

# The need to review the existing guidelines and proposed regulations for stem cell therapy in India based on published scientific facts, patient requirements, national priorities and global trends

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## Abstract

India was amongst the first countries in the world to create a set of dedicated guidelines for stem cell therapy in the year 2002. These guidelines which were created by the Indian Council of Medical Research were comprehensive and progressive when one considers that the field was at that time in its infancy. Subsequent developments including the more recent guidelines created in the year 2007 and 2013 did not keep up with the progressiveness of the initial guidelines. In fact it would not be incorrect to state that the most recent set of guidelines (2013) is regressive and if implemented will destroy the emerging field of regenerative medicine in the country. This paper highlights the limitations and flaws in the existing guidelines and proposed regulations and makes suggestions based on published scientific data from our own clinical work, national priorities, patient requirements and global trends, which could form a basis for a review of our national guidelines and regulations.

**Keywords :** Ethics, Regulations, Cell Therapy, Stem Cells, Regulatory challenges.

## Introduction

Regulations, guidelines, ethics and principles of evidence based medicine form the foundation of modern medical practices. There is no questioning the value of these in maintaining public safety in connection with medical practice. However the emergence of the field of regenerative medicine and cellular therapy has raised new questions about the limitations of the existing systems in the development and availability of emerging technologies. Despite tremendous increase in and availability of both basic science data as well as clinical results of safety and efficacy, the benefits of regenerative medicine are still not available to millions of patients who are potential beneficiaries. A decade ago patients of Duchenne Muscular dystrophy, Motor neuron disease and other incurable

illnesses were dying because there was no treatment available. In 2015 thousands of these patients are dying but the tragedy is that this is happening despite the availability of a treatment whose results have been documented and published. This treatment is Stem cell therapy and it is the guidelines and regulations that are preventing the wider availability of this life saving treatment. It would therefore not be an exaggeration to state that the current regulations and guide lines instead of saving life are actually resulting in the loss of life. Whereas regulatory bodies are correct in having stringent standards to ensure patient safety, we believe there are two sides to this issue. The other side is that many patients are being deprived of treatments that could potentially save their lives, reduce their disability or ease their suffering. A good analogy of what is currently happening would be looking

at a coin. A coin has two sides. But at any one time we can see only one side. Presently the regulators are seeing only one side of the coin and the practitioners of stem cell therapy are seeing the other. But a coin to be whole needs both sides. It is important therefore that both sides (regulators and doctors) agree to look at both sides of the coin and come to a balanced approach. Regulators need to be open to the reality that stem cell therapy is here to stay and should be open to accepting newer indications for this treatment based on safety records, evolving trends and published literature. They need to recognize that stopping or preventing the practice of stem cell therapy in newer indications could do more harm and result in more deaths than its being more easily available. On the other hand Stem cell experts need to accept there need to be checks and balances in place through guidelines and regulations to ensure patient safety and prevent patient exploitation.

### **The present situation in India with regards to guidelines for stem cell therapy**

1. The National guidelines for stem cell research have been formulated by the Indian Council of Medical Research and the Department of Biotechnology in 2013 [1]. These guidelines have retained the 2007 classification of stem cell research into 3 categories namely permitted, restricted and prohibited [2]. However, it has introduced an additional layer of oversight besides the institutional ethics committee (IEC) in the form of Institutional Committee for Stem Cell Research (IC-SCR) and the National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT). A major recommendation has been to omit the word therapy from the title of the guidelines.
2. The Ministry of Health and Family Welfare, Government of India, established a High Powered Committee in June 2013 to suggest a road map for regulation of stem cells and other cell based therapies being practiced in India. Under the chairmanship of Professor Lalji Singh it submitted a Guidance Document for Regulatory Approvals of Stem Cell and Cell Based Products (SCCPs) in December 2013. This Guidance Document

is based on the recommendations of that committee and it is subsidiary to the amendments made in 2013 to the Drugs and Cosmetics Act (DCA), 1940 and the new rules proscribed there under. As per these amendments it has been decided that Government of India, through the DCG (I) and CDSCO, shall regulate all practices related to the use of stem cells, and other cells, for therapeutic purposes in India. The amendment in DCA also mandates that all stem cells and cell based products that can be used for therapeutic purposes shall be referred as Stem Cell and Cell Based Products (SCCPs) and all activities related to their usage i.e. manufacture/isolation/ collection, storage and transplantation into patients must be done only under a license or permission that would be granted by the DCG(I)/CDSCO [3].

3. Another important and major development has been the proposal of the Drug Controller General of India DCG(I) to include "stem cells" in the definition of new drugs in the proposed bill titled "Drugs and Cosmetics (Amendment) Bill 2015"[4].

