

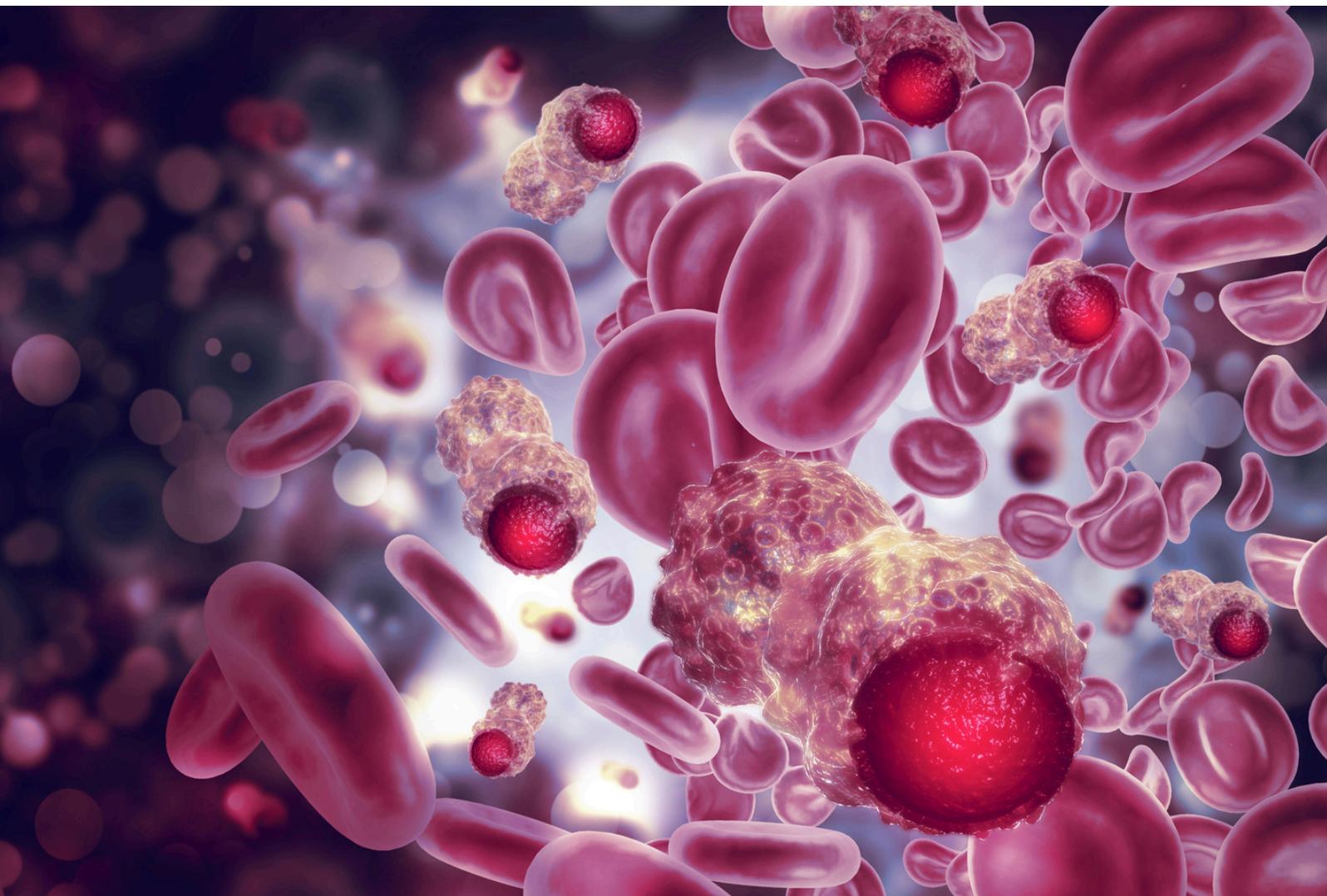


WHITE PAPER

# CIRCLES FOR MESENCHYMAL STEM CELL CARE AND RESEARCH

---

September 2025



---

## TABLE OF CONTENTS

<b>EXECUTIVE SUMMARY</b>	<b>3</b>
<b>MESENCHYMAL STEM CELLS: A NEW THERAPEUTIC PARADIGM</b>	<b>4</b>
<b>KEY CLINICAL ISSUES IN MESENCHYMAL STEM CELL THERAPY</b>	<b>5</b>
<b>REAL-WORLD EVIDENCE: A PARADIGM SHIFT FOR THERAPEUTIC INNOVATION</b>	<b>7</b>
<b>CIRCLES: CLINICALLY-EFFICIENT, VALIDATABLE RWE</b>	<b>10</b>
<b>CIRCLES USE CASES IN MSC CARE AND RESEARCH</b>	<b>11</b>
<b>CONCLUSION</b>	<b>13</b>
<b>WORKS CITED</b>	<b>14</b>

Mesenchymal Stem Cells (MSCs) represent a significant and versatile therapeutic platform, poised to address a wide spectrum of complex diseases through their profound immunomodulatory, anti-inflammatory, and regenerative properties.<sup>1</sup> The global MSC market, valued at \$3.1 billion in 2023 and projected to reach \$7.2 billion by 2030 with a CAGR of 12.8%, underscores the immense scientific and commercial interest in this field. However, the translation of this promise into standard clinical care is constrained by a critical evidence gap.

Traditional research methodologies, particularly randomized controlled trials (RCTs), are often ill-suited to capture the long-term, multi-faceted outcomes of complex cell-based therapies in real-world patient populations.<sup>3</sup> This gap hinders the optimization of treatment protocols, the validation of therapeutic value, and broader clinical adoption. Real-World Evidence (RWE), derived from the analysis of routinely collected Real-World Data (RWD), offers a transformative paradigm for addressing these issues.<sup>3</sup>

The RegenMed Circles platform is engineered to overcome the inherent limitations of conventional RWD sources, which often lack the necessary quality and clinical depth.<sup>4</sup> By utilizing prospectively designed observational protocols within a closed, collaborative system, Circles generate high-fidelity, "validatable" RWE that is clinically relevant, longitudinally robust, and auditable.<sup>3</sup> This report details the key clinical issues in MSC therapy, elucidates the role of RWE, and demonstrates how the Circles methodology can significantly accelerate the generation of evidence needed to optimize treatment strategies, validate therapeutic value, and inform robust regulatory and clinical guidelines for this next frontier of medicine.



