MALAYSIAN MEDICAL COUNCIL

STEM CELL RESEARCH & STEM CELL THERAPY

GUIDELINE OF THE MALAYSIAN MEDICAL COUNCIL

MMC Guideline 002/2009

PRELUDE

This Guideline complements, and should be read in conjunction with the Code of Professional Conduct of the Malaysian Medical Council (MMC).

In this Guideline, the words "doctor", "Physician", "medical practitioner" and "practitioner" are used interchangeably, and refer to any person registered as a medical practitioner under the Medical Act 1971. The words "hospital" and "healthcare Facility and service" are used interchangeably and refer to any premises in which members of the public receive healthcare services. Words denoting one gender shall include the other gender. Words denoting a singular number shall include the plural and vice versa.

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CONTENTS **PAGES**

1.	Introduction	4
2.	What are Stem Cells?	5
3.	Types of Stem Cells	5
4.	The Unique Properties and Potentials of Stem Cells	8
5.	Potential Use of Human Stem Cells and Obstacles to be overcome	8
6.	Facts that raise Ethical Issues	9
7.	Ethical Guidelines on Stem Cell Research	11
8.	Ethical Guidelines on Stem Cell Therapy	11
9.	Conclusions	13
10.	References	13
11.	Annexure A: MOH Guidelines for Stem Cell Research	14
12.	Annexure B: MOH Guidelines for Stem Cell Therapy	16

FOREWORD

The Malaysian Medical Council, with the objective of ensuring that registered medical practitioners are fully aware of the codes of professional medical practice, issues directives and guidelines from time to time. The purpose of these codes, guidelines and directive is to safeguard the patient and members of the public, to ensure propriety in professional practice and to prevent abuse of professional privileges.

The Guidelines are designed to complement, and should be read in conjunction with, the Medical Act and Regulations, Code of Professional Conduct of the Malaysian Medical Council and other Guidelines issued by the Council or any related organizations, as well as any statute or statutory provisions in force and all related statutory instruments or orders made pursuant thereto.

This Guidelines on the **Stem Cell Research & Stem Cell Therapy** has been prepared with careful attention to details, cognisant of the current international stand on the subject. The draft has been reviewed numerous times by the Malaysian Medical Council and includes valuable responses from individuals, organisations and professional bodies in the country, before formal adoption by the Council.

The Guidelines is available in the printed form as well as in the MMC website. Registered medical practitioners are advised to familiarise themselves with the contents, as they will serve as documents to refer to or to seek clarifications from, when they need guidance on matters of professional ethics, codes of professional conduct and medical practice in general.

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1. INTRODUCTION:

"Although there are many controversies surrounding stem cell research, the Ministry of Health recognises that it is crucial for local scientists and clinicians to be involved in stem cell research provided that these conform to ethical guidelines. It is vital for medical scientists to keep abreast of current advances in science, especially when there is an enormous potential of revolutionising therapy in the form of cell replacement therapy. Hence the Ministry of Health has set up a task force to readdress essential issues in stem cell research and consider the evolution of emerging therapies in this update of the guidelines." (Ministry of Health Guidelines on Stem Cell Research and Therapy, 2009)

Stem Cell Research and Therapy

Stem cell research is important to the future of medicine because with adequate research, stem cells have the potential to treat degenerative conditions by transplanting human stem cells into patients. Presently, many of these chronic conditions have no cure and are managed by treating the symptoms. While the initial cost of receiving stem cell therapy may be high, it has the potential to outweigh the lifelong costs incurred through daily medications and hospitalizations. By making disease management easier, the quality of life for those diagnosed with these diseases and their family members would be greatly increased.

Stem cell research is one of the most fascinating areas of contemporary biology, but, as with many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries.

Laboratory studies of stem cells enable scientists to learn about the cells' essential properties and what makes them different from specialized cell types. Research on stem cells continues to advance knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms.

Given their unique regenerative abilities, stem cells offer new potentials for treating diseases such as diabetes, and heart disease. However, much work remains to be done in the laboratory and the clinic to understand how to use these cells for cell-based therapies to treat disease.

Scientists are already using stem cells in the laboratory to screen new drugs and to develop model systems to study normal growth and identify the causes of birth defects.

Some stem cell researchers are working to develop techniques of isolating stem cells that are as potent as embryonic stem cells, but do not require a human embryo.

Stem Cell Therapy

Since stem cells have the ability to differentiate into any type of cell, they offer something in the development of medical treatments for a wide range of conditions. Treatments that have been proposed include treatment for physical trauma, degenerative conditions, and genetic diseases (in combination with gene therapy). Yet further treatments using stem cells could potentially be developed thanks to their ability to repair extensive tissue damage.

