Inspired by research. Driven by compassion. Inspiré par la recherche. Guidé par la compassion.

MANUFACTURING CELL THERAPY PRODUCTS FOR MULTI-CENTRE CLINICAL TRIALS: THE OHRI EXPERIENCE

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The Ottawa Hospital RESEARCH INSTITUTE | L'Hôpital d'Ottawa INSTITUT DE RECHERCHE

CellCAN Regenerative Medicine and Cell Therapy Network

OHRI Multi-Centre Clinical Trials: Stem/Progenitor Cell and Cell Based Gene Therapy

The **eN**OS **A**nd **C**ell **T**herapy – Acute Myocardial Infarction (ENACT- AMI): *opened Q2 2013, 38/100 patients*
Ottawa, Toronto, Montreal, Quebec

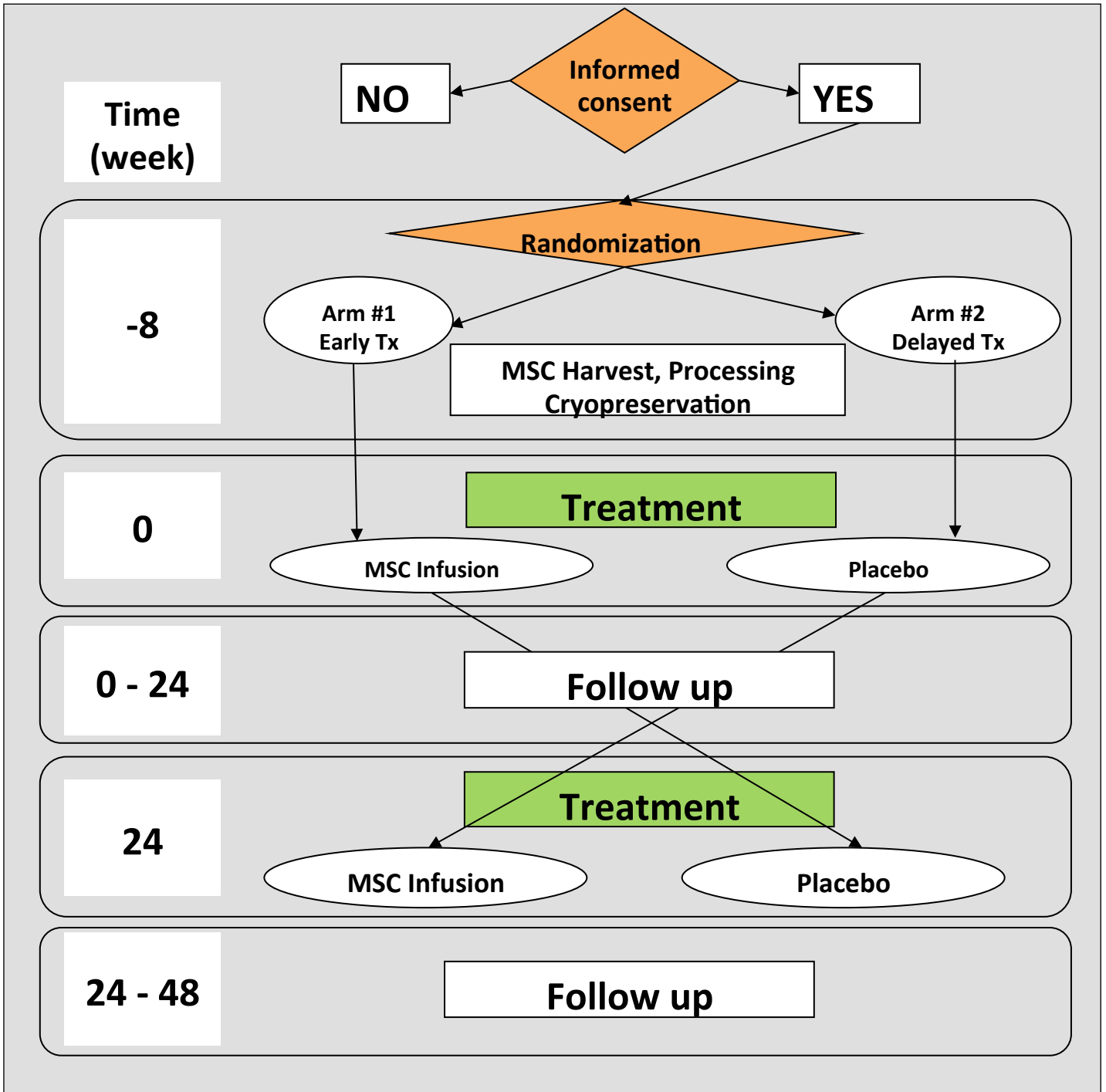
***MESCAMS/MESEMS**-allogenic MSCs for MS*
19/20 patients Ottawa and 3/20 Winnipeg