Mesenchymal Stem Cells are a focal point of modern regenerative medicine, distinguished by a unique combination of biological properties that confer a remarkable therapeutic versatility. To fully appreciate their clinical potential, it is essential to understand their fundamental characteristics, their sophisticated mechanisms of action, and the distinct advantages offered by various tissue sources.

## Defining MSCs: Biological Properties and Therapeutic Promise

MSCs are a class of adult, multipotent progenitor cells that, unlike embryonic stem cells, are not pluripotent but retain the ability to differentiate into a variety of specialized cell types, including bone, cartilage, and fat cells.<sup>5</sup> This distinction is critical, as it allows for significant regenerative potential while avoiding the ethical controversies and safety concerns, such as teratoma formation, associated with embryonic cells.<sup>2</sup> These cells can be isolated from a wide array of postnatal tissues, including bone marrow, adipose (fat) tissue, and perinatal tissues such as the umbilical cord, making them highly accessible for clinical use.<sup>5</sup>

The International Society for Cellular Therapy (ISCT) has established minimal criteria to define MSCs, ensuring a degree of standardization in the field. These criteria state that MSCs must:

1. Adhere to plastic in standard culture conditions.
2. Express specific surface antigens (CD105, CD73, CD90) while lacking others (e.g., CD45, CD34).
3. Possess the multipotent ability to differentiate in vitro into osteoblasts, adipocytes, and chondrocytes.<sup>2</sup>

## Mechanisms of Action and Key Sources

While the ability of MSCs to replace damaged cells was the initial focus of research, their primary therapeutic power lies in their sophisticated ability to modulate the local tissue environment through paracrine signaling — the secretion of bioactive molecules that orchestrate a pro-regenerative and anti-inflammatory milieu.<sup>7</sup> This makes them dynamic "conductors" of tissue repair. Key mechanisms include:

