Evidence Based Status of Stem Cell Therapy for Human Diseases

2021

INDIAN COUNCIL OF MEDICAL RESEARCH
Department of Health Research
Ministry of Health & Family Welfare

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Published by:

Indian Council of Medical Research, New Delhi- 110029

January 2021

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PREFACE

The discovery of several types of stem cells over past half a century has each time promised to revolutionize the future of regenerative medicine. However, the full potential of therapeutic use of stem cells is yet to be achieved as the biology of these cells is not completely understood. A lot of basic and clinical research is required to unravel the mechanistic action of the stem cells. Inspite of this scientific understanding, the stakeholders especially the patient and their caregivers are often left confused and misinformed on the therapeutic use of stem cells for variety of debilitating diseases.

In order to bring clarity, the Ministry of Health and family Welfare had requested ICMR to frame guidelines on the stem cell therapy. ICMR Drafting Committee suggested formulating two documents:

1. National Guidelines for Hematopoietic Stem Cell transplantation for approved or Standard of Care (SOC) indications.
2. Evidence based Status of therapeutic use of stem cells for other/unapproved indications.

The **National Guidelines for Hematopoietic Cell Transplantation (NGHCT) -2021** includes an updated list of approved indications using stem cells as Standard of Care.

The document on '**Evidence Based Status of Stem Cell Therapy for Human Diseases'** is a result of the extensive exercise wherein ICMR invited Level I and Level II evidence writing to professional societies and also through open call on ICMR website. Group of clinicians reviewed the available scientific literature and scrutinized the claims received. Based on the critical review of literature and claims this document has been prepared.

We sincerely hope that both the above documents bring forth clarity on the approved and experimental therapeutic use of stem to the stakeholders and provide adequate information to clinicians and vulnerable diseased groups alike. It is understood that this is a dynamic document and thus going forward, sustained efforts will be made to proactively engage with all stakeholders to incorporate appropriate and timely revisions as per the emerging evidence and/or safety concerns. We hope there will be increasing indications for the evidence-based use of stem cells to alleviate human sufferings and will require basic, translational, and clinical research in compliance with existing guidelines and regulations.

Dr. Balram Bhargava
Secretary
Department of Health Research
Ministry of Health & Family Welfare
&
Director General
Indian Council of Medical Research

ACKNOWLEDGMENT

The compilation of this document required a lot of guidance, expertise and inputs from many eminent clinicians and professional societies. ICMR is extremely thankful to all of them for their precious time and constructive contributions in making of this document.

We profusely thank members of the Core Drafting Committee spearheaded by Dr. Rajiv Sarin, Lt. Gen (Dr) Velu Nair, Dr. HS Chhabra, Dr. Anurag Agrawal Dr. Subrata Sinha and Dr. P.B. Seshagiri for their vision in taking forward this challenging task and continued guidance.

ICMR also acknowledges the efforts and enthusiasm of all the stakeholders for collating and submitting the publications for review. The timely inputs from Indian Orthopaedic Association, Associations from Plastic Surgeons of India and Association of Spine Surgeons of India & Spinal Cord Society are greatly appreciated.

Special thanks are due to senior faculties from major medical institutes including AIIMS, New Delhi; Safdarjung Hospital, New Delhi; Sir Gangaram Hospital, New Delhi, ISIC, New Delhi; PGI, Chandigarh; SGPGI, Lucknow; Medanta Hospital, Gurugram; Fortis Hospital, Delhi & Mohali TMC-ACTREC, Mumbai; Govt. Stanley Medical College, Chennai; AIG, Hyderabad; MDRF, Chhenai etc. Sincere efforts of Dr. Rajesh Malhotra, Dr. Kameshwar Prasad, Dr. V. Padma, Dr. Sudesh Prabhakar, Dr. Sandeep Seth, Dr. Karoon Agrawal, Dr. R.K. Khazanchi, Dr. Shubha Phadke, Dr. Madhulika Kabra, Dr. Rajeev Narang, Dr. Ratna Puri, Dr. Sanjeev Sharma, Dr. Namrata Sharma, Dr. Radhika Tandon, Dr. V. Sangwan, Dr. Shilpa Sharma, Dr. D.K. Gupta, Dr. Sasikala Mitnala, Dr. Anil Arora, Dr. Jeswanth, Dr. V. Mohan and Dr. Deepak Agarwal are highly valued. The finalisation of this document was possible only because of their critical review of the scientific literature, and the comments and evidence provided by medical professionals and societies/associations. This is in addition to the clinicians who have contributed to National Guidelines for Hematopoietic Cell Transplantation (NGHCT)-2021.

It is an extreme privilege to thank Dr. Rajiv Sarin for his relentless efforts and able guidance throughout the exercise.

Sincere thanks are also extended to the staff of Division of BMS for their timely support.

The patronage, constant encouragement, and guidance from Dr. Balram Bhargava are gratefully acknowledged.

Geeta Jotwani

Content

Introduction

Stem cells and their unique properties: Stem cells are special cells which not only have the ability of self-renewal but can also be a lifelong source of specialised functional cells of different human organs. Development of a human embryo into a healthy new-born child is possible because of the unique ability of embryonic stem cells to form different tissues and organs. Most adult human tissues and organs also have stem cells that can produce their functional specialised cells as and when required. The self-renewal ability of stem cells ensures that stem cells are not depleted and enough stem cells remain to produce sufficient number of specialized cells of that organ during the long human lifespan, until aging starts affecting stem cells.

Stem cells in Regenerative Medicine and human diseases: When a disease or injury causes severe depletion of the functional cells of a human organ or system, the function of that organ or organ system is lost. In the natural healing process, some organs such as skin, blood, liver etc. can often regenerate its form and function by producing sufficient numbers of new functional cells from the stem cells present in them. However, specialized cells of some organs like the nerve cells in the brain, spinal cord, eyes and muscles have limited or no capacity to regenerate and restore full function. In the last two decades, medical science has undertaken extensive research to explore the potential of stem cells from the same organ or tissue type (homologous use) or from a different organ or tissue type (non-homologous use) to restore some lost bodily function. These stem cells may be from the same person (autologous source) or from another person (allogeneic source). Research to regenerate the form and function of a human organ or organ system from stem cells or tissue engineering is called 'Regenerative Medicine'.

Status of Stem cells in Regenerative Medicine and human diseases: Unfortunately, the promise of Regenerative Medicine in general, and stem cells in particular, is yet to be realized due to several technical, biological, ethical and medical challenges. To produce sufficient number of specialised cells for restoring a lost body function with just a small number of stem cells or by using stem cells from one organ to restore cells and function of a different organ (such as mesenchymal stem cells in bone marrow or fat tissue to restore nerve or muscle function) has proven to be far more difficult in humans than what was thought based on animal experiments. As a result, the inherent appeal of stem cells has remained largely unfulfilled in human diseases. The exception is however the use of "Haematopoietic Stem Cells" for reconstituting or regenerating the bone marrow in order to start producing blood and immune cells. Transplantation of enough number of "Haematopoietic Stem Cell" in a procedure called Bone Marrow Transplantation or Haematopoietic Stem Cell Transplantation from the same person (autologous) or from another human donor (allogenic) is a recognized medical indication of stem cell use for benign and malignant life threatening haemato-lymphoid diseases or few immune

related diseases. Haematopoetic stem cells are also progenitors for other cells like osteoclasts and have successfully used in osteopetrosis and some inborn errors of metabolism like Gaucher disease, mucopolysaccharidosis. Use of other types of stem cells and even the bone marrow derived stem cells to restore function of other organs remains experimental and is subject of ongoing controlled clinical trials. Not only the efficacy of these experimental stem cell use is uncertain, the process of taking out stem cells, culturing or growing them, storing them and putting them back can cause changes in these cells and sometimes serious side effects, including some reported cases of cancers.

Why Stem cells continue to be used for debilitating or incurable conditions outside controlled research studies: A large number of controlled prospective research studies (phase I, II and III clinical trials) investigating the safety and efficacy of stem cells for different diseases have been completed or are ongoing in Europe, USA, Korea and Japan. A small number of such research studies are also being conducted in other countries, including India. All developed countries have taken a very cautious and stringent regulatory approach regarding how different types of stem cells can be procured, processed, stored and used for preclinical or clinical research or as stem cell therapy outside research studies. Participants of regulated interventional research in any field, including stem cells, are made aware through a detailed written informed consent process about the experimental nature of the therapy, unproven efficacy and uncertainty regarding the benefits and risks of stem cells, the natural history of the disease, current standard therapy for that disease and any alternative treatments. It is the duty of the research sponsors to provide free of cost medical tests and treatments done as part of stem cell clinical trial and research, including the cost of procuring, storing and using stem cells. Circumventing the route of rigorous research studies to establish the safety and efficacy of a particular type of stem cells for a specific disease or aging condition, some unlicensed or even licenced and registered medical practitioners engage in unethical practices of selling unproven stem cell therapy as a magical remedy to desperate families with incurable and potentially fatal diseases with little or no hope of cure from other methods. Desperate patients from around the world including USA and Europe with stricter enforcement of regulations for stem cell use outside clinical trials get lured to stem cell clinics in South America, China, Russia and India. The US FDA and European Medical Agency has warned against this practice through several such advisories.

https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies

https://www.fda.gov/news-events/press-announcements/statement-stem-cell-clinic-permanent-injunction-and-fdas-ongoing-efforts-protect-patients-risks

https://www.fda.gov/news-events/press-announcements/federal-court-issues-decision-holding-us-stem-cell-clinics-and-owner-adulterated-and-misbranded-stem

Is Stem cell research permitted or encouraged by the governmental agencies?

The unethical and unregulated use of stem cells as, often promoted as a magical remedy is not allowed by the government in the developed world and many Low and Middle Income Countries (LMIC) including India. However, considering the incurable nature of many diseases, and the acknowledged potential of stem cells, most countries, including India, encourage and fund scientific, ethical and regulated research in the field of stem cells. The purpose of such research is to obtain safety and efficacy data with the use of a particular type of stem cell in a particular condition. To provide guidance and to facilitate human research in stem cells, while curbing exploitation of vulnerable patients, the Indian government through the Indian Council of Medical Research (ICMR) has come out with successive National Guidelines in this field since 2007. The most recent National Guidelines for Stem Cell Research with inputs from all stakeholders including various government agencies and regulators, patients, medical and scientific experts and the industry, was released in 2017. These guidelines are revised at regular intervals to incorporate any new evidence for the safety or efficacy of stem cells.
https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf

Need for National Guidelines for evidence-based use of Stem cells as a routine or standard treatment option: In many countries including India, there is a lack of clarity among patients, and to some extent among the medical community, whether stem cell therapy can be considered as a standard treatment option for a specific medical condition or should remain as an unproven experimental approach. There are several reports of increasing use of stem cells therapy for a wide range of diseases, often with little or no scientific evidence of efficacy or cure. Unethical promotions with false claims and misleading advertisements have been widely used to promote unscientific stem cell therapy. Several instances of public exploitation and grievances from members of the public have been received by the ICMR and other government agencies from aggrieved patients describing how they were lured into unproven stem cell therapies. Often the complainants demanded actions to be taken by the regulatory agencies and professional bodies to curb such practices. With this background, the Govt. of India has entrusted the ICMR to frame guidelines on stem cell therapy.

In order to develop a scientific and unbiased guideline for evidence based use of stem cell as a routine or standard treatment option in India, the ICMR has solicited opinion from expert clinicians, professional medical societies and through its website from any clinician or member of public to submit level I or level II scientific evidence for clinical efficacy of stem cells in any disease indications with reference for such evidence from peer reviewed Pubmed indexed medical and scientific journals.

https://icmr.nic.in/content/icmr-inviting-level-i-or-level-ii-scientific-evidence-and-grade-or-b-recommendation-use-stem

A critical review of the comments and evidence provided by medical experts and their professional societies or any member of the public and the scientific literature was done to draft guidelines and statements for evidence-based use of stem cell therapy.

Statements have been prepared for individual diseases or groups of diseases or conditions on the "EVIDENCE BASED STATUS FOR THE USE OF STEM CELLS IN (Disease condition)". In these statements the first section is for the public and patients using layman terms while the second section is for doctors, scientists and allied healthcare professionals providing major research studies in the scientific literature, scientific level of evidence and a summary recommendation based on the current scientific evidence.

International Society for Stem Cell Research (ISSCR)

The International Society for Stem Cell Research (https://www.isscr.org/) is the leading professional organization of stem cell scientists and represents over 4,000 members in 67 countries including India. Like ICMR in India, FDA in USA, EMA in Europe, this international society also felt the urgent need to address the growing public concern regarding the unscientific or unethical use of stem cell therapy. The ISSCR has also issued a statement on reporting false marketing claims and adverse events from clinics offering unapproved stem cell therapies.

https://www.closerlookatstemcells.org/patient-resources/how-to-report-false-marketing-claims-and-adverse-events-from-clinics-offering-unapproved-stem-cell-therapies/.

In parallel with the ICMR initiative and public advertisement inviting comments and evidence for stem cell use from public and medical professionals, the ISSCR has also come out with factsheets on current status of stem cell use. The ISSCR document highlights that other than Hematopoietic stem cell (also called Bone Marrow) transplant for certain haematological or immune system disorder, the "list of diseases for which stem cell treatments have been proven to be beneficial and/or have obtained regulatory approval for use is still very short" and that "some bone, skin and corneal (eye) injuries and diseases can be treated by grafting or implanting tissues in which stem cells are essential for the healing process".The ISSCR cautions that "However, clinics around the world continue to provide unproven stem cell treatments and often market them as cures for a variety of diseases and conditions without sound scientific evidence or regulatory approval. These so-called treatments have, in some cases, caused patients great harm physically, and at great expense financially".
https://www.isscr.org/professional-resources/scientific-professional-resources/disease-fact-sheets

https://www.isscr.org/scientific-clinical-resources/disease-fact-sheetshttps://www.closerlookatstemcells.org/2020/01/14/truths-around-stem-cell-treatments/

The ISSCR concise factsheets provide the current state of stem cell science for specific diseases, including background on the disease, rationale for using cell-based therapies, evidence for specific approaches and current status of the field with respect to clinical trials. A total of 11 conditions have been covered so far.

1. Age-related macular degeneration
2. Amyotrophic lateral sclerosis
3. Chronic obstructive pulmonary disease
4. Diabetes
5. Huntington's disease
6. Liver disease
7. Multiple sclerosis
8. Myocardial infarction / Heart failure
9. Osteoarthritis
10. Parkinson's disease
11. Paediatric leukodystrophies

1. Evidence Based Status of Use of Stem Cells in Orthopedic Conditions / Injuries

A. Information for public and patients

What are orthopaedic conditions/injuries?