Study of Angiogenic cell therapy for Progressive Pulmonary Hypertension: Intervention with Repeat dosing of eNOS-enhanced EPCs (SAPPHIRE): opened Q3 2017
Ottawa, Toronto, London, Montreal, Quebec City, Vancouver

Mesenchymal Stem Cell Therapy for Canadians with Multiple Sclerosis (MeSCaMS) Trial

- Phase IIa Multi-center Trial, OHRI is sponsor
- Double blinded, randomized and placebo controlled cross-over study
- Canadian study – targeting enrolment of 40 patients: 20 in Ottawa, 20 in Winnipeg
- Autologous MSCs manufactured in both Ottawa and Winnipeg, target dose 1 to 2 Million/Kg
- Funded by MS Society of Canada and the Manitoba Health Research Council

MeSCaMS Protocol



Primary Outcomes (24 weeks)

Safety: incidence and severity of AEs in the MSC treatment group compared to the placebo group at week 24.

MRI: the cumulative number of gad enhancing lesions on scans obtained at weeks 4, 12 and 24 compared between both groups.

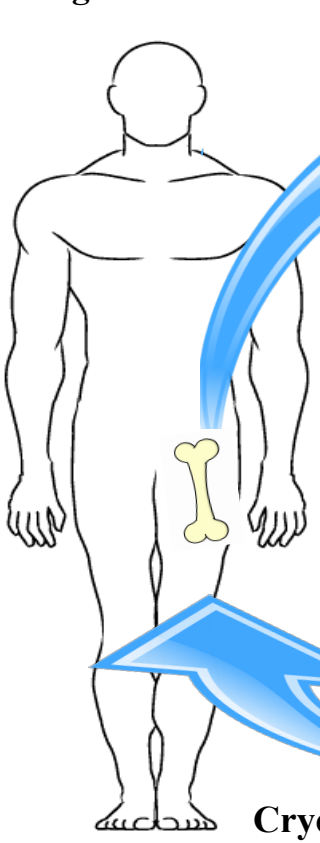
Exploratory Objectives

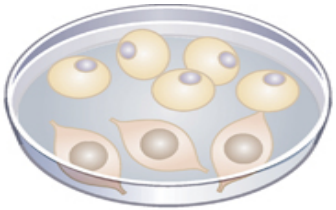
Investigate whether the experimental therapy influences metrics indicative of regeneration or repair of the CNS. These may include non-standard MRI metrics, neuropsychology, visual assessments including visual acuity testing, visual evoked potentials and optical coherence tomography, neurophysiological metrics and patient related outcomes including quality of life and fatigue scores.

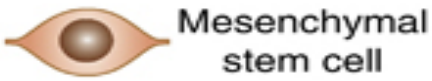
These will vary depending on the centre.

Manufacturing Protocol

Harvested bone marrow from MS patient is plated in DMEM media containing Human Platelet Lysate

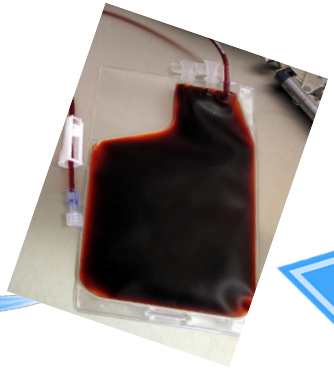






Adherent mesenchymal stem cells form colonies and are passaged to HYPERFlasks to generate 200 to 300 million cells