- **Immunomodulation:** MSCs are potent regulators of the immune system, capable of suppressing pathological inflammation, which is crucial for treating autoimmune diseases.<sup>2</sup>
- **Homing and Tissue Repair:** MSCs can "home" to sites of injury and inflammation, where they secrete trophic factors that inhibit cell death, promote the formation of new blood vessels, and stimulate the body's own intrinsic repair mechanisms.<sup>2</sup>



The choice of tissue source is a critical therapeutic variable. Umbilical cord-derived MSCs (UC-MSCs) are particularly advantageous as they are ethically sourced, highly proliferative, and "immune evasive," reducing the risk of rejection in allogeneic (donor-to-patient) settings and allowing for the development of "off-the-shelf" therapies.<sup>11</sup>

## The Imperative for Robust Evidence in Regenerative Medicine

The long-term trajectory of many conditions treated with MSCs, coupled with the ethical and practical challenges of conducting traditional RCTs, highlights the critical need for alternative, robust evidence generation methodologies.<sup>3</sup> The broad spectrum of applications, from common orthopedic injuries to complex autoimmune diseases and pioneering neurological treatments, means that MSC therapies represent a substantial opportunity to address unmet medical needs. However, the diverse and sometimes subtle effects of these therapies can lead to challenges in demonstrating value, exacerbating long-term evidence gaps and contributing to what can be described as a "hidden burden" of unproven potential.<sup>3</sup>

## KEY CLINICAL ISSUES IN MESENCHYMAL STEM CELL THERAPY

Addressing the full potential of MSC therapies presents a unique set of clinical and commercial challenges, primarily stemming from gaps in protocol standardization, difficulties in demonstrating long-term efficacy, and the complexities of navigating a rapidly evolving market and regulatory landscape.

### Protocol Optimization and Standardization Gaps

Treatment approaches using MSCs are highly variable, depending on the specific condition and its severity. A significant challenge in the field is the lack of standardized protocols. Key questions remain unanswered regarding:

- **Optimal Cell Source:** Cells derived from different tissues (e.g., bone marrow, adipose, umbilical cord) may exhibit variations in their biological properties. For example, bone marrow MSCs are more likely to differentiate into osteoblasts, while umbilical cord MSCs may possess superior immunomodulatory properties.<sup>13</sup>



# KEY CLINICAL ISSUES IN MESENCHYMAL STEM CELL THERAPY

- **Effective Dosage and Administration:** Determining the correct number of cells, the frequency of administration, and the best delivery method (e.g., systemic infusion vs. local injection) is critical for efficacy and is often protocol- and indication-specific.
- **Manufacturing and Quality Control:** Ensuring consistent product quality, viability, and potency through rigorous Good Manufacturing Practice (GMP) is essential for reproducible outcomes and regulatory approval.

This lack of standardization makes it challenging to compare results across studies and establish definitive, evidence-based care pathways that can be widely adopted.

## Demonstrating Long-Term Efficacy and Durability

Many of the conditions targeted by MSCs are chronic or progressive. For example, in osteoarthritis, success is not merely a reduction in pain at three months but sustained functional improvement and delayed joint degeneration over several years.<sup>14</sup> In autoimmune diseases, the goal is not just temporary suppression of a flare-up but the induction of long-term remission.<sup>11</sup>

Understanding and effectively managing these long-term trajectories are critical for optimal patient outcomes. However, capturing these long-horizon outcomes is a central challenge. Traditional clinical trials are often too short and costly to track patients for the years required to fully assess the durability of a regenerative therapy. This evidence gap makes it difficult to fully validate the therapeutic promise of MSCs and justify their use over existing treatments.

## Navigating the Market, Regulatory, and Commercialization Landscape

Beyond the clinical challenges, the MSC field operates within a complex ecosystem of commercial, scientific, and regulatory interests.

- **Market and Industry:** The MSC market is dynamic, with a **global value of \$3.1 billion in 2023** projected to reach **\$7.2 billion by 2030** at a **CAGR of 12.8%**. This growth is driven by major industry players like **Mesoblast, Athersys, Osiris, Pluri Inc., Stempeutics, MEDIPOST, FCB-Pharmicell, Anterogen, CORESTEMCHEMON, Nipro, and Capricor**.