### **The flaws in the existing guidelines & proposed regulations**

1. The current guidelines are uniformly applicable to "Autologous" and "Allogenic" Stem Cells. Autologous Stem Cell Therapy has been practiced for various hematological conditions for the last 3 decades and for other incurable conditions over the last 5 to 10 years. They have a proven track record of safety. On the other hand allogenic stem cells are manufactured commercially by companies and so it may be appropriate to consider them as a new drug. The use of autologous stem cells is a form of therapy and since they are not manufactured commercially, they should not be considered as a product or drug.

We, therefore, suggest that instead of including 'stem cells' in the category of new drugs, it should be changed to "allogenic stem cells". By doing this, stem cells that are being manufactured and sold by companies and are therefore a product will come under

the category of new drug whereas autologous stem cells which are being used by individual doctors will not be included in this category.

2. All medical research is done with the intention of developing newer therapies. So we should be moving from research to therapy. Our 2007 guidelines include therapy but our 2013 ones don't. By dropping the word therapy in the 2013 guidelines, we have taken a step backwards instead of moving forwards. This needs to be reviewed.
3. The foreword to the 2013 National guidelines for stem cell research makes sweeping unjustified and unsubstantiated statements about the clinical indications for stem cell therapy. Deciding what therapy is and what is not therapy comes under the purview of the medical community and treating doctors and this keeps changing with newer developments and publications. The strong inappropriate words and statements made in the foreword would effectively stop all stem cell therapy advancements in the country. The foreword itself reveals the anti stem cell therapy bias that the guidelines have. This needs to be withdrawn and corrected based on the existing scientific medical literature.
4. Whereas the guidelines do make a distinction amongst different stem cell types however when it comes to the practical implementation of policy, all the cell types seem to get bundled into one. This would be like having a common set of regulations for alcohol, aerated drinks like Coke / Pepsi and homemade orange juice calling them all beverages. Stem cell could be broadly divided into three types. Embryonic, umbilical and adult stem cells. Embryonic stem cell could be compared to alcohol, Umbilical cord stem cells to Cold drinks like Pepsi /Coke and Adult autologous stem cells to homemade fruit juice. Whereas alcohol is potentially dangerous and there should definitely be tight regulations so also embryonic stem cell work should be tightly regulated. Cold drinks may not be dangerous but can be harmful so there should be quality checks in place, so also for Umbilical cord cells there should

be quality checks in place and these types of cells should be treated like drugs/ medicines and the same regulations and quality control systems should be in place for them. However there is no need for any strict regulations for home made orange juice and so autologous adult cells should be freed up from regulations and their availability in fact encouraged since they are completely safe and have shown clinical benefits in many conditions in various published scientific papers. If one were to use a traffic light as an analogy we would suggest that there be a green light for autologous, orange light for umbilical cord and red light for embryonic stem cell therapy.

5. The views of the main stakeholders i.e. [1] patients who are suffering from diseases that stem cell therapy could benefit & [2] Doctors who are practicing stem cell therapy have not been taken. Guidelines should not be framed by a handful of researchers and academicians without taking into account the views of the people directly involved in the field. The present committees (including NAC-SCRT) lack clinical experts from different specialties with experience and publications in this field. It is important that any review takes into account their views. Publications in this field particularly from India but from the rest of the world as well should be studied whilst drafting/reviewing any guidelines.

### **The scientific basis for the need to relook at the current guidelines**

There is enough published scientific evidence in medical journals and textbooks to justify the need to make the newly developed cellular therapies more readily available to the patient population. This is more specifically required for those medical conditions for which there are no other treatments available. Whereas, there is a lot of evidence from across the world as well as from India; we now present our own published clinical results in various incurable neurological conditions.

Our own documented and published scientific work is summarized to establish the scientific basis to seek a review of the existing guidelines

## 1. Autism

Sharma et al 2013, published a clinical study which was an open label proof of concept study in 32 patients of autism. They administered autologous bone marrow mononuclear cells (BMMNCs) intrathecally in 32 patients with autism followed by multidisciplinary therapies. All patients were followed up for 26 months (mean 12.7). The outcome measures used were Childhood Autism Rating Scale (CARS), Indian Scale for Autism Assessment (ISAA), Clinical Global Impression (CGI), and Functional Independence Measure (FIM/Wee-FIM) scales. Positron Emission Tomography-Computed Tomography (PET-CT) scan recorded objective changes. It was found that out of 32 patients, a total of 29 (91%) patients improved on total ISAA scores and 20 patients (62%) showed decreased severity on CGI-I. On CGI-II 96% of patients showed global improvement. The efficacy was measured on CGI-III efficacy index. Few adverse events were reported, including seizures in three patients, but these were reversible and easily controlled with medications. The encouraging result of this leading clinical study provides future directions for application of cellular therapy in autism [6].

