

TECHNICAL EVALUATION & CDMO FRAME

Autologous Dendritic Cell — Liver Cancer

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 monocyte-derived dendritic cells, cryopreserved unloaded mature drug product
Modality	Dendritic cell, autologous monocyte-derived, delivered intratumorally
Phase	Phase I/II — MC1641, NCT03942328, recruiting since 19 September 2019, 85 patients planned
Trial	Intratumoral dendritic cells with immune checkpoint inhibition after high-dose conformal external beam radiotherapy , in unresectable primary liver cancer. Mayo Clinic sponsor, NCI collaborator, with Dr. Fonkouda as co-principal investigator
Regulatory status	Trial open and recruiting. Whether a manufacturing site change runs as an amendment or a new IND is open — see §3
Starting material	Leukapheresis, autologous
Drug substance	Mature, unloaded monocyte-derived dendritic cells harvested from the seven-day culture
Drug product	Cryopreserved mature unloaded DC in 1 mL vials, product and reserve vials at defined cell doses; 30–60 × 10 ⁶ mature DC per injection
Current process	LOVO wash, CliniMACS Plus CD14 selection, T-175 differentiation, cytokine maturation; seven days
Governing constraint	A hard 21-day manufacturing window set by the radiotherapy schedule — see §11 and §12
Where MADE would manufacture	Princeton, NJ, with East Norriton, PA in the MADE network for scale
MADE reference	ON23745–2026
MADE technical fit	Strong on unit operations and equipment — every step maps to instruments in service today, with nothing to onboard. On modality experience we are direct: MADE has not manufactured a dendritic cell product. See §13

This is a technical assessment, not a proposal.

2. Program understanding

What your team told us. Your process runs seven days from leukapheresis receipt. Material is washed, concentrated and volume-reduced on the LOVO in a closed system; CD14-positive monocytes are enriched by immunomagnetic selection on the CliniMACS Plus, producing a defined starting population. Selected cells are seeded into T-175 flasks with immature DC media formulated from CellGenix media, IL-4, GM-CSF and Glutamax. Maturation transitions immature cells into an unloaded mature phenotype using defined cytokines including PGE2 and TNF- α , with cells redistributed into T-175 flasks for a defined maturation window under strict timing control. Mature unloaded DCs are harvested, released, formulated with cryoprotectant, aliquoted into product and reserve vials at defined doses, controlled-rate frozen and stored in vapor-phase liquid nitrogen.

What the public record adds, and it changes the manufacturing brief. MC1641 delivers those cells *intratumorally*, into a lesion that has just been treated with high-dose conformal external beam radiotherapy, on a checkpoint-inhibition backbone. Apheresis and the radiotherapy — five or fifteen fractions across one to three weeks — are cycle 1. **The first dendritic cell dose is day 1 of cycle 2, and cycles repeat every 21 days.** That is a hard 21-day manufacturing window, and release, including a fourteen-day sterility read, has to land inside it. The 13-valent pneumococcal conjugate vaccine given alongside the dose is a licensed product and sits outside the manufacturing scope.

We read that as the single most important planning input in the program, and we have written §11 and §12 against it rather than against suite availability.

Two aspects of how you run this make a transfer easier than the modality norm.

You test at three points across the front of the process — apheresis, post-LOVO and post-CliniMACS — for cell count, with flow cytometry on apheresis and post-selection material. That means a low yield can be attributed to the collection, the wash or the selection rather than appearing as an unexplained shortfall at harvest. Many programs test only at the ends.

Your quality position is mature. All methods validated in a phase-appropriate manner, safety methods fully validated or verified, other methods qualified against the relevant ICH Q2(R2) parameters, with release shortly after the fourteen-day sterility result. We have written this assessment accordingly rather than starting from fundamentals.