These are conditions/injuries of the musculoskeletal system – most commonly of the bone or joints. They are generally associated with pain and/or dysfunction of the affected area. These include arthritis (osteoarthritis and rheumatoid arthritis), Osteoporosis, Bursitis and Pain, ligament-tendon injuries, osteonecrosis, cartilage defects, bone-joint injuries, and osteogenesis imperfecta.

What are the treatments available for orthopaedic conditions/injuries?

The treatment options for the orthopaedic condition/ injury depends on the type of condition or injury. Most conditions/injuries respond well to conventional treatments; however, some conditions/injuries may be difficult to manage by conventional methods. Some orthopedic conditions are curable, and some cannot currently be cured, but can be treated to reduce pain and improve quality of life.

Have stem cells been used for orthopaedic conditions/injuries?

Stem cells have shown encouraging results for treatment of orthopaedic condition/injuries in animal experiments and to a certain extent in clinical trials. The evidence from clinical trials is encouraging; however, more studies need to be undertaken before stem cells are used in general clinical practice.

Recommendations (2021): Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Orthopedic Conditions/injuries.

Use of any type of stem cells in spinal cord injury should be restricted to clinical trials after obtaining necessary approval from the regulatory authorities in India. These trials should follow the National Guidelines for Stem Cell Research and the patients participating in clinical trials should be closely monitored for the possibility of any harm with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, trial participants should have read and signed the informed consent form which explains the existing standard of care, alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. **Participants should not be made to pay for any expenses** incurred beyond routine clinical care and which are research related including tests, investigations, and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should

be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

In pre-clinical trials, stem cells demonstrate safety and efficacy in a wide range of orthopaedic applications. Mesenchymal stem cells have been studied the most due to their ease of harvesting and their propensity to differentiate easily into bone and cartilage. Due to this, far more data is available from case studies than validated large scale clinical trials leading to paucity of Level I evidence for use to stem cells in a variety of orthopaedic conditions. Efforts must be made to ensure safe, economical, efficient and effective introduction of stem cells for regular clinical use. Well-developed, randomized, prospective, clinical studies that build on the existing animal data will provide us with much needed information for the correct application of this field of science to well documented needs of orthopaedic surgeons.

ICMR with inputs from experts in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding level of evidence for efficacy and safety of stem cells for orthopaedic applications. A critical review of the published human studies that are either randomized controlled trials or have been submitted as proof of level I or level II evidence supporting the use of stem cells in case of Orthopedic conditions/injuries is outlined below in table:

Orthopedic Condition/injuries	
Disease/Disorders	**Review of Literature** **Critique / Applicability of the study results**
Articular cartilage defects of the knee	i. Source: Autologous bone marrow-derived mesenchymal stem cells RoA: Surgical Nejadnik H, Hui JH, Feng Choong EP, Tai BC, Lee EH. Autologous bone marrow–derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study. The American journal of sports medicine. 2010 Jun;38(6):1110-6. PMID: 20392971 [Claimed Level of Evidence 2b] Cohort study. Evidence level III. The IKDC subjective knee evaluation (P = .861), Lysholm (P = .627), and Tegner (P = .200) scores do not show any significant difference between groups over time. *Further studies with larger sample size and longer follow-up data are needed*. ii. Source: Adipose-derived stem cells RoA: Surgical Koh YG, Kwon OR, Kim YS, Choi YJ, Tak DH. Adipose-Derived Mesenchymal Stem Cells with Microfracture Versus Microfracture

	Alone: 2-Year Follow-up of a Prospective Randomized Trial. Arthroscopy. 2016 Jan;32(1):97-109. PMID: 26585585 [Claimed Level of Evidence 1b] RCT reporting significant improvement in mean KOOS pain and symptom sub scores. Arthroscopy revealed no significant intergroup difference. Level II evidence
Avascular necrosis of femoral head	i. Source: Bone-marrow buffy coat RoA: intra-articular (core decompression + autologous bone graft with bone marrow buffy coat) Ma Y, Wang T, Liao J, Gu H, Lin X, Jiang Q, Bulsara MK, Zheng M, Zheng Q. Efficacy of autologous bone marrow buffy coat grafting combined with core decompression in patients with avascular necrosis of femoral head: a prospective, double-blinded, randomized, controlled study. Stem cell research & therapy. 2014 Dec;5(5):115. PMID: 25315149 [Claimed Level of Evidence 1b] Double blind RCT. Sample size 53 hips. Heterogenous Ficatstage I-III . Core decompression + bone graft Vs Core decompression + bone graft + buffy coat. The etiology and Ficat stages of ANFH are diverse in the participants, and the subclass patient number limited. Further studies with a larger sample size and a longer follow-up period required.
Osteonecrosis of the femoral head	i. Source: Bone marrow-derived cells Li X, Xu X, Wu W. Comparison of bone marrow mesenchymal stem cells and core decompression in treatment of osteonecrosis of the femoral head: a meta-analysis. Int J Clin Exp Pathol. 2014 Jul 15;7(8):5024-30. PMID: 25197374 [Claimed Level of Evidence 1a] Total 4 studies used for meta-analysis. Of these only 2 were clinical trials. *Therefore, even though the data is encouraging, more and larger studies need to be undertaken.* ii. Source: Bone marrow-derived mesenchymal cells RoA: Intra-articular Daltro GC, Fortuna V, de Souza ES, Salles MM, Carreira AC, Meyer R, Freire SM, Borojevic R. Efficacy of autologous stem cell-based therapy for osteonecrosis of the femoral head in sickle cell disease: a five-year follow-up study. Stem cell research & therapy. 2015 Dec;6(1):110. PMID: 26021713 [Claimed Level of Evidence 2b] Phase I/II, non-controlled study. Evidence Level III
Osteonecrotic hips	i. Source: Autologous bone marrow mononuclear cells RoA: Surgical Sen RK, Tripathy SK, Aggarwal S, Marwaha N, Sharma RR, Khandelwal N. Early results of core decompression and autologous bone marrow

	mononuclear cells instillation in femoral head osteonecrosis: a randomized control study.J Arthroplasty. 2012 May;27(5):679-86. PMID: 22000577 [Claimed Level of Evidence 1b] RCT. 51 hips. Core decompression Vs Core decompression + autologous bone marrow mononuclear cell instillation. *Results are encouraging but need large scale trials to confirm findings.*
Unicompartmental osteoarthritis knee	i. Source: Cultured autologous bone marrow-derived mesenchymal stem cell RoA: Intra-articular (in conjunction with microfracture and medial opening-wedge high tibial osteotomy) PMID: 24286801 [Claimed Level of Evidence 1b] Level II randomized controlled trial. Concludes that MSC + HA is better than only HA after high tibial osteotomy. Sample size 56. No blinding.
Chondral lesions	i. Source**:** Peripheral blood stem cells RoA: Intra-articular Saw KY, Anz A, Siew-Yoke Jee C, Merican S, Ching-Soong Ng R, Roohi SA, Ragavanaidu K. Articular cartilage regeneration with autologous peripheral blood stem cells versus hyaluronic acid: a randomized controlled trial. Arthroscopy. 2013 Apr;29(4):684-94. PMID: 23380230 [Claimed Level of Evidence 1a] Level II evidence randomized controlled trial (RCT) with 50 subjects. Uses Peripheral blood stem cells. Study lists limitations like possible confounding due to difference in population age in both groups, use of a new MRI morphologic scoring system and lack of long term data.
Osteochondral lesions of the talus	i. Source: Autologous bone marrow-derived cells RoA: Arthroscopic Cadossi M, Buda RE, Ramponi L, Sambri A, Natali S, Giannini S. Bone marrow-derived cells and biophysical stimulation for talar osteochondral lesions: a randomized controlled study. Foot Ankle Int. 2014 Oct;35(10):981-7. PMID: 24917648 [Claimed Level of Evidence 1b] The RCT was to determine the effect of PEMF not of bone marrow cells. Level II evidence. ii. Source: Autologous bone marrow derived MSC RoA: Arthroscopic Kim YS, Park EH, Kim YC, Koh YG. Clinical outcomes of mesenchymal stem cell injection with arthroscopic treatment in older patients with osteochondral lesions of the talus. Am J Sports Med. 2013 May;41(5):1090-9. PMID: 23460335

	[Claimed Level of Evidence 2b] Cohort study; Level of evidence, 3
Osteoarthritis	i. Source: Allogeneic bone marrow MSCs RoA: Intra-articular Vega A, Martín-Ferrero MA, Del Canto F, Alberca M, García V, Munar A, Orozco L, Soler R, Fuertes JJ, Huguet M, Sánchez A. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. Transplantation. 2015 Aug 1;99(8):1681-90. PMID: 25822648 [Claimed Level of Evidence 1b] Possible efficacy. It is a Phase I/IIa trial with 30 subjects only. Large scale trial needed for confirming the trial findings. ii. Source: Allogeneic mesenchymal stem cells RoA: Intra-articular following meniscectomy Vangsness Jr CT, Jack Farr II, Boyd J, Dellaero DT, Mills CR, LeRoux-Williams M. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study. JBJS. 2014 Jan 15;96(2):90-8 PMID: 24430407 [Claimed Level of Evidence 1b] The difference in the distribution of the presence of osteoarthritis across the groups was not controlled in the study. Double blind RCT, does provide level 1 evidence, however, sample size is small
Knee osteoarthritis	i. Source: Mesenchymal stem cell RoA: Arthroscopic surgery using MSCs, injection of MSCs in combination with platelet-rich plasma Kim YS, Kwon OR, Choi YJ, Suh DS, Heo DB, Koh YG. Comparative Matched-Pair Analysis of the Injection Versus Implantation of Mesenchymal Stem Cells for Knee Osteoarthritis. Am J Sports Med. 2015 Nov;43(11):2738-46. PMID: 26337418 [Claimed Level of Evidence 2b] Cohort study; Level of evidence, 3.

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021): Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Orthopedic Conditions/injuries.

CAUTIONARY NOTE

Use of any type of stem cell in spinal cord injury should be restricted to clinical trials that have all approvals as defined in NGSCR-2017. These trials should follow the National Guidelines on Stem Cell Research and patients participating in these trials should be closely monitored for the possibility of any harm with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, trial participants should have read and signed the informed consent form which explains them existing standard of care, alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Orthopedic Conditions/injuries.

2. Evidence Based Status of Use of Stem Cells in Spinal Cord Injury

A. Information for public and patients

What is Spinal Injury?

A **spinal cord injury** (SCI) is **damage** to the **spinal cord** resulting in temporary or permanent alteration in muscle, sensory or autonomic function in the parts of the body served by the **spinal cord** below the level of the **injury**. Spinal cord injury may be due to traumatic or non-traumatic causes. Traumatic causes include road traffic crashes (RTCs), fall from height, low falls, diving accidents, violence, sports injuries etc. Non traumatic causes include infection, degeneration, tumor, metabolic etc. If there is no residual movement or sensation below the level of the injury, especially in the perianal area, it is labelled as a complete injury. Complete injuries do not have the potential to recover neurologically. If there is any sensation or movement below the level of injury, especially in the perianal region, it is labelled as incomplete injury. Such injuries have a good potential to recover neurologically.

What is the treatment of spinal cord injury?

Treatment of SCI can be better defined as management of SCI and the associated complications. It is targeted towards minimizing the neurological damage due to the injury and maximizing recovery of the damaged nerve cells. In general, SCI management starts from the time of injury even before the patient reaches hospital (pre-hospital care) and spans from emergency room to intensive care management where applicable, management of vertebral fracture, management of complications, comprehensive rehabilitation and lifelong follow up.

In case of incomplete injuries, the chances of regaining full neurological and motor functions are high. In case of complete injuries, neurological and motor function recovery is limited but the patients can have a good quality of life with comprehensive rehabilitation which includes physical, psycho-social, sexual and vocational rehabilitation, community inclusion and lifelong follow up.

Have stem cells been used in spinal cord injury?

ICMR with inputs from medical specialists in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding any evidence-based safety and efficacy of stem cells in spinal cord injury.

In pre-clinical studies / animal experiments, use of stem cells has been shown to be effective and the cells were approved to be tested for clinical use. However, when tested at the clinical level in validated clinical trial studies, these cells/interventions have not been proven to be very effective. Therefore, their use as a standard therapy is not recommended.

Recently completed and some ongoing clinical trials using different types of stem cells have shown some encouraging results. We need to conduct further testing of such cells in clinical trials with large population sizes to understand whether stem cells may be used as a standard therapy for repair of the injured spinal cord. However, until then use of stem cells in case of SCI is limited to conducting validated clinical trials only and their use as a "therapy" with commercial implications is unethical. Critical review of the studies reported so far do not support the use of stem cell therapy over and above the standardised and validated management as mentioned above.

Recommendations (2021): Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with spinal cord injury.

CAUTIONARY NOTE

Use of any type of stem cell in spinal cord injury should be restricted to clinical trials that have necessary approval from regulatory authorities in India. These trials should follow the National Guidelines on Stem Cell Research - 2017 and patients participating in these trials should be closely monitored for the possibility of any harm with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, trial participants should have read and signed the informed consent form which explains existing standard of care, alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

There is substantial evidence at the pre-clinical level for the safety and efficacy of stem cell interventions; setting the stage to move forward with clinical translation. However, so far, this has not translated to generation of substantial evidence at the clinical trial. The factors underlying this are many, ranging from use of appropriate animal models, cell population selection, dose of the intervention, route of transplantation, time of transplantation, clinical trial design, outcome measures and data analysis. Additionally, due to the hope generated by the idea that stem cells could be used as a 'Wonder Drug' and the ease of obtaining autologous stem cell populations,

the path to identifying a scientifically validated Level 1 evidence for safety and efficacy of cellular intervention arising from an ethical and validated clinical trial has been severely hindered.

