ISSCR) Guidelines recommend that preclinical safety testing include assessment of the delivery procedure, evaluation in immune-deficient rodents to assess engraftment, stability of differentiated cells, and cancer risk, and that small animal studies attempt to correlate cell number and potency required for subsequent large animal studies and clinical trials (ISSCR, Guidelines for Stem Cell Research and Clinical Translation, 2021/2025. Available at: https://www.isscr.org/guidelines).

Acute and repeat-dose toxicity. Preclinical toxicology studies in rodents and large animals have generally demonstrated a favourable acute safety profile for MSCs across tissue sources. Acute and chronic tumorigenicity/toxicity experiments in immunocompromised mice using clinically relevant MSC doses have shown no toxic effects on body or organ weight, no biochemical abnormalities following necropsy, and no histopathological changes at injection sites (Bockeria et al., 2013, as cited in Gargett et al.). The majority of preclinical studies in mice and rats infuse approximately 50 million and 10–20 million MSCs per kilogram of body weight, respectively — doses that are substantially higher on a per-kilogram basis than the average clinical dose of approximately 1–2 million cells per kilogram in humans (Rendra et al., 2020, F1000Research. DOI: 10.12688/f1000research.21862.1. PMID: 32148780).

Biodistribution. Biodistribution studies constitute a critical component of the preclinical safety package. A landmark study by Eggenhofer and colleagues examined the localisation and viability of intravenously infused MSCs in immunocompetent C57BL/6 mice using both Cr-51 radioactive labelling and DsRed fluorescent protein tracking. One hour after intravenous administration, more than 60% of total radioactivity was located in the lungs and approximately 10% in the liver. By 24 hours, radioactivity had shifted predominantly to the liver, with the lungs showing markedly reduced signal. Critically, when tissue cultures were established to detect living donor MSCs, viable DsRed-positive MSCs were recoverable from lung tissue at 5 minutes, 1 hour, and 24 hours post-infusion, but were no longer detectable at 72 hours. No viable donor MSCs were recovered from liver, spleen, kidney, or bone marrow at any time point (Eggenhofer et al., 2012, Frontiers in Immunology.).

This finding — that intravenously administered MSCs are mechanically entrapped in the pulmonary capillary bed and cleared within 24–72 hours — has been replicated across multiple models. Following intravenous infusion, most MSCs become trapped in pulmonary vasculature where they form emboli; within approximately 24 hours, the vast majority are cleared from the lungs, with only a minor fraction redistributing to heart, brain, liver, and kidney (Česnik and Švajger, 2024, Frontiers in Cell and Developmental Biology. DOI: 10.3389/fcell.2024.1400347. PMID: 39129786; Lee et al., 2009; Eggenhofer et al., 2014; Luk et al., 2016, as cited therein).

The typical diameter of an MSC is 15–30 µm — considerably larger than lymphocytes (4–12 µm) — and MSCs become larger after serial ex vivo passaging, which further explains the pulmonary first-pass effect (Zhuang et al., 2021 [review of MSC biodistribution]). Redistribution to liver, spleen, and inflamed tissues subsequently occurs, but long-term engraftment of substantial numbers of infused MSCs has not been demonstrated; rather, only a small population (2–10%) remains in the days following administration (Dimmeler et al., 2014, as cited in Gargett et al.).

3.1.2 Tumorigenicity Testing

Tumorigenicity assessment in immunocompromised mice (typically NOD/SCID or nude mice) is a regulatory requirement for MSC products. The Committee for Advanced Therapies (CAT) and the Cell Product Working Party of the European Medicines Agency organised a dedicated meeting to discuss the risk of tumour formation following MSC-based therapies. When discussing the influence of the manufacturing process on inducing cytogenetic abnormalities, it was highlighted that culture duration and conditions present critical risk factors for producing chromosomal aberrations. Notably, aneuploidy was found to be donor-dependent, with three out of five aberrations derived from the same donor (Tarte et al., 2010, Blood. DOI: 10.1182/blood-2009-05-219907. PMID: 20032501). Thus, donor screening and monitoring of long-term expansion and integrity of the cells are a requirement (Barkholt et al., 2013, Cytotherapy. DOI: 10.1016/j.jcyt.2013.03.005. PMID: 23602595).

In humans, MSCs are minimally susceptible to oncogenic transformation in vivo, and long-term culture either does not affect MSC morphology or cause chromosomal alterations (Mareschi et al., 2006, Journal of Cellular Biochemistry. DOI: 10.1002/jcb.20681. PMID: 16229018). Continued passaging leads to loss of already existing aneuploidy, or any resulting aneuploidy leads to senescence, negating the risk of cancer formation (Stultz et al., 2016, Cytotherapy. DOI: 10.1016/j.jcyt.2015.11.017. PMID: 26780865). Early reports of spontaneous malignant transformation of human bone marrow-derived MSCs in vitro (Røsland et al., 2009, Cancer Research. DOI: 10.1158/0008-5472.CAN-08-4630. PMID: 19509230) were subsequently attributed to cross-contamination with malignant cell lines (Torsvik et al., 2010, Cancer Research. DOI: 10.1158/0008-5472.CAN-10-1305. PMID: 20631079; de la Fuente et al., 2010, Cancer Research [retraction]. DOI: 10.1158/0008-5472.CAN-10-2451. PMID: 20710046).

3.1.3 Route-Specific Preclinical Safety

Distinct routes of cell administration — local or systemic, homologous or non-homologous/ectopic — can lead to different adverse events. The ISSCR Guidelines specifically note that local transplantation into organs like the heart or the brain may lead to life-threatening adverse events related to the transplantation itself or to the damage that transplanted cells may cause to vital structures. In cases where cell preparations are infused at anatomic sites distinct from the tissue of origin, care must be exercised in assessing the possibility of local, anatomically specific, and systemic toxicities (ISSCR, Guidelines for Stem Cell Research and Clinical Translation, 2021/2025).

3.1.4 Key Finding: Engraftment Versus Clearance

The weight of preclinical evidence indicates that MSCs act through a "hit-and-run" mechanism rather than stably engrafting in host tissue. Autopsies of patients who received MSC intravenous infusions for different conditions within a year before death confirmed that donor MSCs are not normally retained in host tissue. Detection of donor DNA did not correlate with the degree of HLA mismatch or the clinical response, suggesting that clearance is not immune-mediated (von Bahr et al., 2012, as cited in Maumus et al.). This rapid clearance has important safety implications: it reduces the theoretical risk of long-term engraftment-related complications (ectopic tissue formation, tumorigenicity) but simultaneously raises questions about the durability of therapeutic effects and the need for repeat dosing.

3.2 Clinical Safety — Meta-Analyses and Systematic Reviews

3.2.1 The Lalu et al. Foundational Meta-Analysis (2012)

The first major systematic review of MSC safety was conducted by Lalu and colleagues in 2012, who analysed data from randomised controlled trials (RCTs) to assess the safety of MSC administration. This Canadian group found no significant association between MSC infusion and tumour formation. Malignancies were detected only in patients with ongoing malignancies or as recurrence events. No de novo malignancies were reported, although clinical follow-up in the examined trials ranged from only 3 to 60 months (Lalu et al., 2012, as cited in Godoy et al., 2019, Frontiers in Cell and Developmental Biology. DOI: 10.3389/fcell.2019.00255. PMID: 31824942).

3.2.2 Updated Meta-Analyses (2020–2026)

A subsequent systematic review and meta-analysis reappraised 55 randomised controlled trials encompassing over 2,000 patients to investigate the safety of systemically inoculated MSCs. The principal findings were as follows (Zhuang et al., 2021 [comprehensive MSC review]):

Safety Parameter	Finding
Fever	Risk significantly greater in MSC-treated patients versus controls
Infection	No significant increase in risk
Thromboembolic events	No significant increase in risk
Malignancy	No significant increase in risk
Ectopic tissue formation	No significant increase in risk
Mortality	Risk of death significantly *lower* in MSC-treated patients

Among the included studies, serious adverse events possibly related to MSC treatment included treatment-related fever, in-stent thrombosis with death, acute coronary artery occlusions after intra-coronary delivery, grade 1 anaphylactoid reaction, gastric ulcer perforation, hypersensitivity reaction, and anal cancer (Zhuang et al., 2021).

A further meta-analysis of 55 randomised studies encompassing 2,696 patients confirmed that no study had been suspended because of serious adverse effects, affirming that MSCs are well tolerated across indications and tissue sources, including umbilical cord-derived MSCs (Mebarki et al., 2021, Stem Cell Research & Therapy. DOI: 10.1186/s13287-021-02222-y. PMID: 33637125).

The biosafety profile of MSCs has been further corroborated by meta-analyses combining data from clinical trials exploring bone marrow-derived, umbilical cord-derived, and adipose tissue-derived MSC products across various diseases. Results from these studies suggest there may be transient fever as the most common adverse event, but no consistent safety signals for serious adverse events, with SAE rates comparable to placebo in controlled trials (Česnik and Švajger, 2024, Frontiers in Cell and Developmental Biology. DOI: 10.3389/fcell.2024.1400347. PMID: 39129786).

Pooled data from over 5,000 patients have confirmed transient fever, headache, and flushing in 10–30% of intravenous administrations, typically mild and self-limiting.

3.2.3 Interpretive Caution

It is essential to distinguish "no evidence of harm" from "evidence of no harm." Most clinical trials to date have been Phase I or Phase I/II studies with small sample sizes (typically 10–60 patients), short follow-up periods (6–24 months), and were not statistically powered to detect rare adverse events. Most trials only showed short-term safety and were conducted without examination of tumour-associated biomarkers (Zhuang et al., 2021). The publishing bias — with few or no reports on negative outcomes and/or failed trials — further limits the completeness of the safety evidence base (Guerrouahen et al., 2019, Stem Cells International. DOI: 10.1155/2019/7219297. PMID: 31467564).

3.3 Specific Safety Concerns — Evidence Assessment

3.3.1 Tumorigenicity and Cancer Risk

Theoretical risk. MSCs exhibit tropism for the tumour microenvironment niche, and selective homing into inflammatory tumour sites has been established in various types of cancer (Kidd et al., 2009, Stem Cells. DOI: 10.1002/stem.187. PMID: 19650040). Even if MSCs have intrinsic antitumour properties, they can potentially alter their phenotype towards a protumorigenic role including proangiogenic and immunosuppressive capabilities (Guerrouahen et al., 2019. PMID: 31467564). The immunosuppressive effects exerted by MSCs could theoretically allow tumour formation and development of already existing malignant cells in the host/recipient (Barkholt et al., 2013. PMID: 23602595).

Evidence. There is no official statement on the potential of tumorigenicity in MSC-based therapies, and no observation of tumour formation of MSC origin in patients given cellular therapy (Guerrouahen et al., 2019. PMID: 31467564). The Lalu et al. (2012) meta-analysis found no de novo malignancies attributable to MSC treatment. Although direct evidence linking MSCs to tumorigenesis is lacking, their capacity to remodel the tumour microenvironment raises long-term safety concerns (Zhao et al., 2026, Stem Cell Reviews and Reports. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448). Murine MSCs readily undergo spontaneous transformation in vitro, but reports of similar events in human MSCs have been attributed to culture cross-contamination (Torsvik et al., 2010. PMID: 20631079).

Current consensus. While MSC therapy has been qualified as safe by both the FDA and EMA, the potential long-term risks still have to be considered (Guerrouahen et al., 2019. PMID: 31467564). Patients with concurrent neoplasm or family history of hereditary cancer should be carefully reviewed during MSC treatment. Long-term follow-up is essential to evaluate potential pro-tumorigenic effects (Zhao et al., 2026. PMID: 41254448).

3.3.2 Immunogenicity and Immune Rejection

Theoretical risk. MSCs were historically considered "immune-privileged" owing to low expression of HLA class I, absence of HLA class II and co-stimulatory molecules (CD80, CD86), and potent immunosuppressive properties. This paradigm supported their use across histocompatibility barriers. However, recent data indicate that MSC transplantation may provoke donors' humoral and cellular immune responses, especially in allogeneic settings (Rendra et al., 2020. PMID: 32148780).

Evidence. Repeated intra-articular injection of allogeneic mesenchymal stem cells in an equine model resulted in an adverse clinical response, suggesting there is a potential for immune recognition of allogeneic MSCs upon repetitive exposures (Joswig et al., 2017, Stem Cell Research & Therapy. DOI: 10.1186/s13287-017-0503-8). A certain percentage of patients have been shown to develop alloantibodies and subsequent immune rejection of administered MSCs (Česnik and Švajger, 2024. PMID: 39129786). Only two clinical trials have reported the development of donor-specific antibodies in patients who received allogeneic MSCs, and the authors argued that the increased allo-antibodies had no relevance to clinical outcome or the occurrence of adverse events (Rendra et al., 2020. PMID: 32148780). In two clinical trials using allogeneic MSCs to treat type 2 diabetes and diabetic nephropathy, there was no report of patients developing donor-specific HLA antibodies despite donor–recipient mismatching (Rendra et al., 2020. PMID: 32148780).

Current consensus. While the clinical significance of anti-donor antibody formation remains uncertain, consideration of histocompatibility barriers along with anticipation of immune rejections and immune sensitisation reactions should be kept in mind, particularly for repeated dosing protocols and pooled MSC products from different donors where HLA diversity is further increased (Česnik and Švajger, 2024. PMID: 39129786).

3.3.3 Thromboembolism and Instant Blood-Mediated Inflammatory Reaction (IBMIR)

Theoretical risk. MSCs express tissue factor (TF/CD142), a cell surface glycoprotein that plays an important role in extrinsic coagulation. When MSCs are introduced into systemic circulation, TF/CD142 on their cell surface can trigger procoagulation and instant blood-mediated inflammatory reaction (IBMIR), leading to reduced graft survival and thromboembolism (O'Rourke et al., 2021, Stem Cells Translational Medicine. DOI: 10.1002/sctm.20-0454. PMID: 33527780; Moll et al., 2019, Trends in Molecular Medicine.).

Evidence. TF/CD142 expression levels vary among different tissue origins of MSCs and with culture conditions. Compared with adipose-derived MSCs (AD-MSCs) and umbilical cord-derived MSCs (UC-MSCs), bone marrow-derived MSCs (BM-MSCs) express lower levels of TF (Oeller et al., 2018, Theranostics. DOI: 10.7150/thno.22249). Pulmonary embolism and infarction in three related patients have been reported after adipose MSC infusion (Rendra et al., 2020. PMID: 32148780). Two cases of

thromboembolism induced by umbilical cord MSC infusion have been documented (Wu et al., 2017, Transplantation Proceedings.). MSC infusion has been associated with dose-dependent coagulation abnormalities, with high doses linked to thrombosis and microvascular complications (Zhao et al., 2026. PMID: 41254448).

Mitigation strategies. Several approaches have been proposed:

- **Selection of TF-deficient MSCs:** Selecting TF-deficient BM-MSCs may reduce the risk of IBMIR (Oeller et al., 2018).
- **Co-treatment with anticoagulant:** Adding an anticoagulant during infusion should be considered (Rendra et al., 2020. PMID: 32148780).
- **Post-thaw recovery:** Allowing MSCs to recover for 24 hours post-thaw significantly lowers levels of phosphatidylserine (PS) and TF/CD142, reducing procoagulant potential (O'Rourke et al., 2021. PMID: 33527780).
- **Bioreactor-based delivery:** Immobilising MSCs in hollow-fibre bioreactors significantly prolongs clot formation time relative to direct injection (O'Rourke et al., 2021. PMID: 33527780).

Current consensus. Thromboembolism/IBMIR represents the most clinically actionable safety concern for intravenous MSC administration. A call for improvement in the minimal criteria for MSCs to maximise patient safety was recently raised to include evaluation of tissue factor and hemocompatibility of MSC products (Moll et al., 2022, as cited in Dulak and Pecyna, 2023, Stem Cell Reports. DOI: 10.1016/j.stemcr.2023.05.017. PMID: 37390824).

3.3.4 Ectopic Tissue Formation

Theoretical risk. Given the trilineage differentiation capacity of MSCs (osteogenic, chondrogenic, adipogenic), there is a theoretical concern that MSCs could form unwanted bone, cartilage, or fat tissue at injection sites.

Evidence. No reports of unwanted ectopic differentiation (bone or cartilage formation at injection sites) have been documented in clinical trials. The meta-analysis of 55 RCTs found no significant increase in the risk of ectopic tissue formation in MSC-treated patients versus controls (Zhuang et al., 2021). Concerns of ectopic bone formation on clinical application of BM-MSCs are mitigated by the observation that MSCs from certain sources (e.g., menstrual blood-derived MSCs) have weak osteogenic differentiation capacity, and by the finding that MSCs are rapidly cleared rather than engrafting long-term (Gargett et al.).

Current consensus. Ectopic tissue formation remains a theoretical concern that has not materialised in clinical practice. The rapid clearance of MSCs from the body (typically within 24–72 hours for IV administration) substantially mitigates this risk.

3.3.5 Infection Transmission

Theoretical risk. As with any biological product derived from human tissue, MSC products carry a theoretical risk of transmitting infectious agents from donor to recipient. This risk is amplified in allogeneic products where cells derived from a single donor can potentially be implanted into a large number of patients.

Evidence. The ISSCR Guidelines recommend that donors and/or the resulting cell banks developed for allogeneic stem cell-based interventions should be screened and/or tested for infectious diseases and other risk factors, in compliance with applicable regulatory guidelines. Donor screening should include medical examination, collection of donor history, and blood testing. This process mitigates the risk of potential transmission of adventitious agents from the donor to patients receiving the stem cell products (ISSCR, Guidelines, 2021/2025). The EMA has issued specific guidance on extraneous agents in stem cell-based products, requiring comprehensive pathogen screening during manufacturing (EMA, "Stem cells-based products extraneous agents — problem statement," 2016). GMP-compliant manufacturing with validated sterility testing, mycoplasma testing, and endotoxin testing further mitigates this risk.

Current consensus. Infection transmission risk is manageable through rigorous donor screening, GMP-compliant manufacturing, and validated release testing. No cases of donor-to-recipient infection transmission have been reported in clinical trials using properly manufactured MSC products, though this risk requires ongoing vigilance.

3.4 Route-Specific Safety Profiles

The safety profile of MSC therapy varies meaningfully by route of administration. A scoping review of 42 clinical studies found that the most common routes were intravenous (32%), followed by local injection into musculoskeletal tissue (38% of "other routes"), intra-articular (7%), intrathecal (7%), and intramuscular (10%) (Renesme et al., 2022, Stem Cells Translational Medicine. DOI: 10.1093/stcltm/szab009. PMID: 35641170).

3.4.1 Intravenous (IV)

Intravenous administration is the most widely used route and carries the most extensively characterised safety profile. The principal risks include:

- **Pulmonary first-pass effect:** The majority of IV-infused MSCs are mechanically trapped in pulmonary capillaries due to their large cell size (15–30 μm), creating transient microemboli (Česnik and Švajger, 2024. PMID: 39129786).
- **Infusion reactions:** Transient fever (the most common adverse event), headache, flushing, and mild allergic reactions occur in 10–30% of administrations.
- **Thromboembolism/IBMIR:** As detailed in Section 3.3.3, this is the most significant route-specific risk for IV delivery.
- **Dose considerations:** The average clinical dose is approximately 1–2 million cells per kilogram of body weight. Although increasing the dose might be tempting, safety should be assessed carefully as it may increase the risk for embolism or adverse reactions (Rendra et al., 2020. PMID: 32148780).

3.4.2 Intra-Articular (IA)

Intra-articular injection is the preferred route for osteoarthritis and other joint conditions. Phase I clinical trials have demonstrated the safety of direct IA administration of MSCs in osteoarthritis patients (Centeno et al., 2008; Davatchi et al., 2011, as cited in Maumus et al.). In a long-term follow-up of a multicentre randomised controlled clinical trial, 30 OA patients received intra-articular infusion of autologous BM-MSCs versus hyaluronic acid, with no adverse effects occurring after MSC transplantation or during the 4-year follow-up (Margiana et al., 2022, Stem Cell Research & Therapy. DOI: 10.1186/s13287-022-03054-0. PMID: 35902958). Transient knee joint pain and swelling after local administration have been reported in some patients but are generally self-limiting.

3.4.3 Intrathecal/Intraspinal

Intrathecal administration has been evaluated primarily for spinal cord injury (SCI), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). The CELLTOP Phase I trial (NCT03308565) investigated intrathecal delivery of 1×10^8 autologous adipose-derived MSCs in 10 patients with traumatic SCI, with 96-week follow-up. No serious adverse events occurred throughout the study period, although non-serious adverse events were not infrequent (Bydon et al., 2024, Nature Communications. DOI: 10.1038/s41467-024-46259-y. PMID: 38561341). The safety profile was corroborated in prior studies with ALS patients: Staff et al. (2016) demonstrated that intrathecal treatment of autologous AD-MSCs was safe using a dose-escalation protocol ranging from 1×10^7 to 1×10^8 cells (Staff et al., 2016, Neurology. DOI: 10.1212/WNL.0000000000003359. PMID: 27784774). Oh et al. (2015) reported no serious adverse events during 12-month follow-up of repeated intrathecal autologous BM-MSC injections in ALS patients (Oh et al., 2015, Stem Cells Translational Medicine. DOI: 10.5966/sctm.2014-0212. PMID: 25934946).

However, one case report documented polyclonal lymphocytic infiltrate with arachnoiditis resulting from intrathecal stem cell transplantation, underscoring the need for careful monitoring (Madhavan et al., 2020, Neuroradiology Journal).

3.4.4 Intramuscular (IM)

Intramuscular injection has been used primarily for critical limb ischaemia and ALS (combined with intrathecal delivery). Phase I/II trials of MSC-NTF cells administered via combined intrathecal and intramuscular routes in ALS patients demonstrated safety and provided indications of possible clinical benefits (NCT01051882; NCT01777646) (Margiana et al., 2022. PMID: 35902958).

3.4.5 Topical/Wound Application

Topical application of MSCs or MSC-conditioned medium for wound healing represents the lowest-risk route of administration, as it avoids systemic exposure. No significant safety concerns have been reported in clinical studies of topical MSC application for chronic wounds or burns.

3.4.6 Intracardiac/Intracoronary

Intramyocardial and intracoronary delivery have been evaluated in cardiac indications. A study of 12 participants with hypoplastic left heart syndrome who received allogeneic human MSCs (2.5×10^5 cells/kg) via intramyocardial injection reported no serious adverse effects during the trial (NCT02398604) (Margiana et al., 2022. PMID: 35902958). However, acute coronary artery occlusions after intra-coronary delivery and in-stent thrombosis with death have been reported as serious adverse events possibly related to MSC treatment in the meta-analytic literature (Zhuang et al., 2021). This route carries the highest procedural risk and requires specialised cardiac catheterisation facilities.

3.5 Long-Term Safety Follow-Up Data

3.5.1 Available Long-Term Data

Long-term safety data for MSC therapies remain limited, representing one of the most significant gaps in the evidence base. The longest published follow-up periods include:

- **Ischaemic stroke (5 years):** Lee and colleagues evaluated the long-term safety and efficacy of IV autologous MSC transplantation in 85 patients with severe middle cerebral artery territory infarct, with follow-up up to 5 years. Results showed that MSCs were safe and could promote functional recovery depending on specific patient characteristics (Zhou et al., 2022, Stem Cell Research & Therapy. DOI: 10.1186/s13287-022-02876-2. PMID: 35551643).
- **Systemic lupus erythematosus (6 years):** Wang et al. reported long-term safety of UC-MSCs administered in 9 patients with refractory SLE, with no haematological, liver, or cardiac side effects after 6 years (Wang et al., as cited in Mebarki et al., 2021. PMID: 33637125).
- **Osteoarthritis (4 years):** Intra-articular BM-MSC injection showed no adverse effects during 4-year follow-up in a multicentre RCT (Margiana et al., 2022. PMID: 35902958).
- **Rheumatoid arthritis (3 years):** UC-MSC therapy showed no serious side effects at 1 year and 3 years in a Phase I/II single-arm study of 64 patients (Mebarki et al., 2021. PMID: 33637125).

3.5.2 Cancer Incidence at Extended Follow-Up

No de novo malignancies attributable to MSC treatment have been reported in any published long-term follow-up study. However, this must be interpreted with caution: most follow-up periods are insufficient to detect late-onset malignancies (which may require 10–20 years to manifest), sample sizes are small, and systematic cancer surveillance has not been a standard component of most trial protocols. Most trials only showed short-term safety and were conducted without examination of tumour-associated biomarkers (Zhuang et al., 2021).

3.5.3 Late-Emerging Adverse Events

No pattern of late-emerging adverse events has been identified in the available literature. However, the absence of evidence should not be conflated with evidence of absence. The field lacks the equivalent of the long-term registries that exist for organ transplantation or haematopoietic stem cell transplantation.

3.5.4 Registry Initiatives

The establishment of long-term patient registries for MSC therapy recipients has been recommended by multiple expert bodies. The ISSCR Guidelines emphasise the need for long-term follow-up and risk management of advanced therapy medicinal products. The EMA guideline on safety and efficacy follow-up and risk management of ATMPs (EMEA/149995/2008) provides a framework for post-marketing surveillance that is applicable to MSC products (Mebarki et al., 2021. PMID: 33637125).

3.6 Safety Comparison with Existing Therapies

To contextualise the MSC safety profile for policy decision-making, it is instructive to compare it with the adverse event profiles of conventional therapies used for conditions where MSCs are being investigated — particularly osteoarthritis, inflammatory diseases, and chronic pain.

Therapy	Common Adverse Events	Serious Adverse Events	Long-Term Risks
NSAIDs (oral)	GI upset (15–30%), headache, dizziness	GI bleeding/perforation (1–2%/year), cardiovascular events (MI, stroke), renal impairment	Chronic kidney disease, cardiovascular mortality (elevated with prolonged use)
Corticosteroids (systemic)	Weight gain, hyperglycaemia, mood changes, insomnia	Osteoporosis, adrenal suppression, immunosuppression, avascular necrosis	Diabetes, cataracts, vertebral fractures, increased infection risk
Corticosteroids (intra-articular)	Post-injection flare (2–5%), transient pain	Septic arthritis (rare, ~1:10,000–50,000), cartilage degeneration with repeated use	Accelerated cartilage loss with frequent injections
Hyaluronic acid (IA)	Local pain and swelling (10–20%), pseudosepsis (rare)	Anaphylaxis (very rare)	No significant long-term risks identified
Biologic DMARDs (anti-TNF, anti-IL-6)	Injection site reactions, upper respiratory infections	Serious infections (TB reactivation, opportunistic infections), lymphoma (debated), demyelination	Increased infection risk, possible malignancy risk with long-term use
MSCs (IV)	Transient fever (10–30%), headache, flushing	No consistent safety signals; SAE rates comparable to placebo	Insufficient long-term data; no de novo malignancies reported to date
MSCs (IA)	Transient joint pain/swelling	No serious adverse events in controlled trials with up to 4-year follow-up	Insufficient long-term data

This comparison suggests that the short-term safety profile of MSC therapy compares favourably with many conventional therapies, particularly systemic NSAIDs and corticosteroids, which carry well-documented risks of gastrointestinal, cardiovascular, and renal toxicity. Biologic DMARDs, while effective, carry risks of serious infections and possible malignancy that are at least comparable to the theoretical (but undemonstrated) risks of MSC therapy. However, the critical distinction is that

conventional therapies have decades of post-marketing surveillance data, whereas MSC therapies have at most 5–6 years of systematic follow-up in limited patient populations.

3.7 Regulatory Safety Requirements

3.7.1 European Medicines Agency (EMA)

Under Regulation (EC) No 1394/2007, MSC-based products are classified as advanced therapy medicinal products (ATMPs) — either as somatic cell therapy medicinal products (sCTMPs) or tissue-engineered products (TEPs), depending on the intended indication. The EMA, through the Committee for Advanced Therapies (CAT), maintains stringent requirements for evidence of quality, safety, and efficacy before granting marketing authorisation (Piemonti et al., 2023, Transplant International. DOI: 10.3389/ti.2023.11633. PMID: 37822447).

Key EMA safety-related guidelines applicable to MSC products include:

- **Guideline on human cell-based medicinal products** (EMEA/CHMP/410869/2006)
- **Reflection paper on stem cell-based medicinal products** (EMA/CAT/571134/2009)
- **Guideline on safety and efficacy follow-up and risk management of ATMPs** (EMEA/149995/2008)
- **Guideline on the minimum quality and non-clinical data for certification of ATMPs** (EMA, 2010)

The minimum preclinical safety package for an MSC-based ATMP seeking EMA marketing authorisation includes biodistribution studies, tumorigenicity assessment, toxicology studies (acute and repeat-dose), and immunogenicity evaluation. Post-marketing, the guideline on safety and efficacy follow-up (EMEA/149995/2008) requires a risk management plan including long-term follow-up of treated patients (Mebarki et al., 2021. PMID: 33637125).

3.7.2 United States Food and Drug Administration (FDA)

The FDA regulates MSC products as biological products under Section 351 of the Public Health Service Act when they involve more than minimal manipulation or non-homologous use. The regulatory framework requires an Investigational New Drug (IND) application for clinical trials and a Biologics License Application (BLA) for marketing authorisation. Key safety requirements include:

- GLP-compliant preclinical toxicology and biodistribution studies
- Tumorigenicity testing in immunocompromised animal models
- Chemistry, Manufacturing, and Controls (CMC) documentation demonstrating product safety, identity, purity, and potency
- Long-term follow-up requirements: the FDA requires monitoring of cell therapy recipients for a minimum of 15 years post-treatment to assess delayed adverse events, including malignancy

3.7.3 Japan Pharmaceuticals and Medical Devices Agency (PMDA)

Japan operates under a unique dual-track regulatory system established by the Act on the Safety of Regenerative Medicine (2013) and the Pharmaceuticals and Medical Devices Act (PMD Act). The conditional and time-limited approval pathway allows MSC products to receive marketing authorisation based on demonstrated safety and probable efficacy from early-phase trials, with a requirement for post-marketing confirmatory studies within a defined period (typically 5–7 years). This pathway was used for the approval of Temcell® (remestemcel-L) for acute graft-versus-host disease in 2015 and Stemirac® for spinal cord injury in 2018. The PMDA requires comprehensive preclinical safety data including biodistribution, tumorigenicity, and toxicology, as well as post-marketing safety surveillance (Mebarki et al., 2021. PMID: 33637125).

3.7.4 Korean Ministry of Food and Drug Safety (MFDS)

South Korea has approved multiple MSC products (Cartistem®, Cupistem®, Cellgram®, Neuronata-R®) and requires a preclinical safety package comparable to that of the FDA and EMA, including GLP toxicology, tumorigenicity, and biodistribution studies. The MFDS also requires post-marketing surveillance and periodic safety update reports.

3.7.5 Implications for Fiji

For a nation with a nascent ATMP regulatory framework, the regulatory safety requirements of reference agencies provide a template for minimum standards. A reference-agency reliance pathway — whereby Fiji recognises safety assessments conducted by the TGA, EMA, or PMDA — would enable access to MSC therapies that have already undergone rigorous safety evaluation without requiring Fiji to independently replicate the full preclinical and clinical safety assessment. This approach is consistent with WHO recommendations for small regulatory authorities and is discussed further in subsequent chapters of this report.

3.7.6 Summary of Minimum Safety Package Across Jurisdictions

Safety Requirement	EMA	FDA	PMDA	MFDS
GLP toxicology (acute, repeat-dose)	Required	Required	Required	Required
Biodistribution studies	Required	Required	Required	Required
Tumorigenicity (immunocompromised mice)	Required	Required	Required	Required
Karyotype/chromosomal stability	Required	Required	Required	Required
Immunogenicity assessment	Required	Required	Required	Required
Hemocompatibility/TF expression	Recommended	Recommended	Recommended	Recommended
Long-term follow-up (post-approval)	Risk management plan required	15-year follow-up recommended	Post-marketing confirmatory study	Post-marketing surveillance
Donor screening (allogeneic)	Required per Directive 2004/23/EC	Required per 21 CFR 1271	Required	Required

Summary of Key Safety Findings for Policy Consideration

The evidence base for MSC safety, while reassuring in the short to medium term, carries important caveats that must inform policy decisions:

1. **Short-term safety is well established.** Across thousands of patients in controlled trials, MSCs demonstrate a safety profile comparable to placebo, with transient fever as the most common adverse event.
2. **Thromboembolism/IBMIR is the most clinically significant acute risk** and is mitigable through tissue factor screening, anticoagulant co-administration, and appropriate cell preparation protocols.

3. **Tumorigenicity has not been observed clinically** but cannot be definitively excluded given limited long-term follow-up. Rigorous manufacturing controls (passage limits, karyotyping, donor screening) are essential risk mitigation measures.
4. **Immunogenicity is a consideration for repeated allogeneic dosing** but has not been associated with clinically significant adverse outcomes in the available data.
5. **Long-term safety data are insufficient.** The longest systematic follow-up is approximately 5–6 years, and no large-scale registries exist. This represents the single most important evidence gap for policy-makers.
6. **Route of administration significantly influences the risk profile.** Intravenous delivery carries thromboembolism risk; intrathecal delivery requires specialised monitoring; intra-articular and topical routes have the most favourable safety profiles.
7. **Regulatory safety requirements are broadly harmonised** across major agencies, providing a clear template for any jurisdiction establishing an ATMP framework or adopting a reference-agency reliance pathway.

Chapter 4: MSC Global Clinical Trials — Comprehensive Landscape

4.1 Global Clinical Trial Landscape Overview

4.1.1 Total Registered Trials

Mesenchymal stromal cell (MSC) therapies represent one of the most actively investigated advanced therapy modalities worldwide. As of February 2026, a curated analysis of global clinical trial databases identified **704 MSC-specific clinical trials** that are actively recruiting or planned, representing **14.7% of all cell therapy trials** tracked globally (MSC Clinical Trial Intelligence, Supabase Market Intelligence Database, last updated 5 February 2026). When historical registrations — including completed, terminated, and withdrawn studies — are included, the cumulative total exceeds **1,670 registered MSC clinical trials** worldwide as of 2025 (MSC Comprehensive Report, 2025 market analysis).

This figure represents a dramatic expansion from earlier counts. In 2015, a comprehensive review identified approximately 463 registered MSC trials on ClinicalTrials.gov alone, of which 264 were open for recruitment and 199 were closed (Ullah et al., 2015, *Bioscience Reports*. DOI: 10.1042/BSR20150025. PMID: 25797907). By 2017, the keyword "mesenchymal stem cell" returned nearly 650 active clinical trials globally on ClinicalTrials.gov, excluding studies of unknown status (Samsonraj et al., 2017, *Stem Cells Translational Medicine*. DOI: 10.1002/sctm.17-0129. PMID: 29076267). The field has thus more than doubled its clinical footprint in under a decade.

4.1.2 Year-over-Year Growth Trends (2010–2026)

The growth trajectory of MSC clinical trials can be characterised in three distinct phases:

1. **Foundation Phase (2004–2012):** Fewer than 50 new trials registered annually. Early studies were predominantly Phase I safety assessments, concentrated in North America and Western Europe. The first regulatory approvals — Prochymal in Canada (2012) and Cartistem in South Korea (2012) — marked the transition from exploratory to translational research.
2. **Expansion Phase (2013–2019):** Annual new trial registrations increased to approximately 80–120 per year. Geographic diversification accelerated, with China, Iran, South Korea, and India emerging as major contributors. The approval of Temcell HS in Japan (2015), Stempeucel in India (2016), and Alofisel in the EU (2018) validated the global regulatory pathway.
3. **Acceleration Phase (2020–2026):** The COVID-19 pandemic triggered a surge in MSC trials for ARDS and pneumonia (2020–2021), adding approximately 50–70 pandemic-related registrations. Post-pandemic, the field has maintained momentum, with 89 new MSC trials initiated in the first half of 2025 alone — a 37% year-over-year increase (MSC Comprehensive Report, 2025 market analysis). The December 2024 approval of remestemcel-L (Ryoncil) by the US FDA and the 2025 approval of Ammitel-L (hUC-MSC) in China for steroid-refractory acute GvHD have further catalysed investment (Zhao et al., 2026, *Stem Cell Reviews and Reports*. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448).

4.1.3 Breakdown by Registry

MSC clinical trials are registered across multiple international platforms, reflecting the global distribution of research activity:

Registry	Jurisdiction	Estimated MSC Trials	Notes
ClinicalTrials.gov	Global (US-based)	~1,100+ (cumulative)	Largest single registry; includes trials from >60 countries
Chinese Clinical Trial Registry (ChiCTR)	China	~200+	Rapid growth since 2015; many not cross-listed on ClinicalTrials.gov
EU Clinical Trials Register (EU CTR)	European Union	~40–50	Includes GvHD, Crohn's, MS trials; several Phase III HOVON studies
ANZCTR	Australia/New Zealand	21	Includes GvHD, COPD, Crohn's, cranial reconstruction, renal transplant, COVID-19 trials
Japan Registry of Clinical Trials (jRCT/JPRN)	Japan	~30–40	Stemirac-related SCI trials; GvHD studies under PMDA framework
Clinical Trials Registry – India (CTRI)	India	~30–40	OA, critical limb ischaemia, GvHD, diabetes
Iranian Registry of Clinical Trials (IRCT)	Iran	~25–30	OA, MS, GvHD, diabetes; Kerman and Tehran universities prominent
ISRCTN	International	~15–20	Primarily UK-based MSC studies

(Sources: ANZCTR search for "mesenchymal stromal cell," accessed 2025; EU CTR search for "mesenchymal stromal cell," accessed 2025; ClinicalTrials.gov search, various dates 2015–2026)

It is important to note that substantial cross-listing occurs between registries, and the Chinese Clinical Trial Registry captures a significant volume of trials not reflected in ClinicalTrials.gov. The true global total, accounting for de-duplication, is estimated at 1,500–1,700 unique trial registrations as of early 2026.

4.2 Breakdown by Phase

The phase distribution of MSC clinical trials provides critical insight into the maturity of the field and the translational bottleneck between early safety studies and confirmatory efficacy trials.

4.2.1 Phase Distribution (Active/Recruiting Trials, February 2026)

Phase	Number of Trials	Percentage of MSC Trials	Typical Design
Phase I	183	26.0%	Open-label, dose-escalation, 10–30 patients; primary endpoint: safety/tolerability
Phase I/II	187	26.6%	Combined safety/preliminary efficacy; 20–60 patients; often single-arm
Phase II	214	30.4%	Randomised, controlled; 30–100 patients; efficacy signals as primary endpoint
Phase II/III	17	2.4%	Adaptive designs bridging efficacy confirmation
Phase III	36	5.1%	Multicentre, randomised, controlled; 100–500 patients; pivotal for registration
Phase IV	21	3.0%	Post-marketing surveillance; real-world evidence
Phase 0	44	6.2%	Exploratory/microdosing studies
Phase III/IV	2	0.3%	Combined pivotal/post-marketing

(Source: MSC Clinical Trial Intelligence, Supabase Market Intelligence Database, 5 February 2026)

4.2.2 Interpretation of Phase Distribution

The phase distribution reveals several important features of the MSC clinical landscape:

The Phase II bottleneck. Over half of all active MSC trials (52.6%) are in Phase I or Phase I/II, indicating that the field remains predominantly in the safety-establishment and early-efficacy stage. The Phase II segment (30.4%) represents the critical "valley of death" where many programmes stall due to insufficient efficacy signals, manufacturing scale-up challenges, or funding constraints.

Limited Phase III activity. Only 5.1% of active trials have progressed to Phase III, a figure that is lower than the broader ATMP landscape, where Phase II trials account for approximately 53% of all ongoing advanced therapy trials globally (Alliance for Regenerative Medicine, 2022 data). This suggests that while MSC research is prolific, the conversion rate from early-phase to pivotal trials remains a challenge.

Growing Phase III pipeline. Notwithstanding the low percentage, the absolute number of Phase III trials (36 active/recruiting) represents a meaningful pipeline. An alternative analysis incorporating all registered trials (including completed) estimates that approximately 25% of all MSC trials have reached Phase III or beyond (MSC Comprehensive Report, 2025 market analysis), reflecting the cumulative maturation of programmes initiated in earlier years.

Average enrolment by phase. Historical analysis indicates average enrolment of 25 patients per Phase I trial, 40 per Phase I/II, 54 per Phase II, 93 per Phase II/III, and 145 per Phase III trial (Olsen et al., 2018, *Frontiers in Medicine*. DOI: 10.3389/fmed.2018.00178. PMID: 29977893). These figures are consistent with the dose-escalation and safety-focused nature of early MSC studies and the larger, controlled designs required for registration-enabling trials.

4.3 Breakdown by Indication

4.3.1 Top 15 Indications by Trial Count

The following table ranks the leading therapeutic indications for MSC clinical trials based on curated registry data:

Rank	Indication	Trial Count	Leading Phases	Key Geographies	Notable Results
1	Osteoarthritis (OA)	67	I/II, II, III	South Korea, China, USA, Iran, Spain, India, Australia	CARTISTEM approved (Korea, 2012); Stempeucel Phase III positive (India); multiple Phase II trials showing WOMAC improvement
2	Crohn's Disease / Perianal Fistulas	25	I/II, III	EU, Spain, USA, South Korea, Iran	Alofisel (Cx601) EMA-approved 2018 (withdrawn 2024); Cupistem approved (Korea, 2012); ADMIRE-CD Phase III positive
3	COVID-19 / COVID Pneumonia	23 + 13	I, I/II, II	China, USA, Spain, Iran, Brazil, Mexico, Indonesia	Rapid pandemic response; mixed efficacy results; UC-MSC predominant
4	Graft-versus-Host Disease (GvHD)	23	I/II, II, III	China, USA, Japan, EU, Australia, Malaysia	Ryoncil FDA-approved (2024); Temcell PMDA-approved (2015); Prochymal (Canada/NZ, 2012); Ammitel-L (China, 2025)
5	Type 2 Diabetes	18	I, I/II, II	China, Vietnam, India, Iran	Early-phase; UC-MSC and BM-MSC; glycaemic improvement signals
6	ARDS (non-COVID)	17	I, I/II, II/III	USA, Germany, Spain, Sweden, Iran, Colombia, Australia	BM-MSC and UC-MSC; safety established; efficacy data mixed
7	Ischaemic Stroke	14 + 10	I, I/II, II	China, South Korea, USA, Spain	AT-MSC safe at 24 months; functional improvement signals
8	Liver Cirrhosis / ACLF	13 + 11	I/II, II	China, Iran, Egypt	UC-MSC predominant; improvement in MELD scores reported
9	Spinal Cord Injury (SCI)	11 + 11	I, I/II, III	Japan, China, South Korea, Brazil	Stemirac conditionally approved (Japan, 2018); functional improvements in Phase I/II
10	Systemic Sclerosis / Autoimmune	11	I/II, II	China, USA, France, Spain, Belarus	UC-MSC and BM-MSC; immunomodulatory endpoints
11	Bronchopulmonary Dysplasia	11	I, I/II	South Korea, Australia, USA	Neonatal indication; safety established
12	Chronic Kidney Disease	11	I, I/II	China, USA, Jordan	Renal protection signals; early-phase
13	Multiple Sclerosis (MS)	~20	I/II, II	Iran, Jordan, Sweden, Spain, Italy, Israel, USA	BM-MSC predominant; MESEMS consortium Phase II completed
14	Congestive Heart Failure / AMI	10 + others	I/II, II, III	South Korea, USA, China, EU	Cellgram-AMI approved (Korea, 2011); mixed Phase III results
15	Anal Fistula (non-Crohn's)	11	I/II, III	Spain, EU, South Korea	Alofisel pivotal data; local injection approach

(Sources: MSC Clinical Trial Intelligence, February 2026; Markov et al., 2021, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-021-02265-1. PMID: 33736695; Guerrouahen et al., 2019, *Stem Cells International*. DOI: 10.1155/2019/7219297. PMID: 31467564)

4.3.2 Correlation with Global Disease Burden

There is a strong correlation between the global economic burden of health disorders and the number of MSC clinical trials targeting those conditions (Samsonraj et al., 2017, *Stem Cells Translational Medicine*. DOI: 10.1002/sctm.17-0129. PMID: 29076267). Musculoskeletal conditions (OA, bone/cartilage) collectively represent the largest share (≈ 25.6% of all MSC trials), followed by cardiovascular disease (≈ 14.3% CAGR in trial growth) and immunological/transplant-related conditions (GvHD, autoimmune diseases). This distribution is particularly relevant for Fiji, where the non-communicable disease burden — including diabetes, cardiovascular disease, and osteoarthritis — aligns closely with the most actively investigated MSC indications.

4.4 Breakdown by Geography

4.4.1 Geographic Distribution of MSC Clinical Trials

Country/Region	Estimated Trial Count	Leading Indications	Key Institutions/Sponsors
China	200+	OA, GvHD, liver disease, SCI, diabetes, COVID-19, stroke	Chinese Academy of Sciences; Shanghai East Hospital; Peking University People's Hospital; Southwest Hospital; Nanfang Hospital
United States	150+	OA, GvHD, Crohn's, ARDS, MS, cardiac	Mayo Clinic; MD Anderson Cancer Center; various academic centres
South Korea	60+	OA, GvHD, cardiac, ALS	Medipost; Pharmicell; SCM Lifescience; Corestem; academic hospitals
Iran	40+	OA, MS, GvHD, RA, diabetes	Tehran University of Medical Sciences; Kerman Medical University; Isfahan University
European Union	40–50	GvHD, Crohn's, MS, OA, systemic sclerosis	HOVON Foundation (Netherlands); medac GmbH (Germany); Spanish academic centres; Italian hospitals

Country/Region	Estimated Trial Count	Leading Indications	Key Institutions/Sponsors
Japan	30–40	GvHD, SCI, cardiac	JCR Pharmaceuticals; Sapporo Medical University; Nipro Corporation
India	30+	OA, critical limb ischaemia, diabetes, GvHD	Stempeutics Research Bangalore; academic medical centres
Australia/New Zealand	21 (ANZCTR)	GvHD, COPD, Crohn's, COVID-19, cranial reconstruction, lung transplant rejection	Royal Perth Hospital; Alfred Hospital; various university hospitals
Middle East (excl. Iran)	25+	OA, MS, diabetes	University of Jordan; Stem Cells of Arabia; Jordan, Saudi Arabia, UAE centres
Latin America	20+	OA, COVID-19, ARDS, Crohn's, SCI	Brazil, Mexico, Colombia, Ecuador, Panama centres
Southeast Asia	15+	OA, COVID-19, GvHD	University of Indonesia; Malaysian centres; Taiwanese hospitals
Canada	15+	MS, GvHD, OA	Academic centres; Prochymal approved 2012

(Sources: MSC Clinical Trial Intelligence, February 2026; ANZCTR search results, 2025; EU CTR search results, 2025; Markov et al., 2021. PMID: 33736695)

4.4.2 Asia-Pacific Dominance

The Asia-Pacific region dominates the global MSC clinical trial landscape, accounting for an estimated 71.6% of market share in 2024 with the fastest growth rate (14.9% CAGR). South Korea hosts the highest density of approved commercial MSC products globally, with five products receiving marketing authorisation between 2010 and 2014 (Queencell, Cellgram-AMI, Cartistem, Cupistem, Neuronata-R). Japan's regulatory framework for regenerative medicine — the Act on the Safety of Regenerative Medicine (2013) and the Pharmaceuticals and Medical Devices Act (PMD Act) — enables conditional and time-limited approvals, as exemplified by Temcell HS (2015) and Stemirac (2018). China's rapidly expanding trial portfolio is driven by both academic institutions (68.3% of all MSC trial sponsors are institutional) and a growing biotechnology sector.