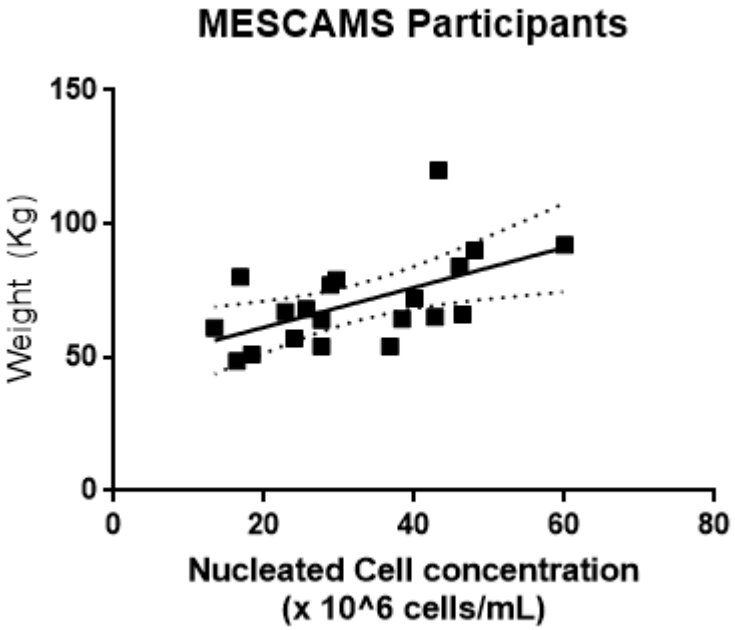
MSCs are harvested from HYPERFlasks once 60 to 70% confluent and cryopreserved in Plasma-Lyte A with 5% human albumin and 10% clinical grade DMSO

