Autologous Cellular Therapies in Neurosurgery Clinical Practice

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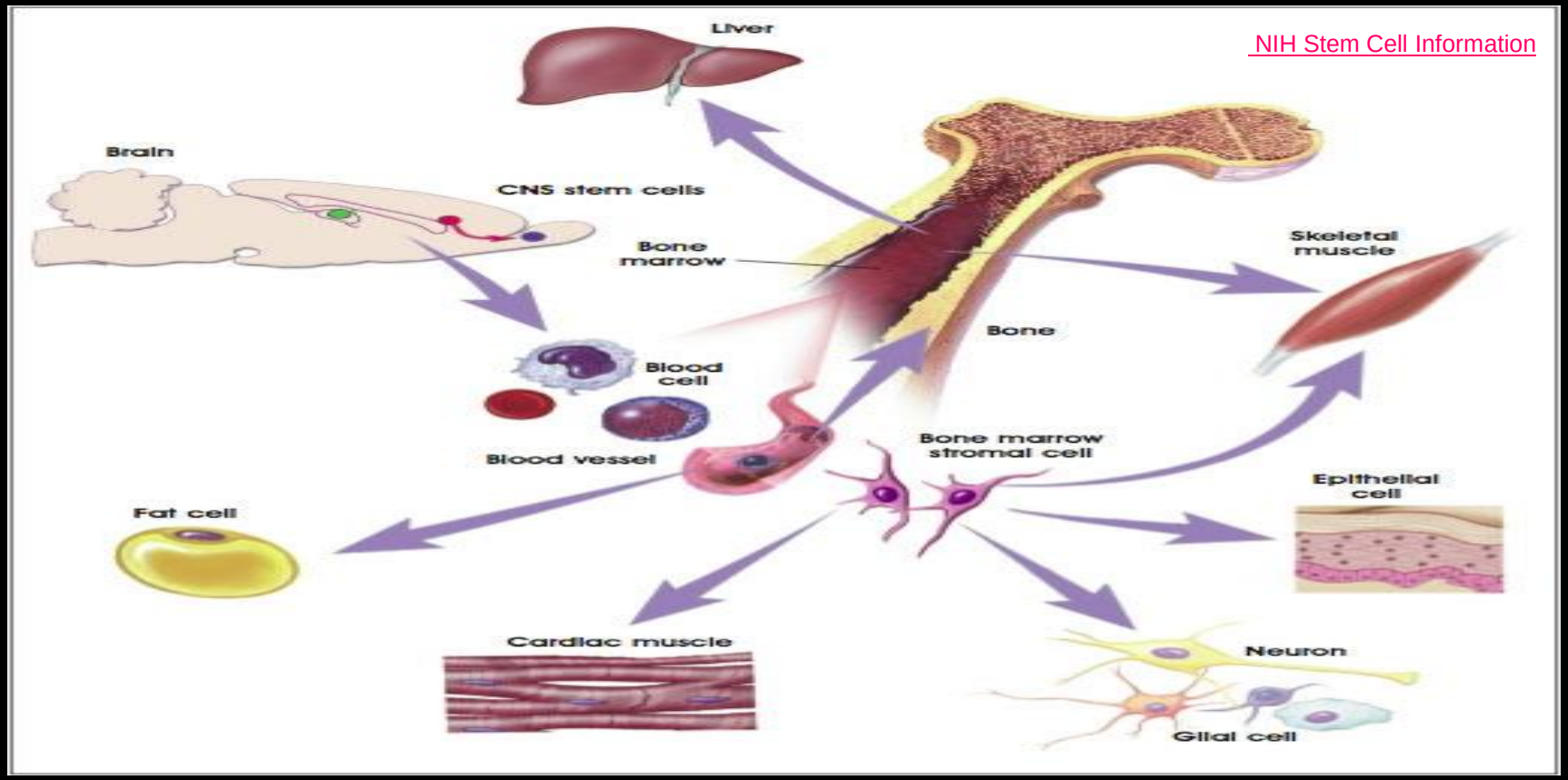
Autologous Cellular Therapies in Neurosurgery Clinical Practice

- **Autologous cellular therapy: Bone marrow concentrate cellular therapy**
- **Bone marrow concentrate cellular therapy : Mechanism of action**
- **Clinical indications in neurosurgery clinical practice**
- **Clinical endpoints in neurosurgery clinical practice**
- **Legal, regulatory and affair parameters**

- **Discussion**

Bone marrow concentrate cellular therapy

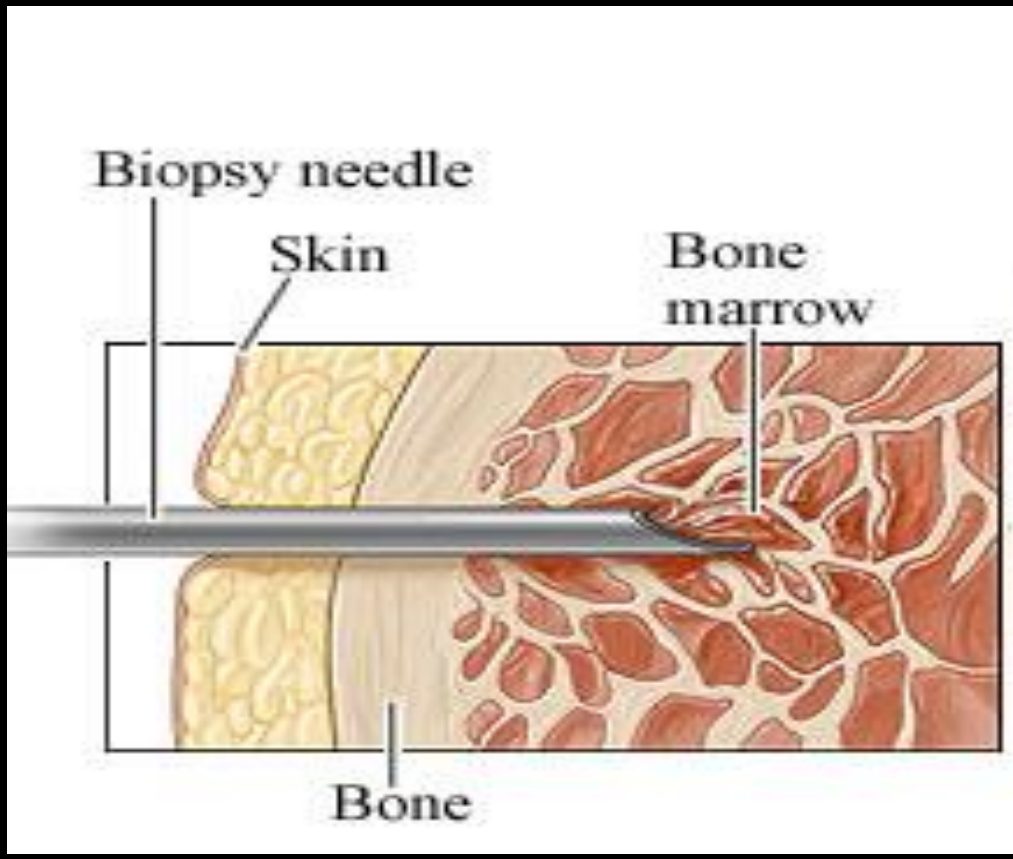
Bone marrow: A niche of multipotential stem cells



