

TECHNICAL EVALUATION & CDMO FRAME

Autologous Adipose MSC

MADE technical evaluation and CDMO frame

PI	MAYO SITE	ON NUMBER	MODALITY	VERSION
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PREPARED				
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1. At a glance

Program	Autologous adipose-derived MSC — frozen drug substance, fresh drug product
Modality	Autologous MSC, adipose-derived
Phase	Phase I/II
Regulatory status	Understood to be NCT06649864 — Phase 1, single group, 20 patients, Mayo-sponsored, Rochester, start February 2027. Not confirmed by Mayo; see §15
Starting material	Patient adipose tissue
Drug substance	Cryopreserved into 1 mL vials, held in liquid nitrogen
Drug product	Thawed from a single vial, cultured, harvested, formulated and loaded into a syringe — administered within 8 hours of loading
Where MADE would manufacture	Princeton, NJ, with East Norriton, PA in the MADE network for scale
MADE reference	ON23735-2026
MADE technical fit	Good on process. The transport design is the substance of the answer — see §9 and §14

This is a technical assessment, not a proposal.

2. Program understanding

Your process runs in two tiers. Patient adipose tissue is collected and processed, adipose-derived MSCs are cultured, and drug substance is cryopreserved into 1 mL vials held in liquid nitrogen. For administration, a single drug substance vial is thawed and plated, cultured, harvested, formulated and loaded into a syringe — with the product administered within eight hours of loading. The drug product is fresh, not frozen.

What the public record adds. The trial is understood to be NCT06649864 — *autologous adipose-derived mesenchymal stromal cells in preventing biliary complications after living donor liver transplant* — Phase 1, 20 patients, Rochester, start February 2027. The cells are applied once at the biliary anastomosis during the transplant operation, which is why the product is fresh and why the clock is eight hours rather than a shelf life. Two consequences follow and both are favorable. The registered dose is approximately $3-5 \times 10^6$ cells in 5 mL of Lactated Ringer solution, two orders of magnitude below the modality's usual 10^8 per dose, so expansion capacity is not the constraint anywhere in this program. And **living-donor transplant is elective, scheduled surgery**, so the manufacturing slot is plannable rather than reactive — the most useful structural property this program has. We have marked the identification as understood rather than settled, and it is the first question in §15.

Two things about this program are stronger than the modality norm. Karyotype on drug substance addresses the passage-dependent quality question directly on an expanded autologous product, and a great many programs omit it. And the identity panel goes beyond the ISCT minimum: CD90, CD73 and CD105 with

CD14, CD45 and HLA-DR negative is the standard core, and you have added CD44 and HLA-ABC. That is a more informative panel than most.

3. Regulatory position and pathway

Current filing status	Phase I/II. Understood to be NCT06649864 — registered, Mayo-sponsored, not yet recruiting, start February 2027; see §15
Designations held	None recorded
What the CMC package must support	Phase 1: the process described with critical parameters identified though not validated; identity by flow; viability; sterility, endotoxin and mycoplasma; a biologically relevant quantitative potency assay qualified rather than validated; and stability sufficient for the proposed storage and shipping with a real-time study started. It does not need validated release methods, reference standards or ICH-compliant long-term stability
What a site change implies	Manufacture moves from Mayo to MADE. Your RFI sets the bar: comparability of at least three runs using the intended in-house analytical methods, with method validation permitted concurrently, and shipping verification performed inside the comparability studies
Applicable guidance	ISCT 2006 minimum criteria; 21 CFR 1271 and 610; USP <71>, <63> and <85>; ICH Q5A. FDA CBER's flexible-CMC position of 11 January 2026 applies: before Phase 2/3 manufacture, 21 CFR Part 211 compliance is not expected, specifications may be permissive, and three PPQ lots are not required
The recurring modality deficiencies	Donor variability not adequately characterized; potency not correlated to clinical mechanism; senescence characterization insufficient; passage-dependent quality changes not controlled. All four are the same problem — a product defined by what it is rather than what it does

