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 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.