Ethical & Regulatory Principles for the Practice of Regenerative Medicine using Cell / Stem Cells.

Important distinction

Regulators from many countries and Courts from countries like the USA & India have made a core legal and regulatory distinction between :-

(1) Cell / Stem cell procedures done by doctors in hospitals using Autologous (taken from same patient) Minimally Manipulated cells in a surgical setting which is a doctor's practice and does not require a regulatory license

And

(2) Stem cell derived Products where Allogenic (taken from Donor) and more than minimally manipulated cells are manufactured by companies that requires an FDA / Equivalent permission and license.

General Principles that Govern the Ethics and Regulations

The following are the general principles that govern the ethical and regulatory aspects of Cell / Stem cell procedures done by doctors in hospitals using Autologous Minimally Manipulated cells in a surgical setting :-

(A) Which Doctors can practice cell / stem cell therapy

There are presently no formal clinical University degrees or post graduate qualifications for regenerative medicine.

Cell / Stem cell therapy requires two sets of doctors – (1) A Clinical team and (2) A laboratory team.

(1) The Head of the Clinical team should be :- A doctor from a "**Domain***" area for the indications he/she is treating patients. Domain refers to an anatomical/ physiological aspect of the human body such as Nervous System , Cardiovascular system etc. So a Neurosurgeon or Neurophysician can do cell / stem cell therapy for any medical condition that is connected to the Nervous system i.e. those involving the brain , spine , nerves etc. A Cardiologist or Cardiovascular surgeon can treat conditions affecting the CardioVascular system i.e. those related to the heart and blood vessels etc . A Nephrologist or Urologist can treat any condition that involves the Genito Urinary system i.e those involving the kidney , bladder, prostate etc.

The Rationale for this is that :-

(a) Better evaluation , better Monitoring and avoidance of missing any conditions that could be a risk factor: - Only a doctor from a particular domain area can fully understand all the clinical aspects , diagnostic investigations etc for medical conditions related to that domain. Only a Neuro doctor can do a proper neurological clinical examination and interpret neurological tests like MRI scans etc. Other specialty doctors cannot do this. Only a cardiac doctor can interpret heart murmurs and read an ECG properly or interpret an 2D Echo etc. Other specialty doctors cannot do this.

(b) Proper Management of complications if any :- The most important fact is that only a doctor from that domain area can identity and comprehensively manage any complications or problems that may occur following cell / stem cell therapy. For example - If a Neurosurgeon treats cardiac conditions and if there is a problem such as arrhythmias post cell / stem cell therapy then he is not qualified or trained to identify or manage such complications. On the other hand if a Cardiothoracic surgeon treats brain problems and if there is a problem such a convulsions after the treatment then the Cardiac surgeon is not qualified or trained to manage such a complication.

(c) To Prevent Medical Mismanagement :- Many patients undergoing cell / stem cell therapy are on other medications and treatments for long periods such as anti convulsant drugs, etc in the case of neurological patients. These medications require adjustment of doses, etc which is not part of a non Neuro doctors practice and therefore can result in medical mismanagement.

In view of all the above from an ethical, regulatory and legal point of view it is inappropriate and incorrect for doctors from one domain area to treat patients from another domain area.

(2) The Head of the Laboratory team should be a Pathologist, Microbiologist, Biochemist or Pharmacologist. This is because the handling of cell / stem cells in the laboratory is a skill that these doctors have been trained in.

(B) In what type of facility / Hospital can Cell / Stem cell therapy be done.

(1) The clinical work should be done in a hospital that is registered with the local governmental health authorities.

(2) The facility should have a cell / stem cell laboratory that is either GLP (Good Laboratory Practice) or GMP (Good Manufacturing Practice).

The Cell / Tissue laboratory Facility should :-

(a) Be designed to prevent infection , extraneous contamination and impurity

(b) Quality of the preparations should be consistent and should be checked at various levels.

(c) Storage containers and storage conditions should be such as to retain potency for the intended purpose.