In addition to the above case series, 5 separate case reports by Sharma et al, [7,8,9,10,11] have also been published documenting the safety, efficacy and objective radiological improvements in patients of Autism following cell therapy.

The results of Sharma et al are coherent with findings of Siniscalco et al. 2012 and Yang-Tao et al, 2013 [12,13].

## 2. Cerebral Palsy

Sharma et al in 2015 carried out an open label, nonrandomized study on 40 cases of all types of cerebral palsy treated with autologous bone marrow mononuclear cells intrathecal administration. Three months after intervention, 14 patients showed improvement in oromotor activities, 11 in neck control, 17 in sitting balance, 15 in standing balance, 9 in walking balance, and 12 in speech. At six months, 38 out of 40 (95%) patients showed improvements and 2 did not show any improvement but remained stable without any deterioration. No major adverse events were noted except for seizures in 2

patients which were self limiting and were controlled by medications. The study, thus demonstrated the safety, feasibility, and efficacy of the intervention [14].

Apart from the above case series, 3 separate case reports by Sharma et al, [15,16,17] have also been published documenting the safety, efficacy and objective radiological improvements in patients of Cerebral Palsy following cell therapy.

The findings of Sharma et al. are similar to those of Chen et al., 2010 [18] & Chernykh et al., 2014 [19] that demonstrate the safety and efficacy of stem cell therapy in cerebral palsy.

## 3. Muscular dystrophy

Sharma et al 2013, carried out a study in 150 patients with muscular dystrophy which included Duchenne Muscular Dystrophy, Limb Girdle Muscular Dystrophy and Becker Muscular Dystrophy variants. They were administered with autologous bone marrow derived mononuclear cells intrathecally and intramuscularly. On a mean follow up of 12 months  $\pm$  1 month, overall 86.67% cases showed symptomatic and functional improvements, 53% cases showed increase in trunk muscle strength, 48% showed increase in upper limb strength, 59% in lower limb strength and about 10 % showed improved gait. Patients showed shift on assessment scales such as Functional Independence Measure (FIM) and Brooke & Vignos scale. 6 patients showed changes on musculoskeletal Magnetic Resonance Imaging (MRI) with respect to muscle regeneration and decrease in fatty infiltration and 9 showed improved muscle electrical activity on Electromyography (EMG). The results show that this treatment is safe, efficacious and also improves the quality of life of patients suffering from Muscular Dystrophy. No significant adverse events were noted [20].

In another study, Sharma et al 2015, carried out a study in 59 patients with limb girdle muscular dystrophy (LGMD) who underwent autologous bone marrow mononuclear cells intrathecal transplantation and extensive rehabilitation. At a follow up of 9 months to 4.5 years, there was a statistically significant improvement in the muscle strength of major body muscles. The results showed maintained FIM scores and thus,

maintained function in patients over time which suggested achievement of plateau phase in the disease progression [21].

Safety and efficacy of cellular therapy has been documented with 4 other case reports by Sharma et al, [22,23,24,25] apart from the case series mentioned above.

#### **4. Traumatic spinal cord injury**

In a study published by Sharma et al in year 2013, fifty six chronic cervical spinal cord injury patients were treated with autologous bone marrow mononuclear cells intrathecally. On a mean follow up of 2 years  $\pm$  1 month, out of the affected patients improvement was seen in 92.31% in trunk stability, 87.5% in sitting balance, 77.78% in trunk muscle strength, 52% in upper limb strength, 48.21% in standing balance, 21.57% in sensation, 20.59% in bladder sensation, 18.37% in spasticity and 14.29% in walking balance. All the patients who suffered from postural hypotension showed an improvement

On ASIA scale, two patients showed a change from level B to C and one from level A to B and one from C to D. On FIM scale, 24 out of 56 patients showed an increase in the score[26].

Sharma et al carried out a study which was published in 2013, 110 patients with thoracolumbar SCI were administered autologous bone marrow derived mononuclear cells intrathecally. On a mean follow up of 2 years  $\pm$  1 month, 100 cases (91%) showed symptomatic, investigational, and functional improvement. A reduction in spasticity was found in 26% of cases, partial sensory recovery in 28%, improved trunk control in 96%, and less postural hypotension in 100%. There was also an improvement in bladder management with respect to a shift from indwelling and condom catheters to intermittent self-catheterization in 33% of cases. Further, 22% of wheelchair-bound cases started walking and 60% of patients whose activities of daily living were affected showed improvement. Two of the 110 patients shifted from grade A to C on the ASIA scale, one shifted from grade B to C, and eight shifted from grade A to B. The median preintervention FIM score was 71 and after intervention was 79.5. Fifty-nine patients showed a significant change in FIM score [27].