# KEY CLINICAL ISSUES IN MESENCHYMAL STEM CELL THERAPY

---

- **Scientific Leadership:** The field is guided by the work of Key Opinion Leaders such as **Catherine M. Verfaillie** (pioneer of MAPCs), **Jan A. Nolta** (Director at UC Davis stem cell program), **Matthew J. Dalby** (bioengineer at University of Glasgow), **Gordana Vunjak-Novakovic** (Columbia University tissue engineering expert), and **Maria Grazia Roncarolo** (Stanford expert in immune regulation).
- **Collaborative Societies:** Progress is fostered by major societies including the **International Society for Cell & Gene Therapy (ISCT)**, **International Society for Stem Cell Research (ISSCR)**, **International Federation for Adipose Therapeutics and Science (IFATS)**, **American Society for Gene and Cell Therapy (ASGCT)**, and the **Tissue Engineering & Regenerative Medicine International Society (TERMIS)**, among others.
- **Legal and Regulatory Issues:** Mesenchymal stem cells (MSCs) occupy a complex regulatory space, as they can be classified as drugs, biologics, or minimally manipulated tissues depending on jurisdiction. Regulatory authorities, such as the **FDA, EMA, and PMDA**, require rigorous GMP manufacturing, standardized potency assays, and thorough safety and efficacy data before clinical use. Legal challenges arise from unapproved clinics marketing MSC therapies without proper trials, raising concerns about immune reactions, tumorigenicity, and variable product quality. Differences in national regulations, combined with evolving scientific understanding, create ongoing challenges for harmonizing MSC clinical translation, commercialization, and ethical oversight globally.

## REAL-WORLD EVIDENCE: A PARADIGM SHIFT FOR THERAPEUTIC INNOVATION

---

The evolving landscape of healthcare data has paved the way for Real-World Evidence to play an increasingly pivotal role in understanding disease, evaluating medical products, and informing clinical practice, especially for novel therapies like MSCs.

### Defining Real-World Data (RWD) and Real-World Evidence (RWE)

As defined by the FDA, Real-World Data (RWD) encompasses information relating to patient health status and/or the delivery of healthcare that is routinely collected from a variety of sources.<sup>3</sup>

# REAL-WORLD EVIDENCE: A PARADIGM SHIFT FOR THERAPEUTIC INNOVATION

Real-World Evidence (RWE), in turn, is the clinical evidence regarding a medical product's use and potential benefits or risks, derived from the analysis of RWD.<sup>3</sup> The 21st Century Cures Act specifically defines RWE as evidence derived from "data regarding the usage, or potential benefits or risks, of a drug derived from sources other than randomized clinical trials."<sup>3</sup>

## Distinction from Randomized Controlled Trials (RCTs) and Complementary Role

As defined by the FDA, Real-World Data (RWD) encompasses information relating to patient health status and/or the delivery of healthcare that is routinely collected from a variety of sources.<sup>3</sup> Real-World Evidence (RWE), in turn, is the clinical evidence regarding a medical product's use and potential benefits or risks, derived from the analysis of RWD.<sup>3</sup> The 21st Century Cures Act specifically defines RWE as evidence derived from "data regarding the usage, or potential benefits or risks, of a drug derived from sources other than randomized clinical trials."<sup>3</sup>

## Distinction from Randomized Controlled Trials (RCTs) and Complementary Role

Randomized Controlled Trials (RCTs) have long been considered the "gold standard" for clinical research. They are meticulously designed to eliminate bias, providing clear results on the *efficacy* of interventions in highly controlled settings.<sup>3</sup> However, RCTs face critiques regarding the generalizability of their findings. They often exclude diverse patient populations, and their controlled environment frequently fails to mirror real-world clinical practice.<sup>3</sup>

RWE studies aim to evaluate the *effectiveness* of interventions in routine clinical practice.<sup>3</sup> RWE thus complements RCTs by providing insights into how medical products perform in heterogeneous, real-world patient cohorts.<sup>3</sup> For a field like regenerative medicine, where ethical and practical limitations often constrain the scope of RCTs, RWE becomes not merely a complementary tool but an essential methodology for generating the necessary evidence.<sup>3</sup>