(d) Records should be kept for volume , number of cells , procedure used to isolate or purify the cell population, cell characterization and most important the Count and Viability of the cells prior to administration.

(e) Labelling to be maintained as per requirement.

(f) The cell / tissue processing facility should be within the Hospital and under control of the hospital.

(C) <u>Who should have oversight over the treatment protocols or clinical indications being treated with cell / stem cell therapy.</u>

(1) <u>Institutional Ethics Committee</u> : Since cell / stem cell therapy is not yet a standard of care for most non hematological conditions but is a Clinical option, therefore, the following are mandatory:

(a) The hospital should have a *Institutional Ethics Committee* (IEC) or IRB (Institutional Review Board) that is registered with a Central / Federal Health Ministry. This IEC / IRB needs to approve all the treatment protocols and clinical indications for which the treatment can be offered. This is called oversight.

(b) <u>Written Informed consent</u> should be taken from the patient or family member / caretaker. Video documentation of the consent process should be done. Making a patient / caretaker just sign on a consent form without explaining the contents of the consent form is not considered real informed consent. In informed consent the following are mandatory and should be explained in a language that the family member/ patient is familiar with :-

(1) The nature , purpose , benefits and effects of the proposed procedure or treatment.

(2) The expected outcome and the likelihood of success.

(3) A detailed explanation of all possible risks.

(4) The alternatives to the procedure and supporting information regarding those alternatives.

(5) The effect of no treatment or procedure, including the effect on the prognosis and the material risks associated with no treatment.

(6) Also included should be instructions concerning what should be done if the procedure turns out to be harmful or unsuccessful.

(D) Peer Review of the Clinical Results of Safety & Efficacy

In a newly involving field like Regenerative Medicine, it is important that the clinical results and safety of the treatments at the center be Peer Reviewed. This means that someone outside of the institute should have evaluated the data and validated the clinical results, scientific content and ethical aspects of work being done. This is done when the hospital submits its data and results to a medical journal for publication. Before publishing any paper the journal's editor / editorial board and 2-3 independent reviewers evaluate the data and only after confirming the authenticity, scientific and ethical aspects do they publish. Amongst medical journals there are those of a higher standard which are referred to as PubMed indexed. So if a hospital has multiple scientific papers published in international or national medical journals and specially if these are in PubMed indexed medical journals then it can be said that the work being done there is Scientific and Ethical.

(E) Guidance to patients/caretakers on how to select a hospital for cell/stem cell therapy

(a) 1st find out whether the hospital is using allogenic, more than minimally manipulated stem cell derived products which are usually given intravenously, if so check whether the hospital has approval from country's FDA/other government regulatory body for use of the same.

(b) In the event the hospital is doing cell/stem cell procedures using autologous minimally manipulated cells in a surgical setting then you should ask the following questions:

1. Is the head of the clinical team a qualified specialist from the domain area for which you are seeking treatment?
   (For autism, cerebral palsy, stroke, etc it should be a neuro doctor, for OA, AVN, etc it should be an ortho doctor, for renal failure, etc it should be a nephro doctor, for cardiac failure, etc it should be a cardiac doctor, for infertility, etc it should be a gynac doctor and so on)
2. Does the hospital have a qualified doctor as head of the laboratory team?
3. Is the treatment being done in a hospital that is registered with the local government health authorities?
4. Does the cell/stem cell laboratory have a GLP/GMP certification?
5. Does the hospital have an Institutional Ethics Committee that is registered with the Health Ministry? Has this IEC given approval to the doctor/ hospital to treat the condition for which you are seeking treatment?
6. Does the hospital take written informed consent and offer you all the explanations of the procedure, its benefits and risks?

7. Has the hospital published the its own clinical results of safety and efficacy in PubMed indexed medical journals? What is the percentage of success and what are the risks of complications documented in their publications?
8. If the doctor or the hospital does not answer the above questions satisfactorily or have negative answers to the above then we suggest that you should look for an alternative hospital for treatment.

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