ICMR with inputs from experts in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding level of evidence for efficacy and safety of stem cells in SCI. A critical review of the published human studies that are either randomized controlled trials or have been submitted as proof of level I or level II evidence supporting the use of stem cells in case of Spinal Cord Injury is outlined below:

Spinal Cord Injury	
S.No	**Review of Literature** **Critique / Applicability of the study results**
i.	Source: BMMMNCs, MNC, UCMSC RoA: Intravenous, subarachchnoid Fan X, Wang JZ, Lin XM, Zhang L. Stem cell transplantation for spinal cord injury: a meta-analysis of treatment effectiveness and safety. Neural Regen Res. 2017 May;12(5):815-825. PMID: 28616040 [Claimed Level of Evidence 1a] Total studies 10 only. All Studies from China only. Has heterogenous SCI group - AIS A-C which leads to data confounding. Hence, level of evidence not strong.
ii.	Source: Mesenchymal stem cell RoA: Intrathecal, subarachnoid injection, intravenous injection Xu P, Yang X. The Efficacy and Safety of Mesenchymal Stem Cell Transplantation for Spinal Cord Injury Patients: A Meta-Analysis and Systematic Review. Cell Transplant. 2019 Jan;28(1):36-46 PMID: 30362373. [Claimed Level of Evidence 1a] 11 studies used for meta analysis. 9 studies from China, 1 Egypt and 1 Iran. Again, has heterogenous SCI group.
iii.	Source: Umbilical cord mesenchymal stem cell RoA: Subarachchnoid Cheng H, Liu X, Hua R, Dai G, Wang X, Gao J, An Y. Clinical observation of umbilical cord mesenchymal stem cell transplantation in treatment for sequelae of thoracolumbar spinal cord injury. J Transl Med. 2014 Sep 12;12:253. PMID: 25209445 [Claimed Level of Evidence 1b] RCT with 34 AIS A subjects, reports significant changes in urodynamics but no change in AIS grade. Results are encouraging, however, level of evidence not strong due to small sample size.
iv.	Source: Bone marrow-derived cells Route: RoA: Intravenous injection Li XC, Zhong CF, Deng GB, Liang RW, Huang CM. Efficacy and safety of bone marrow-derived cell transplantation for spinal cord injury: a systematic review and meta-analysis of clinical trials. Clin Transplant. 2015;29:786–795. PMID: 26115044

	[Claimed Level of Evidence 2a] 24 studies included O**nly one Grade I level of evidence**, six Grade II levels, three Grade III levels, and 14 Grade IV levels. prospective, randomized trials in larger cohorts are still needed

BMMNC= Bone marrow mononuclear cells; MNC= Mononuclear cells; UCMSC= Umbilical cord derived mesenchymal cells

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021):

Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with spinal cord injury.

The experts observed that spinal cord injury can have a major impact on the quality of life of the individual and the family. There is therefore a need to undertake research into the prevention and more effective management of spinal cord injury. Since management does not result in neurological recovery in complete spinal cord injuries, such patients, consumers and families see a hope in some miraculous recovery with the use of stem cells without understanding the risks versus benefit ratio. It is therefore imperative that use of any type of stem cells in spinal cord injury should be restricted to clinical trials that have necessary approvals as defined in NGSCR-2017 including regulatory authorities in India. These trials should follow the national guidelines on stem cell research and patients in these trials should be closely monitored for the possibility of any harm with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, trial participants should have read and signed the informed consent form which explains them alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations, and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Spinal Cord Injury.

3. Evidence Based Status of Use of Stem Cells in Critical Limb Ischemia (CLI)

A. Information for public and patients

What is Critical Limb Ischemia (CLI)?

Critical limb ischemia (CLI) is considered the most severe form of peripheral artery disease (PAD) which is caused by obstruction of peripheral arteries so that the blood supply to the limbs is insufficient to maintain their normal internal functioning. CLI is said to have developed when the blood flow to the limb is insufficient for metabolism of the cells in the limb, even when the person is resting. Patients may experience pain in the feet or in the toes when walking and in some severe cases even when he/she is not walking (rest pain). If the disease is severe, they may develop painful sores / ulcers on the toes or feet or legs. If the circulation does not improve, these ulcers can start as dry, gray, or black sores, and eventually become dead tissue (called gangrene). If no therapeutic intervention is made during this stage of the disease the inevitable outcome is limb amputation. The blockage of arteries is primarily due to atherosclerosis; although in Mediterranean and Asian countries including India this can be due to Thromboangitis obliterance (TAO) or Buerger's disease which has shown to be strongly associated with tobacco / cannabis use.

What is the treatment of CLI?

The treatment options for this condition in general are lifestyle changes such as control of diabetes, hypertension, and hypercholesterolemia, along with dietary restrictions aimed at reducing lipid levels, complete discontinuation of cigarette smoking or other use of tobacco / cannabis in any form, maintaining ideal body weight, and drugs to treat conditions that have primarily caused this condition. There are surgical options to reestablish blood circulation in the limbs. But surgery is usually not possible in all cases.

Have stem cells been used in CLI?

Along with supportive symptomatic therapies, studies have reported their experience with the use of different types of stem cells for patients with CLI. From the published studies, websites and other resources, it has come to our knowledge that many Indian patients with CLI / PAD have been offered different types of stem cell therapies within and outside clinical trial / research. ICMR with inputs from medical / surgical specialists in this field has reviewed the existing scientific and medical literature regarding any evidence based safety and efficacy of stem cells in CLI. Critical review of the studies reported so far and feedback from experts in the field do not support the use of cell therapy in CLI as on date.

Recommendations (2021):

Based on a critical review of the available scientific evidence by the ICMR experts, stem cell based or derived products for CLI should NOT be offered as a standard or routine therapy to patients with CLI unless it is approved by the regulatory agency in India. One such stem cell and cell based product from India, stempeucel® (Adult Human Bone-Marrow Derived, Cultured, Pooled, Allogeneic Mesenchymal Stromal Cells) has been granted manufacturing and marketing license by Central Drugs Standard Control Organisation (CDSCO) for "no-option" patients of CLI due to Buerger's disease and Critical Limb Ischemia due to Atherosclerotic PAD in Rutherford III-5 or III-6, not eligible for or have failed traditional revascularisation treatment, with rest pain and/or ulcers in the affected limb. This is the only approved stem cell and cell-based product for above mentioned conditions in India. These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for CLI.

CAUTIONARY NOTE

From various websites and other sources, it has come to our knowledge that some doctors and clinics in India continue to offer stem cells as a standard treatment option to CLI patients outside the purview of regulated and approved clinical trials. Patients with CLI from India and those coming from outside India should be aware that any type of stem cells therapy for CLI should be offered only as part of ongoing clinical trials that have all the approvals from the regulatory authorities in India. These trials should follow the national guidelines on stem cells research. As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, clinical trial participants should have read and signed the informed consent form which explains them standard and alternative therapies, possible benefits and harms due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred including routine clinical clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator / control groups. Participants in a clinical trial should be provided with compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

Peripheral artery occlusive disease (PAOD) also commonly known as peripheral artery disease (PAD) is a manifestation of atherosclerosis caused by obstruction of peripheral arteries. Critical limb ischemia (CLI) is the severe subset and end stage of PAD which is characterised by severe rest pain, non-healing ischemic skin lesions and finally gangrene of the extremity due to inadequate blood supply to the limb. If no therapeutic intervention is made during this stage of

the disease the inevitable outcome is limb amputation. The blockage of arteries is primarily due to atherosclerosis; although in Mediterranean and Asian countries including India this can be due to Thromboangitis obliterance (TAO) or Buerger's disease which has shown to be strongly associated with tobacco or cannabis use. Other causes include various autoimmune disorders like Systemic Lupus Erythematosus (SLE), and acute conditions like embolism. Various risk factors causally related to PAD include diabetes, hyperlipidemia, hypertension and smoking. Coexistent coronary artery disease (CAD) and cerebrovascular disease (CVD) are highly prevalent in patients with PAD particularly in elderly population.

Diagnostic studies include measurement of hemodynamic changes by Ankle Brachial Pressure Index (ABPI), transcutaneous partial oxygen pressure (TcPO2), toe brachial pressure index, exercise testing to elicit symptoms, segmental pressure monitoring, and Doppler examination of the vascular system. Magnetic resonance angiogram (MRA) and computed tomography (CT) angiography can also aid in the diagnosis. The management of CLI is based on risk factor management and surgical or endovascular revascularization aiming to improve blood flow to the affected extremity. Most patients with CLI are managed with analgesics, antiplatelets and cilostazol in addition to lipid lowering drugs. If revascularization has failed or is not possible, major amputation is often necessary. Approximately 10% of CLI patients will undergo primary amputation with healing rates varying from 30% and 90%, and re-amputation rate stands between 4% and 30%. Overall, approximately 40% and 50% of CLI patients will lose their leg within 6 – 12 months and approximately 15% will also require contralateral amputation within 2 years. In CLI patients, cardiovascular cause of mortality increases substantially with approximately 20% of patients dying during first 6 to 12 months after CLI onset, and 2 -, 5 – and 10 years mortality rates of approximately 35%, 70% and 100% respectively.

Many Indian patients with CLI have been offered different types of stem cells therapies as part of approved clinical trials and also as standard treatment option which is outside the purview of approved clinical trial. ICMR with inputs from experts in this field has reviewed the existing medical and scientific literature regarding level of evidence of evidence and safety of stem cells in CLI.

A critical review of the published human studies supporting the use of stem cells in CLI has been undertaken. Summary of some representative studies are outlined below:

Chronic Limb Ischemia	
S.No.	**Review of Literature** **Critique / Applicability of the study results**
i.	Lafrati MD et al. Early results and lessons learned from a multicenter, randomized, double-blind trial of bone marrow aspirate concentrate in critical limb ischemia. J Vasc Surg. 2011 Dec;54(6):1650-8. doi: 10.1016/j.jvs.2011.06.118. In this multicenter, randomized, double-blind, placebo-controlled trial of autologous bone marrow cell therapy for CLI, the therapy was well tolerated without significant adverse events.

	The BMAC group demonstrated trends toward improvement in amputation, pain, quality of life, Rutherford classification, and ABI when compared with controls.
ii.	Ai M et al. Safety and efficacy of cell-based therapy on critical limb ischemia: A meta-analysis. Cytotherapy. 2016 Jun;18(6):712-24. doi: 10.1016/j.jcyt.2016.02.009. Cell-based therapy has a significant therapeutic effect on CLI, but randomized double-blind placebo-controlled trials are needed to improve the credibility of this conclusion.
iii.	Gupta P K et al. Administration of Adult Human Bone Marrow-Derived, Cultured, Pooled, Allogeneic Mesenchymal Stromal Cells in Critical Limb Ischemia Due to Buerger's Disease: Phase II Study Report Suggests Clinical Efficacy. Stem Cells Transl Med. 2017 Mar;6(3):689-699. doi: 10.5966/sctm.2016-0237. This phase II, open-label nonrandomized study demonstrated the possible effects of allogeneic bone marrow derived Mesenchymal stromal cells in CLI due to Buerger's disease. The patients in the 2 million cells/kg group showed clinical benefit in both the primary endpoints (rest pain relief and ulcer healing) and most secondary endpoints (improvement in total walking distance, ankle brachial pressure index, and quality of life). Hence, it is suggested that in this pathfinder study, BM-MSCs at a dose of 2 million cells/kg body weight may be the best dose in patients with critical limb ischemia due to Buerger's disease.
iv.	Idei N et al. Autologous bone-marrow mononuclear cell implantation reduces long-term major amputation risk in patients with critical limb ischemia: a comparison of atherosclerotic peripheral arterial disease and Buerger disease. Circ Cardiovasc Interv. 2011 Feb 1;4(1):15-25. doi: 10.1161/CIRCINTERVENTIONS.110.955724. BM-MNC implantation reduces major amputation rate and is safe and effective in patients with CLI, especially in patients with Buerger's disease.
v.	Liew A et al. Cell Therapy for Critical Limb Ischemia: A Meta-Analysis of Randomized Controlled Trials. Angiology. 2016 May;67(5):444-55. doi: 10.1177/0003319715595172. In summary, our meta-analysis suggests that cell therapy for patients with CLI is feasible and safe, with preliminary assessments of efficacy of these cell types, encouraging. However, additional, carefully designed future double-blind, sham, and placebo controlled RCTs in a large, homogenous patient cohort, with a clearly defined cell type, cell number, and potency are needed to confirm its true potential therapeutic effect.
vi.	Wahid FSA et al. Efficacy and Safety of Autologous Cell-based Therapy in Patients with No-option Critical Limb Ischaemia: A Meta-Analysis**.** Curr Stem Cell Res Ther. 2018;13(4):265-283. doi: 10.2174/1574888X13666180313141416. Implantation of autologous cell-based therapy may be an effective therapeutic strategy for no-option CLI patients. BM-MNC and mobilized – peripheral blood stem cells more effective than non-cell-based therapy in improving AR and other limb perfusion parameters. BM-MSC may be beneficial in improving perfusion parameters but not AR, however, this observation needs to be confirmed in a larger population of patients. Generally, treatment using various sources and phenotypes of cell products appeared safe and well tolerated.
vii.	Sharma S et al. Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Safety and Therapeutic Efficacy of Angiogenesis Induced by Intraarterial Autologous Bone Marrow-Derived Stem Cells in Patients with Severe Peripheral Arterial Disease. J Vasc Interv Radiol. 2021 Feb;32(2):157-163. doi: 10.1016/j.jvir.2020.09.003. Epub 2020 Nov 25. PMID: 33248918. Intraarterial administration of autologous BMSCs results in significantly greater improvement in hemodynamic parameters such as ABI and TcPO2 in patients with severe PAD and greater freedom from major amputation among patients with CLI, with no adverse effects or 30-day

	mortality. Intraarterial autologous stem cell therapy delivered proximal to the most proximal occlusion is a safe and effective alternative in the management of patients with severe PAD.

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021)

Based on a critical review of the available scientific evidence by the ICMR experts, stem cell based or derived products for CLI should NOT be offered as a standard or routine therapy to patients with CLI unless it is approved by the regulatory agency in India. One such stem cell and cell based product from India, stempeucel® (Adult Human Bone-Marrow Derived, Cultured, Pooled, Allogeneic Mesenchymal Stromal Cells) has been granted manufacturing and marketing license by Central Drugs Standard Control Organisation (CDSCO) for "no-option" patients of CLI due to Buerger's disease and Critical Limb Ischemia due to Atherosclerotic PAD in Rutherford III-5 or III-6, not eligible for or have failed traditional revascularisation treatment, with rest pain and/or ulcers in the affected limb. This is the only approved stem cell and cell-based product for above mentioned conditions in India. These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for CLI.

The experts observed that Peripheral arterial disease (PAD) is a common disorder and a major cause of morbidity and mortality. The most severely affected patients, with rest pain, ulcerations, or gangrene, are given a diagnosis of critical limb ischemia (CLI). These patients have a particularly poor prognosis, with high rates of limb amputation and mortality. Despite improvements in medical therapy for atherosclerosis and associated comorbidities as well as improvements in interventional and surgical techniques to improve limb perfusion, CLI continues to carry a major risk of limb amputation. A significant portion of patients with CLI are considered "no option" for revascularization, and no medical therapy has been shown to be capable of reducing the need for amputation. Therefore, novel therapies are needed to treat this disorder. Therefore there is a need to undertake research into the causes and more effective management of CLI especially reducing the amputation rate and overall cardiovascular mortality. Since conventional management fails to significantly delay control symptoms in many cases of no-option CLI cases, such families see a hope in some recovery with the use of stem cells without understanding the risks versus benefit ratio.