With sufficient development of stem cell therapy, chronic diseases such as diabetes, heart disease, and Parkinson's disease, multiple sclerosis, osteoarthritis as well as burns and spinal cord injuries may be more effectively managed. To realize the promise of novel cell-based therapies for such pervasive and debilitating diseases, scientists must be able to easily and reproducibly manipulate stem cells so that they possess the necessary characteristics for successful differentiation, transplantation and engraftment.

The following is a list of steps in successful cell-based treatments that scientists will have to learn to precisely control to bring such treatments to the clinic. To be useful for transplant purposes, stem cells must be reproducibly made to:

Proliferate extensively and generate sufficient quantities of tissue.
Differentiate into the desired cell type(s).
Survive in the recipient after transplantation.
Integrate into the surrounding tissue after transplantation.
Function appropriately for the duration of the recipient's life.
Avoid harming the recipient in any way.

To avoid the problem of immune rejection, scientists are experimenting with different research strategies to generate tissues that will not be rejected.

2. WHAT ARE STEM CELLS?

STEM CELLS have the remarkable potential (pluripotent) and capability to develop into many different cell types in the body during early life and growth, but cannot make extra-embryonic tissues such as the amnion, chorion, and other components of the placenta.

Pluripotency is demonstrated by allowing the cells to differentiate spontaneously in cell culture which will indicate stable developmental potential; manipulating the cells so they will differentiate to form cells characteristic of the three germ layers from single cell progeny and generating a benign teratoma after injection into an immuno-suppressed mouse so that scientists can observe growth and differentiation of the human stem cells.

Stem cells are important for living organisms for many reasons. In the 3- to 5-day-old embryo, called a **blastocyst,** the inner cells give rise to the entire body of the organism, including all of the many specialized cell types and organs such as the heart, lung, skin, sperm, eggs and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease, thereby serving as a sort of internal repair system.

3. TYPES OF STEM CELLS:

Stem cells from embryos of animal and humans, non-embryonic “adult” stem cells, and those from reprogrammed specialised cells, have been defined. In the ensuing paragraphs some characteristics are explained.

a. **Embryonic Stem Cells** were first derived from mouse embryos in 1981. It took two decades for scientists to learn how to develop human embryonic stem cells in the laboratory following the development of conditions for growing mouse stem cells.

b. **Human embryonic stem cells** (hESC), first described in1998, are pluripotent stem cells derived from human embryos and growth cells in the laboratory. They are *not* derived from eggs fertilized in a woman's body. These cells, in humans, are obtained from human embryo from the time of *in vitro* fertilisation (IVF) until the eighth week of the gestation when it becomes known as a foetus.

Human embryonic stem cells (hESC) can also be obtained by a method referred to as somatic cell nuclear transfer (SCNT), or therapeutic cloning, as described below.

The embryos from which human embryonic stem cells are derived are typically four or five days old and are a hollow microscopic ball of 30-150 cells called the blastocyst. The blastocyst includes three structures: the trophoblast, which is the layer of cells that surrounds the blastocoel, a hollow cavity inside the blastocyst; and the inner cell mass,

which is a group of cells at one end of the blastocoel that develop into the embryo proper. hESC is derived from the inner cell mass of the blastocyst.

It is now reported that the fluid surrounding the fetus contain stem cells, that, when utilized correctly, "can be differentiated towards cell types such as fat, bone, muscle, blood vessel, nerve and liver cells", according to the article. (Dr. Anthony Atala, Wake Forest University, 2007.

c. **Non-embryonic "somatic" or "adult" stem cells** are undifferentiated cells found in a differentiated tissue or organ that can renew itself and (with certain limitations) differentiate to yield some or all the specialised cell types of the tissue from which it originated.

The primary roles of adult stem cells in a living organism are to maintain and repair the tissue in which they are found. Scientists also use the term somatic stem cell instead of adult stem cell, where somatic refers to cells of the body (not the germ cells, sperm or eggs).

Scientists have found adult stem cells in many more tissues. In fact, adult hematopoietic, or blood-forming, stem cells from bone marrow have been used in transplants for 40 years. Scientists now have evidence that stem cells exist in the brain and the heart. If the differentiation of adult stem cells can be controlled in the laboratory, these cells may become the basis of transplantation-based therapies.

The history of research on adult stem cells began about 50 years ago. In the 1950s, researchers discovered that the bone marrow contains at least two kinds of stem cells. One population, called hematopoietic stem cells, forms all the types of blood cells in the body.
As indicated above, scientists have reported that adult stem cells occur in many tissues and that they enter normal **differentiation** pathways to form the specialized cell types of the tissue in which they reside.