NIH Stem Cell Information

Bone marrow concentrate cellular therapy

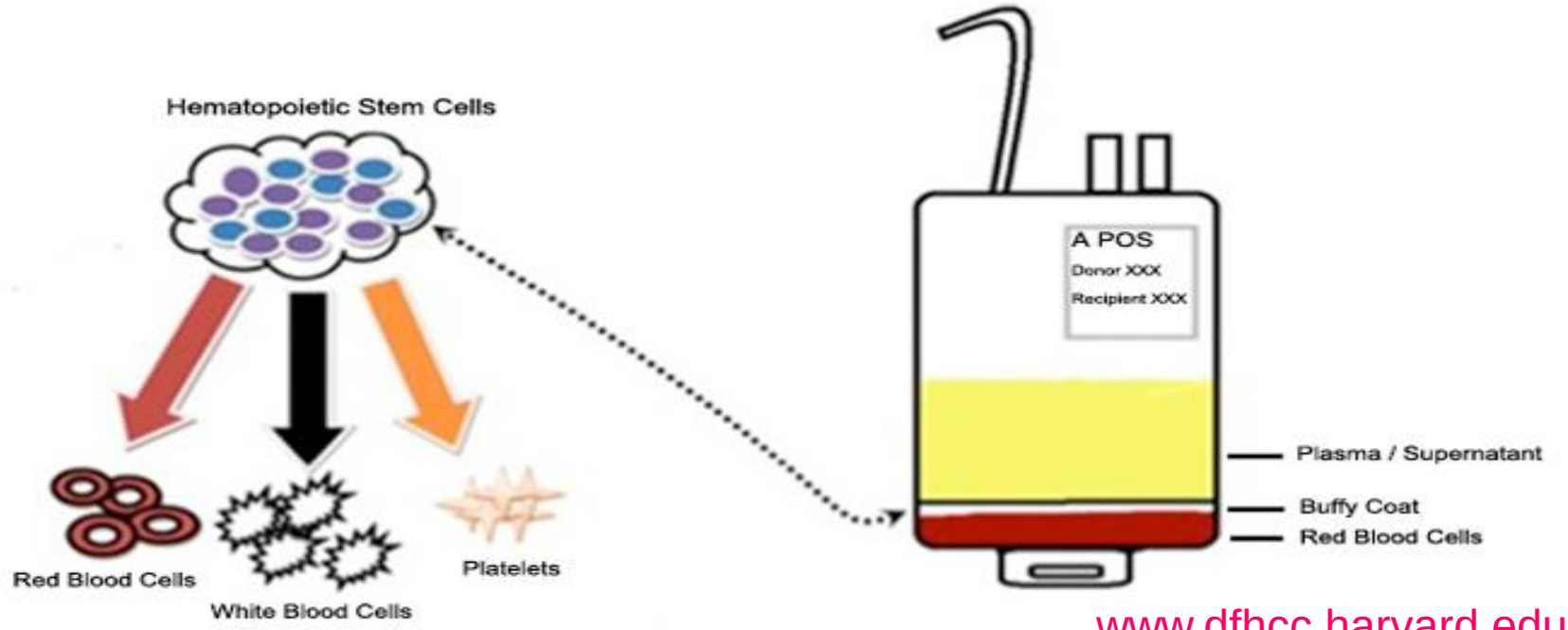
Bone marrow collection: A safe and painless procedure



Bone marrow concentrate cellular therapy

Bone marrow processing: A sterile CE bone marrow concentrate production procedure into the surgery room

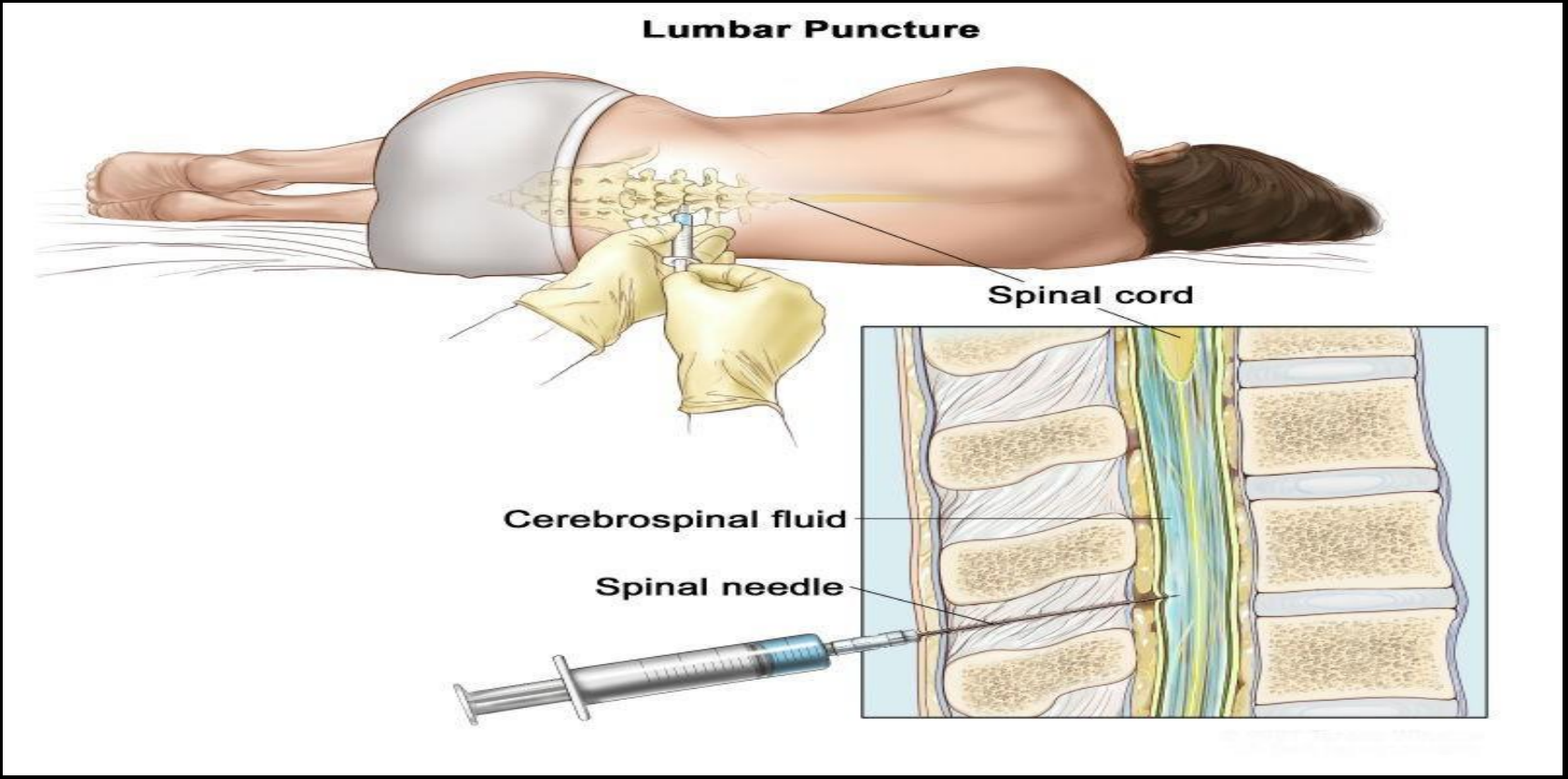
Processing Fundamentals: Clinical stem cell transplant processing typically involves the manipulation of plasma / supernatant and/or red blood cell layers, while maximizing the recovery of the buffy coat layer (containing stem cells) for infusion.



