INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

24 November 2025

Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2025-D-3403, Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations

To whom it may concern:

The International Society for Stem Cell Research (ISSCR) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance for Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations.

The ISSCR is an independent, global, nonprofit organization that promotes excellence in stem cell science and applications to human health. ISSCR represents 4,700 scientists, educators, ethicists, and business leaders across 80 countries. Our vision is a world where stem cell science is encouraged, ethics are prioritized, and discovery improves understanding and advances human health.

ISSCR appreciates FDA's willingness to consider alternative designs for clinical trials of cellular and gene therapy products. Additional guidance from the FDA will support our members, who are leading research and innovation, in their efforts. To complement FDA's efforts, we offer the following comments and recommendations regarding Regenerative Medicine Products (RMPs).

I. General Comments

i. **Manufacturing Changes in Adaptive/Master Protocols**. ISSCR requests additional guidance on how manufacturing changes, which are common in RMPs, should be bridged within adaptive/master protocol designs (e.g. with comparability studies, or cohort splits).

ii. **Decentralized Trials for Small Populations**. Decentralized trials can improve enrollment for small cohorts. ISSCR requests additional guidance on remote consent, home visits, specimen logistics, and tele-assessments while protecting data integrity.

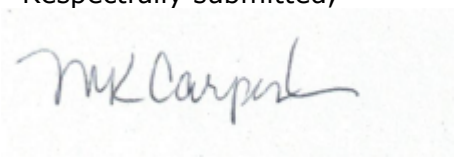
iii. **Long-Term Follow-Up.** ISSCR requests clarity on clinical trial design considerations for long-term follow ups related to long term RMP immune response or mutation risk tracking and how to integrate such data with other pivotal evidence.

iv. **Surrogate Endpoints and Biomarkers.** ISSCR appreciates FDA encouraging the use of surrogate endpoints and biomarkers, but it will be helpful to have more guidance about how such surrogate endpoints can be used as pivotal efficacy evidence. How should these measurements be validated, especially when the patient sample size is small or when disease progression is variable?

v. **Trial Design Selection.** It will be helpful if FDA provided examples of a decision tree or a checklist for choosing among single-arm, external-control, adaptive, Bayesian, or master-protocol approaches based on disease course, expected effect size, and feasibility constraints.

Thank you for considering our views on the draft guidance for Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations. If the ISSCR can clarify any of these views or be of assistance, please contact Tyler Lamb, ISSCR's Director of Policy, at tlamb@isscr.org or Denise de Villa, ISSCR's Manager of Policy, at ddevilla@isscr.org.

Respectfully submitted,



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