SCE 0905 Public Evidence Appendix

Outcomes

Literature review date: September 13, 2026

Controlling principle. Trial outcomes are not interchangeable. Biological activity, imaging change, functional performance, patient experience, quality of life, survival, and safety answer different questions. Findings should be described at the level actually measured, and clinical importance should be considered separately from statistical significance.

Point-by-point framework

Controlling Point	What it measures	Interpretive boundary
Safety endpoints	Adverse effects, complications, serious events, hospitalization, death, and other harms.	Small or short studies may miss uncommon or delayed risks; absence of observed harm is not proof of complete safety.
Biomarkers	Biological state, process, exposure, target engagement, prognosis, or response.	A biomarker change is not automatically clinical benefit; surrogate endpoints require validation.
Imaging	Anatomy, structure, perfusion, inflammation, tissue characteristics, or function.	A statistically detectable imaging change may not improve symptoms or function.
Functional outcomes	What a patient can do or how a body system performs.	Performance can be affected by learning, motivation, rehabilitation, devices, and baseline severity.
Patient-reported outcomes	Symptoms, function, health status, and treatment experience reported directly by patients.	Instrument validity, missing data, recall period, blinding, and meaningful change matter.
Quality of life	Physical, psychological, social, and role-related well-being.	Improvement can be clinically important without changing survival; durability and magnitude remain essential.
Survival	Time to death or other prespecified time-to-event outcomes.	Censoring, follow-up, competing risks, crossover, subsequent therapy, and absolute effect size affect interpretation.
Clinically meaningful differences	Whether the magnitude of change matters to patients or clinical decisions.	Statistical significance alone does not establish clinical importance; thresholds are context-specific.

Evidence-handling rules

Primary, secondary, and exploratory endpoints should remain distinct. Composite endpoints require component-level interpretation. Outcome timing, durability, missing data, multiplicity, effect size, uncertainty, harms, and patient preferences all influence the strength and clinical meaning of a result.

A favorable mechanistic or surrogate result should not be promoted into a patient-benefit claim unless the relevant endpoint has been validated for that use and the clinical evidence supports the inference.

Principal references

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

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

3. 3. U.S. Food and Drug Administration. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Guidance for Industry.

4. 4. U.S. Food and Drug Administration. Multiple Endpoints in Clinical Trials: Guidance for Industry. 2022.

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

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

7. 7. Cella D, Hahn EA, Jensen SE, et al. Patient-Reported Outcomes in Performance Measurement. RTI Press; methodological framework and related validation literature.

8. 8. Contemporary clinical-trial methodology literature on minimal clinically important differences, time-to-event outcomes, surrogate endpoints, and interpretation of effect size.