4.4.3 Oceania Context

Australia and New Zealand have a modest but scientifically rigorous MSC trial portfolio. The ANZCTR lists 21 MSC-related trials, spanning GvHD (Phase I, completed), COPD (Phase I, completed), Crohn's disease (completed), COVID-19 pneumonia (Phase I, recruiting), cranial reconstruction (recruiting), chronic lung allograft dysfunction (Phase II, completed), renal transplant ischaemia-reperfusion injury (recruiting), and neonatal stroke (withdrawn) (ANZCTR, search for "mesenchymal stromal cell," accessed 2025). Australia's proximity and regulatory alignment with Fiji through the Therapeutic Goods Administration (TGA) framework makes this trial portfolio particularly relevant for Fijian policy considerations.

4.5 MSC Source in Clinical Trials

4.5.1 Tissue Source Distribution

MSCs used in clinical trials are derived from three principal tissue sources, with a notable shift in preference over the past decade:

Bone marrow-derived MSCs (BM-MSCs) have historically been the most commonly used source, reflecting the original isolation of MSCs from bone marrow aspirates. BM-MSCs remain the most extensively characterised source and have been used in the majority of approved products (Prochymal, Temcell HS, Cellgram-AMI, Neuronata-R, Stemirac, Stempeucel). However, bone marrow as a source is limited by the invasive and painful aspiration procedure and the very low abundance of MSCs, which typically account for 0.001–0.01% of nucleated cells (Camilleri et al., 2016, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-016-0370-8. PMID: 27515308).

Adipose tissue-derived MSCs (AT-MSCs/AD-MSCs) offer a more accessible and abundant source, with 1–10% of the stromal vascular fraction comprising MSCs (Camilleri et al., 2016. PMID: 27515308). Adipose tissue can be harvested under local anaesthesia with minimal morbidity, yielding approximately 40-fold more MSCs per volume than bone marrow (Pendleton et al., 2013, *PLoS ONE*. DOI: 10.1371/journal.pone.0058198. PMID: 23554877). AT-MSCs have been used in Alofisel (EMA-approved, 2018) and Cupistem (Korea-approved, 2012), and are increasingly favoured in OA and wound-healing trials.

Umbilical cord-derived MSCs (UC-MSCs), including Wharton's jelly-derived MSCs (WJ-MSCs), represent the fastest-growing source in clinical trials. UC-MSCs offer several advantages: non-invasive and ethically acceptable collection from discarded birth tissue, superior proliferative capacity, lower immunogenicity, and greater batch-to-batch consistency compared to adult-tissue-derived MSCs (Česnik & Švajger, 2024, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2024.1400347. PMID: 39129786). UC-MSCs are the predominant source in Chinese clinical trials and are increasingly used in GvHD (Ammitel-L, approved China 2025), COVID-19, and diabetes studies. Cartistem (Korea, 2012) uses umbilical cord blood-derived MSCs.

4.5.2 Trends: Shift from BM-MSC to UC/WJ-MSC

Analysis of trial registrations over time reveals a clear trend toward UC-MSC and WJ-MSC sources, particularly in trials initiated after 2018. This shift is driven by:

- **Scalability:** UC-MSCs can be expanded to clinically relevant numbers more efficiently, supporting the allogeneic "off-the-shelf" model.
- **Donor variability:** UC-MSCs from neonatal tissue exhibit less donor-to-donor variability than BM-MSCs from adult donors, whose MSC quality declines with age.
- **Manufacturing advantages:** UC-MSCs demonstrate superior proliferation rates and can achieve higher passage numbers while maintaining therapeutic potency.

Comparison of single-cell RNA sequencing data has revealed more differences in gene expression between tissue sources than between individual donors, indicating that tissue origin is a primary determinant of MSC phenotype (Česnik & Švajger, 2024. PMID: 39129786).

4.5.3 Allogeneic versus Autologous

The field has shifted decisively toward allogeneic MSC products. Among the 704 actively tracked trials, the majority of newer registrations employ allogeneic sources, reflecting the practical and commercial advantages of off-the-shelf products. There is no clear clinical evidence that autologous MSCs are superior to allogeneic MSCs; indeed, in conditions such as osteoarthritis, patients' own MSCs may display a dysfunctional phenotype, and while patients responded to allogeneic MSC treatment, no response was seen with autologous cell transplantation in some studies (Česnik & Švajger, 2024. PMID: 39129786). Given the numerous advantages associated with allogeneic MSCs — particularly the greater ease of acquisition, production, and quality control — it is probable that allogeneic MSCs will increasingly replace autologous cell sources in clinical practice.

4.6 Trial Status and Completion Rates

4.6.1 Current Status Distribution

Among the 704 actively tracked MSC trials (February 2026):

Status	Count	Percentage
Recruiting	582	82.7%

Status	Count	Percentage
Planned	122	17.3%

(Source: MSC Clinical Trial Intelligence, February 2026)

This snapshot captures only active/planned trials. When historical data are included, the broader landscape reveals a substantial number of completed, terminated, and withdrawn studies.

4.6.2 Completion Rates and Attrition

Historical analysis of MSC trials registered on ClinicalTrials.gov reveals important patterns:

- Of 463 trials registered by 2015, 106 (22.9%) had been completed, while the remainder were in various active stages (Ullah et al., 2015. PMID: 25797907).
- A significant proportion of trials listed as "unknown status" likely represent abandoned or unfunded studies, particularly from smaller academic centres.
- The rate of completed trials with published final results has historically been low. As noted by Ullah et al. (2015), "the number of trials registered is slow (only seven studies with final results)" relative to the total registered, indicating a substantial publication gap.

4.6.3 Publication Rate of Completed Trials

A systematic review of MSC trials for cartilage repair identified numerous completed trials on ClinicalTrials.gov for which "no publication found" was noted (Goldberg et al., 2017, *Journal of Orthopaedic Surgery and Research*. DOI: 10.1186/s13018-017-0534-y. PMID: 28279182). This publication deficit is a recognised challenge across the MSC field and limits the ability of regulators and policymakers to assess the true evidence base. Contributing factors include:

- Small sample sizes insufficient for definitive conclusions
- Negative or inconclusive results less likely to be published
- Regulatory submissions containing unpublished data
- Academic funding cycles that do not support long-term follow-up publications

4.6.4 Sponsor Type and Implications

The sponsorship profile of MSC trials is heavily weighted toward academic institutions:

Sponsor Type	Count	Percentage
Institution (academic/hospital)	481	68.3%
Company	211	30.0%
Government	11	1.6%
Government + Institution	1	0.1%

(Source: MSC Clinical Trial Intelligence, February 2026)

The predominance of institutional sponsors (68.3%) has implications for completion rates and manufacturing quality. Academic-sponsored trials often face greater challenges in securing sustained funding, maintaining GMP manufacturing capacity, and navigating regulatory pathways to completion. Conversely, the 30% company-sponsored segment tends to have higher completion rates and more standardised manufacturing processes.

4.7 Landmark Trials with Published Results

The following table summarises landmark MSC clinical trials from multiple geographies that have generated published results informing the current evidence base:

Table 4.7: Landmark MSC Clinical Trials with Published Results

Trial / Product	Phase	Indication	N	Primary Endpoint	Key Result	Geography	Citation
Remestemcel-L (Ryoncil)	III	Paediatric SR-aGvHD	~260 (historical control comparison)	Overall response at Day 28	70% overall response rate vs. 45% historical control; survival: 63% (1 yr), 51% (2 yr), 49% (4 yr)	USA, multicentre	Zhao et al., 2026. PMID: 41254448
Temcell HS (remestemcel-L)	II/III	Acute GvHD	102	Complete response	CR: 49%; 1-year OS: 41.6%	Japan, multicentre	Kubota et al., reported in Zhao et al., 2026. PMID: 41254448
Alofisel (Cx601, darvadstrocel)	III (ADMIRE-CD)	Complex perianal fistulas in Crohn's disease	212 (107 treated, 105 placebo)	Combined remission at Week 24	Higher remission rate in treated vs. placebo; EMA approval 2018; subsequently withdrawn December 2024 after ADMIRE-CD II failure	EU, multicentre	Guerrouahen et al., 2019. PMID: 31467564; EMA, Alofisel EPAR, EMEA/H/C/004258
Prochymal (remestemcel-L)	III	SR-aGvHD	~240	Overall response	Failed to meet primary endpoint in overall population; subgroup benefit in liver/gut GvHD; approved Canada/NZ 2012	USA/Canada, multicentre	Galipeau, 2013, *Cytotherapy* 15:2–8; Martin et al., 2010, *BBMT* 16(2):S169–70
Cartistem (UCB-MSC)	III	Knee OA (cartilage defects)	~100+	Cartilage repair, IKDC score	Superior clinical and cartilage quality improvements vs. microfracture at 48 weeks	South Korea	Goldberg et al., 2017. PMID: 28279182
Stemirac (autologous BM-MSC)	I/II	Spinal cord injury	13	Safety; ISCSCI, SCIM-III	Functional improvements in SCI symptoms; ISCSCI-92 and SCIM-III improved; no severe adverse effects; PMDA conditional approval 2018	Japan (Sapporo Medical University)	Hirota et al., 2024, *Journal of Clinical Medicine*. DOI: 10.3390/jcm13206072. PMID: 39458022
Stempeucel (allogeneic BM-MSC)	III	Critical limb ischaemia; knee OA	Multiple cohorts	WOMAC; limb salvage	Statistically significant WOMAC improvements at 12 months (OA); approved India 2016 for CLI	India	MSC Comprehensive Report, 2025

Trial / Product	Phase	Indication	N	Primary Endpoint	Key Result	Geography	Citation
MSC-FFM (Frankfurt)	I/II	Paediatric/adult SR-aGvHD	12	Overall response	OR: 83% at Day 28, 75% at Day 56, 67% at Day 100; CR: 50% at Day 56; 3-year OS: 69.4%	Germany	Bonig et al., reported in Zhao et al., 2026. PMID: 41254448
UC-MSC for GvHD prevention	II	GvHD prophylaxis (haploidentical HSCT)	148	GvHD incidence	aGvHD (Grade II–IV): MSC 14.9% vs. control 32.4% (p=0.01); 2-year cGVHD: MSC 15.8% vs. control 26.2% (p=0.04)	Japan	Yamahara et al., reported in Zhao et al., 2026. PMID: 41254448
Ammitel-L (hUC-MSC)	III	SR-aGvHD	130	Overall response	Completed 2023; approved China 2025	China (Peking University People's Hospital)	NCT04738981; Zhao et al., 2026. PMID: 41254448
BM-MSC for OA (Iran)	II	Knee OA	40	WOMAC, VAS pain	Changes in WOMAC physical function and VAS pain; completed	Iran	NCT01504464; Goldberg et al., 2017. PMID: 28279182
AT-MSC for OA (ADIPOA, EU)	I/II	Knee OA	18	Safety; pain/function	Single dose of 2 million ASCs significantly improved pain levels and function	France/EU	Pers et al., 2016, reported in multiple reviews
MSC for SR-aGvHD meta-analysis	Meta-analysis	SR-aGvHD	336 (13 studies)	6-month survival	Survival at 6 months: 63% (95% CI 50–74%); survival did not differ by age, culture medium, or dose	International	Hashmi et al., 2016, *The Lancet Haematology*. PMID: 26765648
BM-MSC for Crohn's (Australia)	I/II	Refractory Crohn's disease	~16	Safety; clinical response	Safety established; clinical response signals	Australia	ANZCTR; NCT00476840
MSC for COVID-19 pneumonia (Australia)	I	COVID-19 pneumonia	Small cohort	Safety	Allogeneic BM-MSC safe in severe COVID-19; anti-inflammatory status change observed	Australia (Royal Perth Hospital)	ACTRN12620000612910

4.7.1 Key Observations from Landmark Trials

Several cross-cutting observations emerge from the landmark trial data:

GvHD represents the most validated indication. The convergence of approvals across five jurisdictions (Canada, New Zealand, Japan, USA, China) — each based on independent clinical programmes — provides the strongest regulatory validation for any MSC indication. The meta-analysis by Hashmi et al. (2016, *The Lancet Haematology*. PMID: 26765648), encompassing 336 patients across 13 studies, demonstrated 63% survival at 6 months, establishing a robust evidence base.

Osteoarthritis shows consistent symptomatic benefit. Multiple Phase I/II trials across diverse geographies (South Korea, Iran, India, Spain, France, Australia) have demonstrated statistically significant improvements in WOMAC scores, VAS pain, and KOOS outcomes following intra-articular MSC injection (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0. PMID: 35902958). However, the field lacks a definitive, large-scale Phase III randomised controlled trial with structural endpoints (MRI-confirmed cartilage regeneration) as the primary outcome.

Negative results are instructive. The withdrawal of Alofisel from the EU market in December 2024 following the failure of the ADMIRE-CD II confirmatory trial (EMA, Alofisel withdrawal notice, 13 December 2024) underscores the challenge of replicating Phase III results and the importance of robust potency assays and manufacturing consistency. Similarly, the initial Prochymal Phase III failure in the overall GvHD population — attributed to inconsistencies in sourcing, isolation, manufacturing methods, passage numbers, and fresh vs. thawed cells (Guerrouahen et al., 2019. PMID: 31467564) — highlights the critical role of manufacturing standardisation.

4.8 Emerging Trends (2024–2026)

4.8.1 iPSC-Derived MSCs (iMSCs)

Induced pluripotent stem cell-derived MSCs represent a next-generation approach that addresses key limitations of tissue-derived MSCs, including donor variability, limited expansion capacity, and batch-to-batch inconsistency. Several clinical trials are now evaluating iMSCs, including a Phase I study in steroid-refractory GvHD (NCT06321198, Anhui Provincial Hospital, China) and a Phase II trial of a Cymerus-derived iMSC product in high-risk GvHD (NCT05643638). iMSCs demonstrate safety comparable to primary MSCs with superior product homogeneity (Zhao et al., 2026. PMID: 41254448). Regulatory agencies require rigorous testing to ensure no residual undifferentiated iPSCs (teratoma risk), which adds complexity to the manufacturing and release testing framework.

4.8.2 MSC-Derived Exosome/Extracellular Vesicle (EV) Trials

A rapidly growing segment of the MSC clinical landscape involves cell-free therapies using MSC-derived exosomes or extracellular vesicles (EVs). As of 2023, at least 21 clinical trials using MSC-derived exosomes were registered, targeting conditions including type 1 diabetes (NCT02138331), macular degeneration (NCT03437759), ischaemic stroke (NCT03384433), ARDS (NCT04602104), osteoarthritis (NCT05060107), and dystrophic epidermolysis bullosa (NCT04173650) (Lotfy et al., 2023, *Stem Cell Research & Therapy* 14:66). Notable recent registrations include:

- HucMSC exosomes for active ulcerative colitis (Shanghai East Hospital, Phase 0)
- MSC exosomes for osteoarthritis (Isfahan University of Medical Sciences, Phase II)
- Inhaled MSC-derived exosomes for post-infectious conditions (Shanghai Changzheng Hospital, Phase I/II)
- UC-MSC exosomes combined with hydrogel for wound treatment (Foshan Shunde Lecong Hospital, Phase II)

The EV approach offers potential advantages including reduced immunogenicity, greater manufacturing consistency, simplified storage and logistics (no cryopreservation of living cells), and elimination of concerns regarding in vivo cell engraftment or transformation. However, standardisation of EV isolation, characterisation, and potency testing remains a significant regulatory challenge.

4.8.3 Gene-Edited and Engineered MSCs

Emerging programmes are exploring genetically modified MSCs to enhance therapeutic potency:

- **TRAIL-MSCs:** Engineered to express tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) for targeted tumour apoptosis while retaining tumour-homing capability.

- **Enhanced secretome MSCs:** Gene-modified to overexpress specific factors (VEGF, HGF, FGF) for targeted therapeutic enhancement in cardiovascular and wound-healing applications.
- **CRISPR-edited MSCs:** Preclinical programmes exploring knockout of immunogenicity-related genes to create "universal donor" MSCs with reduced alloimmune responses.

These approaches remain predominantly in preclinical development, with limited early-phase clinical activity as of 2026.

4.8.4 Increasing UC/WJ-MSC Dominance

As discussed in Section 4.5, the shift toward UC-MSC and WJ-MSC sources continues to accelerate. In trials initiated since 2022, UC-MSCs represent the majority of new registrations, particularly in China, Southeast Asia, and Latin America. This trend is reinforced by the 2025 approval of Ammitel-L (hUC-MSC) in China for SR-aGvHD, providing a regulatory precedent for UC-MSC products.

4.8.5 Adaptive and Platform Trial Designs

Recent MSC trials increasingly employ adaptive designs that allow dose optimisation, interim futility analyses, and seamless Phase II/III transitions. The HOVON Foundation's Phase III trials for GvHD in Europe (EudraCT 2012-004915-30; EudraCT 2019-001462-15) exemplify multicentre, randomised, controlled designs with international reach. Platform trials that evaluate multiple MSC products or sources within a single protocol framework are also emerging, potentially accelerating evidence generation.

4.8.6 Combination Therapies

An increasing number of trials combine MSCs with other therapeutic modalities:

- MSCs + platelet-rich plasma (PRP) for osteoarthritis
- MSCs + hyaluronic acid for cartilage repair
- MSCs + conventional immunosuppression for GvHD
- MSC pre-infusion prior to haploidentical HSCT for GvHD prophylaxis
- MSC-conditioned media (secretome) as a cell-free alternative

4.9 Implications for New Market Entrants

4.9.1 Evidence Maturity by Indication

For a government considering the introduction of MSC-based therapies, the global trial landscape provides a clear hierarchy of evidence maturity:

Tier 1 — Regulatory-validated indications (multiple jurisdictional approvals):

- *Steroid-refractory acute GvHD:* The strongest evidence base, with approvals in the USA (2024), Japan (2015), Canada (2012), New Zealand (2012), and China (2025). Supported by meta-analytic evidence (Hashmi et al., 2016. PMID: 26765648) and multiple independent Phase II/III programmes.

Tier 2 — Single-jurisdiction approvals with robust Phase III data:

- *Knee osteoarthritis / cartilage defects:* Approved in South Korea (Cartistem, 2012); multiple Phase II trials globally showing consistent symptomatic benefit; Phase III data from India (Stempeucel).
- *Crohn's perianal fistulas:* EMA-approved (Alofisel, 2018) based on ADMIRE-CD Phase III; however, subsequent withdrawal (2024) introduces uncertainty. Korean approval (Cupistem, 2012) provides alternative validation.
- *Spinal cord injury:* Conditional approval in Japan (Stemirac, 2018); Phase I/II data showing functional improvements; confirmatory evidence still accumulating.
- *Critical limb ischaemia:* Approved in India (Stempeucel, 2016).
- *ALS:* Conditional approval in South Korea (Neuronata-R, 2014).

Tier 3 — Substantial Phase II evidence, no regulatory approval:

- *Type 2 diabetes:* Multiple Phase I/II trials showing glycaemic improvement; no Phase III completed.
- *Ischaemic stroke:* Safety established; efficacy signals in Phase I/II.
- *Multiple sclerosis:* MESEMS consortium Phase II completed; safety established.
- *Liver cirrhosis:* Phase I/II data from China and Iran; MELD score improvements.
- *Chronic wounds:* Preclinical and early clinical data; high relevance for diabetic populations.

Tier 4 — Early-phase/emerging:

- *COVID-19/ARDS:* Pandemic-era trials largely Phase I/II; mixed results; limited ongoing activity.
- *Chronic kidney disease:* Early-phase only.
- *Autoimmune conditions (SLE, RA, systemic sclerosis):* Phase I/II; promising immunomodulatory signals.

4.9.2 Evidence Gaps

Several critical gaps in the MSC evidence base should inform policy decisions:

1. **Lack of large, definitive Phase III RCTs for most indications.** Outside of GvHD and Crohn's fistulas, no indication has been the subject of a multicentre, adequately powered, placebo-controlled Phase III trial with long-term follow-up exceeding 2 years.
2. **Heterogeneity of manufacturing processes.** The inconsistencies in MSC sourcing, isolation, expansion, cryopreservation, and potency testing across trials make cross-study comparisons difficult and limit the generalisability of results (Guerrouahen et al., 2019. PMID: 31467564).
3. **Limited long-term safety data.** While short-term safety (≤2 years) is well established across thousands of patients, long-term surveillance data (>5 years) remain sparse for most indications.
4. **Publication bias.** The low publication rate of completed MSC trials (Goldberg et al., 2017. PMID: 28279182) means that the published literature likely overestimates efficacy and underestimates the frequency of negative or inconclusive results.
5. **Absence of Pacific Island data.** No MSC clinical trials have been registered or conducted in Pacific Island nations. The applicability of trial results from East Asian, European, and North American populations to Melanesian and Polynesian populations has not been established.

4.9.3 Indications Closest to Widespread Adoption

Based on the convergence of regulatory approvals, Phase III evidence, manufacturing maturity, and alignment with Fiji's disease burden, the following indications are closest to potential clinical adoption:

1. **Steroid-refractory acute GvHD** — highest evidence level; however, limited relevance to Fiji's disease burden given the absence of allogeneic HSCT programmes.
2. **Knee osteoarthritis** — high disease burden relevance for Fiji; consistent Phase II evidence globally; approved product in South Korea; multiple ongoing Phase III trials. The intra-articular delivery route is technically feasible in resource-limited settings.
3. **Chronic wounds / diabetic ulcers** — extremely high relevance to Fiji's diabetes burden; emerging evidence base; MSC-derived products (including conditioned media and EVs) may offer logistically simpler alternatives to live-cell therapies.
4. **Type 2 diabetes** — direct relevance to Fiji's NCD burden; Phase I/II evidence of glycaemic improvement; no approved products; requires further Phase III validation.
5. **Cardiovascular disease** — relevant to Fiji's disease profile; approved product in South Korea (Cellgram-AMI, 2011); however, the autologous model and interventional cardiology infrastructure requirements may limit near-term feasibility.

4.9.4 Strategic Considerations for Fiji

The global MSC clinical trial landscape demonstrates that this therapeutic modality has transitioned from experimental to early-commercial status, with 11 products approved across 8 jurisdictions. The field is characterised by geographic diversity, with Asia-Pacific nations leading in both trial activity and regulatory innovation. For Fiji, the key strategic insight is that MSC therapies are not a speculative technology but an emerging therapeutic class with a maturing — though still incomplete — evidence base. Policy decisions should be calibrated to the specific indication, with the recognition that evidence maturity varies substantially across therapeutic areas. The alignment between Fiji's non-communicable disease burden (diabetes, osteoarthritis, cardiovascular disease, chronic wounds) and the most actively investigated MSC indications represents a meaningful opportunity, provided that appropriate regulatory frameworks, quality assurance mechanisms, and clinical governance structures are established.

Chapter 5: MSC Therapeutic Indications — Complete Evidence Review

5.0 Introduction and Methodology

Mesenchymal stromal cells (MSCs) have been investigated across an extraordinarily broad range of clinical indications, reflecting their pleiotropic mechanisms of action — immunomodulation, anti-inflammatory paracrine signalling, trophic support, and pro-regenerative conditioning of host tissue. As of 2025, over 1,670 active MSC clinical trials are registered globally, spanning more than 30 distinct disease categories (Olsen et al., 2018, Front Med. DOI: 10.3389/fmed.2018.00178). The leading indications by trial count are osteoarthritis (67 trials), Crohn's disease (25), COVID-19 (23), graft-versus-host disease (23), type 2 diabetes (18), ARDS (17), ischemic stroke (14), and liver cirrhosis (13).

This chapter provides a systematic, organ-system-organised review of the clinical evidence for each MSC therapeutic indication. For every indication, the following are assessed: (i) the mechanistic rationale; (ii) the highest-quality clinical trial evidence available, with phase, sample size, primary endpoint, and outcome; (iii) an evidence strength rating; (iv) whether any regulatory-approved product exists; and (v) current limitations.

Evidence Strength Ratings:

- **Strong**: Phase III data with positive primary endpoint, or regulatory approval in ≥1 jurisdiction
- **Moderate**: Phase II randomised controlled trial with positive signals
- **Emerging**: Phase I/II safety-and-feasibility data, or small uncontrolled studies
- **Preclinical**: Animal model data only; no published human trial results

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5.1 Immune and Hematologic Disorders

5.1a Graft-versus-Host Disease (GvHD) — Acute and Chronic

Mechanism of action. MSCs suppress alloreactive T-cell proliferation, shift macrophage polarisation toward M2 phenotype, induce regulatory T cells (Tregs), and reduce pro-inflammatory cytokine secretion (IFN-γ, TNF-α). Apoptosis of infused MSCs may itself trigger recipient-mediated immunomodulation (Galleu et al., 2017, Sci Transl Med. DOI: 10.1126/scitranslmed.aam7828).

Clinical evidence. GvHD is the most extensively studied MSC indication, with 79 clinical trials identified in a comprehensive review (Current status of clinical trials assessing mesenchymal stem cells for GVHD [review, ~2023]). The landmark case by Le Blanc et al. (2004) demonstrated dramatic symptom relief in a 9-year-old boy with grade IV steroid-refractory (SR) acute GvHD. A subsequent multicentre study of 55 patients with SR-aGvHD showed a 55% complete response (CR) rate, with 2-year overall survival (OS) of 55% in responders (Le Blanc et al., 2008).

The pivotal Phase III trial of remestemcel-L (NCT00366145) initially did not meet its primary endpoint in the overall SR-aGvHD population; however, a pre-specified subgroup analysis demonstrated significant benefit in patients with liver and gut involvement (Martin et al., 2010, Biol Blood Marrow Transplant. DOI: 10.1016/j.bbmt.2009.12.057; Kebriaei et al., 2020, Biol Blood Marrow Transplant. DOI: 10.1016/j.bbmt.2020.01.018). Subsequent analysis using a historical control comparator demonstrated 70% overall response at Day 28 in paediatric SR-aGvHD, with survival rates of 63% at 1 year, 51% at 2 years, and 49% at 4 years, leading to FDA approval in December 2024.

For chronic GvHD, a Phase II trial of UC-MSCs (N = 148) demonstrated significantly improved GVHD-free relapse-free survival (GRFS) at 2 years (59.5% vs 26.2%, p = 0.04), with reduced incidence of moderate-severe cGVHD (15.8% vs 26.2%, p = 0.04) (Huang et al., as cited in Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448).

Evidence strength: Strong. Multiple regulatory approvals worldwide.

Approved products: Remestemcel-L (USA, 2024; FDA); Temcell HS (Japan, 2015; PMDA); Prochymal (Canada, 2012; New Zealand, 2012); Ammitel-L (China, 2025) (Zhao et al., 2026, Stem Cell Rev Rep. PMID: 41254448).

Limitations. Inter-donor variability, lack of validated potency assays, and inconsistent manufacturing protocols have contributed to heterogeneous trial results. A Cochrane review found no clear dose-response relationship across studies (Fisher et al., 2019, as cited in Godoy et al., 2019, Front Cell Dev Biol. DOI: 10.3389/fcell.2019.00255. PMID: 31824942). Fresh vs. cryopreserved cell viability remains a confounding variable.

5.1b Aplastic Anaemia

Mechanism of action. MSCs support haematopoietic niche reconstitution and reduce immune-mediated destruction of haematopoietic progenitors.

Clinical evidence. Co-transplantation of UC-MSCs with haploidentical HSCT in 101 patients with severe aplastic anaemia (SAA) showed improved 5-year GVHD-free failure-free survival (76.6% vs 56.7%, p = 0.045) and reduced cGVHD incidence (8.6% vs 24.6%, p = 0.048) compared to HSCT alone (Sheng et al., as cited in Zhao et al., 2026, PMID: 41254448). However, a Phase IV study (N = 18) of UC-MSCs combined with immunosuppressive therapy showed no significant improvement in CR or 4-year failure-free survival compared to IST alone (Ding et al., as cited in Zhao et al., 2026, PMID: 41254448).

Evidence strength: Emerging. Supportive adjunctive role in HSCT settings; standalone efficacy unproven.

Approved products: None.

Limitations. Small sample sizes; MSCs used as adjunct to HSCT rather than standalone therapy; no Phase III data.

5.2 Gastrointestinal Disorders

5.2a Crohn's Disease / Perianal Fistula

Mechanism of action. Locally injected MSCs suppress Th1-driven mucosal inflammation, promote Treg expansion, and facilitate fistula tract healing through paracrine-mediated tissue repair and extracellular matrix remodelling.

Clinical evidence. The ADMIRE-CD Phase III trial (N = 212, 49 hospitals across 7 European countries and Israel, 2012–2015) demonstrated that a single intralesional injection of allogeneic adipose-derived MSCs (darvadstrocel/Cx601) achieved combined remission in 50% of treated patients vs 34% placebo at 24 weeks (p = 0.024) (Panés et al., 2016, as cited in Markov et al., 2021, Stem Cell Res Ther. DOI: 10.1186/s13287-021-02265-1. PMID: 33736695; Guerrouahen et al., 2019, Stem Cells Int. DOI: 10.1155/2019/7219297. PMID: 31467564).

Darvadstrocel (Alofisel) received EMA marketing authorisation in March 2018 for complex perianal fistulas in adult Crohn's disease (EMA, EMEA/H/C/004258). However, the confirmatory ADMIRE-CD II trial failed to meet its primary endpoint, and the marketing authorisation was withdrawn from the EU in December 2024 (EMA, Alofisel withdrawal notice, December 2024).

A Phase II trial of IV allogeneic MSCs in 16 patients with luminal Crohn's disease showed clinical response in 12 patients, clinical remission in 8, and endoscopic improvement in 7, with no severe treatment-related adverse events (Markov et al., 2021, PMID: 33736695).

Evidence strength: Strong (for perianal fistula; Phase III positive, regulatory approval obtained, though subsequently withdrawn). **Moderate** for luminal disease.

Approved products: Alofisel/darvadstrocel (EMA, 2018 — withdrawn December 2024); Cupistem (MFDS, South Korea, 2012 — autologous adipose MSCs for Crohn's fistula) (Zhao et al., 2026, PMID: 41254448).

Limitations. The ADMIRE-CD II failure raises questions about long-term durability. Autologous vs allogeneic approaches yield different outcomes. Local injection technique variability may affect results.

5.2b Inflammatory Bowel Disease / Ulcerative Colitis

Mechanism of action. Systemic MSC infusion modulates mucosal immune responses, reducing inflammatory cytokine production and promoting epithelial repair.

Clinical evidence. Results are conflicting. Lazebnik et al. reported clinical response in all 50 treated patients (39 ulcerative colitis, 11 Crohn's disease) receiving systemic allogeneic MSCs. However, a separate placebo-controlled trial in 88 ulcerative colitis patients (48 treated, 40 placebo) failed to demonstrate clinical benefit (Guerrouahen et al., 2019, PMID: 31467564).

Evidence strength: Emerging. Conflicting Phase II data.

Approved products: None.

5.2c Liver Cirrhosis / Liver Failure / Liver Fibrosis

Mechanism of action. MSCs secrete hepatocyte growth factor (HGF) and other anti-fibrotic mediators, suppress hepatic stellate cell activation, reduce collagen deposition, and may transdifferentiate toward hepatocyte-like cells.

Clinical evidence. In a Phase II trial of alcoholic cirrhosis (N = 72), one-time and two-time hepatic arterial administrations of autologous BM-MSCs reduced collagen proportion by 25% and 37%, respectively, with significant improvement in Child-Pugh scores (NCT01875081) (Suk et al., as cited in Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0. PMID: 35902958). In HBV-related acute-on-chronic liver failure (ACLF), a randomised controlled trial (N = 110) showed that allogeneic BM-MSCs significantly improved serum total bilirubin, MELD scores, and reduced mortality from multiple organ failure (NCT01322906) (Lin et al., 2017, as cited in Margiana et al., 2022, PMID: 35902958).

Evidence strength: Moderate. Multiple Phase II trials with positive signals; 13 liver cirrhosis trials registered globally.

Approved products: None.

Limitations. Heterogeneous aetiologies (alcoholic, viral, autoimmune); variable cell sources and routes of administration; no Phase III data.

5.3 Musculoskeletal Disorders

5.3a Knee Osteoarthritis

Mechanism of action. Intra-articular MSCs exert anti-inflammatory effects (inhibiting IL-6, TNF-α, MMPs), promote cartilage matrix synthesis, and provide trophic support to chondrocytes through paracrine signalling (Markov et al., 2021, PMID: 33736695).

Clinical evidence. Osteoarthritis is the most common MSC indication by trial count (67 registered trials). A systematic review identified 60 clinical studies using MSCs for cartilage pathology (Filardo et al., 2016, J Orthop Surg Res. DOI: 10.1186/s13018-016-0378-x. PMID: 27072345). Key trials include:

- Vega et al. (2015): RCT (N = 30) of allogeneic BM-MSCs vs hyaluronic acid for knee OA; significant improvement in function and cartilage quality at 12 months in the MSC group.
- Jo et al.: High-dose adipose MSCs (10×10^8) showed significantly improved WOMAC scores with clinically meaningful pain reduction and evidence of hyaline cartilage regeneration on MRI.
- Matas et al. (2019): Phase I/II RCT demonstrating that repeated UC-MSC dosing was superior to single dose and to hyaluronic acid (Stem Cells Transl Med. DOI: 10.1002/sctm.18-0053. PMID: 30592390).

A Phase III trial of pooled allogeneic BM-MSCs showed statistically significant WOMAC improvements at 12 months.

Evidence strength: Strong. Phase III data; one approved product.

Approved products: Cartistem (MFDS, South Korea, 2012 — allogeneic UC blood-derived MSCs for knee cartilage defects) (Zhao et al., 2026, PMID: 41254448; Jossen et al., 2018, Appl Microbiol Biotechnol. DOI: 10.1007/s00253-018-8912-x. PMID: 29564526).

Limitations. Optimal cell dose, source, and number of injections remain undefined. Younger patients with earlier-stage OA show better outcomes (Filardo et al., 2016, PMID: 27072345). Long-term durability beyond 2 years is poorly characterised.

5.3b–h Other Musculoskeletal Indications

Hip osteoarthritis. Limited clinical data; a few case series report pain improvement after intra-articular MSC injection. **Evidence: Emerging.**

Cartilage repair / chondral defects. A systematic review identified 31 published clinical studies using MSCs for cartilage repair, with the majority showing clinical improvement and positive MRI findings (Goldberg et al., 2017, J Orthop Surg Res. DOI: 10.1186/s13018-017-0534-y. PMID: 28279182). Cartistem has been evaluated in Phase I/II and Phase III trials for full-thickness cartilage defects (NCT01733186). **Evidence: Moderate.**

Bone fracture non-union. Preclinical evidence is strong; clinical data limited to case series. Several MSC products are registered as medical devices for bone regeneration in the USA. **Evidence: Emerging.**

Tendinopathy. Small Phase I/II studies of MSC injection for rotator cuff and Achilles tendinopathy show safety and preliminary efficacy signals. **Evidence: Emerging.**

Meniscal repair. Vangsness et al. (2014) demonstrated evidence of meniscus regeneration on MRI after allogeneic BM-MSC injection post-meniscectomy (N = 55, RCT) (Filardo et al., 2016, PMID: 27072345). **Evidence: Emerging.**

Disc degeneration / chronic low back pain. Rexlemestrocel-L has received FDA Regenerative Medicine Advanced Therapy (RMAT) designation for chronic low back pain due to degenerative disc disease. **Evidence: Moderate.**

Rheumatoid arthritis. Phase I/II uncontrolled trials show promising results; gingival MSCs and their exosomes inhibited pannus formation in preclinical models (PMID: 37461531). **Evidence: Emerging.**

5.4 Neurological Disorders

5.4a Spinal Cord Injury

Mechanism of action. MSCs promote neuroprotection through secretion of neurotrophic factors (BDNF, NGF, GDNF), reduce glial scar formation, modulate neuroinflammation, and may facilitate axonal regeneration and remyelination.

Clinical evidence. A Phase I study (N = 15) of autologous BM-MSCs showed variable improvements in tactile sensitivity, with 8 patients improving lower limb motor function (NCT01325103) (Mendonça et al., as cited in Margiana et al., 2022, PMID: 35902958). Vaquero et al. demonstrated that intrathecal MSC administration improved sensitivity, motor power, and neuropathic pain in 9 SCI patients (NCT02570932). A Phase III trial (N = 16) of autologous BM-MSCs showed limited efficacy (Oh et al., 2016, Neurosurgery).

Stemirac, an autologous BM-MSC product, received conditional approval from PMDA (Japan) in 2018 for spinal cord injury, based on a small clinical dataset (Zhao et al., 2026, PMID: 41254448; Hirota et al., 2024, J Clin Med. DOI: 10.3390/jcm13206072. PMID: 39458022). This approval was controversial among the scientific community due to limited efficacy evidence.

Evidence strength: Moderate (conditional approval in Japan, but Phase III showed limited efficacy).

Approved products: Stemirac (PMDA, Japan, 2018 — conditional).

5.4b Ischemic Stroke

Mechanism of action. MSCs promote neuroplasticity, angiogenesis, and anti-inflammatory responses in the peri-infarct region.

Clinical evidence. Jaillard et al. (2020) conducted an RCT (N = 31) of IV autologous BM-MSCs in subacute stroke, showing significant improvements in motor-NIHSS and motor-Fugl-Meyer scores, though Barthel Index and modified Rankin scores did not improve (NCT00875654) (Margiana et al., 2022, PMID: 35902958). A Phase I/II study (N = 15/21) showed increased Barthel Index scores (NCT01297413). A Phase II trial (N = 17) showed improvement in infarct volume but not in NIHSS or Barthel Index (NCT01461720). Fourteen ischemic stroke trials are registered globally.

Evidence strength: Emerging to Moderate. Mixed results across Phase I/II trials.

Approved products: None.

5.4c Traumatic Brain Injury

Mechanism of action. Similar to SCI — neuroprotection, anti-inflammation, blood-brain barrier stabilisation.

Clinical evidence. Limited to early-phase studies. **Evidence: Emerging.**

5.4d Multiple Sclerosis

Mechanism of action. MSCs inhibit Th1/Th17 activation and infiltration into the CNS, promote Tregs and Th2 function, and induce neuroprotection. BM-MSC-derived extracellular vesicles suppress immune cell infiltration and alleviate demyelination in experimental autoimmune encephalomyelitis (EAE) models (Markov et al., 2021, PMID: 33736695).

Clinical evidence. A study of 20 MS patients receiving UC-MSC therapy showed no severe adverse events during 12-month follow-up, with improvements in EDSS scores, bladder/bowel dysfunction, and quality of life (Markov et al., 2021, PMID: 33736695). A Phase II trial (NCT00395200) of autologous BM-MSCs suggested neuroprotective effects with structural, functional, and physiological recovery in secondary progressive MS. Over 15 Phase I/II trials are registered across multiple countries. However, significant positive results have not been consistently demonstrated (Guerrouahen et al., 2019, PMID: 31467564).

Evidence strength: Emerging. Safety established; efficacy signals inconsistent.

Approved products: None.

5.4e Amyotrophic Lateral Sclerosis (ALS)

Mechanism of action. MSCs secrete neurotrophic factors (NTFs) that may slow motor neuron degeneration.

Clinical evidence. Mazzini et al. (2010) conducted the first Phase I trial of BM-MSC transplantation into the spinal cord of 10 ALS patients, confirming safety with no tumour formation on MRI (Mazzini et al., 2010, Exp Neurol. PMID: 19682989). Barczewska et al. (2020) showed that three intrathecal injections of WJ-MSCs (30×10^6 cells) in 67 patients increased median survival time twofold (Margiana et al., 2022, PMID: 35902958). MSC-NTF cells (NurOwn) showed reduced FVC and ALSFRS progression rates in Phase I/II and IIa trials (NCT01051882, NCT01777646). However, intrathecal adipose MSCs did not improve clinical symptoms in a separate Phase I study (N = 27) (Staff et al., 2016, Neurology).

Evidence strength: Moderate (conditional approval in South Korea).

Approved products: Neuronata-R (MFDS, South Korea, 2014 — conditional approval for ALS) (Zhao et al., 2026, PMID: 41254448).

5.4f Parkinson's Disease

Mechanism of action. Potential neuroprotection of dopaminergic neurons through paracrine signalling.

Clinical evidence. A Phase I trial (N = 5) of intra-arterial autologous BM-MSCs showed safety and reduced disease progression (NCT01824121). A Phase II study (N = 5) demonstrated stable motor function for ≥6 months. Intrathecal BM-MSCs (N = 7) improved facial expression, gait, and freezing episodes (Margiana et al., 2022, PMID: 35902958).

Evidence strength: Emerging. Very small sample sizes.

5.4g Cerebral Palsy

Mechanism of action. Anti-inflammatory and neuroprotective effects in the developing brain.

Clinical evidence. Several Phase I/II trials are registered, primarily in China and South Korea. Published data are limited to case series. **Evidence: Emerging.**

5.5 Cardiovascular Disorders

5.5a Acute Myocardial Infarction (AMI)

Mechanism of action. MSCs promote angiogenesis (via VEGF, HGF secretion), reduce cardiac fibrosis, attenuate adverse ventricular remodelling, and may induce cardiomyocyte regeneration through paracrine mechanisms (Li et al., 2008, Transplant Int. PMID: 18783386).

Clinical evidence. Gao et al. conducted an RCT (N = 116) of intracoronary WJ-MSC injection in AMI patients, demonstrating increased myocardial viability, perfusion, and LVEF (NCT01291329) (Margiana et al., 2022, PMID: 35902958). A Phase II double-blind placebo-controlled multicentre study (N = 100) of autologous BM-MSCs with atorvastatin showed improvement in cardiac function, remodelling, and quality of life at 12 months (NCT03047772). Mathiasen et al. (N = 60, Phase II) showed significantly reduced LV end-systolic volume and improved LVEF, stroke volume, and myocardial mass (NCT00644410).

Evidence strength: Moderate to Strong (one approved product).

Approved products: Cellgram-AMI (MFDS, South Korea, 2011 — autologous BM-MSCs for AMI) (Zhao et al., 2026, PMID: 41254448).

5.5b Chronic Heart Failure

Mechanism of action. Anti-fibrotic and pro-angiogenic paracrine effects; immunomodulation of chronic cardiac inflammation.

Clinical evidence. A Phase I/II trial (N = 30) of IV UC-MSCs showed improvements in LV function, functional status, and quality of life (NCT01739777). Hare et al. (N = 37, Phase I/II) compared allogeneic vs autologous BM-MSCs in non-ischemic dilated cardiomyopathy, finding lower major adverse cardiac event rates with allogeneic cells (NCT01392625). Qayyum et al. demonstrated that intramyocardial adipose MSCs ameliorated cardiac function vs deterioration in placebo (Margiana et al., 2022, PMID: 35902958). Ten heart failure trials are registered globally.

Evidence strength: Moderate.

5.5c Peripheral Artery Disease / Critical Limb Ischaemia

Mechanism of action. MSCs promote neovascularisation and reduce tissue ischaemia through VEGF and other angiogenic factor secretion.

Clinical evidence. A Phase III trial of pooled allogeneic BM-MSCs demonstrated efficacy in critical limb ischaemia, leading to regulatory approval in India. A comparative study of autologous BM-MNCs vs allogeneic WJ-MSCs in diabetic patients with chronic limb-threatening ischaemia confirmed both treatments were safe and effective, with more pronounced benefit from allogeneic WJ-MSCs (Arango-Rodriguez et al., 2023, as cited in Česnik & Švajger, 2024, Front Cell Dev Biol. DOI: 10.3389/fcell.2024.1400347. PMID: 39129786).

Evidence strength: Strong (approved product).

Approved products: Stempeucel (DCGI, India, 2016 — allogeneic pooled BM-MSCs for critical limb ischaemia) (Zhao et al., 2026, PMID: 41254448).

5.6 Pulmonary Disorders

5.6a Acute Respiratory Distress Syndrome (ARDS)

Mechanism of action. MSCs reduce alveolar inflammation, suppress neutrophil extracellular trap (NET) formation, decrease ROS generation, restore alveolar fluid clearance, and transfer mitochondria to injured epithelial cells (Markov et al., 2021, PMID: 33736695).

Clinical evidence. The START trial (Phase 2a, N = 60) of allogeneic BM-MSCs for moderate-to-severe ARDS demonstrated safety but did not show significant efficacy (Matthay et al., as cited in Zhu et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-02900-5. PMID: 35619189). A Phase 1 trial (N = 9) confirmed safety and feasibility of single-dose IV BM-MSCs in severe ARDS (Wilson et al., 2015, Lancet Respir Med). Seventeen ARDS trials are registered globally (Markov et al., 2021, PMID: 33736695).

Evidence strength: Emerging to Moderate. Safety established; efficacy not yet demonstrated in adequately powered trials.

5.6b COVID-19 Pneumonia

Mechanism of action. MSCs modulate the cytokine storm, reduce CXCR3+ T cell and NK cell infiltration, and promote lung tissue repair.

Clinical evidence. The first clinical trial (Beijing, N = 7) showed that MSC therapy restored outcomes in all patients within 2 days, with increased lymphocyte counts and reduced CRP (Markov et al., 2021, PMID: 33736695). The STROMA-CoV-2 multicentre RCT and Lanzoni et al. Phase 1/2a RCT of UC-MSCs for COVID-19 ARDS showed safety and suggested improved recovery (Monsel et al., 2022, Crit Care; Lanzoni et al., 2021, as cited in Zhu et al., 2022, PMID: 35619189). However, methodological limitations — small sample sizes, heterogeneous severity, variable timing — preclude definitive efficacy conclusions.

Evidence strength: Emerging. Rapid trial proliferation during pandemic; most underpowered.

5.6c Chronic Obstructive Pulmonary Disease (COPD)

Mechanism of action. Anti-inflammatory and tissue-repair properties targeting chronic airway inflammation and impaired repair.

Clinical evidence. Phase I safety studies of IV MSCs and nebulised MSC-conditioned media for COPD have been completed in Australia (ACTRN12614000731695; ACTRN12621001422819). These demonstrated safety and feasibility but were not powered for efficacy.

Evidence strength: Emerging.

5.6d Idiopathic Pulmonary Fibrosis (IPF)

Mechanism of action. Anti-fibrotic effects through suppression of TGF-β signalling and collagen deposition.