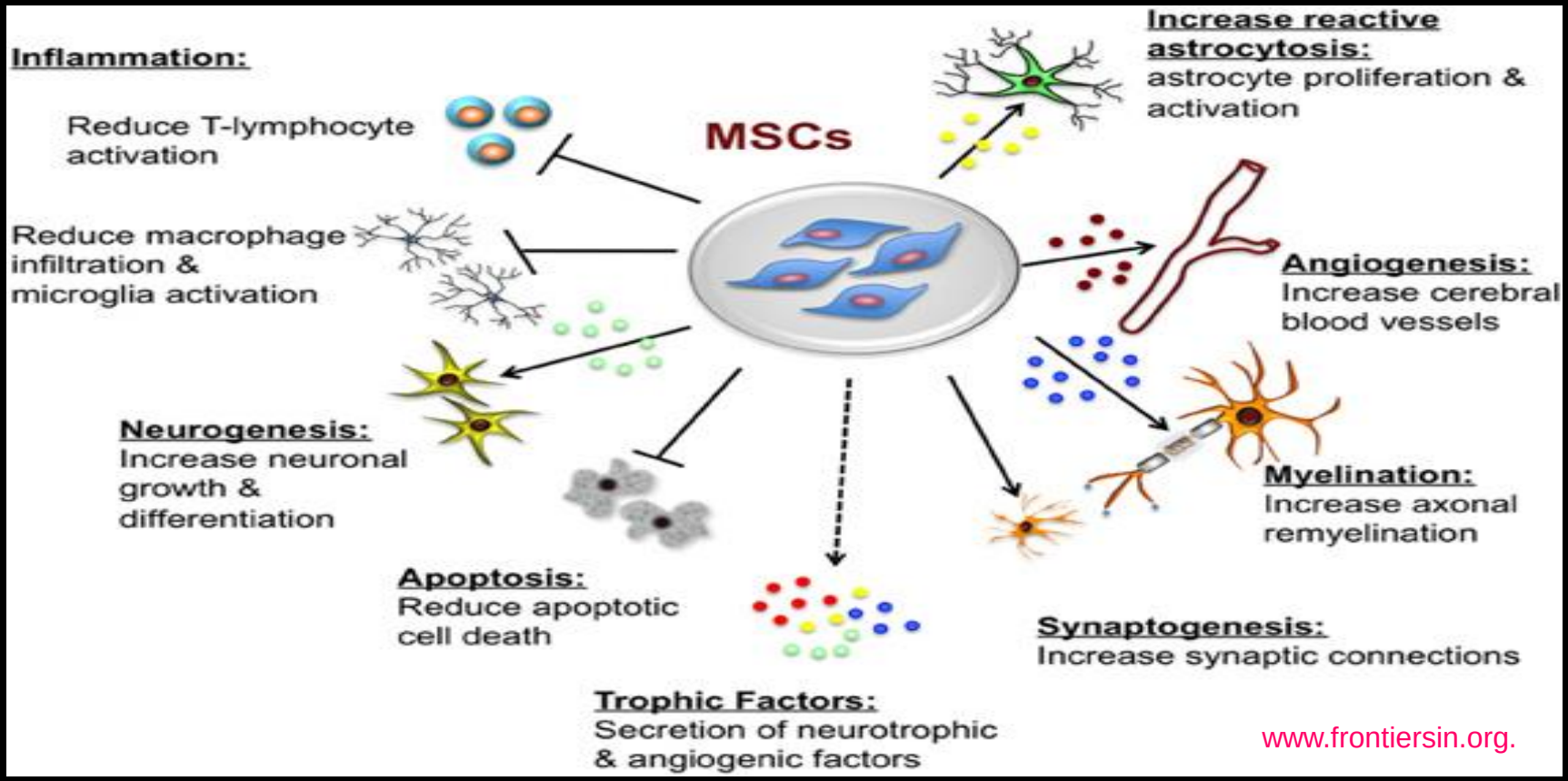
www.dfhcc.harvard.edu

Bone marrow concentrate cellular therapy

Bone marrow concentrate infusion: intra venous and/or intra lumbar



Bone marrow concentrate cellular therapy : Mechanism of action



Bone marrow concentrate cellular therapy: Clinical indications in neurosurgery clinical practice

- 1. Parkinson's Disease
- 2. Amyotrophic Lateral Sclerosis
- 3. Spinal Cord Injury
- 4. Epilepsy
- 5. Stroke
- 6. Cerebral Pulsy / Autism

1. Parkinson's Disease

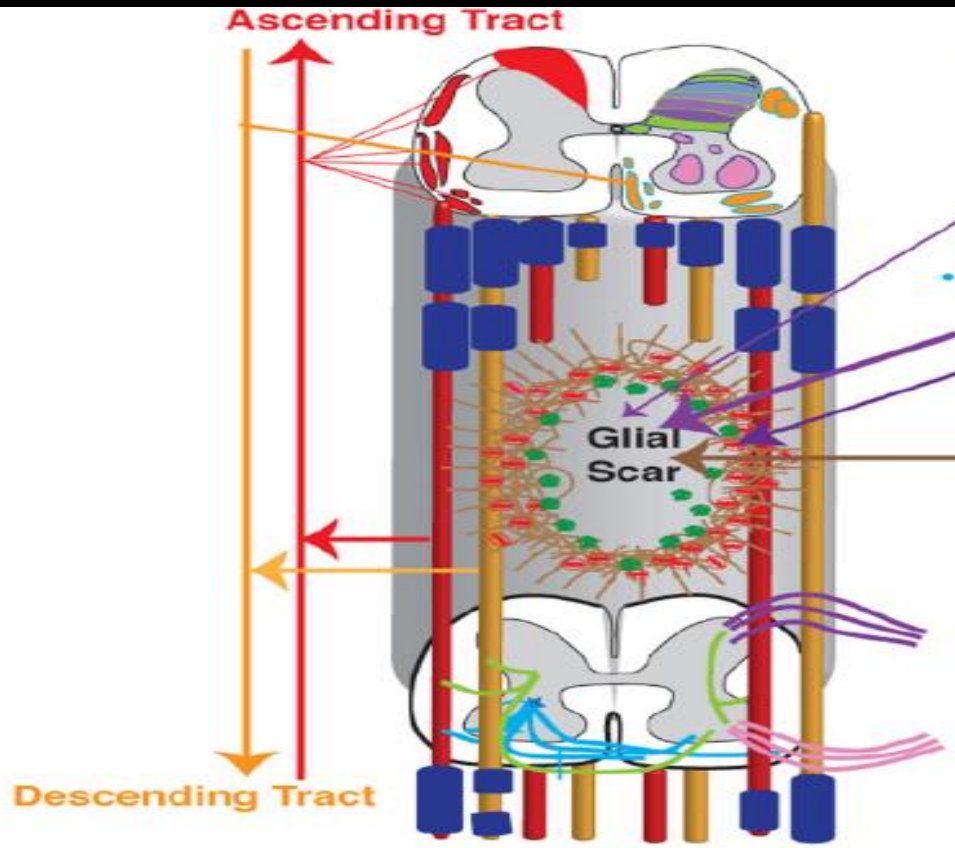
Name of the study location/clinicaltrials.gov identifier	Status start and end of the study	Number of recruited patients	Type of cells/ intervention	Study design/primary purpose	Outcome measures	Preclinical/clinical literature
Autologous mesenchymal stem cell transplant for Parkinson's disease India/NCT00976430	November 2011 (final data collection date for primary outcome measure)	5	Autologous bone marrow derived stem cells transplant	Endpoint classification: safety/efficacy study Intervention model: single group assignment Masking: open label	Primary: improvement in clinical condition of the patient assessed using UPDRS (UNIFIED PARKINSON'S DISEASE RATING SCALE)	Arias-Carrion and Yuan, 2009/no publications associated to the trial
Mesenchymal stem cells transplantation to patients with Parkinson's disease Cina/NCT01446614	Recruiting October 2011 June 2014	20	Intravenous administration of autologous bone marrow derived mesenchymal stem cells	Endpoint classification: safety/efficacy study Intervention model: single group assignment Masking: open label primary purpose: treatment	Primary: number of participants with adverse events 1 month after transplantation Secondary: effect assessment 1 month after transplantation and later	Park et al., 2008; Shetty et al., 2009; Glavaski-Joksimovic et al., 2010; Somoza et al., 2010/no publications associated to the trial
Evaluation of safety and tolerability of fetal mesencephalic dopamine neuronal precursor cells for Parkinson's disease Republic of Korea/NCT01860794	Recruiting May 2013 February 2018	15	Evaluation of safety and tolerability of Fetal mesencephalic dopamine neuronal precursor cells as a treatment for patients with Parkinson's disease	Intervention model: single group assignment Masking: single blind (outcomes assessor) Primary purpose: treatment	Primary: presence or absence of cancer formation and infection within 5 years after transplantation Secondary: score UPDRS) within 5 years after transplantation. Detection of positron emission in Putamen. Dyskinesia Pronation-supination test	No publications provided/no publications associated to the trial
Rajavtihi neuronal adult stem cells project Thailand/NCT00927108	Unknown/July 2009 December 2011	10	Oligodendrocyte progenitor cell	Basic science	Not described	No publications provided/no publications associated to the trial
Study to assess the safety and effects of autologous adipose-derived stromal in patients with Parkinson's disease Mexico/NCT01453803	Recruiting/May 2011 June 2015	10	Autologous adipose-derived stromal cells	Allocation: non-randomized Endpoint classification: safety/efficacy study Intervention model: single group assignment Masking: open label primary purpose: treatment	Primary: presence or absence adverse effects, mesure of UPDRS Secondary: reduction of Parkinson's medication	No publications provided/no publications associated to the trial
Molecular analysis of human neural STEM Cells USA(company) /NCT01329926	Enrolling by invitation/June 2011 June 2014	20	The aim of this study is to develop and optimize methods to isolate, propagate and differentiate adult human neural stem cells from patients with degenerative neurological disorders like Parkinson's disease	Basic science	Isolation and propagation of adult human neural stem cells from patients with Parkinson's disease	No publications provided/no publications associated to the trial
Clinical trial to evaluate Bone marrow stem cell Therapy for progressive supranuclear Palsy a rare form of Parkinsonism Italy/NCT01824121	December 2012 December 2014	25	Mesenchymal stem cells (MSCs) isolated from Bone marrow collected from the iliac crest	Randomized Endpoint classification: safety/efficacy study: double blind Primary purpose: treatment	Primary: incidence of adverse events. Secondary: striatal density of dopamine	No publications provided/no publications associated to the trial
Derivation of induced pluripotent stem cells from somatic cells donated by patients with neurological diseases for the study of the pathogenesis of the disorders and development of novel therapies Israel/NCT00874783	April 2009 December 2014	120	Human fibroblasts and possibly other human somatic cells reprogrammed.120 donors to cover 10 different neurodegenerative disorders based on 10 donors per disorder and 20 healthy control donors	Basic science Preparation of iPs from people with neurodegenerative pathology to study their biological differences	Not provided	Yu et al., 2007/no publications associated to the trial
Peripheral blood stem cell collection from adult volunteers USA/NCT00033774	April 2002 last update January 2013	Not provided	Bone marrow stem cells collection	Basic science	Not provided	Orkin, 2000; Wei et al., 2000; Lemischka, 2001/no publications associated to the trial