The safety and efficacy of cellular therapy is

further supported with 2 additional published case reports by Sharma et al [28,29].

Clinical studies conducted in various parts of the world by Huang et al 2012 [30], Saberi et al 2008 [31], Moviglia et al 2009 [32] and Tabakow et al 2013 [33] also highlight the safety and efficacy of stem cell therapy.

#### **5. Stroke**

Sharma et al in 2014 published a study in which the effect of intrathecal administration of autologous bone marrow mononuclear cells (BMMNCs) was analyzed on the recovery process of patients with chronic stroke. 24 patients diagnosed with chronic stroke were administered cell therapy, followed by multidisciplinary neurorehabilitation. They were assessed on functional independence measure (FIM) objectively, along with assessment of standing and walking balance, ambulation, and hand functions. Out of 24 patients, 12 improved in ambulation, 10 in hand functions, 6 in standing balance, and 9 in walking balance. Further factor analysis was done. Patients of the younger groups showed higher percentage of improvement in all the areas. Patients who underwent cell therapy within 2 years after the stroke showed better changes. Ischemic type of stroke had better recovery than the hemorrhagic stroke. This study demonstrates the potential of autologous BMMNCs intrathecal transplantation in improving the prognosis of functional recovery in chronic stage of stroke [34].

Apart from the above case series 2 separate case reports are published by Sharma et al that provide evidence about the safety and efficacy of stem cell therapy [35,36].

A Li et al in 2013 conducted a controlled clinical study with 60 patients who received stem cell therapy and 40 patients who did not and found that there was neurological and functional improvement in higher percentage of the patients that received stem cell therapy as compared to the control group [37].

#### **6. Traumatic Brain Injury**

Sharma et al in 2015 published a study carried out in 17 patients with Traumatic brain Injury (TBI) who had attained a plateau stage, treated with autologous bone marrow mononuclear cells

transplantation. Symptomatic analysis was done for the common symptoms observed in these patients and was graded as no change, mild moderate and significant improvements. The symptoms included higher mental functions, posture, trunk activity, upper limb activity, lower limb activity, coordination, oromotor, ambulation and Activities of Daily Living. Mild improvement was defined as improvements till 3 of the symptoms mentioned. Moderate was considered when 4 to 6 symptoms showed improvement, whereas significant improvements were considered when there were improvements recorded in 7 to 9 of the symptoms.

Analysis revealed that out of 17 patients, 29.41% of patients showed significant improvements in higher mental functions, posture, trunk activity, upper limb activity, lower limb activity, coordination, oromotor, ambulation and Activities of Daily Living; 23.52% of patients showed moderate improvement, 41.17% of patients showed mild improvements and 5.88% of patients showed no improvements in any of the symptoms. There were 4 patients that showed improvement in brain metabolism on PET CT scan of brain. Since TBI causes widespread brain damage to multiple areas of the CNS, most of the patients showed mild improvements [38].

## 7. Motor neuron disease

Sharma et al analyzed the survival duration of 46 ALS patients treated with intrathecal autologous bone marrow mononuclear cells transplantation since August 2008 till February 2014 compared with 20 patients who did not undergo intrathecal autologous BMMNCs transplantation using Kaplan-Meier survival analysis. Comparison of the survival duration suggested that the mean survival duration of the patients treated with intrathecal autologous BMMNCs transplantation was longer [104.069 months] than those who were not treated with intrathecal autologous BMMNCs transplantation [57.38 months]. A clinically significant difference of 47 months in the survival duration suggests the potential of intrathecal autologous BMMNCs transplantation in the treatment of ALS [39].

In addition to the above case series, 1 separate case report by Sharma et al also provides evidence about safety and efficacy of stem cell therapy [40].

Clinical study published by Prabhakar et al. 2012 [41], Blanquer et al. 2012w [42], Mazinni et al [43,44] & Martinez et al [45,46] also demonstrated a similar effect on progression of the disease. Also the case reports by Huang et al. [47,48,49] demonstrate the slowing down of the progression of the disease.

8 other publications by Sharma et al, document clinical outcomes in various other incurable neurological conditions [50,51,52,53,54,55,56,57]

## Objective neuroradiological and electrophysiological improvements that document the improvements of cell therapy

An argument given by critics of stem cell therapy is that the clinical improvements reported after stem cell therapy may be the result of the placebo effect. To counter this argument we present from our own clinical work a few representative cases where objective improvements have been clearly documented on investigations. This scientifically shows that biologically beneficial changes are occurring in damaged tissues following stem cell therapy.