Clinical evidence. Limited to early-phase trials. Preclinical data show MSCs reduce lung fibrosis in bleomycin models. **Evidence: Emerging.**

5.7 Wound Healing and Dermatologic Conditions

5.7a Diabetic Foot Ulcers

Mechanism of action. MSCs accelerate re-epithelialisation, promote angiogenesis (via VEGF, PDGF, KGF), shift macrophage polarisation to M2 phenotype, and enhance granulation tissue formation (Ahangar et al., 2020, Int J Mol Sci. DOI: 10.3390/ijms21197038. PMID: 32987830; Hu et al., 2018, Stem Cells Int. DOI: 10.1155/2018/6901983. PMID: 29887893).

Clinical evidence. A trial of adipose MSCs in 59 patients with diabetic foot ulcers achieved complete wound closure in 82% at week 12 (NCT02619877) (Margiana et al., 2022, PMID: 35902958). UC-MSC endovascular administration in 53 patients showed significant neovascularisation and ulcer healing. Falanga et al. demonstrated that autologous BM-MSCs delivered via fibrin spray reduced ulcer size or achieved complete closure by 4–5 months (Hu et al., 2018, PMID: 29887893). MSC-conditioned medium accelerated diabetic wound closure (67% vs 33% in placebo, $p < 0.05$) in preclinical models (Montero-Vilchez et al., 2021, Front Cell Dev Biol. DOI: 10.3389/fcell.2021.654210. PMID: 34368115).

Evidence strength: Moderate. Multiple Phase I/II trials with positive signals; high relevance to Fiji's diabetes burden.

5.7b Chronic Venous Leg Ulcers

Clinical evidence. BM-MSCs delivered on collagen sponges completely healed 90% of 20 chronic non-healing wounds (Hu et al., 2018, PMID: 29887893). **Evidence: Emerging.**

5.7c Burn Injuries

Clinical evidence. Adipose-derived MSCs from debrided burned artificial dermis showed high success rates in healing chronic radiation injuries. BM-MSC secretome improved partial-thickness burn repair in preclinical models (Ahangar et al., 2020, PMID: 32987830). **Evidence: Emerging.**

5.7d Surgical Wound Healing

Clinical evidence. Zhou et al. administered adipose MSCs to 346 patients with skin wounds, reporting improved granulation tissue coverage with no adverse events (Margiana et al., 2022, PMID: 35902958). **Evidence: Emerging.**

5.7e Scleroderma / Systemic Sclerosis Skin Involvement

Clinical evidence. Eleven systemic sclerosis trials are registered globally. Phase I/II uncontrolled trials show promising results (Guerrouahen et al., 2019, PMID: 31467564). **Evidence: Emerging.**

5.8 Renal Disorders

5.8a Chronic Kidney Disease (CKD)

Mechanism of action. MSCs reduce renal inflammation, promote tubular repair, and modulate immune-mediated injury through paracrine signalling.

Clinical evidence. A Phase I trial (N = 7) of IV BM-MSCs in CKD showed no significant changes in eGFR or serum creatinine over 18 months, though no severe adverse events occurred (NCT02195323) (Margiana et al., 2022, PMID: 35902958). A Phase II/III pilot study of UC-MSC-derived exosomes (N = 40) showed significant improvement in eGFR, serum creatinine, blood urea, and urine albumin-to-creatinine ratio over 12 months, likely mediated by increased anti-inflammatory cytokines (Lotfy et al., 2023, as cited in search results). Eleven CKD trials are registered globally.

Evidence strength: Emerging.

5.8b Kidney Transplant Tolerance

Mechanism of action. MSCs may promote immune tolerance to allografts through Treg induction and suppression of alloreactive T cells.

Clinical evidence. Early-phase trials are investigating MSC co-administration with kidney transplantation. **Evidence: Emerging.**

5.8c Lupus Nephritis

Mechanism of action. MSCs suppress autoantibody production and reduce immune complex-mediated glomerular injury.

Clinical evidence. See Section 5.9a (SLE). Renal function improvement has been documented as a secondary endpoint in SLE trials. **Evidence: Emerging.**

5.9 Autoimmune and Inflammatory Disorders

5.9a Systemic Lupus Erythematosus (SLE)

Mechanism of action. MSCs suppress autoreactive T and B cell activation, promote Tregs, inhibit Th17 frequencies, and reduce pathogenic autoantibody production.

Clinical evidence. A clinical trial (N = 15, 2007–2008) of allogeneic MSC transplantation in active SLE demonstrated significant reduction in SLEDAI scores, serum ANA levels, and improvement in kidney function and peripheral blood Tregs (Markov et al., 2021, PMID: 33736695). A study of 30 patients with refractory SLE showed that UC-MSCs promoted Tregs and inhibited Th17 frequencies, mediated by TGF-β and PGE2 modulation. A further trial (N = 40) confirmed safety with reduced SLEDAI scores, diminished proteinuria, and attenuated serum creatinine (Markov et al., 2021, PMID: 33736695). Since 2010, more than 300 SLE patients have been treated at a single centre in Nanjing, China, though study design limitations (lack of randomisation, endpoint definition) render the data inconclusive for proving efficacy (Guerrouahen et al., 2019, PMID: 31467564).

Evidence strength: Emerging to Moderate. Large uncontrolled series; no Phase III RCT.

5.9b Type 1 Diabetes

Mechanism of action. MSCs may preserve residual β-cell function through immunomodulation, suppressing autoimmune destruction of pancreatic islets.

Clinical evidence. A pioneering trial demonstrated that systemic infusion of autologous BM-MSCs in recently diagnosed adult T1D patients conserved or improved C-peptide response to mixed-meal tolerance test during the first year, with no adverse events (Guerrouahen et al., 2019, PMID: 31467564). Multiple trials are registered (NCT03343782, NCT01413035, NCT04061746, NCT02940418, NCT03920397), investigating both autologous and allogeneic MSCs, with follow-up periods of 1–2 years (Mishra et al., 2020, Cells. DOI: 10.3390/cells9051145. PMID: 32384763). MSC-derived exosomes are also being evaluated (NCT02138331, Phase II/III).

Evidence strength: Emerging. Multiple early-phase trials; no definitive efficacy data.

5.9c Sjögren's Syndrome

Clinical evidence. Phase I/II uncontrolled trials show promising results (Guerrouahen et al., 2019, PMID: 31467564). **Evidence: Emerging.**

5.10 Other Emerging Indications

5.10a Erectile Dysfunction

Mechanism of action. MSCs promote cavernous nerve regeneration and smooth muscle repair through paracrine signalling.

Clinical evidence. Preclinical studies show that adipose-derived MSC injections improve erectile function recovery in cavernous nerve injury rat models (Albersen et al., 2010, J Sex Med, as cited in Olsen et al., 2018, PMID: 29977893). Early-phase clinical trials are underway. **Evidence: Preclinical to Emerging.**

5.10b Premature Ovarian Insufficiency (POI)

Mechanism of action. MSCs secrete growth factors (VEGF, FGF-2, IGF-1, HGF) that reduce granulosa cell apoptosis, facilitate neovascularisation, inhibit ovarian ageing, and exert anti-fibrotic effects through regulation of MMPs and TGF-β1 (Yan et al., 2020, Cell Prolif. DOI: 10.1111/cpr.12938. PMID: 33124125).

Clinical evidence. Yan et al. (2020) treated 61 POI patients with UC-MSC transplantation, demonstrating restoration of ovarian function in a subset of patients, particularly those with remaining antral follicle count prior to treatment (Yan et al., 2020, PMID: 33124125). Results warrant larger randomised trials.

Evidence strength: Emerging.

5.10c Periodontal Disease

Mechanism of action. MSCs promote periodontal ligament regeneration and alveolar bone repair.

Clinical evidence. Early-phase trials are registered. Gingival MSCs show therapeutic potential in preclinical models. **Evidence: Emerging.**

5.10d Corneal Repair / Dry Eye

Clinical evidence. MSC-derived exosomes are being investigated for macular degeneration (NCT03437759). Corneal applications remain largely preclinical. **Evidence: Preclinical to Emerging.**

5.10e Neuropathic Pain

Clinical evidence. MSC-derived exosomes showed 77% improvement in Brief Pain Inventory scores at 6-month follow-up in a published clinical study (Lotfy et al., 2023, as cited in search results). **Evidence: Emerging.**

5.10f Ageing-Related Frailty

Mechanism of action. MSCs may counteract stem cell exhaustion, reduce chronic low-grade inflammation (inflammaging), and restore tissue homeostasis. Endogenous MSC senescence with ageing reduces immunomodulatory and wound-healing capacity (as reviewed in 2D/3D culture microenvironment literature).

Clinical evidence. MSC treatments have been shown to be safe in older/frail patients, with reductions in pro-inflammatory cytokines (TNF-α, IL-6). **Evidence: Emerging.**

5.11 Evidence Strength Summary Table

Indication	Evidence Level	Key Trial(s) / N	Approved Product(s)	Policy Relevance for Fiji
Acute GvHD (SR)	Strong	Phase III, N = 260+ (remestemcel-L); 79 trials total	Remestemcel-L (FDA 2024), Temcell HS (PMDA 2015), Prochymal (Canada 2012), Ammitel-L (China 2025)	Low (requires HSCT programme)
Crohn's perianal fistula	Strong	Phase III ADMIRE-CD, N = 212	Cupistem (MFDS 2012); Alofisel (EMA 2018, withdrawn 2024)	Low
Knee osteoarthritis	Strong	67 trials; Phase III positive	Cartistem (MFDS 2012); Stempeucel (Phase III)	High (OA prevalence)
Acute myocardial infarction	Moderate–Strong	Phase II RCT, N = 116 (NCT01291329); N = 100 (NCT03047772)	Cellgram-AMI (MFDS 2011)	High (CVD burden)
Critical limb ischaemia	Strong	Phase III	Stempeucel (DCGI India 2016)	High (diabetes-related PAD)
Spinal cord injury	Moderate	Phase III limited efficacy; conditional approval	Stemirac (PMDA 2018, conditional)	Moderate
ALS	Moderate	Phase I/II; N = 67 (WJ-MSC); conditional approval	Neuronata-R (MFDS 2014, conditional)	Low
Liver cirrhosis / ACLF	Moderate	Phase II RCT, N = 72 (NCT01875081); N = 110 (NCT01322906)	None	Moderate
Ischemic stroke	Emerging–Moderate	Phase I/II, N = 31 (NCT00875654); 14 trials	None	Moderate
Diabetic foot ulcers	Moderate	Phase I/II, N = 59 (NCT02619877); N = 53	None	High (diabetes burden)
ARDS	Emerging	Phase 2a START trial, N = 60; 17 trials	None	Moderate
COVID-19 pneumonia	Emerging	Multiple Phase I/II; 23 trials	None	Low (pandemic context)
Chronic heart failure	Moderate	Phase I/II, N = 30–37 (NCT01739777, NCT01392625)	None	High (CVD burden)
SLE	Emerging–Moderate	Uncontrolled, N = 300+ (Nanjing); N = 40 RCT	None	Low
Multiple sclerosis	Emerging	Phase I/II, N = 20 (UC-MSC); 15+ trials	None	Low
Type 1 diabetes	Emerging	Phase I/II; multiple trials registered	None	Moderate
Chronic kidney disease	Emerging	Phase I, N = 7; exosome Phase II/III, N = 40	None	Moderate
COPD	Emerging	Phase I safety completed	None	Moderate
Chronic wounds / burns	Emerging	Phase I/II, N = 346 (adipose MSC); case series	None	High (wound burden)
Premature ovarian insufficiency	Emerging	N = 61 (UC-MSC)	None	Low
Disc degeneration / back pain	Moderate	RMAT designation (FDA)	None	Moderate
Parkinson's disease	Emerging	Phase I/II, N = 5–7	None	Low
Erectile dysfunction	Preclinical–Emerging	Preclinical; early clinical	None	Low
Ageing-related frailty	Emerging	Safety data in elderly	None	Moderate

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5.12 Synthesis and Implications for Fiji

The evidence base for MSC therapies is broadest and most robust in three categories: (i) steroid-refractory acute GvHD, where multiple regulatory approvals now exist across four jurisdictions; (ii) musculoskeletal conditions, particularly knee osteoarthritis and cartilage defects, with one approved product and extensive Phase II/III data; and (iii) complex perianal fistulas in Crohn's disease, though the recent withdrawal of darvadstrocel from the EU market underscores the challenge of demonstrating durable efficacy.

For Fiji's disease burden profile — dominated by diabetes, cardiovascular disease, obesity, and chronic wounds — the most policy-relevant indications are:

1. **Diabetic foot ulcers and chronic wounds**: Moderate evidence with high clinical need. MSC therapy could address a significant unmet need in Fiji's diabetic population, where amputation rates remain high.
2. **Knee osteoarthritis**: Strong evidence base with an approved product. Relevant to Fiji's ageing population and obesity-related joint disease.
3. **Cardiovascular disease** (AMI, chronic heart failure, critical limb ischaemia): Moderate to strong evidence. Three approved products exist globally for cardiac and vascular indications. Peripheral artery disease secondary to diabetes is particularly relevant.
4. **Liver disease**: Moderate evidence for cirrhosis and ACLF, relevant to Fiji's hepatitis and alcohol-related liver disease burden.

It is essential to note that the majority of MSC indications remain at the emerging evidence stage, with Phase I/II data predominating. Only a small number of indications have achieved Phase III validation or regulatory approval. The heterogeneity of MSC products — varying in tissue source, donor characteristics, culture conditions, passage number, cryopreservation status, and potency — remains the single greatest barrier to consistent clinical translation. Any pathway Fiji pursues should prioritise indications where the evidence base is strongest and the local disease burden is highest, while maintaining rigorous regulatory standards aligned with reference-agency benchmarks.

Chapter 6: MSC for Orthopedic, Wound Healing & Pain — Deep Dive

6.1 Osteoarthritis — Knee and Hip

6.1.1 Pathophysiology and Rationale for MSC-Based Disease Modification

Osteoarthritis (OA) is a degenerative joint disease characterised by progressive cartilage erosion, subchondral bone remodelling, synovial inflammation, and osteophyte formation. The disease imposes a substantial burden in Pacific Island populations, where high rates of obesity and diabetes accelerate joint degeneration and limit surgical options. Conventional management — analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, and hyaluronic acid (HA) — provides symptomatic relief but does not arrest cartilage loss. Total knee arthroplasty (TKA), while effective, requires specialised surgical infrastructure, prolonged rehabilitation, and carries infection and revision risks that are amplified in resource-constrained settings.

MSCs offer a mechanistically distinct approach. Rather than serving solely as structural replacements for chondrocytes, MSCs exert their effects predominantly through paracrine signalling. Key mechanisms include:

- **Anti-inflammatory modulation**: MSCs secrete interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and tumour necrosis factor-α-stimulated gene-6 (TSG-6), which collectively suppress synovial inflammation and reduce levels of pro-inflammatory monocytes/macrophages and IL-2 in synovial fluid (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0).
- **Anti-catabolic effects**: MSC-conditioned medium interferes with the NF-κB pathway, inhibiting IL-6, TNF-α, and various matrix metalloproteinases (MMPs), while upregulating IL-10 and promoting collagen II production (Platas et al., 2013; van Buul et al., 2012 — cited in Mancuso et al., *Frontiers in Bioengineering and Biotechnology*).
- **Trophic cartilage support**: MSCs promote endogenous chondrocyte proliferation, extracellular matrix (ECM) homeostasis, and subchondral bone maintenance. Preclinical models demonstrate that MSC intra-articular injection obstructs central sensitisation of pain and promotes expression of the anti-inflammatory and cartilage-protective factor TSG-6 (Markov et al., 2021, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-021-02265-1).
- **Hit-and-run mechanism**: Autopsy studies of patients who received MSC intravenous infusions confirm that donor MSCs are not normally retained in host tissue long-term. Detection of donor DNA did not correlate with HLA mismatch or clinical response, suggesting that therapeutic benefit derives from transient paracrine activity rather than stable engraftment (von Bahr et al., 2012 — cited in Mancuso et al.).

6.1.2 Clinical Trial Evidence

The evidence base for MSC therapy in knee OA has expanded substantially, with over 60 clinical studies published and numerous registered trials. The following key studies illustrate the range of cell sources, dosing strategies, and outcomes.

Bone Marrow-Derived MSCs (BM-MSCs)

1. **Chahal et al. (Phase I/IIa, NCT02351011)**: Twelve patients with late-stage Kellgren–Lawrence knee OA received a single intra-articular injection of 1×10^6, 10×10^6, or 50×10^6 BM-MSCs. Patients demonstrated improved KOOS pain, symptoms, and quality of life scores, as well as improved WOMAC stiffness relative to baseline. Cartilage catabolic biomarkers and MRI synovitis were meaningfully lower at higher doses. No serious adverse events occurred (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0).
2. **Vega et al. (RCT, NCT01586312)**: Thirty patients with knee OA were randomised to receive allogeneic BM-MSCs (40×10^6 cells) or HA via intra-articular injection. At 12 months, the MSC group demonstrated significantly better functional outcomes and cartilage quality improvements compared to HA controls (Vega et al., 2015, *Transplantation*. DOI: 10.1097/TP.0000000000000678 — cited in Filardo et al., 2016, *Journal of Orthopaedic Surgery and Research*. PMID: 27072345).
3. **Orozco et al. (Case series)**: Twelve patients with knee OA received intra-articular BM-MSC injection. Rapid and progressive clinical improvement was observed at 12 months, with 11 of 12 patients showing increased cartilage quality on MRI. Pain improvement at 12 months was maintained at 24-month follow-up, with further cartilage quality improvement on MRI (Orozco et al., 2013/2014, *Transplantation* — cited in Filardo et al., 2016, *Journal of Orthopaedic Surgery and Research*. PMID: 27072345).
4. **Hernigou et al.**: In a study of 140 patients with OA, subchondral infusion of BM-MSCs on one side was compared with TKA on the contralateral knee. Subchondral MSC injection had a significant effect on pain and delayed or avoided TKA in the contralateral joint. Subchondral delivery was found to be more effective than intra-articular injection of the same dose (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0).
5. **Espinosa et al. (Multicentre RCT, 4-year follow-up)**: Thirty OA patients received intra-articular infusion of autologous BM-MSCs at two dose levels (10×10^6 or 100×10^6) versus HA. No adverse effects occurred during the 4-year follow-up. Intra-articular infusion of BM-MSCs together with HA was demonstrated to be a safe and viable process leading to clinical and functional improvement in knee OA (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0).

Adipose Tissue-Derived MSCs (AT-MSCs)

6. **Jo et al.**: Higher doses of AT-MSCs (up to 1×10^8 cells) yielded significantly improved WOMAC scores with clinically meaningful pain reduction and, critically, regenerated hyaline articular cartilage at the most severely degenerated site in the knee (Jo et al., 2014 — cited in Mancuso et al., *Frontiers in Bioengineering and Biotechnology*).
7. **ADIPOA Trial (Pers et al.)**: A single dose of 2×10^6 AT-MSCs significantly improved pain levels and function in knee OA patients (Pers et al., 2016 — cited in Mancuso et al., *Frontiers in Bioengineering and Biotechnology*).
8. **Phase Ia study (18 patients)**: Three groups received single intra-articular administration of 2×10^6, 10×10^6, and 50×10^6 AT-MSCs. Significant improvement in pain levels and function was observed. MRI Osteoarthritis Knee Score indicated modification of disease progression (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0).

Umbilical Cord-Derived MSCs (UC-MSCs)

9. **Dilogo et al. (Phase I/II, NCT02580695)**: Forty patients received 20×10^6 UC-MSCs via intra-articular injection. Significantly improved pain levels and function were observed, with VAS pain scores significantly lower in the MSC group compared to controls (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0).
10. **NCT03800810**: Twenty-nine patients received 1×10^6 UC-MSCs. VAS showed decreased pain and WOMAC scores were reduced (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0).

Amniotic MSCs

11. **hAMSC trial (18 participants)**: Intra-articular administration of 5×10^7 human amniotic MSCs reduced pain and restored knee joint function and cartilage, supporting their candidacy for knee OA therapy (Markov et al., 2021, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-021-02265-1).

Comparative and Long-Term Observations

A systematic review by Filardo et al. (2016) identified 60 clinical studies on MSCs for cartilage pathology and noted that younger age, lower BMI, smaller lesion size, and earlier OA stages correlated with better outcomes. The review concluded that while evidence is promising, the lack of standardisation and heterogeneity across studies preclude definitive dose–response conclusions (Filardo et al., 2016, *Journal of Orthopaedic Surgery and Research*. PMID: 27072345). A further systematic review by Goldberg et al. (2017) catalogued over 30 registered clinical trials for MSC-based cartilage repair, noting that the majority used WOMAC, VAS pain, and MRI cartilage assessment as primary endpoints (Goldberg et al., 2017, *Journal of Orthopaedic Surgery and Research*. DOI: 10.1186/s13018-017-0534-y. PMID: 28279182).

Davatchi et al. reported that while significant improvement persisted at 5 years following BM-MSC injection in three patients with knee OA, there was gradual worsening after the initial 6-month follow-up, suggesting that repeated dosing may be necessary for sustained benefit in advanced disease (Davatchi et al., 2015 — cited in Filardo et al., 2016, *Journal of Orthopaedic Surgery and Research*. PMID: 27072345).

6.1.3 CARTISTEM — First Approved MSC Product for Cartilage

CARTISTEM represents the first regulatory-approved MSC product specifically indicated for cartilage repair. Approved by the Korean Ministry of Food and Drug Safety (MFDS) in January 2012, it consists of allogeneic umbilical cord blood-derived MSCs (UCB-MSCs) combined with sodium hyaluronate gel. The product is indicated for the treatment of knee cartilage defects in patients with osteoarthritis (Mello et al., 2024, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms25116063. PMID: 38892249; Jossen et al., 2018, *Applied Microbiology and Biotechnology*. DOI: 10.1007/s00253-018-8912-x. PMID: 29564526).

CARTISTEM is delivered via arthroscopic implantation into the cartilage defect site after microfracture preparation. A Phase III trial (NCT01733186) compared CARTISTEM with microfracture alone in patients with knee articular cartilage injury or defect, with a 48-week primary endpoint (Goldberg et al., 2017, *Journal of Orthopaedic Surgery and Research*. DOI: 10.1186/s13018-017-0534-y. PMID: 28279182). The product's allogeneic nature eliminates the need for autologous cell harvest, reducing procedural burden and enabling off-the-shelf availability — a significant advantage for settings with limited cell-processing infrastructure.

6.1.4 Dosing, Delivery, and Outcomes

Typical Dose Ranges: Clinical trials have explored a wide dose range:

- Low dose: 1–2 × 10^6 cells (ADIPOA trial)
- Medium dose: 10–50 × 10^6 cells (most Phase I/II trials)
- High dose: 100 × 10^6 cells (Jo et al.; Phase II multicentre trials)

Delivery Methods:

- **Intra-articular injection**: The most common route; performed under ultrasound or fluoroscopic guidance. Typical injection volume is 2–5 mL.
- **Subchondral injection**: Hernigou et al. demonstrated superior outcomes with subchondral delivery compared to intra-articular injection of the same dose.
- **Arthroscopic implantation**: Used for CARTISTEM and scaffold-based approaches; requires surgical infrastructure.

Outcome Measures:

- **WOMAC score**: The most widely used composite measure of pain, stiffness, and physical function. Significant improvements have been reported across multiple trials.
- **VAS pain**: Consistent reductions in pain scores, typically reaching clinical significance by 3–6 months.
- **MRI cartilage assessment**: Increased cartilage thickness, improved cartilage quality (T2 mapping), and reduction of subchondral oedema have been documented in multiple studies.
- **Joint space width**: Less commonly reported but relevant for long-term structural assessment.

6.1.5 Relevance to Fiji

The high prevalence of obesity-associated knee OA in Fiji, combined with limited access to joint replacement surgery, makes MSC-based intra-articular injection a potentially transformative intervention. The procedure requires only outpatient-level infrastructure (ultrasound guidance, sterile injection suite) and could substantially reduce the need for surgical referral abroad.

6.2 Bone Healing and Fracture Non-Union

6.2.1 MSCs for Critical-Size Bone Defects and Non-Unions

Fracture non-union — defined as failure of bone healing after 6–9 months — affects approximately 5–10% of fractures and represents a significant clinical challenge, particularly in settings where revision surgery and prolonged immobilisation impose substantial socioeconomic costs. MSCs offer a biologically rational approach to non-union repair through their capacity for osteogenic differentiation, paracrine stimulation of angiogenesis, and immunomodulation of the fracture microenvironment.

Pioneering Clinical Work

Quarto et al. (2001) first reported the application of culture-expanded BM-MSCs combined with hydroxyapatite biomaterial for the treatment of large bone defects resulting from traumatic fractures in three patients. Abundant callus formation along the implants and good integration at the interfaces with host bone were observed at 2 months post-surgery. All three patients recovered full limb function with no adverse reactions (Marolt Presen et al., 2019, *Frontiers in Bioengineering and Biotechnology*. DOI: 10.3389/fbioe.2019.00352. PMID: 31828066).

Tibial Non-Union Trials

Hernigou et al. (2005) demonstrated that percutaneous injection of concentrated bone marrow aspirate into tibial non-unions resulted in mineralised callus at 4 months, with a negative correlation between time to union and the concentration of colony-forming units (CFUs) in the graft. Le Nail et al. (2014) analysed 43 patients with open tibial fractures at risk of non-union and determined a threshold number of transplanted progenitors above which healing was 100% successful (Marolt Presen et al., 2019, *Frontiers in Bioengineering and Biotechnology*. DOI: 10.3389/fbioe.2019.00352. PMID: 31828066).

Multicentre European Trial (NCT01813188)

Gómez-Barrena et al. (2019) reported that surgical delivery of culture-expanded BM-MSCs combined with biphasic calcium phosphate bioceramic granules for the treatment of delayed unions and non-unions in tibia, femur, and humerus was safe and feasible, with 26 of 28 patients exhibiting radiologic healing at 1 year after treatment. No severe adverse events were recorded (Gómez-Barrena et al., 2019, *Biomaterials.* DOI: 10.1016/j.biomaterials.2018.03.033 — cited in Marolt Presen et al., 2019. PMID: 31828066).

Percutaneous BM-MSC Injection (NCT02020590)

Twenty-two patients with bone fractures received percutaneous injection of 50–100 × 10^6 BM-MSCs. Ultrasound scores and global disease evaluation improved, and pain at palpation at the fracture site was reduced. No serious adverse events were observed (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0).

Tibial Fracture Acceleration (NCT00250302)

Liebergall et al. (2013) reported that prophylactic injection of magnetically-separated BM-MSCs mixed with platelet-rich plasma and demineralised bone matrix resulted in shorter time to union (1.5 months) compared to the control group (3 months) in a 24-patient study (Marolt Presen et al., 2019, *Frontiers in Bioengineering and Biotechnology*. DOI: 10.3389/fbioe.2019.00352. PMID: 31828066).

6.2.2 Avascular Necrosis of the Femoral Head

Osteonecrosis of the femoral head (ONFH) is characterised by impaired vascularisation with ischaemia resulting in bone cell death, leading to hip joint deterioration. Without intervention, the majority of patients progress to femoral head collapse requiring total hip replacement.

Phase I/II Clinical Trial (NCT01700920)

Blanco et al. (2023) conducted a prospective, open-label, non-randomised Phase I/II trial in eight patients with idiopathic ONFH (ARCO classification < IIC). Autologous BM-MSCs were expanded under GMP conditions, and a single dose of 0.5–1.0 × 10^6 cells/kg body weight (approximately 80 × 10^6 MSCs total) was administered intraosseously via trocar under radioscopic control following core decompression. Key findings at 8-year follow-up included:

- No adverse effects related to cell administration
- VAS and Oswestry Disability Index (ODI) scores improved after surgery
- Radiographic stabilisation was achieved in 62.5% of patients during the first year
- MRI staging stabilisation was observed in 87.5% of patients (7 of 8)
- 50% of patients showed clinical improvement; 25% were stabilised
- None of the patients required total hip replacement within the first year

(Blanco et al., 2023, *Journal of Clinical Medicine*. DOI: 10.3390/jcm12062117. PMID: 36983120)

Meta-Analytic Evidence

Yuan et al. conducted a meta-analysis of seven case–control studies of autologous BM-MNC implantation for ONFH. The cell-therapy group demonstrated delayed disease progression (OR = 0.17; $p < 0.001$), reduced total hip arthroplasty incidence (OR = 0.3; $p < 0.01$), and increased Harris Hip Score (mean difference = 4.76; $p < 0.01$).

6.2.3 Dosing and Delivery for Bone Applications

- **Percutaneous injection**: 50–100 × 10^6 BM-MSCs, typically in 5–10 mL suspension
- **Surgical delivery with scaffold**: Culture-expanded MSCs seeded on bioceramic granules (hydroxyapatite, tricalcium phosphate, or biphasic calcium phosphate)
- **Core decompression + MSC infusion**: For ONFH, MSCs are delivered intraosseously through the decompression channel

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6.3 Tendon and Ligament Repair

6.3.1 Rotator Cuff Augmentation

Rotator cuff tendons heal to bone with interposed scar tissue, making repairs prone to failure. Gulotta et al. (2009) investigated the application of BM-MSCs in a rat rotator cuff repair model. Ninety-eight Lewis rats underwent unilateral detachment and repair of the supraspinatus tendon, receiving either 10^6 MSCs in a fibrin carrier, the carrier alone, or nothing at the repair site. While MSCs were confirmed to be present and metabolically active at the repair site at both 2 and 4 weeks, there were no differences in new cartilage formation, collagen fibre organisation, biomechanical strength, cross-sectional area, peak stress to failure, or stiffness between groups. The authors concluded that the repair site may lack the cellular and/or molecular signals necessary to induce appropriate differentiation of transplanted cells, and that cell-based strategies may need to be combined with growth and differentiation factors to be effective (Gulotta et al., 2009, *American Journal of Sports Medicine*. PMID: 19684297).

6.3.2 Anterior Cruciate Ligament (ACL) Augmentation

Kouroupis et al. (2016) described the generation of stem cell-based bioartificial ACL grafts using infrapatellar fat pad-derived MSCs, demonstrating feasibility for ACL rupture repair in preclinical models (Kouroupis et al., 2016 — cited in Kouroupis et al., 2021, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-020-02107-6. PMID: 33413649). Priming MSCs with hyaluronan has been shown to alter growth kinetics and increase attachment to articular cartilage, suggesting potential for enhancing tendon-to-bone healing (Succar et al., 2016 — cited in Guerrouahen et al., 2019, *Stem Cells International*. DOI: 10.1155/2019/7219297. PMID: 31467564).

6.3.3 Medial Collateral Ligament and Achilles Tendon

Saether et al. demonstrated that primed MSCs improved rat medial collateral ligament healing (Saether et al. — cited in Guerrouahen et al., 2019, *Stem Cells International*. DOI: 10.1155/2019/7219297. PMID: 31467564). Costa-Almeida et al. (2019) reviewed the role of MSCs in empowering tendon regenerative therapies, noting that MSC-derived paracrine factors — rather than direct cellular engraftment — are the primary mediators of tendon repair (Costa-Almeida et al., 2019, *International Journal of Molecular Sciences* — cited in secondary source).

6.3.4 Summary Assessment

The evidence for MSC-based tendon and ligament repair remains predominantly preclinical. While the biological rationale is sound — MSCs secrete growth factors that promote tenocyte proliferation and matrix remodelling — clinical translation has been limited by the complexity of tendon-to-bone healing and the lack of appropriate differentiation signals at the repair site. This indication is not yet ready for clinical implementation and should be monitored as the evidence base matures.

6.4 Chronic Wound Healing

6.4.1 Biological Rationale

Chronic wounds — defined as those persisting for at least three months — are generally classified as vascular, diabetic, or pressure ulcers. They typically result from prolonged or exacerbated inflammatory processes that prevent dermal or epidermal cells from responding to regenerative stimuli. MSCs promote wound healing through multiple mechanisms: migration into the skin damage site, suppression of inflammation, stimulation of angiogenesis, promotion of re-epithelialisation, enhancement of granulation tissue formation, and increasing the growth and differentiation ability of fibroblasts, epidermal cells, and endothelial cells (Hu et al., 2018, *Stem Cells International*. DOI: 10.1155/2018/6901983. PMID: 29887893; Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0).

MSCs encourage a regenerative rather than fibrotic wound healing microenvironment. Treatment increases wound tensile strength, reduces scarring, reduces wound contraction, and increases collagen expression. The relative increase in anti-inflammatory M2 to pro-inflammatory M1 macrophage ratio may help reduce scarring, as increased M1 macrophage activity is thought to be a major regulator of impaired wound healing and tissue fibrosis (Hu et al., 2018, *Stem Cells International*. DOI:

10.1155/2018/6901983. PMID: 29887893).

6.4.2 Diabetic Foot Ulcers

Diabetic foot ulcers represent the most clinically relevant wound-healing application for Fiji, given the nation's high diabetes prevalence.

Falanga et al.: Autologous BM-MSCs delivered via fibrin spray to lower-extremity wounds accelerated healing of acute surgical wounds (n = 5) and significantly decreased wound size of chronic venous and diabetic ulcer wounds (n = 6) at 20 weeks. Histologically, MSCs migrated into the upper layers of the wound bed and differentiated into cells with a fibroblast phenotype. The surface density of MSCs correlated with reduction in ulcer size (Hu et al., 2018, *Stem Cells International*. DOI: 10.1155/2018/6901983. PMID: 29887893).

Collagen sponge delivery (n = 20 patients): Autologous BM-MSCs impregnated onto a collagen sponge were applied to 20 chronic, non-healing wounds in 13 patients. Ninety percent of wounds healed completely, including chronic burns, lower-extremity ulcers, and decubitus ulcers (Hu et al., 2018, *Stem Cells International*. DOI: 10.1155/2018/6901983. PMID: 29887893).

Randomised study (2009): Cultured autologous BM-MSCs simultaneously administered topically onto 24 chronic, non-healing ulcers of the lower extremities and via intramuscular injection into the affected limb significantly decreased wound size (72% versus 25%) and decreased ulcer-associated wound pain at 12 weeks compared to standard wound care (Hu et al., 2018, *Stem Cells International*. DOI: 10.1155/2018/6901983. PMID: 29887893).

Zhou et al. (346 patients): Adipose MSCs were administered to 346 patients with skin wounds. No adverse events occurred during the trial. The granulation tissue coverage rate and wound healing were improved in the MSC-treated group (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0).

6.4.3 Venous Leg Ulcers and Pressure Ulcers

Clinical evidence for MSC therapy in venous leg ulcers and pressure ulcers is more limited but consistent with the diabetic ulcer data. BM-MSCs have been administered to chronic cutaneous ulcerations and pressure ulcers, resulting in accelerated wound closure and improved healing properties (Ahangar et al., 2020, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms21197038. PMID: 32987830).

6.4.4 Delivery Methods for Wound Applications

Multiple delivery strategies have been investigated:

- **Topical spray (fibrin polymer)**: MSCs suspended in fibrin are sprayed directly onto the wound surface. Allows even distribution across irregular wound beds.
- **Direct injection**: Intradermal or subcutaneous injection at wound margins. Typical dose: 1–5 × 10^6 cells per injection site, multiple sites per wound.
- **Scaffold/matrix delivery**: MSCs impregnated onto collagen sponges, fibrin glue matrices, or hydrogel scaffolds. Provides a microenvironment more suitable for cell adhesion, proliferation, and differentiation. Collagen-based scaffolds enhance wound epithelialisation and granulation and downregulate inflammation (Hu et al., 2018, *Stem Cells International*. DOI: 10.1155/2018/6901983. PMID: 29887893).
- **Exosome-based dressings**: MSC-derived exosomes applied topically have shown promise in reducing scar formation and promoting wound closure without the regulatory complexity of live-cell products (Ha et al., 2020, *Cells*. DOI: 10.3390/cells9051157. PMID: 32392899).
- **Conditioned medium**: MSC-conditioned medium (MSC-CM) applied topically can recapitulate many therapeutic effects of cell therapy. One systematic review reported that topical MSC-CM improved wound closure and vascularisation across multiple in vivo models compared to control treatments, for wounds with origins ranging from diabetes, psoriasis, burns, and radiation (Montero-Vilchez et al., 2021, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2021.654210. PMID: 34368115).

6.4.5 Relevance to Fiji

Diabetic foot ulcers are a leading cause of lower-limb amputation in Fiji. Current wound care relies on debridement, offloading, and conventional dressings. MSC-based wound therapies — particularly cell-free approaches using conditioned medium or exosomes — could be implemented with relatively modest infrastructure requirements and may substantially reduce amputation rates.

6.5 Burn Injury Treatment

6.5.1 Acute Burn Treatment

Burn injuries represent a significant clinical challenge in Pacific Island communities, where cooking-related burns and occupational injuries are common. MSC-based therapies for burns have been investigated primarily in preclinical models, with emerging clinical evidence.

Preclinical Evidence

In a second-degree burn injury mouse model, MSC-conditioned medium derived from human fetal placental MSCs (2 × 10^6 cells) promoted wound healing compared to PBS and DMEM controls when injected subcutaneously near the wound at four sites (Li J. Y. et al., 2019 — cited in Montero-Vilchez et al., 2021, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2021.654210. PMID: 34368115).

BM-MSC conditioned medium promoted wound healing in deep second-degree burns in male rats, with increased numbers of fibroblasts, accelerated wound closure, promoted angiogenesis, and enhanced collagen deposition (Aryan et al., 2019 — cited in Ahangar et al., 2020, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms21197038. PMID: 32987830).

In burn wound models, MSC-CM showed faster wound healing, increased re-epithelialisation, and vascularisation compared to controls (unconditioned medium, PBS, or DMEM). Twenty-eight mice with burn wounds treated with MSC-CM demonstrated significantly increased wound closure area compared to controls. The volume of epidermis and dermis in the burn wound was preserved in the MSC-CM group compared to control, DMEM, and silver sulfadiazine groups (Montero-Vilchez et al., 2021, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2021.654210. PMID: 34368115).

6.5.2 Scar Reduction

MSC-CM has demonstrated significant anti-scarring effects:

- MSC-CM had a greater effect in scar reduction than control groups, decreasing hypertrophic scar weight by 34% compared to untreated groups and by 23% compared to DMEM groups. MSC-CM reduced the proportion of both cellularity/inflammatory cells and blood vessel density (Montero-Vilchez et al., 2021, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2021.654210. PMID: 34368115).
- MSC-derived exosomes attenuated the thickness of the dermal layer and the length of scars. Collagen in the dermis was well distributed with less crosslinking, and the ratio of collagen III to collagen I was increased (Choi et al., 2017 — cited in Montero-Vilchez et al., 2021. PMID: 34368115).
- Hypoxic MSC-CM reduced scar formation and decreased wound size compared to normoxic MSC-CM, with decreased levels of TGF-β1 and collagen I (Du et al., 2016 — cited in Montero-Vilchez et al., 2021. PMID: 34368115).

6.5.3 Clinical Translation

Clinical evidence for MSC therapy in burns remains limited. MSC-CM has been tested in combination with fractional laser therapy for acne scars in four studies evaluating 71 patients, with combined therapy showing greater scar volume reduction (23.5% on the MSC-CM side versus 15.0% on the control side) (Park C. S. et al., 2019 — cited in Montero-Vilchez et al., 2021. PMID: 34368115). No clinical study has specifically evaluated MSC-CM for acute burn treatment, though the preclinical evidence is robust and consistent.

6.6 Pain Management

6.6.1 Chronic Lower Back Pain

Chronic lower back pain (CLBP) due to degenerative disc disease represents one of the most prevalent musculoskeletal conditions globally and is a significant contributor to disability in working-age populations. Intradiscal injection of MSCs has been investigated as a disease-modifying approach that addresses the underlying disc degeneration rather than merely masking symptoms.

A Phase III clinical programme has evaluated allogeneic BM-MSCs (rexlemestrocel-L) for CLBP, which has received Regenerative Medicine Advanced Therapy (RMAT) designation from the US FDA, indicating that the agency recognises preliminary evidence of the product's potential to address an unmet medical need.

Wharton's jelly-derived MSCs (WJ-MSCs) have been investigated for bone fracture healing with relevance to pain outcomes. In a Phase I/IIa trial, 20 patients received intramedullary delivery of 4×10^7 to 2×10^8 WJ-MSCs. VAS, ODI, and SF-36 scores significantly improved, with promoted bone architecture (Margiana et al., 2022, *Stem Cell Research & Therapy.* DOI: 10.1186/s13287-022-03054-0).

6.6.2 Neuropathic Pain — MSC Anti-Inflammatory Mechanism

MSCs modulate pain through multiple pathways:

- **Central sensitisation blockade**: Intra-articular MSC injection has been shown to obstruct central sensitisation of pain in OA models, promoting expression of the anti-inflammatory and cartilage-protective factor TSG-6 (Markov et al., 2021, *Stem Cell Research & Therapy.* DOI: 10.1186/s13287-021-02265-1).
- **Macrophage polarisation**: MSCs shift the macrophage phenotype from pro-inflammatory M1 to anti-inflammatory M2, reducing the inflammatory mediators that drive nociceptor sensitisation.
- **Neurotrophic factor secretion**: MSCs secrete brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell-derived neurotrophic factor (GDNF), which may promote nerve repair and modulate pain signalling.

6.6.3 MSCs as an Alternative to Chronic Opioid Use

The public health implications of MSC-based pain management extend beyond individual patient outcomes. In Pacific Island nations, access to chronic pain management is limited, and the risks of opioid dependence — even with controlled prescribing — are well documented. MSC therapies that address the underlying pathology (cartilage degeneration, disc disease, chronic inflammation) rather than masking pain signals could reduce long-term analgesic requirements.

Clinical evidence from OA trials consistently demonstrates that MSC injection reduces VAS pain scores and WOMAC pain subscores, with effects persisting for 12–24 months in many studies. The Hernigou et al. study of 140 OA patients demonstrated that MSC treatment had a significant effect on pain sufficient to postpone or avoid TKA (Margiana et al., 2022, *Stem Cell Research & Therapy.* DOI: 10.1186/s13287-022-03054-0).

6.6.4 Comparison with Conventional Pain Management

Parameter	Conventional Management	MSC-Based Approach
Mechanism	Symptom masking (analgesics, NSAIDs)	Disease modification (anti-inflammatory, trophic)
Duration of effect	Hours to weeks	Months to years (single injection)
Repeated dosing	Daily medication	Single or infrequent injections
Side effects	GI bleeding, renal toxicity, opioid dependence	Transient local swelling; no systemic toxicity reported
Disease progression	Not modified	Potential cartilage preservation/regeneration
Infrastructure	Pharmacy supply chain	Cell processing or off-the-shelf product

6.7 Dosing and Administration Protocols — Summary Table

Indication	Route	Cell Source	Dose Range	Frequency	Key Outcomes
Knee OA	Intra-articular injection	BM-MSC	1–100 × 10^6 cells	Single or repeated at 6-month intervals	WOMAC improvement, VAS pain reduction, MRI cartilage quality improvement
Knee OA	Intra-articular injection	AT-MSC	2–100 × 10^6 cells	Single injection	WOMAC improvement, hyaline cartilage regeneration at high doses
Knee OA	Intra-articular injection	UC-MSC	1–20 × 10^6 cells	Single or double dose at 6-month interval	VAS pain reduction, WOMAC improvement
Knee cartilage defect	Arthroscopic implantation	UCB-MSC (CARTISTEM)	Product-specific (allogeneic)	Single surgical procedure	Cartilage repair, IKDC score improvement
Fracture non-union	Percutaneous injection	BM-MSC	50–100 × 10^6 cells	Single injection	Radiologic healing, pain reduction
Fracture non-union	Surgical delivery + scaffold	BM-MSC	Culture-expanded (variable)	Single surgical procedure	93% radiologic healing at 1 year
Tibial fracture	Percutaneous injection + PRP	BM-MSC	Variable (with PRP/DBM)	Single injection	Shortened time to union (1.5 vs 3 months)
Femoral head AVN	Intraosseous (core decompression)	BM-MSC	0.5–1.0 × 10^6/kg (≈ 80 × 10^6 total)	Single procedure	VAS/ODI improvement, MRI stabilisation, THR avoidance
Diabetic foot ulcer	Topical spray (fibrin)	BM-MSC	Variable (fibrin suspension)	Single or repeated application	Wound size reduction, complete healing
Chronic wound	Scaffold (collagen sponge)	BM-MSC	Variable (impregnated)	Single application	90% complete healing rate
Chronic wound	Topical + intramuscular	BM-MSC	Variable	Single combined application	72% wound size reduction at 12 weeks

Indication	Route	Cell Source	Dose Range	Frequency	Key Outcomes
Burn injury	Subcutaneous injection	MSC-CM (cell-free)	200 µL per injection site	Repeated every 2–3 days	Accelerated wound closure, reduced scarring
Scar reduction	Subcutaneous/topical	MSC-CM or exosomes	200 µL per injection site	Weekly for 4 weeks	34% scar weight reduction
Chronic low back pain	Intradiscal injection	BM-MSC (allogeneic)	Under investigation (Phase III)	Single injection	VAS, ODI improvement (Phase III ongoing)

6.8 Commercial Products for These Indications

6.8.1 Approved Products

CARTISTEM (UCB-MSC, allogeneic)

- **Indication**: Knee cartilage defects in OA
- **Regulator**: MFDS (South Korea), 2012
- **Cell source**: Allogeneic umbilical cord blood-derived MSCs combined with sodium hyaluronate
- **Delivery**: Arthroscopic implantation
- **Significance**: First approved MSC product for cartilage repair; off-the-shelf allogeneic product eliminates autologous harvest requirement

(Mello et al., 2024, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms25116063. PMID: 38892249)

Stemirac (BM-MSC, autologous)

- **Indication**: Spinal cord injury
- **Regulator**: PMDA (Japan), 2018 (conditional and time-limited approval)
- **Cell source**: Autologous BM-MSCs expanded in autologous serum
- **Delivery**: Intravenous infusion
- **Relevance to pain**: While approved for spinal cord injury, the underlying MSC platform and intravenous delivery approach have implications for pain management through neuroprotection and neurotrophic factor secretion

(Mello et al., 2024, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms25116063. PMID: 38892249; Zhao et al., 2026, *Stem Cell Reviews and Reports*. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448)

Stempeucel (BM-MSC, allogeneic, pooled donor)

- **Indication**: Critical limb ischaemia (India, 2016)
- **Additional data**: Phase III success in knee OA using pooled donor strategy, with statistically significant WOMAC improvements at 12 months
- **Relevance**: Demonstrates feasibility of pooled allogeneic MSC approach for musculoskeletal indications

Alofisel (darvadstrocel) (AT-MSC, allogeneic)

- **Indication**: Complex perianal fistulas in Crohn's disease
- **Regulator**: EMA (EU), 2018 — subsequently withdrawn from EU market in December 2024 following ADMIRE-CD II trial failure
- **Relevance to wound healing**: The product's mechanism — local immunomodulation and tissue repair at the fistula site — is mechanistically analogous to wound healing applications. The withdrawal underscores the importance of robust Phase III confirmation

(Mello et al., 2024, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms25116063. PMID: 38892249)

6.8.2 Products in Development for Orthopedic and Wound Indications

Several MSC-based products are in advanced clinical development for indications covered in this chapter:

- **Rexlemestrocel-L** (allogeneic BM-MSC): Under investigation for chronic low back pain due to degenerative disc disease. Has received RMAT designation. Phase III programme ongoing.
- **JOINTSTEM** (autologous AT-MSC, 100 × 10^6 cells): Phase II trial (NCT02658344) for degenerative arthritis, with WOMAC as primary endpoint (Goldberg et al., 2017, *Journal of Orthopaedic Surgery and Research*. DOI: 10.1186/s13018-017-0534-y. PMID: 28279182).
- **MSC-conditioned medium products**: Cell-free approaches using MSC secretome for wound healing are in early-stage development. These products offer significant advantages for resource-limited settings: they can be manufactured, quality-controlled, and stored more readily than live-cell products, and they avoid the regulatory complexity of cell-based ATMPs.
- **MSC-derived exosome products**: Exosome-based wound dressings are in preclinical and early clinical development. MSC-derived exosomes have demonstrated wound healing, anti-scarring, and anti-inflammatory effects comparable to whole-cell therapy in multiple preclinical models (Ha et al., 2020, *Cells*. DOI: 10.3390/cells9051157. PMID: 32392899).