The Table describes: in row 1 the name of the clinical trial, the location and the ClinicalTrials.gov identifier; in row 2 the Status, the Start and end of the study and the number of recruited patients; in row 3 the type of cells used and the method of administration; in row 4 the study design and the primary purpose; in row 5 the outcomes; in row 6 the preclinical and clinical literature.

2. Amyotrophic Lateral Sclerosis

Name of the study location/clinicaltrials.gov identifier	Status start and end of the study	Number of recruited patients	Type of cells/ intervention	Study design/primary purpose	Outcome measures	Preclinical/clinical literature
Clinical trial on the use of autologous bone marrow stem cells in amyotrophic lateral sclerosis Spain/NCT01254539	Active not recruiting October 2010 November 2014	63	Laminectomy and bone marrow stem cells transplantation Intrathecal infusion of autologous bone marrow stem cells Intrathecal infusion of placebo (saline solution)	Randomized safety/efficacy study Double blind Primary purpose: treatment	Primary: forced vital capacity. Secondary: absence of adverse events; neurophysiological, neuroradiological, and respiratory variables	No publications provided/no publications associated to the trial
Dose escalation and safety study of human spinal cord derived neural stem cell transplantation for the treatment of amyotrophic lateral sclerosis USA/NCT01730716	Enrolling by invitation only May 2013 April 2014	18	5 sequential cohorts with 3 subjects in each cohort. Each cohort will follow a dose escalation plan. No control group is included. All patients will received spinal cord injections of HSSC	Safety Study Primary purpose: treatment	Primary: safety, toxicity, and maximum tolerated (safe) dose of human spinal cord-derived Secondary: (1) attenuation of motor function loss; (2) maintenance of respiratory capacity; (3) stabilization of the pathology; (4) reduction of spasticity/rigidity if present; and (5) graft survival at autopsy if and when there is mortality	No publications provided/Glass et al., 2012
Human spinal cord derived neural stem cell transplantation for the treatment of amyotrophic lateral sclerosis (ALS) USA/ NCT01348451	Active not recruiting January 2009 August 2013	18	Transplantation of human spinal cord derived neural stem cell for the treatment of ALS	Safety study Primary purpose: treatment	Primary: safety Secondary: (1) attenuation of motor function loss; (2) changes in muscle performance and pain assessment	Robberecht and Philips, 2013/Glass et al., 2012
Clinical trial on the use of autologous bone marrow stem cells in amyotrophic lateral sclerosis Spain/NCT00855400	Completed February 2007 February 2010	11	Autologous bone marrow cells collection Procedure: laminectomy and bone marrow stem cells transplantation	Safety/efficacy study Primary purpose: treatment	Primary: forced vital capacity Secondary: absence of adverse events	Blanquer et al., 2012/no publications associated to the trial
The Clinical trial on the use of umbilical cord mesenchymal stem cells in amyotrophic lateral sclerosis	Enrolling by invitation only March 2012 April 2015	30	Heterologous umbilical cord mesenchymal stem cells transplantation	Safety/efficacy study Primary purpose: treatment	Primary: forced vital capacity and nerve functional evaluation. Secondary: electrophysiology examination, blood and urinary tests	No publications provided/no publications associated to the trial
A dose-escalation safety trial for intrathecal autologous mesenchymal stem cell therapy in amyotrophic lateral sclerosis USA/NCT01609283	Recruiting May 2012 May 2014	25	Autologous mesenchymal stem cell transplantation dose escalation	Safety/efficacy study Primary purpose: treatment	Primary: number of patients with dose-limiting toxicities Secondary: adverse effects, blood analysis, development of cancer within 2 years after transplantation	No publications provided/no publications associated to the trial
Safety study of HLA-haplo matched allogenic bone marrow derived stem cell treatment in amyotrophic lateral sclerosis Republic of Korea/NCT01758510	Recruiting December 2012 June 2014	18	HLA-haplo matched allogenic bone marrow derived stem cells	Safety/efficacy study Primary purpose: treatment	Primary: adverse effects Secondary: motor performance changes	Choi et al., 2010b; Kim et al., 2010; Koh et al., 2012a,b; Kwon et al., 2012/no publications associated to the trial
Effect of intrathecal administration of hematopoietic stem cells in patients with amyotrophic lateral sclerosis (ALS) Mexico/NCT01933321	Recruiting December 2012 January 2014	14	Autologous hematopoietic stem cells intrathecal transplantation	Safety/efficacy study Primary purpose: treatment	Primary: adverse effects	No publications provided/no publications associated to the trial
Human neural stem cell	Recruiting	18	Intra-spinal cord delivery	Safety/efficacy study	Primary: safety of a	Robberecht and Philips,

3a. Spinal Cord Injury (Cellular Therapy: Mode of Action)



Stem Cell Transplant

Mitochondria

Microvesicle
Exosome

Trophic Factors

- VEGF
- FGF-2
- HGF
- IGF-1
- TGF-β
- VEGF
- TSG-6
- PGE2
- Galectin 1 & 9
- IFNγ
- TNF-α etc...