### 1. Autism

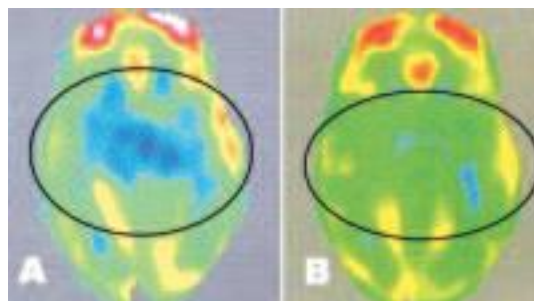


Figure 1: In the figure, A & B show PET-CT scan images before and after stem cell therapy, respectively. PET-CT scan after Stem cell therapy shows increase in the metabolism as outlined by the circles. Blue areas depicting hypometabolism in the pre SCT image which have changed to green areas depicting normal metabolism.

### 2. Cerebral Palsy

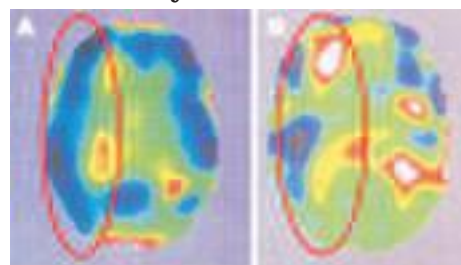


Figure 2: (A) Before stem cell therapy blue areas representing severe hypometabolism (B) Reduction in the blue areas suggesting increase in the metabolism and a positive response to the treatment.

**3. Muscular dystrophy**

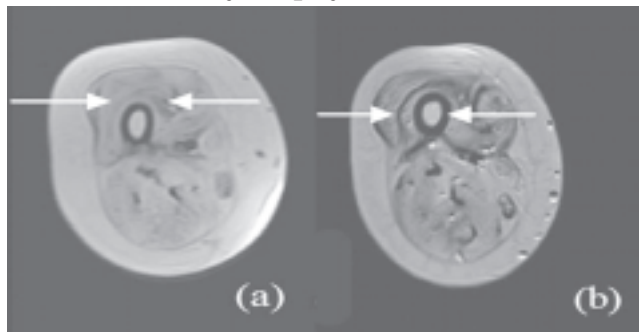


Figure 3: In the figure, A & B show MRI Musculoskeletal images before and after stem cell therapy, respectively showing regeneration of muscle in vastus medialis and vastus radialis.

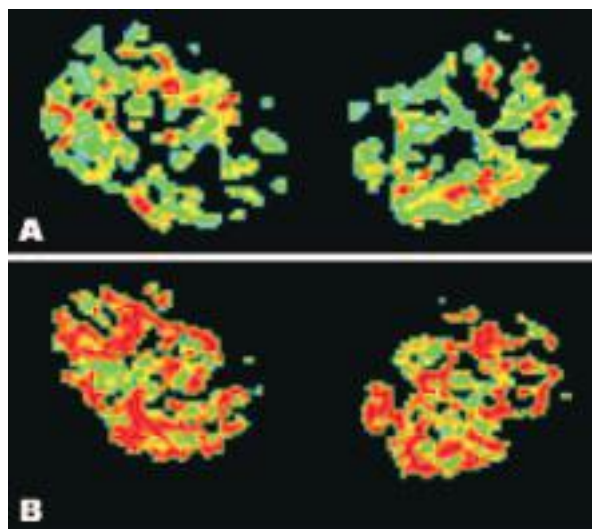


Figure 4: In the figure, A & B show MRI MSK DTI images before and after stem cell therapy, respectively showing increased red areas depicting increased activity of muscles.

**4. Traumatic spinal cord injury**

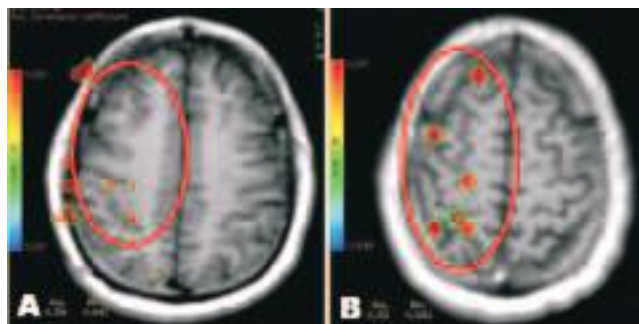


Figure 5: Figure A, shows the areas activated in the brain before stem cell therapy; Figure B shows increased activation of brain areas post stem cell therapy, new areas of activation are recorded in red and green color in the functional MRI of the brain.