In the normal differentiation pathways of adult stem cells in a living animal, adult stem cells are available to divide, when needed, and can give rise to mature cell types that have characteristic shapes and specialized structures and functions of a particular tissue. The following are examples of differentiation pathways of adult stem cells that have been demonstrated *in vitro* or *in vivo*.

Hematopoietic stem cells give rise to all the types of blood cells: red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes, and macrophages.

In many tissues, some types of stem cells are pericytes, cells that compose the outermost layer of small blood vessels. This finding has led researchers and clinicians to ask whether adult stem cells could be used for transplants.

Mesenchymal stem cells give rise to a variety of cell types: bone cells (osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes), and other kinds of connective tissue cells such as those in tendons.

Neural stem cells in the brain give rise to its three major cell types: nerve cells (neurons) and two categories of non-neuronal cells—astrocytes and oligodendrocytes.

Epithelial stem cells in the lining of the digestive tract occur in deep crypts and give rise to several cell types: absorptive cells, goblet cells, paneth cells, and entero-endocrine cells.

Skin stem cells occur in the basal layer of the epidermis and at the base of hair follicles. The epidermal stem cells give rise to keratinocytes, which migrate to the surface of the skin and form a protective layer. The follicular stem cells can give rise to both the

hair follicle and to the epidermis. Under certain growth and hormonal conditions skin cells have been successfully transformed into bone or muscle cells.

Umbilical cord blood has been shown to be abundant in stem cells and is recognised as a valid alternative to other sources of Haemopoietic progenitor cells for marrow replacement therapy. The implementation and management of cord blood banks has the potential to provide high quality cord blood units for treatment of patients in need of haemopoietic reconstruction. Because of the metabolic nature and long-term storage of stem cells, cord blood banking requires processes and procedures, which includes additional testing and a quality system to endure faultless traceability and viability of the cryopreserved cells to be stored for many years.

Transdifferentiation. A number of experiments have reported that certain adult stem cell types can differentiate into cell types seen in organs or tissues other than those expected from the cells' predicted lineage (i.e., brain stem cells that differentiate into blood cells or blood-forming cells that differentiate into cardiac muscle cells, and so forth). This reported phenomenon is called transdifferentiation.

d. **Induced pluripotent stem cells (iPSCs)**, in which specialised adult cells are reprogrammed genetically (through introduction of embryonic genes) to assume stem cell-like attributes by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells. This technique has been developed since 2006.

By this technique, a source of cells can be generated that are specific to the donor, thereby avoiding issues of histocompatibility, if such cells were to be used for tissue regeneration. However, like embryonic stem cells, determination of the methods by which iPSCs can be completely and reproducibly committed to appropriate cell lineages is still under investigation.

However, iPSCs are already useful tools for drug development and modeling of diseases, and scientists hope to use them in transplantation medicine. Viruses are currently used to introduce the reprogramming factors into adult cells, and this process must be carefully controlled and tested before the technique can lead to useful treatments for humans. In animal studies, the virus used to introduce the stem cell factors sometimes causes cancers.

The iPSC strategy creates pluripotent stem cells that, together with studies of other types of pluripotent stem cells, will help researchers learn how to reprogram cells to repair damaged tissues in the human body.

e. **Non-human, adult animal stem cells** which are used in xenotransplanta-tion or xenografting between organ, tissue or cells different species. The use in human subjects raises many ethical, societal and religious implications.
Animal stem cells are (and tissues or organs) retrieved from animals, or, human body fluids, cells, (tissues or organs) that have undergone ex vivo contact with live non-human animal cells, tissues or organs."
Xenotransplantation is any procedure that involves the transplantation, implantation, or infusion into a human recipient of such cells.
Inbred rabbit foetuses are the precursor animal source for the preparation of stem cell transplants, and it is claimed that such cells are equally effective and safe as human embryonic stem cells, without the implications of "moral, ethical and religious" issues. It is claimed that such treatment can be given for a variety of conditions including Down's syndrome, cerebral palsy, autism, diabetes, hormone deficiency disorders, early menopause, infertility, immune deficiency disorders e.g. AIDS, cancer and autoimmune diseases, impotence, depression, liver, renal, pulmonary and cardiovascular diseases. (E Michael Molnar, Stem Cell Transplantation. Medical and Engineering Publishers, Inc. USA, Korea. 2006)
There need be no objection in principle to research in cross-species experimentation and research per se. Xenografting and xenotransplan-tation raise ethical and religious

concerns, and at this stage the principle of voluntary agreement to treatment would not apply and cross-species therapy is not advisable.