TRANSPLANTED STEM CELLS

- Homing
- Surviving in hostile environment
- Inducing axonal regeneration
- Inducing remyelination
- Improving decavitation

Transplantaion of differentiated, specialized cells unlikely to accomplish all these roles

Transplantation of naive stem cells producing trophic factors more likely to achieve these roles

3b. Spinal Cord Injury (Clinical Trials)

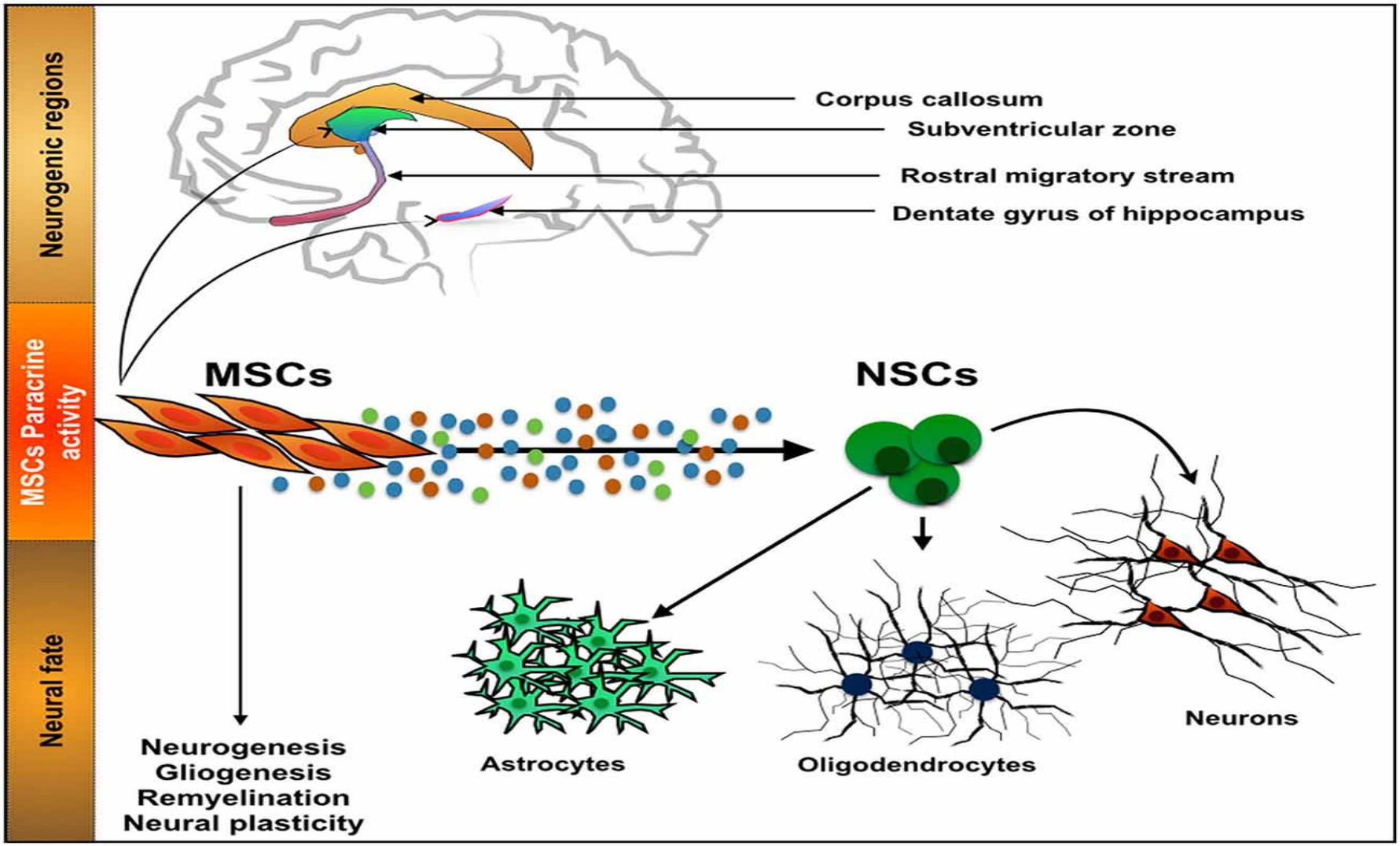
Therapeutic modulator	Biological actions	Status	Study title	ClinicalTrials.gov Identifier
Exercise	Increases skeletal muscle mass as well as cellular, biochemical, and cardiovascular functions; Improves neuroprotection, regeneration and rehabilitative processes	Currently recruiting participants	Study About Acting of Adaptive Sport in Musculoskeletal, Cardiovascular System and the Quality of Life of Individuals With Spinal Cord Injury Through Biomedical Instrumentation	NCT02177929
Minocycline	Neuroprotective, functional recovery, tissue sparing, down-regulation of pro-inflammatory species	Recruiting	Phase III Study of Minocycline in Acute Spinal Cord Injury	NCT01828203
Cethrin (BA-210)	Inhibitor of Rho/ROCK signalling; reduced apoptosis; decreased glial scarring; regenerative growth of axons	Completed	A Safety Study for Cethrin (BA-210) in the Treatment of Acute Thoracic and Cervical Spinal	NCT00500812
Erythropoietin	Anti-apoptogenic; anti-inflammatory; improves vascular integrity	Suspended participant recruitment	Evaluation of the Tolerability and Efficacy of Erythropoietin (EPO) Treatment in Spinal Shock: Comparative Study vs Methylprednisolone (MP)	NCT00561067
Riluzole	Blocks [Na^+] influx; inhibits glutamatergic neurotransmission; and improves neurological outcome	Currently recruiting participants	Riluzole in Spinal Cord Injury Study (RISCIS)	NCT01597518
Hypothermia	Reduces anti-inflammatory species; decreases microglia activation;suppresses neurotoxicity and mitigates blood spinal cord barrier disruption; Anti-apoptogenic	Currently recruiting participants	Hypothermia Following Acute Spinal Cord Injury	NCT01739010
Cellular Approach: *Macrophages*	Phagocytosis of cell debris; regeneration of axons; and neurological benefits	Suspended participant recruitment	A Phase II Multicenter, Randomized-Controlled Study to Evaluate the Safety and Efficacy of Autologous Incubated Macrophages for the Treatment of Patients With Complete Spinal Cord injuries	NCT00073853
Cellular Approach: *Bone marrow derived mesenchymal stem cells*	Promote neuronal regeneration; provide neuroprotection; replace neurons; and neurotrophic factors	Completed	Cell Transplant in Spinal Cord Injury Patients	NCT00816803

4. Epilepsy

Name of the study location/clinicaltrials.gov identifier	Status start and end of the study	Number of recruited patients	Type of cells/intervention	Study design/primary purpose
Autologous bone marrow stem cells transplantation in patients with temporal lobe epilepsy Brazil/NCT00916266	Ongoing, but not recruiting participants	20	Transplantations with autologous bone marrow mononuclear stem cells by selective posterior cerebral artery angiography	Non-randomized safety/efficacy study Primary purpose: treatment