Numerous regulatory approved clinical trials (many trials are in phase 2 or phase 3) are being conducted in this condition across the world including India and the patients are being followed up for adequate time to see the safety and efficacy of the stem cells. Till date no stem cells drug is approved by the regulatory agency for this condition. It is therefore imperative that use of any type of stem cells in CLI should be restricted to clinical trials with due approvals from regulatory authority in India and as per the National Guidelines on Stem Cell Research. As part of the regulated clinical trials, patients should be closely monitored not only for objective measures of

clinical benefit but also for any possible harms with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, trial participants should have read and signed the informed consent form which explains them alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay any expenses incurred including routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator / control groups. Participants in a clinical trial should be provided with compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for CLI.

4. Evidence Based Status of Use of Stem Cells in Duchenne Muscular Dystrophy

A. Information for public and patients

What is Duchenne Muscular Dystrophy (DMD)?

Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle degeneration and weakness due to the alterations of a protein called *dystrophin* that helps keep muscle cells intact. DMD occurs because of a change in the DMD gene that results in the decrease of the dystrophin protein in the muscle cells. As a result of this the muscle becomes frail and does not work efficiently. DMD is one of four conditions known as dystrophinopathies. The other three diseases that belong to this group are Becker Muscular dystrophy (BMD, a mild form of DMD); an intermediate clinical presentation between DMD and BMD; and DMD-associated dilated cardiomyopathy (heart-disease) with little or no clinical skeletal, or voluntary, muscle disease. DMD symptom onset is in early childhood, usually between ages 2 and 3. The disease primarily affects boys, but in rare cases it can affect girls. The children have difficulty in climbing stairs, jumping and running. They develop a waddling walk and can have prominent calf muscles.

What is the standard treatment for DMD?

Patients with Duchenne Muscular Dystrophy are advised supportive physical therapies along with steroids as the standard of care. The two options for steroids are prednisolone or deflazacort, as indicated. They increase muscular strength and retard the progression of disease. They also reduce the need for scoliosis surgery, improve lung and cardiac function. Other drugs that are used for older patients include beta-blockers and angiotensin-converting enzyme inhibitors to delay DMD cardiomyopathy.

Recently precision therapy using the mutation type is FDA approved. Exon skipping with ASO (antisense oligonucleotides) bind to a specific mRNA to allow exon skipping. and formation of a normal short dystrophin protein. This restores the reading frame of the protein. There is some expression of the shortened but functional dystrophin protein. Exon skipping related to exons 51and 53 are currently approved for treatment of patients amenable to this therapy. Ataleuren, a small molecule for treatment of a specific type of DMD mutation is used under conditional approval in Europe. It is important to follow up with a doctor who has experience in managing patients with DMD

Have stem cells been used in DMD?

Along with this management, few studies have tested the use of various forms of stem cells to treat patients with DMD and repair the function of damaged muscle. Cell therapy approaches aim to provide new cells to patients to compensate for their deteriorated cells in the targeted

tissue. Cells can be from a donor or from the patient himself. Both approaches have advantages and disadvantages. While cells from the donor are mutation free; an immune reaction is a risk. Autologous cells have lower risk of causing an immune reaction; however, the cells would need to be repaired prior to reinjection. However most of these studies have one or more flaws and do not support the use of stem cells over the current standard of care treatment for patients with DMD.

The muscles in the human body are of various types eg trunk muscle, limbs muscle. Their origin and programming is different as is the type of muscle fibre they are composed of. To derive each kind from a stem cell in the correct position is currently not achieved. Making a mature skeletal muscle from the stem cell using current methods is limited.

We are aware that many patients with DMD in India are offered and have undergone stem cell therapy for DMD. ICMR with expert inputs from various specialists in this field, has reviewed extensively and discussed existing scientific and medical literature related to stem cell therapy in DMD. Consensus statements from various professional societies world over has also been reviewed and they also do not recommend use of stem cells in DMD without genetically engineering them to correct the gene defect. The latter are also in clinical trials and not the standard of care world over.

Recommendations (2021): Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Duchenne Muscular Dystrophy (DMD). These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Duchenne Muscular Dystrophy.

CAUTIONARY NOTE

Use of any type of stem cell in DMD should be restricted to clinical trials that have necessary approval from regulatory authorities in India. These trials should follow the National Guidelines on Stem Cell Research and patients in these trials should be closely monitored for the possibility of any harm with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, trial participants should have read and signed the informed consent form which explains them existing standard of care, alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

Duchenne Muscular Dystrophy occurs due to a mutation in the dystrophin gene. The disorder causes progressive muscular damage and degeneration occurs in people with DMD, resulting in muscular weakness, associated motor delays, loss of ambulation, respiratory impairment, and cardiomyopathy. In 2018 DMD care considerations, were published which were supported by the US Centers for Disease Control and Prevention (CDC) with involvement of the TREAT-NMD network for neuromuscular diseases, the Muscular Dystrophy Association, and Parent Project Muscular Dystrophy
(Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan)

The details of some of the studies of the use of stem cells in DMD are given below:

Duchenne Muscular Dystrophy	
S.No.	**Review of Literature** **Critique / Applicability of the study results**
i.	Source: Wharton jelly-derived MSCs (WJ-MSCs) RoA: four doses of intramuscular and four doses of intra-arterial Dai A, Baspinar O, Yeşilyurt A, Sun E, Aydemir Çİ, Öztel ON, Capkan DU, Pinarli F, Agar A, Karaöz E. Efficacy of stem cell therapy in ambulatory and nonambulatory children with Duchenne muscular dystrophy - Phase I-II. Degener Neurol Neuromuscul Dis. 2018 Oct 26;8:63-77. 4 ambulatory and 5 non-ambulatory children. Well define criteria. Only one patient (patient number 3) has shown remarkable new myoblastic signal activity quantitative analysis of muscle strength, did not show a significant difference though EMG showed increase amplitude. Improved quality of life in first year but progressive decline thereafter. Small sample size. Follow up with possible requirement of additional doses not available. In the analysis, no comparison between ambulatory and non-ambulatory patients.
ii.	Source: Umbilical cord derived mesenchymal stem cells (UCMSCs); RoA: Intravenous and intramuscular Rajput BS, Chakrabarti SK, Dongare VS, Ramirez CM, Deb KD. Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Duchenne Muscular Dystrophy: Safety and Feasibility Study in India. J Stem Cells. 2015;10(2):141-56 Single blinded study on 11 patients. One of the inclusion criteria - mutation in dystrophin gene in cytogenetic analysis. As this is not possible the definitive diagnosis is uncertain. Small underpowered study.

iii.	Source: Allogeneic, umbilical cord donors RoA: peripheral IV infusion 6 Kang PB, Lidov HG, White AJ, Mitchell M, Balasubramanian A, Estrella E, Bennett RR, Darras BT, Shapiro FD, Bambach BJ, Kurtzberg J, Gussoni E, Kunkel LM. Inefficient dystrophin expression after cord blood transplantation in Duchenne muscular dystrophy. Muscle Nerve. 2010 Jun;41(6):746-50. Single case report. Primary stem cell transplant to treat chronic granulomatous disease. On follow up he was diagnosed to have DMD as well. Analysis of myofibers demonstrated no definite donor cell engraftment. Even though this is done on one patient it shows that the concept of stem cell transplant is not efficacious on its own.
iv.	Source: Autologous bone marrow-derived mononuclear cells RoA: intrathecally and intramuscularly Sharma A, Sane H, Badhe P, Gokulchandran N, Kulkarni P, Lohiya M, Biju H, Jacob VC. A clinical study shows safety and efficacy of autologous bone marrow mononuclear cell therapy to improve quality of life in muscular dystrophy patients. Cell Transplant. 2013;22 Suppl 1:S127-38 This non-randomized, open-label, single center trial from India on 150 patients with muscular dystrophy. Limb girdle muscular dystrophies and DMD and BMD are clubbed together. No molecular diagnosis of the dystrophies is provided. 86.67% of cases showed symptomatic and functional improvements. However specific muscles tested are not defined. Patients were not grouped based on the severity of affection at the onset of treatment. Long term follow-up of this cohort is not available. The author acknowledges that this is a single-center study with no control group and a limited follow up
v.	Source: Autologous transplantation of muscle derived CD133+ stem cells RoA: Intramuscular Torrente Y, Belicchi M, Marchesi C, D'Antona G, Cogiamanian F, Pisati F, Gavina M, Giordano R, Tonlorenzi R, Fagiolari G, Lamperti C, Porretti L, Lopa R, Sampaolesi M, Vicentini L, Grimoldi N, Tiberio F, Songa V, Baratta P, Prelle A, Forzenigo L, Guglieri M, Pansarasa O, Rinaldi C, Mouly V, Butler-Browne GS, Comi GP, Biondetti P, Moggio M, Gaini SM, Stocchetti N, Priori A, D'Angelo MG, Turconi A, Bottinelli R, Cossu G, Rebulla P, Bresolin N. Autologous transplantation of muscle-derived CD133 + stem cells in Duchenne muscle patients. Cell Transplant. 2007; 16 (6): 563-77 Small sample size – 5 patients; double-blind phase I clinical trial. Increased capillaries per muscle fibre - angiogenic potential of the injected CD133+ stem cells. But not clear how the cells will promote the switch of slow-to-fast muscle fiber type. This is the first step for future clinical trials for DMD based on the autologous transplantation of engineered stem cells and need at least four potential improvements. • isolate cells from easily accessible site as blood • Expand in vitro without loss of stem cell property • transduce them with viral vectors that promote the expression of dystrophin by exon skipping • to deliver them to diseased muscle through arterial circulatory routes. The authors say that better understanding of the stem cell behaviour in the human muscle structures is required to gain the route for stem cell therapy.

vi.	Source: Autologous bone marrow mononuclear cell transplantation RoA: Intrathecal ClinicalTrials.gov Identifier: NCT02241434. The Role of Autologous Bone Marrow Mononuclear Cell Therapy in Duchenne Muscular Dystrophy Recruitment Status: Withdrawn First Posted: September 16, 2014 Last Update Posted: October 25, 2018 Study was to start in January 2009. Completion date 2016 There are no updates of any results and recruitment withdrawn

None of the studies are of an appropriate level of evidence based on the methodological quality of their design, validity, and applicability to patient care. None of them are randomized double blind studies or multicentric studies as are usually performed for rare genetic disorders. Many are single case reports or use a small number of patients. The criteria to assess benefit for use of stem cell therapy in the studies are not well defined or uniform and thus the presence or absence of improvement in muscle function is ambiguous.

In summary, the studies, case series, including one aborted clinical trial reported so far do not show clear scientific evidence to support the use of stem cell therapy in DMD. Hence, based on current knowledge, stem cell therapy should not be offered as one of the standard or routine therapy to patients with DMD. Currently the role of stem cell use in DMD should be in a research setting with a rigorously designed and executed protocol as per the national guidelines, with appropriate approval from recognized regulatory authorities in India. These studies should be closely monitored for the possibility of any harm to the patients by the use of stem cells. Participants of any such trials should have read and signed the informed consent form which has to clearly explain the alternative therapies, the design and phase of the clinical trial, possible benefit and harm due to stem cell therapy and what compensation will be provided to the patient or the family in the event of any harm or death due to the use of experimental stem cell therapy. The real utility of stem cells is where they are combined with genome editing to correct the patient mutation in the induced pluripotent stem cell.

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021)

Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Duchenne Muscular Dystrophy.

The experts observed that Duchenne Muscular Dystrophy is a severe disorder with premature death and can have a major impact on the quality of life of the affected child and the family. There are standards of care that are published for the care and patients of patients with DMD. Recently definitive therapy targeting the type of mutation has also recently been approved for use. In September 2016, the US Food and Drug Administration (FDA) granted accelerated approval of Eteplirsen, an exon skipping drug that has shown to increase dystrophin in patients with a mutation of the dystrophin gene amenable to exon 51 skipping. Ataluren is licensed in the European Union and United Kingdom to treat patients aged 2 years and older with DMD caused by nonsense mutations. Golodirsen and Viltolarsen, drugs for use in patients with mutations amenable to exon 53 skipping were approved by FDA in December 2019 and August 2020 respectively.

Currently there is no recommendation of the use of stem cells treatment in patients with DMD. The real utility of stem cells is where they are combined with genome editing to correct the patient mutation in the induced pluripotent stem cell. It is therefore imperative that use of any type of stem cell in DMD should be restricted to clinical trials with due approvals from regulatory authorities in India and as per the national guidelines on stem cell research. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, trial participants should have read and signed the informed consent form which explains them alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Duchenne Muscular Dystrophy.

5. Evidence Based Status of Therapeutic Use of Stem Cells in Autism Spectrum Disorder (ASD)

A. Information for public and patients

What is Autism or Autism Spectrum Disorder?

It is a neurological and developmental disorder which is first noticed in childhood and the condition remains the same or worsen in later life. It is termed "Autism Spectrum Disorder" as may cause a range of problems from difficulties in speaking, avoiding eye contact and doing or saying things repetitively. If ASD is suspected in your child, a more detailed evaluation is done by a team of specialists to make a diagnosis of ASD. Some genetic disorders namely, fragile X syndrome, Rett syndrome, Tuberous sclerosis have autistic features. However, there are no known or well-established causes for most of the cases of ASD.

What is the treatment of autism?

Patients with autism are advised behavioural and occupational therapy along with other forms of supportive therapies as required. Sometimes pharmacological agents are used for symptomatic management of certain manifestations of Autism spectrum disorder.

Have stem cells been used in ASD?