**5. Stroke**

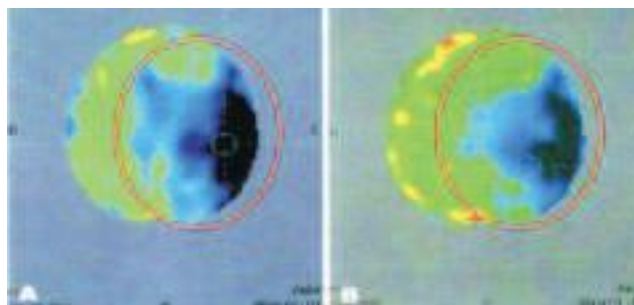
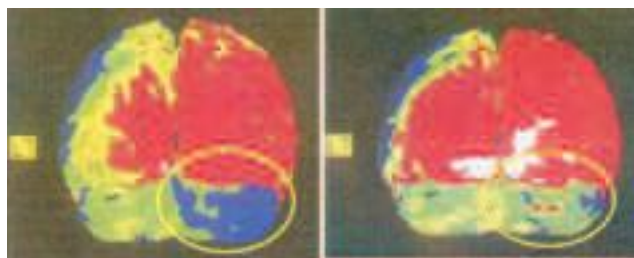


Figure 6: In the figure, A & B show PET-CT scan images before and after stem cell therapy, respectively. PET-CT scan after Stem cell therapy shows increase in the metabolism as outlined by the circles. Blue/black areas depicting hypometabolism in the pre SCT image which have reduced after Stem cell therapy.

**6. Traumatic Brain Injury**



(A) Before stem cell therapy (B) After stem cell therapy

Figure 7: Figure A, reduction in the metabolism of the brain, shown in blue color on the PET CT scan. Figure B, showing improved metabolic activity post stem cell therapy which is indicated by decrease in blue areas and increase in the green areas.

**Review of internationally published work documenting the safety and efficacy of stem cell therapy in various neurological disorders.**

A review of International scientific literature reveals a large number of published articles that clearly document the safety and efficacy of stem cell therapy in various conditions. In spinal cord injury (SCI) there are over 66 published papers

in which 1599 patients have been treated using various different types of cellular therapies and in these 844 patients have shown functional and neurological improvements and with no major adverse events reported. In cerebro vascular accident, there are more than 11 published studies including over 334 patients. In motor neuron disease, there are 9 studies evaluating the effects of cellular therapy in 203 patients (41-49). There are over 19 published studies in cerebral palsy including 344 patients. These published clinical results are only part of a larger group of work that definitively establishes the role of stem cell therapy as a safe and effective treatment option.

Medical Textbooks too have started including chapters on stem cell therapy. The Internationally accepted "Harrisons Principles of Internal Medicine, 19th Edition" has a separate section on stem cell therapy and mentions several indications for the clinical use of stem cells [58]. An international book on cerebral palsy "Cerebral palsy challenges for the future" has a chapter on "stem cell therapy in cerebral palsy" written by Sharma et al 2014 [59].

### **International documents that need to be referred to before formulating guidelines & regulations for stem cell therapy**

#### **1. World Medical Association' declaration of Helsinki for Ethical Principles for Medical Research Involving Human Subjects [60]**

Clause 37 of the Helsinki declaration states that, *"In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available."*

This implies that it is ethical for a physician to treat patients with an unproven therapy when no other treatments are available. This part of the Helsinki Declaration should be considered as

an important inclusion for any regulations regarding stem cell therapy. This would mean that clinical work with stem cell therapy being done by centers following this aspect of the Helsinki declaration would be ethical and legitimate.

#### **2. The International Society for Cellular Therapy (ICST) "White paper" published in 2010 in Cytotherapy [61]**

The following important aspects of this paper need to be taken into consideration for any stem cell therapy regulations.

##### **a. Distinction between clinical trials and medical innovation**

Regulations should make a distinction between clinical trials and medical innovation. According to the ICST white paper the distinction can be made as follows,

*"Medical innovation in cellular therapy may be viewed as ethical and legitimate use of non-approved cell therapy by qualified healthcare professionals in their practice of medicine. Patients not eligible for controlled clinical trials should be able to choose unproven but scientifically validated cell therapy medical innovations, if the researchers are competent and those seeking treatment are truthfully and ethically informed. There is a place for both paradigms in the cell therapy global community."*

As per this it can be said that non approved cell therapy should be considered as ethical and legitimate part of medical innovation if (i) It is done by qualified healthcare professionals in their practice of medicine (ii) The researchers are competent & (iii) Those seeking treatment are informed truthfully and ethically. There is a role for both, clinical trials and medical innovation, in the cell therapy global community.