6.8.3 Implications for Fiji

For a Pacific Island nation evaluating MSC therapy implementation, the orthopedic and wound healing indications present the most compelling near-term opportunities. The key considerations are:

1. **Knee OA (intra-articular injection)**: The strongest evidence base, with multiple cell sources validated. Requires only outpatient injection infrastructure. Allogeneic products (e.g., CARTISTEM model) would eliminate the need for autologous cell processing.
2. **Diabetic wound healing**: High unmet need in Fiji. Cell-free approaches (conditioned medium, exosomes) may be implementable with lower infrastructure requirements than live-cell therapies.
3. **Fracture non-union**: Relevant to occupational injuries. Percutaneous MSC injection combined with standard orthopaedic fixation could reduce non-union rates and shorten rehabilitation.
4. **Burn injury**: Preclinical evidence is strong but clinical translation is early. MSC-CM-based dressings represent a practical near-term option.

The evidence reviewed in this chapter supports the conclusion that MSC-based therapies for musculoskeletal and wound healing indications have progressed beyond proof-of-concept to a stage where clinical implementation pathways can be rationally designed. The choice between autologous, allogeneic, and cell-free approaches should be guided by the specific indication, available infrastructure, and regulatory pathway selected by the Ministry.

Chapter 7: MSC for Health Longevity and Regenerative Wellness

7.1 Biological Rationale for MSC in Aging

7.1.1 Hallmarks of Aging Relevant to MSC Biology

The biology of aging is characterised by a set of interconnected molecular and cellular hallmarks that collectively drive the progressive decline in physiological function. López-Otín and colleagues identified nine canonical hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, altered intercellular communication, and stem cell exhaustion (López-Otín et al., 2013, Cell. DOI: 10.1016/j.cell.2013.05.039). Three of these hallmarks are directly relevant to the rationale for exogenous MSC administration as a potential intervention in aging.

Stem cell exhaustion. The progressive depletion and functional decline of endogenous stem cell pools is a defining feature of organismal aging. MSCs, as tissue-resident progenitor cells, are not exempt from this process. Colony-forming unit-fibroblast (CFU-f) analysis demonstrates that MSC numbers obtained from bone marrow aspiration decline significantly from childhood to adulthood, accompanied by age-related increases in oxidative damage, reactive oxygen species (ROS) levels, and expression of senescence markers p21 and p53 (Stolzing et al., 2008, Mechanisms of Ageing and Development. PMID: 18241911). Adipose-derived MSCs from elderly donors similarly exhibit increased senescence-associated β-galactosidase (SA-β-gal) positivity, elevated mitochondrial ROS production, and upregulated p21 expression (Liu et al., 2017, Cell Transplantation. DOI: 10.1177/0963689717721221).

Inflammaging. The term "inflammaging," coined by Franceschi and colleagues, describes the chronic, low-grade, sterile inflammation that accompanies aging and underpins many age-related diseases (Franceschi et al., 2000, Annals of the New York Academy of Sciences. DOI: 10.1111/j.1749-6632.2000.tb06651.x). The senescence-associated secretory phenotype (SASP) — comprising pro-inflammatory cytokines (IL-6, TNF-α, IL-1β), chemokines, and matrix metalloproteinases — is a major driver of inflammaging (Ha et al., 2020, Cells. DOI: 10.3390/cells9051157). Inflammaging has been mechanistically linked to type 2 diabetes, cardiovascular disease, neurodegeneration, and osteoarthritis — conditions of particular relevance to Fiji's non-communicable disease burden.

Immunosenescence. Age-related remodelling of the immune system results in diminished adaptive immunity, reduced vaccine responsiveness, and impaired tumour surveillance, while innate immune activation becomes dysregulated. This immunosenescence is both a consequence and a driver of inflammaging.

7.1.2 How Aging Affects Endogenous MSC Function

Aging exerts profound effects on endogenous MSC populations across multiple functional dimensions:

- **Reduced numbers and proliferative capacity.** Bone marrow MSC frequency declines with donor age, and remaining cells exhibit slower proliferation kinetics (Stolzing et al., 2008, PMID: 18241911; Choudhery et al., 2014, Journal of Translational Medicine. DOI: 10.1186/1479-5876-12-8).
- **Impaired differentiation potential.** Aged MSCs show diminished osteogenic capacity with a concomitant shift toward adipogenesis, contributing to age-related bone loss and marrow adiposity (Yang et al., 2018, Stem Cell Research & Therapy. DOI: 10.1186/s13287-018-0876-3; Liu et al., 2017, PMID: 29113467).
- **Epigenetic dysregulation.** Long-term culture and donor aging are associated with altered histone acetylation patterns and DNA methylation changes that drive spontaneous differentiation and loss of stemness (Li et al., 2011, PLoS ONE. DOI: 10.1371/journal.pone.0020526).
- **Reduced migration and homing.** Expression of chemokine receptors CXCR4 and CXCR7 declines with age, impairing the ability of MSCs to migrate toward sites of injury (Liu et al., 2017, PMID: 29113467).
- **Altered secretome.** Senescent MSCs exhibit a SASP-like secretory profile, with increased production of pro-inflammatory cytokines and decreased immunomodulatory capacity (Turinetto et al., 2016, International Journal of Molecular Sciences. DOI: 10.3390/ijms17071164).

7.1.3 Theoretical Mechanisms for Exogenous MSC Benefit

The rationale for administering exogenous MSCs to counteract aging rests on several theoretical mechanisms:

1. **Paracrine anti-inflammatory signalling.** Young, allogeneic MSCs secrete anti-inflammatory cytokines (IL-10, TGF-β, TSG-6) and immunomodulatory factors that may counteract SASP-driven inflammaging.
2. **Senescent cell modulation.** MSC-derived exosomes have been shown in preclinical models to reduce senescence markers in target cells, induce proliferation, and reduce SASP components through transfer of specific miRNAs (Ha et al., 2020, DOI: 10.3390/cells9051157). Highly purified human extracellular vesicles from stem cells have been reported to alleviate aging cellular phenotypes of senescent human cells (Liu et al., 2019, Stem Cells. DOI: 10.1002/stem.2996).
3. **Immune reconstitution.** MSCs may partially restore aged immune cell function through modulation of T-cell subsets, promotion of regulatory T-cells, and suppression of Th17-mediated inflammation.
4. **Trophic support.** MSC-secreted growth factors (VEGF, HGF, IGF-1, BDNF) may support tissue maintenance and repair in aging organs.

It is essential to note that these mechanisms remain largely demonstrated in preclinical models. The translation of these effects to clinically meaningful anti-aging outcomes in humans requires substantially more evidence than is currently available.

7.2 Published Clinical Evidence — Aging and Frailty

7.2.1 The CRATUS Trial Programme

The most significant body of clinical evidence for MSC therapy specifically targeting aging and frailty derives from the CRATUS (allogeneiC human mesenchymal stem cells in patients with aging fRailTy via intravenoUS delivery) trial programme conducted at the University of Miami.

Phase I (Golpanian et al., 2017). The initial phase I dose-escalation study enrolled 15 patients with aging frailty (mean age ≥60 years, meeting Fried frailty criteria) who received a single intravenous infusion of allogeneic bone marrow-derived MSCs at doses of 20, 100, or 200 million cells. The primary endpoint was safety at one month. No treatment-related serious adverse events were reported. Exploratory efficacy signals included improvements in 6-minute walk distance and quality of life measures.

Phase II (Tompkins et al., 2017). The subsequent randomised, double-blind, placebo-controlled phase II CRATUS trial enrolled 30 patients with aging frailty who were randomised to receive 100 million cells, 200 million cells, or placebo. Key findings included:

- **6-minute walk test (6MWT):** Significant improvement in the 100-million-cell group at 6 months compared to baseline, with a mean increase reported in walking distance.
- **TNF-α levels:** Significant reduction in serum TNF-α in the 100-million-cell group, suggesting an anti-inflammatory effect.
- **Quality of life:** Improvements in quality of life scores were observed in the treatment groups.
- **Immune biomarkers:** Improvements in B-cell intracellular TNF-α were noted.
- **Pulmonary function:** FEV1 showed improvement in the treatment groups.

(Tompkins et al., 2017, Journals of Gerontology: Series A.)

7.2.2 Subsequent Studies and Follow-up

Following the CRATUS programme, additional studies have explored MSC therapy in the context of aging:

- **Golpanian et al. (2016)** reported on the rationale and design of the CRATUS trial, establishing the frailty phenotype as a measurable clinical endpoint for MSC therapy.
- **Hare et al. (2017)** demonstrated in the POSEIDON-DCM trial that allogeneic MSCs reduced TNF-α to a greater extent than autologous MSCs in non-ischaemic dilated cardiomyopathy patients (mean age >50 years), with improvements in Minnesota Living with Heart Failure Questionnaire scores (Hare et al., 2017, Journal of the American College of Cardiology. DOI: 10.1016/j.jacc.2016.11.009). While not a frailty trial per se, these findings in an elderly population with cardiac disease are relevant to the aging-frailty nexus.

7.2.3 Limitations of the Evidence Base

The clinical evidence for MSC therapy in aging and frailty must be interpreted with considerable caution:

Limitation	Detail
Sample size	The CRATUS Phase II enrolled only 30 patients — far too few for definitive efficacy conclusions
Follow-up duration	Maximum 6–12 months; long-term effects of MSC infusion on aging trajectories are unknown
Single-centre design	All CRATUS data originate from a single academic centre
Surrogate endpoints	6MWT and TNF-α are surrogate markers; no hard clinical endpoints (mortality, hospitalisation, disability progression) have been assessed
Replication	No independent replication of the CRATUS findings has been published to date
Frailty definition	Fried frailty criteria, while validated, capture only one dimension of the aging phenotype

In summary, the CRATUS programme provides proof-of-concept that allogeneic MSC infusion is safe in frail elderly patients and may produce measurable improvements in physical performance and inflammatory biomarkers. However, the evidence is insufficient to support clinical use of MSCs for aging or frailty outside of well-designed clinical trials.

7.3 Immunosenescence and Immune Rejuvenation

7.3.1 Age-Related Immune Decline

Immunosenescence encompasses a constellation of changes in both innate and adaptive immunity that accumulate with age: thymic involution and reduced naïve T-cell output, expansion of memory and senescent T-cell populations, impaired B-cell diversity and antibody responses, and dysregulated innate immune activation. These changes contribute to increased susceptibility to infections, diminished vaccine efficacy, and heightened risk of autoimmunity and malignancy.

7.3.2 MSC Effects on Aged Immune Cells

MSCs exert broad immunomodulatory effects that are theoretically relevant to immunosenescence reversal:

- **T-cell modulation.** MSCs suppress proliferation of both CD4+ and CD8+ T-cells, inhibit Th1 and Th17 polarisation, and promote regulatory T-cell (Treg) generation (Turinetto et al., 2016, DOI: 10.3390/ijms17071164). In aged individuals with expanded pro-inflammatory T-cell subsets, this rebalancing could be beneficial.
- **B-cell effects.** MSCs inhibit B-cell proliferation and terminal differentiation, potentially modulating age-related autoantibody production.
- **NK cell regulation.** MSCs can suppress NK cell activation and cytotoxicity, which may be relevant in the context of age-related NK cell dysfunction.
- **Macrophage polarisation.** MSCs promote M2 (anti-inflammatory) macrophage polarisation, counteracting the M1-skewed phenotype characteristic of inflammaging.

7.3.3 Preclinical Evidence for Immune Rejuvenation

Preclinical studies have demonstrated that extracellular vesicles derived from young donor serum can attenuate inflammaging by partially rejuvenating aged T-cell immunotolerance in mice (Wang et al., 2018, FASEB Journal. DOI: 10.1096/fj.201800059R). Implantation of hypothalamic stem/progenitor cells engineered to survive aging-related inflammation was reported to retard aging and extend lifespan in mid-aged mice, partly through exosomal miRNA signalling (Zhang et al., 2017, Nature. DOI: 10.1038/nature23282). Extracellular vesicle-contained eNAMPT from young organisms has been shown to delay aging and extend lifespan in mice (Yoshida et al., 2019, Cell Metabolism. DOI: 10.1016/j.cmet.2019.05.015).

7.3.4 Clinical Evidence

Direct clinical evidence for MSC-mediated immune rejuvenation in aging is extremely limited. The CRATUS trial reported reductions in TNF-α and improvements in B-cell intracellular TNF-α as secondary endpoints, but comprehensive immunophenotyping of aged immune cell subsets before and after MSC therapy has not been published in a controlled trial setting. This remains a significant gap in the evidence base.

7.4 Organ-Specific Rejuvenation Evidence

The following summarises the current evidence for MSC-mediated rejuvenation effects across organ systems. It is critical to note that the vast majority of this evidence is preclinical, and extrapolation to human anti-aging applications is premature.

7.4.1 Skin Aging

Evidence level: Preclinical and early clinical (cosmetic studies).

MSC-conditioned medium (MSC-CM) has been evaluated in UV-induced photoaged mouse models, where it reduced wrinkle formation, improved transepidermal water loss, and increased collagen fibre density (Montero-Vilchez et al., 2021, Frontiers in Cell and Developmental Biology. DOI: 10.3389/fcell.2021.654210). Twelve clinical studies have evaluated MSC-CM for skin wrinkles and acne scars, with generally positive but heterogeneous results. MSC-derived exosomes promote collagen I and elastin synthesis in skin models and have shown anti-senescence effects on dermal fibroblasts in vitro (Ha et al., 2020, DOI: 10.3390/cells9051157). However, these studies are predominantly small, uncontrolled, and often conducted in cosmetic rather than medical settings.

7.4.2 Brain Aging and Neurodegeneration

Evidence level: Preclinical with early-phase clinical trials in specific diseases.

Systematic reviews and meta-analyses of preclinical studies demonstrate that MSC transplantation significantly improves memory loss and cognitive impairment in Alzheimer's disease (AD) animal models, rotational behaviour and limb function in Parkinson's disease (PD) models, and neurobehavioural outcomes in amyotrophic lateral sclerosis (ALS) models. MSC-derived secretome and exosomes have shown neuroprotective effects through modulation of microglial activation, reduction of

amyloid-β plaques, and promotion of neurotrophic factor secretion (Ullah et al., 2015, Bioscience Reports. DOI: 10.1042/BSR20150025). A phase 1/2 clinical trial (NCT04388982) is evaluating allogeneic adipose-derived MSC exosomes administered via nasal drip for mild-to-moderate AD. These studies address specific neurodegenerative diseases rather than generalised brain aging; no clinical trial has evaluated MSCs for age-related cognitive decline in the absence of diagnosed neurological disease.

7.4.3 Cardiovascular Aging

Evidence level: Phase I–II clinical trials for cardiac disease; no trials for cardiovascular aging per se.

Extensive clinical trial data exist for MSCs in myocardial infarction and heart failure. The RIMECARD trial demonstrated that intravenous infusion of umbilical cord MSCs improved left ventricular ejection fraction and functional status in heart failure patients (Bartolucci et al., 2017, Circulation Research. DOI: 10.1161/CIRCRESAHA.117.310712). The POSEIDON-DCM trial showed that allogeneic MSCs reduced TNF-α and improved quality of life in dilated cardiomyopathy (Hare et al., 2017, PMID: 28011450). Preclinical studies demonstrate that MSC paracrine factors increase angiogenesis and reduce apoptosis in ischaemic myocardium (Tang et al., 2005, Annals of Thoracic Surgery. PMID: 15975372). However, these studies target established cardiac disease, not age-related cardiovascular decline in otherwise healthy individuals.

7.4.4 Kidney Aging

Evidence level: Preclinical only for aging; early clinical for acute kidney injury.

MSC-derived extracellular vesicles have shown renoprotective effects in preclinical models of acute kidney injury and diabetic nephropathy. No clinical trials have specifically evaluated MSCs for age-related renal decline.

7.4.5 Musculoskeletal System — Sarcopenia and Osteoporosis

Evidence level: Preclinical and mechanistic.

The age-related shift in MSC differentiation from osteogenesis toward adipogenesis is well documented and contributes to osteoporosis and marrow fat accumulation (Justesen et al., 2001, Biogerontology. PMID: 11708718; Yang et al., 2018, DOI: 10.1186/s13287-018-0876-3). BM-MSC-derived exosomes have been shown to alleviate radiation-induced bone loss by restoring recipient BM-MSC function and activating Wnt/β-catenin signalling in animal models (Zuo et al., 2019, Stem Cell Research & Therapy. DOI: 10.1186/s13287-018-1121-9). For sarcopenia, the evidence is even more limited, with no published clinical trials evaluating MSC therapy for age-related muscle wasting.

7.5 Commercial Longevity Clinics — Published Outcomes

7.5.1 The Commercial Landscape

A rapidly growing number of clinics worldwide market MSC-based therapies for "anti-aging," "rejuvenation," and "longevity" purposes. Turner and Knoepfler (2016) documented over 570 clinics in the United States alone marketing direct-to-consumer stem cell interventions, many of which include anti-aging claims (Turner & Knoepfler, 2016, Cell Stem Cell. DOI: 10.1016/j.stem.2016.06.007). Berger et al. (2016) mapped the global distribution of such businesses, identifying operations across the Americas, Asia, and Europe (Berger et al., 2016, Cell Stem Cell. DOI: 10.1016/j.stem.2016.07.015).

7.5.2 Common Protocols

Commercial longevity clinics typically offer:

- **Cell source:** Allogeneic umbilical cord-derived MSCs (UC-MSCs) or autologous adipose tissue-derived MSCs (AT-MSCs)
- **Route:** Intravenous infusion
- **Dose:** 100–200 million cells per infusion, often repeated at 6–12 month intervals
- **Claimed indications:** General rejuvenation, energy enhancement, immune boosting, skin improvement, cognitive enhancement
- **Cost:** Typically USD $5,000–$25,000 per treatment cycle, not covered by insurance

7.5.3 Published Outcomes and Their Limitations

Peer-reviewed publications from commercial longevity clinics are exceedingly rare. The published literature is dominated by:

- **Case reports and case series** without control groups, blinding, or standardised outcome measures
- **Retrospective analyses** with significant selection and publication bias
- **Patient satisfaction surveys** that conflate subjective well-being with objective clinical improvement

No randomised controlled trial has demonstrated that MSC infusion extends lifespan, reverses biological aging markers (e.g., epigenetic clocks, telomere length), or prevents age-related disease in otherwise healthy individuals. The absence of controlled data makes it impossible to distinguish genuine biological effects from placebo responses, regression to the mean, or the well-documented benefits of the clinical encounter itself.

7.5.4 Publication Bias

The commercial incentive structure strongly favours publication of positive results. Clinics that charge patients for treatments have no motivation to publish negative findings. This creates a systematically distorted evidence base that overstates efficacy and understates risk. The ISSCR has specifically noted that "researchers should always report the results of preclinical research irrespective of whether they are positive, negative, or inconclusive" (ISSCR, Guidelines for Stem Cell Research and Clinical Translation, 2016/2021).

7.6 Ethical and Regulatory Considerations

7.6.1 The Therapeutic–Enhancement Distinction

A fundamental ethical question in MSC longevity applications is the distinction between treating disease and enhancing normal function. Established medical ethics frameworks prioritise the treatment of disease and the alleviation of suffering. The use of MSCs to treat age-related diseases (e.g., osteoarthritis, heart failure, diabetic wounds) falls within conventional therapeutic paradigms. The use of MSCs to "reverse aging" or "enhance vitality" in otherwise healthy individuals represents a qualitatively different proposition — one that raises questions about:

- **Medical necessity:** Whether aging itself constitutes a disease requiring treatment
- **Resource allocation:** Whether scarce healthcare resources should be directed toward enhancement rather than treatment
- **Equity:** Whether longevity interventions available only to the wealthy exacerbate health disparities
- **Informed consent:** Whether patients can meaningfully consent to interventions with unknown long-term risks and unproven benefits

7.6.2 Regulatory Grey Zones and Stem Cell Tourism

The global regulatory landscape for stem cell-based longevity interventions is characterised by significant heterogeneity and enforcement gaps. The direct-to-consumer marketing of unproven stem cell interventions has proliferated in both developing and developed countries, with recent reports documenting a significant rise of clinics in the USA, UK, Australia, and Japan (Horner et al., 2018, npj Regenerative Medicine. DOI: 10.1038/s41536-018-0043-6). Stem cell tourism — the practice of patients travelling to jurisdictions with less stringent regulation to receive unproven treatments — poses particular risks:

- **Physical harm:** Documented cases include bilateral blindness following intravitreal injection of autologous adipose-derived stem cells for age-related macular degeneration (Kuriyan et al., 2017, New England Journal of Medicine. DOI: 10.1056/NEJMoa1609583), tumour formation, and infections from non-GMP-compliant manufacturing.
- **Financial exploitation:** Patients typically pay substantial out-of-pocket costs for treatments lacking evidence of efficacy.
- **Delayed access to proven treatments:** Patients who pursue unproven stem cell therapies may forgo or delay evidence-based interventions.

7.6.3 ISSCR Guidelines

The International Society for Stem Cell Research (ISSCR) has issued clear guidance on unproven stem cell interventions:

> *"The ISSCR condemns the administration of unproven stem cell- and other cell- and tissue-based interventions outside of the context of clinical research or medical innovation... particularly when it is performed as a business activity." (ISSCR, Guidelines for Stem Cell Research and Clinical Translation, Recommendation 3.5)*

> *"The clinical use of unproven stem cell-based interventions should be limited to well-regulated clinical trials and medical innovations compliant with these guidelines and local laws, policies, and regulations. Government authorities and professional organizations should establish and strictly enforce policies and regulations governing the commercial use of stem cell based medical interventions." (ISSCR, Recommendation 3.5.1)*

The ISSCR further specifies that "it is a breach of professional medical ethics and responsible scientific practices to market or provide stem cell-based interventions prior to rigorous and independent expert review of safety and efficacy and appropriate regulatory approval" (ISSCR Guidelines, Section 3.6).

7.6.4 Regulatory Enforcement Actions

Regulatory authorities have taken enforcement actions against clinics marketing unproven stem cell therapies. In the United States, the FDA issued a warning letter to a Florida-based stem cell clinic in 2017 for marketing an unapproved stromal vascular fraction product, and the Department of Justice subsequently filed a lawsuit to halt operations (FDA Warning Letter, 24 August 2017; DOJ filing, 9 May 2018). FDA Commissioner Scott Gottlieb stated: "Stem cell clinics that mislead vulnerable patients into believing they are being given safe, effective treatments that are in full compliance with the law are dangerously exploiting consumers and putting their health at risk" (FDA Press Release, 28 August 2017).

A survey of 2,030 individuals in Saudi Arabia found that 72.1% were unaware that unapproved stem cell treatments may cause serious health complications, and over 63% would be willing to try stem cell therapy if offered — illustrating the scale of public misinformation (Aboalola et al., 2022, Frontiers in Medicine. DOI: 10.3389/fmed.2022.789695).

7.6.5 Distinguishing Legitimate Research from Premature Commercialisation

For governments evaluating MSC-based longevity claims, the following criteria can help distinguish legitimate research from premature commercialisation:

Feature	Legitimate Clinical Research	Premature Commercialisation
Regulatory oversight	Approved by national regulator (IND/CTA)	No regulatory approval; claims "practice of medicine" exemption
Trial registration	Prospectively registered (e.g., ClinicalTrials.gov, ANZCTR)	Not registered, or registered as "pay-to-participate"
Informed consent	Comprehensive, IRB/ethics-approved consent	Minimal disclosure; marketing language in consent forms
Cost to patient	Free or reimbursed	Patient pays $5,000–$25,000+
Data collection	Standardised endpoints, independent monitoring	Testimonials, patient satisfaction surveys
Publication	Peer-reviewed, positive and negative results	Selective publication of positive outcomes only
Manufacturing	GMP-compliant facility	Variable or undisclosed manufacturing standards

7.7 Evidence Assessment for Longevity Applications

7.7.1 What Is Supported by Evidence?

The following MSC applications in age-related conditions are supported by Phase II–III clinical trial evidence:

- **Osteoarthritis:** Multiple randomised controlled trials demonstrate symptomatic improvement following intra-articular MSC injection (see Chapter 5).
- **Chronic wounds and diabetic ulcers:** Clinical evidence supports MSC-mediated wound healing acceleration (see Chapter 5).
- **Graft-versus-host disease:** Approved MSC products (e.g., Temcell/Prochymal) demonstrate efficacy in steroid-refractory GvHD.
- **Heart failure:** Phase I–II trials show safety and preliminary efficacy signals for MSCs in ischaemic and non-ischaemic cardiomyopathy.

These represent disease-specific applications with defined endpoints, not generalised anti-aging interventions.

7.7.2 What Is Promising but Unproven?

The following applications show biological plausibility and early-phase clinical signals but lack definitive evidence:

- **Frailty syndrome:** The CRATUS trial provides proof-of-concept (safety, improvements in 6MWT and TNF-α) but requires replication in larger, multi-centre trials.
- **Immunosenescence reversal:** Preclinical evidence is compelling; clinical data are limited to secondary endpoints in small trials.
- **Skin rejuvenation:** MSC-conditioned medium shows promise in small clinical studies, but rigorous controlled trials are lacking.
- **Neurodegenerative disease prevention:** Preclinical data are strong for disease models (AD, PD, MS); clinical translation for age-related cognitive decline is in its infancy.

7.7.3 What Is Speculative?

The following claims lack sufficient scientific evidence and should be regarded as speculative:

- **Lifespan extension in humans:** No clinical evidence supports the claim that MSC infusion extends human lifespan. Preclinical lifespan extension data (e.g., hypothalamic stem cell implantation in mice) cannot be extrapolated to humans.

- **Biological age reversal:** No published trial has demonstrated that MSC therapy reverses epigenetic clock measurements or other validated biomarkers of biological age.
- **General "rejuvenation" or "wellness enhancement":** Claims of improved energy, vitality, or cognitive function in healthy individuals are not supported by controlled clinical data.
- **Telomere lengthening:** While MSCs exhibit telomerase activity in culture, no clinical evidence demonstrates that MSC infusion lengthens telomeres in recipient tissues.

7.7.4 Policy Recommendation

For the Republic of Fiji, the evidence assessment leads to a clear policy hierarchy:

1. **Prioritise disease treatment.** MSC-based therapies should be evaluated and, where appropriate, enabled for conditions with established clinical evidence — particularly those aligned with Fiji's disease burden (diabetic wounds, osteoarthritis, cardiovascular disease). These applications have defined regulatory pathways, measurable endpoints, and a growing evidence base.
2. **Permit longevity research only within regulated frameworks.** Any investigation of MSC therapy for aging or frailty should occur exclusively within the context of properly designed clinical trials, with ethics committee approval, prospective registration, and independent data monitoring. The ISSCR's recommendation that "government authorities and professional organizations should establish and strictly enforce policies and regulations governing the commercial use of stem cell based medical interventions" (ISSCR, Recommendation 3.5.1) should guide Fiji's approach.
3. **Prohibit unsubstantiated longevity claims.** Commercial marketing of MSC-based "anti-aging" or "rejuvenation" therapies without regulatory approval and adequate clinical evidence should be explicitly prohibited. Consumer protection legislation should be strengthened to address health claims related to stem cell products.
4. **Invest in public education.** Given the documented susceptibility of populations to stem cell misinformation (Aboalola et al., 2022, DOI: 10.3389/fmed.2022.789695), Fiji should develop public education initiatives — in partnership with clinical and scientific experts — to help citizens distinguish evidence-based stem cell therapies from unproven commercial offerings. This is particularly important given the proximity of stem cell tourism destinations in the Asia-Pacific region.

The gap between the biological promise of MSC therapy in aging and the current clinical evidence base is substantial. Responsible stewardship of this emerging field requires that policy decisions be anchored in the evidence as it exists today — not in the aspirational claims of commercial actors. As the ISSCR has cautioned, "the potential benefits of stem cell-based interventions are sometimes exaggerated and the challenges, including their clinical application and risks, are often understated" (ISSCR Guidelines, Section 4). Fiji's regulatory framework should reflect this reality, ensuring that patients are protected while legitimate research pathways remain open for the future.

Chapter 8: Global Regulatory Landscape for MSC Products

8.1 Regulatory Classification of MSC Products

Cell Therapy, Drug, Biologic, or Medical Device: Classification by Jurisdiction

The regulatory classification of mesenchymal stromal cell (MSC) products varies substantially across jurisdictions, creating a fragmented global landscape that directly affects how products are developed, approved, and made available to patients. In the European Union, MSC-based therapies are classified as advanced therapy medicinal products (ATMPs) under Regulation (EC) No 1394/2007, which encompasses gene therapy medicinal products, somatic cell therapy medicinal products (SCTMP), and tissue-engineered products (TEP) (Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products, 2007). The Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA) provides formal classification recommendations; as of 2024, out of 69 MSC-based classification requests submitted to the CAT, 21 concerned umbilical cord-derived MSCs, with 17 classified as TEP and 4 as SCTMP (Mebarki et al., 2021, Journal of Stem Cell Research & Therapy. DOI: 10.1186/s13287-021-02222-y).

In the United States, MSC products are regulated as biological products under Section 351 of the Public Health Service Act (PHSA), requiring an Investigational New Drug (IND) application for clinical trials and a Biologics License Application (BLA) for marketing authorisation. The US framework distinguishes between "human cells, tissues, and cellular and tissue-based products" (HCT/Ps) regulated under Section 361 of the PHSA (21 CFR Part 1271) and biological products requiring full premarket review under Section 351 (Iglesias-López et al., 2019, Frontiers in Pharmacology. DOI: 10.3389/fphar.2019.00921).

In Japan, MSC products are classified as "regenerative medicine products" under the Pharmaceutical and Medical Device (PMD) Act, Chapter 1, Article 2, Paragraph 2 (Kim et al., 2022, Regenerative Therapy. DOI: 10.1016/j.reth.2022.04.004). In Australia, MSC products are classified as "biologicals" under Part 3-2A of the Therapeutic Goods Act 1989 (TGA, Biologicals Framework, 2025). In South Korea, they are classified as cell therapy products under the Safety and Support of Advanced Regenerative Medicine and Advanced Therapy Medicinal Products Act (Kim et al., 2022, Regenerative Therapy. DOI: 10.1016/j.reth.2022.04.004). Notably, in the United States, certain MSC-containing products have been registered as medical devices (e.g., structural tissue allografts containing MSCs for bone regeneration), illustrating the classification ambiguity that persists even within a single jurisdiction (Jossen et al., 2018, Applied Microbiology and Biotechnology. DOI: 10.1007/s00253-018-8912-x. PMID: 29564526).

"Minimally Manipulated" Versus "More Than Minimally Manipulated"

A pivotal regulatory distinction across all major jurisdictions is whether a cell-based product has been "minimally manipulated" or "more than minimally manipulated." This determination dictates whether a product can be marketed under lighter-touch tissue regulations or must undergo full premarket review as a drug or biologic.

In the US framework, culture expansion of MSCs is explicitly defined as "more than minimal manipulation," and use of MSCs for immunomodulation (e.g., in graft-versus-host disease or autoimmune conditions) constitutes "non-homologous use" — both criteria triggering regulation under Section 351 as a biological product requiring IND/BLA (US FDA, 21 CFR Part 1271; ISSCR, Guidelines for Stem Cell Research and Clinical Translation, 2021/2025). The ISSCR Guidelines reinforce this principle: "Stem cells, cells, and tissues that are substantially manipulated or used in a non-homologous manner must be proven safe and effective for the intended use before being marketed to patients" (ISSCR, Recommendation 3.1.1, 2021/2025). The EMA, PMDA, and TGA have issued analogous standards delineating when manipulation can no longer be considered minimal (ISSCR Guidelines, 2021/2025).

Consequently, virtually all therapeutic MSC products intended for systemic immunomodulation or tissue repair via culture-expanded cells are regulated under the most stringent pathway in every major jurisdiction. Products based on minimally processed adipose tissue (e.g., micro-fragmented fat) occupy a contested regulatory grey zone, with regulators in several countries actively clarifying that enzymatic digestion or ultrasonic cavitation of adipose tissue constitutes substantial manipulation (ISSCR Guidelines, Recommendation 3.1.1, 2021/2025).

Autologous Versus Allogeneic Regulatory Differences

Autologous MSC products (cells harvested from and returned to the same patient) and allogeneic products (cells from a healthy donor administered to an unrelated recipient) face different regulatory considerations, though both require full premarket review when culture-expanded. Allogeneic products are manufactured as standardised, off-the-shelf batches, enabling conventional pharmaceutical-style quality control, batch release testing, and scalable manufacturing. This model aligns more readily with existing regulatory frameworks for biologics. Autologous products, by contrast, are manufactured as single-patient batches, creating challenges for batch-to-batch consistency, potency assurance, and logistics (Mello et al., 2024, International Journal of Molecular Sciences. DOI: 10.3390/ijms25116063. PMID: 38892249).

In the EU, both autologous and allogeneic culture-expanded MSC products are classified as ATMPs. In Australia, the TGA provides a specific sub-classification for "autologous human cell and tissue products" within the biologicals framework, defined as products "that comprise, contain, or are derived from human cells and tissues and are removed from, and applied to, the same person" (Australian Regulatory Guidelines for Biologics, ARGB; Kim et al., 2022, Regenerative Therapy. DOI: 10.1016/j.reth.2022.04.004).

8.2 United States — FDA

21 CFR Part 1271 (HCT/Ps), Section 351 (BLA) Versus Section 361 Pathway

The US regulatory framework for cell-based products is bifurcated. Under 21 CFR Part 1271, HCT/Ps that meet all four criteria — (i) minimal manipulation, (ii) homologous use, (iii) no combination with another article (except water, crystalloids, or sterilising/preserving agents), and (iv) either no systemic effect/dependence on metabolic activity, or autologous/first- or second-degree relative use — are regulated under Section 361 of the PHSA and require only registration and listing with the FDA. All other cell-based products, including culture-expanded MSCs, fall under Section 351 and require an IND for clinical investigation and a BLA for marketing (US FDA, 21 CFR Part 1271; Iglesias-López et al., 2019, Frontiers in Pharmacology. DOI: 10.3389/fphar.2019.00921).

RMAT Designation and Approved MSC Products

The Regenerative Medicine Advanced Therapy (RMAT) designation, established under Section 3033 of the 21st Century Cures Act (2016), provides expedited development and review for regenerative medicine products intended to treat serious or life-threatening conditions. RMAT-designated products may benefit from early interactions with the FDA, priority review, and potential use of surrogate or intermediate endpoints for accelerated approval. The designation applies to cell therapies, therapeutic tissue-engineering products, human cell and tissue products, and combination products, but explicitly excludes products regulated solely under Section 361 (Iglesias-López et al., 2019, Frontiers in Pharmacology. DOI: 10.3389/fphar.2019.00921).

In December 2024, the FDA approved RYONCIL (remestemcel-L) for the treatment of pediatric steroid-refractory acute graft-versus-host disease (SR-aGvHD), representing the first allogeneic MSC therapy cleared for commercial use in the United States. This approval followed a Phase III trial (NCT02336230) demonstrating significant improvement in paediatric patients who failed steroid treatment (Mello et al., 2024, International Journal of Molecular Sciences. DOI: 10.3390/ijms25116063. PMID: 38892249). A second MSC-based product, rexlemestrocel-L for chronic low back pain, holds RMAT designation and is in advanced clinical development.

Enforcement Actions Against Unapproved Clinics

The FDA has progressively intensified enforcement against clinics marketing unapproved stem cell interventions. In 2019, the FDA published its "Framework for the Regulation of Regenerative Medicine Products," clarifying that culture-expanded MSC products and stromal vascular fraction (SVF) obtained via enzymatic digestion are regulated as biological products requiring premarket approval (US FDA, Framework for the Regulation of Regenerative Medicine Products, 2019). The ISSCR has condemned the administration of unproven stem cell-based interventions outside clinical research, particularly when performed as a business activity, noting that "for the vast majority of medical conditions for which putative 'stem cell therapies' or 'regenerative therapies' are currently being marketed, there is insufficient evidence of safety and efficacy to justify routine or commercial use" (ISSCR Guidelines, Recommendation 3.5.1, 2021/2025). The EMA and Heads of Medicines Agencies (HMA) issued a parallel joint statement in March 2025 warning against unregulated advanced therapies, including dendritic cell therapies marketed for cancer in the EU (EMA/HMA Joint Statement on Unregulated ATMPs, March 2025).

8.3 European Union — EMA

ATMP Regulation (EC) No 1394/2007 and Hospital Exemption

In the EU, all ATMPs — including MSC-based products — are subject to centralised marketing authorisation through the EMA. Regulation (EC) No 1394/2007 establishes the legal framework, supplemented by Directive 2001/83/EC and Regulation (EC) No 726/2004. The Committee for Advanced Therapies (CAT) prepares a draft opinion on quality, safety, and efficacy, which is transmitted to the Committee for Medicinal Products for Human Use (CHMP) for adoption; the European Commission makes the final authorisation decision (EMA, Advanced Therapy Medicinal Products: Overview, 2025).

A notable feature of the EU framework is the "hospital exemption" (Article 28 of Regulation 1394/2007), which permits the use of ATMPs prepared on a non-routine basis for individual patients within a hospital, under the exclusive professional responsibility of a medical practitioner, without requiring centralised marketing authorisation. This provision has been used in several EU member states to provide MSC therapies — for example, pooled MSC products for steroid-refractory GvHD in Germany (Česnik & Švajger, 2024, Frontiers in Cell and Developmental Biology. DOI: 10.3389/fcell.2024.1400347. PMID: 39129786). However, the ISSCR has cautioned that hospital exemptions "should not be used as a vehicle for providing unapproved stem cell-based interventions or avoiding regulatory oversight" (ISSCR Guidelines, 2021/2025).

In October 2017, the European Commission and EMA published a joint action plan on ATMPs to streamline procedures and better address the specific requirements of ATMP developers (European Commission–EMA Action Plan on ATMPs, 2017). EMA also launched a pilot programme in September 2022 providing enhanced regulatory support to academic and non-profit ATMP developers targeting unmet clinical needs, including guidance, fee reductions, and waivers (EMA, ATMP Academic Development Support Pilot, EMA/797476/2022/Rev1).

Alofisel (Darvadstrocel): Approval and Market Withdrawal

Alofisel (darvadstrocel, EMEA/H/C/004258) was the first allogeneic, adipose tissue-derived MSC product to receive centralised marketing authorisation in the EU, approved in March 2018 for the treatment of complex perianal fistulas in adult patients with non-active or mildly active luminal Crohn's disease who have shown an inadequate response to at least one conventional or biologic therapy (EMA, Alofisel EPAR, 2018). The approval was supported by the ADMIRE-CD Phase III trial involving 212 patients (Panés et al., 2016).

However, Alofisel was withdrawn from the EU market in December 2024, coinciding with the failure of the confirmatory ADMIRE-CD II trial to meet its primary endpoint. The marketing authorisation was formally withdrawn from the Community Register of Medicinal Products by the European Commission in December 2024 (EMA, "Alofisel withdrawn from the EU market," 13 December 2024). This withdrawal has significant implications for the EU ATMP landscape: the EMA is expected to demand more rigorous potency assays and longer follow-up periods for future MSC product applications (Mello et al., 2024, International Journal of Molecular Sciences. DOI: 10.3390/ijms25116063. PMID: 38892249). The Alofisel experience illustrates both the promise and the fragility of conditional or early approvals for cell-based products and underscores the importance of robust confirmatory trials.

8.4 Japan — PMDA

Act on Safety of Regenerative Medicine (2014) and Conditional/Time-Limited Approval

Japan has established one of the most progressive regulatory frameworks for regenerative medicine globally. The Act on the Safety of Regenerative Medicine (Act No. 85, 2013; effective November 2014) and the revised Pharmaceutical and Medical Device (PMD) Act created a unique conditional and time-limited approval pathway for regenerative medicine products. Under this system, products may receive marketing authorisation based on results from early-phase clinical trials demonstrating safety and probable efficacy (a lower evidentiary threshold than "substantial evidence" required by the FDA or EMA). Conditional approval is granted for a defined period (typically 7 years), during which the manufacturer must conduct post-marketing studies to confirm efficacy. If confirmatory data are insufficient, the approval may be revoked (Kim et al., 2022, Regenerative Therapy. DOI: 10.1016/j.reth.2022.04.004).

This framework reflects Japan's deliberate policy choice to enable faster patient access to regenerative therapies while maintaining safety oversight through mandatory post-market surveillance. The ISSCR has acknowledged the legitimacy of conditional marketing authorisations but emphasises that "regulators must ensure there is a robust post-market surveillance system whereby regulators have the capacity and power to remove products from the market as appropriate" (ISSCR Guidelines, Recommendation 3.6.1.3, 2021/2025).

Temcell HS and Stemirac

Two MSC products have received marketing authorisation in Japan under this framework:

1. **Temcell HS Inj.** — An allogeneic bone marrow-derived MSC product licensed to JCR Pharmaceuticals, approved by the PMDA in 2015 for the treatment of acute graft-versus-host disease. Temcell HS was originally developed as remestemcel-L and received market authorisation under a fast-track protocol (Jayaraman et al., 2021, Frontiers in Cell and Developmental Biology. DOI: 10.3389/fcell.2021.648472. PMID: 33928083).
2. **Stemirac** — An autologous bone marrow-derived MSC product developed for the treatment of spinal cord injury, which received conditional and time-limited approval from the PMDA in 2018. Stemirac represents a notable case of the Japanese conditional approval pathway applied to a neurological indication with high unmet need (Mello et al., 2024, International Journal of Molecular Sciences. DOI: 10.3390/ijms25116063. PMID: 38892249).

Japan's approach has been both praised for enabling early patient access and critiqued for the limited evidence base at the time of conditional approval. The system's success depends critically on the rigour and completion of post-marketing confirmatory studies — a challenge that has proven difficult in practice for some conditionally approved products.

8.5 South Korea — MFDS

First MSC Product Approvals

The Republic of Korea, regulated by the Ministry of Food and Drug Safety (MFDS), hosts the highest density of approved commercial MSC products globally. Four MSC products have received marketing authorisation:

1. **Cellgram-AMI** — An autologous bone marrow-derived MSC product approved in 2011 for the treatment of acute myocardial infarction (MFDS, 2011).
2. **CARTISTEM** — An allogeneic umbilical cord blood-derived MSC product approved in 2012 for the treatment of knee osteoarthritis (cartilage defects) (MFDS, 2012).
3. **Cupistem** — An autologous adipose tissue-derived MSC product approved in 2012 for the treatment of Crohn's disease-associated perianal fistulas (MFDS, 2012).
4. **Neuronata-R** — An autologous bone marrow-derived MSC product that received conditional approval in 2014 for amyotrophic lateral sclerosis (ALS) (MFDS, 2014).

(Mello et al., 2024, International Journal of Molecular Sciences. DOI: 10.3390/ijms25116063. PMID: 38892249; Jossen et al., 2018, Applied Microbiology and Biotechnology. DOI: 10.1007/s00253-018-8912-x. PMID: 29564526)

Regulatory Pathway and Post-Market Surveillance

South Korea's regulatory pathway for cell therapy products is governed by the Safety and Support of Advanced Regenerative Medicine and Advanced Therapy Medicinal Products Act. The MFDS classifies MSC products as cell therapy products and has established a dedicated approval process within its Bio & Cosmetics division. The MFDS also operates a Global Innovative products on Fast Track (GIFT) programme and a Global Harmonization Center (GHC) to facilitate international regulatory convergence (MFDS, 2025). Post-market surveillance is mandatory for all approved cell therapy products, and the MFDS requires periodic safety update reports and re-examination of new drugs within defined timeframes. The concentration of MSC approvals in South Korea reflects both a supportive regulatory environment and substantial government investment in regenerative medicine infrastructure.

8.6 Australia — TGA

Biologicals Framework

In Australia, MSC products are regulated as "biologicals" under Part 3-2A of the Therapeutic Goods Act 1989. The Therapeutic Goods Administration (TGA) defines biologicals as entities that "comprise, contain, or are derived from human cells or human tissues" and are intended for therapeutic, diagnostic, or physiological purposes (Therapeutic Goods Act 1989, Part 3-2A, Section 32A; TGA, Biologicals, 2025).

The approval procedure for a new biological entity (NBE) involves submission of an application, preliminary assessment within 30 days, departmental reviews with data requests at days 130, 180, and 230, consultation with the Advisory Committee on Biologicals (ACB) if necessary, and final approval within a total of 290 days (Kim et al., 2022, Regenerative Therapy. DOI: 10.1016/j.reth.2022.04.004).

Exclusion Categories and CTN/CTX Schemes

The TGA provides specific exclusion categories for certain low-risk biological products. Autologous human cell and tissue products that are minimally manipulated and used homologously may be excluded from full regulatory oversight under the Australian Regulatory Guidelines for Biologics (ARGB). However, culture-expanded MSC products — whether autologous or allogeneic — are fully regulated as biologicals.

For clinical trials, Australia operates two pathways: the Clinical Trial Notification (CTN) scheme and the Clinical Trial Exemption (CTX) scheme. Under CTN, the sponsor notifies the TGA after receiving ethics committee approval, and the TGA does not evaluate the trial protocol before commencement. Under CTX, the TGA evaluates the clinical trial proposal before it can proceed. The CTN pathway is widely used for cell therapy trials and provides a relatively streamlined mechanism for initiating clinical research, making Australia an attractive jurisdiction for early-phase MSC clinical trials.

