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

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 ICMR National Bioethics guidelines 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. Further- more, 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 ICMR National Bioethics guidelines 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.