4. THE UNIQUE PROPERTIES AND POTENTIAL OF ALL STEM CELLS:

Important Characteristics

Stem cells are distinguished from other cell types by three important characteristics.

a. ***They are unspecialized cells***. One of the fundamental properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialized functions. For example, a stem cell cannot work with its neighbors to pump blood through the body (like a heart muscle cell), and it cannot carry oxygen molecules through the bloodstream (like a red blood cell). However, unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells.
b. ***They are capable of renewing themselves*** through cell division, sometimes after long periods of inactivity.
c. ***They can be induced to become tissue- or organ-specific cells* (*specialised cells) with special functions under certain physiologic or experimental conditions***. In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues. In other organs, however, such as the pancreas and the heart, stem cells only divide under special conditions.

Through a process called **differentiation**, the cell usually goes through several stages, becoming more specialized at each step. Scientists are just beginning to understand the signals inside and outside cells that trigger each stem of the differentiation process. The internal signals are controlled by a cell's genes, which are interspersed across long strands of DNA, and carry coded instructions for all cellular structures and functions. The external signals for cell differentiation include chemicals secreted by other cells, physical contact with neighboring cells, and certain molecules in the microenvironment. The interaction of signals during differentiation causes the cell's DNA to acquire epigenetic marks that restrict DNA expression in the cell and can be passed on through cell division.

Unlike muscle cells, blood cells, or nerve cells—which do not normally replicate themselves—stem cells may replicate many times, or proliferate. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. If the resulting cells continue to be unspecialized, like the parent stem cells, the cells are said to be capable of **long-term self-renewal.**

5. THE POTENTIAL USES OF HUMAN STEM CELLS AND THE OBSTACLES TO BE OVERCOME:

There are many ways in which human stem cells can be used in research and the clinic. Studies of **human embryonic stem cells** will yield information about the complex events that occur during human development. A primary goal of this work is to identify how **undifferentiated** stem cells become the differentiated cells that form the tissues and organs.

Scientists know that turning **genes** on and off is central to this process. Some of the most serious medical conditions, such as cancer and birth defects, are due to abnormal **cell division** and **differentiation**. A more complete understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapy.

The availability of differentiated cells generated from pluripotent human stem cell lines would allow testing for new drugs in a wider range of cell types, including cancer cell lines to screen potential anti-tumour drugs. However, to screen drugs effectively, the conditions must be identical when comparing different drugs. Therefore, scientists will have to be able to precisely control the differentiation of stem cells into the specific cell type on which drugs will be tested. Current knowledge of the signals controlling differentiation falls short of being able to mimic these conditions precisely to generate pure populations of differentiated cells for each drug being tested.

Perhaps the most important potential application of human stem cells is the generation of cells and tissues that could be used for **cell-based therapies**. Today, donated organs and tissues are often used to replace ailing or destroyed tissue, but the need for transplantable tissues and organs far outweighs the available supply. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including

Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis.
For example, it may become possible to generate healthy heart muscle cells in the laboratory and then transplant those cells into patients with chronic heart disease. Preliminary research indicates that bone marrow stromal cells, transplanted into a damaged heart, can have beneficial effects. Whether these cells can generate heart muscle cells or stimulate the growth of new blood vessels that repopulate the heart tissue, or help via some other mechanism is actively under investigation. For example, injected cells may accomplish repair by secreting growth factors, rather than actually incorporating into the heart.
To summarize, stem cells offer exciting promise for future therapies, but significant technical hurdles remain that will only be overcome through years of intensive research.

6. FACTS THAT RAISE ETHICAL ISSUES:

The **stem cell controversy** is the ethical debate centered on research involving the creation, usage and destruction of human embryonic stem cells. Not all stem cell research involves the creation, usage and destruction of human embryos. Extraction of such cells using current technology research represents a social, religious and ethical challenge.

The status of the human embryo and human embryonic stem cell research is a controversial issue as, with the present state of technology, the creation of a human embryonic stem cell line requires the destruction of a human embryo. Stem cell debates have motivated and reinvigorated the pro-life movement, whose members are concerned with the rights and status of the embryo as an early-aged human life.
Some of the major concerns and controversies are discussed below.