Australia's geographic proximity to the Pacific Islands and its membership in the Pharmaceutical Inspection Co-operation Scheme (PIC/S) make the TGA a natural reference agency for Fiji's regulatory considerations.

8.7 Other Key Jurisdictions

Canada

Canada approved Prochymal (remestemcel-L) in 2012 for the treatment of paediatric acute graft-versus-host disease, making it one of the earliest MSC product approvals globally (Jossen et al., 2018, Applied Microbiology and Biotechnology. DOI: 10.1007/s00253-018-8912-x. PMID: 29564526). Health Canada regulates cell therapies under the Food and Drugs Act and the Biologics and Radiopharmaceuticals Regulations. Notably, GMP compliance is not as strictly mandated at early clinical phases as in the EU, where GMP is required from Phase I (Jayaraman et al., 2021, Frontiers in Cell and Developmental Biology. DOI: 10.3389/fcell.2021.648472. PMID: 33928083). Canada's regulatory approach has been characterised as pragmatic, with provisions for special access programmes and conditional approvals.

Brazil (ANVISA)

Brazil's Agência Nacional de Vigilância Sanitária (ANVISA) regulates cell therapy products under Resolution RDC No. 508/2021, which establishes requirements for clinical research with advanced therapy products. Brazil has an active MSC clinical trial landscape, particularly for cardiovascular and autoimmune indications, but has not yet approved a commercial MSC product. ANVISA participates in international harmonisation efforts and has observer status at ICH.

India (CDSCO)

India's Central Drugs Standard Control Organization (CDSCO), under the Drug Controller General of India (DCGI), approved Stempeucel in 2016 for the treatment of critical limb ischaemia in Buerger's disease. This allogeneic bone marrow-derived MSC product was approved on a limited basis (200 patients, cost-recovery), with mandatory post-marketing surveillance (Mello et al., 2024, International Journal of Molecular Sciences. DOI: 10.3390/ijms25116063. PMID: 38892249). India's New Drugs and Clinical Trials Rules (2019) provide a framework for cell and gene therapy clinical trials, though the regulatory infrastructure for ATMPs remains under development.

Singapore (HSA)

The Health Sciences Authority (HSA) of Singapore regulates cell therapy products under the Health Products Act and the Health Products (Cell, Tissue and Gene Therapy Products) Regulations 2021. Singapore has positioned itself as a regional hub for cell therapy manufacturing and clinical trials, with a well-resourced regulatory agency and strong GMP infrastructure. The HSA participates in ASEAN pharmaceutical harmonisation initiatives.

Thailand

Thailand's Food and Drug Administration (Thai FDA) has developed guidelines for stem cell and cell therapy products, and the country has an active clinical research programme in MSC therapies. Thailand's regulatory framework is evolving, with increasing alignment to international standards through ASEAN harmonisation.

Iran

Iran's Food and Drug Administration approved MeseStroCell, a bone marrow-derived MSC product for knee osteoarthritis, in 2018 (Mello et al., 2024, International Journal of Molecular Sciences. DOI: 10.3390/ijms25116063. PMID: 38892249). Iran has a growing regenerative medicine sector with several academic centres conducting MSC clinical trials.

Saudi Arabia (SFDA)

The Saudi Food and Drug Authority (SFDA) regulates cell and gene therapy products and has been developing its regulatory framework for advanced therapies. Saudi Arabia has invested substantially in regenerative medicine infrastructure, including GMP cell therapy manufacturing facilities, and the SFDA engages with international regulatory bodies for harmonisation of standards.

Malaysia, Indonesia, and ASEAN Harmonisation

The Association of Southeast Asian Nations (ASEAN) has initiated pharmaceutical harmonisation efforts through the ASEAN Pharmaceutical Product Working Group, though cell therapy-specific harmonisation remains at an early stage. Malaysia's National Pharmaceutical Regulatory Agency (NPRA) and Indonesia's Badan Pengawas Obat dan Makanan (BPOM) regulate cell-based products under their respective pharmaceutical laws, but dedicated ATMP frameworks are still under development. For Pacific Island nations considering regulatory alignment, the ASEAN harmonisation model offers instructive lessons in regional regulatory cooperation among resource-constrained jurisdictions.

8.8 Fiji and Pacific Islands — Regulatory Context

Fiji Medicines Regulatory Authority: Current Framework

Fiji's pharmaceutical regulation is administered by the Ministry of Health and Medical Services (MHMS) through the Fiji Pharmaceutical and Biomedical Services Centre (FPBSC). The current regulatory framework is designed primarily for conventional pharmaceutical products — small-molecule drugs, vaccines, and medical devices — and is governed by the Fiji Medicines Act. The MHMS has been actively engaged in strengthening its regulatory capacity, including recent legislative reviews such as the Review of the Nursing Act 2011 (MHMS Fiji, 2025/2026).

Cell Therapy/ATMP-Specific Regulation: Gap Analysis

At present, Fiji does not have a dedicated regulatory framework for advanced therapy medicinal products, cell therapies, or regenerative medicine products. The existing Medicines Act does not contain provisions specifically addressing the classification, manufacturing, quality control, clinical trial oversight, or post-market surveillance of living cell-based therapeutics. This regulatory gap is not unique to Fiji — it is characteristic of most small island developing states (SIDS) and many low- and middle-income countries globally.

The absence of ATMP-specific regulation means that any MSC-based therapy introduced in Fiji would currently lack a defined legal pathway for evaluation, approval, and oversight. This creates both a patient safety risk (potential for unregulated interventions) and a barrier to legitimate clinical development.

WHO Prequalification Reliance and Reference Agency Models

For small nations with limited regulatory capacity, the World Health Organization (WHO) has promoted the concept of "reliance" — whereby a national regulatory authority bases its regulatory decisions, in whole or in part, on the assessments of a trusted reference agency. Fiji already employs elements of this approach for conventional pharmaceuticals.

For MSC products, several reference agency options merit consideration:

- **TGA (Australia):** Geographic proximity, shared Commonwealth legal traditions, existing bilateral health cooperation, PIC/S membership, and a well-established biologicals framework make the TGA the most natural reference agency for Fiji. The TGA's 290-day biologicals approval pathway and CTN/CTX clinical trial schemes could serve as templates.
- **EMA:** The EU's centralised ATMP framework is comprehensive but complex. The EMA's experience with Alofisel — including both approval and withdrawal — provides valuable precedent. The hospital exemption model may be relevant for Fiji's consideration of limited, controlled clinical use.
- **FDA:** While the FDA's framework is the most extensively documented, its complexity and US-specific requirements (e.g., BLA process) may be less directly transferable to a small Pacific Island context.
- **WHO Prequalification (PQ):** WHO PQ does not currently cover cell therapy products, but the WHO has issued guidance on cell-based therapeutics and is developing frameworks for the evaluation of advanced therapies in resource-limited settings.

Regulatory Pathway Options for Fiji

Four principal regulatory pathway options are available to Fiji:

1. **Full national ATMP framework:** Developing a comprehensive, standalone regulatory framework for cell therapies. This approach provides maximum sovereignty but requires substantial investment in regulatory expertise, laboratory infrastructure, and ongoing capacity that may exceed Fiji's current resources.
2. **Reference agency reliance:** Adopting a formal reliance pathway whereby Fiji recognises approvals and assessments from one or more designated reference agencies (e.g., TGA, EMA). This is the most resource-efficient approach and is consistent with WHO recommendations for SIDS.
3. **Hybrid model:** Establishing a minimal national framework that defines classification criteria, clinical trial oversight, and pharmacovigilance requirements, while relying on reference agency assessments for product quality and efficacy evaluation. This balances sovereignty with practicality.
4. **Regional cooperation:** Engaging with Pacific Island Forum countries and/or ASEAN harmonisation initiatives to develop a shared regional framework for advanced therapies. This approach distributes the regulatory burden across multiple nations.

Regional Context: Tonga, Samoa, Papua New Guinea

Other Pacific Island nations face similar regulatory gaps. Tonga and Samoa have small national medicines regulatory authorities with limited capacity beyond conventional pharmaceuticals. Papua New Guinea has a somewhat larger regulatory infrastructure but similarly lacks ATMP-specific provisions. A coordinated Pacific regional approach — potentially facilitated through the Pacific Community (SPC) or the Pacific Islands Forum — could enable shared regulatory capacity, joint assessments, and harmonised standards for advanced therapies. Such cooperation would be consistent with the ISSCR's recommendation that "government authorities and professional organizations should establish and strictly enforce policies and regulations governing the commercial use of stem cell-based medical interventions" (ISSCR Guidelines, Recommendation 3.5.1, 2021/2025).

8.9 International Harmonisation

ICH Guidelines

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has developed guidelines relevant to cell therapy products, including ICH Q5A (Viral Safety Evaluation of Biotechnology Products), ICH Q5D (Derivation and Characterisation of Cell Substrates), ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System). While these guidelines were originally developed for conventional biologics, they provide foundational quality principles applicable to MSC manufacturing. ICH membership and observer status are available to regulatory authorities worldwide, and adoption of ICH guidelines provides a recognised quality benchmark for cell therapy products.

WHO Guidance on Cell-Based Therapeutics

The WHO has published guidance documents on the evaluation of cell-based therapeutics, emphasising the need for appropriate regulatory oversight, donor screening, manufacturing quality, and clinical evidence. The WHO's role in prequalification and its technical assistance programmes for regulatory strengthening in low- and middle-income countries make it a critical partner for nations like Fiji that are developing regulatory capacity for advanced therapies. The WHO's Essential Medicines framework does not currently include cell therapy products, but the organisation's normative guidance provides a foundation for national regulatory development.

ISSCR Guidelines

The International Society for Stem Cell Research (ISSCR) published comprehensive Guidelines for Stem Cell Research and Clinical Translation (originally 2006, updated 2016, 2021, and 2025). These guidelines address the full spectrum of stem cell research and clinical application, including classification of cell-based interventions, cell processing and manufacture, preclinical development, clinical trial design, regulatory approval, and post-market surveillance (ISSCR, Guidelines for Stem Cell Research and Clinical Translation, 2021/2025). Key recommendations relevant to regulatory framework development include:

- Products containing substantially manipulated cells or cells used non-homologously must be evaluated as drugs, biologics, or ATMPs (Recommendation 3.1.1).
- Conditional marketing authorisations must be accompanied by robust post-market surveillance (Recommendation 3.6.1.3).
- Government authorities should establish and strictly enforce regulations governing commercial use of stem cell-based interventions (Recommendation 3.5.1).
- Clinical trials should not be conducted in foreign countries solely due to less stringent regulation (Recommendation 3.4.5.1).

These guidelines serve as an internationally recognised normative framework that can inform national regulatory development, particularly for jurisdictions without existing ATMP legislation.

PIC/S for GMP

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) provides a framework for harmonised GMP standards and mutual recognition of GMP inspections among participating regulatory authorities. PIC/S membership is particularly relevant for cell therapy manufacturing, as GMP compliance is a prerequisite for product quality and safety. Australia (TGA) is a PIC/S member, and adoption of PIC/S-aligned GMP standards would facilitate Fiji's recognition of TGA-inspected manufacturing facilities.

How Small Nations Can Leverage International Standards

For small nations with limited regulatory resources, international harmonisation offers a practical pathway to ensure patient safety without duplicating the full regulatory infrastructure of larger jurisdictions. Key strategies include:

- **Formal reliance agreements** with one or more reference agencies for product assessment.
- **Adoption of ICH quality guidelines** as national standards for manufacturing and quality control.
- **Alignment with ISSCR Guidelines** as a normative framework for clinical translation.
- **PIC/S-aligned GMP recognition** to accept manufacturing facilities inspected by PIC/S member authorities.
- **Participation in WHO regulatory strengthening programmes** to build national capacity incrementally.
- **Regional cooperation** with neighbouring Pacific Island nations to share regulatory expertise and costs.

The ISSCR has specifically noted that "these guidelines do not supersede local laws and regulations. However, they complement existing legal frameworks and can inform the interpretation and development of laws applicable to stem cell research" (ISSCR Guidelines, 2021/2025) — a principle directly applicable to Fiji's regulatory development process.

8.10 Comparative Regulatory Table

Jurisdiction	Classification	Approval Pathway	Approved MSC Products	Typical Timeline	Key Feature
United States (FDA)	Biological product (Section 351 PHSA)	IND → Phase I/II/III → BLA; RMAT designation available	RYONCIL (remestemcel-L), 2024 — paediatric SR-aGvHD	10–15 years (development); 10-month BLA review	First US MSC approval in 2024; RMAT expedites development; active enforcement against unapproved clinics
European Union (EMA)	ATMP (Regulation 1394/2007)	Centralised authorisation via CAT/CHMP; hospital exemption available	Alofisel (darvadstrocel), 2018 — withdrawn December 2024	~210 days (assessment); years of development	Hospital exemption permits non-routine individual use; Alofisel withdrawal highlights confirmatory trial importance
Japan (PMDA)	Regenerative medicine product (PMD Act)	Conditional/time-limited approval (7 years); post-market confirmatory studies required	Temcell HS (2015, GvHD); Stemirac (2018, spinal cord injury)	Faster than FDA/EMA due to conditional pathway	Enables early patient access; conditional approval may be revoked if confirmatory data insufficient
South Korea (MFDS)	Cell therapy product (Advanced Regenerative Medicine Act)	Full approval or conditional approval; GIFT programme	Cellgram-AMI (2011); CARTISTEM (2012); Cupistem (2012); Neuronata-R (2014, conditional)	Variable	Highest density of approved MSC products globally; strong government investment in regenerative medicine
Australia (TGA)	Biological (Therapeutic Goods Act 1989, Part 3-2A)	New Biological Entity application; CTN/CTX for clinical trials	None (MSC trials conducted under CTN)	290 days (NBE assessment)	CTN scheme enables streamlined clinical trial initiation; natural reference agency for Pacific Islands
Canada (Health Canada)	Biologic (Food and Drugs Act)	New Drug Submission; Special Access Programme	Prochymal (2012, paediatric GvHD)	Standard biologic review	Early MSC approval (2012); pragmatic regulatory approach

Jurisdiction	Classification	Approval Pathway	Approved MSC Products	Typical Timeline	Key Feature
India (CDSCO/DCGI)	Cell therapy (New Drugs and Clinical Trials Rules, 2019)	New drug approval; limited/conditional	Stempeucel (2016, critical limb ischaemia — limited to 200 patients)	Variable	Conditional approval with mandatory post-market surveillance; cost-recovery basis
Iran (Iran FDA)	Cell therapy	National approval	MeseStroCell (2018, knee osteoarthritis)	Variable	Growing regenerative medicine sector
Brazil (ANVISA)	Advanced therapy product (RDC 508/2021)	Clinical trial authorisation; no commercial MSC approval yet	None	Variable	Active MSC trial landscape; evolving regulatory framework
Singapore (HSA)	Cell, tissue and gene therapy product	Health Products Act; CTGTP Regulations 2021	None	Variable	Regional manufacturing hub; strong GMP infrastructure
Fiji (MHMS/FPBSC)	No ATMP-specific classification	No defined pathway for cell therapies	None	N/A	Regulatory gap; reference agency reliance (TGA) recommended as interim pathway

This comparative analysis demonstrates that the global regulatory landscape for MSC products is characterised by significant heterogeneity in classification, evidentiary requirements, and approval timelines. Asia-Pacific jurisdictions — particularly South Korea and Japan — have adopted the most progressive frameworks, resulting in the highest concentration of approved MSC products. The EU and US maintain more stringent evidentiary requirements, with the US achieving its first MSC approval only in late 2024. For Fiji, the absence of ATMP-specific regulation represents a critical gap that must be addressed before MSC therapies can be safely and legally introduced. A reference agency reliance model, anchored to the TGA and supplemented by adherence to ISSCR Guidelines and ICH quality standards, offers the most pragmatic and resource-efficient pathway for ensuring that any future MSC-based interventions in Fiji meet internationally recognised standards of quality, safety, and efficacy.

Chapter 9: Commercially Approved MSC Products Worldwide

9.1 Overview

Scope of Regulatory Approvals

As of mid-2026, a total of approximately 13 MSC-based products have received marketing authorisation from national or supranational regulatory agencies worldwide, though the precise count varies depending on whether conditional approvals, hospital exemptions, and medical-device-classified products are included (Mello et al., 2024, *Int J Mol Sci*. DOI: 10.3390/ijms25116063; Zhao et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448). When restricted to products classified as advanced therapy medicinal products (ATMPs) or their regulatory equivalents — that is, culture-expanded MSC preparations approved through pharmaceutical-grade review pathways — the number stands at 12 distinct products across seven jurisdictions. This figure includes the landmark approval of remestemcel-L (Ryoncil) by the United States Food and Drug Administration (FDA) in December 2024, the first allogeneic MSC therapy cleared for commercial use in the United States, and the approval of Ammitel-L by China's National Medical Products Administration (NMPA) in 2025 for steroid-refractory acute graft-versus-host disease (SR-aGvHD) (Zhao et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448).

Timeline and Geographic Distribution

The regulatory history of MSC products spans 15 years, from the first approval in 2010 to the most recent in 2025. The geographic distribution is heavily concentrated in the Asia-Pacific region, which accounts for the majority of approvals:

- **Republic of Korea (MFDS):** Four products approved between 2010 and 2014 — Queencell (2010), Cellgram-AMI (2011), Cartistem (2012), Cupistem (2012), and Neuronata-R (2014, conditional). Korea hosts the highest density of approved commercial MSC products globally (Zhao et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448; Jossen et al., 2018, *Appl Microbiol Biotechnol*. PMID: 29564526).
- **Japan (PMDA):** Two products — Temcell HS Inj. (2015) and Stemirac (2018, conditional).
- **India (DCGI):** One product — Stempeucel (2016), with restricted use.
- **Iran (Iran FDA):** One product — MesestroCell (2018).
- **Canada (Health Canada) and New Zealand (Medsafe):** Prochymal (2012).
- **European Union (EMA):** One product — Alofisel (2018), subsequently withdrawn in December 2024.
- **United States (FDA):** One product — Ryoncil/remestemcel-L (2024).
- **China (NMPA):** One product — Ammitel-L (2025).

This distribution reflects the progressive regulatory frameworks established in South Korea and Japan, which enabled conditional and expedited approvals for regenerative medicine products earlier than Western regulators (Fernández-Santos et al., 2022, *Front Immunol*. PMID: 35812460).

Commercial Success Versus Market Challenges

The commercial trajectory of approved MSC products has been mixed. Several products remain on the market with stable but modest revenues, while others have faced significant challenges:

- **Alofisel (darvadstrocel)** was withdrawn from the EU market in December 2024 following the failure of the confirmatory ADMIRE-CD II trial to meet its primary endpoint, representing the most prominent commercial failure in the MSC field (EMA, "Alofisel withdrawn from the EU market," 13 December 2024, EMEA/H/C/004258).
- **Prochymal** was approved in Canada and New Zealand but never achieved broad commercial uptake and was subsequently superseded by the development of remestemcel-L (Ryoncil) for the US market.
- Korean products (Cellgram-AMI, Cartistem, Cupistem) remain marketed domestically but have had limited international expansion.
- **Stemirac** was granted conditional approval in Japan under the PMDA's expedited pathway for regenerative medicine products, with full approval contingent on confirmatory post-marketing data.

These experiences underscore a recurring theme: regulatory approval of MSC products is achievable, but commercial sustainability requires adequate reimbursement frameworks, robust confirmatory evidence, and scalable manufacturing (Olsen et al., 2018, *Front Med*. PMID: 29977893).

9.2 Detailed Product Profiles

9.2.a Cellgram-AMI (Pharmicell Co., Ltd., Republic of Korea, 2011)

Product characteristics: Cellgram-AMI (also known as Hearticellgram-AMI) is an autologous bone marrow-derived MSC (BM-MSC) product. Cells are harvested from the patient's own iliac crest, culture-expanded, and re-administered via intracoronary infusion.

Indication: Improvement of left ventricular ejection fraction (LVEF) following acute myocardial infarction (AMI).

Regulatory pathway and approval: Approved by the Korean Ministry of Food and Drug Safety (MFDS) in July 2011 as a cell therapy product (Mello et al., 2024, *Int J Mol Sci*. PMID: 38892249; Zhao et al., 2026, *Stem Cell Rev Rep*. PMID: 41254448).

Pivotal clinical evidence: The approval was supported by a Phase II/III clinical trial in which patients with AMI who had undergone percutaneous coronary intervention received intracoronary infusion of autologous BM-MSCs. The study demonstrated improvements in LVEF and reductions in infarct size at 6-month follow-up compared to baseline. The trial was relatively small by international standards.

Dosing and administration: Autologous BM-MSCs are administered as a single intracoronary infusion following culture expansion. The dose is patient-specific, typically in the range of 5–7 × 10^7 cells.

Current market status: Marketed in the Republic of Korea. International expansion has been limited.

Cost: Estimated at approximately USD 18,000–20,000 per treatment in Korea.

9.2.b Cartistem (Medipost Co., Ltd., Republic of Korea, 2012)

Product characteristics: Cartistem is an allogeneic umbilical cord blood-derived MSC (UCB-MSC) product combined with sodium hyaluronate as a scaffold. It is the first allogeneic MSC product approved for a musculoskeletal indication.

Indication: Treatment of knee cartilage defects in patients with osteoarthritis (grade IV cartilage defects of the knee).

Regulatory pathway and approval: Approved by the Korean MFDS in January 2012 (Jossen et al., 2018, *Appl Microbiol Biotechnol.* PMID: 29564526; Zhao et al., 2026, *Stem Cell Rev Rep.* PMID: 41254448).

Pivotal clinical evidence: A Phase III randomised controlled trial compared Cartistem implantation with microfracture surgery for knee cartilage defects. The study demonstrated non-inferiority or superiority of Cartistem in cartilage repair as assessed by the International Knee Documentation Committee (IKDC) score, Visual Analogue Scale (VAS) for pain, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at 48 weeks. A follow-up study (NCT01626677) extended observation to 60 months (Goldberg et al., 2017, *J Orthop Surg Res.* PMID: 28279182).

Dosing and administration: Approximately 2.5 × 10^6 cells per cm^2 of defect area, applied surgically via arthrotomy with the hyaluronate gel scaffold directly to the debrided cartilage defect.

Current market status: Actively marketed in the Republic of Korea. The manufacturer has been expanding into ankle cartilage defects and developing a next-generation platform (SMUP-Cell).

Cost: Approximately USD 5,000–7,000 per treatment in Korea.

9.2.c Cupistem (Anterogen Co., Ltd., Republic of Korea, 2012)

Product characteristics: Cupistem is an autologous adipose tissue-derived MSC (AT-MSC) product.

Indication: Treatment of complex perianal fistulas in patients with Crohn's disease.

Regulatory pathway and approval: Approved by the Korean MFDS in January 2012 (Mello et al., 2024, *Int J Mol Sci.* PMID: 38892249; Zhao et al., 2026, *Stem Cell Rev Rep.* PMID: 41254448).

Pivotal clinical evidence: The approval was based on clinical trial data demonstrating fistula closure following local injection of autologous AT-MSCs into the fistula tract. The pivotal study reported combined remission (clinical assessment of fistula closure plus absence of collections >2 cm on MRI) in a significant proportion of treated patients.

Dosing and administration: Autologous AT-MSCs are harvested via lipoaspiration, culture-expanded, and injected directly into the fistula tract and surrounding tissue. Dose is typically 3 × 10^7 to 6 × 10^7 cells per injection.

Current market status: Marketed in the Republic of Korea.

Cost: Approximately USD 10,000–15,000 per treatment.

9.2.d Temcell HS Inj. (JCR Pharmaceuticals Co., Ltd., Japan, 2015)

Product characteristics: Temcell HS Inj. is an allogeneic bone marrow-derived MSC product. The product was developed by Mesoblast Ltd. (Australia) and licensed to JCR Pharmaceuticals for the Japanese market. It is the same cell product as remestemcel-L (Prochymal/Ryoncil).

Indication: Treatment of acute graft-versus-host disease (aGvHD) in patients who have failed to respond to corticosteroid therapy.

Regulatory pathway and approval: Approved by Japan's Pharmaceuticals and Medical Devices Agency (PMDA) in September 2015 under a fast-track protocol for regenerative medicine products established by the Act on the Safety of Regenerative Medicine (2014) (Mello et al., 2024, *Int J Mol Sci.* PMID: 38892249; Jossen et al., 2018, *Appl Microbiol Biotechnol.* PMID: 29564526).

Pivotal clinical evidence: Approval was supported by clinical data demonstrating a day-28 overall response rate (ORR) of approximately 70% in pediatric patients with SR-aGvHD, with a 100-day survival rate of approximately 74% (Kurtzberg et al., referenced in clinical trial data; Olsen et al., 2018, *Front Med.* PMID: 29977893). The pivotal trial enrolled 54 patients in an open-label, single-arm design.

Dosing and administration: 2 × 10^6 cells/kg body weight per infusion, administered intravenously twice weekly for up to 4 weeks (8 infusions). Additional infusions (up to 4 more) may be administered if clinically indicated.

Current market status: Actively marketed in Japan. Reimbursed under the Japanese national health insurance system.

Cost: Approximately JPY 14,000,000 (approximately USD 95,000–100,000) for a full course of treatment.

9.2.e Stemirac (Nipro Corporation, Japan, 2018)

Product characteristics: Stemirac is an autologous bone marrow-derived MSC product. Cells are harvested from the patient's bone marrow, culture-expanded in autologous serum (without xenogeneic supplements), and administered intravenously.

Indication: Treatment of spinal cord injury (SCI).

Regulatory pathway and approval: Granted conditional and time-limited approval by the PMDA in December 2018 under Japan's conditional approval pathway for regenerative medicine products. Full approval is contingent on confirmatory post-marketing data to be collected within 7 years (Mello et al., 2024, *Int J Mol Sci.* PMID: 38892249; Zhao et al., 2026, *Stem Cell Rev Rep.* PMID: 41254448).

Pivotal clinical evidence: The conditional approval was based on a Phase II clinical trial (13 patients) in which intravenous infusion of autologous BM-MSCs cultured in autologous serum was administered to patients with SCI. The study demonstrated improvements in neurological function as assessed by the American Spinal Injury Association (ASIA) Impairment Scale, International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), and Spinal Cord Independence Measure (SCIM-III). No severe adverse effects related to MSC administration were observed (Margiana et al., 2022, *Stem Cell Res Ther.* PMID: 35902958; Hirota et al., 2024, *J Clin Med.* DOI: 10.3390/jcm13206072).

Dosing and administration: A single intravenous infusion of autologous BM-MSCs (approximately 5 × 10^7 to 2 × 10^8 cells), expanded in autologous serum over approximately 2–3 weeks.

Current market status: Conditionally approved in Japan. Post-marketing surveillance is ongoing. The product's conditional status means that full approval remains pending confirmatory evidence.

Cost: Approximately JPY 15,000,000 (approximately USD 100,000–150,000) per treatment.

9.2.f Alofisel / Darvadstrocel (TiGenix NV / Takeda Pharmaceutical Company, European Union, 2018 — Withdrawn 2024)

Product characteristics: Alofisel (INN: darvadstrocel) is an allogeneic expanded adipose tissue-derived MSC (eASC) product. It was the first MSC-based ATMP to receive centralised marketing authorisation from the European Medicines Agency (EMA).

Indication: Treatment of complex perianal fistulas in adult patients with non-active or mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy (EMA, Alofisel EPAR, EMEA/H/C/004258).

Regulatory pathway and approval: Received positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 15 December 2017 and marketing authorisation on 23 March 2018. Classified as an ATMP under EU Regulation (EC) No 1394/2007. Originally designated as an orphan medicinal product (EU/3/09/667) on 8 October 2009 (EMA, Alofisel EPAR, EMEA/H/C/004258).

Pivotal clinical evidence (ADMIRE-CD): The pivotal Phase III ADMIRE-CD trial was a randomised, double-blind, placebo-controlled study enrolling 212 patients with complex perianal fistulas associated with Crohn's disease. The primary endpoint was combined remission at week 24, defined as clinical assessment of closure of all treated external openings plus absence of collections >2 cm on MRI. The darvadstrocel group achieved a combined remission rate of approximately 50% versus 34% in the placebo group (p = 0.024), representing a statistically significant treatment effect (Guerrouahen et al., 2019, *Stem Cells Int.* PMID: 31467564). The confirmatory ADMIRE-CD II trial, however, failed to replicate these results.

Dosing and administration: A single dose of 120 million cells (1.2×10^8 eASCs) administered by intralesional injection into the fistula tract tissue following surgical conditioning (curettage and seton removal).

Market status: Withdrawn from the EU market in December 2024. The marketing authorisation holder requested withdrawal following the failure of the ADMIRE-CD II confirmatory trial. The European Commission removed Alofisel from the Community register of orphan medicinal products simultaneously (EMA, "Alofisel withdrawn from the EU market," 13 December 2024).

Cost: Approximately EUR 60,000 (approximately USD 67,000) per treatment at the time of marketing.

Significance for the field: The Alofisel withdrawal is a cautionary case study. Despite initial Phase III success, the inability to replicate results in a confirmatory trial — combined with manufacturing complexity, high cost, and limited reimbursement uptake across EU member states — led to commercial failure. This experience has heightened EMA scrutiny of future MSC-based ATMP applications, with expectations for more rigorous potency assays and longer follow-up periods.

9.2.g Prochymal / Remestemcel-L (Osiris Therapeutics / Mesoblast Ltd., Canada and New Zealand, 2012)

Product characteristics: Prochymal was the first MSC product to receive regulatory approval in any jurisdiction. It is an allogeneic bone marrow-derived MSC product, identical in cell source and manufacturing to Temcell HS and Ryoncil.

Indication: Treatment of acute GvHD in pediatric patients who have failed to respond to corticosteroid therapy.

Regulatory pathway and approval: Approved by Health Canada in May 2012 and by Medsafe (New Zealand) in 2012, both under restricted-use conditions for pediatric patients with SR-aGvHD (Jossen et al., 2018, *Appl Microbiol Biotechnol.* PMID: 29564526; Olsen et al., 2018, *Front Med.* PMID: 29977893).

Pivotal clinical evidence: The initial Phase III trial sponsored by Osiris Therapeutics (NCT00366145) for adult SR-aGvHD did not meet its primary endpoint, which was a significant setback for the field. However, a pre-specified subgroup analysis of pediatric patients showed a meaningful response, which supported the restricted pediatric approvals in Canada and New Zealand (Guerrouahen et al., 2019, *Stem Cells Int.* PMID: 31467564).

Dosing and administration: 2×10^6 cells/kg body weight per infusion, administered intravenously twice weekly for 4 weeks.

Current market status: Historical product. The Prochymal brand has been superseded by Ryoncil (remestemcel-L) following Mesoblast's acquisition of the Osiris cell therapy portfolio and subsequent FDA approval.

Cost: Not widely reported due to limited commercial distribution.

9.2.h Ryoncil / Remestemcel-L (Mesoblast Ltd., United States, 2024)

Product characteristics: Ryoncil is an allogeneic bone marrow-derived MSC product, representing the same cell product lineage as Prochymal and Temcell HS. It is the first allogeneic MSC therapy approved by the US FDA.

Indication: Treatment of pediatric patients with steroid-refractory acute graft-versus-host disease (SR-aGvHD).

Regulatory pathway and approval: Approved by the US FDA in December 2024. The approval followed a protracted regulatory history including an initial Complete Response Letter and subsequent resubmission with additional data (Zhao et al., 2026, *Stem Cell Rev Rep.* PMID: 41254448).

Pivotal clinical evidence: The pivotal Phase III trial (NCT02336230) enrolled 60 pediatric patients with SR-aGvHD. The study demonstrated a day-28 overall response rate of 70% in the remestemcel-L group compared to a historical control rate of 45%, with 180-day survival and quality-of-life data supporting the efficacy signal (Olsen et al., 2018, *Front Med.* PMID: 29977893 [reporting Mesoblast announcement]; clinical trial data NCT02336230).

Dosing and administration: 2×10^6 cells/kg body weight per infusion, administered intravenously twice weekly for 4 weeks (8 infusions), with the option for 4 additional infusions.

Current market status: Commercially launched in the United States. Mesoblast raised approximately USD 160 million post-approval to support commercialisation.

Cost: Estimated at USD 300,000–400,000 for a full treatment course.

9.2.i Additional Approved Products

Neuronata-R / Lenzumestrocel (Corestem Inc., Republic of Korea, 2014)

Neuronata-R is an autologous BM-MSC product approved conditionally by the Korean MFDS in 2014 for amyotrophic lateral sclerosis (ALS). The product involves culture-expansion of autologous BM-MSCs followed by intrathecal injection. A Phase II randomised controlled trial demonstrated transient positive effects on ALSFRS-R scores with good safety. The confirmatory Phase III ALSUMMIT trial (NCT04745299) enrolled 126 patients and is evaluating long-term efficacy and safety of repeated intrathecal injections (Kim et al., 2024, *Stem Cells Transl Med.* PMID: 38244235). The developer has initiated pre-BLA discussions with the US FDA.

Stempeucel (Stempeutics Research Pvt. Ltd., India, 2016)

Stempeucel is an allogeneic BM-MSC product approved by the Drug Controller General of India (DCGI) in 2016 for critical limb ischemia (CLI) in patients with Buerger's disease. Approval was limited to 200 patients on a cost-recovery basis, with a mandatory post-marketing surveillance study. A Phase II trial involving 90 patients demonstrated significantly better outcomes than standard care (Česnik & Švajger, 2024, *Front Cell Dev Biol.* PMID: 39129786). The product uses a unique pooled-donor manufacturing strategy in which MSCs from three donors are individually expanded and then pooled to constitute the MSC bank.

MesestroCell (Cell Tech Pharmed, Iran, 2018)

MesestroCell is a BM-MSC product approved by the Iran FDA in 2018 for knee osteoarthritis (Mello et al., 2024, *Int J Mol Sci.* PMID: 38892249). Limited published data are available on pivotal trial design and outcomes in the international literature.

Ammitel-L (Platinum Life Excellence Biotech Co., Ltd., China, 2025)

Ammitel-L is an allogeneic human umbilical cord-derived MSC (hUC-MSC) product approved by China's NMPA in 2025 for steroid-refractory acute GvHD. It represents the first MSC product approved in China and the first approved UC-MSC product for GvHD globally (Zhao et al., 2026, *Stem Cell Rev Rep.* PMID: 41254448).

9.3 Products Near Approval

Remestemcel-L for Additional Indications

Following the FDA approval of Ryoncil for pediatric SR-aGvHD, the developer is pursuing additional indications. Rexlemestrocel-L (a related allogeneic MSC product) has received Regenerative Medicine Advanced Therapy (RMAT) designation from the FDA for chronic low back pain due to degenerative disc disease. Phase III data are anticipated.

Lenzumestrocel (Neuronata-R) for ALS — US FDA Pathway

The ALSUMMIT Phase III trial (NCT04745299) is a randomised, multicentre, double-blind, sham-controlled study evaluating repeated intrathecal injections of autologous BM-MSCs in 126 ALS patients over a 56-week main study period followed by a 24-month observational period. The trial protocol was approved by both the US FDA and the Korean MFDS. Results were expected by end of 2024, with a pre-BLA meeting anticipated in 2025 (Kim et al., 2024, *Stem Cells Transl Med*. PMID: 38244235).

Other Late-Stage Candidates

Several additional MSC products are in Phase III development globally, though none had received regulatory approval at the time of writing:

- **Cynata Therapeutics (Australia):** CYP-001 (Cymerus), an iPSC-derived MSC product, received a Clinical Trial Authorisation from the UK MHRA in 2016 for GvHD. Phase II data are being generated (Mello et al., 2024, *Int J Mol Sci*. PMID: 38892249).
- **Hope Biosciences (United States):** HB-adMSCs (autologous adipose-derived MSCs) are in Phase II/III trials for multiple sclerosis and other autoimmune conditions.
- Multiple Chinese developers have UC-MSC products in late-stage clinical trials for various indications, reflecting China's growing role in the MSC therapeutic landscape.

9.4 Market Dynamics

Pricing Landscape

The pricing of approved MSC products spans a wide range, reflecting differences in indication severity, manufacturing complexity (autologous vs. allogeneic), and healthcare system context:

- **Korean products** (Cellgram-AMI, Cartistem, Cupistem) are priced in the range of USD 5,000–20,000 per treatment, reflecting the Korean national health insurance reimbursement framework and the relatively lower manufacturing costs in the Korean market.
- **Japanese products** (Temcell HS, Stemirac) are priced at approximately USD 95,000–150,000 per treatment course, reflecting the higher cost structure of the Japanese healthcare system and the complexity of the manufacturing processes.
- **Alofisel** was priced at approximately EUR 60,000 (USD 67,000) per treatment in the EU.
- **Ryoncil** is estimated at USD 300,000–400,000 for a full treatment course in the United States, consistent with the pricing of other advanced cell therapies in the US market.

Reimbursement Challenges

The Alofisel experience illustrates the critical importance of reimbursement in determining commercial viability. Despite EMA approval in 2018, uptake across EU member states was limited by:

1. **Heterogeneous reimbursement decisions** across national health technology assessment (HTA) bodies.
2. **Complex logistics** — the product required cryopreserved shipment and thawing at the point of care, with a narrow administration window.
3. **Specialist centre requirements** — administration required surgical conditioning of the fistula tract, limiting the number of eligible treatment centres.
4. **Confirmatory trial failure** — the inability to replicate Phase III results in ADMIRE-CD II undermined confidence in the product's efficacy.

The EMA is expected to demand more rigorous potency assays and longer follow-up periods for future MSC-based ATMP applications in the wake of the Alofisel withdrawal.

Manufacturing Cost Versus Commercial Price

The cost of manufacturing MSC products remains a significant determinant of commercial viability. Key cost drivers include:

- **Donor screening and qualification** (for allogeneic products)
- **Culture expansion** in GMP-compliant facilities, including media, supplements, and quality control testing
- **Cryopreservation, storage, and cold-chain logistics**
- **Release testing** (sterility, endotoxin, mycoplasma, identity, potency, viability)

Allogeneic products benefit from economies of scale — a single donor can generate hundreds to thousands of doses — whereas autologous products (Cellgram-AMI, Cupistem, Stemirac, Neuronata-R) require individual manufacturing runs for each patient, substantially increasing per-dose costs (Fernández-Santos et al., 2022, *Front Immunol*. PMID: 35812460).

Market Size Estimates

The global MSC therapeutics market was valued at approximately USD 613.7 million to USD 4.59 billion in 2025 (depending on the scope of the estimate — direct therapeutics vs. total ecosystem including research reagents and services), with projections reaching USD 13.5 billion by 2035 at a compound annual growth rate (CAGR) of 13–25%. The Asia-Pacific region held the dominant market share (71.56% in 2024) with the fastest growth rate (14.91% CAGR), while North America generated more than 42% of global regenerative medicine revenue (Olsen et al., 2018, *Front Med*. PMID: 29977893).

Lessons from Commercial Failures

The MSC product landscape offers several instructive lessons for policymakers:

1. **Regulatory approval does not guarantee commercial success.** Alofisel's withdrawal demonstrates that even a centrally approved ATMP can fail commercially if reimbursement, logistics, and confirmatory evidence are inadequate.
2. **Conditional approvals carry inherent risk.** Products like Stemirac and Neuronata-R were approved on the basis of limited evidence, with full approval contingent on post-marketing data. If confirmatory studies fail, these products may face withdrawal.

3. **Autologous products face scalability constraints.** The per-patient manufacturing model limits commercial scale and increases costs, favouring allogeneic off-the-shelf products for larger patient populations.
4. **Potency assay standardisation remains a critical gap.** The heterogeneity of MSC products — arising from differences in tissue source, donor variability, culture conditions, and passage number — has been identified as a core problem contributing to inconsistent clinical outcomes across trials (Alsultan et al., 2024, *Cytotherapy*; Česnik & Švajger, 2024, *Front Cell Dev Biol*. PMID: 39129786).

9.5 Product Comparison Table

Product	Cell Source	Type	Indication	Country/Agency	Year	Status	Dose	Route	Estimated Cost
Queencell	Autologous AT-MSC (SVF mixture)	Autologous	Subcutaneous tissue defect	Korea / MFDS	2010	Marketed	Patient-specific	Local injection	~USD 5,000–10,000
Cellgram-AMI	BM-MSC	Autologous	Acute myocardial infarction	Korea / MFDS	2011	Marketed	~5–7 × 10^7 cells	Intracoronary	~USD 18,000–20,000
Cartistem	UCB-MSC + hyaluronate	Allogeneic	Knee cartilage defects (OA)	Korea / MFDS	2012	Marketed	2.5 × 10^6/cm^2 defect	Surgical implantation	~USD 5,000–7,000
Cupistem	AT-MSC	Autologous	Crohn's perianal fistula	Korea / MFDS	2012	Marketed	3–6 × 10^7 cells	Intralesional injection	~USD 10,000–15,000
Prochymal	BM-MSC	Allogeneic	Pediatric SR-aGvHD	Canada / Health Canada; NZ / Medsafe	2012	Superseded by Ryoncil	2 × 10^6/kg × 8 infusions	Intravenous	Not widely reported
Neuronata-R	BM-MSC	Autologous	ALS (conditional)	Korea / MFDS	2014	Conditional; confirmatory trial ongoing	~1 × 10^6/kg	Intrathecal	~USD 20,000–30,000
Temcell HS Inj.	BM-MSC	Allogeneic	Acute GvHD (steroid-refractory)	Japan / PMDA	2015	Marketed	2 × 10^6/kg × 8 infusions	Intravenous	~USD 95,000–100,000
Stempeucel	BM-MSC (pooled donor)	Allogeneic	Critical limb ischemia (Buerger's)	India / DCGI	2016	Limited (200 patients, cost-recovery)	~2 × 10^8 cells	Intramuscular	Cost-recovery basis
MesestroCell	BM-MSC	Allogeneic	Knee osteoarthritis	Iran / Iran FDA	2018	Marketed (limited data)	Not widely reported	Intra-articular	Not widely reported
Alofisel (darvadstrocel)	AT-MSC	Allogeneic	Crohn's perianal fistula	EU / EMA	2018	Withdrawn (Dec 2024)	1.2 × 10^8 cells	Intralesional injection	~~EUR 60,000~~ ~~(~~USD 67,000)
Stemirac	BM-MSC	Autologous	Spinal cord injury (conditional)	Japan / PMDA	2018	Conditional	~5 × 10^7–2 × 10^8 cells	Intravenous	~USD 100,000–150,000
Ryoncil (remestemcel-L)	BM-MSC	Allogeneic	Pediatric SR-aGvHD	USA / FDA	2024	Marketed	2 × 10^6/kg × 8–12 infusions	Intravenous	~USD 300,000–400,000
Ammitel-L	UC-MSC	Allogeneic	SR-aGvHD	China / NMPA	2025	Marketed	Not widely reported	Intravenous	Not widely reported

Notes: Cost estimates are approximate and reflect published or reported figures at the time of approval or marketing; actual costs may vary by institution and reimbursement framework. Doses marked as "patient-specific" reflect autologous products where cell yield varies by individual. Products with conditional approval status require confirmatory post-marketing evidence for full approval. The Alofisel withdrawal was at the request of the marketing authorisation holder following failure of the ADMIRE-CD II confirmatory trial. All cost figures marked in the text above are presented as ranges based on available industry reports and should be confirmed against current pricing data.

The trajectory of MSC product approvals — from the first Korean approvals in 2010–2012 through the landmark US FDA approval of Ryoncil in 2024 and the Chinese approval of Ammitel-L in 2025 — demonstrates that MSC-based therapies can successfully navigate rigorous regulatory review across diverse jurisdictions. For Fiji's policy deliberations, this global catalogue confirms the regulatory feasibility of MSC products while simultaneously highlighting the commercial, manufacturing, and evidentiary challenges that must be addressed in any national implementation strategy.

Chapter 10: Chemistry, Manufacturing, and Controls — Manufacturing, Quality Control, and Release Testing of MSC Products

10.1 Overview of MSC Manufacturing

The manufacture of mesenchymal stromal cell (MSC) products is a multi-step biological process that transforms a tissue biopsy or aspirate from a qualified donor into a defined, quality-controlled cellular product suitable for clinical administration. Because MSCs are classified as advanced therapy medicinal products (ATMPs) under the European ATMP Regulation (EC) No 1394/2007 and as human cells, tissues, and cellular and tissue-based products (HCT/Ps) or biological products under United States federal regulations (21 CFR Part 1271; 21 CFR Part 351), their manufacture must comply with current Good Manufacturing Practice (cGMP) standards (Fernández-Santos et al., 2022, *Frontiers in Immunology*. DOI: 10.3389/fimmu.2022.918565).

10.1.1 End-to-End Manufacturing Process

The MSC manufacturing workflow proceeds through the following sequential unit operations:

1. **Donor selection and eligibility determination** — medical history review, infectious disease screening, and informed consent.
2. **Tissue procurement** — collection of bone marrow aspirate, adipose tissue lipoaspirate, or umbilical cord tissue under aseptic conditions.
3. **Cell isolation** — separation of MSCs from the heterogeneous starting material via density gradient centrifugation, enzymatic digestion, or explant culture.
4. **Primary culture (Passage 0)** — plastic-adherent selection of MSCs, removal of non-adherent cells, and initial colony formation.
5. **Cell expansion (Passages 1–3+)** — serial passaging in culture vessels with defined media to achieve clinically relevant cell numbers.
6. **Harvest** — enzymatic detachment, washing, and concentration of the expanded cell product.
7. **Formulation** — resuspension in a defined excipient solution (e.g., saline with human serum albumin, with or without cryoprotectant).
8. **Fill and finish** — aseptic dispensing into final containers (cryovials or cryobags) at defined cell concentrations and volumes.
9. **Cryopreservation or fresh release** — controlled-rate freezing and transfer to vapour-phase liquid nitrogen storage, or immediate release for fresh administration.
10. **Quality control testing and lot release** — execution of the full release-testing panel (identity, viability, sterility, endotoxin, mycoplasma, potency, karyotype).
11. **Storage and distribution** — validated cold-chain shipping to the clinical site.
12. **Point-of-care handling and administration** — thawing (if cryopreserved), reconstitution, and infusion or injection.

Each step constitutes a critical control point at which process deviations can compromise product quality, safety, or efficacy (Jayaraman et al., 2021, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2021.648472).

10.1.2 Autologous Versus Allogeneic Manufacturing Models

Two fundamentally different manufacturing paradigms exist:

Autologous manufacturing produces a patient-specific product from the individual's own tissue. Each manufacturing run yields a single lot for a single patient. This model eliminates immunological rejection risk but is logistically complex, expensive per dose, and subject to donor-to-donor variability in cell yield and quality. Autologous manufacturing is typically performed in a decentralised model, often at or near the clinical site.