*Rows as in **Table 3**.*

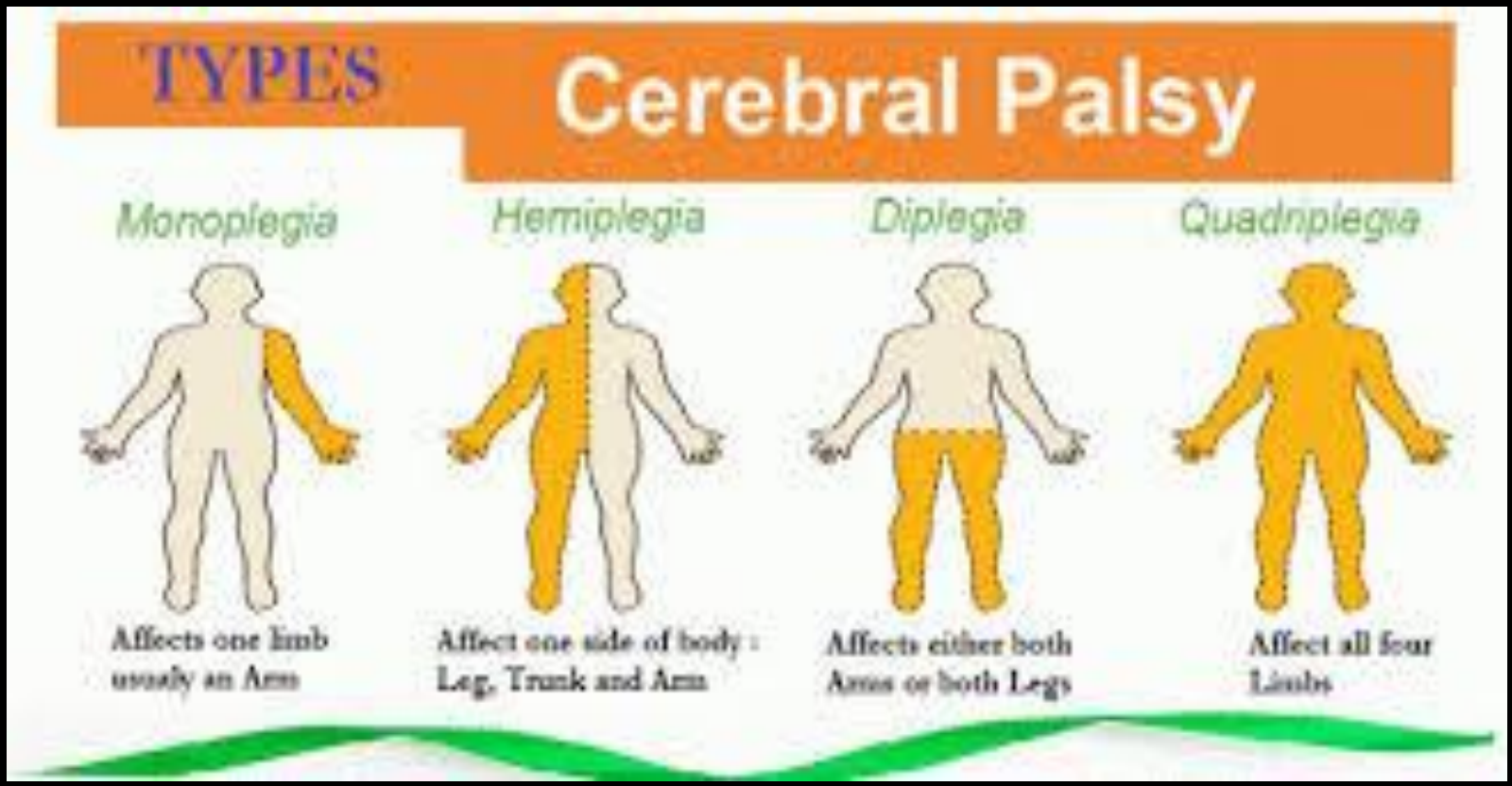
5a. Stroke (Mode of Action)



5b. Stroke (Clinical Trials)

Name of the study location/clinicaltrials.gov identifier	Status start and end of the study	Number of recruited patients	Type of cells/intervention	Study design/primary purpose	Outcome measures	Preclinical/clinical literature
Efficacy study of CD34 stem cell in chronic stroke patients China/NCT00950521	Completed June 2009 December 2010	30	Autologous peripheral blood CD34 stem cell/ phase II study	Randomized Efficacy study Double blind Primary purpose: treatment	Primary: NIH-stroke scale (NIHSS) Secondary: European stroke scale (ESS)/ European stroke motor subscale (EMS)	Mackie and Losordo, 2011/Chen et al., 2014
Autologous bone marrow stem cells in middle cerebral artery acute stroke treatment Spain/NCT00761982	Completed September 2008 August 2011	20	Autologous bone marrow stem cells/phase II study	Non randomized/safety-efficacy study Double blind Primary purpose: treatment	Primary: absence of new neurological deficits and adverse effects during the timeframe Secondary: improvement in clinical function as assessed by the modified rankin score, barthel scale and NIH stroke scale	Mackie and Losordo, 2011/Moniche et al., 2012
Intravenous autologous bone marrow-derived stem cells therapy for patients with acute ischemic stroke India/ NCT01501773	Completed October 2008 October 2011	120	Intravenous autologous bone marrow-derived stem cells/phase II study	Randomized/ Safety-efficacy study	Primary: barthel index score Secondary: NIHSS score and functional status	No publications provided/Prasad et al., 2012