4. Starting material

Source	Patient adipose tissue — autologous, one patient per batch
Collection	Collection method and typical tissue quantity are not stated in the RFI — see §15
Acceptance criteria	Not established — see §15. The controlling variables are time from collection to processing start, transport temperature and container, and we would agree them with your team before the first run rather than propose them unilaterally
Fresh or cryopreserved	Fresh tissue, shipped inbound to the manufacturing site
Time from collection to processing	Not established — see §15
Isolation	Not stated in the RFI. Enzymatic digestion liberates cells in hours and allows same-day plating, at the cost of residual enzyme and matrix fragments that need clearing and controlling; explant outgrowth is purer and slower — see §15
Chain of identity and custody	Autologous, so identity is patient-linked from collection through to the operating room. The identity chain and the transport lane are the same problem and would be designed together

Scheduling	Living-donor liver transplant is elective, scheduled surgery. The manufacturing slot is booked against a known surgical date rather than against an unplanned admission, which is the difference between a plannable autologous program and a reactive one
Failed collection or failed expansion	Not established — whether re-collection is protocol-permitted, and whether the surgical date waits, is an open question. See §15

5. Process flow

Unit operation	Your approach	MADE capability	Read
Adipose tissue receipt	Patient tissue, collected and shipped	Standard receipt, with a defined time-and-temperature window to agree	Fits — window to agree, see §4
Isolation	Not stated in the RFI	Standard; enzyme residual clearance controlled as part of the process	Fits
MSC culture and expansion, drug substance	Not stated in the RFI	Corning CellSTACK-scale flask work, Terumo Quantum Flex hollow fiber, PBS Biotech vertical-wheel, Sartorius Biostat STR	Fits at any of these. At a $3-5 \times 10^6$ cell dose, scale is not the constraint
Drug substance harvest and formulation	Final collection, then cryopreservation	LOVO and CTS Rotea for harvest and wash	Fits
Drug substance freeze and storage	1 mL vials, liquid nitrogen	Controlled-rate freezing and LN2 storage at both sites	Fits — freeze profile transfers with the process
Drug product thaw and plate	Thaw a single DS vial, plate	Standard	Fits
Drug product culture	Culture to dose	Standard	Fits
Drug product harvest, formulate, load	Harvest, formulate, load into a syringe	Standard aseptic operation, Grade B background with Grade A biological safety cabinet	Fits
Release and administration	Interim in-process sterility supports administration; final sterility follows treatment	Release turnaround designed around the eight-hour clock	This is the constraint — see §9 and §14

6. Key equipment

Instrument	Your platform	MADE's installed position	Onboarding required
Corning CellSTACK — multi-layer flask	Not stated	Publicly named platform option; a consumable vessel rather than a tracked asset	None

Instrument	Your platform	MADE's installed position	Onboarding required
Terumo BCT Quantum Flex — hollow fiber	Not stated	1 at Princeton	None. The lowest-comparability-risk route out of an open flask process, because it closes and automates the work while preserving 2D growth geometry
PBS Biotech vertical-wheel	Not stated	6 at Princeton	None
Sartorius Ambr 15 — small-scale screening	Not stated	1 at Princeton	None
LOVO — harvest and wash	Not stated	3 at Princeton, 1 at East Norriton	None
CTS Rotea — harvest and wash	Not stated	3 at Princeton, 2 at East Norriton	None
Controlled-rate freezer	Used for drug substance	2 at Princeton, 7 at East Norriton	Freeze profile and post-thaw plating performance transfer with the process
NucleoCounter NC-200 — count and viability	NucleoCounter NC-200	7 at Princeton	None — the same instrument you specify
Beckman Coulter CytoFLEX — flow cytometry	Not stated	4 at Princeton, 13-color	Panel and gating strategy transfer with the method
Endosafe nexgen-PTS — endotoxin	Endosafe nexgen-PTS	4 at Princeton, 3 at East Norriton	None — the same platform you specify
BioFire — mycoplasma by PCR	BioFire	1 at Princeton, 2 at East Norriton	None — the same platform you specify

7. Analytical panel and release

Tier	Attribute	Your method	MADE position	In house or outsourced
Drug substance	Sterility, no growth after 14 days	BacT/Alert, USP <71>	USP <71> run in house	In house
Drug substance	Endotoxin, informational	Endosafe nexgen-PTS, USP <85>	Same platform, 7 units across both sites	In house
Drug substance	Mycoplasma, not detected	PCR, BioFire, USP <63>	Same platform, 3 units across both sites	In house
Drug substance	Identity — CD90 ≥85%, CD73 ≥85%, CD105 ≥85%, CD44 ≥85%, HLA-ABC ≥60% of gated; CD14 ≤5%, CD45 ≤5%, HLA-DR ≤5%	Flow cytometry	Beckman Coulter CytoFLEX, 13-color. A viability dye and the gating strategy are part of the method and transfer with it	In house

Tier	Attribute	Your method	MADE position	In house or outsourced
Drug substance	Genetic stability, no clonal abnormalities	Karyotype, G-banding	Standard	Outsourced, as across the industry
Drug product	Cell dose, consistent with order and trial group	NucleoCounter NC-200	Same instrument	In house
Drug product	Viability $\geq 70\%$	NucleoCounter NC-200	Same instrument	In house
Drug product	In-process sterility, 48 h before harvest — pending at administration	BacT/Alert, USP <71>	USP <71> run in house	In house
Drug product	Final sterility, no organisms seen	Gram stain	Standard	In house
Drug product	Final sterility, result follows treatment	BacT/Alert, USP <71>	USP <71> run in house	In house
Drug product	Endotoxin <0.2 EU/kg	Endosafe nexgen-PTS, USP <85>	Same platform	In house
Drug product	Mycoplasma, not detected — rapid, available before treatment	BioFire, USP <63>	Same platform, and the rapid result before treatment is preserved	In house
Both	Potency	None in either panel	See §7a	—

On a positive sterility. Your process notifies the physician within 24 hours and identifies the organism to species level. That path transfers as it stands; we would want to understand whether MADE is expected to replicate it exactly or to feed into it — see §15.

Every test in both panels sits within MADE's in-house capability, with karyotype outsourced as is standard everywhere. Your panel transfers as it stands; we would add nothing and remove nothing without your agreement.

7a. Potency

Neither panel carries a functional attribute, and that is a more defensible position for an autologous product than it would be for an allogeneic bank. The donor is the patient, so donor variability cannot be managed, only characterized — and a functional release gate would put a patient's dose at risk against an acceptance range that does not yet exist. Identity by ISCT-style markers does not distinguish an MSC from a fibroblast, and it says nothing about whether this patient's cells are functional.

Our recommendation is characterization rather than release. An IDO or PGE2 readout on every batch, run as characterization data and not as a release gate, uses instruments already in our laboratories, accumulates the dataset that makes a Phase 2 specification defensible, and risks nothing clinically. Population doubling

time tracked per passage belongs alongside it as the cheapest available signal of the senescence that silently degrades MSC function. Which readout is mechanistically right at a biliary anastomosis is a question for your laboratory, not ours.

8. Fill, finish and presentation

Container closure — drug substance	1 mL vials
Container closure — drug product	Syringe
Fill volume — drug substance	1 mL per vial
Fill volume — drug product	Not stated in the RFI. The registered trial describes approximately $3-5 \times 10^6$ cells in 5 mL of Lactated Ringer solution — see §15
Dose form	Fresh cell suspension, applied once at the biliary anastomosis during the transplant operation
Labeling	Not established — see §15
Controlled-rate freeze	Drug substance only. Controlled-rate freezers are deployed at both MADE sites; the profile transfers with the process
Storage	Drug substance in liquid nitrogen. Drug product has no storage step — the clock runs from loading

There is no terminal aseptic fill-finish operation on the drug product in the conventional sense: the product is formulated and loaded into a syringe for immediate use, and the release design is built around that rather than around a shelf life.

9. Stability, storage and shipping

Stability status — drug substance	Not established for this program — see §15. The modality position is stability assessed at 6, 12, 24 and 36 months at $\leq -150^\circ\text{C}$ in vapor-phase liquid nitrogen, testing post-thaw viability, marker expression and potency, with a loss of more than 10% in viability or potency triggering investigation
Stability status — drug product	Not applicable in the usual sense. The eight-hour window is the stability claim, and it has to be demonstrated at the far end of the window rather than the near end
Storage condition — drug substance	Liquid nitrogen
Storage condition — drug product	None — administered within 8 hours of loading
Inbound shipper, adipose tissue	Not established — see §15. A well-understood shipment; the controlling variables are time, temperature and container
Outbound shipper, drug product	Not established — see §15. This is the harder leg, and the design has to establish how much of the eight hours transport may consume and what remains for the site

Qualification status	Neither lane is qualified today. Your RFI places shipping verification inside the comparability studies, and we have scoped it there rather than as a precondition
Chain of custody, outbound leg	Not established — see §15. The registered trial lists Rochester only while the RFI names Rochester, Jacksonville and Phoenix; which governs the design changes the answer materially
Distance	MADE is not within a few hours of Rochester, Jacksonville or Phoenix. We would rather say that plainly than soft-pedal it. Your RFI names validated transport as the alternative, and that is the route we would take — see §14

10. Comparability

The comparability exercise here is a site change on an academic-origin process, which sets the expectation honestly at the start: academic or research-lab origin normally carries three to five bridging lots with equivalence margins on critical quality attributes. **Your RFI sets the bar at a minimum of three runs using the intended in-house analytical methods, with method validation permitted concurrently and shipping verification included.** We would design to your number and tell you if the data argues for more.

What the protocol has to cover, weighted: identity by flow and purity HIGH; immunomodulatory activity CRITICAL where a functional readout exists; viability HIGH; proliferative capacity HIGH; karyotype MEDIUM and rising with passage; endotoxin HIGH; sterility and mycoplasma every lot. We would add population doubling time, which is the cheapest early senescence signal available and the one most often not tracked.

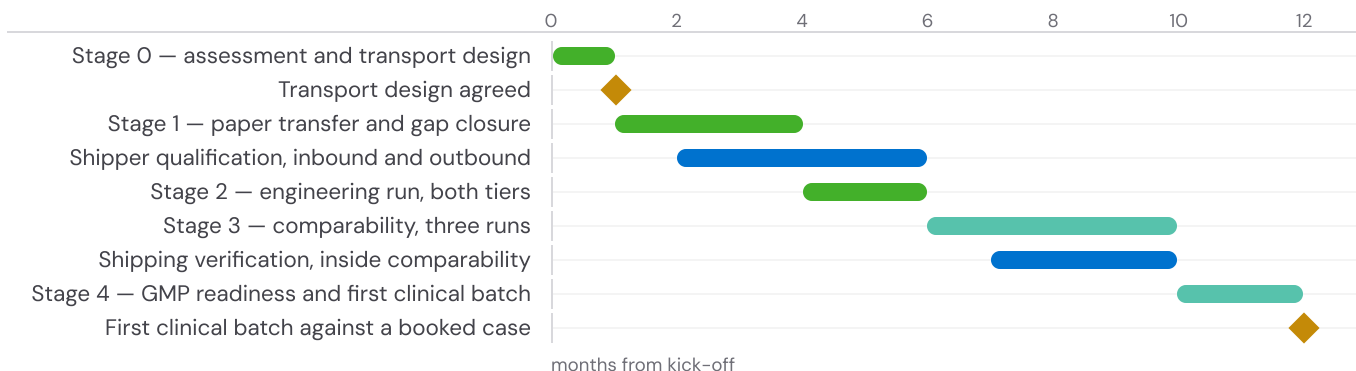
Change	Risk	What has to bridge it
Transport — inbound tissue and outbound fresh drug product	Highest, and named by you as a comparability item	Dose and viability demonstrated across the full window under worst-case conditions, on both legs
Site change, Mayo to MADE	High	Three runs minimum on the intended in-house methods
Culture platform and vessel	High	If your process runs open flasks and MADE proposes a closed platform, that is a comparability exercise in its own right. Hollow fiber is the lowest-risk route because it preserves 2D growth geometry
Media and supplement — serum, human platelet lysate or xeno-free	High	Not stated in the RFI. If serum, the conversion plan and its timing is a live question — a conversion shifts growth rate and cell behavior and needs comparability
Passage budget	Medium-High	Autologous, so the budget is per patient. Limits and their justification need stating
Analytical methods	Medium	Your methods transferred, MADE equivalents qualified, or a combination, with equivalency demonstrated
Cryopreservation of drug substance	Medium	Controlled-rate profile and post-thaw plating performance

11. Technology transfer approach

Stage	What happens	Gate
Stage 0 — technical assessment and transport design	This document, plus a worked transport design for both legs against the eight-hour window	Transport design agreed with your team before scope is fixed
Stage 1 — paper transfer and gap closure	Batch records mapped; culture format, media and passage budget confirmed; shipper qualification planned; analytical gap assessment across both panels. In this modality the analytical gap is usually larger than the process gap, so it starts first	Gap list closed and materials sourced
Stage 2 — engineering run	Non-GMP through both tiers on healthy-donor tissue, with population doubling time tracked per passage and both transport legs exercised end to end	Engineering run meets both release panels
Stage 3 — comparability	Three runs minimum on the intended in-house methods, method validation concurrent, shipping verification included as your RFI specifies	Comparability accepted
Stage 4 — GMP manufacture, release and clinical supply	GMP readiness, then batches scheduled against booked surgical dates. Because living-donor transplant is elective, the manufacturing slot is set from a known operating-room date rather than from an unplanned admission — the slot, the release turnaround and the transport lane are planned as one interval	First clinical batch released against a booked case

12. Indicative timeline

Stage	Duration
Stage 0 — assessment and transport design	3–5 weeks
Stage 1 — paper transfer and gap closure	1–3 months
Stage 2 — engineering run, both tiers	1–2 months
Stage 3 — comparability, three runs plus shipping verification	2–4 months
Stage 4 — GMP readiness and first clinical batch	1–2 months
Total	12–18 months [industry range], plus approximately one month for autologous scheduling complexity



The two transport bars are drawn separately because your RFI places shipping verification inside comparability, and we have scoped it that way rather than as a precondition. A February 2027 first patient sets the direction of travel for everything on this chart, and it is the second question in §15.

13. MADE experience that supports this

On adipose MSC. MADE has manufactured GMP MSC lots for global customers since technology transfer began in Q3 2025, at approximately 0.5 billion viable cells per CS10. The RoosterBio strategic partnership, announced 5 May 2026, brings xeno-free MSC expansion media and bioprocess-ready starting material into our GMP operations. For per-patient batch sizes at this dose, CellSTACK-scale flask work and Quantum Flex hollow-fiber expansion are both directly applicable, and neither is stretched by the scale.

On the analytical bench. Every attribute in both of your panels is covered in house, on instruments deployed today — flow on CytoFLEX, count and viability on the same NucleoCounter NC-200 you specify, endotoxin on the same Endosafe platform, mycoplasma on the same BioFire platform.

On quality. MADE's quality leadership carries collective experience from prior organizations across cell therapy quality systems, aseptic manufacture, comparability and inspection readiness. This is experience held by individuals now at MADE; the company itself has not yet completed a client audit.

On facilities. Princeton, NJ and East Norriton, PA. Grade B background with Grade A biological safety cabinets for open manipulations; closed-system steps as Grade B / Closed System.

14. Guidance and suggestions

On transport, which is the question your RFI puts first. We see two structural options and would want your view on both.

Option A — ship the drug product. A qualified courier lane and a validated shipper, with data supporting viability and dose across the full window under worst-case conditions. This keeps everything in one place and spends part of the eight hours in transit.

Option B — ship drug substance and perform the final culture-and-formulate step near the clinical site. This preserves the whole eight-hour window at the site rather than consuming part of it in transit. It implies a presence or a qualified partner near your clinical site and is a different commercial conversation — but it is the option that solves the constraint rather than working within it.

Our preliminary view is that Option B deserves serious examination, and the registry makes the case stronger rather than weaker: NCT06649864 is registered at Rochester only, while the RFI names three campuses. If Rochester is the whole footprint, Option B has one destination to serve rather than three, which changes the shape of the problem entirely. We would not commit to it without your view of the site mix and the regulatory implications, which is why it is a question in §15 rather than a recommendation here.

On the surgical date. A living-donor operation books two people into an operating room. Nothing in our scheduling design should imply that a manufacturing slot could move that date; the date sets the slot, never the reverse. What we would want to understand is how far ahead a case is booked and what fraction move or cancel inside that window, because that number designs the whole slot.

On potency, stated plainly. Run an IDO or PGE2 readout on every batch as characterization data, not as a release gate, with population doubling time tracked per passage alongside it. See §7a.

On endotoxin. It is informational at drug substance and specified at <0.2 EU/kg on drug product. That is a coherent design for an intermediate, and it does mean the entire endotoxin control point sits on a fresh product with an eight-hour clock. We would want to establish that the assay turnaround supports that comfortably rather than marginally.

15. Open questions

The program. Is NCT06649864 the trial behind ON23735–2026, and is the February 2027 start still the plan? Is this Phase I/II starting fresh or continuing existing work? Who holds the IND, and where does manufacture sit in the current submission?

Scheduling — this one designs the manufacturing slot. How far ahead is a living-donor case scheduled, and what fraction move or cancel inside that window? What happens to the case if the product is late, and what happens to a batch already in manufacture if the case moves? Expected patients per month?

Logistics. What is the acceptable time and temperature window for adipose tissue from collection to processing start? Of the eight-hour post-loading window, how much may transport consume? **Would you consider Option B — shipping drug substance with final drug product preparation near the clinical site?** The registration lists Rochester only and the RFI names three campuses; which governs the transport design?

Starting material. What is the adipose collection method and typical tissue quantity? Is isolation enzymatic or by explant outgrowth? What acceptance criteria would you want on incoming tissue? If a patient's cells fail to expand to dose, is re-collection protocol-permitted, and does the surgery wait?

Process. What culture vessel and format is used today? What media and supplement — fetal bovine serum, human platelet lysate, or xeno-free — and if serum, is a conversion planned? What passage and population-doubling limits apply, and what justifies them? What is the target cell dose, and does it vary by trial group? Three anticipated biliary anastomoses is an exclusion criterion — does the dose scale between one and two anastomoses, and does that change the batch?

Analytics and release. Would you prefer your methods transferred or MADE equivalents qualified? Is population doubling time tracked per passage? **Would you support an IDO or PGE2 characterization assay on every batch to build the Phase 2 potency dataset?** What is the working mechanistic hypothesis at the

anastomosis — anti-fibrotic, immunomodulatory, or both — and is there a preclinical readout we could carry forward as a batch characterization assay? What is the endotoxin assay turnaround against the eight-hour window? On a positive sterility, is MADE expected to replicate your 24-hour physician-notification path exactly, or to feed into it?

Presentation and stability. What is the drug product fill volume and formulation buffer? What labeling applies at each tier? What drug substance stability data exists today, and at what timepoints?

16. Suggested next step

A working session on the transport design specifically. It is the question your RFI puts first, it is the one where our answer needs your input rather than the other way round, and settling it — with the Rochester-only question answered alongside it — makes every other part of the scope estimable.