##### **b. Distinction between legitimate cell therapy medical services and fraudulent services.**

Regulations need to differentiate between legitimate cell therapy medical services and fraudulent services. ICST "White paper" highlights how this can be done,

*"The following guidelines are useful in assessing scientific rigor and for differentiating between legitimate cell therapy medical services (including clinical trials and medical innovation) and fraudulent cell therapies."*



1. *Peer review and transparency: consumers of cell therapy medical innovation should evaluate evidence from peer-reviewed publications, professional society presentations and scientific recognition. They should be encouraged to seek multiple professional opinions and have all questions answered to their satisfaction.*
2. *Safety and regulatory history: patients should consider the reputation of the investigator and clinic, as well as the record of disciplinary activities against these entities.*
3. *Informed consent: patients should expect to be informed fully and accurately of the risks, benefits, costs, safety, compensation for injury, investigator conflicts of interest and alternative therapies, as a minimum."*

Therefore institutes whose clinical results are peer reviewed and transparent through peer reviewed publications, professional society presentations & scientific recognition, who have a good safety & regulatory history and who take informed consent may be considered as centers offering legitimate cell therapy.

#### **c. The basic right of a patient to seek treatment should be respected**

Regulations may violate the basic bioethical principle of autonomy of the patients with reference to cellular therapy. Implementing evidence based guidelines alone implies that the patients' rights of choosing a treatment which is safe are being denied. The ICST White Paper is in agreement with this and states,

*"Patients seeking medical treatment for cellular therapies have the following rights that must be respected by healthcare providers and all associated with their care.*

- a. *The right to seek treatment: patients and their families/partners have the right to seek treatments for their diseases. No entity should withhold this fundamental right unless there is a high probability of harm to the patients.*
- b. *The right to information: patients have the right to an accurate representation regarding the safety and efficacy record of the cell treatment. This includes probable side-effects and a truthful record of efficacy.*
- c. *The right to informed consent: patients have a*

*right to a true informed consent process that includes all the elements described above."*

This implies that the right to seek treatment is the fundamental right of the patients and their families and this should not be taken away by any regulatory or professional body. Patients also have a right to information and a right to informed consent which should be made available to the patients and their families by the treating physicians.

#### **d. Distinguishing various centers offering cellular therapy**

The ICST White Paper distinguishes various centers offering cell therapy as follows

1. *Approved/standard therapies (e.g. hematopoietic stem cell transplant and other cellular therapies approved for marketing)*
2. *Controlled clinical trials*
3. *Valid compassionate use of unapproved therapies*
4. *Treatments not subject to independent scientific and ethical review."*

At present most regulations only recognize (1) approved/standard therapies (e.g. hematopoietic stem cell transplant and other cellular therapies approved for marketing) (2) controlled clinical trials. Anything apart from this is not recognized as ethical or legal. It is important that as per the ICST white paper, (3) Valid compassionate use of unapproved therapies, be recognized as a separate, ethically accepted and legitimate alternative.

#### **3. The United States Food and Drug Administration article 1271 15B (Human cells, Tissues, and Cellular and Tissue based products) [5]**

This states that :- *"You are not required to comply with the requirements of this part if you are an establishment that removes Human cells, Tissues and cellular and tissue-based products from an individual and implants such products into the same individual during the same surgical procedure"*

What this implies is that autologous and minimally manipulated cell therapy should not have regulations that are in place for other human cells, tissues, tissue based products and drugs. This is the single most important distinction that

any guideline or regulation for stem cell therapy should make. Having common regulations for all cellular therapy would be like having common regulations for alcohol, sodas and homemade orange juice covering them all under the category of beverages.

#### 4. The new Japanese legislation on stem cell therapies [62]

In their recent amendment to their pharmaceutical law, Japan has created a separate approval channel for regenerative medicine. Instead of, using phased clinical trials, researchers will have to demonstrate efficacy in pilot studies of as few as 10 patients in one study if the change is dramatic enough or a few hundred if the improvements are marginal. If the efficacy can be surmised it will be approved for marketing. At that stage the treatment would be approved for commercial use as well as national insurance coverage. Thus the Japanese government has lowered the bar for regenerative therapies dramatically by requiring limited safety and efficacy data. Other regulatory bodies should study the new Japanese legislation and incorporate the relevant aspects of this path breaking regulation for regenerative medicine [44].

#### National Policies: Views of the Government and the Prime Minister of India

The importance the Government of India and our Honorable Prime Minister gives to the field of stem cell therapy is highlighted by the following :-

[1] In the address by President of India to the joint session of the Lok Sabha at the central hall of parliament where the President shared the governments agenda for the country in paragraph 38 it states *"My government will build world class research centers in the fields of nanotechnology, material sciences, thorium technology, brain research, stem cells etc"*.