Along with supportive therapies and drug treatment, few studies have tested the use of various forms of stem cells to improve the outcome in children with Autism. We are aware that many Indian patients with ASD have been offered different types of stem cell therapies as a standard treatment option and not as part of any approved clinical trial / research. ICMR with inputs from medical specialists in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding any evidence-based safety and efficacy of stem cells in ASD. ***Critical review of the studies reported so far do not support the use of stem cell therapy over and above the behavioural and supportive therapies for ASD.***

Recommendations (2021): **Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Autism. These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Autism Spectrum Disorder.** Therapeutic use of any type of stem cell in Autism should be restricted to clinical trials only after obtaining necessary regulatory approval as defined in National Guidelines for Stem Cell Research-2017. The patients participating in these clinical trials should be closely monitored for the possibility of any harm with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human

Participants - 2017, trial participants should have read and signed the informed consent form which explains them the alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

The diagnosis of Autism Spectrum Disorder is made after a detailed evaluation by a multidisciplinary team. There are very few established causes of ASD and this remains an active area of research. Based on their symptoms and signs, ASD patients are managed with behavioural and occupational therapy along with other forms of supportive therapies. In some ASD cases, pharmacological agents are used in an attempt to control some manifestations. Along with these supportive therapies and drug treatment, there are several reports of the use of stem cells to children with Autism. Many Indian patients with ASD have also been offered different types of stem cell therapies as part of research studies and also as a standard treatment option which is outside the purview of approved clinical trial. ICMR with inputs from experts in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding level of evidence for efficacy and safety of stem cells in ASD. A critical review of the published human studies that are either randomized controlled trials or have been submitted in response to the ICMR call for Level I/II evidence supporting the use of stem cells in Autism Spectrum Disorder has been undertaken. Summary of some representative studies is outlined below:

Autism Spectrum Disorder	
S.No.	Review of Literature Critique / Applicability of the study results

i.	Source: Human embryonic stem cell RoA: IV, IM, Epidural, popliteal block, brachial plexus block, intrathecal, epidural catheter caudal, deep spinal muscle Shroff G. Human Embryonic Stem Cells in the treatment of Autism: A case series. InnovClin Neurosciences. 2017, 14 (3-4), 12-16 PMID: 28584692 Three cases studied. No control used. The patients were treated with 3 to 4 sessions from 2011 to 2013. 'Results: The patients showed improvements in eye coordination, writing, balancing, cognition, and speech and showed reduced hypersensitivity to noises and smells.' The time period of post-treatment evaluation has not been given. The patients were given occupational and physical therapy additionally. It is mentioned that there was improvement but tools for assessing behavioural & intellectual functions have not been described and there is no objective assessment pre- and post-therapy. The paper is published in 2017, but there is no data about follow up after therapies given in 2012-13. The weakness in this study prevents its findings from being used to support the use of stem cells.
ii.	Source: Human cord blood mononuclear cells (CBMNCs) & umbilical cord derived mesenchymal stem cells (UCMSCs) RoA: Combined IV and IT transplantation Lv YT, Zhang Y, Liu M, Qiuwaxi JN, et al. Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism. J Transl Med. 2013;11:196. doi: 10.1186/1479-5876-11-196. This non-randomized, open-label, single center phase I/II trial from China showed that combined (CBMNC and UCMSC) therapy showed significant improvement in CARS score by 24 weeks. However, it is a small study of 37 cases. It was an open label and non-randomized study. After the 2013 publication, there has been no follow up publication to see if there was any long-term benefit or harm
iii.	Source: Autologous umbilical cord blood (AUCB) RoA: Peripheral IV infusion Chez M, Lepage C, Parise C, et al. Safety & Observations from a Placebo-Controlled, Crossover Study to Assess Use of Autologous Umbilical Cord Blood Stem Cells to Improve Symptoms in Children with Autism. Stem Cells Transl Med. 7(4):333-341 A randomized, blinded, placebo-controlled trial but in only 29 children with autism. With autologous umbilical cord blood infused intravenously a trend towards improvement, particularly in socialization, was seen but there was no statistically significant differences for any endpoints

iv.	Source: Fetal stem cells RoA: IV or subcutaneous Bradstreet JJ, Sych N, Antonucci N, et al Efficacy of fetal stem cell transplantation in autism spectrum disorders: an open-labeled pilot study. Cell Transplant. 2014;23Suppl 1:S105-12. doi:10.3727/096368914X684916 This study used Fetal stem cells and relied on Autism Treatment Evaluation Checklist (ATEC) Structure to judge efficacy. ATEC is a caregiver-administered questionnaire designed to measure changes in severity of ASD after treatment. Caregiver's assessment is likely to be a source of bias. Also the ATEC scores decrease with increasing age and this has not accounted for while interpreting the decrease in score as the efficacy of stem cell treatment. (See study on ATEC -Mahapatra S, Vyshedsky D, Martinez S, Kannel B, Braverman J, Edelson SM, Vyshedskiy A. Autism Treatment Evaluation Checklist (ATEC) Norms: A "Growth Chart" for ATEC Score Changes as a Function of Age. Children (Basel). 2018. 16;5(2). pii: E25. doi: 10.3390/children5020025)
v.	Source: Autologous bone marrow mononuclear cells RoA: Intrathecal Sharma A, Gokulchandran N, Sane H et al. Autologous bone marrow mononuclear cell therapy for autism: an open label proof of concept study. Stem Cells Int. 2013;2013:623875. doi: 10.1155/2013/623875. In a small study of 32 patients with Autism, autologous bone marrow mononuclear cells (BMMNCs) were given intrathecally along with multidisciplinary therapies. A significant improvement in certain scores was reported at a mean follow up of 12 months. Under the heading limitations and future directions, the authors acknowledge that *"The study is an open label proof of concept. A small sample size, the absence of randomization, and the absence of control group were the limitations. Large scale, multicentre, and randomized controlled trials are recommended. A longer period of follow up may be required to further establish the safety and efficacy. Few patients had increased episodes of seizures after the intervention, which were controlled with medications…".* In fact, the 9% seizure rate after this therapy is a matter of concern. Without any follow up randomized or larger Phase II study after the 'Proof of Concept' study of 2013, its findings cannot be used to justify stem cells as a standard therapy option.
vi.	Source: Autologous umbilical cord blood RoA: IV Dawson G, Sun JM, Davlantis KS, et al. Autologous Cord Blood Infusions are Safe and Feasible in Young Children with Autism Spectrum Disorder: Results of a Single-Center Phase I Open-Label Trial. Stem Cells Transl Med. 2017; 6(5):1332-1339 Pre and post assessments were done based on caregiver and clinician administered tools. Out of multiple scales used, most did not show significant p values. Discussion mentions about improvement in scores but does not refer to the p value for statistical significance.

vii.	Source: Autologous bone marrow aspirate concentrate RoA: Intrathecal Bansal H, Verma P, Agrawal A et al. A Short Study Report on Bone Marrow Aspirate Concentrate Cell Therapy in Ten South Asian Indian Patients with Autism. J Stem Cells. 2016;11:25-36 In this study, intrathecal transplantation of bone marrow aspirate concentrate stem cells was performed. The maximal effect of cell therapy was observed within the first 12 months following the treatment. Interestingly, they also found that improvement decreased with increasing age of the child. The authors acknowledge it was a pilot study and its findings cannot be used to justify stem cells as a standard therapy option.
viii.	Sharifzadeh N, Ghasemi A, Tavakol Afshari J, Moharari F, Soltanifar A, Talaei A, Pouryousof HR, Nahidi M, Fayyazi Bordbar MR, Ziaee M. Intrathecal autologous bone marrow stem cell therapy in children with autism: A randomized controlled trial. Asia Pac Psychiatry. 2020 Nov 4:e12445. doi: 10.1111/appy.12445. Epub ahead of print. PMID: 33150703. Overall, 32 patients in two groups of intervention (n = 14) and control (n = 18) completed the study, of which 27 (84.4%) were male. Mean age was 9.50 ± 2.14 years. The improvements in CARS total score, GARS-II autism index, and CGI global improvement showed **no significant differences between the groups over 12 months.**
ix.	Price J. Cell therapy approaches to autism: a review of clinical trial data. Mol Autism. 2020 May 24;11(1):37. doi: 10.1186/s13229-020-00348-z. PMID: 32448347; PMCID: PMC7245880. The author is from the institute of psychiatry, Kings College, London. In this article all publications and clinical trials are reviewed. The author concludes that, these studies present a mixed picture. The only placebo-controlled study resulted in a negative outcome, while the open-labelled studies provided mixed and, in most cases ambiguous, outcomes. The author gives the following conclusions and raises a strong question about exposing the children to probably unsafe and ineffective therapies. "A number of reservations arise from this tranche of studies, specifically the absence of identified therapeutic targets, and deficiencies in the therapeutic approach that is being employed. " "The data on advanced therapies is currently too sparse to analyse robustly, but the experimental nature of these therapies means that their success rate is unlikely to be higher. This means that the overwhelming majority of patients taking part in trials such as those considered here are receiving treatments that are unsafe, ineffective, or both. Parents and clinicians would do well to remember that these patients, for the most part, are children, unable themselves to give consent. In many cases, the future quality of life is very difficult to assess. How legitimate is it to expose these individuals to risk with such a low probability of success?

Unfortunately, most of these studies have one or more flaws which prevent us from drawing an unbiased and valid conclusion to support the use of stem cell therapy over and above the behavioural and supportive therapies. These studies are not double-blind randomized studies and have other shortcomings like small number of patients, not using unbiased tools for objective quantification of pre- and post-stem cell therapy cognitive function and behaviour, absence of long term follow up data and relying on caregivers assessment for benefit with stem cell therapy. As these studies have used behavioural therapy along with the stem cell therapy it is not clear if

the observed benefit is from intensive supportive therapy during the initial period and at long term follow up.

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021)

Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Autism Spectrum Disorder.

CAUTIONARY NOTE

The experts observed that severe autism can have a major impact on the quality of life of the affected child and the family. There is therefore a need to undertake research into the causes and more effective management of ASD. Since conventional management fails to control symptoms in many cases, such families see hope in some miraculous recovery with the use of stem cells without understanding the risks versus benefit ratio. It is therefore imperative that use of any type of stem cells in ASD should be restricted to clinical trials with necessary approval from regulatory authorities in India and as per the National Guidelines on Stem Cell Research - 2017.

https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017 https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf, trial participants should have read and signed the informed consent form which explains them alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Autism Spectrum Disorder

6. Evidence Based Status of Use of Stem Cells in Lysosomal Storage Disorders (LSD)

A. Information for public and patients

What are Lysosomal Storage Disorders?

Lysosomal storage disorders (LSDs) are a group of more than 50 different inherited diseases, with an overall incidence of 1:7,000 new-borns, though individually rare. In India the exact incidence is not known but these are probably the commonest inherited metabolic disorders encountered in clinical practice. Lysosomal storage disorders (LSD) basically mean that there is something wrong with the special chemicals called enzymes that are required to break down certain substances in the body. As the enzymes are found in special compartments in the body's cells called lysosomes, hence the name LSDs. LSDs are inherited genetic defects. As a result of this deficiency, various materials are inappropriately stored in the cell. Over time, the amount of material building up in each lysosome causes it to swell and occupy more space in the cell, leading to additional problems for normal cellular function. Cells thus become dysfunctional and may die, resulting in a wide variety of clinical symptoms. The ultimate result of these genetic alterations is defective substrate degradation, leading to abnormal accumulation of undegraded substrates usually causing multisystem involvement. The common organs involved are brain, liver, spleen bones, joints, heart, and connective tissue. LSDs affect multiple organs and cause progressive physical and/or cognitive deterioration over time. Some LSDs may present in a "mild" form, and others with a more severe impact on the patient. Some patients survive into adulthood, but others with more severe symptoms may die in their teens or earlier.

How are LSDs managed?

The management is multidisciplinary primarily supportive for most, but definitive therapies are available already for few in the form of enzyme replacement therapy [ERT- eg Gaucher's disease, Mucopolysaccharidosis (MPS) type I, II, IV, VI, VII, Pompe disease and Fabry disease] and there are few awaiting FDA approval. Supportive therapy includes physical therapy, blood component therapy (eg Gaucher's disease) Interventions for cognitive and behavioural problems, surgical interventions etc. Substrate reduction therapy (SRT) is also available for some LSDs.

Have stem cells been used in LSDs?

Hematopoietic Stem Cell Transplantation (HSCT) has been tried in LSDs for many years though the evidence base for efficacy is still weak except for Hurler syndrome (MPS IH) as there are no randomized controlled trials and experience is limited to relatively small number of cases with phenotypic variability. Stem cell transplantation in LSDs provides a constant source of enzyme replacement from the engrafted donor cells, which can cross the blood-brain barrier unlike ERT. The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of functional cells. The potential advantage of HSCT over ERT is possible benefit in neurological manifestations and much lower- and one-time cost. But the evidence is limited and old with very few recent trials being available. The potential morbidity and mortality associated with the procedure and availability of donors makes this modality less acceptable. There is lack of experience even at tertiary care centers in India which needs to be built.

Recommendations (2021): Based on the review of available scientific evidence, stem cell therapy NOT be offered as a standard or routine therapy to patients with LSDs and should only be used in selected LSDs as per details given below in consultation with experts. These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for LSDs.

CAUTIONARY NOTE

Use of HSCT in LSDs should be restricted to MPS 1H before 2 years of age that too under supervision and in consultation with the experts . For others the decision has to be taken on case to case basis and individualized as there is lack of sufficient and good quality evidence in literature .

If any trials are conducted approval from regulatory authorities in India should be obtained . These trials should follow the National Guidelines on Stem Cell Research and patients in these trials should be closely monitored for the possibility of any harm with use of stem cells. As per the ICMR National Bioethics guidelines 2017, trial participants should have read and signed the informed consent form which explains them existing standard of care, alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

Lysosomal storage disorders are a group of disorders with multisystem involvement and clinical heterogeneity . All require multidisciplinary care and some have specific therapies available. Role of HSCT has not been evaluated extensively and there is very limited published literature .