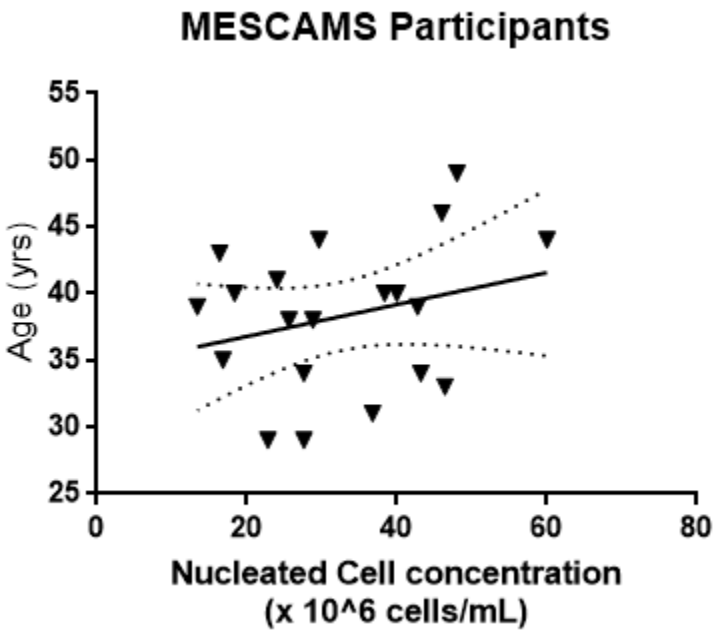


Cryopreserved MSCs are thawed and transfused into the same patient

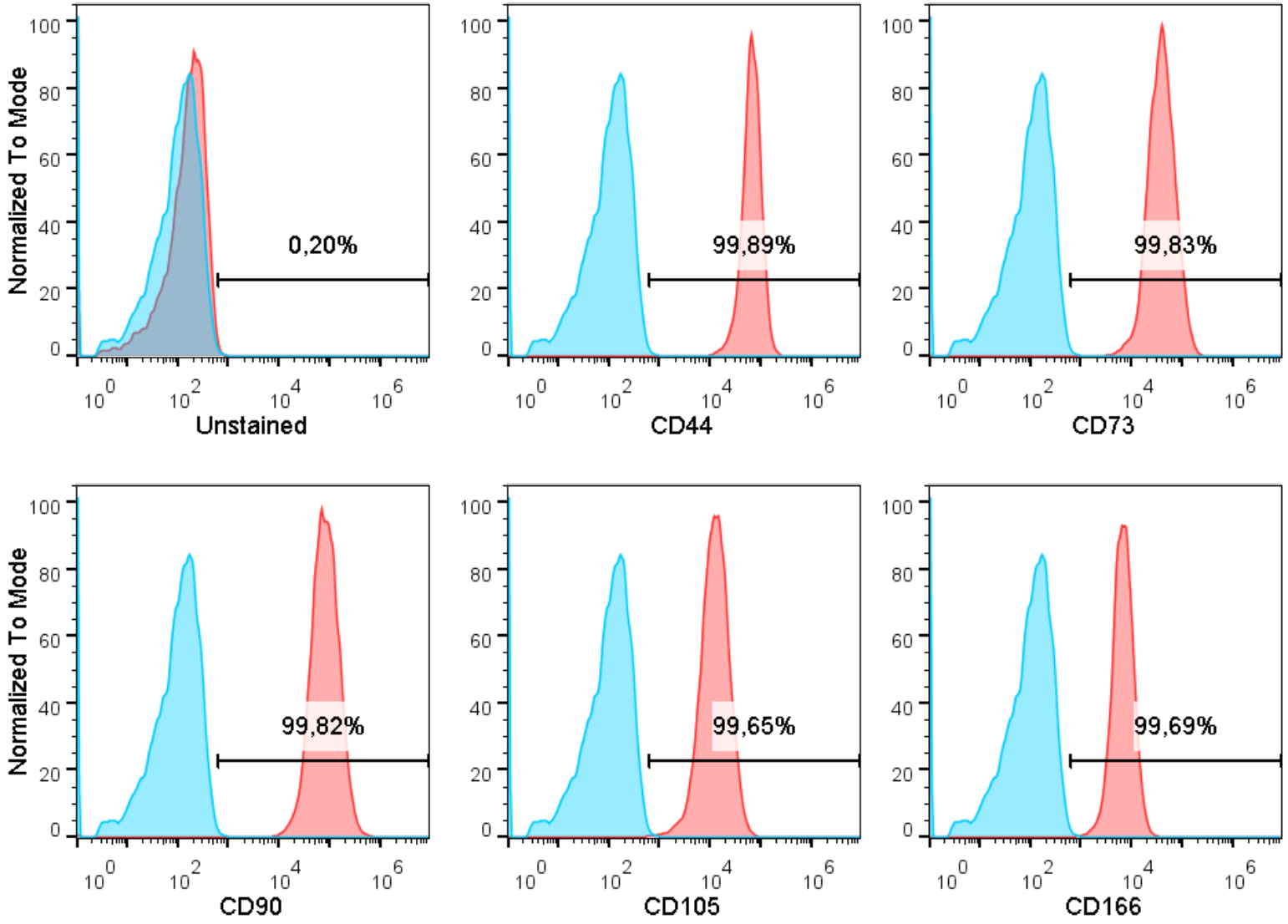
Patient and BMA characteristics

Patient Characteristics	N = 20
Age (Yrs; Range)	38.3 (29 – 49)
Sex (Female; %)	11 (55%)
Weight (Kg; Range)	70.7 (49 – 120)
BMA volume (mL; Range)	25.4 (23 – 29)
Nucleated cell [ ] in BMA (cells/mL; Range)	32.0×10^6 ($22.8 – 60.0 \times 10^6$)