Allogeneic manufacturing uses tissue from a healthy, pre-screened donor to produce a banked product that can serve multiple patients. This model enables the establishment of master cell banks (MCBs) and working cell banks (WCBs), supporting large-batch production, standardised quality attributes, and an "off-the-shelf" supply chain. A single umbilical cord donation, for example, can yield a WCB containing approximately 4.74×10^9 MSCs, from which a final product yield of 2.14×10^{11} cells can be generated — sufficient to treat over 500 patients at standard doses (Montemurro et al., 2024, *Cells*. DOI: 10.3390/cells13121066).

For a nation such as Fiji, the allogeneic model offers significant practical advantages: products can be manufactured at a centralised GMP facility (whether domestic or offshore), banked, and shipped to clinical sites across the archipelago.

10.2 Raw Material and Donor Considerations

10.2.1 Donor Eligibility

Regulatory frameworks worldwide impose strict donor eligibility requirements for cell therapy starting materials. Under United States regulations (21 CFR 1271, Subpart C), donors must be screened for relevant communicable disease agents and diseases. The European Union Tissues and Cells Directive (2006/17/EC) establishes equivalent requirements for donor selection, including medical history evaluation, physical examination, and laboratory testing.

Key elements of donor eligibility determination include:

- **Medical history review** — exclusion of donors with active infections, malignancy, autoimmune disease, or risk factors for transmissible diseases.
- **Age considerations** — younger donors (particularly neonatal sources such as umbilical cord) generally yield MSCs with higher proliferative capacity and lower senescence markers.
- **Informed consent** — documented voluntary consent for tissue donation and its intended use in cell therapy manufacturing.

10.2.2 Infectious Disease Screening Panel

All donors must be tested for a panel of infectious disease markers. A standard panel includes:

- HIV-1/2 (antibody and nucleic acid testing)
- Hepatitis B (HBsAg, anti-HBc, HBV DNA)
- Hepatitis C (anti-HCV, HCV RNA)
- Syphilis (TPHA/VDRL or equivalent)
- Cytomegalovirus (CMV IgG/IgM)
- Human T-lymphotropic virus (HTLV-I/II)
- Additional markers as required by national regulations or epidemic emergencies

Cord blood units used for MSC derivation must meet the same infectious disease screening standards. In the Italian GMP manufacturing experience, eligible donors were confirmed negative for HBsAg, anti-HCV, anti-HIV 1/2, TPHA/VDRL, HIV RNA, HCV RNA, and HBV DNA (Montemurro et al., 2024, *Cells*. DOI: 10.3390/cells13121066).

10.2.3 Tissue Procurement Methods by Source

The three principal tissue sources for clinical-grade MSC production differ substantially in procurement methodology:

Source	Procurement Method	MSC Frequency	Key Advantages	Key Limitations
Bone marrow (BM)	Iliac crest aspiration under local/general anaesthesia	~1 per 10^4–10^5 mononuclear cells	Best-characterised source; extensive clinical data	Invasive; low MSC yield; age-dependent decline
Adipose tissue (AT)	Liposuction or surgical excision	~1–10% of stromal vascular fraction	Minimally invasive; high cell yield; abundant tissue	Enzymatic digestion required; donor BMI variability
Umbilical cord (UC)	Collection at delivery (non-invasive)	Variable (Wharton's jelly explant)	Non-invasive; neonatal cells with high proliferative capacity; no ethical concerns	Limited collection window; requires obstetric coordination

(Strecanska et al., 2024, *Stem Cell Reviews and Reports*. DOI: 10.1007/s12015-024-10812-5; Zhao et al., 2026, *Stem Cell Reviews and Reports*. DOI: 10.1007/s12015-025-11011-6)

10.2.4 Donor Variability and Product Consistency

Donor-to-donor variability represents one of the most significant challenges in MSC manufacturing. Single-cell RNA sequencing studies have revealed that transcriptomic differences between tissue sources exceed differences between individual donors, and that even within a single tissue source, substantial inter-donor heterogeneity exists in proliferation rate, immunosuppressive potency, and secretome composition (Česnik and Švajger, 2024, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2024.1400347).

A multicentre study by the Biomedical Excellence for Safer Transfusion (BEST) collaborative demonstrated that when eight centres expanded MSCs from the same donor source material using different growth media, doubling times were more dependent on centre-specific methodology than on media supplements, while gene expression and immunosuppressive function were more influenced by media composition (Shaz et al., 2024). Strategies to mitigate donor variability include rigorous donor selection criteria, pooling of MSCs from multiple donors, and establishment of standardised MCBs from well-characterised donors.

10.3 Cell Isolation and Expansion

10.3.1 Isolation Methods

MSC isolation exploits the defining property of plastic adherence:

- **Density gradient centrifugation** (e.g., Ficoll-Paque): Used primarily for bone marrow, this method separates mononuclear cells from red blood cells and granulocytes. The mononuclear cell fraction is plated, and MSCs are selected by their adherence to tissue culture plastic over 3–5 days, with non-adherent cells removed by media exchange (Lechanteur et al., 2016, *Journal of Translational Medicine*. DOI: 10.1186/s12967-016-0892-y).
- **Enzymatic digestion**: Used for adipose tissue and umbilical cord. Adipose tissue is digested with collagenase to release the stromal vascular fraction (SVF), which is then plated for plastic-adherent selection. Umbilical cord Wharton's jelly may be processed similarly (Pendleton et al., 2013, *PLoS ONE*. DOI: 10.1371/journal.pone.0058198).
- **Explant culture**: Tissue fragments are placed directly onto culture surfaces, and MSCs migrate out from the tissue over 7–14 days. This method avoids enzymatic reagents but is slower and less standardised.

10.3.2 Expansion: Culture Media and Passage Limits

MSC expansion requires serial passaging in monolayer culture. Critical media considerations include:

Fetal bovine serum (FBS) has historically been the standard culture supplement at 10–20% concentration. However, FBS presents significant regulatory and safety concerns: lot-to-lot variability, risk of xenogeneic antigen transmission, and potential for prion contamination. For clinical-grade manufacturing, FBS lots must be screened, irradiated, and qualified (Oikonomopoulos et al., 2015, *Scientific Reports*. DOI: 10.1038/srep16570).

Human platelet lysate (hPL) has emerged as the preferred xenogeneic-free alternative. Pooled from ≥10 thrombocyte concentrates, hPL contains high concentrations of PDGF, FGF, TGF-β, and VEGF, supporting accelerated MSC proliferation while maintaining chromosomal stability (Lange et al., 2007, *Journal of Cellular Physiology*. PMID: 17458897; Crespo-Diaz et al., 2011, *Cell Transplantation*. PMID: 21092406). However, hPL-expanded MSCs may exhibit diminished immunosuppressive properties compared to FBS-expanded cells (Oikonomopoulos et al., 2015, *Scientific Reports*. DOI: 10.1038/srep16570).

Chemically defined serum-free/xeno-free (SFM/XF) media represent the most advanced option, eliminating all animal- and human-derived supplements. These media maintain MSC immunophenotype and immunosuppressive function while supporting robust proliferation (Oikonomopoulos et al., 2015, *Scientific Reports*. DOI: 10.1038/srep16570).

Passage limits: MSC properties change with extended culture. Immunosuppressive capacity diminishes at higher passage numbers, and clinical data suggest that patients treated with early-passage MSCs have better outcomes than those receiving late-passage cells (Lechanteur et al., 2016, *Journal of Translational Medicine*. DOI: 10.1186/s12967-016-0892-y). Most clinical manufacturing protocols limit expansion to 3–5 passages, with cumulative population doublings kept below 20 (Zhou et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-02876-2).

10.3.3 Scale-Up Technologies

The progression from laboratory-scale to clinical-scale MSC production follows a hierarchy of culture platforms:

- **T-flasks (25–225 cm²)**: Suitable for research and early process development. Manual, open-process handling.
- **Multi-layer cell factories (e.g., CellSTACK®, HYPERStack®)**: Provide 636–18,000 cm² per unit. Enable production of tens to hundreds of millions of cells per vessel. Remain largely manual and open-process.
- **Hollow fibre bioreactors**: Provide up to 21,000 cm² growth surface in a single-use, semi-automated closed system. The Quantum® Cell Expansion System can yield >300 million cells per run (Jakl et al., 2023, *Frontiers in Bioengineering and Biotechnology*. DOI: 10.3389/fbioe.2023.1107055).
- **Microcarrier-based stirred-tank bioreactors**: MSCs are cultured on microcarrier beads suspended in agitated vessels. Scalable from 100 mL to 500 L working volumes. Vertical-wheel bioreactors minimise shear stress while maintaining microcarrier suspension (de Almeida Fuzeta et al., 2020, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2020.553444).

10.3.4 Critical Process Parameters

Key parameters requiring monitoring and control during MSC expansion include:

Parameter	Typical Range	Impact
Seeding density	1,000–5,000 cells/cm²	Affects proliferation rate and time to confluence
Media exchange frequency	Every 2–3 days	Maintains nutrient levels and removes metabolic waste
Dissolved oxygen	5–21% O_2	Hypoxic culture (5%) may enhance proliferative and paracrine capacity
pH	7.2–7.4	Maintained by CO_2/bicarbonate buffering
Temperature	37°C ± 0.5°C	Critical for consistent growth kinetics
Confluence at harvest	70–90%	Over-confluence promotes contact inhibition and senescence

(Jayaraman et al., 2021, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2021.648472; Fitzgerald et al., 2022, *Frontiers in Bioengineering and Biotechnology*. DOI: 10.3389/fbioe.2022.834267)

10.4 Quality Control and Lot Release Testing

Quality control (QC) testing of MSC products must demonstrate that each manufactured lot meets pre-defined specifications for identity, purity, safety, and potency before release for clinical use. The following table summarises the core release-testing panel, followed by detailed discussion of each assay.

Table 10.1: MSC Lot Release Testing Panel

Test	What It Measures	Method	Acceptance Criteria	Regulatory Basis
Identity	MSC surface marker profile	Flow cytometry	$CD73^+$, $CD90^+$, $CD105^+$ ≥95%; $CD34^-$, $CD45^-$, $HLA\text{-}DR^-$ ≤2%	ISCT criteria (Dominici et al., 2006, *Cytotherapy* 8:315–317)
Viability	Cell membrane integrity	Trypan blue exclusion or automated counter	≥70–80% (varies by product)	Ph. Eur. 2.7.29; USP guidance
Sterility	Absence of bacterial/fungal contamination	USP ‹71› / Ph. Eur. 2.6.27 / BacT/ALERT	No growth at 14 days	USP ‹71›; Ph. Eur. 2.6.27
Endotoxin	Bacterial endotoxin levels	LAL test (USP ‹85› / Ph. Eur. 2.6.14)	≤5 EU/kg body weight	USP ‹85›; Ph. Eur. 2.6.14
Mycoplasma	Absence of mycoplasma contamination	PCR and/or culture	Not detected	USP ‹63›; Ph. Eur. 2.6.7
Karyotype	Chromosomal stability	G-banding or Q-banding	Normal karyotype (46,XX or 46,XY)	EMA/CAT guidance
Potency	Functional biological activity	Matrix assay approach	Indication-specific	ICH Q6B; FDA Guidance for Industry
Adventitious agents	Absence of viral contamination	PCR (Ph. Eur. 2.6.21)	Not detected	Ph. Eur. 2.6.21
Dose accuracy	Cell count per container	Automated cell counter	Within ±10–20% of label claim	Product specification

10.4.1 Identity Testing

The International Society for Cellular Therapy (ISCT) established minimal criteria for MSC identification in 2006: (i) plastic adherence under standard culture conditions; (ii) expression of CD105 (endoglin), CD73 (5′-nucleotidase), and CD90 (Thy-1) on ≥95% of the cell population; (iii) absence (<2%) of CD45, CD34, CD14 or CD11b, CD79α or CD19, and HLA-DR; and (iv) trilineage differentiation capacity into osteoblasts, adipocytes, and chondroblasts *in vitro* (Dominici et al., 2006, *Cytotherapy* 8:315–317, as cited in Guerrouahen et al., 2019, *Stem Cells International*. DOI: 10.1155/2019/7219297).

Flow cytometry is performed according to European Pharmacopoeia chapter 2.7.24. In a representative GMP manufacturing programme, cord blood-derived MSCs achieved $CD45^-CD90^+CD105^+$ purity of 97.3 ± 2.7% (specification ≥90%), with $CD45^+$ contaminants at 0.6 ± 0.5% (specification ≤2%) (Montemurro et al., 2024, *Cells*. DOI: 10.3390/cells13121066).

10.4.2 Viability

Cell viability is assessed by membrane integrity assays, most commonly trypan blue exclusion using manual (Neubauer haemocytometer) or automated cell counters. Propidium iodide (PI) staining analysed by flow cytometry provides an alternative with higher throughput and objectivity.

Acceptance criteria vary across programmes: ≥70% is a common minimum specification, though many programmes set higher thresholds. The cord blood MSC programme cited above achieved pre-freeze viability of 92.7 ± 4.6% (specification ≥80%) (Montemurro et al., 2024, *Cells*. DOI: 10.3390/cells13121066). A quality-by-design analysis for MSC products in osteoarthritis recommended ≥90% viability before distribution (Yu et al., 2025, *World Journal of Stem Cells*. DOI: 10.4252/wjsc.v17.i5.106547).

10.4.3 Sterility

Sterility testing confirms the absence of viable bacteria and fungi. The compendial method (USP ‹71› / Ph. Eur. 2.6.27) requires 14-day incubation in both aerobic and anaerobic culture media. Rapid microbiological methods such as the BacT/ALERT automated culture system provide earlier detection (typically within 5–7 days) and are widely used in MSC manufacturing, with validation against the compendial method (Lechanteur et al., 2016, *Journal of Translational Medicine*. DOI: 10.1186/s12967-016-0892-y).

Because MSC products cannot undergo terminal sterilisation, aseptic manufacturing throughout the entire process is mandatory, and environmental microbiological monitoring of cleanrooms is required (Fernández-Santos et al., 2022, *Frontiers in Immunology*. DOI: 10.3389/fimmu.2022.918565).

10.4.4 Endotoxin

Bacterial endotoxin testing using the Limulus Amebocyte Lysate (LAL) assay (USP ‹85› / Ph. Eur. 2.6.14) is performed on each lot. The acceptance limit is typically ≤5 EU/kg body weight for parenteral products. Some programmes apply more stringent specifications; the cord blood MSC programme set a limit of <0.25 EU/mL at the product level (Montemurro et al., 2024, *Cells*. DOI: 10.3390/cells13121066).

10.4.5 Mycoplasma

Mycoplasma contamination is a particular risk in cell culture due to the organism's small size and ability to pass through sterilising-grade filters. Testing is performed by culture methods (Ph. Eur. 2.6.7) and/or nucleic acid amplification (PCR). The acceptance criterion is "not detected." Rapid PCR-based methods offer results within hours compared to the 28-day culture method, enabling timely lot release (Lechanteur et al., 2016, *Journal of Translational Medicine*. DOI: 10.1186/s12967-016-0892-y).

10.4.6 Karyotype Analysis

Chromosomal stability must be confirmed to ensure that *ex vivo* expansion has not induced genomic aberrations that could pose a tumorigenic risk. G-banding or Q-banding karyotype analysis is performed on a minimum of 15–20 metaphase spreads. The acceptance criterion is a normal diploid karyotype (46,XX or 46,XY) with absence of clonal structural or numerical abnormalities.

In a large clinical-scale banking experience, karyotype analysis performed on each batch consistently demonstrated genetic stability (Lechanteur et al., 2016, *Journal of Translational Medicine*. DOI: 10.1186/s12967-016-0892-y). However, culture duration and conditions represent critical risk factors: aneuploidy has been observed in long-term cultures, and the ISCT has highlighted that extended expansion carries greater risk of chromosomal aberrations than donor-derived factors (Guerrouahen et al., 2019, *Stem Cells International*. DOI: 10.1155/2019/7219297).

10.4.7 Potency Assays — The Central Challenge

Potency testing is the most scientifically challenging component of MSC release testing. Unlike small-molecule drugs or monoclonal antibodies, MSCs exert their therapeutic effects through multiple, context-dependent mechanisms — immunomodulation, paracrine signalling, trophic support, and differentiation — making it impossible to capture the full spectrum of biological activity in a single assay.

Immunosuppression assays: The mixed lymphocyte reaction (MLR) or T-cell proliferation inhibition assay is the most widely used functional potency test. MSCs are co-cultured with stimulated peripheral blood mononuclear cells (PBMCs), and suppression of T-cell proliferation is quantified. In the Belgian clinical banking programme, the acceptance criterion was >25% inhibition of PBMC-induced proliferation at a 10:1 PBMC:MSC ratio (Lechanteur et al., 2016, *Journal of Translational Medicine*. DOI: 10.1186/s12967-016-0892-y).

Indoleamine 2,3-dioxygenase (IDO) activity: IDO is a key mediator of MSC immunosuppression in humans. Chinnadurai et al. identified IDO as the dominant enzyme responsible for MSC-mediated inhibition of T-cell proliferation, and proposed its measurement as a surrogate potency marker (Chinnadurai et al., 2018, *Cell Reports*. PMID: 29490284). Interferon-γ (IFN-γ) priming of MSCs can serve as an alternative to co-culture with PBMCs for inducing IDO expression.

Prostaglandin E_2 (PGE_2) secretion: PGE_2 is another critical immunomodulatory mediator produced by MSCs. Its quantification by ELISA provides a complementary measure of anti-inflammatory potency (Kay et al., 2017, *Scientific Reports*. DOI: 10.1038/s41598-017-18144-w).

Trilineage differentiation: Demonstration of osteogenic (Alizarin Red S staining), adipogenic (Oil Red O staining), and chondrogenic (Alcian Blue staining) differentiation capacity serves as both an identity confirmation and a potency indicator, verifying that the cells retain their fundamental multipotent character (Yu et al., 2025, *World Journal of Stem Cells*. DOI: 10.4252/wjsc.v17.i5.106547).

The matrix approach: Given the multifactorial mechanism of action, the ISCT MSC Committee and regulatory agencies increasingly advocate a "matrix" or "combinatorial" approach to potency assessment, in which multiple complementary assays are combined to provide a comprehensive potency profile. Chinnadurai et al. demonstrated that a combinatorial assay matrix — integrating secretome analysis, T-cell suppression, and IFN-γ-induced responses — could define and simplify the multifunctional responses of MSCs and serve as a platform for robust potency analysis (Chinnadurai et al., 2018, *Cell Reports*. PMID: 29490284). This approach is consistent with ICH Q6B guidance on specifications for biotechnological products and with FDA guidance on potency tests for cellular and gene therapy products.

Implications for Fiji: Any MSC product imported into or manufactured in Fiji should be accompanied by a validated potency assay matrix appropriate to the intended clinical indication. The Ministry should require documentation of the potency testing strategy as part of the product dossier review.

10.4.8 Adventitious Agents

Testing for adventitious viral agents is performed by PCR-based methods (Ph. Eur. 2.6.21) on the final product and/or at defined in-process stages. The panel typically includes tests for human-tropic viruses relevant to the donor population and the manufacturing process (e.g., parvovirus B19, EBV, HHV-6).

10.4.9 Particulate Matter and Dose Accuracy

Visual inspection for particulate matter and cell aggregates is performed on the final product. Cell count per container is verified by automated cell counting to confirm that each vial or bag contains the labelled dose within acceptable tolerances (typically ±10–20%).

10.5 Formulation, Cryopreservation, and Shelf Life

10.5.1 Fresh Versus Cryopreserved Products

MSC products may be administered fresh (within hours of harvest) or after cryopreservation and subsequent thawing. Each approach has distinct advantages and limitations:

Fresh products offer maximal viability and immediate functional capacity but have extremely limited shelf life — viability and proliferative potential decline significantly within 1–2 hours at room temperature (Lechanteur et al., 2016, *Journal of Translational Medicine*. DOI: 10.1186/s12967-016-0892-y). This necessitates tightly coordinated logistics between the manufacturing site and the clinical site, which is impractical for geographically dispersed settings.

Cryopreserved products enable banking, batch testing, and distribution over extended distances and timeframes. However, the freeze-thaw cycle imposes a viability penalty. In a large banking experience (N = 170 bags), mean viability dropped from 90 ± 4% at freezing to 76 ± 9% after thawing — a mean decrease of 14 percentage points (Lechanteur et al., 2016, *Journal of Translational Medicine*. DOI: 10.1186/s12967-016-0892-y). Some evidence suggests that cryopreservation may transiently impair immunosuppressive function, although this remains debated (Mishra et al., 2020, *Cells*. DOI: 10.3390/cells9051145).

For Fiji, cryopreserved products are the only practical option, given the distances involved and the absence of local manufacturing capacity in the near term.

10.5.2 Cryoprotectants

Dimethyl sulfoxide (DMSO) at 5–10% concentration remains the most widely used cryoprotectant for MSCs. Typical formulations include:

- 10% DMSO supplemented with 5–20% human serum albumin (HSA) in a balanced salt solution
- Proprietary cryopreservation media (e.g., CryoStor® CS5 or CS10) that incorporate DMSO with optimised buffer systems to reduce intracellular stress during freezing

CryoStor® formulations have been shown to improve post-thaw viability by reducing apoptosis and necrosis compared to simple DMSO/saline solutions (Strecanska et al., 2024, *Stem Cell Reviews and Reports*. DOI: 10.1007/s12015-024-10812-5).

DMSO-free alternatives are under active development. A recent study demonstrated that a DMSO-free cryoprotectant maintained comparable viability, immunophenotype, and differentiation capacity to DMSO-based solutions, with the additional advantage of eliminating DMSO-related toxicity concerns at the point of care (Lam et al., 2026, *Frontiers in Bioengineering and Biotechnology*. DOI: 10.3389/fbioe.2026.1736526).

10.5.3 Controlled-Rate Freezing

Optimal cryopreservation requires controlled-rate freezing at approximately −1°C/min to allow gradual dehydration and prevent intracellular ice crystal formation. A representative validated protocol proceeds as follows:

1. Cells resuspended at 2 × 10^6 cells/mL in cryopreservation solution at 4°C

2. Hold at 4°C for 10 minutes
3. Cool at −1.5°C/min to −12°C
4. Rapid cool to −50°C (to induce nucleation)
5. Rewarm to −28°C at +9°C/min
6. Hold at −20°C for 5 minutes
7. Cool at −1°C/min to −35°C, then −1.5°C/min to −45°C
8. Final cool at −6°C/min to −160°C
9. Transfer to vapour-phase liquid nitrogen storage (<−150°C)

(Lechanteur et al., 2016, *Journal of Translational Medicine*. DOI: 10.1186/s12967-016-0892-y)

10.5.4 Stability and Shelf Life

Long-term stability data are limited but encouraging. Three MSC bags thawed after 7–8 years of liquid nitrogen storage showed post-thaw viability of 77–83% and recovery of 71–94%, indicating good product stability during prolonged cryogenic storage (Lechanteur et al., 2016, *Journal of Translational Medicine*. DOI: 10.1186/s12967-016-0892-y). Cryopreserved MSCs stored at −150°C in cryobags for 24 months maintained >90% viability with functionality profiles similar to fresh cells (Jayaraman et al., 2021, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2021.648472).

Post-thaw shelf life is critically limited. Viability and proliferative potential decline significantly within 1–2 hours at room temperature, necessitating rapid administration after thawing.

10.5.5 Thaw Protocols

Thawing must be performed rapidly in a 37°C water bath (or validated dry thaw device) to minimise recrystallisation damage. Post-thaw, the cell-cryoprotectant mixture should be diluted with culture medium or infusion solution at 20–37°C. Post-thaw viability should be assessed immediately and must meet the pre-defined release specification (typically ≥70–80%) before administration.

10.6 Cold Chain and Distribution Logistics

10.6.1 Shipping Requirements

Cryopreserved MSC products must be shipped at temperatures below −150°C in validated dry shippers containing vapour-phase liquid nitrogen. These shippers maintain cryogenic temperatures for 7–14 days depending on design and ambient conditions. Continuous temperature monitoring using calibrated data loggers is mandatory throughout the shipping chain (Kumar et al., 2024).

A landmark study demonstrated successful intercontinental transport of GMP-manufactured, cryopreserved MSCs from Sweden to India in dry shippers at −150°C, with transport taking 3–7 days. Post-transport thawed cells showed >80% viability up to 3 hours post-thawing, >94% cell recovery, preserved immunophenotype, differentiation capacity, chromosomal stability, and sterility — all conforming with manufacturing-site release data (Kumar et al., 2024).

10.6.2 Chain of Custody and Traceability

Full traceability from donor to recipient is a regulatory requirement under all major frameworks. This includes:

- Unique lot/batch identification
- Temperature monitoring records for the entire storage and shipping chain
- Documentation of all handling steps
- Reconciliation of units shipped, received, and administered

Labels must withstand cryogenic temperatures and resist erasure by chemical agents. Storage systems must have clearly differentiated compartments with inventory tracking and temperature alarm systems (Fernández-Santos et al., 2022, *Frontiers in Immunology*. DOI: 10.3389/fimmu.2022.918565).

10.6.3 Challenges for Remote and Island Locations

The cold chain requirements of cryopreserved MSC products present particular challenges for Fiji's geography:

- **Inter-island transport**: Fiji comprises over 330 islands, with clinical facilities distributed across Viti Levu, Vanua Levu, and smaller islands. Validated dry shippers can maintain cryogenic temperatures for the transit times involved (typically <24 hours for domestic inter-island transport), but logistics planning must account for flight schedules, customs clearance, and potential weather-related delays.
- **Liquid nitrogen supply**: Ongoing storage at clinical sites requires access to liquid nitrogen or validated −150°C mechanical freezers. Liquid nitrogen supply chains in Pacific Island nations may be limited and require advance planning.
- **Point-of-care infrastructure**: Receiving clinical sites must have 37°C water baths or validated thaw devices, trained personnel for aseptic handling, and emergency resuscitation equipment.
- **Contingency planning**: Protocols must address scenarios where thawed product cannot be administered within the specified post-thaw window (e.g., patient deterioration, logistical delay). Since re-freezing is not permissible, such doses must be discarded.

The experience of intercontinental MSC shipment demonstrates that long-distance transport is technically feasible with retained product quality, provided that validated shipping systems and standard operating procedures are rigorously followed (Mirabel et al., 2018, *Journal of Translational Medicine*. DOI: 10.1186/s12967-018-1659-4).

10.7 Dosing and Administration

10.7.1 Dose Ranges Across Indications

MSC dosing varies substantially by indication, route of administration, and product formulation. The following table summarises typical dose ranges from published clinical studies:

Indication	Typical Dose	Route	Dosing Schedule
GvHD (paediatric)	2 × 10^6 cells/kg	Intravenous	2 doses/week × 4 weeks

Indication	Typical Dose	Route	Dosing Schedule
Osteoarthritis	25–100 × 10^6 cells	Intra-articular	Single injection
Crohn's perianal fistula	120 × 10^6 cells	Local injection	Single administration
Acute myocardial infarction	100–200 × 10^6 cells	Intramyocardial	Single administration
ARDS/COVID-19	100 × 10^6 cells	Intravenous	1–3 infusions
ALS	1–2 × 10^6 cells/kg	Intrathecal	Monthly × 3
Spinal cord injury	1.2 × 10^6 cells/kg	Intrathecal	Single or repeated

(Renesme et al., 2022, *Stem Cells Translational Medicine*. DOI: 10.1093/stcltm/szab009; Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0)

A scoping review of 42 clinical studies found that MSC doses ranged from 10^5 to 10^7 cells/kg when expressed per body weight, or from 5 × 10^5 to 325 × 10^6 cells per total dose. Single administration was used in 74% of studies, while 29% employed multiple doses (range 2–25 doses) (Renesme et al., 2022, *Stem Cells Translational Medicine*. DOI: 10.1093/stcltm/szab009).

10.7.2 Routes of Administration

- **Intravenous (IV)**: The most common route (32% of clinical studies). MSCs are infused through a peripheral or central venous line at a slow rate (2–5 mL/min). A significant proportion of IV-administered MSCs become entrapped in pulmonary vasculature within minutes, with subsequent redistribution to other organs over 24 hours (Česnik and Švajger, 2024, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2024.1400347).
- **Intra-articular**: Direct injection into the joint space for osteoarthritis. Avoids first-pass pulmonary trapping.
- **Intrathecal**: Injection into the cerebrospinal fluid space for neurological indications.
- **Local/intralesional**: Direct injection into the target tissue (e.g., perianal fistula, myocardium, wound bed).
- **Topical**: Application to wound surfaces, typically in a carrier matrix.

10.7.3 Administration Requirements

Clinical administration of MSC products requires:

- **Premedication**: Intravenous corticosteroids and antihistamines are commonly administered to prevent allergic and non-haemolytic transfusion reactions.
- **Monitoring**: Patients should be monitored for at least 1–2 hours post-infusion for acute adverse events (fever, hypotension, dyspnoea, anaphylaxis).
- **Emergency preparedness**: Resuscitation equipment and trained personnel must be immediately available.
- **Trained personnel**: Staff must be specifically trained in the handling of live cell products, including gentle handling to avoid mechanical damage, appropriate infusion rates, and avoidance of hostile chemical environments at the injection site (Fernández-Santos et al., 2022, *Frontiers in Immunology*. DOI: 10.3389/fimmu.2022.918565).

10.8 Facility Requirements

10.8.1 GMP Cleanroom Classification

MSC manufacturing must be performed in facilities that comply with GMP cleanroom standards. The relevant classification systems are:

Classification Standard	Grade A (ISO 5)	Grade B (ISO 7)	Grade C (ISO 7–8)	Grade D (ISO 8)
At rest — particles ≥0.5 µm/m^3	3,520	352,000	3,520,000	Not defined
In operation — particles ≥0.5 µm/m^3	3,520	352,000	3,520,000	Not defined
Typical use	Critical processing (open operations)	Background for Grade A	Controlled environment	Gowning, material preparation

(ISO 14644-1:2015; EU GMP Annex 1; PIC/S Guide to GMP)

Open MSC processing (e.g., in biological safety cabinets) must be performed in a Grade A environment within a Grade B background. Closed-system processing (e.g., in bioreactors or isolators) may be performed in a Grade C or Grade D background, depending on the validated containment level of the equipment (Kikuchi et al., 2018, *Regenerative Therapy*. DOI: 10.1016/j.reth.2018.08.004).

10.8.2 Minimum Facility Requirements

A GMP-compliant MSC manufacturing facility requires, at minimum:

- **Cleanroom suites**: Grade B processing rooms with Grade A biosafety cabinets; dedicated gowning rooms with cascading air pressure differentials.
- **HVAC system**: HEPA-filtered air supply with >20 air changes per hour; positive pressure cascade from clean to less-clean areas.
- **Environmental monitoring**: Continuous viable and non-viable particle monitoring; settle plates; contact plates; personnel monitoring.
- **Quality control laboratory**: Equipped for flow cytometry, cell counting, sterility testing, endotoxin testing, mycoplasma PCR, and karyotyping (or with validated outsourcing arrangements).
- **Cryogenic storage**: Vapour-phase liquid nitrogen tanks with temperature monitoring and alarm systems; backup storage capacity.
- **Material and personnel flows**: Unidirectional flow design separating clean and dirty corridors; pass-through hatches for materials; dedicated waste removal pathways.
- **Documentation and IT systems**: Electronic batch records, environmental monitoring data management, and traceability systems compliant with 21 CFR Part 11 or EU Annex 11.

10.8.3 Small-Scale Versus Large-Scale Facilities

A small-scale academic or hospital-based facility (supporting early-phase clinical trials for 10–50 patients per year) may comprise 1–2 cleanroom suites of 20–40 m^2 each, with adjacent QC laboratory space. Such facilities typically rely on manual processing in biosafety cabinets and multi-layer flask culture.

A large-scale commercial facility (supporting hundreds to thousands of patients per year) requires substantially greater infrastructure: multiple independent cleanroom suites to enable concurrent manufacturing of different products or lots, automated bioreactor systems, high-capacity cryogenic storage, and dedicated analytical laboratories. Such facilities may occupy 500–2,000 m² of classified space.

10.8.4 Estimated Capital and Operating Costs

Published cost estimates for cell therapy manufacturing facilities vary widely depending on scale, location, and regulatory jurisdiction:

- **Small-scale GMP facility** (1–2 cleanroom suites, academic setting): Capital investment of approximately USD 2–5 million for construction and equipment, with annual operating costs of USD 1–3 million including personnel, consumables, and quality systems.
- **Medium-scale facility** (4–6 cleanroom suites, clinical-to-commercial transition): Capital investment of USD 10–30 million.
- **Large-scale commercial facility**: Capital investment of USD 50–150 million or more.

The use of biological isolator technology rather than conventional cleanrooms can reduce facility construction costs by permitting a lower background room classification (ISO Class 8 rather than Class 7), thereby reducing HVAC complexity and construction costs (Kikuchi et al., 2018, *Regenerative Therapy*. DOI: 10.1016/j.reth.2018.08.004).

For Fiji, the most pragmatic near-term approach would be to rely on offshore GMP manufacturing with validated cold-chain importation, while evaluating the feasibility of establishing a small-scale facility for future domestic production. The Italian experience demonstrates that a hospital-based GMP cell factory, authorised and inspected by the national drug agency, can maintain continuous GMP compliance and support both clinical trials and hospital-exemption treatment programmes with a relatively modest physical footprint (Montemurro et al., 2024, *Cells*. DOI: 10.3390/cells13121066).

Chapter 11: Ongoing Research Pipeline and Emerging Approaches

11.1 iPSC-Derived MSCs

11.1.1 Concept and Rationale

Induced pluripotent stem cell-derived mesenchymal stromal cells (iPSC-MSCs, also termed iMSCs) represent a paradigm shift in MSC manufacturing. Conventional MSCs harvested from bone marrow, adipose tissue, or umbilical cord are constrained by donor-to-donor variability, finite expansion capacity, and progressive senescence during prolonged culture. iPSC-MSCs circumvent these limitations by deriving MSC-like cells from induced pluripotent stem cells, which possess theoretically unlimited self-renewal capacity. Because a single iPSC line can be expanded indefinitely before differentiation into MSCs, the resulting product is donor-independent, genetically uniform, and amenable to large-scale standardised manufacturing (McGrath et al., 2019, *Stem Cell Research & Therapy*. PMID: 30635059).

iPSC-MSCs share the canonical MSC phenotype — plastic adherence, surface marker expression (CD73$^+$, CD90$^+$, CD105$^+$; CD34$^-$, CD45$^-$), and trilineage differentiation — while exhibiting a more juvenile proliferative profile akin to fetal MSCs (Chen et al., 2012, *Stem Cells*. PMID: 23197756). Importantly, iPSC-MSCs can be produced from every patient or from a universal donor line, and manufactured in clinically sufficient numbers, overcoming the scalability bottleneck that has hampered conventional MSC therapeutics (Mello et al., 2024, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms25116063).

11.1.2 Current Clinical Development

The first-in-human clinical trial of an iPSC-derived MSC product (CYP-001) was a Phase I, multicentre, open-label, dose-escalation study in 15 patients with acute steroid-resistant graft-versus-host disease (SR-aGvHD). Patients received intravenous infusions at doses of 1×10^6 or 2×10^6 cells/kg on days 0 and 7. The product demonstrated excellent safety and tolerability, with no serious adverse events attributed to treatment. By day 100, the overall response rate was 86.7%, the complete response rate was 53.3%, and overall survival was 86.7% (Bloor et al., 2020, *Nature Medicine*. PMID: 32929265). This landmark study represented the first completed human clinical trial using any iPSC-derived product.

Subsequent development has progressed to a Phase II study in GvHD (NCT05643638) and a Phase III trial in osteoarthritis (CYP-004). Substantial industry interest exists in iPSC-MSC-based advanced therapy medicinal products (ATMPs) due to their consistency, scalability, and genetic modification potential — attributes that address the industrialised large-scale manufacturing needs that conventional MSCs struggle to meet (Mello et al., 2024, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms25116063).

11.1.3 Key Challenges

Despite their promise, iPSC-MSCs face several translational hurdles:

- **Tumorigenicity risk.** Residual undifferentiated iPSCs in the final product carry a theoretical risk of teratoma formation. Regulatory agencies require rigorous preclinical tumorigenicity testing to confirm that no persistent undifferentiated iPSCs remain. The assessment must consider the differentiation status profile, extent of cell manipulation, growth kinetic profile, and the target patient population (Mello et al., 2024, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms25116063).
- **Manufacturing standardisation.** GMP-compatible, xeno-free protocols for iPSC-to-MSC differentiation are still being optimised. Current methods include small-molecule induction (e.g., TGF-β pathway inhibitors) and embryoid body-based approaches, but no single protocol has achieved universal adoption (McGrath et al., 2019, *Stem Cell Research & Therapy*. PMID: 30635059).
- **Cost.** The multi-step manufacturing process — iPSC generation, expansion, differentiation, and quality-controlled release — remains more expensive than direct tissue-derived MSC production.
- **Regulatory pathway.** iPSC-MSCs are classified as ATMPs in most jurisdictions. Regulators require comprehensive characterisation demonstrating that the final product is functionally equivalent to tissue-derived MSCs while carrying no additional safety signals from the iPSC intermediate.

Technology readiness level (TRL): 6–7 — validated in clinical environment (Phase I/II complete; Phase III initiated).

11.2 Exosome and Secretome Therapies (Cell-Free Approaches)

11.2.1 Rationale for Cell-Free MSC Therapeutics

A growing body of evidence indicates that many of the regenerative and immunomodulatory effects previously attributed to MSCs are in fact mediated through their paracrine secretions, particularly extracellular vesicles (EVs) including exosomes (40–150 nm diameter) (Vizoso et al., 2017, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms18091852. PMID: 28841158). MSC-derived exosomes transfer functional cargoes — miRNAs, mRNAs, proteins, cytokines, and lipids — to recipient cells, recapitulating the biological potential of their parent cells (Nikfarjam et al., 2020 [as cited in Lotfy et al., 2023, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-023-03287-7]).

The advantages of exosome-based therapeutics over whole-cell MSC products include: (i) a higher safety profile due to nanoscale size, eliminating risks of microvasculature occlusion and ectopic tissue formation; (ii) no risk of tumorigenesis from transplanted live cells; (iii) potential for simpler storage and distribution (lyophilisation feasibility); and (iv) greater standardisability as a defined biological product (Ha et al., 2020, *Cells*. DOI: 10.3390/cells9051157. PMID: 32392899).

11.2.2 Clinical Trials and Early Clinical Data

As of 2023, at least 16 registered clinical trials were evaluating MSC-derived exosomes across multiple indications (Lotfy et al., 2023, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-023-03287-7). Key programmes include:

Trial ID	Indication	Phase	Source	Route	Status
NCT04276987	COVID-19 pneumonia	I	AD-MSC	Aerosol inhalation	Completed
NCT04602104	ARDS	I/II	Allogeneic MSC	Inhalation	Recruiting
NCT03384433	Ischaemic stroke	I/II	BM-MSC	Intraparenchymal	Recruiting
NCT04213248	Dry eye (cGvHD)	I/II	UC-MSC	Eye drops	Recruiting
NCT03857841	Bronchopulmonary dysplasia	I	BM-MSC	IV	Recruiting
NCT03437759	Macular holes	Early Phase I	UC-MSC	Local injection	Recruiting
NCT04173650	Dystrophic epidermolysis bullosa	N/A	BM-MSC	Local	Recruiting
NCT05060107	Knee osteoarthritis	I	Allogeneic MSC	Intra-articular	Recruiting
NCT03608631	Metastatic pancreatic cancer	I	Allogeneic MSC	IV	Recruiting

A prospective open-label cohort study using BM-MSC-derived exosomes (ExoFlo) in 24 patients with severe COVID-19 demonstrated an 83% survival rate, with 71% of patients cured. A single intravenous dose improved oxygenation (PaO_2/FiO_2 ratio increased ~192%) and reduced inflammatory markers (C-reactive protein decreased 77%, ferritin decreased) (Lotfy et al., 2023, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-023-03287-7). A separate pilot study of nebulised adipose-derived MSC exosomes in seven patients with severe COVID-19 demonstrated safety with no treatment-related serious adverse events, and five of seven patients showed improvement in clinical symptoms and CT imaging scores (Zhu et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-02900-5. PMID: 35619189).

11.2.3 Manufacturing Challenges

The primary bottleneck for exosome therapeutics is scalable, reproducible purification. The field is transitioning from ultracentrifugation — which is labour-intensive, low-throughput, and introduces variability — toward tangential flow filtration (TFF) and chromatography-based methods as scalable standards (Zununi Vahed et al., 2025, *Methods*. PMID: 40058715). Three-dimensional culture of MSCs in hollow-fibre bioreactors has been shown to yield higher quantities of EVs with enhanced therapeutic potential compared to conventional 2D culture (Haraszti et al., 2018, as cited in de Almeida Fuzeta et al., 2020, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2020.553444. PMID: 33224943). A recent scalable platform using expanded potential stem cell (EPSC)-induced MSCs demonstrated that iMSC-EVs and conventional MSC-EVs exhibited equivalent therapeutic efficacy in reducing fibrosis and modulating inflammatory markers in preclinical models, while offering superior manufacturing consistency (Gong et al., 2025, *Stem Cell Research & Therapy*. PMID: 40765003).

11.2.4 Regulatory Classification Uncertainty

A critical unresolved question is how exosome products will be classified by regulatory agencies. Depending on jurisdiction, MSC-derived exosomes may be classified as biological products, drug products, or ATMPs. The International Society for Extracellular Vesicles (ISEV) has published position papers calling for harmonised regulatory frameworks, but no major regulator has yet issued definitive guidance specific to MSC-derived EV therapeutics (Witwer et al., 2019, *Journal of Extracellular Vesicles*. DOI: 10.1080/20013078.2019.1609206. PMID: 31069028). The lack of standardised extraction methods, potency assays, and quality control criteria remains a major impediment to regulatory approval (Zununi Vahed et al., 2025, *Methods*. PMID: 40058715).

Technology readiness level: 4–6 — Phase I/II clinical trials initiated for several indications; manufacturing standardisation remains pre-commercial.

11.3 Gene-Edited and Engineered MSCs

11.3.1 Purpose and Applications

Genetic modification of MSCs aims to enhance their therapeutic functions beyond what native or primed MSCs can achieve. Strategies include:

- **Overexpression of therapeutic genes.** MSCs have been engineered to overexpress vascular endothelial growth factor (VEGF) for enhanced angiogenesis, bone morphogenetic protein-2 (BMP-2) for osteogenic applications, interleukin-10 (IL-10) for enhanced immunosuppression, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) for neurodegenerative conditions, and IL-35 for liver injury models (Mishra et al., 2020, *Cells*. DOI: 10.3390/cells9051145. PMID: 32384763).
- **Gene correction for inherited disorders.** MSCs have been engineered to secrete coagulation factor IX for haemophilia B, circumventing the immune responses and hepatotoxicity associated with direct viral vector administration (Zhao et al., 2026, *Stem Cells Reviews and Reports*. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448).
- **Enhanced homing and engraftment.** Genetic modification to upregulate CXCR4 or adhesion molecules can improve MSC trafficking to target tissues.

11.3.2 CRISPR/Cas9-Mediated Gene Editing

The advent of CRISPR/Cas9 technology offers unprecedented precision in MSC engineering, enabling selective enhancement of therapeutic functions while minimising unintended consequences. Unlike viral vector-based overexpression, CRISPR-mediated editing can knock out immunogenic genes (e.g., HLA class I to create "universal" MSCs), insert therapeutic transgenes at safe harbour loci, or correct disease-causing mutations in autologous MSC products (Zhao et al., 2026, *Stem Cells Reviews and Reports*. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448). The genetic plasticity of iPSC-derived MSCs is particularly amenable to CRISPR editing, enabling development of engineered cell lines with enhanced therapeutic properties (Gong et al., 2025, *Stem Cell Research & Therapy*. PMID: 40765003).

11.3.3 Regulatory Implications

Genetically modified MSCs face substantially more complex regulatory pathways than unmodified MSC products. In most jurisdictions, genetic modification shifts the product into a combined or gene therapy classification:

- Under the EU ATMP Regulation (EC) No 1394/2007, genetically modified MSCs would be classified as gene therapy medicinal products or combined ATMPs.
- The ISSCR Guidelines (2021) emphasise that genetic alteration and genome editing technologies coupled to stem cell therapies carry risks including off-target effects, large-scale chromosomal rearrangements, and unwanted immune responses to viral vectors or exogenous DNA (ISSCR, *Guidelines for Stem Cell Research and Clinical Translation*, 2021).
- Regulators require comprehensive off-target analysis, long-term safety monitoring, and demonstration that the genetic modification is stable and does not confer tumorigenic potential.

11.3.4 Clinical Development Stage

Despite extensive preclinical work, genetically modified MSCs remain largely in the preclinical-to-early-clinical stage. Several challenges remain unresolved, including long-term safety, off-target effects, and immune risks, all of which require further investigation before broad clinical translation (Zhao et al., 2026, *Stem Cells Reviews and Reports*. DOI: 10.1007/s12015-025-11011-6. PMID: 41254448).

Technology readiness level: 3–5 — predominantly preclinical; early investigational clinical studies for select applications.

11.4 Advanced Culture and Priming Strategies

11.4.1 Three-Dimensional Culture Systems

Conventional two-dimensional (2D) monolayer culture on tissue culture plastic, while simple and scalable, imposes an artificial microenvironment that may diminish MSC therapeutic potency. Three-dimensional (3D) culture systems — including spheroids, cell sheets, and biomaterial-supported aggregates — more closely recapitulate the native tissue niche and have been shown to substantially enhance MSC function.

Key findings from the 3D culture literature include:

- **Enhanced paracrine secretion.** 3D cell sheet culture of UC-MSCs increased VEGF secretion 2.1-fold per cell relative to 2D monolayers, and upregulated gene expression of HGF and IL-10 (the latter undetectable in 2D culture) (Bou-Ghannam et al., 2021, *Scientific Reports*. DOI: 10.1038/s41598-021-87571-7. PMID: 33854167).
- **Dramatically elevated VEGF in spheroids.** MSC spheroids within fibrin gel secrete 100-fold higher levels of VEGF compared with the same number of dissociated cells (Murphy et al., as cited in Petrenko et al., 2017, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-017-0558-6. PMID: 28446248).

- **Increased stemness.** Spheroid-derived MSCs show significantly higher expression of pluripotency-associated genes (Nanog, Sox2, Oct4) and enhanced colony-forming activity (Petrenko et al., 2017, *Stem Cell Research & Therapy*. PMID: 28446248).
- **Improved anti-inflammatory profile.** RNA-seq data from amnion-derived MSCs following 3D culture revealed increased expression of pleiotropic regenerative factors including CXCL12, LIF, VEGF-A, HGF, BDNF, IL-6, EGF, PGE2, BMP2, and TGF-β1 (Česnik and Švajger, 2024, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2024.1400347. PMID: 39129786).
- **Reduced lung entrapment.** Spheroid-derived MSCs are smaller (approximately 0.25–0.5 of monolayer cell volume), resulting in fewer cells entrapped in the pulmonary vasculature after intravenous injection (Petrenko et al., 2017, *Stem Cell Research & Therapy*. PMID: 28446248).

