SCE 0903 Public Evidence Appendix

Trial design

Literature review date: September 13, 2026

Controlling principle. Trial design determines how confidently an observed difference can be attributed to an intervention rather than baseline imbalance, expectations, co-interventions, outcome assessment, chance, center effects, or selective analysis. Design features are complementary and must be interpreted together.

Point-by-point framework

Controlling Point	Primary purpose	Key limitation / boundary
Randomization	Assign treatment by chance and reduce systematic baseline imbalance.	Does not prevent post-assignment bias, dropout, crossover, or selective reporting.
Allocation concealment	Prevent foreknowledge of the next assignment during enrollment.	Distinct from blinding; inadequate concealment can undermine randomization.
Blinding	Reduce expectation, behavioral, assessment, and analytic bias after assignment.	May be incomplete or impossible for visible products or procedures; alternative protections are then needed.
Placebo controls	Separate active treatment effects from expectation, attention, natural history, and nonspecific effects.	Not always ethical or practical when proven therapy must not be withheld.
Active controls	Compare an investigational treatment with established care.	Interpretation depends on superiority/noninferiority question, margin, adherence, and assay sensitivity.
Sham procedures	Control procedural and expectancy effects in invasive-intervention trials.	Can impose real risk without therapeutic intent and requires strong scientific and ethical justification.
Multicenter trials	Test reproducibility and generalizability across sites and increase recruitment/diversity.	Center heterogeneity in selection, skill, product handling, background care, and outcomes must be controlled.

Evidence-handling rules

Positive, negative, mixed, null, and inconclusive results are interpreted in light of randomization, concealment, blinding, comparator choice, protocol adherence, endpoint integrity, missing data, multiplicity, center effects, and clinically meaningful effect size.

Methodological rigor and ethics are complementary: a control must be scientifically informative and ethically defensible, with risk minimized and proven effective care not inappropriately withheld.

Principal references

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

2. 2. International Council for Harmonisation. E9 Statistical Principles for Clinical Trials and E9(R1) Addendum on Estimands and Sensitivity Analysis.

3. 3. U.S. Food and Drug Administration. Frequently Asked Questions — Developing Potential Cellular and Gene Therapy Products. Guidance for Industry. August 2026.

4. 4. U.S. Food and Drug Administration. Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations. Draft Guidance for Industry. September 2025.

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

6. 6. International Society for Cell & Gene Therapy and International Society for Extracellular Vesicles. Contemporary methodological guidance relevant to cell and EV clinical translation.

7. 7. National Research Council and contemporary clinical-trial methodology literature addressing missing data, multiplicity, estimands, and intention-to-treat principles.

8. 8. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants. 2024 revision.