C) Evidence for HSCT in LSDs (Selected Studies)

Lysosomal Storage Disorder	
Disease/Disorders	**Review of Literature** **Critique / Applicability of the study results**
MPS IH	i. Multiple sources: Cord blood, related and unrelated donors parenteral Systemic review of case series/reports No RCTs Marleen H. van der Linden, Moyo C. et all. Orthopaedic management of Hurler's disease after hematopoietic stem cell transplantation: a systematic review. J Inherit Metab Dis (2011) 34:657–669. The donor source that was used for HSCT treatment was described by 16 studies; eight had included multiple donor types, four used cord blood transplantations only, three were confined to unrelated donors, and one to related donors. ii. Aldenhoven M, Wynn RF, Orchard PJ, et al. Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study. Blood 2015; 125:2164. Focus of the study was on post HSCT Orthopedic management. Total of 32 studies (31 case series and one case report) published between 1993 and 2009 were included. These studies described a total of 399 patient reports. The vast majority of studies (29) were longitudinal and retrospective. A total of 26 studies described only Hurler patients, the other six studies described mixed patient populations. The average age of the patients at HSCT was 18.8±7.0 months (25 studies,n=348 patients, range across studies 13–48 months). The average duration of follow-up was 3.3±35.4 months after HSCT (23 studies, n=321 patients, range across studies 10.5-134.4 months).. The success rate of HSCT was described by 14 papers, with full engraftment at the first attempt in on average 76% of the cases (range 47-100%). Factors that determine the long-term outcomes of different organ systems after successful HSCT. Age at HCT and the intelligence quotient (IQ) at HCT are the strongest predictors of neurodevelopmental outcome
Other MPS	i. Wang J, Luan Z, Jiang H, Fang J, Qin M, Lee V, Chen J. Allogeneic Hematopoietic Stem Cell Transplantation in Thirty-Four Pediatric Cases of Mucopolysaccharidosis—A Ten-Year Report from the China Children Transplant Group */ Biol Blood Marrow Transplant 22 (2016) 2100–2108* Limited data over all. Recent study from China -efficacy of HSCT was evaluated in 34 children with MPS. There were 12 children each of MPS I & II , 4 each of MPS IV & VI and two were unclassified. The estimated overall survival at 3 years was 84.8% and 91.2% of the patients (31 of 34) achieved full donor

		chimerism. Twenty-seven children were evaluable and all but 1 (carrier sibling donor; enzyme level improved but failed to reach normal) achieved normal enzyme level after transplantation.
Gaucher Disease	i.	Somaraju UR, Tadepalli K. Hematopoietic stem cell transplantation for Gaucher disease. Cochrane Database Syst Rev 2017;10:CD006974. Hematopoietic stem cell transplantation (HSCT or HCT) can provide a definitive cure for GD. However, this procedure is associated with substantial morbidity and mortality and therefore has been effectively replaced by ERT and SRT in clinical practice. No randomised controlled trials (RCTs), quasi-RCTs or controlled clinical trials (CCTs) on the efficacy of hemotopoietic stem cell transplantation (HSCT) were identified for inclusion in the Cochrane review till March 2017

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021):

The following is the summary based on the available evidence for common LSDs.

1. Hematopoietic Stem Cell Transplantation in MPS

HSCT is the treatment of choice for and has been used most successfully to treat Hurler syndrome (MPS IH), which is the most severe phenotype and the results are best if HSCT is done in patients before two years of age. The intervention related risks are considerably reduced compared with previous years in expert hands and better conditioning regimens .HSCT is less commonly used in milder MPS I and II and MPS VI and VII and is not considered as standard of care

- **MPS IH –** There are no RCTs or high level evidence available in literature, but HSCT is the recommended treatment for MPS IH early in life ideally before 2 years of age . If engrafted well most of the patients benefit as there is reduction in hepatosplenomegaly, improved joint mobility, airway obstruction, and cardiac function. Improvement or stabilization of hearing, and if done early especially in younger patients, may stabilize cognitive regression. Clinical outcomes after transplant are most clearly related to the age at transplant (the younger the better). The delivered enzyme dose is better when the donor is fully rather than partially engrafted and when the donor is not a carrier of the disease. HSCT has been performed in more than 600 patients with Hurler syndrome. Results have improved greatly in series from both single institutions and from registry studies. Event-free survival at five years of around 80 percent after transplantation with an HLA-matched sibling donor or a six-out-of-six matched, unrelated, cord blood donor has been reported. Factors that determine the long-term outcomes of different organ systems after successful HSCT. Age at HSCT and the intelligence quotient (IQ) at HSCT are the strongest predictors of neurodevelopmental outcome

- **Other MPS:** Limited Data is available, but HSCT has been tried in many MPS with improved clinical outcomes . These include patients with milder MPS I and II and MPS VI and VII.HSCT has not prevented the central nervous system (CNS) decline in patients with severe MPS II in most series and has not been successful. Patients with MPS III usually do

not benefit and the skeletal abnormalities in MPS IV also do not correct well. The reason for the lack of success of HSCT in some types of MPS is uncertain, although it is possible that the transplanted cells do not secrete sufficient enzyme or the enzyme may not be taken up sufficiently to correct the deficiency

2. Hematopoietic Stem Cell Transplantation in Gaucher's Disease

Hematopoietic stem cell transplantation (HSCT) can provide a definitive cure for Gaucher's disease . However, this procedure is associated with substantial morbidity and mortality and therefore has been effectively replaced by ERT and SRT in clinical practice.No randomised controlled trials (RCTs), quasi-RCTs or controlled clinical trials (CCTs) on the efficacy of hematopoietic stem cell transplantation (HSCT) were identified and literature is limited to case reports.

3. HSCT in other LSDs: Not enough data and no clear recommendations for other LSDs like Metachromatic Leukodystrophy, Krabbes disease, etc are available .

None of the studies are of an appropriate level of evidence based on the methodological quality of their design, validity, and applicability to patient care. None of them are randomized double blind studies or multicentric studies as are usually performed for rare genetic disorders. Many are single case reports or use a small number of patients.

7. Evidence Based Status of Use of Stem Cells in Amyotrophic Lateral Sclerosis (ALS) Or Motor Neuron Disease (MND)

A. Information for public and patients

What is Amyotrophic lateral sclerosis (ALS) OR Motor Neuron Disease (MND)?

This is a group of progressive neuro-degenerative diseases in which the special nerve cells called Motor Neurons in the brain and spine are affected. Whenever ALS / MND is suspected, a more detailed evaluation and special tests are done by the Neurologists before making a diagnosis. As the nerve cells continue to die, the muscles supplied by these nerves are unable to function or move. As a result, the patient gradually becomes wheelchair bound and eventually when the muscles needed for breathing movement are affected, breathing becomes increasingly difficult and may be fatal. Some forms of ALS or MND can be familial and genetic testing in such cases helps to confirm this.

What is the treatment of ALS?

The current multidisciplinary management of this condition includes supportive and rehabilitative care to relieve symptoms, manage complications and improve the quality of life. Currently there are no proven treatment methods which can permanently reverse the damage to motor neurons and the resultant difficulty in movements or breathing. However this condition has variable progression and some patients can live for a longer period with good supportive care and rehabilitation.

Have stem cells been used in ALS / MND?

Along with supportive therapies and rehabilitation, few studies have reported their experience with the use of different types of stem cells for patients with ALS or MND. From the published studies, websites and other sources, it has come to our knowledge that many Indian patients with ALS/MND have been offered different types of stem cell therapies within and outside clinical trial / research. ICMR with inputs from medical specialists in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding any evidence based safety and efficacy of stem cells in ALS / MND. Critical review of the studies reported so far do not support the use of stem cell therapy over and above the behavioural and supportive therapies for ALS or MND

RECOMMENDATIONS (2021)

Based on a critical review of the available scientific evidence by the ICMR experts, stem cell therapy should NOT be offered as a standard or routine therapy to patients with ALS / MND. These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for ALS/ MND.

CAUTIONARY NOTE

From various websites and other sources, it has come to our knowledge that some doctors and clinics in India continue to offer stem cells as a standard treatment option to ALS / MND patients outside the purview of regulated and approved clinical trials. Patients with ALS / MND from India and those coming from outside India should be aware that any type of stem cell therapy for ALS / MND should be offered only as part of ongoing clinical trials that have all the approvals from the regulatory authorities in India. These trials should follow the National Guidelines on Stem Cell Research.
(https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf). As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017.
(https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf)
clinical trial participants should have read and signed the informed consent form which explains them standard and alternative therapies, possible benefits and harms due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

The diagnosis of ALS / MND is made after a detailed neurological and if required genetic evaluation. There are no established causes of ALS / MND and it is an active area of research. Patients with ALS/ MND are managed with supportive care and rehabilitation and management of complications. Along with these supportive and rehabilitative therapies, several studies have been reported on the use of stem cells in this condition. Many Indian patients with ALS/MND have also been offered different types of stem cell therapies as part of research studies and also as a standard treatment option which is outside the purview of approved clinical trial. ICMR with inputs from experts in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding level of evidence for efficacy and safety of stem cells in ALS/MND.

A critical review of the published human studies that are either randomized controlled trials or have been submitted in response to the ICMR call for Level I/II evidence supporting the use of stem cells in ALS/MND has been undertaken. Summary of some representative studies is outlined below:

Amyotrophic Lateral Sclerosis/ Motor Neuron Disease	
S. No.	**Publications and Author's conclusions or critique**

I	Stem cell treatments for amyotrophic lateral sclerosis: a critical overview of early phase trials. Goutman SA et al. Expert Opin Investig Drugs. 2019 Jun;28(6):525-543. doi: 10.1080/13543784.2019.1627324. Study conclusion (expert opinion): Clinical trials in humans are still in the nascent stages of development. It will be critical to ensure that powered, well-controlled trials are conducted, that optimal treatment windows are identified, and that the ideal cell type, cell dose, and delivery site and method are determined. Several trials have used more invasive procedures, and ethical concerns of sham procedures on patients in the control arm and on their safety should be considered.
ii	Advances in stem cell therapy for amyotrophic lateral sclerosis. Mazzini L et al. Expert Opin Biol Ther. 2018 Aug;18(8):865-881. DOI: 10.1080/14712598.2018.1503248 Study conclusion: While data from individual studies are encouraging, stem-cell-based therapies do not yet represent a satisfactory, reliable clinical option. The field will critically benefit from the introduction of well-designed, randomized and reproducible, powered clinical trials. Comparative studies addressing key issues such as the nature, properties, and number of donor cells,the delivery mode and the selection of proper patient populations that may benefit the most from cell-based therapies are now of the essence. Multidisciplinary networks of experts should be established to empower effective translation of research into the clinic.
iii	Cell based therapies for amyotrophic lateral sclerosis/motor neuron disease S Fadilah Abdul Wahid et al. Cochrane Systematic Review - Intervention Version published: 08 November 2016 https://doi.org/10.1002/14651858.CD011742.pub2. Author's conclusion: Currently, there is a lack of high quality evidence to guide practice on the use of cell based therapy to treat ALS/MND. We need large, prospective RCTs to establish the efficacy of cellular therapy and to determine patient, disease and cell treatment related factors that may influence the outcome of cell based therapy. The major goals of future research should be to determine the appropriate cell source, phenotype, dose, and route of delivery, as these will be key elements in designing an optimal cell based therapy programme for people with ALS/MND. Future research should also explore novel treatment strategies, including combinations of cellular therapy and standard or novel neuroprotective agents, to find the best possible approach to prevent or reverse the neurological deficit in ALS/MND, and to prolong survival in this debilitating and fatal condition.
Iv	Efficacy of Stem Cell Therapy in Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis. Moura MC et al. J Clin Med Res. 2016 Apr;8(4):317-24. RESULTS AND CONCLUSIONS: A meta-analysis confirmed the efficacy of stem cell therapy in improving survival in preclinical trials, where a mean difference of 9.79 days (95% confidence interval: 4.45 - 15.14) in lifespan favoured stem cell therapy. In contrast, the number of clinical studies is still insufficient to assess their effectiveness, and these studies only demonstrate the absence of serious adverse events. However, even this conclusion should be interpreted with caution because clinical studies are retrospective & heterogeneous and have unsatisfactory quality.

V	The effect of autologous bone marrow mononuclear cell (BMNC) transplantation on the survival duration in Amyotrophic Lateral Sclerosis - a retrospective controlled study. Alok Sharma, **Hemangi Sane,** Amruta Paranjape et al. American J Stem Cell 2015; 4(1): 50–65. Of the 57 patients with ALS, 37 received BMNC transplantation and 20 patients did not receive and served as controls. Authors conclusion: Prospective randomized controlled studies with a larger sample size and rigorous methodology are required for conclusive findings.

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021)

Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Amyotrophic lateral sclerosis (ALS) OR Motor Neuron Disease (MND)

The experts observed that ALS/MND through rare is a progressive and fatal disease. There is therefore a need to undertake research into the causes and more effective management of ALD/MND. Since conventional management fails to significantly delay control symptoms in many cases, such families see hope in some miraculous recovery with the use of stem cells without understanding the risks versus benefit ratio. It is therefore imperative that use of any type of stem cell in ALS/MND should be restricted to clinical trials with due approval from regulatory authority in India and as per the national guidelines on stem cell research.(https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf). As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017 (https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf). trial participants should have read and signed the informed consent form which explains them alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for ALS/MND

8. Evidence Based Status of Use of Stem Cells in Stroke

A. Information for public and patients

What is stroke?

Stroke is a sudden onset brain disease when the blood supply to any part of the brain is suddenly blocked (Ischemic stroke) or when a blood vessel in the brain bursts (Haemorrhagic stroke). Stroke symptoms consists of sudden onset weakness or numbness, particularly on one side of the body; difficulty in speaking or understanding speech, sudden confusion; sudden difficulty in seeing; loss of balance or coordination; or sudden severe headache with loss of consciousness. The diagnosis of stroke is made clinically and using CT scan or MRI Brain.

What is the treatment of Stroke?

Stroke treatment consists of immediate management, rehabilitation and prevention. Immediate treatment in Stroke is to try to stop it while it is happening by restoring the patency of blocked blood vessel in ischemic stroke or by halting the bleeding of a haemorrhagic stroke. In acute ischemic stroke patency of blood vessel is restored by using intravenous thrombolysis (the breakdown of blood clots formed in blood vessels, using medication) and endovascular mechanical thrombectomy (surgical removal of clot), given within a few hours of stroke onset, to a few eligible patients. In chronic stroke, management consists of drugs to prevent recurrent stroke (antiplatelets, statins and control of risk factors like diabetes, hypertension) and rehabilitation.

Have stem cells been used in Stroke?

Research on stem cell therapy (injecting cells that may save or replace damaged nerve tissue) has been predominantly conducted on Ischemic stroke. A systematic review (a scientific summary) of all major (randomized trials) that recruited adults with ischemic stroke, at any time after onset and used any stem cell or method of administration, identified seven randomized trials, involving 401 participants. The review found that stem cell transplantation was associated with a reduced neurological impairment, but not with a better functional outcome. There were no safety concerns. But the certainty of evidence was low or very low. Hence more well designed studies are needed and current available evidence do not support the use of stem cell therapy in Ischemic stroke. The certainty of the evidence ranged from low to very low because of the risk of bias in the included studies, the lack of precision of the results, and different designs. More well-designed randomized controlled trials are needed. Till then, the current evidence do not support the use of stem cell therapy in Ischemic stroke. Hence stem cell therapy should not be offered as one of the standard or routine therapy to patients with Stroke. Use of any type of stem cell in Stroke should therefore be restricted to rigorously designed and executed clinical trials which are initiated after obtaining approval from all regulatory authorities in India, follow the national guidelines and are closely monitored for the possibility of any harm to the patients by the use of

stem cell. Participants of any such trials should have read and signed the informed consent form which has to clearly explain the alternative therapies, the design and phase of the clinical trial, possible benefit and harm due to stem cell therapy and what compensation will be provided to the patient or the family in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

RECOMMENDATIONS (2021)

Based on a critical review of the available scientific evidence by the ICMR experts, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Stroke. These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Stroke.