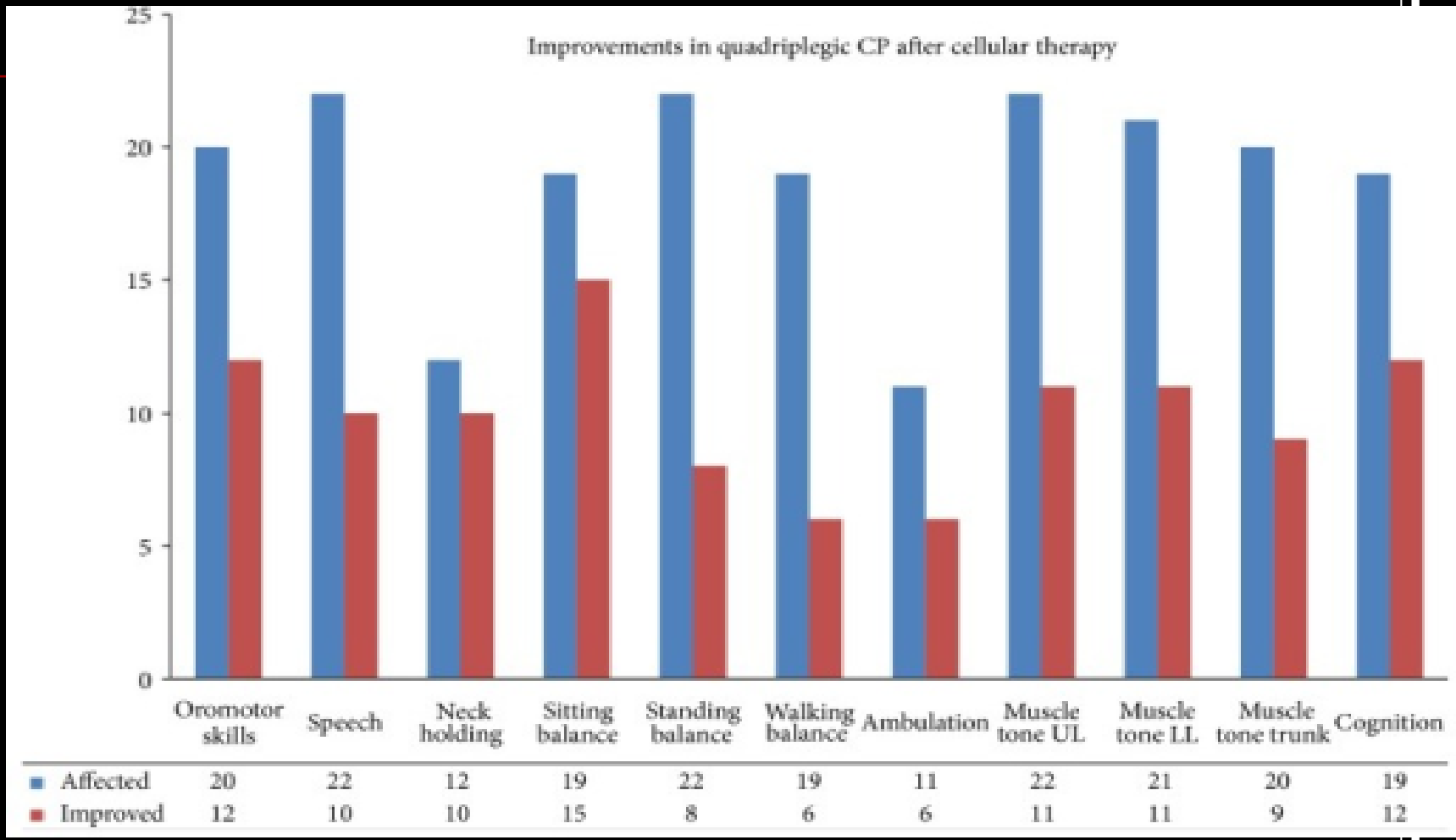
6. Cerebral Palsy Types



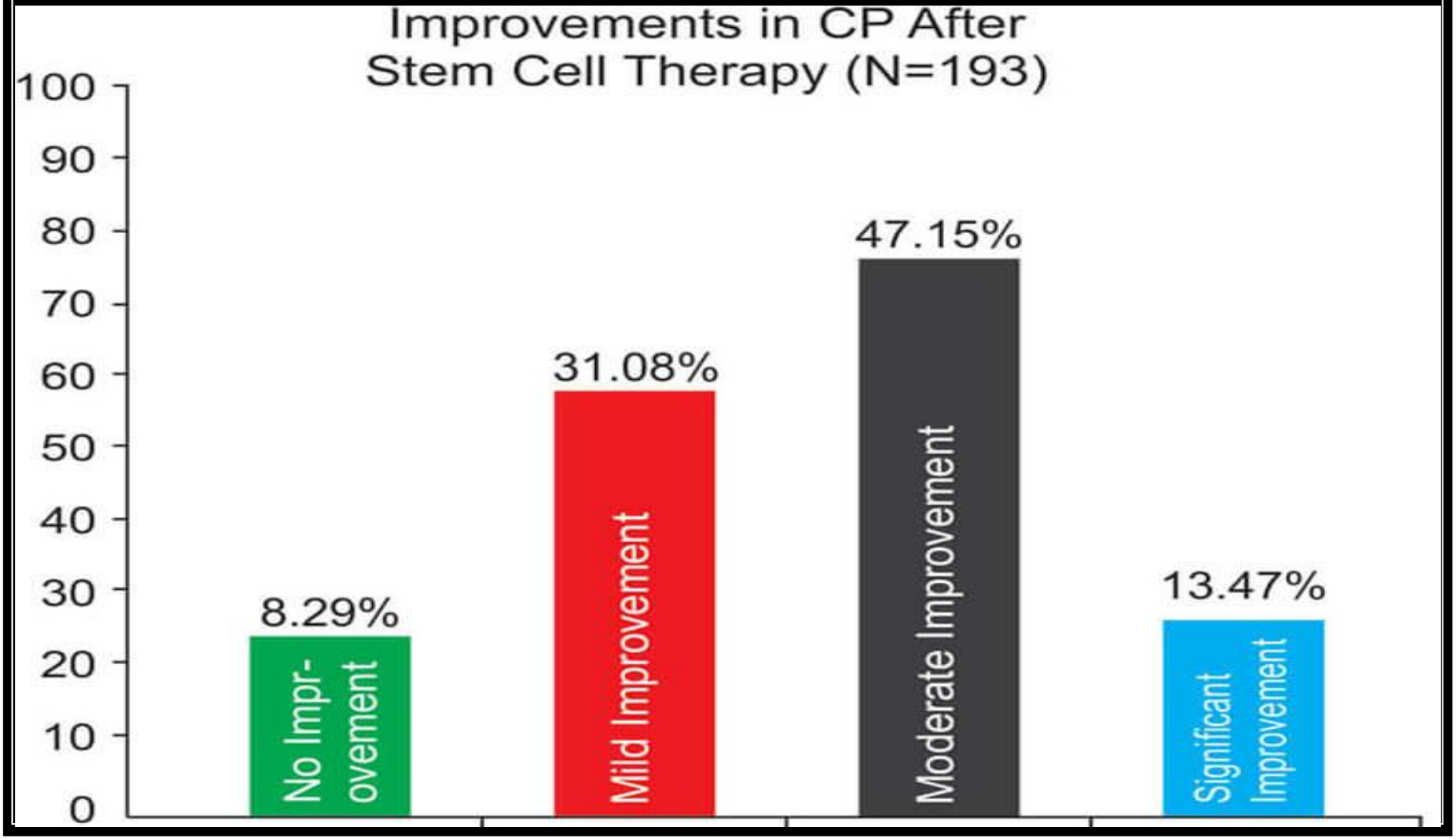
6a. Cerebral Palsy

A clinical study of autologous bone marrow mononuclear cells for cerebral palsy patients: a new frontier.

Sharma A, Sane H, Gokulchandran N, Kulkarni P, Gandhi S, Sundaram J, Paranjape A, Shetty A, Bhagwanani K, Biju H, Badhe P - Stem Cells Int (2015)



6b. Cerebral Palsy (Clinical Endpoints)