3. Regulatory position and pathway

Item	Position
Current filing status	Trial open and recruiting since 19 September 2019, 85 patients planned, primary completion May 2030. Mayo Clinic sponsor with NCI as collaborator
Designations held	Not established — see §15
What the CMC package must support at this phase	The process described with critical parameters identified; identity by flow; viability; sterility, endotoxin and mycoplasma; and a biologically relevant, quantitative potency assay that is qualified rather than validated. Before Phase 2/3 manufacture, 21 CFR Part 211 compliance is not expected, IND specifications may be permissive, and there is no requirement for three PPQ lots
Amendment versus a new IND	You asked this directly on 18 August, and it deserves a framed answer rather than a ruling. An amendment to the existing IND normally moves faster and preserves the trial's manufacturing and clinical history, in exchange for carrying a comparability package that satisfies a reviewer already familiar with the product. A new IND resets that history and the review clock, and is generally reached for when the product or the process has changed enough that a bridge is not credible. Which applies here turns on how much of the process moves and what the existing IND already commits to — we would not offer a definitive view without having read the IND , and MADE's regulatory lead would take that on with your team
What a site change implies either way	A comparability exercise against your historical batches and a site-change assessment. Transfer risk on the standard matrix sits at the harder end of its band for this modality, because DC processes are institution-specific with no platform reference to fall back on — see §10
Long-term follow-up	Non-integrating dendritic cell products do not carry the fifteen-year follow-up expectation that applies to integrating vectors

Item	Position
Applicable guidance	FDA CBER, <i>Potency Assurance for Cell and Gene Therapy Products</i> , draft, December 2023; <i>Long-Term Follow-Up After Administration of Human Gene Therapy Products</i> , final, January 2020; and the CBER flexible-CMC announcement of 11 January 2026
What to expect the agency to ask	There is no published dendritic-cell deficiency list to work from. Reasoning from the framework, the questions to expect are what measures potency and whether it is mechanism-correlated; how maturation state is controlled and demonstrated batch to batch; and how product consistency is assured across an unloaded product whose antigen is supplied in situ by the irradiated tumor

4. Starting material

Item	Position
Source	Autologous leukapheresis
Collection	Apheresis is performed in cycle 1, alongside the radiotherapy course. Radiation oncology sets the front edge of the manufacturing slot
Acceptance criteria	Not established — monocyte content is patient-dependent and is the variable that decides whether this process yields a dose. See §15
Fresh or cryopreserved	Not established — see §15
Time from collection to processing	Not established. It matters more here than in most programs, because it consumes the 21-day window before manufacture starts. See §15
Chain of identity and custody	MADE runs standard incoming handling with chain of identity and chain of custody. The collection-to-manufacture leg would need designing against the radiotherapy calendar rather than against a manufacturing calendar
On a failed collection	Not established. In a schedule owned by a second department, a re-collection is not simply a repeat — it re-enters the radiotherapy sequence. See §15
Monocyte yield	Not established — what yield is typically achieved post-CliniMACS, and what the acceptance threshold is, are the two numbers we would want first. See §15

5. Process flow

Unit operation	Your approach	MADE capability	Read
Leukapheresis receipt and acceptance	Standard receipt; count and flow on the incoming material	Standard incoming handling, chain of identity and custody	Fits
Wash and volume reduction	LOVO, closed system	Four LOVO systems in service — see §6	Fits
CD14 monocyte enrichment	CliniMACS Plus immunomagnetic selection	Five CliniMACS Plus units in service — see §6	Fits

Unit operation	Your approach	MADE capability	Read
In-process control, front of chain	Count at apheresis, post-LOVO and post-CliniMACS; flow at apheresis and post-selection	Transfers unchanged. Your counts run on a Sysmex analyzer; at MADE these would run on the NucleoCounter NC-200 your panel already names for viability	Fits, with an instrument note
Differentiation	T-175 flasks, CellGenix media with IL-4, GM-CSF, Glutamax	Grade B suites with Grade A biological safety cabinets are built for exactly this kind of open flask work	Fits
Maturation	PGE2, TNF- α ; strict timing controls; redistribution into T-175 flasks	Transfers as validated parameters. Cytokines specified by specific activity rather than mass concentration, since activity differs between vendors and lots	Fits
Harvest and release	Release testing on the final cell harvest before freezing	Standard	Fits
Formulation, fill, freeze	Cryoprotectant, product and reserve vials, controlled-rate freeze	Nine controlled-rate freezers in service — see §6 and §8	Fits
Distribution	Validated LN2 shipping to Mayo sites	Standard capability — see §9	Fits

No antigen loading is in scope. The product is an unloaded mature dendritic cell; the antigen is supplied in situ by the irradiated tumor. That removes the hardest supply chain in this modality — per-patient peptide, lysate or mRNA — and a whole class of comparability question with it. We would confirm that boundary explicitly, because it changes what MADE is being asked to make.

Culture is flask-based and manual, and that is a scheduling fact rather than a problem. There is no closed automated platform for dendritic cell manufacture with the maturity of the closed systems used for T cells. Batch size is bounded by operator capacity and suite time rather than by vessel volume, which is why the throughput conversation for this program is about people and slots.

6. Key equipment

Instrument	Your platform	MADE's installed position	Onboarding required
LOVO	Wash and volume reduction	4 in service — 3 Princeton, 1 East Norriton in room L-140	None
CliniMACS Plus	CD14-positive selection	5 in service , Princeton	None
Controlled-rate freezer and LN2 storage	Controlled-rate freeze, vapor-phase LN2	9 in service — 2 Princeton, 7 East Norriton	None
NucleoCounter NC-200	Viability and count	7 in service, Princeton — the same instrument your panel names	None

Instrument	Your platform	MADE's installed position	Onboarding required
Beckman Coulter CytoFLEX, 13-color	Flow cytometry, run on Navios at Mayo	4 in service, Princeton	Equivalency bridge, not onboarding — see §7
BioFire	Mycoplasma by PCR	3 in service — 1 Princeton, 2 East Norriton	None
Endosafe	Endotoxin	7 in service — 4 Princeton, 3 East Norriton	None
CTS Rotea	Not used in your process	5 in service — 3 Princeton, 2 East Norriton	Available if a closed counterflow alternative to LOVO is ever of interest
Elutra	Not used in your process	Held, but not in service	Would be an acquisition-and-qualification conversation if a process ever required it

Every unit operation in your process maps to an instrument in service today, and nothing needs onboarding for this transfer. Your RFP's Areas of Interest ask about new equipment onboarding timeframes, IQ/OQ ownership and how a site determines what requires validation. For this process the answer is that none of it is on the critical path, and we would answer those questions in that context rather than as a hypothetical.

7. Analytical panel and release

Attribute	Your method	Specification	MADE position	In house or outsourced
Sterility, 14 days	BacT/Alert USP <71> or direct inoculation USP <71>	No growth	See the method note below	In house
Endotoxin	Endosafe nexgen-PTS, USP <85>	Informational use only	Same instrument family	In house
Mycoplasma	BioFire PCR, USP <63>	Not detected	Same instrument	In house
CD83	Flow cytometry, Navios	≥70% gated	CytoFLEX — equivalency bridge required	In house
CD197, CD14, CD86, CD274, B7H2, CD80, HLA-DR, CD45	Flow cytometry, Navios	For information only	CytoFLEX, same bridge	In house
Viability, post-harvest	NucleoCounter NC-200	≥70% of total cells	Same instrument	In house

The Navios-to-CytoFLEX bridge is routine work, and your RFP already invites in-house equivalents where equivalency is demonstrated. We would run it as part of analytical gap closure rather than as a separate exercise.

Sterility method for a cryopreserved product. Your panel lists USP <71> by BacT/Alert or direct inoculation. For a cryopreserved product carrying cryoprotectant, MADE's standard is USP <71> by membrane filtration, because cryoprotectant carryover can inhibit direct inoculation and mask a contaminated unit; BacT/Alert

then serves as the rapid interim read. This is a method–suitability point to settle during analytical transfer, not a criticism of the current method — and given the 21-day window, how quickly a reliable interim read is available is a scheduling question as much as a quality one.

7a. Potency

There is no potency assay in the panel. CD83 at $\geq 70\%$ gated is the only flow specification and everything else is informational, which is a defensible Phase 1 position and precisely the one that does not survive the move toward pivotal. This modality has no default assay to adopt later, which is why starting during transfer matters more here than elsewhere.

An unloaded, intratumorally delivered product raises the stakes on this. Where a loaded product can be characterized partly by what it carries, an unloaded one cannot — release rests entirely on maturation phenotype and function.

Your informational panel is more valuable than its label implies. CD80, CD86 and HLA-DR, with CD83, describe whether the product can prime a T cell rather than tolerize one; CD14 down-regulation evidences that differentiation happened; CD274 and B7H2 speak to polarization. Collecting all of them and specifying only CD83 is a deliberate, phase-appropriate choice — but the data accumulating is exactly the dataset from which Phase 2 specifications should be set.

CD197 is CCR7, and it is already in your panel. The ability to migrate to a draining lymph node is not reported by any other marker, and you are already measuring its surface expression.

Our recommendation: convert that into a functional CCR7-directed chemotaxis assay, paired with IL-12p70 secretion on maturation, as a Phase 2 potency matrix. Both run on instruments already in our laboratories — CytoFLEX and a multi-mode plate reader — and both build on measurements your process already generates.

8. Fill, finish and presentation

Item	Position
Container closure	1 mL vials, filled as product vials and reserve vials
Fill volume and dose	1 mL per vial. Dose is $30\text{--}60 \times 10^6$ mature DC per injection; the target cell dose per vial and the number of product and reserve vials per manufacture are not established — see §15
Dose form	Cryopreserved cell suspension, thawed and drawn into a syringe at the treating site
Labeling	Not established — see §15
Controlled-rate freeze	Controlled-rate freeze followed by vapor-phase LN2. The profile itself is not stated in what we have seen; confirming it transfers, and that post-thaw phenotype is retained, is Stage 1 and Stage 3 work
Storage	Vapor-phase liquid nitrogen
Presentation at the point of use	This product goes to an interventional or radiotherapy setting rather than an infusion chair, in small volume and under image guidance. Hold time after thaw and transport within the hospital have to be specified against that destination, and they are not the same specifications an infused product needs. See §15

There is no aseptic fill-finish operation in the small-molecule sense — cells are formulated and aliquoted into vials as the terminal step of the manufacture.

9. Stability, storage and shipping

Item	Position
Stability status	Not established. Shelf life of the frozen product and the stability data supporting it are among the first things we would ask for. See §15
Storage condition	Vapor-phase liquid nitrogen
Shipper	Validated liquid-nitrogen shipping is a stated requirement in your RFP and is a standard MADE capability. The specific shipper and lane are not established — see §15
Qualification status of the shipping lane	To be qualified as part of Stage 1, against the receiving Mayo sites once those are confirmed
Chain of custody, outbound leg	Frozen drug product shipped to Mayo sites for thawing, syringe loading and administration. An instruction-for-use covering thaw and bedside handling is part of the deliverable, because these products are commonly thawed and drawn by site staff rather than prepared in a pharmacy
The three questions a cryopreserved DC product has to answer	Post-thaw viability, post-thaw maturation phenotype retention, and whether function survives the freeze. The third is the one most often unmeasured, and it is the one an unloaded product can least afford to leave open
What cryopreservation buys	Frozen product decouples manufacture from the dosing appointment, which is the only reason a fourteen-day sterility read is compatible with a 21-day cycle at all

10. Comparability

Dendritic cell programs sit at the harder end of their transfer-risk band, because the source process is institution-specific with no platform reference to fall back on. Against that, this transfer has two things going for it: you have instructed that the vendor use your existing processes, supported by batch records, test records and reports — which makes this a process transfer rather than a platform proposal — and the product carries no antigen, which removes the change with the highest risk in the modality.

The analytical bridge is the Navios-to-CytoFLEX equivalency demonstration in §7. It is planned before the engineering run, because comparability is only as good as the assays carrying it.

Attribute	Method	Priority
Maturation phenotype — CD83, CD80, CD86, HLA-DR, CD14	Flow	HIGH
Functional potency	CCR7 chemotaxis, IL-12p70	CRITICAL where an assay exists; identified as a gap where it does not — see §7a
Viability	NucleoCounter NC-200	HIGH
Purity and residual non-DC populations	Flow	HIGH

Attribute	Method	Priority
Post-thaw phenotype retention	Flow	HIGH
Yield across the three front-of-process control points	Count	HIGH
Endotoxin	Endosafe	HIGH
Sterility and mycoplasma	Per method	Required every lot

The change inventory, and what carries real risk. Site, operators and suite — with T-175 flask work and many manual steps, operator qualification against your batch records is the substance of the transfer. Cytokine lots for IL-4, GM-CSF, PGE2 and TNF- α , specified by specific activity rather than mass. CellGenix media lot, with incoming performance testing. The flow bridge. The maturation window and its timing, preserved as validated parameters. And the controlled-rate freeze profile, confirmed rather than assumed.

11. Technology transfer approach

The 21-day window is the design constraint, not an output of the plan. In MC1641 the interval between the last radiation fraction and cycle 2 day 1 is 21 days, and a seven-day manufacture plus a fourteen-day sterility read consumes it. Every stage below is designed against that arithmetic, and the first thing we would want to establish is how much of the interval remains today after release.

Stage	What happens	Gate
Stage 0 — technical assessment	This document, the equipment answer in §6, and the questions in §15	—
Stage 1 — paper transfer and gap closure	Batch records, test records and reports mapped to our document system; cytokine and media sourcing qualified by specific activity; the Navios-to-CytoFLEX flow bridge planned; LN2 shipping lane qualified; the release-to-dose timeline modeled against the 21-day window before any run is scheduled	—
Stage 2 — engineering run	Non-GMP on healthy-donor apheresis, with your three in-process count points measured to establish our own yield chain, and a maturation-marker time course rather than a single endpoint reading — so the maturation window is characterized on our equipment rather than inherited	Go / no-go sits here
Stage 3 — comparability	Head-to-head on CD83, the informational panel, viability and yield, plus post-thaw phenotype retention	—
Stage 4 — GMP manufacture, release and distribution	First clinical batch, release, and shipment to the treating site against a qualified LN2 lane	Readiness assessment before GMP activity

You have asked that the vendor use your existing processes, supported by tech transfer with batch records, test records and reports. That is a clear instruction and we would follow it.

How this becomes a proposal. A MADE proposal presents this plan as numbered work orders grouped into milestones — process establishment and feasibility, process and analytical development, GMP readiness, and GMP manufacture — with each work order carrying its own deliverables, assumptions and exclusions, and Mayo's deliverables stated alongside ours, so both teams always know what the critical path needs next. The first milestone concludes in a joint review of the data with a penalty-free go/no-go decision, and the move from development into GMP activity is a formal stage-gate readiness assessment. The plan above is written to drop into that structure without translation.

12. Indicative timeline

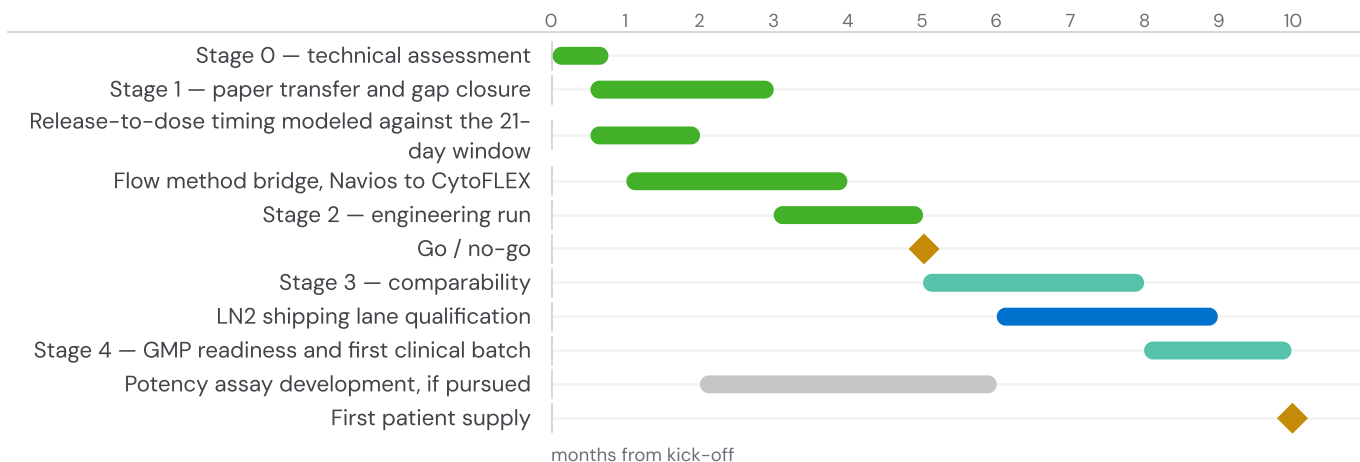
Two clocks run on this program, and they should not be confused.

The per-patient clock is 21 days, from the last radiation fraction to cycle 2 day 1. Apheresis and radiotherapy are cycle 1; the first dendritic cell dose is day 1 of cycle 2; cycles repeat every 21 days. Manufacture is seven days and the compendial sterility read is fourteen. The closed pilot in this lineage ran 28-day cycles, and one protocol in the same family allows cycle 1 to extend by seven days to allow for dendritic cell production — which tells us the constraint is recognized in the protocol design. What we do not yet know is how much of the 21 days remains after release today, and that question governs everything about how a transferred process would be scheduled.

The transfer clock is the program timeline below.

Stage	Duration
Stage 0 — assessment	2–4 weeks
Stage 1 — paper transfer and gap closure	1–3 months
Analytical alignment, in parallel from Stage 1	2–4 months [industry range]
Stage 2 — engineering run	1–2 months
Stage 3 — comparability	2–3 months
Stage 4 — GMP readiness and first clinical batch	1–2 months
Total	12–18 months [industry range]

Autologous scheduling complexity adds approximately one month to GMP readiness [industry range]. If a potency assay is developed in parallel, it adds 2–4 months to the analytical path but not to the critical path.