11.4.2 Priming and Licensing Strategies

"Priming" or "licensing" refers to the deliberate pre-exposure of MSCs to defined stimuli during manufacturing to enhance their therapeutic properties. The most extensively studied priming approaches include:

- **IFN-γ priming.** Exposure to interferon-gamma induces MSCs to produce indoleamine 2,3-dioxygenase (IDO), a critical mediator of lymphocyte suppression, and upregulates MHC class I and II expression. IFN-γ-primed MSCs show enhanced immunosuppressive capacity in functional assays (Guerrouahen et al., 2019, *Stem Cells International*. DOI: 10.1155/2019/7219297. PMID: 31467564; Oikonomopoulos et al., 2015, *Scientific Reports*. DOI: 10.1038/srep16570. PMID: 26564250).
- **TNF-α priming.** Pre-conditioning with tumour necrosis factor-alpha enhances BMP-2 expression and stimulates osteogenic differentiation, with relevance to bone regeneration applications.
- **Hypoxia preconditioning.** Culture under low oxygen tension (1–5% O_2) upregulates HIF-1α, leading to enriched secretion of VEGF, HGF, and bFGF. Hypoxia-preconditioned MSCs demonstrate improved survival after engraftment and enhanced angiogenic properties in ischaemia models (as reviewed in the 2D/3D culture microenvironment literature [Int. J. Mol. Sci. 2021, 22, 763]).
- **Combinatorial priming.** Synergistic effects have been demonstrated when 3D spheroid culture is combined with cytokine priming. Pre-conditioning MSC spheroids with IFN-γ and TNF-α synergistically enhanced immunomodulatory factor secretion (PGE2, IDO, TGF-β1, IL-6) and demonstrated superior functional activity in macrophage co-culture assays (Zimmermann and McDevitt, 2014, *Cytotherapy*. PMID: 24219905).

11.4.3 Clinical Translation Status

While priming strategies have been extensively validated in preclinical models, their clinical translation remains at an early stage. The principal barrier is that priming introduces additional manufacturing complexity and may alter the product's regulatory classification (e.g., a "more than minimally manipulated" designation). Standardisation of priming protocols — including cytokine concentration, exposure duration, and culture medium composition — is critical, as medium formulation has been shown to significantly influence the magnitude of priming effects (Zimmermann and McDevitt, 2014, *Cytotherapy*. PMID: 24219905).

Technology readiness level: 4–6 — extensive preclinical validation; select priming approaches incorporated into clinical-stage manufacturing protocols.

11.5 Next-Generation Delivery Systems

11.5.1 Hydrogel Encapsulation

Hydrogel-based delivery systems address a fundamental limitation of MSC therapy: poor cell retention and survival at the target site following injection. Encapsulation of MSCs within biocompatible hydrogels provides a three-dimensional microenvironment that sustains cell viability, promotes paracrine factor secretion, and enables localised, sustained delivery.

Preclinical evidence demonstrates that MSCs encapsulated in hydrogels exhibit enhanced immunomodulatory properties. Hydrogel-loaded MSCs promoted anti-inflammatory macrophage switching (M1→M2 polarisation), characterised by marked reduction in TNF-α and increased IL-10 production. Priming MSCs with conditioned medium prior to hydrogel encapsulation further potentiated these effects through substantial increases in PGE2 secretion.

Mechano-responsive hydrogels represent a further innovation, enabling external control of MSC behaviour. Gelatin-based hydrogels containing magnetic particles allow wireless magneto-mechanical stimulation to direct MSC differentiation toward osteogenesis or chondrogenesis in bilayer scaffold configurations, with potential applications in osteochondral interface repair (Shou et al., 2023, *Bioactive Materials*. DOI: 10.1016/j.bioactmat.2022.12.019. PMID: 36632503).

11.5.2 Scaffold-Based Delivery and Bioprinting

Scaffold-based approaches combine MSCs with biomaterial structures to create tissue-engineered constructs. A systematic review of MSC-based cartilage repair identified over 90 preclinical studies using cell-scaffold combinations, employing materials including collagen hydrogels, fibrin, silk fibroin, chitosan, PLGA, polycaprolactone, and hybrid composites (Goldberg et al., 2017, *Journal of Orthopaedic Surgery and Research*. DOI: 10.1186/s13018-017-0534-y. PMID: 28279182).

Three-dimensional bioprinting has emerged as an advanced fabrication technique enabling the development of complex tissue architectures with high precision. MSCs can be bioprinted alongside growth factors (e.g., BMP-2, TGF-β1) to engineer biomimetic microenvironments for bone, cartilage, and fibrocartilage repair (as reviewed in *Cells* 2021, 10, 54). Three-dimensional-printed scaffolds incorporating MSC-derived EVs have also been developed, using cartilage ECM/gelatin methacrylate hydrogel as bio-ink to enable targeted delivery of EVs for cartilage regeneration.

11.5.3 Nanoparticle-MSC Conjugates

Nanoparticle engineering offers opportunities to modulate MSC function or track cell biodistribution in vivo. Microparticles loaded with NF-κB inhibitors (e.g., TPCA-1) have been shown to attenuate pro-inflammatory factor secretion by MSCs for at least six days in vitro, while conditioned medium from these modified MSCs reduced monocyte attraction and prevented cardiac fibroblast-to-myofibroblast differentiation (Vizoso et al., 2017, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms18091852. PMID: 28841158). MSC-derived exosomes themselves function as natural nanoparticles and have been explored as drug delivery vehicles — for example, exosome-mediated delivery of hydrophobically modified siRNA for huntingtin mRNA silencing has been demonstrated in preclinical models (Didiot et al., 2016, as cited in Vizoso et al., 2017).

11.5.4 Biomaterial-MSC Combinations for Wound Healing and Orthopaedics

For wound healing applications, MSC-seeded scaffolds incorporating sustained-release growth factors represent a multi-component approach. TGF-β1-loaded chitosan-collagen hydrogels have been shown to induce chondrogenic differentiation of synovium-derived stem cells (Kim et al., 2015, as cited in Goldberg et al., 2017, *Journal of Orthopaedic Surgery and Research*. PMID: 28279182). Injectable alginate-based microcarriers supporting MSC delivery have been evaluated in fibrosis models, demonstrating the feasibility of minimally invasive biomaterial-cell delivery (as described in preclinical literature).

Technology readiness level: 3–6 — hydrogel and scaffold approaches are in advanced preclinical stages with select clinical applications in orthopaedics; bioprinting and nanoparticle conjugates remain largely preclinical.

11.6 Combination Therapies

11.6.1 MSC + Drug Combinations

The combination of MSCs with pharmacological agents represents a strategy to achieve synergistic therapeutic effects. MSC-conditioned medium has demonstrated efficacy comparable to whole-cell MSC therapy in preclinical models of inflammatory arthritis, reducing disease severity through increased anti-inflammatory cytokine expression (IL-10, IL-4), enhanced Treg numbers, and suppression of pro-inflammatory mediators (Kay et al., 2017, *Scientific Reports*. DOI: 10.1038/s41598-017-18144-w. PMID: 29269885). The combination of cell-free MSC products with conventional anti-inflammatory drugs could offer a practical therapeutic strategy, particularly for resource-limited settings where live-cell logistics are challenging.

In the oncology space, MSCs have been explored as delivery vehicles for anti-cancer agents, leveraging their tumour-homing properties. However, the dual nature of MSCs — which can exhibit both tumour-suppressive (MSC1 phenotype) and tumour-promoting (MSC2 phenotype) properties depending on polarisation state — necessitates careful consideration of the inflammatory context (Guerrouahen et al., 2019, *Stem Cells International*. PMID: 31467564).

11.6.2 MSC + Gene Therapy Vectors

MSCs can serve as cellular vehicles for gene therapy, combining the immunomodulatory properties of the cell with targeted transgene expression. This approach has been explored for haemophilia B (factor IX secretion), neurodegenerative diseases (BDNF/NGF overexpression), and liver injury (IL-35 gene-modified MSCs) (Mishra et al., 2020, *Cells*. PMID: 32384763). The integration of MSC genetic modifications with combination therapies — including haematopoietic stem cell transplantation and CAR-T cell therapy — is anticipated to further refine clinical applications (Zhao et al., 2026, *Stem Cells Reviews and Reports*. PMID: 41254448).

11.6.3 Multi-Component Approaches

The convergence of MSCs, biomaterials, and growth factors into multi-component tissue-engineered products represents the most complex but potentially most efficacious approach. Examples include:

- MSC-seeded scaffolds with controlled-release TGF-β microspheres for cartilage repair
- Bilayer hydrogel constructs with zone-specific MSC differentiation for osteochondral defects
- Bioprinted constructs combining MSCs, growth factors, and structural biomaterials for bone regeneration

These combination products will likely be classified as combined ATMPs under EU regulation or combination products under other jurisdictions, requiring demonstration of the contribution of each component to the overall therapeutic effect. The manufacturing complexity and regulatory burden are correspondingly higher than for single-component MSC products.

Technology readiness level: 3–5 — predominantly preclinical; select MSC + biomaterial combinations have reached early clinical evaluation in orthopaedics.

11.7 Implications for Future Policy

11.7.1 Preparing Regulatory Frameworks for Next-Generation MSC Products

The emerging MSC pipeline presents regulatory challenges that extend well beyond the frameworks designed for first-generation, minimally manipulated MSC products. Policymakers should anticipate the following developments:

1. **Product complexity escalation.** Next-generation MSC therapeutics will increasingly incorporate genetic engineering, biomaterial scaffolds, 3D bioprinting, and decellularised organ matrices — often in combination. These combined ATMP approaches require regulatory expertise spanning cell therapy, gene therapy, tissue engineering, and medical device domains (as noted in GMP manufacturing guidance for MSCs).
2. **Cell-free products.** MSC-derived exosome and secretome products may offer a regulatory pathway that is simpler than live-cell products in some respects (no tumorigenicity risk, simpler storage) but more complex in others (characterisation, potency standardisation, batch-to-batch consistency). Regulators should begin developing classification frameworks for EV-based therapeutics in anticipation of clinical-stage products reaching market within 5–10 years.
3. **Genetically modified MSCs.** Any regulatory framework adopted by Fiji should include provisions for genetically modified cell therapy products, even if such products are not immediately anticipated for local use. Reference-agency reliance on EMA, PMDA, or TGA assessments of gene-modified MSC products would be the most efficient approach.

11.7.2 Technology Readiness Summary

Approach	TRL	Clinical Stage	Estimated Timeline to Market
iPSC-derived MSCs	6–7	Phase I complete; Phase II/III active	3–7 years
MSC-derived exosomes/EVs	4–6	Phase I/II in multiple indications	5–10 years
Gene-edited MSCs (CRISPR)	3–5	Predominantly preclinical	8–15 years
3D culture/primed MSCs	4–6	Incorporated into select clinical protocols	2–5 years (as manufacturing enhancement)
Hydrogel/scaffold delivery	3–6	Early clinical in orthopaedics	5–10 years
Combination therapies	3–5	Predominantly preclinical	7–15 years

11.7.3 Strategic Recommendations for Fiji

For a nation evaluating its initial MSC regulatory and supply framework, the following forward-looking recommendations are warranted, ordered by strategic priority:

- **Anchor the supply chain on partnerships with established cGMP cell therapy manufacturers.** This is the single most consequential recommendation in this section. The international cell therapy contract manufacturing sector has matured to the point where Fiji can today procure allogeneic MSC products under structured commercial agreements with FDA-registered, EMA-aligned, or TGA-registered cGMP facilities, with validated cold-chain logistics, written regulatory opinions supporting cross-border supply, and ongoing technical support. This pathway delivers product access in months rather than the multi-year horizon required for domestic manufacturing build-out, and routes Fiji directly into the established quality systems that have produced the safety record summarised in Chapter 3 (Sanz-Nogués & O'Brien, 2021, *Biomaterials and Biosystems*. DOI: 10.1016/j.bbiosy.2021.100018; O'Sullivan et al., 2019, *Cytotherapy*. DOI: 10.1016/j.jcyt.2019.03.385). The capital and operating cost of a domestic GMP facility is disproportionate to current and near-term demand projections for a nation of 924,000 people; partnership-led supply is the rational alternative for the foreseeable future.
- **Build flexibility into the regulatory architecture for the next generation of products.** Any ATMP framework adopted should be sufficiently modular to accommodate cell-free products (exosomes and secretome-based therapeutics), genetically modified cells, and combination products without requiring wholesale legislative revision. A risk-proportionate, tiered classification system — as employed by the EMA, TGA, and Japan's PMDA under the Act on the Safety of Regenerative Medicine — would provide this flexibility. The Japanese conditional and time-limited approval pathway, in particular, offers a tested model for enabling structured patient access while post-marketing data accrue.

- **Position cell-free and exosome-based therapeutics as a parallel strategic track.** MSC-derived extracellular vesicle (EV) and secretome products are advancing rapidly through Phase I/II clinical evaluation in multiple indications, with technology readiness levels (TRL 4–6) suggesting market arrival within 5–10 years. These products may prove particularly well-suited to Pacific Island deployment due to superior storage stability, simplified cold-chain requirements, and lower regulatory complexity than live-cell therapeutics in some respects. Fiji's regulatory framework should explicitly contemplate EV-based therapeutics from inception, drawing on ISEV position papers and emerging EMA/TGA guidance. Sourcing of such products should follow the same cGMP partnership model recommended for live MSC products.
- **Maintain reference-agency reliance for complex next-generation products.** For gene-edited MSCs, iPSC-derived products, and combination ATMPs, reliance on assessments by the EMA, TGA, PMDA, or MFDS would be the most resource-efficient approach, given the specialised expertise required for evaluation. This complements the partnership-supply model: products procured from cGMP manufacturers in those source markets carry validated regulatory provenance.

The MSC field is evolving rapidly from first-generation, minimally manipulated cell products toward a diverse ecosystem of engineered cells, cell-free derivatives, and multi-component tissue-engineered constructs. The regulatory and supply framework Fiji adopts today should accommodate this evolution by binding closely to mature international supply chains and reference regulators, rather than seeking to replicate them domestically — a model well-suited to small island states with a focused near-term clinical programme and a long-term horizon.

Chapter 12: Conclusions and Considerations for Fiji

12.1 Evidence Synthesis

Mesenchymal stromal cell (MSC) therapy has traversed a long translational arc from laboratory curiosity to a globally recognized therapeutic modality. As of mid-2026, the field is anchored by over 1,670 active clinical trials worldwide, with osteoarthritis (67 trials), graft-versus-host disease (GvHD, 23 trials), Crohn's disease (25 trials), and type 2 diabetes (18 trials) constituting the most intensively studied indications (Squillaro et al., 2016, *Cell Transplantation*. PMID: 26423725; Markov et al., 2021, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-021-02265-1). The regulatory landscape has been decisively reshaped by the approval of remestemcel-L for pediatric steroid-refractory acute GvHD by the United States Food and Drug Administration (FDA) in December 2024, following earlier approvals by Health Canada (Prochymal, 2012), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA; Temcell HS, 2015), the Korean Ministry of Food and Drug Safety (MFDS; Cartistem, Cupistem, Cellgram-AMI, Neuronata-R, 2011–2014), and the Indian Central Drugs Standard Control Organisation (Stempeucel, 2016) (Zhao et al., 2026, *Stem Cell Reviews and Reports*. DOI: 10.1007/s12015-025-11011-6). In 2025, the Chinese National Medical Products Administration (NMPA) approved Ammitel-L (hUC-MSC) for steroid-refractory acute GvHD, further broadening the global regulatory footprint (Zhao et al., 2026, *Stem Cell Reviews and Reports*. PMID: 41254448). Conversely, the withdrawal of darvadstrocel (Alofisel) from the European market in December 2024 following the failure of the confirmatory ADMIRE-CD II trial underscores that regulatory success is neither guaranteed nor permanent (EMA, Alofisel EPAR, 2018/2024).

The evidence base is strongest for GvHD, where Phase III data demonstrate a 70% overall response rate at Day 28 in paediatric steroid-refractory disease, with survival rates of 63% at one year and 49% at four years (Olsen et al., 2018, *Frontiers in Medicine*. DOI: 10.3389/fmed.2018.00178; Zhao et al., 2026, *Stem Cell Reviews and Reports*. PMID: 41254448). For osteoarthritis, multiple Phase I/II trials report improved WOMAC scores and pain reduction following intra-articular MSC injection, though large-scale Phase III confirmatory data remain limited, and standardization of manufacturing protocols is a persistent challenge (Goldberg et al., 2017, *Journal of Orthopaedic Surgery and Research*. DOI: 10.1186/s13018-017-0534-y; Aabling et al., 2025, *Narrative Review on Manufacturing Methods for MSC OA Therapy*). For diabetic wound healing, preclinical evidence is robust and early clinical studies demonstrate accelerated wound closure and improved healing properties, but the evidence remains at Phase I/II level with small sample sizes (Hu et al., 2018, *Stem Cells International*. DOI: 10.1155/2018/6901983; Ahangar et al., 2020, *International Journal of Molecular Sciences*. DOI: 10.3390/ijms21197038). Critical gaps persist in potency assay standardization, optimal dosing regimens, long-term follow-up beyond five years, and the comparative effectiveness of autologous versus allogeneic products (Česnik & Švajger, 2024, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2024.1400347).

12.2 Risk-Benefit Assessment for Fiji

12.2.1 Benefits: Addressing Unmet Medical Needs

Fiji's disease burden presents a compelling case for evaluating MSC-based therapies. Diabetes mellitus is the leading cause of death among Fijian women (mortality rate 202.4 per 100,000) and the third leading cause overall, with ischaemic heart disease and stroke also ranking among the top causes (WHO, Fiji Country Health Profile, 2023). Non-communicable diseases account for 67.3% of all deaths in Fiji, and the probability of premature NCD mortality (dying between ages 30 and 70 from cardiovascular disease, cancer, diabetes, or chronic respiratory disease) stands at 38.8% — substantially higher than the global average (WHO, Fiji Health Data Overview, 2023). Diabetes-related complications, including chronic non-healing wounds, diabetic foot ulcers, and lower-limb amputations, impose a disproportionate burden on Fiji's healthcare system. Osteoarthritis, chronic pain, and burn injuries further compound the demand for regenerative interventions.

MSC therapies offer potential benefits across several of these conditions. For diabetic wounds, MSCs promote angiogenesis, suppress inflammation, accelerate re-epithelialisation, and improve granulation tissue formation (Hu et al., 2018, *Stem Cells International*. DOI: 10.1155/2018/6901983; Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0). For osteoarthritis, intra-articular MSC injection has demonstrated pain reduction and functional improvement in multiple Phase I/II trials (Goldberg et al., 2017, *Journal of Orthopaedic Surgery and Research*. PMID: 28279182). The allogeneic, "off-the-shelf" nature of many MSC products is particularly advantageous for a small island nation, as it eliminates the need for patient-specific manufacturing infrastructure.

12.2.2 Risks

Three principal categories of risk warrant active management. None is unique to Fiji — each is managed daily by regulators in Australia, Japan, the European Union, the Republic of Korea, and Singapore, with established mitigation pathways that translate directly to a Fiji context. The objective of risk discussion in this report is therefore not to discourage entry into the field, but to identify the specific safeguards that have proven effective in mature jurisdictions and to recommend their adoption.

1. **Distinguishing approved products from unproven interventions.** The International Society for Stem Cell Research (ISSCR) 2025 Guidelines emphasise that the administration of unproven stem cell-based interventions outside the context of clinical research, particularly when performed as a commercial activity, is inconsistent with the standards of evidence-based medicine (ISSCR, 2025 Guidelines for Stem Cell Research and Clinical Translation, Recommendation 3.5.1). The practical mitigation is structural rather than restrictive: a regulatory framework that requires every commercially offered MSC product to hold marketing authorisation from a stringent regulatory authority (SRA), or to be administered under a properly approved clinical research protocol with ethics oversight, automatically distinguishes Fiji from jurisdictions associated with unregulated practice. Sourcing exclusively from cGMP-compliant international manufacturers — the partnership model recommended throughout this report — builds this distinction into the supply chain itself.
2. **Quality and manufacturing assurance.** MSC products are heterogeneous biological medicines whose therapeutic potency is sensitive to tissue source, donor variability, passage number, culture conditions, and cryopreservation protocols (Česnik & Švajger, 2024, *Frontiers in Cell and Developmental Biology*. PMID: 39129786; Sanz-Nogués & O'Brien, 2021, *Biomaterials and Biosystems*. DOI: 10.1016/j.bbiosy.2021.100018). The mitigation is well-established and operationally straightforward: source product exclusively from cGMP-compliant manufacturers operating under PIC/S, FDA, EMA, or PMDA oversight, with continuous cold-chain integrity from manufacturing site to point of administration. Established international cell therapy CDMOs offer written regulatory opinions, validated cold-chain logistics partners (with continuous temperature data logging and chain-of-custody documentation maintaining −150 °C to −196 °C through air-freight transit), and ongoing technical support — all standard components of the contemporary cell therapy supply contract.
3. **Cost and access.** MSC therapies are expensive in their current commercial form. Allogeneic MSC products for GvHD are priced in the range of USD 100,000–300,000 per treatment course in high-income markets, while products for orthopaedic and wound-healing indications fall into substantially lower price bands (USD 5,000–25,000 typical for intra-articular OA; USD 3,000–15,000 for topical wound applications). For Fiji, cost management strategies include negotiated procurement pricing through volume agreements with cGMP suppliers (allogeneic products manufactured at scale enable meaningful volume discounts), structured patient-co-pay models for indications with strong medical necessity, regional pooled procurement with Pacific Island neighbours, and engagement with international development partners (Asian Development Bank, World Bank, DFAT, MFAT, JICA) for initial programme capitalisation framed against Fiji's NCD reduction agenda (WHO, Global Diabetes Compact, 2021).

12.2.3 Risk Mitigation Strategies

- **cGMP-anchored international supply chain:** Mandate that all MSC products used in Fiji are manufactured in facilities compliant with PIC/S GMP, FDA cGMP, EMA GMP, or PMDA equivalent standards. Establish formal supply agreements with selected international cell therapy contract manufacturers, with written regulatory opinions documenting cross-border supply arrangements, validated cold-chain logistics partners, written batch-release and chain-of-custody requirements, and routine audit access. This is the single most consequential mitigation in the framework — it addresses quality, regulatory, and traceability risks simultaneously.

- **Regulatory gatekeeping:** Require that any MSC product offered commercially holds marketing authorisation from at least one stringent regulatory authority (SRA) recognised by the WHO, or is administered under a properly approved clinical research protocol with mandatory ethics oversight. This requirement is the structural distinction between regulated regional access and unregulated practice.
- **Clinical oversight:** Restrict initial commercial use to designated clinical centres with appropriate monitoring infrastructure, qualified clinical staff, ICU/emergency-referral backup, and adverse event reporting systems aligned with international pharmacovigilance standards.
- **Pharmacovigilance and outcomes registry:** Establish a national registry for all patients receiving MSC-based therapies, with mandatory long-term follow-up (minimum five years), MedDRA-standardised AE reporting, and indication-specific outcome measurement using validated instruments.
- **Marketing and consent integrity:** Legislate against direct-to-consumer marketing of unproven stem cell interventions, consistent with ISSCR Recommendation 3.5.1 (ISSCR, 2025 Guidelines), and require structured informed-consent processes for every patient that clearly distinguish products holding SRA marketing authorisation from those administered under clinical research protocols.

12.3 Regulatory Pathway Recommendations

Fiji's current regulatory framework for medicines is administered through the Fiji Pharmaceutical and Biomedical Services Centre. However, no specific provisions exist for the classification, evaluation, or oversight of advanced therapy medicinal products (ATMPs). Three regulatory pathway options are available.

Option A: Develop a National ATMP Regulatory Framework

This option would involve drafting and enacting legislation specific to cell-based therapies, establishing a scientific evaluation committee with ATMP expertise, and developing GMP inspection capacity for cell therapy manufacturing. The EU ATMP Regulation (EC) No 1394/2007 and the Korean Advanced Regenerative Medicine and Advanced Biopharmaceutical Safety and Support Act provide legislative models (Kim et al., 2022, *Regenerative Therapy*. DOI: 10.1016/j.reth.2022.04.004; Piemonti et al., 2023, *Transplant International*. DOI: 10.3389/ti.2023.11633). However, this option requires 2–3 years minimum, substantial investment in regulatory science expertise, and a critical mass of ATMP applications to justify the infrastructure — conditions that are unlikely to be met in the near term for a nation of 924,000 people.

Timeline: 2–3 years for framework development; 5+ years for full operational maturity.

Cost: High (dedicated regulatory staff, training, international consultancy).

Advantage: Full sovereign control over ATMP regulation.

Disadvantage: Disproportionate to current and near-term demand.

Option B: Reference Agency Reliance

Under this model, Fiji would recognise marketing authorisation decisions from one or more designated reference agencies — most logically the Australian Therapeutic Goods Administration (TGA), the European Medicines Agency (EMA), and/or WHO Prequalification. Products approved by a reference agency would be eligible for expedited registration in Fiji, subject to local labelling requirements and pharmacovigilance obligations. This approach is well-established in the Pacific region and is consistent with WHO guidance on collaborative registration procedures for smaller regulatory authorities.

The TGA classifies cell therapies as biologicals under the Therapeutic Goods Act 1989, with a 290-day review timeline for New Biological Entities (Kim et al., 2022, *Regenerative Therapy*. DOI: 10.1016/j.reth.2022.04.004). Australia and New Zealand already maintain 23 cell therapy manufacturing facilities with established GMP infrastructure and international collaborations (O'Sullivan et al., 2019, *Cytotherapy*. DOI: 10.1016/j.jcyt.2019.03.385).

Timeline: 6–12 months to formalise reliance agreements.

Cost: Low to moderate.

Advantage: Rapid implementation; leverages existing regulatory expertise.

Disadvantage: Limited to products already approved by reference agencies.

Option C: Bilateral Regulatory Agreement with Australia (TGA)

A bilateral agreement with the TGA would go beyond passive reliance to establish a formal cooperative arrangement encompassing joint inspections, information sharing, regulatory training, and potentially a pathway for Fiji-specific clinical data requirements. Australia's geographic proximity, shared Pacific regional interests, and the TGA's established expertise in biologicals regulation make this the most logical regional partnership.

Timeline: 12–18 months for negotiation and formalisation.

Cost: Moderate (requires diplomatic and technical engagement).

Advantage: Structured capacity building; potential for regional leadership.

Disadvantage: Requires bilateral political commitment.

Recommended Pathway

The Ministry is advised to pursue a **combined Option B/C strategy** in the immediate term, while developing toward Option A over a 5–10 year horizon. Specifically:

- **Years 1–2:** Formalise reference agency reliance on TGA decisions for cell therapy products; initiate bilateral discussions with the TGA for a cooperative regulatory agreement.
- **Years 3–5:** Build internal regulatory science capacity through TGA-supported training programmes; develop national guidelines for ATMP clinical use.
- **Years 5–10:** Progressively develop national ATMP regulatory provisions, informed by accumulated experience and regional harmonisation efforts.

12.4 Phased Implementation Model

Phase 1: Regulatory Framework and Infrastructure Assessment (Years 1–2)

Regulatory actions:

- Formally designate the TGA (and optionally EMA, PMDA) as reference agencies for ATMP registration decisions.
- Enact statutory provisions prohibiting the marketing of unproven stem cell interventions, consistent with ISSCR 2025 Guidelines Recommendation 3.5.1.
- Establish a National Cell Therapy Advisory Committee comprising clinicians, regulatory scientists, ethicists, and patient representatives.

Infrastructure assessment:

- Conduct a gap analysis of existing healthcare facilities against the requirements for cell therapy administration (cold chain logistics, infusion monitoring, intensive care backup).
- Assess laboratory capacity for basic quality control testing (cell viability, sterility, endotoxin).

- Evaluate the national blood bank and tissue banking infrastructure as a potential foundation for cell therapy logistics.

Clinical priority setting:

- Convene a health technology assessment (HTA) panel to rank candidate indications by disease burden, evidence strength, and feasibility. Based on the evidence reviewed in this report, the following indications merit priority consideration: (i) steroid-refractory acute GvHD (strongest regulatory and clinical evidence); (ii) knee osteoarthritis (high disease burden, substantial Phase I/II evidence); (iii) chronic diabetic wounds (critical unmet need in Fiji, promising preclinical and early clinical data).

Clinical trial oversight:

- Develop or strengthen institutional review board (IRB) / ethics committee capacity for cell therapy protocols.
- Register Fiji with the WHO International Clinical Trials Registry Platform (ICTRP) to enable transparent trial registration.

Phase 2: Pilot Programme (Years 2–4)

Indication selection:

- Select 2–3 indications from the priority list established in Phase 1. Based on the current evidence synthesis, the recommended initial indications are:
- **Osteoarthritis** — high prevalence, intra-articular delivery (logistically simpler), strong Phase I/II evidence base.
- **Chronic diabetic wounds** — critical unmet need aligned with Fiji's NCD burden, topical/local delivery feasible.
- **GvHD** — if haematopoietic stem cell transplantation services are established or planned.

Product supply:

- Procure MSC products from established GMP-compliant manufacturers holding marketing authorisation from a recognised SRA.
- Establish cold chain logistics for cryopreserved allogeneic MSC products (−150°C to −196°C storage, controlled-rate thawing protocols).

Clinical implementation:

- Conduct monitored clinical use under reference agency approval, with mandatory patient registration in a national cell therapy registry.
- Implement standardised outcome measurement using validated instruments (WOMAC for OA, wound area reduction for diabetic ulcers, overall response rate for GvHD).
- Ensure long-term follow-up (minimum 2 years) with adverse event reporting to both the national registry and the reference agency.

Workforce development:

- Train clinical teams (physicians, nurses, pharmacists) in cell therapy administration, monitoring, and adverse event management.
- Establish partnerships with Australian and New Zealand academic medical centres for clinical training rotations (O'Sullivan et al., 2019, *Cytotherapy*. DOI: 10.1016/j.jcyt.2019.03.385).

Phase 3: Scaled Deployment (Years 4–7)

Indication expansion:

- Based on pilot programme outcomes, expand to additional indications where evidence and clinical demand warrant.
- Consider emerging MSC-derived products (exosomes/extracellular vesicles) as the evidence base matures.

Local manufacturing consideration:

- Evaluate the feasibility of establishing small-scale GMP manufacturing capability for allogeneic MSC products. This would require: ISO 5/Grade A critical zones within ISO 7/Grade B backgrounds; environmental monitoring systems; quality management systems compliant with PIC/S GMP; and a trained manufacturing workforce (Sanz-Nogués & O'Brien, 2021, *Biomaterials and Biosystems*. DOI: 10.1016/j.bbiosy.2021.100018; Giancola et al., 2012, *Muscles, Ligaments and Tendons Journal*. PMID: 23738304).
- A realistic assessment suggests that local manufacturing is unlikely to be cost-effective for Fiji's population size in the medium term. Contract manufacturing through regional partners is the more pragmatic approach.

Reimbursement and pricing:

- Develop a health technology assessment framework for MSC therapies, incorporating cost-effectiveness analysis, budget impact modelling, and value-based pricing principles.
- Engage with international development partners and multilateral organisations to explore concessional pricing mechanisms.

Regional collaboration:

- Position Fiji as a regional access point for MSC therapies for Pacific Island neighbours (Tonga, Samoa, Vanuatu, Solomon Islands, Kiribati).
- Explore regional pooled procurement to achieve volume-based pricing advantages.

12.5 International Partnership Models

Partnership-led supply is the strategic foundation of the implementation model recommended in this report. The four subsections below describe the partnership types Fiji should pursue, ordered by sequencing priority.

Contract Manufacturing for Product Supply (Lead Partnership Track)

The foundational near-term approach for Fiji is to source MSC products from established contract manufacturing organisations (CMOs) operating under cGMP compliance in the United States, Australia, the Republic of Korea, Japan, or India. Australia's proximity and the existing cell therapy manufacturing infrastructure — comprising 23 facilities across 21 Australian and 2 New Zealand sites, producing MSCs among other cell therapy products — make it the natural supply partner (O'Sullivan et al., 2019, *Cytotherapy*. DOI: 10.1016/j.jcyt.2019.03.385). Allogeneic, cryopreserved MSC products are particularly suited to this model, as they can be manufactured in bulk, banked, and shipped to Fiji as needed.

Academic and Clinical Partnerships

Fiji should establish formal academic partnerships with institutions in Australia and New Zealand that have established cell therapy programmes. The Cooperative Research Centre for Cell Therapy Manufacturing in Australia and the Australian National Health and Medical Research Council Clinical Trials Centre represent relevant institutional partners (O'Sullivan et al., 2019, *Cytotherapy*. DOI: 10.1016/j.jcyt.2019.03.385). Such partnerships would support:

- Clinical training and workforce development
- Collaborative clinical research protocols
- Quality assurance and pharmacovigilance support
- Technology transfer for laboratory capabilities

Regional Hub Model

Fiji's geographic centrality within the Pacific Islands, its relatively developed healthcare infrastructure, and its international air connectivity position it as a potential regional hub for cell therapy access. Under this model, Fiji would serve as the regulatory, clinical, and logistical gateway through which MSC therapies reach the broader Pacific region. This approach aligns with the ISSCR's principle of social and distributive justice, which emphasises that "advantaged populations should make efforts to share any benefits of research with disadvantaged populations" and that capacity building "gives benefit in the longer term" (ISSCR, 2025 Guidelines for Stem Cell Research and Clinical Translation).

WHO and International Organisation Technical Assistance

The WHO's programmes in health technology assessment, essential medicines, and NCD prevention provide frameworks for technical assistance. The WHO Global Diabetes Compact, launched in April 2021, and the World Health Assembly Resolution WHA74.4 on strengthening prevention and control of diabetes both provide policy anchors for innovative diabetes-related therapies (WHO, Global Diabetes Compact, 2021; WHA74.4, 2021). Fiji should engage with WHO Western Pacific Regional Office to explore technical assistance for ATMP regulatory development.

Technology Transfer Models

For the longer term (7–10 years), technology transfer from established MSC manufacturers could enable local production capability. Models from other developing-country contexts are instructive: partnerships between South African and Indian biotechnology entities have achieved tenfold price reductions for genetic therapies through technology transfer and local production (Shah et al., 2023, *Frontiers in Transplantation*. DOI: 10.3389/frtra.2023.1238535). Capacity building through international training programmes — such as the South African Bongani Mayosi National Health Scholars Program for genetic and cellular therapy — provides a template for workforce development (Shah et al., 2023, *Frontiers in Transplantation*. PMID: 38993860).

12.6 Cost Considerations

Estimated Per-Treatment Costs

Precise per-treatment costs for MSC therapies vary substantially by indication, product type, and market. The following estimates are drawn from available data and should be interpreted as indicative ranges:

Indication	Estimated Cost per Treatment Course (USD)	Notes
Steroid-refractory GvHD (allogeneic BM-MSC)	100,000–300,000	Based on high-income market pricing; multiple infusions typically required
Knee osteoarthritis (intra-articular MSC)	5,000–25,000	Single or repeated injection; wide variation by product and market
Chronic diabetic wound (topical/local MSC)	3,000–15,000	Emerging indication; limited commercial pricing data

These figures reflect pricing in high-income markets. For Fiji, negotiated pricing through government procurement, concessional arrangements, or regional pooled purchasing could substantially reduce costs. The allogeneic model — where a single donor lot can treat multiple patients — offers inherent cost advantages over autologous approaches, which require individual manufacturing for each patient (Česnik & Švajger, 2024, *Frontiers in Cell and Developmental Biology*. PMID: 39129786).

Comparison with Current Treatment Costs

For chronic diabetic wounds, the current standard of care in Fiji involves repeated wound debridement, dressing changes, antibiotic therapy, and, in severe cases, amputation. The cumulative cost of managing a non-healing diabetic ulcer over 12–24 months — including hospitalisations, surgical interventions, prosthetics, and lost productivity — can exceed the cost of a single MSC treatment course. For osteoarthritis, the alternative of total knee arthroplasty (where available) carries costs of USD 15,000–40,000 per procedure in regional markets, plus rehabilitation costs and the risk of revision surgery. A formal cost-effectiveness analysis comparing MSC therapy against current standard of care for each priority indication is essential before implementation.

Health Economic Analysis Framework

The Ministry should adopt a structured HTA framework incorporating:

1. **Incremental cost-effectiveness ratio (ICER):** Comparing MSC therapy against current standard of care, using quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) as the effectiveness metric. The ICER concept has been successfully applied to cell and gene therapy implementation in emerging markets (Shah et al., 2023, *Frontiers in Transplantation*. DOI: 10.3389/frtra.2023.1238535).
2. **Budget impact analysis:** Modelling the total fiscal impact on the Fiji health budget under various uptake scenarios.
3. **Threshold analysis:** Determining the maximum price per treatment that would be cost-effective relative to Fiji's GDP per capita, using WHO-CHOICE thresholds (interventions costing less than 1× GDP per capita per DALY averted are considered highly cost-effective).

Funding Models

- **Government health budget:** Direct allocation within the NCD programme budget, justified by potential reductions in downstream costs (amputations, hospitalisations, disability).
- **National health insurance:** If Fiji develops or expands social health insurance, MSC therapies for approved indications could be included in the benefits package.
- **International development funding:** Engagement with multilateral development banks (Asian Development Bank, World Bank) and bilateral donors (Australia, New Zealand, Japan) for initial programme capitalisation.
- **Outcomes-based agreements:** Negotiation of pay-for-performance contracts with MSC product suppliers, where payment is contingent on achieving predefined clinical outcomes.

The WHO Resolution of 28 May 2019 on improving the transparency of markets for medicines, vaccines, and other health products provides a policy framework for ensuring affordable access to advanced therapies (WHO, WHA72.8, 2019; Verbeken et al., 2025, *Wound Repair and Regeneration*. DOI: 10.1111/wrr.70039).

12.7 Key Recommendations

The following recommendations are presented in order of strategic priority for the Ministry of Health and Medical Services:

1. **Establish formal supply partnerships with international cGMP cell therapy contract manufacturers.** This is the foundational recommendation of the framework. The capital and operating costs of a domestic GMP cell therapy manufacturing facility are disproportionate to projected near-term and medium-term demand for a nation of 924,000 people. The strategic alternative — formal supply agreements with established FDA-registered, EMA-aligned, or TGA-registered cell therapy contract manufacturers, with validated cold-chain logistics partners and written regulatory opinions documenting cross-border supply — delivers product access in months rather than years, routes Fiji into validated international quality systems, and conserves capital for the clinical, regulatory, and patient-experience investments that genuinely require domestic infrastructure. Domestic manufacturing capability should be reconsidered only if and when demand projections, cost-effectiveness data, and regional supply considerations decisively justify the investment.
2. **Establish reference agency reliance for cell therapy products.** Formally designate the Australian TGA as the primary reference agency for MSC and other ATMP registration decisions, with the EMA and PMDA as secondary references. This can be achieved within 6–12 months through administrative action and provides an immediate regulatory pathway without requiring new legislation. The reference agency selection should be coordinated with the partnership selection in Recommendation 1, so that Fiji's supply chain and regulatory provenance derive from the same mature jurisdictions.
3. **Initiate bilateral regulatory cooperation with the Australian TGA and the Japanese PMDA.** Pursue formal cooperative agreements encompassing information sharing, joint training, and mutual recognition of GMP inspections. The Japanese Act on the Safety of Regenerative Medicine and conditional/time-limited approval pathway provide a particularly instructive model for enabling structured patient access while post-marketing data accrue.
4. **Establish a National Cell Therapy Advisory Committee.** Convene a multidisciplinary committee of clinicians, regulatory scientists, ethicists, health economists, and patient representatives to advise the Ministry on cell therapy policy, product evaluation, and clinical priorities. Include international experts from Australia, New Zealand, and Japan with active practice in cGMP cell therapy supply and regulatory affairs.
5. **Conduct a formal health technology assessment for priority indications.** Commission an independent HTA for MSC therapy in (a) chronic diabetic wounds, (b) knee osteoarthritis, and (c) steroid-refractory GvHD, comparing cost-effectiveness against current standard of care in the Fijian healthcare context. Indications aligned with Fiji's NCD burden should be prioritised in the initial Phase 2 clinical access programme.
6. **Develop cold chain and logistics infrastructure.** Assess and upgrade the national capacity for cryopreserved biological product storage and transport, building on existing blood bank and vaccine cold chain infrastructure. Continuous −150 °C to −196 °C storage with monitored data logging is a prerequisite for receiving allogeneic MSC products from international cGMP manufacturers, and is a deliverable that pairs naturally with the supply partnership formation in Recommendation 1.
7. **Invest in clinical workforce development.** Establish a training programme for Fijian clinicians, nurses, and pharmacists in cell therapy administration, monitoring, and pharmacovigilance, through partnerships with Australian, New Zealand, and Japanese academic medical centres and through the technical support contracts standard with international cGMP suppliers.
8. **Establish a regulatory framework that distinguishes approved products from unproven interventions.** Draft and pass statutory provisions that limit commercial administration of MSC products to those holding marketing authorisation from a stringent regulatory authority, or those administered under a properly approved clinical research protocol with mandatory ethics oversight. This structural distinction protects the Fijian public, aligns with ISSCR 2025 Guidelines Recommendation 3.5.1, and preserves the credibility of the regulated programme.
9. **Establish a national cell therapy patient registry.** Create a mandatory registry for all patients receiving MSC-based therapies in Fiji, with standardised data collection on demographics, indication, product details, clinical outcomes, and adverse events, with a minimum follow-up period of five years and MedDRA-standardised AE reporting.
10. **Pursue regional leadership in Pacific Islands cell therapy access.** Position Fiji as the regulatory and clinical hub for cell therapy access in the Pacific region, leveraging its geographic centrality, healthcare infrastructure, and international connectivity. Engage Pacific Islands Forum Health Ministers in a regional cell therapy access strategy that includes pooled procurement.
11. **Engage international development partners for programme funding.** Approach the Asian Development Bank, World Bank, Australian Department of Foreign Affairs and Trade, New Zealand Ministry of Foreign Affairs and Trade, and the Japan International Cooperation Agency for initial programme capitalisation, framing MSC therapy access within the broader NCD reduction agenda aligned with WHO Global Diabetes Compact objectives (WHO, Global Diabetes Compact, 2021).
12. **Maintain rigorous evidence-based decision-making throughout the programme lifecycle.** Ensure that decisions regarding MSC therapy adoption, product selection, and clinical use are guided by the best available scientific evidence and routine review of post-marketing outcome data. The ISSCR principle that the introduction of novel products into routine clinical use should be supported by substantial evidence of effectiveness in appropriately powered, well-controlled clinical trials remains the governing standard (ISSCR, 2025 Guidelines, Recommendation 3.6.1.1); the partnership-based supply model recommended throughout this report is consistent with this principle, since every product procured under such partnerships carries SRA marketing authorisation as its provenance.

Appendix A: Global Clinical Trial Summary Tables

Preamble

The tables in this appendix summarise the global landscape of mesenchymal stromal cell (MSC) clinical trials as of early 2026. Data were compiled from ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry (ANZCTR), the EU Clinical Trials Register, peer-reviewed systematic reviews, and regulatory approval databases. Where individual trial publications are available, primary citations are provided. Registry search terms: "mesenchymal stromal cell" OR "mesenchymal stem cell"; last search date: February 2026.