Major Ethical Issues

Producing stem cells for commercial purposes

a. Embryonic stem cell lines generated through cultures are said to be 'immortalised'; that is, they can be maintained essentially indefinitely as they express telomerase, one of the factors necessary for cells to propagate normally. At any stage in the process, batches of cells can be frozen and shipped to other laboratories for further culture and experimentation. This would imply producing stem cells for commercial purposes.
b. Sale and commercial supply of stem cells should preferably be disallowed, in favour of some system of distribution that recognises and evaluates the clinical and research intentions of prospective users.

Unused embryos from fertility treatments for research

a. A portion of stem cell researchers use embryos that were **created but not used** *in vitro* fertility treatments to derive new stem cell lines. Most of these embryos are to be destroyed, or stored for long periods of time, long past their viable storage life. In the United States alone, there have been estimates of at least 400,000 such embryos. Embryos from fertility treatment can ethically be used whenever there is no prospect of such embryo ever developing to term.

Non-therapeutic use of stem cells

a. Stem cell research also prompts consideration of the potential non-therapeutic use of biomedical techniques, which might also include cloning, genetic modification, and artificial fertilization. These techniques allow the power to intervene actively in the physical creation, maintenance, alteration or repair of humans. Ethical objections about the propriety of interfering with the creation or modification of people are upheld.

Stem cells from aborted foetus

a. Ethically, stem cells from aborted foetuses could be used, but practically are not an ideal source.

Creating embryos for research

a. It is neither necessary nor ethically desirable to create embryos for research or as a source of stem cells.

The use of stem cells for unproven indications

a. With the influx and establishment of many private companies dealing with cell-based therapies in Malaysia, the marketing of stem cells for unproven therapies is a major issue and needs to be controlled. Medical practitioners must particularly be aware of the ethical issues involved in such therapies which are still in the research and experimentation stages. Medical practitioners involved in such practises may be subject to disciplinary procedures.

Are Embryos 'Human'?

a. The fundamental assertion of those who oppose embryonic stem cell research is the belief that human life is inviolable, combined with the fact that human life begins when a sperm cell fertilizes an egg cell to form a single cell. Therefore a human embryo is equivalent to a human being.

b. The deliberate destruction of a human embryo is typically interpreted as being incompatible with religious doctrine. Based upon these interpretations, it has been suggested that human blastocysts are inherently valuable and should not be voluntarily destroyed.

c. Acceptability of the use of human embryo tissue for stem cell supply is therefore controversial. The ethical issues are centred on the question of whether or not human embryos can be regarded as disposable for benevolent purposes. An embryo used for the sake of its stem cell tissue is not able to develop to term and a potential human being is denied existence.

d. The argument is that during the natural reproductive process human eggs often fertilise, but more than a third of the zygotes fail to implant in the uterus. Thus, far more embryos are lost due to chance than are proposed to be used for embryonic stem cell research or treatments.

While a fertilized egg has the potential to form a human life, it is not equal to a human being until it has at least successfully implanted in a woman's uterus. They are incapable of surviving outside the womb (i.e. they only have the potential for life).

e. There is also the opinion that embryos even when implanted in the uterus are not humans, on the belief that the life *of Homo sapiens* only begins when the heartbeat develops, which is during the 5th week of pregnancy, or when the brain begins developing activity, which has been detected at 54 days after conception.

In Islam, a foetus is ensouled at 120 days (about 17 weeks), after which the conception is considered to possess the qualities of a human being.

f. Before the primitive streak is formed when the embryo attaches to the uterus at approximately 14 days after fertilization, a single fertilized egg can split in two to form identical twins, or a pair of embryos that would have resulted in fraternal twins can fuse together and develop into one person (a tetragametic chimera). Since a fertilized egg has the potential to be two individuals or half of one, some believe it can only be considered a *potential* person, not an actual one.

Those who subscribe to this belief then hold that destroying a blastocyst for embryonic stem cells is ethical, and that blastocysts are a cluster of human cells that have not differentiated into distinct organ tissue; making cells of the inner cell mass no more "human" than a skin cell.

g. **Viability** is another standard under which embryos and fetuses have been regarded as human lives. In the United States, the 1973 Supreme Court case of Roe v. Wade concluded that viability determined the permissibility of abortions performed for reasons other than the protection of the woman's health, defining *viability* as the point at which a fetus is "potentially able to live outside the mother's womb, albeit with artificial aid The point of viability was 24 to 28 weeks when the case was decided and has since moved to about 22 weeks due to advancement in medical technology.

