SCE 0904 Public Evidence Appendix

Study populations

Literature review date: September 13, 2026

Controlling principle. Clinical evidence applies most directly to the population actually studied. Extrapolation to different disease stages, prior-treatment histories, comorbidity burdens, ages, demographic groups, or practice settings should be proportional to the directness and consistency of the evidence.

Point-by-point framework

Controlling Point	Primary issue	Interpretive boundary
Eligibility criteria	Define who may enter the study and protect safety and interpretability.	Overly restrictive criteria can reduce applicability; overly broad criteria can combine biologically distinct groups.
Disease severity	Severity affects baseline risk, room for improvement, reversibility, and detectable treatment effect.	Results from mild disease cannot automatically be applied to advanced disease, or vice versa.
Prior treatment	Previous therapy can alter biology, prognosis, tissue state, and treatment responsiveness.	Treatment-naive, refractory, and heavily pretreated populations answer different clinical questions.
Comorbidities	Additional disease and polypharmacy can alter efficacy, safety, procedures, and competing outcomes.	Early exclusions may be justified for safety but can limit later applicability to routine clinical populations.
Age	Age can affect disease phenotype, immunity, regenerative capacity, organ reserve, and adverse-event risk.	Evidence should not be extrapolated across substantially different age groups without support.
Sex	Sex-related biology can affect disease, immune responses, hormones, pharmacology, and outcomes.	Underrepresentation limits certainty; subgroup findings require adequate design and interaction testing.
Race and ethnicity	Enrollment and outcomes may reflect ancestry, environment, access, social conditions, comorbidity, and treatment patterns.	Racial or ethnic categories should not be treated automatically as simple biological causes.
Generalizability	Assesses whether findings apply beyond the enrolled participants, sites, and treatment conditions.	Excellent internal validity can coexist with limited external validity; conclusions should not exceed the studied population.

Evidence-handling rules

Positive, negative, mixed, null, and inconclusive findings are interpreted in relation to who was enrolled, who was excluded, baseline risk, disease stage, prior therapy, comorbidity, demographic representation, site characteristics, and the exact product and clinical setting.

Subgroup findings require particular caution: prespecified hypotheses, adequate sample size, formal interaction testing, and replication are more informative than comparing statistical significance separately within subgroups.

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. Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies. Guidance for Industry. 2024.

4. 4. U.S. Food and Drug Administration. Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs. Guidance for Industry. 2020.

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. National Academies and contemporary clinical-trial literature on inclusion, representation, recruitment, retention, and generalizability.

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