SCE 0909 Public Evidence Appendix

Evidence grading

Literature review date: September 13, 2026

Controlling principle. Evidence grading is a transparent judgment about confidence in a body of evidence, not a count of positive studies. Certainty, magnitude, consistency, directness, precision, and benefit-risk should be assessed explicitly and kept separate from development stage, regulatory status, guideline position, and manufacturing quality.

Point-by-point framework

Controlling Point	Primary question	Interpretive boundary
Certainty of evidence	How confident are we that the estimated effect is sufficiently close to the true effect for the decision?	Study design alone does not determine certainty; bias, inconsistency, indirectness, imprecision, and reporting concerns matter.
Magnitude of effect	How large is the observed benefit or harm?	Relative effects should be interpreted with absolute effects, baseline risk, confidence intervals, durability, and clinical importance.
Consistency	Do independent studies produce reasonably compatible findings?	Inconsistency may reflect genuine product, dose, population, endpoint, or methodological heterogeneity rather than random noise.
Directness	How closely does the evidence match the actual population, intervention, comparator, and patient-important outcomes?	Extrapolation across species, diseases, surrogate outcomes, routes, or materially different products lowers directness.
Precision	How narrowly is the treatment effect estimated?	Wide confidence intervals can leave important benefit, little effect, and harm simultaneously plausible.
Risk-benefit balance	Do expected benefits outweigh known and potential harms in the defined clinical context?	Benefit-risk depends on severity, alternatives, certainty, durability, reversibility of harm, baseline risk, and patient preferences.

Evidence-handling rules

Positive evidence should lose confidence when bias, inconsistency, indirectness, or imprecision weakens the inference. Negative evidence becomes more convincing when direct, precise, consistent studies exclude a clinically important effect. Evidence remains inconclusive when materially different outcomes remain compatible with the data.

For MSC and extracellular-vesicle studies, certainty cannot be transferred automatically between products with different tissue sources, manufacturing processes, characterization, potency, dose, route, storage, populations, or indications.

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. Schünemann HJ, Bro■ek J, Guyatt G, Oxman A, eds. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. GRADE Working Group.

3. 3. Cochrane Handbook for Systematic Reviews of Interventions. Current methodological guidance on certainty, risk of bias, heterogeneity, imprecision, and synthesis.

4. 4. Alonso-Coello P, Schünemann HJ, Moberg J, et al. GRADE Evidence to Decision frameworks: a systematic and transparent approach to making well informed healthcare choices. BMJ. 2016.

5. 5. U.S. Food and Drug Administration. Benefit-Risk Assessment for New Drug and Biological Products. Guidance for Industry. 2023.

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

7. 7. CONSORT Group. CONSORT 2025 Statement and explanatory materials for randomized trials.

8. 8. Contemporary evidence-synthesis and regenerative-medicine methodology literature addressing product comparability, directness, heterogeneity, and clinically meaningful effect interpretation.