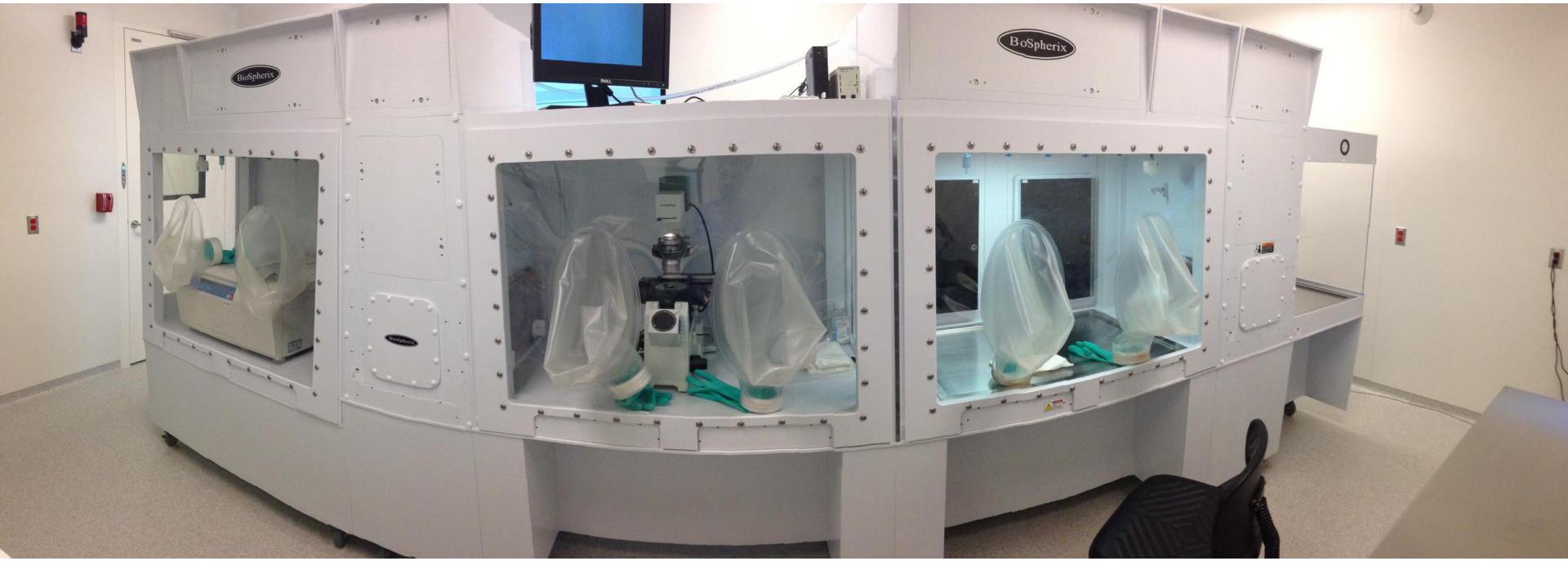


Identity Testing: Surface Markers



Negative for: Cd11b, CD14, CD19, CD34, CD45 ,CD79a, HLA-DR

MSC Processing at OHRI



- All cell processing performed in self contained ISO5 closed isolation systems (Biospherix XVivo) within ISO-8 clean rooms.
- Stable constant environment to enhance yield and reproducibility

MESCAMS

Funding agencies mandated decentralized manufacturing (Ottawa and Winnipeg) and limited number of enrolment (20) at each site
OHRI as sponsor developed all SOPS and submitted CTA
OHRI supplied SOPS and oversight to Winnipeg

MEsenchymal StEm cells for Multiple Sclerosis

Central CRO (Italy) to randomize patients and collect data
Target of 170 patients (154 as of Sept. 2017)

Genoa: A. Uccelli
Milan: G. Comi
G. Martino
Verona: B. Bonetti

London: P. Muraro

Malaga: O. Fernandez
Badalona: C. Ramo-Tello
Sevilla: I. Ayuso
Cordoba: F. Sánchez López

Copenhagen: Per S. Sorensen
R. S. Oliveri

Ottawa: M. Freedman
Winnipeg: J. Marriot

Toulouse: Michel Clanet

Clayton: Martin Short

Stockholm: L. Brundin
K. Le Blanc

http://www.mesems.org/centri.php

MESEMS

- In 2010, a consensus paper on the utilization of MSCs for the treatment of MS was published describing the synopsis of a phase II clinical trial which led to the development of the MESEMS trial in Italy.

- MESCAMS is one of a series of parallel, independent but related, national studies all adopting the MESEMS protocol as part of the International MSCT study Group, now involving 9 countries.

- Results of all national trials will be pooled and should provide enough statistical power to draw conclusions regarding the safety and efficacy of autologous MSC transplantation in MS.

- Cell product cryopreserved, growth in FBS or platelet lysate

MESEMS APPROACH TO MULTI-CENTER TRIALS

Pros

May be the only way to fund a large (>100 patients) academic cell therapy trial and thus reach statistical significance

Assists in regulatory approval, pooling protocols, preclinical data, initial safety findings

Realistic test of autologous therapy produced at multiple centers

If successful it supports a worldwide application of the therapy

Cons

No guarantee that all countries will be timely funded

Each trial is stand alone and governed independently by regulatory agencies, requires duplicating pre-clinical safety, identity, potency and stability assays

Cell product may be highly variable between countries

Requires central coordination and robust funding at central site

Timelines may be prolonged

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Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa