The CARE trial: experience with a Canadian multicentre cell therapy trial (CNTRP)

Imran Ahmad, M.D., M.Sc.(Epid.)
Hematologist - *Hôpital Maisonneuve-Rosemont*
Assistant Clinical Professor - *Université de Montréal*

CellCAN workshop
Till & McCulloch Meetings
Mont-Tremblant, QC
November 7, 2017

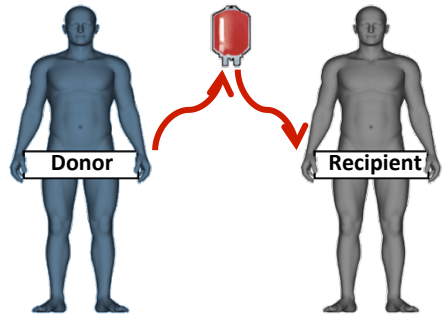
Centre d'excellence en thérapie cellulaire
Hôpital Maisonneuve-Rosemont
Centre affilié à l'Université de Montréal

Canadian National TRANSPLANT Research Program

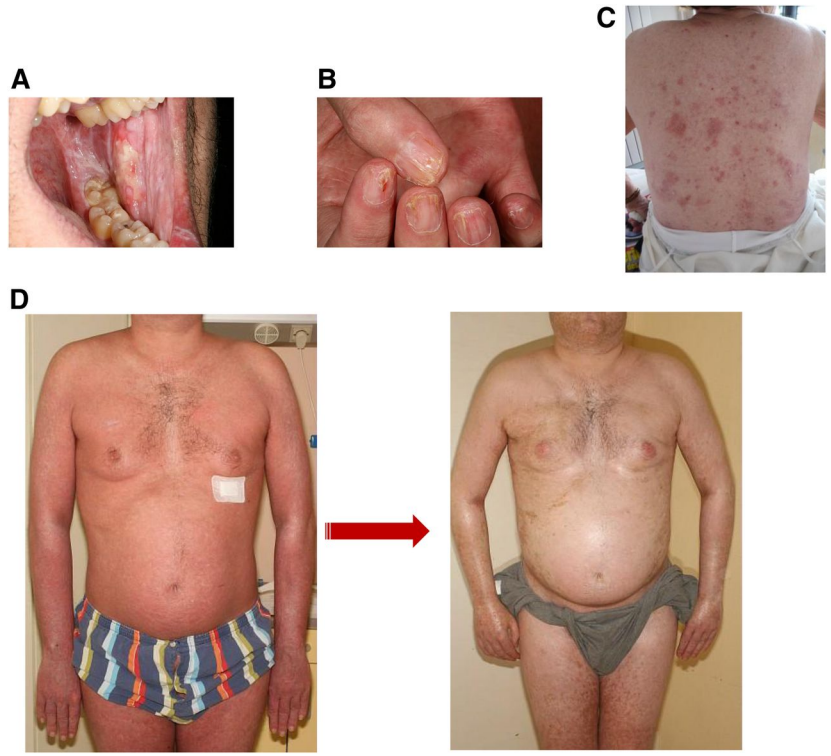
CARE: **C**ontinuous **A**lloreactive cell depletion and **R**egulatory cell **E**xpansion

- Cell therapy for chronic graft-versus-host disease (GVHD)
- Involves « autologous » cell collection (leukapheresis), manipulation and reinfusion after allogeneic transplant
- Pilot trial showed feasibility, biological & clinical activity (Blood 2010)

Chronic GVHD

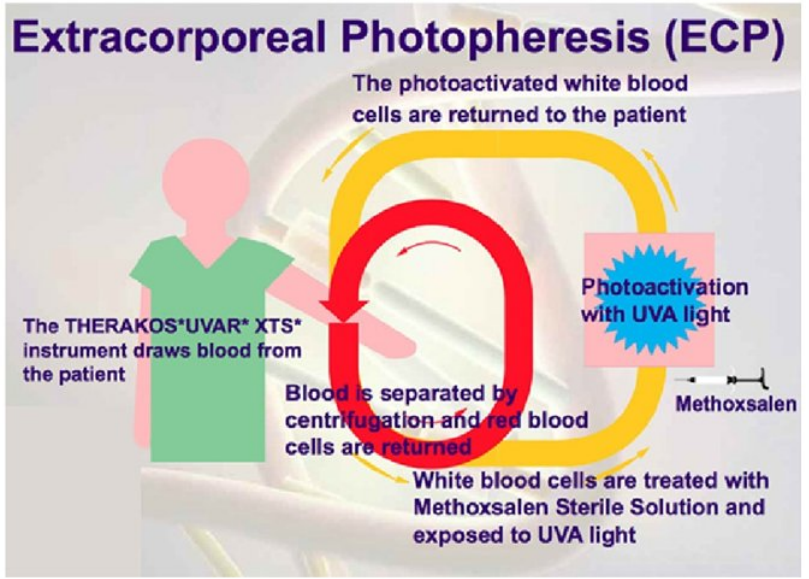


- Clinically significant immune reaction from hematopoietic graft toward the recipient's organs
- Affects ~50% patients, can last years
- Impact on morbidity, mortality and quality of life
- No specific treatment, therapy based on immune suppression



Phototherapy for chronic GVHD

- Phototherapy involves depletion of immune cells (T cells mostly)
- Extracoporeal photopheresis (ECP) is one method

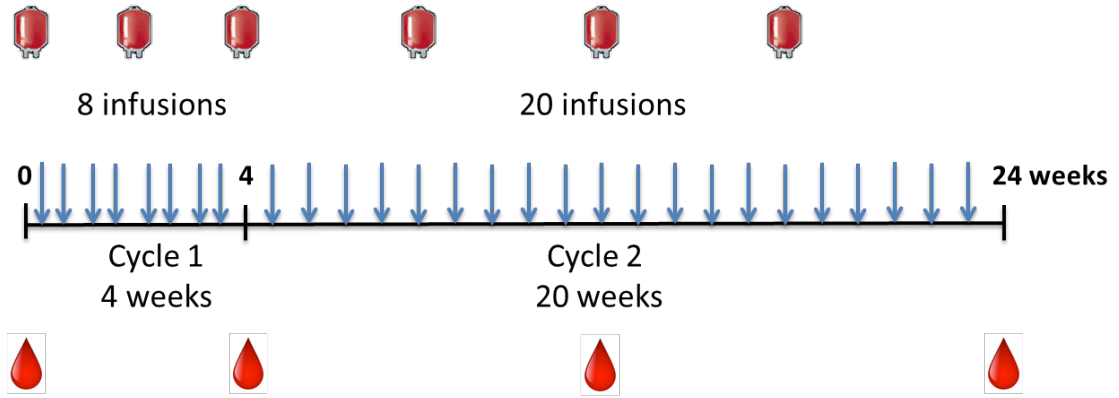


Disadvantages:

- **Cell exposure to UV**
- **Non-specific elimination of T cells**
- **Costly**
- **Frequent visits (twice a week)**
- **Long treatment duration (months of treatment)**

Phototherapy used in CARE trial

- Different modality developed in Montreal induces more selective depletion of alloreactive T cells, as well as expansion of regulatory T cells (Bastien, Blood 2010)
- One cell collection can be treated ex vivo to produce several batches of treated cells for reinfusion

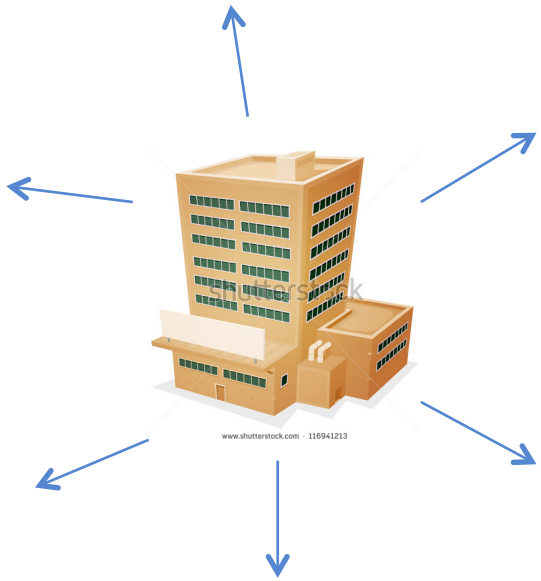


Now, design the trial!

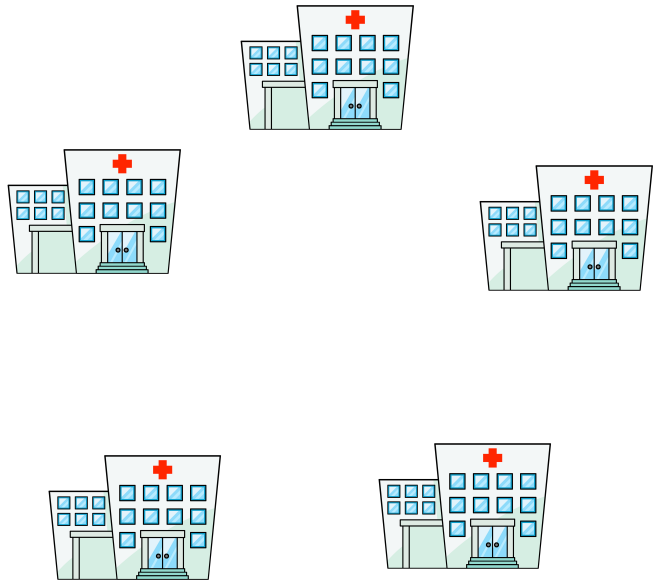
- Scientific aim: test biological activity AND clinical efficacy
  - Clinical endpoints
  - Standardized immune monitoring
- Essential element: collaborative trial = various expertises
  - Cell production
  - Immune monitoring
  - Clinical considerations
- Inescapable budget restrictions: small sample size (n=25)
  - Guidance on sample size determination in cell therapy trials: lacking!

Cell Manufacturing Models

Centralized Manufacturing



Decentralized Manufacturing



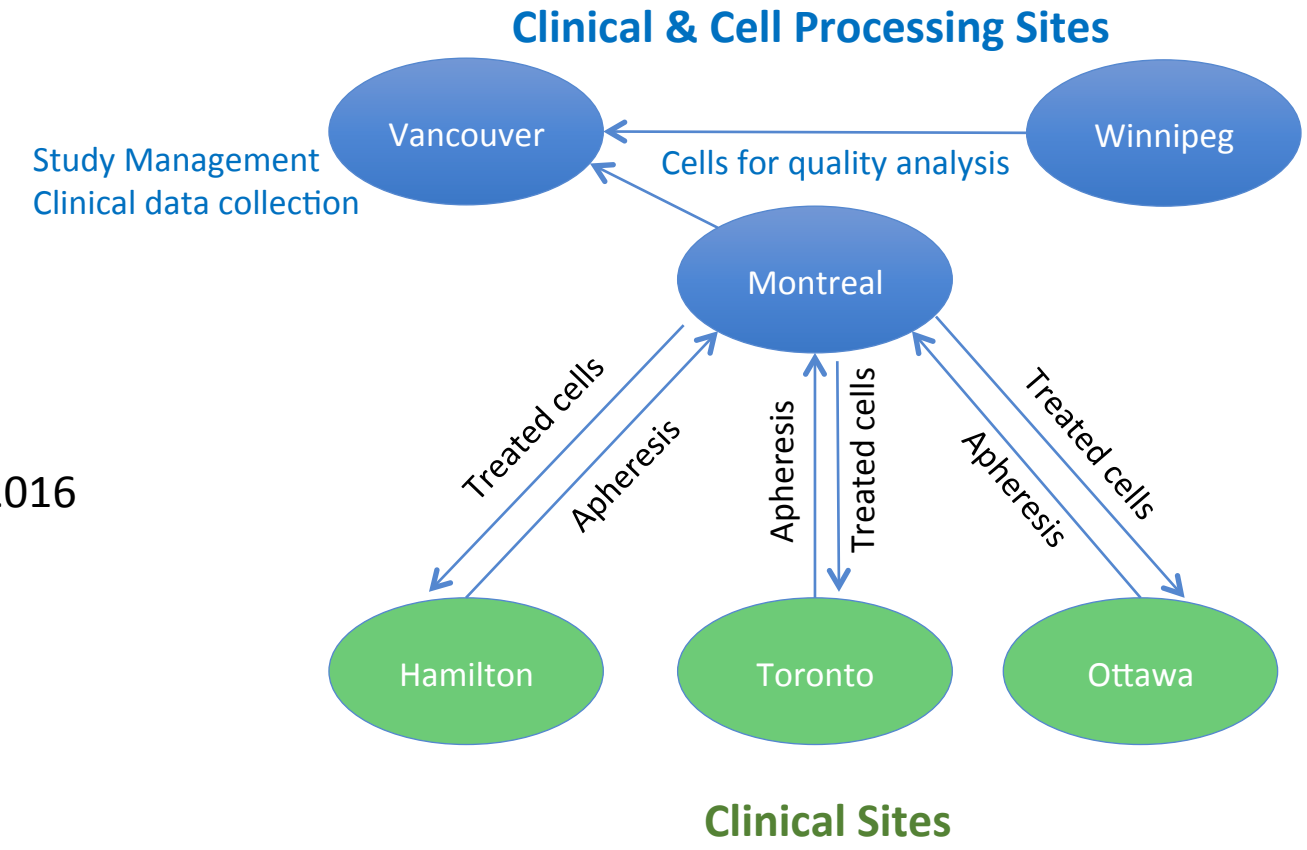
Centralized vs decentralized manufacturing

Centralized	Decentralized
(Allogeneic cell product)	(Autologous cell product)
Frozen product	Fresh product
Consistent quality easier to achieve	Multiple validation of processes (but « stronger » product?)
No complicated technology transfer	Knowledge and skill dissemination
Cold storage chain (shipping): extra variability due to manipulation	Shorter chain, less variability
Economy of scale	Greater upfront capital investment
Tighter expense control	Cost variability
Maximum capacity	Flexibility (CARE: repeated treatments for same patient)

No single model suits all cases!

Combination of centralized and on-site cell production for 6 treating clinical sites

All sites opened between
November 2015 & June 2016



Steps toward a multi-site trial

Clinical sites

- Contracts (statement of work for each parties, budget)
- Ethical approvals
- Training : data handling
- Site initiation visit

Cell Manufacturing

- Implementation of the cell production protocol (local SOPs + Batch Record)
- Installation of equipment (+ reagents)
- Training of personnel (dry & wet runs)
- Site visit (incl. accreditation of local trainers)
- Proficiency testing*
- Cell product release

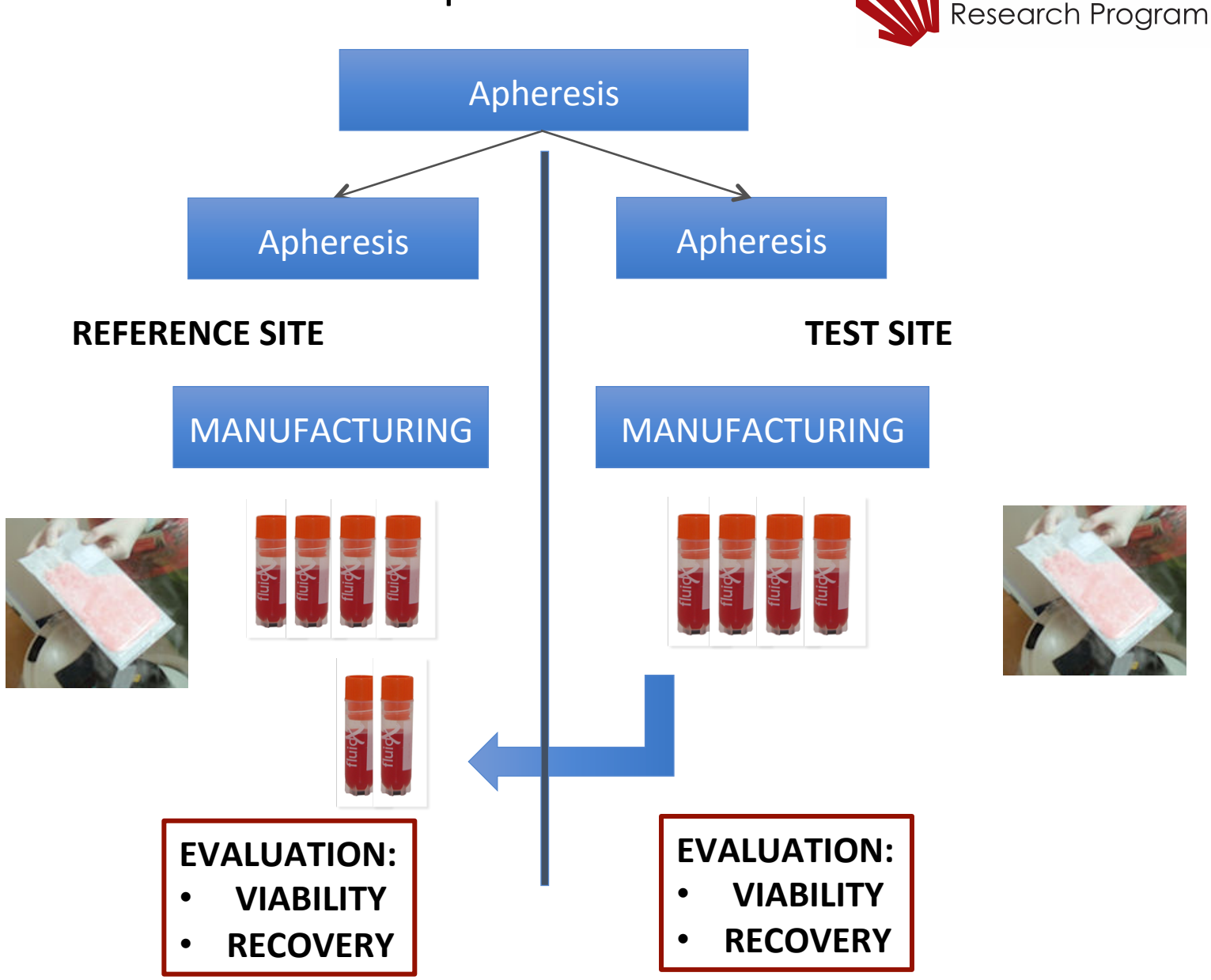
Proficiency Testing

Qualification Run (comparative)
- Two runs with each center

Reference site – Test site
- CETC Montreal vs Winnipeg or Vancouver

Run performed on the same material
- (GVHD patient or healthy donor)

Quality Analysis parameters: next slide



Canadian National TRANSPLANT Research Program

Centre d'excellence en thérapie cellulaire
Hôpital Maisonneuve-Rosemont
Centre affilié à l'Université de Montréal

Quality analysis for proficiency evaluation

Tests:

1. Viability analysis, using Trypan Blue exclusion
2. Live cell recovery (cell count)

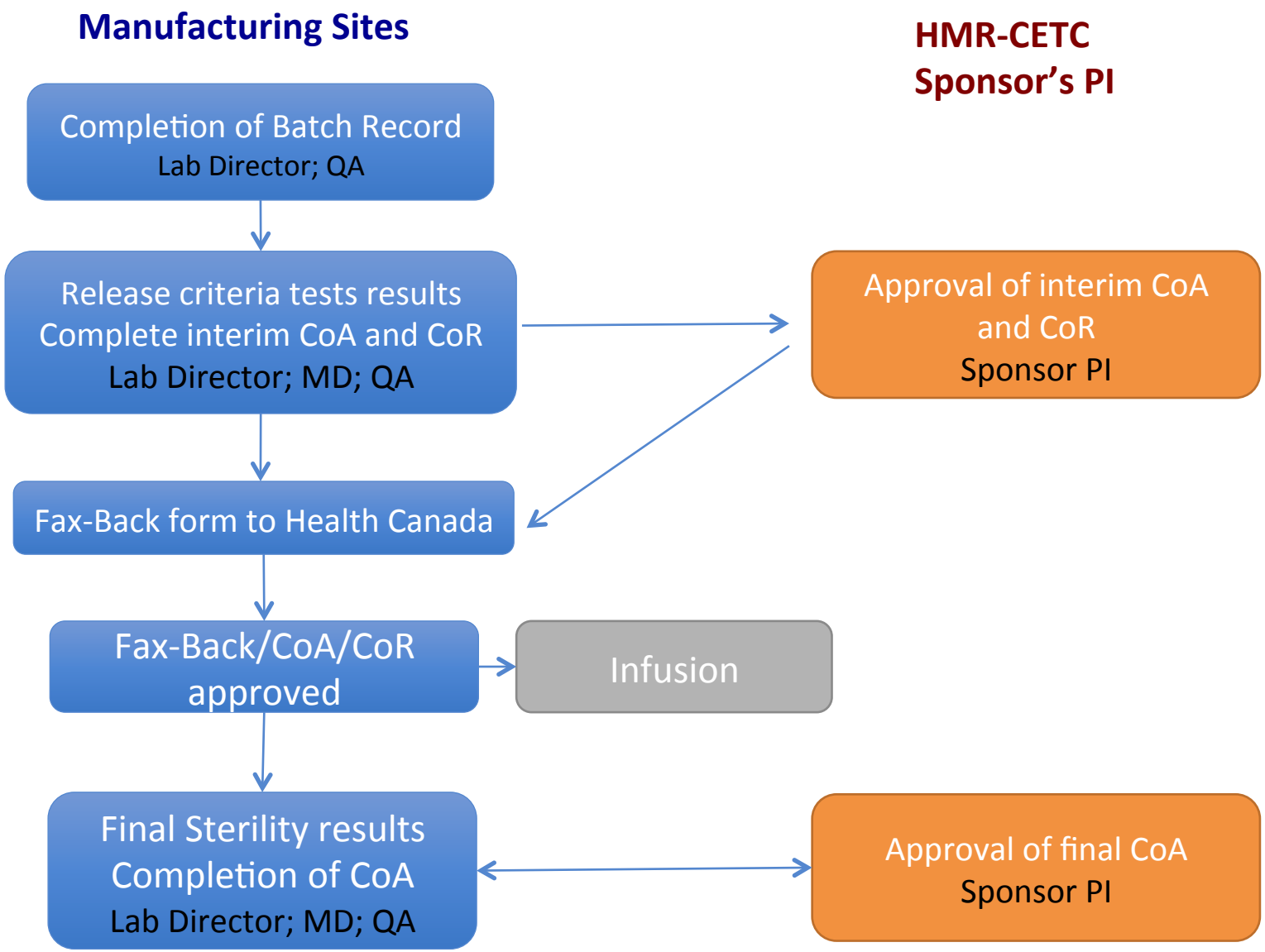
Samples:

1. In-process cells – triplicates
2. Final cell product - triplicates

- Criteria for viability:
  - Intra-center precision: replicates % CV
  - Inter-center precision: between 20% LL and UL

- Live cell recovery >50%

Release of Cell Product

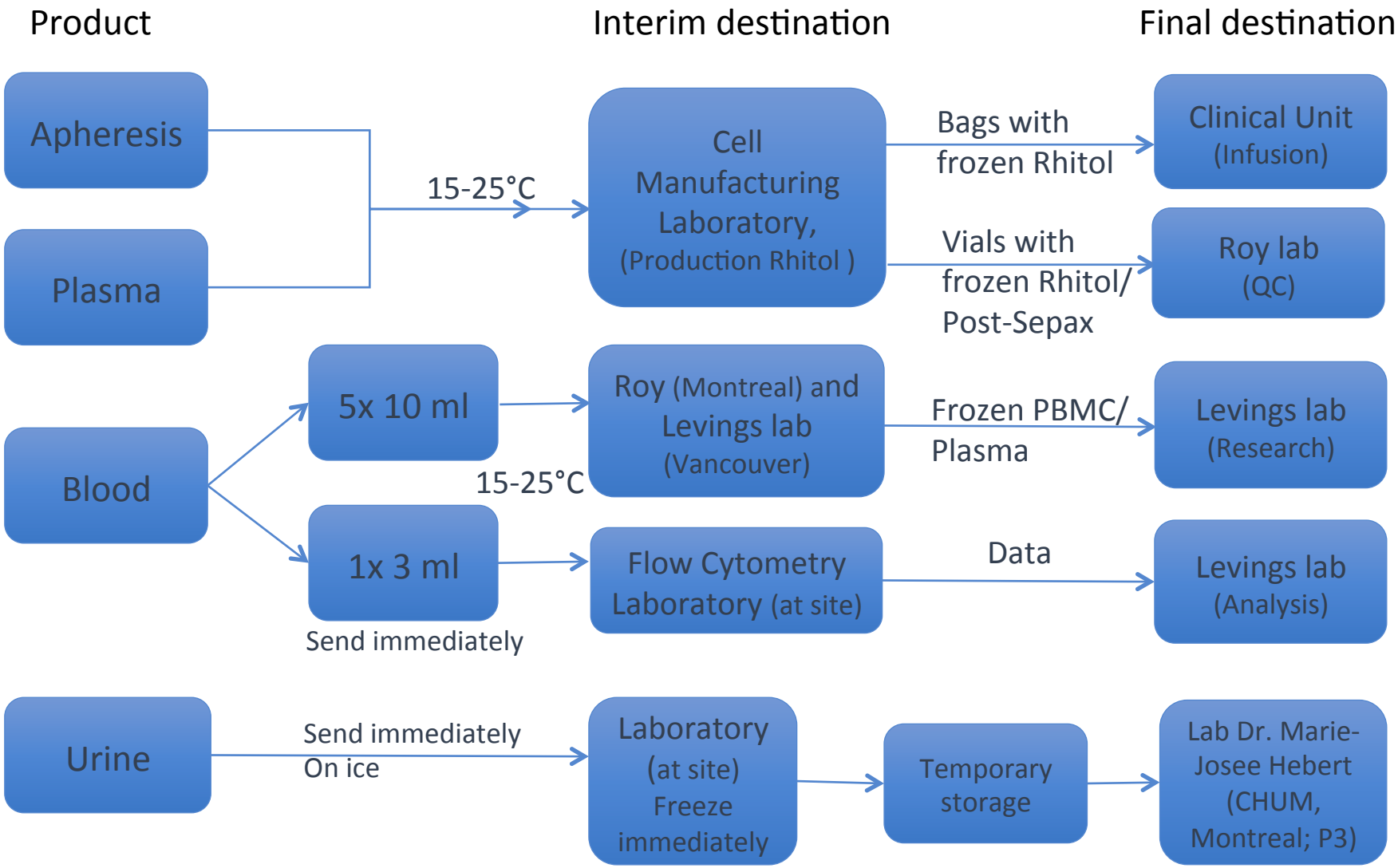


Immune monitoring of cell product & patient blood

- Also a hybrid model of on-site (limited panel) an centralized (advanced CNTRP standard, Vancouver)

- Involves shipping of samples from
  - patient blood at various time points
  - cell product pre- and post-manipulation

Overview of all Material/Sample and Data collection



Logistics of the bio-materials collections

- Shipments of apheresis material and frozen cell products by validated couriers
  - Provide data on the temperatures (winter/summer)
  - Hermex Courier and World Courier

- Manual for all the handling and shipments
  - Patient identifiers
  - Labeling of the products
  - Contact Information

Lessons learned

- Hybrid production model, 6 clinical sites, 3 production sites
  → flexibility, dissemination of knowledge, cooperation

- One production hub responsible for the manufacturing supervision and training
  → expertise has to come from somewhere (CETC Montreal)

- Shipping and production capacity are always logistic challenges
  → close cooperation between sites

- Clinical coordination: one centre (CRO in Vancouver) + PI (Montreal)
  → no advantage for decentralization


©2016 INDYSTAR CREATORS.COM
LEARNING CURVE
TRUMP
garyvarvel.com


CLINICAL SITES
SHIPMENTS
CELL MANUFACTURING FACILITIES
SAMPLE/DATA COLLECTION

CARE people

Denis-Claude Roy

Imran Ahmad

Protocol Chairs

Janetta Bijl

Trial Development &

Lab Coordination

Daphne Brockington

Study Management

STATISTICIAN

Tony Panzarella

CLINICAL TEAMS

Hamilton

Ronan Foley (co-PI)

Irwin Walker (co-PI)

Amiee Hill

Montreal

Stephanie Thiant

Dalal Yared

Ottawa

David Allen (co-PI)

Christopher Bredeson (co-PI)

Kimberly Paquin

Toronto

Dennis Kim (co-PI)

Frank Michelis (co-PI)

Irene Tang

Vancouver

Raewyn Broady (co-PI)

Donna Hogge (co-PI)

Ben Chernoff

Winnipeg

David Szwajcer (co-PI)

Amber Delisle Corps

CELL THERAPY

Montreal (CETC)

Marie-Pier Giard

Cynthia Thérien

Jinane Darwiche

Martin Giroux

Vancouver

Giovanna Cameron

Karen Filer

Winnipeg

Angeline Giftakis

Qingdong Guan

IMMUNE MONITORING

Megan Levings (co-PI)

Sabine Ivison

& lab members

CNTRP

(Central – Core 2 - Project 4)

Lori West

Megan Levings

Donna Wall

Kirk Schultz

Denis-Claude Roy

David Hartell

Stephanie Maier

Peter Subrt