SCE 0908 Public Evidence Appendix

Evidence hierarchies

Literature review date: September 13, 2026

Controlling principle. Evidence hierarchies are useful for understanding what different study designs can contribute, but they are not automatic rankings of truth. Study design and study quality remain separate dimensions, and higher-level synthesis is only as reliable as the evidence it accurately represents.

Point-by-point framework

Evidence type	Primary contribution	Key limitation / boundary
Case reports	Identify unusual outcomes, adverse events, or early hypotheses.	No concurrent comparator; cannot establish treatment efficacy.
Case series	Describe patterns across multiple treated patients and early feasibility or safety signals.	Lacks an adequate counterfactual and remains vulnerable to selection and reporting bias.
Observational studies	Study associations, real-world populations, uncommon harms, and long-term outcomes.	Confounding and treatment-selection differences can limit causal inference.
Controlled trials	Provide a concurrent comparison group for estimating treatment effects.	Nonrandomized controls can retain important selection and confounding problems.
Randomized trials	Strengthen causal inference through chance assignment when properly conducted.	Randomization does not repair poor blinding, attrition, weak endpoints, product inconsistency, or inadequate follow-up.
Systematic reviews	Use reproducible methods to identify, appraise, and synthesize eligible evidence.	Conclusions depend on review methods, completeness, and quality of included studies.
Meta-analyses	Pool sufficiently compatible studies to increase precision and explore heterogeneity.	Pooling biologically or clinically incompatible studies can produce a misleading precise estimate.
Guidelines	Translate evidence into recommendations using benefit, harm, certainty, values, feasibility, equity, and context.	Recommendations are not identical to evidence estimates and may vary across panels, jurisdictions, and time.

Evidence-handling rules

The most appropriate evidence depends on the question. Randomized trials are generally strong for comparative efficacy, whereas large observational systems may be better positioned to identify rare or delayed harms. Risk of bias, directness, precision, consistency, and applicability should be assessed within each evidence type.

For MSC and extracellular-vesicle evidence, synthesis requires verification of product source, manufacturing, characterization, potency, dose, route, indication, population, comparator, endpoint, and follow-up before studies are treated as estimates of the same intervention.

Principal references

1. 1. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-926.

2. 2. Cochrane Handbook for Systematic Reviews of Interventions. Current methodological guidance on study designs, risk of bias, synthesis, and meta-analysis.

3. 3. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

4. 4. Sterne JAC, Savovi■ J, Page MJ, et al. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials.

5. 5. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

6. 6. International Council for Harmonisation. E6(R3) Good Clinical Practice. 2025.

7. 7. Institute of Medicine/National Academies. Clinical Practice Guidelines We Can Trust. National Academies Press. 2011; principles remain foundational to guideline development.

8. 8. Contemporary evidence-synthesis and regenerative-medicine methodology literature addressing clinical heterogeneity, product comparability, and appropriate pooling of cell and extracellular-vesicle studies.