Legislation Cellular Therapies

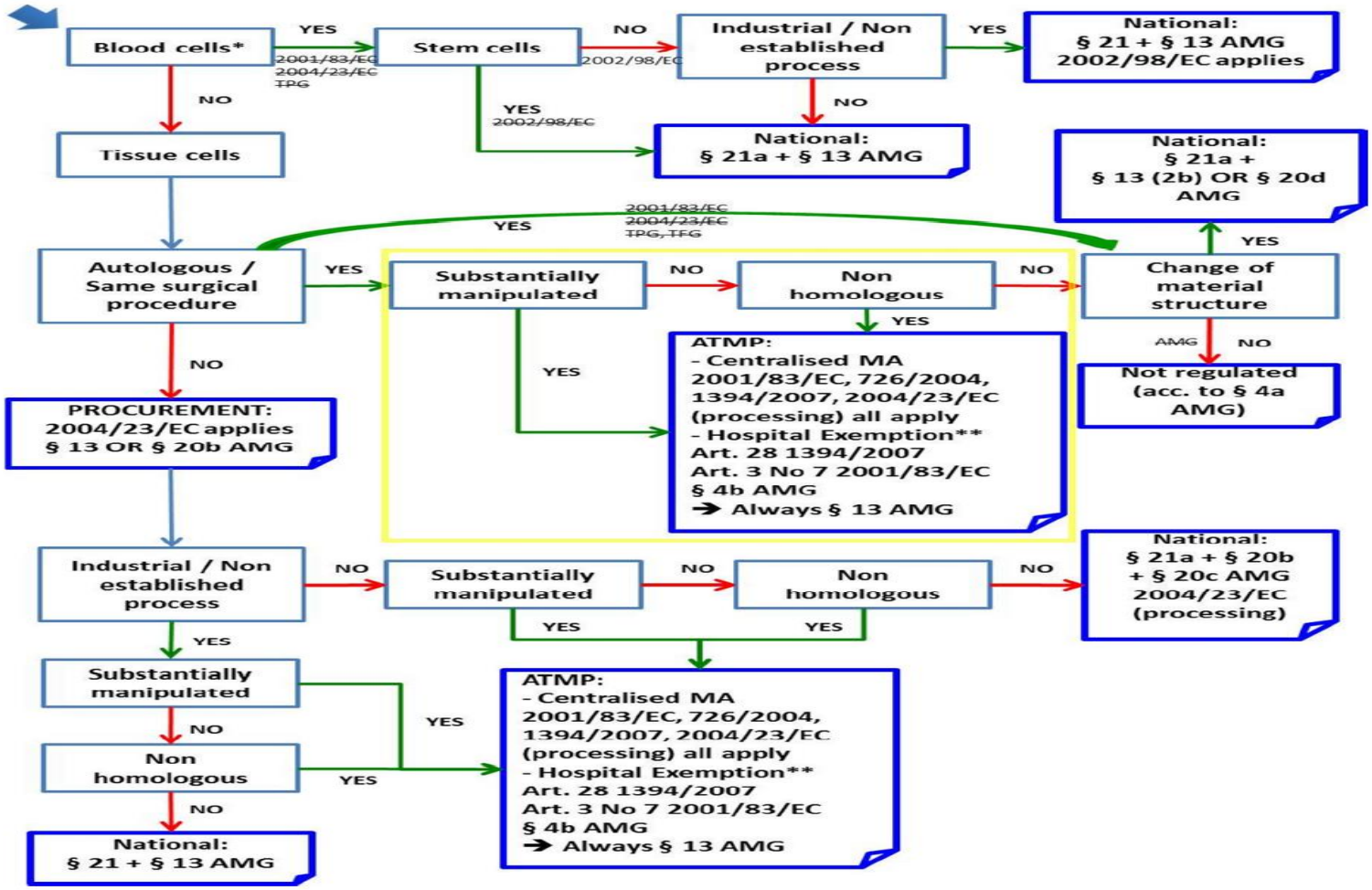


Figure 3: General cell and tissue classification flowchart

If a legislation is crossed out, it is not applicable in the considered regulatory pathway
The yellow frame represents a regulatory pathway that will be discussed in chapter 3.2
*: Blood cells, if substantially manipulated or used in a non-homologous way, are classified as ATMP, § 13 AMG applies
**: ATMP prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient

Quality and quantity control (ISO:9001/ ISO:15189)

Q-CERT

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έχει καθιερώσει ένα σύστημα διαχείρισης ποιότητας το οποίο είναι σε συμμόρφωση με το Διεθνές Πρότυπο

ΕΛΟΤ ΕΝ ISO 9001:2008

14 Σεπτεμβρίου, 2018 — Τέλος Περιόδου Πιστοποίησης

9 Σεπτεμβρίου, 2013 — Ημ/νία Αρχικής Πιστοποίησης

9 Σεπτεμβρίου, 2016 — Ημερομηνία Πιστοποίησης

IAF/EA Υποτομέας: 38.1

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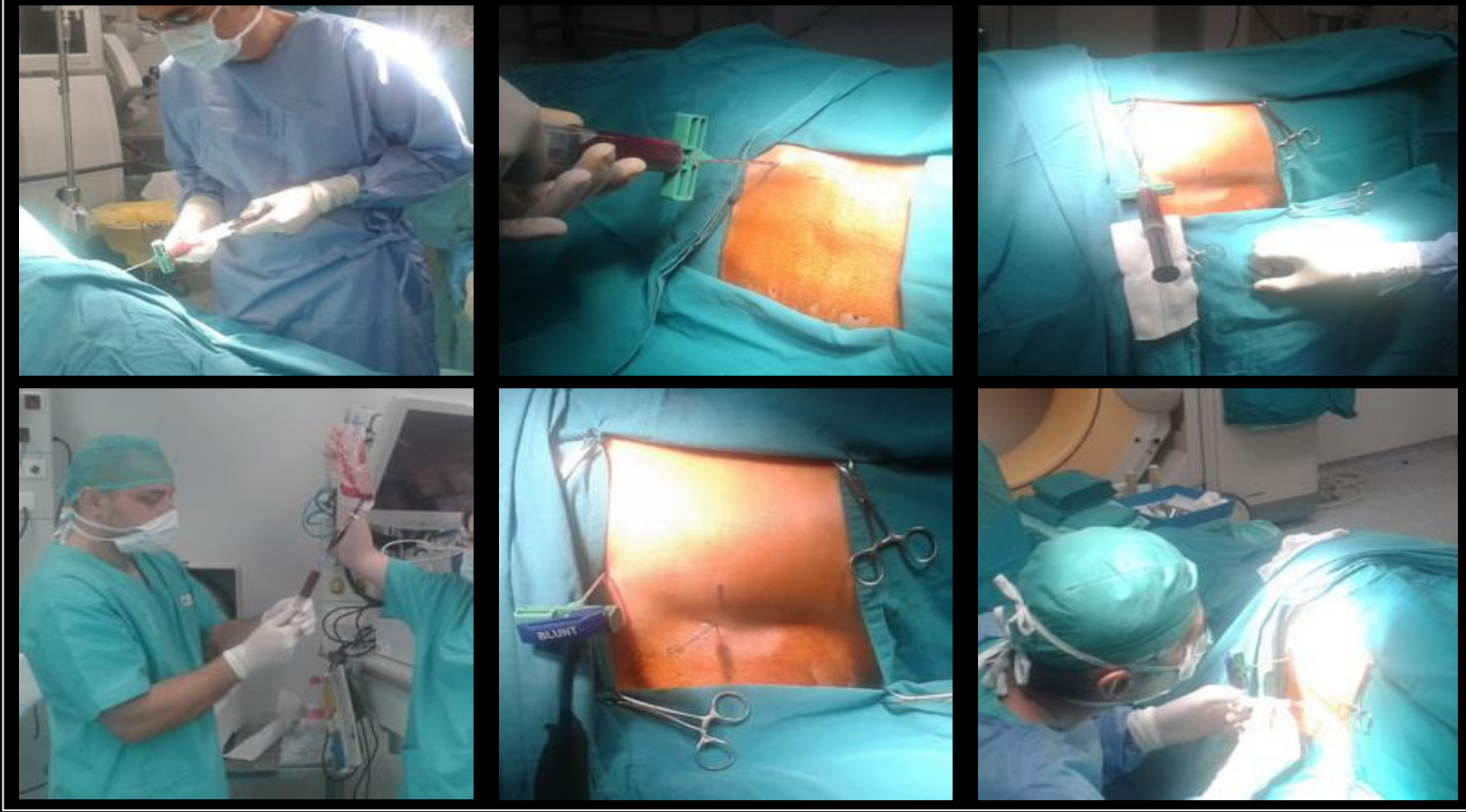
Πιστοποίηση ΣΑ Αρ. Πιστ. 110-3

QMSCERT 26th OCTOBER Str. 90 - GR 546 27 - THESSALONIKI - HELLAS

Example of bone marrow concentrate cellular therapy

Woman 40Y old, clinical indication: stroke / cerebral palsy.
Combined infusion I.V. & I.L. (*Point-of-Care Stem Cell Transplant*)



Thank you!