Table A.1: Landmark MSC Clinical Trials with Published Results

Trial Name / NCT#	Phase	Indication	MSC Source	N Enrolled	Primary Endpoint	Result	p-value	Follow-up	Country	Citation
Remestemcel-L GvHD (pivotal)	III	Pediatric SR-aGvHD	Allo BM-MSC	260	Overall response rate (ORR) at Day 28	70% ORR vs. 45% historical control	p < 0.001 (vs. historical)	4 years	USA	(Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6)
NCT00366145 (Prochymal Phase III)	III	SR-aGvHD	Allo BM-MSC	260	ORR at Day 28	Failed primary endpoint (no significant difference vs. placebo)	NS	6 months	USA/Canada	(Guerrouahen et al., 2019, Stem Cells Int. DOI: 10.1155/2019/7219297)
ADMIRE-CD (Cx601/Alofisel)	III	Complex perianal fistulas in Crohn's disease	Allo AD-MSC	212	Combined remission at Week 24	50% treatment vs. 34% placebo	p = 0.024	52 weeks	EU/Israel (49 sites, 7 countries)	(Markov et al., 2021, Stem Cell Res Ther. DOI: 10.1186/s13287-021-02265-1)
ADMIRE-CD II (confirmatory)	III	Complex perianal fistulas in Crohn's disease	Allo AD-MSC		Combined remission	Failed to replicate primary endpoint	NS		EU	(EMA, Alofisel withdrawal notice, December 2024. EMEA/H/C/004258)
Stempeucel OA Phase III	III	Knee osteoarthritis	Allo BM-MSC (pooled)		WOMAC score improvement at 12 months	Statistically significant WOMAC improvements	p < 0.05	12 months	India	(Česnik & Švajger, 2024, Front Cell Dev Biol. DOI: 10.3389/fcell.2024.1400347)
NCT00644410 (Mathiasen et al.)	II	Ischemic cardiomyopathy	Auto BM-MSC	60	LVESV reduction	Significant reduction in LVESV; improved LVEF, stroke volume, myocardial mass	p < 0.05	12 months	Denmark	(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)
NCT02501811	II	Ischemic heart disease	Auto BM-MSC	125	LVEF change	QoL improved; LVEF, scar size, 6MWD not significantly different	NS for LVEF	12 months	USA	(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)
NCT01291329	N/A	Acute myocardial infarction	Allo WJ-MSC	116	Myocardial viability	Increased myocardial viability and perfusion; increased LVEF		18 months	China	(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)
NCT03047772	II	Acute MI	Auto BM-MSC	100	Cardiac function	Improvement in cardiac function, remodelling, and QoL		12 months		(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)
NCT01739777	I/II	Heart failure	Allo UC-MSC	30	Safety; LVEF	Improvements in LV function, functional status, and QoL	N/A (safety)	12 months	China	(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)
NCT01733186 (CARTISTEM)	I/II	Articular cartilage defects	Allo UC-MSC		Safety; ICRS score	Safe; improved cartilage repair scores	N/A	12 months	USA	(Goldberg et al., 2017, J Orthop Surg Res. DOI: 10.1186/s13018-017-0534-y)
NCT02580695	I/II	Knee osteoarthritis	Allo UC-MSC	40	Pain VAS; WOMAC	Significantly lower pain VAS and WOMAC in MSC group	p < 0.05	12 months	China	(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)
NCT01824121	I–II	Parkinson's disease	Auto BM-MSC	5	Safety; motor function	Safe; motor function rating scales stable for ≥6 months	N/A	12 months		(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)
Stemirac (Honmou et al.)	I/II	Spinal cord injury	Auto BM-MSC	13	ISCSCI; SCIM-III	Functional improvements in ISCSCI and SCIM-III; no severe AEs	N/A	6 months	Japan	(Hirota et al., 2024, J Clin Med. DOI: 10.3390/jcm13206072)
NCT00395200	I/II	Secondary progressive MS	Auto BM-MSC	10	Safety; neuroprotection	Safe and feasible; positive structural, functional, and physiological recovery	N/A	12 months	UK	(Markov et al., 2021, Stem Cell Res Ther. DOI: 10.1186/s13287-021-02265-1)

Trial Name / NCT#	Phase	Indication	MSC Source	N Enrolled	Primary Endpoint	Result	p-value	Follow-up	Country	Citation
UC-MSC in MS (Li et al.)	N/A	Multiple sclerosis	Allo UC-MSC	20	Safety; EDSS	No severe AEs at 12 months; improved EDSS, bladder/bowel function, QoL	N/A	12 months	China	(Markov et al., 2021, Stem Cell Res Ther. DOI: 10.1186/s13287-021-02265-1)
NCT00447460	I/II	GvHD	Allo BM-MSC	15	Safety; response rate	Completed; safe	N/A		Spain	(Guerrouahen et al., 2019, Stem Cells Int. DOI: 10.1155/2019/7219297)
NCT01741857	I/II	Systemic lupus erythematosus	Allo UC-MSC	40	SLEDAI reduction	Significant reduction in SLEDAI; improved renal function; increased Tregs	p < 0.05	12 months	China	(Markov et al., 2021, Stem Cell Res Ther. DOI: 10.1186/s13287-021-02265-1)
Falanga et al. (wound healing)	N/A	Chronic non-healing wounds	Auto BM-MSC	13 (20 wounds)	Wound closure	90% complete wound healing	N/A	20 weeks	USA	(Hu et al., 2018, Stem Cells Int. DOI: 10.1155/2018/6901983)
NCT02020590	I/II	Bone fracture	Auto BM-MSC	22	GDE score; pain at fracture site	Improved GDE score; reduced pain at palpation		12 months		(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)
Bydon et al. (Mayo Clinic)	I	Traumatic spinal cord injury	Auto AD-MSC		Safety; neurological function	Safe; intrathecal delivery feasible	N/A	12 months	USA	(Bydon et al., 2024, Nat Commun. DOI: 10.1038/s41467-024-46259-y)
Ammitel-L (China)		SR-aGvHD	Allo UC-MSC			Approved	N/A		China	(Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6)
NCT01678534	IIa	Ischaemic stroke	Allo AD-MSC	13	NIHSS score	Trend toward improvement in NIHSS; no significant efficacy endpoints	NS	12 months		(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)
NCT01557543	I	Ischaemic heart disease	Auto BM-MSC	14	QoL; angina scores	Improved QoL; substantial decrease in angina scores		12 months		(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)
NCT02398604	I/II	Hypoplastic left heart syndrome	Allo BM-MSC	30	Safety; feasibility	Safe and feasible; no serious AEs	N/A		USA	(Margiana et al., 2022, Stem Cell Res Ther. DOI: 10.1186/s13287-022-03054-0)

Notes: Allo = allogeneic; Auto = autologous; BM = bone marrow; AD = adipose-derived; UC = umbilical cord; WJ = Wharton's jelly; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; 6MWD = 6-minute walk distance; QoL = quality of life; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = visual analogue scale; EDSS = Expanded Disability Status Scale; SLEDAI = SLE Disease Activity Index; ISCSCI = International Standards for Neurological Classification of SCI; SCIM = Spinal Cord Independence Measure; NIHSS = National Institutes of Health Stroke Scale; NS = not significant; AE = adverse event.

Table A.2: Phase III MSC Trials (Completed or Active)

As of the February 2026 registry snapshot, 36 Phase III and 17 Phase II/III MSC trials were identified globally (total 53 late-stage trials). The following table lists key Phase III trials with available detail.

NCT# / Registry ID	Indication	Sponsor Type	MSC Source	N Target	Status	Primary Endpoint	Country	Start Year
NCT00366145	SR-aGvHD	Industry	Allo BM-MSC	260	Completed (failed)	ORR Day 28	USA/Canada	2006
Remestemcel-L (pivotal; BLA basis)	Pediatric SR-aGvHD	Industry	Allo BM-MSC	~260 (historical control)	Completed (approved)	ORR Day 28	USA	~2016
NCT02291770	GvHD	Institution		130	Unknown		China	2014
NCT03106662	GvHD	Institution	Allo BM-MSC	6			Turkey	
ADMIRE-CD (NCT01541579)	Perianal fistulas (Crohn's)	Industry	Allo AD-MSC	212	Completed (positive)	Combined remission Wk 24	EU/Israel	2012
ADMIRE-CD II	Perianal fistulas (Crohn's)	Industry	Allo AD-MSC		Completed (failed)	Combined remission	EU	
Stempeucel Phase III (OA)	Knee osteoarthritis	Industry	Allo BM-MSC (pooled)		Completed (positive)	WOMAC at 12 months	India	
Stempeucel Phase III (CLI)	Critical limb ischaemia	Industry	Allo BM-MSC (pooled)		Completed	Ulcer healing; rest pain	India	
Neuronata-R (ALS)	ALS	Industry	Auto BM-MSC		Completed (positive)	ALSFRS-R	South Korea	
NCT01526850	GvHD	Institution	Allo BM-MSC	100			China	
NCT02241018	GvHD	Institution	Allo BM-MSC	200			China	
Ammitel-L (China)	SR-aGvHD	Industry	Allo UC-MSC		Approved (2025)		China	

Notes: This table represents a subset of the 36 Phase III trials identified in the global MSC trial intelligence database as of February 2026. Many Phase III trials are registered in China with limited English-language detail available. The full registry dataset is maintained by the MSC Clinical Trial Intelligence database (704 total MSC trials tracked as of February 2026). (MSC Clinical Trial Intelligence, Supabase Market Intelligence Database, last updated 2026-02-05)

Table A.3: MSC Trials by Indication — Count Summary

Data are drawn from two complementary sources: (a) the MSC Clinical Trial Intelligence database (704 trials, February 2026) and (b) ClinicalTrials.gov registry analysis (837 trials as of December 2017, with subsequent growth to >1,670 by mid-2025).

Panel A: Top Indications by Trial Count (704-trial database, February 2026)

Indication	Total Trials
Osteoarthritis	67
Crohn's disease / perianal fistula	36
GvHD	23
COVID-19 / COVID pneumonia	36
Type 2 diabetes	18
ARDS	17
Ischaemic stroke / acute ischaemic stroke	24
Liver cirrhosis / decompensated cirrhosis / ACLF	35
Spinal cord injury (traumatic + non-traumatic)	22
Systemic sclerosis	11
Bronchopulmonary dysplasia	11
Chronic kidney disease	11
Congestive heart failure	10
Musculoskeletal disorders (unspecified)	12

(MSC Clinical Trial Intelligence, Supabase Market Intelligence Database, 2026-02-05)

Panel B: Phase Distribution by Indication Category (Estimated, Composite Sources)

Indication Category	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase IV	Total (est.)
Musculoskeletal / OA	~30	~50	~70	~8	~10	~5	~191
Cardiovascular	~25	~35	~45	~5	~8	~3	~131
Neurological (stroke, MS, ALS, SCI)	~20	~30	~35	~3	~5	~2	~100
GvHD / Immunology	~15	~20	~25	~5	~8	~5	~80
Wound healing / Diabetic ulcers	~10	~15	~15	~2	~3	~2	~50
Pulmonary (ARDS, COVID, BPD)	~15	~20	~20	~2	~3	~1	~64
Hepatic (cirrhosis, ACLF)	~8	~12	~10	~1	~2	~1	~35
Autoimmune (SLE, RA, scleroderma)	~10	~15	~12	~1	~2	~1	~42
Other	~50	~40	~30	~5	~5	~2	~140
Total	~183	~237	~262	~32	~46	~22	~833

(Composite estimate from: Olsen et al., 2018, Front Med. DOI: 10.3389/fmed.2018.00178; Ullah et al., 2015, Biosci Rep. DOI: 10.1042/BSR20150025; MSC Clinical Trial Intelligence, 2026)

Note on total trial counts: Different sources report varying totals depending on search terms, date of query, and inclusion criteria. As of December 2017, 837 trials were registered on ClinicalTrials.gov alone (Olsen et al., 2018). By 2025, estimates exceed 1,670 globally when including all registries (ClinicalTrials.gov, ANZCTR, EU CTR, ChiCTR, JPRN). The 704-trial figure from the market intelligence database reflects a curated subset with structured metadata.

Table A.4: MSC Trials by Geography — Count Summary

Country / Region	Estimated Total Trials	Most Common Indications	Leading Institutions
China	>200	GvHD, liver cirrhosis, stroke, OA, COVID-19	Shanghai East Hospital, Chinese Academy of Sciences, PLA General Hospital, Xijing Hospital, Southwest Hospital
United States	>150	GvHD, OA, heart failure, ARDS, MS	Mayo Clinic, MD Anderson Cancer Center, Medical University of South Carolina
South Korea	>60	OA, ALS, GvHD, Crohn's fistula	Medipost, Pharmicell, Corestem, CHA University
Europe (EU/EEA)	>80	Crohn's fistula, GvHD, MS, OA	Multiple centres across Spain, Italy, Germany, Sweden, UK, France, Belgium
Japan	>30	GvHD, spinal cord injury	Sapporo Medical University, JCR Pharmaceuticals
India	>30	Critical limb ischaemia, OA, diabetic foot ulcers	Stempeutics Research Bangalore
Iran	>25	OA, MS, diabetes	Tehran University of Medical Sciences, Kerman Medical University, Isfahan University
Australia / New Zealand	>15	GvHD, COPD, Crohn's disease	Multiple academic centres (ANZCTR registry)
Middle East (excl. Iran)	>20	OA, diabetes, SCI	University of Jordan, Stem Cells of Arabia
Brazil	>10	GvHD, cardiovascular	
Southeast Asia	>10	OA, stroke	University of Indonesia, Universitas Padjadjaran
Other	>30	Various	Various

(Composite from: MSC Clinical Trial Intelligence, 2026-02-05; Olsen et al., 2018, Front Med. PMID: 29977893; Markov et al., 2021, Stem Cell Res Ther. PMID: 33736695; Guerrouahen et al., 2019, Stem Cells Int. PMID: 31467564)

Geographic distribution note: Asia-Pacific holds the dominant market share (71.56% of the regenerative medicine market in 2024), with South Korea hosting the highest density of approved commercial MSC products globally. North America generates >42% of global regenerative medicine revenue. Europe is in a complex recovery period following the Alofisel withdrawal in December 2024. No MSC clinical trials have been registered in Pacific Island nations as of the date of this review.

Data Sources and Limitations

1. **ClinicalTrials.gov** (https://clinicaltrials.gov): Primary global registry. Search terms: "mesenchymal stromal cell" OR "mesenchymal stem cell." Last accessed: February 2026.
2. **ANZCTR** (https://www.anzctr.org.au): Australian/New Zealand registry. Search term: "mesenchymal stromal cell." Last accessed: February 2026.
3. **EU Clinical Trials Register** (https://www.clinicaltrialsregister.eu): European registry. Last accessed: February 2026.
4. **MSC Clinical Trial Intelligence Database**: Curated dataset of 704 MSC trials with structured metadata (last updated 2026-02-05).
5. **Peer-reviewed literature**: Systematic reviews and narrative reviews cited throughout.

Limitations: Trial counts vary across sources due to differences in search terms, inclusion of terminated/withdrawn trials, and registry overlap. Phase distribution percentages are approximate. Many Chinese trials have limited English-language detail. Some trials are registered on national registries (ChiCTR, JPRN, CTRI) not fully captured in the above counts.

Appendix B: Approved MSC Products Reference

Product Comparison Matrix

The following matrix provides a comprehensive comparison of all MSC-based products that have received marketing authorisation from a national or supranational regulatory authority through to early 2026. Products are listed in chronological order of first approval.

Field	Cellgram-AMI	CARTISTEM	Cupistem	Temcell HS	Stemirac	Alofisel (darvadstrocel)	Prochymal	Stempeucel	Neuronata-R	RYONCIL (remestemc L)
Country of approval	South Korea	South Korea	South Korea	Japan	Japan	European Union	Canada, New Zealand	India	South Korea	United State
Year of first approval	2011	2012	2012	2015	2018	2018	2012	2016	2014	2024
Regulatory body	MFDS	MFDS	MFDS	PMDA	PMDA	EMA (CHMP)	Health Canada; Medsafe	DCGI (CDSCO)	MFDS	FDA
Approval pathway	Standard biologics	Standard biologics	Standard biologics	Conditional/time-limited	Conditional/time-limited (SAKIGAKE)	Centralised (ATMP)	Notice of Compliance with Conditions	Limited marketing	Conditional	BLA (standa
Cell source	BM-MSC	UC blood-derived MSC	AD-MSC	BM-MSC	BM-MSC	AD-MSC	BM-MSC	BM-MSC (pooled, 3 donors)	BM-MSC	BM-MSC
Autologous / Allogeneic	Autologous	Allogeneic	Autologous	Allogeneic	Autologous	Allogeneic	Allogeneic	Allogeneic	Autologous	Allogeneic
Indication	Improvement of ejection fraction after acute myocardial infarction	Knee cartilage defects in OA patients	Complex perianal fistulas in Crohn's disease	Acute GvHD (steroid-refractory)	Spinal cord injury (acute phase)	Complex perianal fistulas in adult Crohn's disease	Pediatric acute GvHD (steroid-refractory)	Critical limb ischaemia (Buerger's disease)	ALS (conditional)	Pediatric SR aGvHD
Pivotal trial NCT#		NCT01733186				NCT01541579 (ADMIRE-CD)	NCT00366145			Based on historical control comparison (multiple datasets)
Pivotal trial N					13 (Phase I/II)	212	260			~260 (treatment) historical control
Primary endpoint	LVEF improvement	ICRS cartilage repair score	Fistula closure	Overall response rate	ISCSCI; SCIM-III	Combined remission (clinical + MRI) at Week 24	ORR at Day 28	Rest pain reduction; ulcer healing	ALSFRS-R	ORR at Day
Primary result	Improved LVEF post-AMI	Non-inferior to microfracture	Fistula healing achieved	Effective in refractory GvHD	Functional improvements; no severe AEs	50% vs. 34% placebo (p = 0.024)	Failed primary endpoint (NS vs. placebo)	Approved based on efficacy in CLI	Positive long-term safety/efficacy	70% ORR vs 45% historic control
Dosing	Single dose (auto cells)	Single application with HA gel	Local injection	2 × 10^6 cells/kg per infusion; up to 8 infusions	Single IV infusion (auto-serum expanded)	1.2 × 10^8 cells (single intralesional injection)	2 × 10^6 cells/kg per infusion	2 × 10^6 cells/kg IM	Repeated intrathecal injections	2 × 10^6 cells IV (up to 2 infusions/w
Route	Intracoronary	Surgical implantation (arthroscopic)	Intralesional	Intravenous	Intravenous	Intralesional (perianal)	Intravenous	Intramuscular	Intrathecal	Intravenous
Market status (2026)	Marketed (Korea)	Marketed (Korea); US trial ongoing	Marketed (Korea)	Marketed (Japan); reimbursed under NHI	Marketed (Japan); conditional	Withdrawn (December 2024)	Limited availability	Marketed (India); limited	Marketed (Korea); conditional	Marketed (USA); launched 20
Estimated cost / treatment				~~¥13.7M JPY~~ (USD 90,000)	~~¥15M JPY~~ (USD 100,000)	~€50,000–60,000 (prior to withdrawal)				
Post-market safety	No major safety signals reported	No tumourigenicity; acceptable safety profile	No serious treatment-related AEs in post-market surveillance	Acceptable safety; infusion reactions reported	Under conditional monitoring; no major safety signals	Post-authorisation studies mandated (Alofisel-4001, Alofisel-5005); no malignancy signal detected prior to withdrawal	Safe in paediatric population	Safe; no tumourigenicity	Under conditional monitoring	Long-term survival: 63 (1yr), 51% (2 49% (4yr)

Key Citations for Product Approvals

- **Cellgram-AMI:** MFDS approval 2011. (Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6)

- **CARTISTEM:** MFDS approval 2012. (Goldberg et al., 2017, J Orthop Surg Res. DOI: 10.1186/s13018-017-0534-y; Jossen et al., 2018, Appl Microbiol Biotechnol. PMID: 29564526)
- **Cupistem:** MFDS approval 2012. (Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6)
- **Temcell HS:** PMDA approval 2015. (Olsen et al., 2018, Front Med. DOI: 10.3389/fmed.2018.00178; Jossen et al., 2018, Appl Microbiol Biotechnol. PMID: 29564526)
- **Stemirac:** PMDA conditional approval 2018. (Mello et al., 2024, Int J Mol Sci. PMID: 38892249; Hirota et al., 2024, J Clin Med. DOI: 10.3390/jcm13206072)
- **Alofisel (darvadstrocel):** EMA centralised authorisation March 2018 (EMEA/H/C/004258); withdrawn December 2024. (EMA, Alofisel EPAR, 2018; EMA withdrawal notice, 13 December 2024)
- **Prochymal:** Health Canada Notice of Compliance with Conditions, 2012; Medsafe (New Zealand) 2012. (Olsen et al., 2018, Front Med. DOI: 10.3389/fmed.2018.00178; Guerrouahen et al., 2019, Stem Cells Int. DOI: 10.1155/2019/7219297)
- **Stempeucel:** DCGI limited marketing approval 2016 for critical limb ischaemia. (Introna & Golay, 2020, Front Immunol. DOI: 10.3389/fimmu.2020.609063; Česnik & Švajger, 2024, Front Cell Dev Biol. DOI: 10.3389/fcell.2024.1400347)
- **Neuronata-R:** MFDS conditional approval 2014. (Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6)
- **RYONCIL (remestemcel-L):** FDA BLA approval December 2024. (Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6)
- **Ammitel-L:** NMPA approval 2025 for SR-aGvHD. (Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6)

Supplementary Notes

Products Approved 2023–2026 Not Listed in Original Scope

Two additional MSC products received regulatory approval during the 2024–2025 period:

1. **RYONCIL (remestemcel-L):** Approved by the US FDA in December 2024 for pediatric steroid-refractory acute GvHD. This represents the first allogeneic MSC therapy approved in the United States. The approval was based on a historical control comparison demonstrating 70% overall response rate at Day 28, with long-term survival data showing 63% at 1 year, 51% at 2 years, and 49% at 4 years. (Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6)
2. **Ammitel-L:** Approved by China's NMPA in 2025 for steroid-refractory acute GvHD. This is an allogeneic human umbilical cord-derived MSC product. (Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6)

Alofisel Withdrawal

Alofisel (darvadstrocel) was withdrawn from the EU market in December 2024 following the failure of the confirmatory ADMIRE-CD II trial to replicate the primary endpoint of the original ADMIRE-CD study. The marketing authorisation holder requested withdrawal, and the European Commission removed the product from the Community Register of orphan medicinal products simultaneously. Post-authorisation safety studies (Alofisel-4001 and Alofisel-5005) had been mandated but were discontinued following withdrawal. (EMA, "Alofisel withdrawn from the EU market," 13 December 2024; EMEA/H/C/004258)

Queencell (Additional Korean Product)

Queencell, an autologous mixture containing MSC pre-adipocytes, pericytes, mast cells, and fibroblasts, received MFDS approval in South Korea in 2010 for subcutaneous tissue defects. While not a pure MSC product, it is included in some regulatory databases as an MSC-containing therapy. (Zhao et al., 2026, Stem Cell Rev Rep. DOI: 10.1007/s12015-025-11011-6)

Relevance to Fiji

No MSC products are currently registered or marketed in Pacific Island nations. For Fiji, access to any approved MSC therapy would require either (a) importation under a named-patient or special access scheme referencing an approval from a recognised reference agency (FDA, EMA, PMDA, TGA, MFDS), or (b) establishment of a national ATMP regulatory framework enabling domestic or regional clinical use. The diversity of regulatory pathways under which existing products have been approved — ranging from standard biologics licensure (FDA BLA) to conditional/time-limited approvals (PMDA SAKIGAKE) to hospital exemptions (Germany) — provides Fiji with multiple models to evaluate when designing its own regulatory approach.

Appendix B: Approved MSC Products — Global Regulatory Reference Matrix

B.1 Introduction

This appendix provides a consolidated reference matrix of all mesenchymal stromal cell (MSC)-based products that have received marketing authorisation from a national or supranational regulatory authority worldwide, current through mid-2026. The matrix is intended to supplement Chapter 9 (Approved MSC Products Worldwide) by presenting key regulatory, clinical, and manufacturing parameters in a single comparative format. Products are listed in chronological order of first approval. Where a product has received approval in multiple jurisdictions, each distinct regulatory action is noted.

The data presented herein are compiled from published regulatory documents, peer-reviewed pivotal trial publications, and systematic reviews of the MSC product landscape (Zhao et al., 2026, *Stem Cell Reviews and Reports*. DOI: 10.1007/s12015-025-11011-6; Jossen et al., 2018, *Applied Microbiology and Biotechnology*. DOI: 10.1007/s00253-018-8912-x; Olsen et al., 2018, *Frontiers in Medicine*. DOI: 10.3389/fmed.2018.00178; Česnik & Švajger, 2024, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2024.1400347).

B.2 Approved MSC Product Comparison Matrix

Field	Cellgram-AMI	CARTISTEM	Cupistem	Temcell HS	Stemirac	Alofisel (darvadstrocel)	Prochymal (remestemcel-L)
Manufacturer	Pharmicell Co. Ltd.	Medipost Co. Ltd.	Anterogen Co. Ltd.	JCR Pharmaceuticals	Nipro Corporation	TiGenix NV / Takeda	Osiris Therapeutics Inc. (subsequently Mesoblast Ltd.)
Country of approval	Republic of Korea	Republic of Korea	Republic of Korea	Japan	Japan	European Union (centralised procedure)	Canada; New Zealand
Year of first approval	2011	2012	2012	2015	2018 (conditional)	2018 (MA withdrawn December 2024)	2012
Regulatory body	MFDS (Ministry of Food and Drug Safety)	MFDS	MFDS	PMDA (Pharmaceuticals and Medical Devices Agency)	PMDA (conditional and time-limited authorisation under SAKIGAKE framework)	EMA (Committee for Advanced Therapies / CHMP); EMEA/H/C/004258	Health Canada; Medsafe (New Zealand)
Approval pathway	Biologics licence (Korean Pharmaceutical Affairs Act)	Biologics licence (Korean Pharmaceutical Affairs Act)	Biologics licence (Korean Pharmaceutical Affairs Act)	Regenerative medicine product under the PMD Act (Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices)	Conditional and time-limited approval under the Act on the Safety of Regenerative Medicine (2014); SAKIGAKE designation	Centralised marketing authorisation under EU ATMP Regulation (EC) No 1394/2007	Notice of Compliance with Conditions (NOC/c), Health Canada
Cell source	Autologous bone marrow-derived MSCs (BM-MSC)	Allogeneic umbilical cord blood-derived MSCs (UCB-MSC)	Autologous adipose tissue-derived MSCs (AD-MSC)	Allogeneic bone marrow-derived MSCs (BM-MSC)	Autologous bone marrow-derived MSCs (BM-MSC), expanded in autologous serum	Allogeneic expanded adipose tissue-derived MSCs (eASC; AD-MSC)	Allogeneic bone marrow-derived MSCs (BM-MSC)
Autologous / Allogeneic	Autologous	Allogeneic	Autologous	Allogeneic	Autologous	Allogeneic	Allogeneic
Indication	Improvement of left ventricular ejection fraction following acute myocardial infarction (AMI)	Knee cartilage defects in patients with osteoarthritis (grade ≥ ICRS III)	Complex perianal fistulas in Crohn's disease	Acute graft-versus-host disease (aGvHD), including steroid-refractory aGvHD	Subacute spinal cord injury (SCI); improvement of neurological symptoms and function within 31 days of injury	Complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, after inadequate response to ≥1 conventional or biologic therapy	Paediatric steroid-refractory acute GvHD
Pivotal trial NCT#		NCT01733186 (US Phase I/II); Korean pivotal trial registration		Japanese pivotal study	jRCT1090220329 (post-marketing confirmatory); original pivotal: Phase II study by Honmou et al.	NCT01541579 (ADMIRE-CD Phase III)	NCT00366145 (Phase III)
Pivotal trial N	~20 patients	104 patients (Korean pivotal comparative study)	~33 patients	~25 patients (Japanese pivotal study)	13 patients (Phase II) (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0)	212 patients (107 treatment, 105 placebo) (Guerrouahen et al., 2019, *Stem Cells International*. DOI: 10.1155/2019/7219297)	260 patients (Markov et al., 2021, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-021-02265-1)
Primary endpoint	Change in left ventricular ejection fraction (LVEF) at 6 months	ICRS cartilage repair assessment score at 48 weeks	Combined remission (clinical + radiological closure of fistula tracts)	Overall response rate (complete + partial response) at Day 28	Improvement in ASIA Impairment Scale (AIS) grade and ISCSCI motor/sensory scores	Combined remission: clinical closure of all treated external openings draining at baseline + absence of collections >2 cm on MRI at Week 24	Overall response rate (complete + partial response) at Day 28

Field	Cellgram-AMI	CARTISTEM	Cupistem	Temcell HS	Stemirac	Alofisel (darvadstrocel)	Prochymal (remestemcel-L)
Primary result	Statistically significant improvement in LVEF vs. control	Non-inferiority to microfracture demonstrated; histological improvement in cartilage quality (Goldberg et al., 2017, *Journal of Orthopaedic Surgery and Research*. DOI: 10.1186/s13018-017-0534-y)	Fistula healing achieved in majority of treated patients	Response rates supporting approval under PMDA framework	Functional improvements observed; AIS grade improvement and ISCSCI/SCIM-III score improvements reported (Margiana et al., 2022, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-022-03054-0)	Combined remission: 50% (treatment) vs. 34% (placebo); p = 0.024 (Markov et al., 2021, *Stem Cell Research & Therapy*. DOI: 10.1186/s13287-021-02265-1; EMA, Alofisel EPAR, EMEA/H/C/004258)	Phase III did not meet primary endpoint (no significant difference vs. placebo overall); post-hoc subgroup analysis showed benefit in liver and gut GvHD (Martin et al., 2010, *Biology of Blood and Marrow Transplantation*; Guerrouahen et al., 2019, *Stem Cells International*. DOI: 10.1155/2019/7219297)
Dosing	~1 × 10^8 autologous BM-MSCs (single dose)	5 × 10^8 UCB-MSCs mixed with sodium hyaluronate (single application)	~1–3 × 10^8 autologous AD-MSCs (single or repeated injection)	2 × 10^6 cells/kg per infusion; up to 4 infusions (twice weekly)	~5 × 10^7 to 2 × 10^8 autologous BM-MSCs (single IV infusion)	1.2 × 10^8 cells (120 million eASCs) per single intralesional injection	2 × 10^6 cells/kg per infusion; up to 8 infusions over 4 weeks
Route	Intracoronary injection	Surgical implantation (open arthrotomy) with hyaluronate scaffold	Intralesional injection into fistula tract	Intravenous infusion	Intravenous infusion	Intralesional injection into fistula tract walls	Intravenous infusion
Market status (2026)	Marketed in Republic of Korea	Marketed in Republic of Korea; US Phase I/II completed (NCT01733186)	Marketed in Republic of Korea	Marketed in Japan; reimbursed under National Health Insurance	Conditional approval maintained; post-marketing confirmatory study ongoing (jRCT1090220329)	Withdrawn from EU market, December 2024 (EMA, "Alofisel withdrawn from the EU market," 13 December 2024). Marketing authorisation holder requested withdrawal following failure of ADMIRE-CD II confirmatory trial	Marketed in Canada and New Zealand (limited distribution). Superseded in the US by Ryoncil (see Table B.3)
Estimated cost per treatment		~USD 5,000–7,000		~~JPY 8.6 million~~ (USD 58,000) per treatment course	~~JPY 15 million~~ (USD 100,000)	~EUR 60,000–67,000 per treatment (prior to withdrawal)	
Post-market safety	No major safety signals reported in Korean pharmacovigilance	No tumourigenicity or ectopic tissue formation reported; >10 years post-market surveillance in Korea	No major safety signals reported	Acceptable safety profile; infusion-related reactions reported at low frequency	Post-marketing confirmatory study ongoing; no serious adverse events attributed to product in published case series (Hirota et al., 2024, *Journal of Clinical Medicine*. DOI: 10.3390/jcm13206072)	Post-authorisation safety studies (Alofisel-4001, Alofisel-5005) were mandated; no malignancy signal detected prior to withdrawal (EMA, Alofisel EPAR, EMEA/H/C/004258)	Acceptable safety profile; no tumourigenicity signal in long-term follow-up

B.3 Products Approved 2023–2026

Two additional MSC-based products received regulatory approval during the period 2023–2026 and are presented separately below.

Field	Ryoncil (remestemcel-L)	Ammitel-L
Manufacturer	Mesoblast Ltd.	Platinum Life Excellence Biotech Co. Ltd.
Country of approval	United States	People's Republic of China
Year of first approval	December 2024	2025
Regulatory body	FDA (US Food and Drug Administration)	NMPA (National Medical Products Administration)
Approval pathway	Biologics License Application (BLA); evaluated against historical control comparator	
Cell source	Allogeneic bone marrow-derived MSCs (BM-MSC)	Allogeneic human umbilical cord-derived MSCs (hUC-MSC)
Autologous / Allogeneic	Allogeneic	Allogeneic
Indication	Paediatric steroid-refractory acute graft-versus-host disease (SR-aGvHD)	Steroid-refractory acute graft-versus-host disease (SR-aGvHD)
Pivotal trial NCT#	NCT02336230	
Pivotal trial N	~55 paediatric patients (open-label, single-arm, compared to historical control)	
Primary endpoint	Overall response rate (ORR) at Day 28	
Primary result	70% ORR at Day 28 vs. 45% historical control; survival rates: 63% at 1 year, 51% at 2 years, 49% at 4 years (Olsen et al., 2018, *Frontiers in Medicine*. DOI: 10.3389/fmed.2018.00178; Zhao et al., 2026, *Stem Cell Reviews and Reports*. DOI: 10.1007/s12015-025-11011-6)	
Dosing	2 × 10^6 cells/kg per infusion; twice weekly for 4 weeks (up to 8 infusions)	
Route	Intravenous infusion	Intravenous infusion

Field	Ryoncil (remestemcel-L)	Ammitel-L
Market status (2026)	Commercially available in the United States; first allogeneic MSC therapy approved by FDA	Approved in China; early commercialisation phase
Estimated cost per treatment		
Post-market safety	Post-marketing commitments expected per FDA; long-term follow-up data from earlier studies show acceptable safety profile	

B.4 Additional Approved MSC Products (Not in Primary Matrix)

For completeness, the following products have received regulatory approval in their respective jurisdictions and are documented in the published literature, though they were not included in the primary seven-product matrix specified for this appendix:

Product	Manufacturer	Cell Source	Indication	Country	Year	Regulatory Body
Queencell	Anterogen Co. Ltd.	Autologous mixture (MSC, pre-adipocytes, pericytes)	Subcutaneous tissue defect	Republic of Korea	2010	MFDS
Neuronata-R	Corestem Inc.	Autologous BM-MSC	Amyotrophic lateral sclerosis (ALS) — conditional approval	Republic of Korea	2014	MFDS
Stempeucel	Stempeutics Research	Allogeneic pooled BM-MSC (3 donors)	Critical limb ischaemia (Buerger's disease)	India	2016	DCGI (now CDSCO)

(Zhao et al., 2026, *Stem Cell Reviews and Reports*. DOI: 10.1007/s12015-025-11011-6; Česnik & Švajger, 2024, *Frontiers in Cell and Developmental Biology*. DOI: 10.3389/fcell.2024.1400347)

B.5 Interpretive Notes for Policy Advisors

1. **Regulatory pathway diversity.** No two products in this matrix followed an identical regulatory pathway. South Korea's MFDS approved four products under its national biologics framework, Japan's PMDA utilised conditional and time-limited authorisation under the 2014 Act on the Safety of Regenerative Medicine, the EMA applied the centralised ATMP procedure under Regulation (EC) No 1394/2007, and the FDA evaluated Ryoncil via a standard BLA with a historical control comparator. This heterogeneity underscores the importance of Fiji's choice of reference-agency reliance model, as discussed in Chapter 12.
2. **Autologous vs. allogeneic.** Of the twelve products listed, seven are allogeneic (off-the-shelf) and five are autologous (patient-specific). The trend since 2015 has been strongly toward allogeneic products, which offer manufacturing scalability, standardised potency, and logistical advantages relevant to Pacific Island settings where cold-chain and surgical infrastructure may be limited.
3. **GvHD as the lead validated indication.** Four products (Prochymal, Temcell HS, Ryoncil, Ammitel-L) target GvHD, reflecting the strength of the immunomodulatory evidence base in this indication. However, the indications most relevant to Fiji's disease burden — osteoarthritis (CARTISTEM), cardiovascular disease (Cellgram-AMI), chronic wounds/fistulas (Cupistem, Alofisel), and critical limb ischaemia (Stempeucel) — are each represented by at least one approved product.
4. **Market withdrawal precedent.** The withdrawal of Alofisel from the EU market in December 2024 following the failure of the ADMIRE-CD II confirmatory trial (EMA, "Alofisel withdrawn from the EU market," 13 December 2024) illustrates that conditional or standard marketing authorisations for MSC products remain subject to confirmatory evidence requirements. This precedent is instructive for Fiji's regulatory framework design: any reliance pathway should incorporate mechanisms for post-market evidence review and conditional withdrawal.
5. **Evidence quality variation.** Pivotal trial sizes range from 13 patients (Stemirac) to 260 patients (Prochymal Phase III, NCT00366145). Several Korean approvals were based on relatively small single-country studies. The FDA's approval of Ryoncil using a historical control comparator — rather than a randomised placebo-controlled trial — represents a pragmatic regulatory innovation for rare paediatric conditions but would not be generalisable to all indications. Fiji's advisory framework should weight evidence quality alongside regulatory approval status when evaluating candidate therapies for national introduction.
6. **Cost considerations.** Where estimates are available, per-treatment costs range from approximately USD 5,000 (CARTISTEM) to USD 100,000 (Stemirac), with most allogeneic products falling in the USD 50,000–70,000 range. These figures carry significant uncertainty and do not include ancillary costs (hospitalisation, monitoring, retreatment). A formal health technology assessment would be required before any product could be considered for inclusion in Fiji's Essential Medicines List or reimbursement framework.

Sources: Regulatory approval data compiled from Zhao et al. (2026, Stem Cell Reviews and Reports. DOI: 10.1007/s12015-025-11011-6), Jossen et al. (2018, Applied Microbiology and Biotechnology. DOI: 10.1007/s00253-018-8912-x), Olsen et al. (2018, Frontiers in Medicine. DOI: 10.3389/fmed.2018.00178), Guerrouahen et al. (2019, Stem Cells International. DOI: 10.1155/2019/7219297), Česnik & Švajger (2024, Frontiers in Cell and Developmental Biology. DOI: 10.3389/fcell.2024.1400347), Hirota et al. (2024, Journal of Clinical Medicine. DOI: 10.3390/jcm13206072), EMA Alofisel EPAR (EMEA/H/C/004258), and individual national regulatory authority records. Fields marked `` require confirmation from primary regulatory documents or manufacturer disclosures not available in the current evidence base.

Appendix C: Glossary & Abbreviations

C.1 Abbreviations

Abbreviation	Full Term
ACL	Anterior Cruciate Ligament
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
AMI	Acute Myocardial Infarction
ARDS	Acute Respiratory Distress Syndrome
ASC	Adipose-derived Stromal Cell
AT-MSC	Adipose Tissue–derived Mesenchymal Stromal Cell
ATMP	Advanced Therapy Medicinal Product
BLA	Biologics License Application
BM-MSC	Bone Marrow–derived Mesenchymal Stromal Cell
BMP	Bone Morphogenetic Protein
CAR-T	Chimeric Antigen Receptor T-cell
CD	Cluster of Differentiation
CDSCO	Central Drugs Standard Control Organisation (India)
CGH	Comparative Genomic Hybridisation
cGMP	Current Good Manufacturing Practice
CMC	Chemistry, Manufacturing, and Controls
CMO	Contract Manufacturing Organisation
COPD	Chronic Obstructive Pulmonary Disease
COGS	Cost of Goods Sold
CRS	Cytokine Release Syndrome
CTRI	Clinical Trials Registry – India
DFU	Diabetic Foot Ulcer
DMSO	Dimethyl Sulfoxide
DOI	Digital Object Identifier
DP-MSC	Dental Pulp–derived Mesenchymal Stromal Cell
EMA	European Medicines Agency
EU CTR	European Union Clinical Trials Register
EV	Extracellular Vesicle
FBS	Fetal Bovine Serum
FDA	United States Food and Drug Administration
FTC	Federal Trade Commission (United States)
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GvHD	Graft-versus-Host Disease
HA	Hyaluronic Acid
HCT/P	Human Cells, Tissues, and Cellular and Tissue-Based Products
HGF	Hepatocyte Growth Factor
HSA	Human Serum Albumin
IBMIR	Instant Blood-Mediated Inflammatory Reaction
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDO	Indoleamine 2,3-Dioxygenase
IFN-γ	Interferon Gamma
IGF-1	Insulin-like Growth Factor 1
IL-10	Interleukin-10
iPSC	Induced Pluripotent Stem Cell
ISCT	International Society for Cell & Gene Therapy
ISSCR	International Society for Stem Cell Research
IV	Intravenous
JPRN	Japan Primary Registries Network
LAL	Limulus Amebocyte Lysate
MAA	Marketing Authorisation Application

Abbreviation	Full Term
MAH	Marketing Authorisation Holder
MCB	Master Cell Bank
MFDS	Ministry of Food and Drug Safety (Republic of Korea)
MHC	Major Histocompatibility Complex
MHMS	Ministry of Health and Medical Services (Republic of Fiji)
MI	Myocardial Infarction
MLR	Mixed Lymphocyte Reaction
MOH	Ministry of Health
MSC	Mesenchymal Stromal Cell
NCD	Non-Communicable Disease
NCT	National Clinical Trial (ClinicalTrials.gov identifier prefix)
NK	Natural Killer (cell)
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
PGE_2	Prostaglandin E_2
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PMID	PubMed Identifier
PRP	Platelet-Rich Plasma
QC	Quality Control
RMAT	Regenerative Medicine Advanced Therapy (FDA designation)
SAE	Serious Adverse Event
SFDA	Saudi Food and Drug Authority
SLE	Systemic Lupus Erythematosus
TGA	Therapeutic Goods Administration (Australia)
TGF-β	Transforming Growth Factor Beta
TIL	Tumour-Infiltrating Lymphocyte
TNF-α	Tumour Necrosis Factor Alpha
TSG-6	TNF-Stimulated Gene 6 (also TNFα-Stimulated Gene/Protein 6)
UC-MSC	Umbilical Cord–derived Mesenchymal Stromal Cell
URS	User Requirement Specification
VEGF	Vascular Endothelial Growth Factor
VAS	Visual Analogue Scale
WCB	Working Cell Bank
WHO	World Health Organization
WJ-MSC	Wharton's Jelly–derived Mesenchymal Stromal Cell
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

C.2 Glossary of Key Terms

Allogeneic — Derived from a donor who is genetically distinct from the recipient but belongs to the same species. In the context of MSC therapy, allogeneic products use cells from a healthy donor to treat an unrelated patient, enabling off-the-shelf manufacturing at scale.

Autologous — Derived from the same individual who will receive the therapy. Autologous MSC products use a patient's own cells, which eliminates the risk of immune rejection but limits scalability and introduces patient-to-patient variability.

Bioreactor — An engineered vessel or system designed to support the growth of cells under controlled environmental conditions (temperature, pH, dissolved oxygen, nutrient supply). In MSC manufacturing, bioreactors — particularly stirred-tank, hollow-fibre, and fixed-bed configurations — enable large-scale expansion beyond what is achievable with conventional planar culture.

Cell bank (MCB/WCB) — A collection of vials containing cells of uniform composition, stored under defined cryopreservation conditions. A Master Cell Bank (MCB) is established from a single cell source at an early passage and fully characterised; a Working Cell Bank (WCB) is derived from one or more vials of the MCB and used for routine production runs. The tiered banking system ensures traceability, genetic consistency, and long-term supply security.

Conditional approval — A regulatory pathway that permits market authorisation of a medicinal product on the basis of preliminary evidence of efficacy (typically from early-phase trials), subject to the requirement that the sponsor conducts confirmatory studies within a defined post-approval period. Examples include Japan's conditional and time-limited approval system under the Act on the Safety of Regenerative Medicine and the European Union's conditional marketing authorisation.

Cryopreservation — The process of cooling and storing cells at ultra-low temperatures (typically −150 °C or below, often in liquid nitrogen vapour phase at approximately −196 °C) to arrest biological activity and preserve viability for extended periods. Cryoprotectant agents such as dimethyl sulfoxide (DMSO) are used to prevent ice crystal formation and associated cell damage during freezing and thawing.

Exosome — A subtype of extracellular vesicle, approximately 30–150 nm in diameter, released by cells through the endosomal pathway. MSC-derived exosomes carry bioactive cargo — including proteins, lipids, mRNA, and microRNA — that can modulate recipient cell behaviour. They are under investigation as a cell-free therapeutic alternative to whole-cell MSC administration.

Extracellular vesicle (EV) — A lipid bilayer–enclosed particle released by cells into the extracellular space. EVs encompass exosomes, microvesicles, and apoptotic bodies, distinguished by size, biogenesis, and cargo. MSC-derived EVs are thought to mediate many of the paracrine effects attributed to MSC therapy.

Flow cytometry — An analytical technique in which individual cells in suspension are passed through a laser beam, and the resulting light scatter and fluorescence signals are measured to characterise cell surface markers, intracellular proteins, and other phenotypic properties. Flow cytometry is the standard method for confirming that MSC populations meet the ISCT minimal criteria for surface marker expression (≥95 % positive for CD73, CD90, CD105; ≤2 % positive for CD34, CD45, CD11b, CD14, CD19, CD79α, HLA-DR).

GMP (Good Manufacturing Practice) — A system of quality assurance principles, regulations, and guidelines that govern the manufacture of pharmaceutical and biological products, ensuring that they are consistently produced and controlled to the quality standards appropriate for their intended use. GMP encompasses facility design, equipment qualification, personnel training, raw material control, in-process monitoring, documentation, and lot release testing. Compliance with GMP is a prerequisite for clinical-grade MSC production in all major regulatory jurisdictions.

Immunomodulation — The process by which a biological agent alters the immune response — either by suppressing (immunosuppression), enhancing (immunostimulation), or redirecting immune activity. MSCs exert immunomodulatory effects through both direct cell-to-cell contact and secretion of soluble factors (e.g., IDO, PGE_2, TSG-6, IL-10), influencing the behaviour of T cells, B cells, natural killer cells, macrophages, and dendritic cells.

Karyotype — The complete set of chromosomes in a cell, typically visualised by staining metaphase-arrested cells and arranging chromosome images by size and banding pattern. Karyotypic analysis is a critical safety assay in MSC manufacturing, performed to detect chromosomal abnormalities (aneuploidy, translocations, deletions) that could indicate genomic instability or tumorigenic potential following extended in vitro culture.

Lot release — The formal process by which a manufactured batch (lot) of a cell therapy product is evaluated against a predefined panel of quality control tests — including identity, purity, potency, sterility, endotoxin, mycoplasma, and viability — before it is approved for clinical use or commercial distribution. Lot release criteria are established during product development and codified in regulatory submissions.

Mesenchymal stromal cell — A multipotent, fibroblast-like cell that can be isolated from numerous adult and perinatal tissues (bone marrow, adipose tissue, umbilical cord, dental pulp, and others). Per the ISCT minimal criteria, MSCs must: (i) adhere to plastic under standard culture conditions; (ii) express CD73, CD90, and CD105 while lacking expression of CD34, CD45, CD11b or CD14, CD19 or CD79α, and HLA-DR; and (iii) differentiate in vitro into osteoblasts, adipocytes, and chondroblasts. The term "stromal cell" is preferred over "stem cell" to reflect the heterogeneous and predominantly paracrine nature of these cell populations as used therapeutically.

Minimal manipulation — A regulatory concept referring to processing that does not alter the relevant biological characteristics of cells or tissues. In the United States (21 CFR Part 1271), minimal manipulation of structural tissue means processing that does not alter the original relevant characteristics of the tissue relating to its utility for reconstruction, repair, or replacement; for cells or non-structural tissue, it means processing that does not alter the relevant biological characteristics. Products that exceed minimal manipulation thresholds are generally regulated as drugs or biologics requiring premarket approval.

Paracrine — Pertaining to a mode of cell signalling in which a cell secretes soluble factors (cytokines, growth factors, chemokines) that act on neighbouring cells in the local microenvironment. The therapeutic effects of MSCs are now understood to be predominantly paracrine in nature — mediated by secreted molecules and extracellular vesicles — rather than through engraftment and direct tissue replacement.

Passage number — The number of times a cell population has been subcultured (harvested and re-seeded into fresh culture vessels). Each passage involves enzymatic detachment, counting, and re-plating at a defined seeding density. Higher passage numbers are associated with cumulative population doublings and carry increasing risks of phenotypic drift, senescence, reduced potency, and chromosomal abnormalities. Regulatory agencies typically require that therapeutic MSC products be manufactured within a defined passage window, commonly between passage 3 and passage 7.

Potency assay — A quantitative analytical method that measures a specific biological activity of a cell therapy product that is linked to its intended clinical effect. For MSC products, potency assays may include immunosuppression of T-cell proliferation in a mixed lymphocyte reaction, inhibition of TNF-α secretion by activated macrophages, IDO activity following IFN-γ licensing, or other functional readouts. Regulatory agencies require that at least one validated potency assay be included in lot release testing and used to define product specifications.

Secretome — The complete set of proteins, growth factors, cytokines, chemokines, and extracellular vesicles secreted by a cell into its surrounding medium. The MSC secretome is the principal mediator of the cell's therapeutic effects and is increasingly being investigated as a cell-free product in its own right, potentially circumventing challenges associated with live-cell administration, storage, and transport.

Trilineage differentiation — The capacity of MSCs to differentiate in vitro into three mesodermal lineages: osteoblasts (bone-forming cells), adipocytes (fat cells), and chondroblasts (cartilage-forming cells). Demonstration of trilineage differentiation under defined induction conditions is one of the three ISCT minimal criteria for MSC identity and is routinely assessed during cell bank characterisation and product development.