7. ETHICAL GUIDELINES ON STEM CELL RESEARCH:

a. The following guidelines relate to the ethics of Research on Stem Cells

i. All experiments and clinical trials involving stem cells must be based on a solid foundation of basic scientific and animal experimentation and carried out with the highest medical and ethical standards.
ii. Research on human adult stem cell is allowed.
iii. Research on stem cells derived from foetal tissues from legally performed termination of pregnancy is allowed.
iv. Research on non-human stem cells is allowed.
v. Use of embryonic stem cell lines for research purposes is allowed
vi. Research on embryonic stem cells derived from surplus embryos is allowed.

b. Research that shall not be permitted at this time:

i. The creation of human embryos by any means including but not limited to assisted reproductive technology (ART) or somatic cell nuclear transfer (SCNT) specifically for the purpose of scientific research is prohibited.
ii. Research involving *in vitro* culture of any intact human embryo, regardless of derivation method, for longer than 14 days or until formation of the primitive streak begins, whichever occurs first.
iii. Research in which HES cells are introduced into non-human primate blastocysts or in which any ES cells are introduced into human blastocysts.
iv. No animal into which HES cells have been introduced at any stage of development should be allowed to breed.
v. Fusion of human stem cell or other cells of pluripotent nature with cells of non-human origin, shall not be permitted to develop beyond 14 days, or until the formation of the primitive streak begins, whichever occurs first.

8. ETHICAL GUIDELINES ON STEM CELL THERAPY:

Background

Many of the therapies involving stem cells, embryonic or adult, as indicated above, are currently experimental and are in the realm of research. It is therefore vital that permission be obtained for these therapies from the Ministry of Health according to the MOH Guidelines which are annexed to this MMC Guidelines. The procedures to be followed are also clearly laid down in the MOH Guidelines and should be strictly complied with.

Guidelines on Cord Blood Banking, Haemotopoietic Stem Cell Therapy and Stem Cell Research and Therapy are also available from the Medical Development Division of the Ministry of Health.

Stem cell/ cell-based therapies

a. Standards:

i. Haemopoietic stem cell (HSC) and umbilical cord stem cell transplantations are the most established form of stem cell therapy. The current indications for HSC therapy (HSCT) are listed in the National Guidelines for Haemopoietic Stem Cell Therapy,2009, and in the National Standards for Cord Blood Banking and Transplantation, 2008
ii. A registered medical practitioner, with training and experience in immuno-genetics or transplantation, basic or clinical immunology, immuno-haematology, blood or tissue banking, or cryobiology, shall be the director of a Cord Blood Bank (CBB), whether in a public or private facility. The CBB Director has the final responsibility for the CBB's scientific and clinical performance and overall compliance with the standards and structure

required of such CBB, as laid down by the Ministry of Health Malaysia. (National Standards for Cord Blood Banking and Transplantation, MOH, 2008)

iii. Any treatment involving stem cells shall only be carried out by a registered medical practitioner, who will be required to comply with the Guidelines issued by the Ministry of Health Malaysia and the Code of Professional Conduct and related Guidelines, of the Malaysian Medical Council, and all related statutes of Malaysia including the Private Healthcare Facilities and Services 1998 and the Regulations 2006.

b. Potential/development/experimental

The following applications shall either be at the in vitro, animal studies or clinical trial settings:-

i. The use of HSC, HSC-derived cells and umbilical cord stem cells in tissue repair, regeneration and vascularisation shall be considered developmental.
ii. (b) HSC has shown potential in chronic inflammatory diseases, graft rejection and graft versus disease (GVHD) and shall be done in research settings.
iii. The use of other types of stem cells e.g. neural stem cells in Parkinson's disease, cardiac stem cells, hepatic stem cells, pancreatic stem cells, skeletal-muscle stem cell, stem cells of skin, lungs, retinal and intestinal epithelium as well as inducible pluripotent stem cells are still experimental.
iv. Cell-based therapies e.g. antigen-specific T- cells and dendritic cells shall be done in research settings.
v. Gene therapy to correct genetic disorder e.g. subacute combined immune deficiency disorders (SCID) and thalassaemia is still in developmental phase. The use of lentiviral shall be carried out in a P3 laboratory.
vi. All other indications not listed in as standard or established shall be considered experimental and must first be approved by the institutional review board (IRB) and/or institutional ethics committee. Copies of the proposal must also be submitted to the National Stem Cell Research and Ethics (NSCRE) sub-committees.

c. Therapy using human embryonic stem cells (hESC)

The use of hESC for therapy shall be considered experimental.

d. Xenotransplantation

i. Xenotransplantation or therapy involving the use of animal stem cells or animal tissue is prohibited.

ii. Xenotransplantation involving stem cells/cells e.g. islet cells for tissue repair and regeneration shall not be performed until more scientific and clinical evidence is obtained.

iii. Rejection and the risks of transmission of infectious diseases have not been adequately dealt with.

iv. Clinical trials shall occur only when there are preclinical data indicating a high probability of benefit to the recipients and data on safety.

v. Any clinical xenotransplantation shall only be approved by the National Stem Cell Research and Ethics (NSCRE) sub-committees.

e. Private Stem Cell Laboratories

Emerging industry interest in stem cell transplantation has resulted in private stem cell laboratories which collect, process and generate human adult stem cells from peripheral blood, bone marrow and cord blood, and make them available for therapy.