CAUTIONARY NOTE

From various websites and other sources, it has come to our knowledge that some doctors and clinics in India continue to offer stem cells as a standard treatment option to Stroke patients outside the purview of regulated and approved clinical trials. Patients with Stroke from India and those coming from outside India should be aware that any type of stem cell therapy for Stroke should be offered only as part of ongoing clinical trials that have all the approvals from the regulatory authorities in India. These trials should follow the National Guidelines for Stem Cell Research (https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf). As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, (https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf), clinical trial participants should have read and signed the informed consent form which explains them standard and alternative therapies, possible benefits and harms due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

Stroke is a major cause for mortality and morbidity in India and worldwide. There is a strong demand for alternate therapeutic approaches including stem cell transplantation. Preclinical studies in stroke were promising. But clinical trials in humans have not shown any significant evidence for benefit in Ischemic or haemorrhagic stroke.

Many Indian patients with Stroke have also been offered different types of stem cell therapies as part of research studies and also as a standard treatment option which is outside the purview of approved clinical trial. ICMR with inputs from experts in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding level of evidence for efficacy and safety of stem cells in Stroke.

A critical review of the published human studies that are either randomized controlled trials or have been submitted in response to the ICMR call for Level I/II evidence supporting the use of stem cells in Stroke has been undertaken. Summary of the latest systematic review and metanalysis is outlined below:

A systematic review (a scientific summary) of all major (randomized trials) that recruited adults with ischemic stroke, at any time after onset and used any stem cell or method of administration, identified seven randomized trials, involving 401 participants. The follow up ranged from 6 months to 7 years. Stem cell transplantation was associated with a reduced neurological impairment, but not with a better functional outcome. No safety concerns were raised. There was low to very low certainty of the evidence because of the risk of bias in the included studies, the lack of precision of the results, and different designs. The authors concluded that more well-designed randomized controlled trials are needed. Till then, the current evidence do not support the use of stem cell therapy in Ischemic stroke. Hence stem cell therapy should not be offered as one of the standard or routine therapy to patients with Stroke. Use of any type of stem cell in Stroke should therefore be restricted to rigorously designed and executed clinical trials which are initiated after obtaining approval from all regulatory authorities in India, follow the national guidelines and are closely monitored for the possibility of any harm to the patients by the use of stem cell. Participants of any such trials should have read and signed the informed consent form which has to clearly explain the alternative therapies, the design and phase of the clinical trial, possible benefit and harm due to stem cell therapy and what compensation will be provided to the patient or the family in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

Stroke	
S. No	**Publications and Author's conclusions or critique**

I	Stem cell transplantation for ischemic stroke. Boncoraglio GB et al. Cochrane Database Syst Rev. 2019 May 5;5:CD007231. Study conclusion (expert opinion): A comprehensive systematic review has shown that in participants with ischemic stroke, stem cell transplantation was associated with a reduced neurological impairment, but not with a better functional outcome. Moreover, these results come from small RCTs with high risk of bias and low to very low certainty of evidence. More well-designed trials are needed
Ii	Mesenchymal stem cells for haemorrhagic stroke: status of preclinical and clinical research. Turnbull MT et al. NPJ Regen Med. 2019; 4: 10. doi: 10.1038/s41536-019-0073-8 Study conclusion: Only limited studies are available in Haemorrhagic stroke. Even though preclinical and limited clinical studies are promising, further well designed randomised trials are required to prove its efficacy
Iii	Stem Cell Therapy: A Promising Therapeutic Method for Intracerebral Hemorrhage. Gao L et al. Cell Transplantation 2018, Vol. 27(12) 1809–1824. Author's conclusion: “The detailed therapeutic strategies for ICH treatment such as cell type, the number of cells, time window, and the routes of medication delivery, varied greatly among different studies and had not been determined. Moreover, the safety issues of stem cell therapy for ICH should not be ignored. Stem cell therapy showed good therapeutic effect in ICH, making it a promising treatment. However, safety should be carefully evaluated, and more clinical trials are required before stem cell therapy can be extensively applied to clinical use.”

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021)

Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Stroke

Stroke is a major cause for mortality and morbidity in India and worldwide. There is a strong demand for alternate therapeutic approaches including stem cell transplantation. Preclinical studies in stroke were promising. But clinical trials in humans have not shown any significant evidence for benefit in Ischemic or hemorrhagic stroke. It is therefore imperative that use of any type of stem cell in Stroke should be restricted to clinical trials with due approvals from regulatory authorities in India and as per the National Guidelines for Stem Cell Research (https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf) As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017, (https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf), trial participants should have read and signed the informed consent form which explains them alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Stroke

9. Evidence Based Status of Use of Stem Cells in Multiple Sclerosis (MS)

A. Information for public and patients

What is Multiple Sclerosis (MS)?

Multiple sclerosis (MS) is an autoimmune disease due to breakdown of immunological tolerance toward the central nervous system. MS is initially characterized by repeated acute attacks of focal inflammation causing neurologic events called relapses, characterized by the development of neurological disabilities and lesions in MRI Brain. As the acute inflammation resolves over the course of several weeks, neurologic symptoms may partially or completely resolve. Over time, these attacks tend to occur less frequently, and patients experience progression, an accumulation of long-lasting disabilities from the consequences of repeated damage to the central nervous system.

What is the treatment of MS?

At present, there is no cure for MS. Acute attacks are treated with steroids though they do not affect the course of the disease. Several drugs are used to treat various forms of MS. They act by decreasing attack frequency/severity, delaying disease progression or treating relapses. Some drugs are taken intravenously, some by infusion, and some oral. All drugs should be prescribed and closely monitored by specially trained physicians, as some medications have serious side effects. Symptomatic treatment consists of treatment of spasticity (increased stiffness of muscles), urinary symptoms, psychological symptoms and physiotherapy.

Have stem cells been used in MS?

Along with disease modifying therapies, supportive therapies and rehabilitation, few studies have reported their experience with the use of different types of stem cells for patients with MS. From the published studies, websites and other sources, it has come to our knowledge that many Indian patients with MS have been offered different types of stem cell therapies within and outside clinical trial / research. ICMR with inputs from medical specialists in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding any evidence-based safety and efficacy of stem cells in MS. Critical review of the studies reported so far do not support the use of stem cell therapy over and above the disease modifying treatment, behavioural and supportive therapies for MS

RECOMMENDATIONS (2021)

Based on a critical review of the available scientific evidence by the ICMR experts, stem cell therapy should NOT be offered as a standard or routine therapy to patients with MS. These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for MS.

CAUTIONARY NOTE

From various websites and other sources, it has come to our knowledge that some doctors and clinics in India continue to offer stem cells as a standard treatment option to MS patients outside the purview of regulated and approved clinical trials. Patients with MS from India and those coming from outside India should be aware that any type of stem cell therapy for MS should be offered only as part of ongoing clinical trials that have all the approvals from the regulatory authorities in India. These trials should follow the national guidelines on stem cell research(https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf). As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017 (https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf) clinical trial participants should have read and signed the informed consent form which explains them standard and alternative therapies, possible benefits and harms due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

The diagnosis of MS is made after a detailed neurological and neuroimaging evaluation, after ruling out many conditions which can mimic MS. There are no established causes of MS and it is an active area of research. Patients with MS are managed with disease modifying therapies, supportive care, rehabilitation and management of complications. Several studies have been reported on the use of stem cells in this condition. Many Indian patients with MS have also been offered different types of stem cell therapies as part of research studies and also as a standard treatment option which is outside the purview of approved clinical trial. ICMR with inputs from experts in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding level of evidence for efficacy and safety of stem cells in MS.

A critical review of the published human studies that are either randomized controlled trials or have been submitted in response to the ICMR call for Level I/II evidence supporting the use of stem cells in MS has been undertaken. Summary of some representative studies is outlined below:

Autologous hematopoietic stem cell transplantation (HSCT) have been studied to improve outcomes in aggressive MS. A randomised controlled trial of 110 patients with MS whose disease remained immunologically active despite treatment with DMT compared outcomes following treatment with either HSCT or a different conventional DMT selected by the treating neurologist. The study focused on whether HSCT offers an advantage by preventing development or worsening of permanent disability over a 5-year follow-up period. A validated EDSS scale was used to assess the outcome. The authors found that clinically significant progression occurred much less frequently in the HSCT-treated group compared with the DMT-treated group. Furthermore, the benefit of HSCT was apparent in other measures of disease activity, including fewer relapses, improved MRI lesion load, higher proportion of patients maintaining no evidence of disease activity, and better quality of life. However, this is a preliminary study and further research is needed to replicate these findings and to assess long-term outcomes and safety. Till then, the current evidence does not support the routine use of stem cell therapy in Multiple Sclerosis. Hence stem cell therapy should not be offered as one of the standard or routine therapy to patients with MS. Use of any type of stem cell in MS should therefore be restricted to rigorously designed and executed clinical trials which are initiated after obtaining approval from all regulatory authorities in India, follow the national guidelines and are closely monitored for the possibility of any harm to the patients by the use of stem cell. Participants of any such trials should have read and signed the informed consent form which has to clearly explain the alternative therapies, the design and phase of the clinical trial, possible benefit and harm due to stem cell therapy and what compensation will be provided to the patient or the family in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

Multiple Sclerosis	
S. No	**Publications and Author's conclusions or critique**
i	Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: a randomized clinical trial [published January 15, 2019]. JAMA. Burt RK, Balabanov R, Burman J et al. doi:10.1001/jama.2018.18743 Study conclusion (expert opinion): The authors found that clinically significant progression occurred much less frequently in the HSCT-treated group compared with the DMT-treated group. But there are concerns about the rigor of HSCT and the risks associated with the procedure as many patients experienced moderate to severe acute toxicity in the immediate period after HSCT. Even though no treatment related mortality was reported in this study, deaths have been reported using the same HSCT procedure in other autoimmune diseases. Moreover the DMT cohort probably did not have access to the most effective DMT. The study included highly active MS only and in routine practice only a small proportion of MS patients

	exhibit this kind of activity. Overall, this is a preliminary study and further research is needed to replicate these findings and to assess long-term outcomes and safety.
Ii	Cell-based therapeutic strategies for multiple sclerosis. Scolding NJ et al. BRAIN 2017: 140; 2776–2796 Study conclusion: The authors reviewed the evidence regarding cell based therapeutic strategies for MS. The concluded that "Immunoablation followed by autologous haematopoietic stem cell transplantation appears to have potent and durable efficacy in relapsing-remitting multiple sclerosis though with significant safety concerns. Mostly the cell-based therapy of multiple sclerosis should be pursued in clinical trials. All forms of cell-based therapy for multiple sclerosis should be considered experimental at this time. When it is pursued, comprehensive safety and efficacy data should be collected and submitted to existing registries, with the expectation that the results will be published. Because important biological questions remain for all forms of cell-based therapy, mechanistic studies should be included."

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021)

Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Multiple Sclerosis (MS)

The experts observed that MS is an immunological disease affecting central nervous system with disease severity varies from mild to highly active state. Even though there are various disease modifying treatments available, there is no curative therapy available as of now. Preliminary research on Stem cell therapy in MS has shown some promise but with safety concerns. When conventional management fails to significantly delay control symptoms in many cases, such families see a hope in some miraculous recovery with the use of stem cells without understanding the risks versus benefit ratio. It is therefore imperative that use of any type of stem cell in MS should be restricted to clinical trials with due approvals from regulatory authorities in India and as per the national guidelines on stem cell research (https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf) As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017. (https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf), trial participants should have read and signed the informed consent form which explains them alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond

routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for MS

10. Evidence Based Status of Use of Stem Cells in Heart Failure

A. Information for public and patients

What is Heart Failure?

Heart failure is a complex clinical syndrome that underlines the inability of the heart to perform its circulatory function with the desired efficiency due to structural and/or functional (systolic or diastolic) alterations. The prevalence of HF increases with age. Of the array of biomarkers available for the diagnosis of HF, BNP and NT-pro-BNP are the ones that are extensively used clinically.

What is the treatment of Heart Failure?

There are a number of therapies available for heart failure ranging from drugs like ACE inhibitors, beta blockers, angiotensin receptor- neprisyln inhibitors, ivabradine and left ventricular assist devices and when all else fails there is the option of a heart transplant. Advanced options like heart transplant are limited due to lack of donor hearts and LV assist devices are expensive and out of reach of many. There is, therefore, need for alternative forms of therapy and stem cell and gene therapy have been tried to repair the heart.

Have stem cells been used in Heart Failure?

The current status of research in stem cell therapy suggests that the therapy could reduce the risk of mortality in chronic ischemic heart disease with heart failure and that there are no major adverse events associated with it. This benefit has not been shown in acute myocardial infarction these studies still need to be confirmed in larger clinical trials before cell-based treatment for these patients can be developed as standard treatment. The next studies have to focus on better understanding, and improvement of the cell therapies used (eg, mononuclear cells, circulating progenitor cells, mesenchymal stem cells, embryonal or haematopoietic progenitor cells). Predictors of responders and outcomes need to be carefully assessed and perhaps therapy needs to be tailored to each patient.

Recommendations (2021):

Since the benefit of stem cells has not been shown consistently in all clinical trials, it is still recommended that all stem cell therapies be given within the framework of clinical trials and not as standard or routine therapy outside clinical trials.

CAUTIONARY NOTE

From various websites and other sources, it has come to our knowledge that some doctors and clinics in India continue to offer stem cells as a standard treatment option to Heart Failure patients outside the purview of regulated and approved clinical trials. Patients with Heart Failure from India and those coming from outside India should be aware that any type of stem cell therapy for Heart Failure should be offered only as part of ongoing clinical trials that have all the approvals from the regulatory authorities in India. These trials should follow the National Guidelines for Stem Cell Research - 2017 (https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf). As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants - 2017 (https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf) clinical trial participants should have read and signed the informed consent form which explains them standard and alternative therapies, possible benefits and harms due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

Stem cells are cells that have the ability to develop into different cell types. In some cases, they also have the ability to repair damaged tissues. The two broad types of stem cells are embryonic stem cells and adult stem cells. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells act as a repair system for the body. Stem cell therapy was first established in the treatment of blood malignancies in the form of a bone marrow transplant. Two decades ago this was extended to non-blood disorders in an attempt to repair non-blood disorders by using the pluripotent nature of stem cells to repair other organs.