## Advantages of RWE in Regenerative Medicine

RWE offers several compelling advantages for a field like MSC therapy:

# REAL-WORLD EVIDENCE: A PARADIGM SHIFT FOR THERAPEUTIC INNOVATION

- **Broader Patient Representation:** RWE can encompass a diverse patient population, including individuals with complex comorbidities who might be excluded from traditional trials, providing a more comprehensive understanding of how interventions perform in the real world. <sup>3</sup>
- **Long-term Data:** RWE enables the assessment of long-term safety and effectiveness, which is critical for regenerative therapies where the impact of interventions manifests over extended periods. <sup>3</sup>
- **Cost-effectiveness:** Generating RWE is generally less resource-intensive than conducting traditional clinical trials. <sup>3</sup>
- **Enhanced Safety Surveillance:** RWE has a long history of use by regulatory bodies for post-market safety monitoring and can inform decisions regarding new indications, populations, or dosing information. <sup>3</sup>

## Limitations and Methodological Considerations in RWE Generation

Despite its advantages, RWE generation has inherent limitations when relying on passively collected "big data" from sources like Electronic Health Records (EHRs) or claims data:

- **Data Quality:** RWE relies on existing healthcare data, which can vary significantly in quality, completeness, and consistency, potentially leading to biases. <sup>3</sup>
- **Lack of Clinical Depth:** These datasets often lack the granular detail needed to answer specific research questions, such as the specific source, dose, or viability of an administered MSC product.
- **Confounding Factors:** Patient outcomes can be influenced by numerous unmeasured variables in real-world settings. <sup>3</sup>
- **Lack of Randomization:** The absence of randomization makes it more difficult to establish direct causality. <sup>3</sup>



While RWE offers significant promise, its utility is dependent on the quality and structure of the underlying data. The patented Circles platform represents a structured and innovative approach to generating high-quality, validatable RWE, particularly well-suited for the complexities of MSC therapy.

## Overview of the Circles Methodology and Technical Platform

Circles are designed to capture RWD and develop RWE in a minimally burdensome and cost-efficient manner. The **Observational Protocol (OP)** underlying each Circle is prospectively designed to address a particular RWE objective, with the goal of generating demonstrable clinical, scientific, and financial value for all participating members.<sup>4</sup> The platform encompasses the physician-facing **inCytes™** and patient-facing **Benchmarc™** modules, and associated processes ensuring clinical efficiency as well as seamless collaboration within and across institutional and even national borders.<sup>3</sup>

## Mechanism of Data Collection, Aggregation, and Validation

A Circle represents the coherent integration within a closed system of (i) clinically significant diagnosis and associated treatment data, (ii) pertaining to a specific and statistically significant patient cohort, (iii) well correlated to the long-term outcomes of that cohort.<sup>3</sup> Each Circle focuses on a specific pathology, treatment protocol, and outcomes assessment, ensuring focused and relevant datasets.<sup>3</sup>

Circles inherently foster collaboration among investigators treating similar patient cohorts. For MSC therapies, where patient populations for specific protocols may be small at any single institution, aggregating data across multiple practices through Circles becomes a powerful mechanism for achieving statistical significance and generalizability.<sup>3</sup> The core objective is to produce "**validatable real-world evidence**," defined as high-quality, longitudinal datasets suitable for clinical decision-making, regulatory submissions, and value-based care.<sup>3</sup> Because Circles Datasets are generated within a controlled, closed system, they are unambiguously owned and free of error and artifacts, directly addressing the inherent limitations of traditional RWE generation.<sup>4</sup>

## Specific Benefits of Circles for MSC Research and Clinical Application

Circles offer several important advantages for MSC research:

- **Minimizing Administrative Burden:** The platform is designed to integrate into normal clinical flow, which is valuable for busy providers.<sup>17</sup>



- **Emphasis on Patient Engagement:** Circles prioritize patient (or caregiver) engagement, ensuring comprehension and fostering long-term compliance for data collection. <sup>3</sup>
- **Inherent Collaboration Support:** The model is highly beneficial for studying specific MSC applications or rare conditions where patient cohorts are geographically dispersed. <sup>18</sup>
- **Data Ownership and Value Creation:** In the Physician-Owned Circle (POC) model, participating physicians own and control the data they generate, receiving 85% of license fees from its use by industry partners. This transforms data collection from a burden into a value-creating activity.

## CIRCLES USE CASES IN MSC CARE AND RESEARCH

The true power of the Circles platform is best understood through its application to the specific, real-world evidence challenges facing the field of Mesenchymal Stem Cell therapy. By moving from the abstract capabilities of the platform to concrete use cases, it becomes clear how Circles can accelerate innovation, optimize treatment protocols, and generate the definitive evidence needed to establish MSCs as a standard of care.

### Optimizing Treatment Protocols and Standardization

- **The Challenge:** The use of MSCs in orthopedics for conditions like osteoarthritis is hampered by a lack of definitive, long-term evidence and protocol standardization. Critical questions remain regarding the optimal cell source (e.g., bone marrow vs. adipose), effective dosage, and best delivery methods. <sup>13</sup>
- **The Circles Solution:** A Circle focused on knee osteoarthritis can generate unparalleled RWE on the long-term efficacy of intra-articular MSC injections. The Observational Protocol would mandate the collection of key baseline data and detailed specifics of the MSC treatment administered (source, concentration, etc.). The patient-facing Benchmarc™ module would then longitudinally capture validated patient-reported outcome measures (e.g., KOOS, VAS for pain) over several years. By aggregating this high-fidelity data from hundreds of patients across multiple sites, investigators can analyze long-term trends, directly compare the effectiveness of different treatment protocols, and identify patient characteristics that predict a successful outcome.



## Validating Long-Term Efficacy in Autoimmune Disease

- **The Challenge:** Autoimmune diseases like SLE and RA are notoriously heterogeneous. An RCT might show a modest average benefit, masking a profound effect in a specific subgroup. Furthermore, critical questions, such as whether allogeneic (donor) MSCs are more effective than autologous (patient's own) MSCs — especially given that MSCs from autoimmune patients may be dysfunctional — remain unresolved.<sup>20</sup>
- **The Circles Solution:** A multi-center Circle for SLE provides the ideal framework to address this complexity. By collecting granular data on large, diverse cohorts, the platform is perfectly suited for the powerful subgroup analysis needed to unravel this heterogeneity. Investigators can use the platform to aggregate data from clinicians using different MSC protocols (e.g., allogeneic UC-MSCs vs. autologous AD-MSCs). The OP would capture detailed patient characteristics, disease activity scores, and quality-of-life PROs. Researchers could then build and compare custom cohorts to identify which patient sub-phenotypes respond best to specific MSC sources or dosing regimens, moving beyond a one-size-fits-all approach.

## Generating Foundational Evidence for Pioneering Applications

- **The Challenge:** For pioneering applications like Autism Spectrum Disorder (ASD), the central challenge is to objectively measure the impact of a biological intervention on complex behavioral and functional outcomes. It is one thing to demonstrate a reduction in inflammatory markers; it is another to prove this translates into meaningful improvement in a child's ability to communicate.<sup>21</sup>
- **The Circles Solution:** An ASD-focused Circle is the ideal tool to bridge this gap. The Observational Protocol would capture precise details of the MSC product administered (via inCytes™) and use the Benchmarc™ module for caregivers to complete validated assessment scales (e.g., Vineland Adaptive Behavior Scale, Aberrant Behavior Checklist) at regular intervals. By integrating these datasets, researchers can perform powerful correlational analyses to answer critical questions: Does a higher dose of MSCs lead to greater improvement? Are patients with higher baseline inflammation more likely to respond? This approach moves research beyond "does it work?" to "how does it work, and for whom does it work best?"<sup>23</sup>



## Informing Regulatory Decisions and Clinical Guidelines

- **The Challenge:** Regulatory bodies like the FDA are increasingly leveraging RWE to inform decisions, but the evidence must be of high quality and rigor.<sup>3</sup> The complex regulatory status of MSCs necessitates transparent, verifiable data to support submissions.
- **The Circles Solution:** The validatable RWE generated through Circles meets the quality standards necessary to support regulatory submissions for new indications, expanded populations, or post-approval studies. The continuous cycle of improvement inherent in the Circles methodology, coupled with its ability to develop and confirm standards of care, facilitates the direct translation of robust RWE insights into updated and more effective clinical guidelines for MSC therapies.<sup>3</sup>

## CONCLUSION

Real-World Evidence offers unparalleled opportunities to address the complex clinical questions, optimize treatment strategies, and fully realize the therapeutic potential of Mesenchymal Stem Cells. By leveraging data from routine clinical practice, RWE moves beyond the limitations of traditional clinical trials, providing a more comprehensive and representative understanding of intervention effectiveness in diverse patient populations.

With their structured, collaborative, patient-engaged, and financially sustainable approach, Circles are well positioned to generate the high-quality, validatable RWE needed to advance the field. Circles Datasets can bridge critical evidence gaps in regenerative medicine, accelerating the translation of insights into improved clinical practice and robust regulatory decisions. To fully realize this transformative potential, we invite clinicians, researchers, and industry partners to join this collaborative effort, building the evidence base that will shape the next standard of care.



1. Regenerative Medicine's Therapeutic Potential of Mesenchymal Stem Cells. Open Access Journals.
2. Mesenchymal stem cells: a new treatment for autoimmune disease? (2013). *Arthritis Research & Therapy*, 15(3), 1-3.
3. Circles Overview. RegenMed.
4. Latest News on Real-World Evidence and Circles Use Cases. RegenMed.
5. Clinical applications of mesenchymal stem cells. ResearchGate.
6. Mesenchymal Stem Cells Are Leading the Future of Regenerative Medicine. *American Pharmaceutical Review*.
7. Biological properties of Mesenchymal Stem Cells from different sources. ResearchGate.
8. The Role of Purinergic Signaling in Mesenchymal Stem Cell-Mediated Immunomodulation in Autism Spectrum Disorder. (2024). MDPI.
9. Role of Mesenchymal Stem Cells (MSCs) in Autism Treatment. Advancells.
10. Recent advances in the role of mesenchymal stem cells as regulators of immune and inflammatory disorders. (2024). *Frontiers in Immunology*.
11. Stem Cell Therapy for Autoimmune Diseases. Stem Cell Institute.
12. Everything Parents Should Know About Stem Cell Therapy for Autism. Parent's Guide to Cord Blood Foundation.
13. Orthopedic applications of stem-cell therapy, including allografts and bone substitutes used with autologous bone marrow. BlueCross BlueShield of South Carolina.
14. Mesenchymal Stem Cell Therapy for Arthritis. (2021). *Frontiers in Immunology*.
15. Mesenchymal stem cells (MSCs) for treatment of orthopedic conditions. (2023). *PM&R*, 15(1), 107-123.
16. Mesenchymal stromal cells as a treatment for inflammatory and autoimmune diseases. (2015). *World Journal of Stem Cells*.
17. Physician-Owned Circles (POC) - How It Works. RegenMed.
18. RegenMed Circles: Influence Through Evidence. RegenMed.
19. Physicians-Owned Circles. RegenMed.
20. Mesenchymal Stem Cells: Allogeneic MSC May Be Immunosuppressive but Autologous MSC Are Dysfunctional in Lupus Patients. *Frontiers in Cell and Developmental Biology*.
21. Mesenchymal stromal cells (MSC) immunoregulatory and immunosuppressive properties constitute a strong rationale for their use to improve ASD clinical symptoms. *Frontiers in Cell and Developmental Biology*.
22. A review of mesenchymal stem cells as a treatment for autism spectrum disorder. (2023). *Regenerative Medicine*, 18(3), 245-263.
23. Unlocking Potential: Mesenchymal Stem Cell Therapy for Autism Spectrum Disorder. Stem Cell Medical Center.

24. Stem Cell Therapy for Autism: Success Rate & Patient Outcomes. Swiss Medica.
25. Repeated-dose umbilical cord-derived mesenchymal stem cells in children with autism spectrum disorder: a single-arm, open-label, phase I/II clinical trial. (2020). *Stem Cells Translational Medicine*, 9(10), 1147-1156.