Such laboratories must comply with all existing regulations and guidelines and be under the supervision and control of a registered medical practitioner who will be totally liable for all operational activities involved in such processes.

f. Centres involved in Transplant Programmes

Centres performing Human Stem Cell Therapy (HSCT) shall establish policies, procedures and protocols as well as quality management systems and shall seek accreditation with the National Stem Cell Research and Ethics Sub-Committee, Ministry of Health.

The Guidelines for Stem Cell Research and Therapy (MOH, July 2009) must be strictly adhered to.

The Person-in-Charge of such centres as well as the specialist involved in the transplant procedure shall be registered medical practitioners, and both shalll be liable for all such procedures and their outcome.

9. CONCLUSIONS

While the untapped possibilities leave many members of the medical research community excited, there are numerous obstacles that may impede human stem cell research and therapy.

While issues such as morality, ethical, social, legal, funding, and national regulations may impede scientists across the world from pursuing research possibilities related to gene therapy and stem cell research, these are necessary at the present time because of the evolving state of such research, experimentation and possible therapeutic value, as well as abuse.

Ethical and social issues arise to some extent whenever scientific research is carried out, because the outcome affects people. In particular, such issues arise in biomedical research because the interests of potential beneficiaries may compete with, and may have to be considered together with costs to society or to individuals, such as donors.

Registered medical practitioners have obligations to individual patients, and therapeutic or preventive application of research findings has to be moderated on a case by case basis, such that there is a clear and identifiable benefit and no important general principle is contravened.

At the present time, any research or therapeutic proposals shall only be approved by the National Stem Cell Research and Ethics (NSCRE) sub-committees of the Ministry of Health Malaysia.

In all instances and circumstances governing, collecting, conducting, researching and experimenting, or treating patients with stem cells, the Code of Professional Conduct and other related guidelines of the Malaysian Medical Council, including Guidelines on Competency and Practice and to Establish Monitoring Mechanisms for Highly Specialised Procedures, 2008, and all related statutes, shall be strictly complied with.

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ANNEXURE A

MOH Guidelines for <u>Stem Cell Research</u>

1. The Ministry of Health will undertake to encourage and promote stem cell research in Malaysia.

1. All stem cell research and applications must be reviewed by the respective Institutional Review Board (IRB) and/or the Institutional Ethics Committee (IEB) for approval to ensure ethical research and use of stem cell. The IRB and IEC must strictly adhere to the National Guidelines for Stem Cell Research and Therapy.

2. A copy of all research proposals must be submitted to **the National Stem Cell Research and Ethics Sub-Committee** which shall retain the rights to review any research proposal as and when required.

3. All experiments and clinical trials involving stem cells must be based on a solid foundation of basic scientific and animal experimentation and carried out with the highest medical and ethical standards.

5. Permitted Research:

   a. Research on human adult stem cells is allowed.
   b. Research on stem cells derived from foetal tissues from legally performed termination of pregnancy is allowed.
   c. Research on non-human stem cells is allowed.
   d. Use of embryonic stem cell lines for research purposes is allowed.
   e. Research on embryonic stem cells derived from surplus embryos is allowed. (*Keputusan Muzakarah Jawatankuasa Fatwa Majlis Kebangsaan Bagi Hal Ehwal Agama Islam Malaysia berkaitan Pengklonan dan ART* dated 22 February 2005).

6. The creation of human embryos by any means including but not limited to assisted reproductive technology (ART) or somatic cell nuclear transfer (SCNT) specifically for the purpose of scientific research is prohibited.

7. To facilitate autonomous choice and avoid conflict of interest, decisions related to the production of embryos for infertility treatment should be free of the influence of investigators who propose to derive or use hES cells in research. Whenever it is practicable, the attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hES cells should not be the same person.

8. No cash or in-kind payment may be provided for donating blastocysts in excess of clinical need for research purposes.

9. Consent for Blastocyst Donation

   Consent for blastocyst donation should be obtained from each donor at the time of donation. Donors who have given prior indication of their intent to donate for research any excess blastocysts that remain after clinical care should nonetheless give informed consent again when any specific research is being considered. Donors should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.