Stem cell therapy and its types:

A. First Generation cell therapy

01. Skeletal Myoblasts

Skeletal myoblasts were the first cells tested in preclinical and clinical trials. The advantages include that they have minimum ethical concerns, their expansion in-vitro is quick, resistant to ischemic conditions, and there will be minimal risk of

tumorigenicity. Contrarily disadvantages include there will be no transdifferentiation into functional cardiomyocytes, Due to lack of electrochemical coupling, risks of ventricular arrhythmias are high.

After the initial promising preclinical and clinical trials, the large MAGIC trial was conducted and it showed no benefit and a high incidence of arrhythmias. Trials with myoblasts have since diminished.

02. Bone marrow-derived cells

The bone marrow contains a mix of mature and immature cells. Experiments have shown that an injury causes the recruitment of Bone marrow-derived cells to the injured/inflamed area and they can aid in repair. After the initial clinical experiments with bone marrow-derived cells, the interest shifted to Bone marrow-derived mononuclear cells [MNCs]. Trials with MNCs have shown mixed results showing a benefit of improvement in the ventricular function of about 2-5% in some trials while not showing a benefit in some.

03. Mesenchymal stem cells

Mesenchymal cells are non-hematopoietic stem cells, which are multipotent, and immune privileged. A number of clinical trials have shown a benefit of mesenchymal cells on ventricular function. In the PROCHYMAL (EF improved 7.3%) and the POSEIDON (EF improved 5-8%), the improvement was significant.

B. Second Generation cell therapy

01. Cardiac stem/progenitor cells /Propagated cells.

Several cardiac stem cells (CSCs) and cardiac progenitor cells (CPCs), such as cardiosphere-derived cells (CDCs), stem cell antigen (Sca)-1+ cells and many other types of cardiac stem cells have been found. The clinical trials SCIPIO, CADUCEUS, All-Star and DYNAMIC used an intracoronary infusion of propagated cells or autologous c-Kit+ CSCs and CDCs grown from endomyocardial biopsy respectively and showed improvements in regional ventricular function.

02. Embryonic Stem Cells

ESCs are derived from the inner cell mass of the blastocyst and have the properties of self-renewal and differentiation into cell types of all 3 germ layers ie.: endoderm, mesoderm, ectoderm. There is a demonstrated risk of teratomas shown in animal experiments. They have the potential of forming cardiomyocytes. In phase one ESCORT trial human ESC derived cardiac

progenitors embedded in a fibrin matrix were implanted in patients with severe heart failure. In the first patient, there was an improvement in ventricular function with no tumor formation or arrhythmia.

Mechanism of Action:

A number of mechanisms have been proposed and these include direct cardiac differentiation of injected cells into cardiac muscle and the integration into the myocardium. However, this has been seen more in animal experiments and is probably a highly inefficient mechanism. However, data obtained from numerous *in vitro and in vivo* studies have shown paracrine signaling is the fundamental mechanism that mediates the beneficial effects of stem cell therapy. They can have immunomodulatory and effects. They can also recruit resident cardiac stem cells.

Improving Stem Cell therapy:

Attempts are being made to improve the homing ability of the stem cells and the proangiogenic properties by incubating the stem cells with growth factors and cytokines. Stem cells can also be modified to over express cytokines by transducing with a lentivirus construct. Using machine learning , responders to stem cell therapy can be picked up based on clinical and biochemical markers leading towards personalized stem cell therapy. Primarily to repair cardiocytes efficiently with the help of SCs, two considerable to formulate "next generation" is A) genetic engineering modifications and B) non genetic modification.

The interest in Stem Cell in India started to work that started with AIIMS, Delhi by Prof P Venugopal. This was a series of studies which was started in patients undergoing coronary artery bypass surgery who had a scar and had a non-viable myocardium which received a stem cell injection during the bypass surgery. This area showed improvement on subsequent evaluation on Echocardiograms and PET scan. This study was followed by a study in patients with dilated cardiomyopathy (The ABCD trial) in which patients with dilated cardiomyopathy were injected with bone marrow-derived stem cells injected into the coronary arteries. They showed an improvement in ventricular function and quality of life at 3 and 6 months, which was sustained at 3 years. The biopsies done in these patients showed that there was a trend towards increased vascularity but no new muscle seen. Subsequent studies done with labeling at AIIMS have shown interesting results with technetium-labeled stem cells showing inconsistent homing to the infarct area, which could be one reason why bone marrow-derived stem cells do not always result in an improvement in cardiac function after an intra-coronary injection.. An ICMR sponsored study was then done in patients with recent myocardial infarction where the infarct-related artery had not been opened up within 24 hours. The artery was opened between 24 hours and 30 days and then

stem cells were injected. There was a significant improvement in ventricular function (article in press).

The ICMR also sponsored a multicentric study in India where stem cells were injected in patients who were successfully treated for myocardial infarction and were then injected with intracoronary stem cells. The study did not result in positive results.

The ICMR also sponsored a multicentric study in India where stem cells were injected in patients who were successfully treated for myocardial infarction and were then injected with intracoronary stem cells. The study did not result in positive results.

Current Status of Stem Cell Therapy

The current status of research in stem cell therapy suggests that the therapy could reduce the risk of mortality in chronic ischemic heart disease with heart failure and that there are no major adverse events associated with it. This benefit has not been shown in acute myocardial infarction these studies still need to be confirmed in larger clinical trials before cell-based treatment for these patients can be developed as standard treatment. The next studies have to focus on better understanding, and improvement of the cell therapies used (eg, mononuclear cells, circulating progenitor cells, mesenchymal stem cells, embryonal or haematopoietic progenitor cells). Predictors of responders, outcomes need to be carefully assessed and perhaps therapy needs to be tailored to each patient.

Heart Failure	
S.No.	**Review of Literature** **Critique / Applicability of the study results**
i.	Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LEJ, Berman D *et. al.* Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. The Lancet 2012; 379: 895-904 It showed that intracoronary infusion of autologous CDCs after myocardial infarction is safe, warranting the expansion of such therapy to phase 2 study. The unprecedented increases we noted in viable myocardium, which are consistent with therapeutic regeneration, merit further assessment of clinical outcomes.
ii.	Menasche P, vanneaux V, Fabreguettes JR, Bel A, Tosca L, Garcia S et. al. Towards a clinical use of human embryonic stem cell-derived cardiac progenitors: a translational experience.Eur Heart J 2015; 36 : 743-750 Although several facets of this manufacturing process still need to be improved, these data may yet provide a useful platform for the production of hESC-derived cardiac progenitor cells under safe and cost-effective GMP conditions.
iii.	S. Seth, R. Narang, B. Bhargava, et. al. Percutaneous Intracoronary Cellular Cardiomyoplasty for Nonischemic Cardiomyopathy: Clinical and Histopathological

	Results: The First-in-Man ABCD (Autologous Bone Marrow Cells in Dilated Cardiomyopathy) Trial. J Am Coll Cardiol,48 (2006),pp.2350-2351 In summary, 24 patients underwent intracoronary stem cell injection with coronary sinus blockage. Four patients died during the 6-month follow-up. Overall EF showed a small but significant improvement of 5.4%. There was a decrease in end-systolic volumes, but no change in end-diastolic volumes. Endomyocardial biopsy done at 3 months showed no significant change in the number of myocytes or capillaries, but the ratio of capillaries to myocytes showed an insignificant increase. There were soft data to suggest cell proliferation (binucleate cells and Ki 67 positivity)
iv.	Seth S, Bhargava B, Narang R, Ray R, Mohanty S, Gulati G, et.al The ABCD (Autologous Bone Marrow Cells in Dilated Cardiomyopathy) Trial A Long-Term Follow-Up Study. J Am Coll Cardiol. 2010 Apr 13 ; 55(15) : 1643-4. Doi:10.1016/j.jacc.2009.11.070 Mortality was not significantly different between the treatment and control arms. The EF improved in the treatment arm by 5.9% with a reduction in end-systolic volumes and no change in end-diastolic volumes. Both NYHA functional class III and IV groups in the treatment arm showed improvement, although the effect on the NYHA functional class III patients (EF: 23.6 10.6.% to 30.1 11%) was greater than that on the NYHA functional class IV patients (EF: 20.1 9% to 24 13.8%). There was no significant improvement in the EF in the control patients. There was a significant improvement in quality of life as assessed by KCCQ and functional status on long-term follow-up in the treatment group. Endomyocardial biopsies showed a trend toward improvement in vascularity with no definite evidence of transdifferentiation. This was in the form of significantly increased capillary density with no increase in the supporting pericytes. No new myocardial cells or any immature cells were seen.
v.	Chetan D Patel, Agarwal S, Seth S, Mohanty S, Agarwal H, Gupta N. Detection of homing-in of stem cells labeled with technetium-99m hexamethylpropyleneamine oxime in infarcted myocardium after intracoronary injection. :2014 |29|4|276-277 Bone marrow stem cells having myogenic potential are promising candidates for various cell-based therapies for myocardial disease. We present here images showing homing of technetium-99m (Tc-99m) hexamethylpropyleneamine oxime (HMPAO) labeled stem cells in the infarcted myocardium from a pilot study conducted to radio-label part of the stem cells in patients enrolled in a stem cell clinical trial for recent myocardial infarction.
vi.	Nair Velu , Madan Hemant, Sofat Sunil, Ganguli Prosenjit, Jacob M.J. Data et.al. Efficacy of stem cell in improvement of left ventricular function in acute myocardial infarction - MI3 Trial. The Indian Journal of medical research (2015). 142. 165-74.10.4103/0971-5916.164245 Infusion of stem cells was found to have no benefit in ST elevation AMI. However, the procedure was safe. A possible benefit was seen when the predefined cell dose was administered which was noted upto three weeks post AMI, but this was not significant and needs confirmation by larger trials
vii.	Menasche P, Alfieri O, Janssens S, McKenna W, Reichenspurner H, Triquart L, et.al. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. Circulation 2008;117: 1189-1200. Myoblast injections combined with coronary surgery in patients with depressed LV function failed to improve echocardiographic heart function. The increased number of early postoperative arrhythmic events after myoblast transplantation, as well as the

	capability of high-dose injections to revert LV remodeling, warrants further investigation.
viii.	Choudhury T, Mozid A, Hamshere S, yeo C, Pellaton C, Arnous S, Saunders N, et. al. An exploratory randomized control study of combination cytokine and adult autologous bone marrow progenitor cell administration in patients with ischaemic cardiomyopathy: the REGENERATE-IHD clinical trial. Eur J Heart Fail 2017;19:138-147. It showed that G-CSF combined with autologous i.m. BMCs has a beneficial effect on cardiac function and symptoms. However, this result should be considered preliminary in support of a clinical benefit of i.m. stem cell infusion in 'no option' patients and needs further exploration in a larger study.
ix.	Wollert KC, Meyer GP, Lotz J, Ringes Lichtenburg S, Lippolt P, Breidenbach C et. al: Intracoronary Autologous bone- marrow cell transfer after myocardial infarction: The BOOST randomized controlled clinical trial. The Lancet 2004; 364:141-148. Intracoronary transfer of autologous bone-marrow cells promotes improvement of left ventricular systolic functions after acute myocardial infarction.
x.	Lee JW, Lee SH, Youn YJ, Ahn MS, Kim JY, Yoo BS, et.al: A randomized, open-label, multicenter trial for the safety and efficacy of adult mesenchymal stem cells after acute myocardial infarction. K Korean Med Sci 2014; 29: 23-31. The main finding is that the intracoronary administration of autologous purified BM-derived MSCs at 1 Month after STEMI is tolerable without serious complications and provides modest improvement in LVEF at 6-month follow-up by SPECT.
xi.	Chen SL, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, et.al.: Effect on Left Ventricular Function of Intracoronary Transplantation of Autologous Bone Marrow Mesenchymal Stem Cell in Patients With Acute Myocardial Infarction. Am J Cardiol 2004; 94: 92-95 The results showed that BMSCs 3 months after transplantation were viable, with high left line local shortening and unipolar voltage in the infarcted area and increased cardiac functional indexes as demonstrated by cardiac echocardiography, which encouraged our further study. The results clinically resolved the assessment of viability of implanted BMSCs and confirmed that BMSCs function with host cardiomyocytes. Serial cardiac echocardiographic monitoring demonstrated improvement of cardiac function 1 to 3 months after implantation of BMSCs, and improvement was maintained nearly 6 months after the procedure
xii.	Chugh AR, Beache GM, Loughran JH, Mewton N, Elmore JB, Kajstura J et. al. Administration of cardiac stem cells in patients with ischemic cardiomyopathy: The SCIPIO trial: surgical aspects and interim analysis of myocardial function and viability by magnetic resonance. Circulation 2012; 126:S 54-64 Isolation of CSCs from cardiac tissue obtained in the operating room is feasible and does not alter practices during CABG surgery. CMR shows that CSC infusion produces a striking improvement in both global and regional LV functiona, a reduction in infarct size, and an increase in viable tissue that persist atleast 1 year and are consistent with cardiac regeneration.
xiii.	Mathiasen AB, Qayyum AA, Jorgensen E, Helqvist S, Fischer – Nielsen A, Kofoed KF, et al.Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial). Eur Heart J 2015; 36: 1744-1753 Intra-myocardial injections of autologous culture expanded MSCs were safe and improved myocardial function in patients with severe ischaemic heart failure.

xiv.	Balram A, Talwar S, Choudhary S.K, Bisoi A, Chowdhury UK, Hote M.K, et.al. Application of stem cell technology for coronary artery disease at the All India Institute of Medical Sciences, The Heart Surgery Forum # 2007-0701 10(2), 2007,1-4,doi:10.1532/HSF98 CABG along with Intramyocardial infection of bone marrow stem cells showed improvement in contraction of infracted segments of the heart.

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021)

Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Heart Failure.

The current status of research in stem cell therapy suggests that the therapy could reduce the risk of mortality in chronic ischemic heart disease with heart failure and that there are no major adverse events associated with it. This benefit has not been shown in acute myocardial infarction these studies still need to be confirmed in larger clinical trials before cell-based treatment for these patients can be developed as standard treatment. The next studies have to focus on better understanding, and improvement of the cell therapies used (e.g. mononuclear cells, circulating progenitor cells, mesenchymal stem cells, embryonal or haematopoietic progenitor cells). Predictors of responders, outcomes need to be carefully assessed and perhaps therapy needs to be tailored to each patient. Since the benefit of stem cells has not been shown consistently in all clinical trials, it is still recommended that all stem cell therapies be given within the framework of clinical trials and not as standard or routine therapy outside clinical trials.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for Heart Failure.


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