13. MADE experience that supports this

Said first, because it should not be discovered later: MADE has not manufactured a dendritic cell product. No MADE document claims otherwise. What is true is that every unit operation in your process, and every instrument it names, is in service at MADE today — four LOVO systems, five CliniMACS Plus units, controlled-rate freezing and LN2 storage, Grade B suites with Grade A biological safety cabinets for the open flask work, and the analytical bench for the release panel, with nothing to onboard. That is the accurate answer to the question you raised on 18 August about whether a dendritic cell platform is available and operational at our site: the platform this process needs is, and the modality experience is not.

On the manufacturing environment. Dendritic cell manufacture is flask-based with many open manipulations, and Grade B background with Grade A biological safety cabinets is precisely the environment it requires. Batch sizes are small and per-patient, so suite time and operator capacity set throughput rather than vessel scale — which is a planning input we would work through with you.

On the analytical bench. Beckman Coulter CytoFLEX 13-color flow cytometry, multi-mode plate readers for IL-12 and cytokine ELISA, NucleoCounter NC-200 and Beckman Vi-CELL for count and viability, Endosafe for endotoxin and BioFire for mycoplasma.

On quality. MADE's quality leadership carries collective experience from prior organizations across cell therapy quality systems, aseptic manufacture, method qualification and comparability, spanning commercial cell therapy quality leadership and regulatory CMC covering forty-plus products through FDA INDs. This is experience held by individuals now at MADE; the company itself has not yet completed a client audit.

On sites. Princeton, NJ and East Norriton, PA.

14. Guidance and suggestions

Model the release-to-dose timeline before anything else. In a program where a second department owns the front edge of the manufacturing slot, the schedule is a design input rather than an operational detail. A manufacturer who learns the radiotherapy calendar late designs the wrong process timing. We would want the actual apheresis-to-release duration in hand at Stage 1.

Trend the informational flow panel and use it to set Phase 2 specifications. If that panel has been trended across batches, it is worth looking at before the next protocol amendment rather than after — the specifications are already sitting in the data you have.

Build the potency assay from what you already measure. The CCR7 and IL-12p70 route in §7a starts from your existing panel rather than from nothing, which is worth more in this modality than in most, since there is no default assay to adopt later.

One question rather than a recommendation. Endotoxin is informational-only on this program and specified on other Mayo programs we have reviewed. We assume that is deliberate for a cryopreserved product, and would want to confirm rather than change it.

15. Open questions

Scope boundary — we would confirm this first. Is the transferred product the unloaded mature dendritic cell only, with any antigen contribution left to the irradiated tumor in situ? If loading might come into scope later, what is the antigen and its source?

Regulatory. Has Mayo's regulatory group formed a view on amendment versus new IND, and what would MADE need to supply to support the amendment route? Does the program hold any FDA designations?

The 21-day window. What is the actual time from apheresis to release today, and how much of the 21-day interval remains after the fourteen-day sterility result? What happens on a manufacturing failure — does the patient re-enter the radiotherapy sequence, and is re-collection permitted?

Starting material and process. Leukapheresis acceptance criteria, and maximum age from collection to processing? What monocyte yield is typically achieved post-CliniMACS, and what is the acceptance threshold? Exact cytokine concentrations, and are they specified by specific activity? What is the maturation window, and was it established as a time course?

Equipment. Is LOVO required, or would an equivalent closed wash system with comparability be acceptable? The same question for CliniMACS Plus versus an alternative CD14 selection route. Which CliniMACS tubing set is in use?

Fill, storage and shipping. Target cell dose per vial, and how many product and reserve vials per manufacture? What labeling applies? What is the controlled-rate freeze profile? What is the shelf life of the frozen product and the stability data supporting it? What shipper and lane are in use today, and which Mayo sites receive product?

Presentation at the point of use. What is the permitted hold time after thaw, and what does transport from the receiving pharmacy or laboratory to the interventional suite require? Who thaws, loads and administers, and what does the instruction-for-use require of them?

Analytics. Would you prefer your Navios methods transferred, or a CytoFLEX equivalency bridge? Has the informational flow panel been trended across batches? Is there appetite for a CCR7 migration assay and IL-12p70 secretion as a Phase 2 potency matrix?

Clinical. Expected patients per month across the open groups?

16. Suggested next step

A technical call with your process development and quality teams covering the 21-day window and the current apheresis-to-release timing, the maturation window, and the potency proposal — plus a written response to the Areas of Interest in your RFP, which we would answer specifically rather than generically.