[2] The Prime Minister of our country, Shri Narendra Modi has shown special interest in the field of Stem Cell Therapy as is evident from the fact that :-

When he visited Japan in August 2014, he visited the Stem Cell Institute in Kyoto and personally met with Stem Cell pioneer and Nobel Prize winner Prof. Shinya Yamanaka.

In February 2015 he visited the NCBS and inStem in Bangalore and visited the laboratories to see Stem cell research. He also had a vibrant and truly interactive engagement with the faculty and students on the use of stem cell based therapies.

#### Discussion

Stem Cell Therapy is an upcoming and developing field in modern medicine in which India has played a pioneer and leadership role. Many medical conditions that were earlier considered incurable or untreatable can now be treated with stem cell therapy. This has resulted in Indian Scientists and Doctors playing a lead role in the field due to which many patients from all over the world are now coming to India to take this treatment. The primary job of the various regulatory authorities is to ensure the safety of patients with the country and to see that there is no violation of scientific and ethical principles. Our regulators have done a great job in this. However with reference to the field of stem cell therapy, this has also resulted in a slowness in the availability of this form of treatment to people at large. It is our view that whilst ensuring safety the regulatory authorities should also permit and in fact encourage the wider availability of the safer forms of this treatment (such as adult stem cell therapy) since stem cell therapy has shown significant benefit to children of autism / cerebral palsy / mental retardation / blindness as well as patients who are paralyzed because of spine injury / brain stroke. We believe that there are thousands of patients deteriorating and dying presently with serious neurological and other diseases. (motor neuron disease, muscular dystrophy, heart failure, liver failure etc etc) whose lives could be saved if this treatment was more easily available. There are many scientific publications in international medical journals (many of them from India) that have shown the safety and efficacy of Stem Cell therapy. The existing guidelines are not in our National interest. These will have a negative impact on the health of the people of this country since many people are today dying or suffering from serious diseases who could be treated by a treatment that is available but cannot be given since the regulatory bodies will not permit its greater availability. Whilst thousands of people are dying or suffering today because they cannot get stem cell therapy

for their otherwise incurable diseases on the other hand there are no patients who have either died or suffered due to stem cell therapy. There may be a few cases of complications or adverse events but then which established medical treatment is 100 % free from complications or side effects. As compared to all other treatment forms cell therapy is one of the safest forms of therapy and there are now many scientific papers that have clearly established the safety of cell therapy. These draft guidance have been prepared with a anti stem cell therapy bias as well as without study of the present literature available in international and national journals that show its efficacy and safety. of cell therapy in various diseases. The drafting committee did not have practicing doctors from the clinical specialties who are the appropriate people to judge whether stem cell therapy is useful in their fields of specializations. The main stakeholders (i.e. patients who have received stem cell therapy and doctors practicing stem cell therapy) have not been consulted. We are suggesting simple easy to implement methods that will simultaneously achieve two goals. We will have strict regulations as well as greater availability of this form of treatment.

### Conclusions

We are proposing that the existing guidelines and proposed regulations for stem cell therapy for India be reviewed and those reviewing these should consider the following:

1. Make a distinction between autologous and allogenic stem cell therapy by having a more permissive approach towards autologous stem cell therapy. In continuation with this, in the definition of new drugs "stem cells" be replaced by " allogenic stem cells." This will ensure that stem cells that are been manufactured and are marketed commercially as products (allogenic stem cells) are kept under strict regulations whereas autologous stem cells which are safe, have a published track record of efficacy in several incurable conditions and which are not a product are easily available for patient's benefit in different medical conditions.
2. Study the new Japanese legislation that ensures a fast track approval for regenerative medicine.
3. Evaluate published clinical results of individual practitioners from within the country as well as those from other countries and take these into consideration for deciding approved indications.
4. Criteria be evolved for recognizing legitimate cell therapy medical services, medical innovation and the valid compassionate use of unapproved therapies.
5. The patients' right to seek treatments for their diseases and suffering be respected.
6. The socioeconomic conditions of India be kept in mind. The majority of our population cannot afford expensive treatments. Therefore a more permissive approach be taken to the less expensive autologous therapies that can be easily done in our public hospitals and smaller private hospitals as compared to the more expensive allogeneic therapies manufactured by the large corporates.
7. The views of the people as reflected by the views of the elected representatives in particular our Honorable Prime Minister Shri Narendra Modi be taken into consideration whilst reviewing the guidelines and regulations.
8. That the various expert committees, including NAC-SCRT, be reconstituted with greater representation from different clinical specialties and practicing doctors with clinical experience and publications in stem cell therapy.
9. That free and frank discussions are held with the main stake holders who are the patients suffering from diseases that stem cell therapy could benefit and the doctors who have expertise and are practicing this therapy and their views be respected and reflected in the reviews.

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