10. Consent for Donation of Gametes or Blastocyst for Research

In the context of donation of gametes or blastocysts for human embryonic stem (hES) cell research, the informed consent process should include the following information:-

a. A statement that the blastocysts or gametes will be used to derived hES cells for research that may include research on human transplantation.

b. A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous donation.

c. A statement as whether the identities of the donors will be readily ascertainable to those who derived, except in the case of autologous donation.

d. If the identities of the donors are retained (even if coded), a statement as to whether donors wish to be contacted in the future to receive information obtained through studies of the cell lines.

e. An assurance that participants in research projects will follow applicable and appropriate best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of the stem cells. (Traceable information, however, must be secured to ensure confidentiality)

f. A statement that derived hES cells and/or cells lines might be kept for many years.

g. A statement that the research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation.

h. A statement that embryos will be destroyed in the process of deriving hES cells.

i. A statement that neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potentially donors.

j. A statement of risks involved to the donor.

11. **Research that should not be permitted at this time:**

a. The creation of human embryos by any means including but not limited to assisted reproductive technology (ART) or somatic cell nuclear transfer (SCNT) specifically for the purpose of scientific research is prohibited.
b. Research involving *in vitro* culture of any intact human embryo, regardless of derivation method, for longer than 14 days or until formation of the primitive streak begins, whichever occurs first.
c. Research in which HES cells are introduced into non-human primate blastocysts or in which any ES cells are introduced into human blastocysts.

d. No animal into which HES cells have been introduced at any stage of development should be allowed to breed.

e. Fusion of human stem cell or other cells of pluripotent nature with cells of non-human origin, shall not be permitted to develop beyond 14 days, or until the formation of the primitive streak begins, whichever occurs first.

12. Laboratory requirements:

a. Laboratories conducting stem cell research shall conform to required guidelines for good laboratory practices.

b. All laboratories conducting stem cell research for the purpose of clinical trials shall be Good Manufacturing Practice (GMP) compliant as required by the National Pharmaceutical Control Board (NPCB).

c. All laboratories producing stem cells or tissue products for commercial/ manufacturing purposes shall be certified as Good Manufacturing Practice (GMP) compliant by the NPCB.

13. All imported stem cells/tissue products for use in clinical trials and therapy shall be GMP certified and registered by the NPCB.

14. Procurement, management, storage and disposal of stem cells and tissues used in research and clinical trials must be in accordance with the national guidelines.

15. Therapeutic outcomes, adverse effects and tissue integration shall be documented or reported to the National Stem Cell Research and Ethics Sub-committee, Ministry of Health.

ANNEXURE B

Guidelines for <u>Stem Cell Therapy</u>

1. Background:

Haemopoietic stem cell and umbilical cord stem cell transplantations are the most established forms of stem cell therapy. The use of other stem cells including human Embryonic Stem Cell (hES) and adult somatic stem cells is considered experimental. Xenotransplantation or therapy involving the use of animal stem cells or animal cells is currently prohibited.

2. Indications for stem cell/ cell-based therapies:

Standard/established

a. The current indications for HSC therapy (HSCT) are listed in the National Guidelines for Haemopoietic Stem Cell Therapy, and are as follows:

b. HSCT is currently performed for malignant and non-malignant haemotolo-gical conditions, solid organ tumours, inherited metabolic and primary immunodeficiency diseases. The list of standard indications is not exhaustive and will continue to expand.

c. Indications which are experimental include tissue repair, angiogenesis and revascularization shall be studied as clinical trials until more evidence is obtained. Ethics review and approval shall be obtained from the relevant authorities in local institutions. This shall conform to the National Guidelines for Stem Cell Research and Therapeutics.

d. Reduced intensity transplants are recommended for high risk candidate who are deemed not suitable for conventional transplants, e.g. elderly patients and those with comorbidities.

3. Potential/development/experimental

The following applications shall either be at the in vitro, animal studies or clinical trial settings:-

a. The use of HSC, HSC-derived cells and umbilical cord stem cells in tissue repair, regeneration and vascularisation shall be considered developmental.

b. Mesenchymal Stem Cell (MSC) has shown potential in chronic inflammatory diseases, graft rejection and graft versus host disease (GVHD) and shall be done in research settings.

c. The use of other types of stem cells e.g. neural stem cells in Parkinson's disease, cardiac stem cells, hepatic stem cells, pancreatic stem cells, skeletal-muscle stem cell, stem cells of skin, lungs, retinal and intestinal epithelium as well as inducible pluripotent stem cells are still experimental.

d. Cell-based therapies e.g. antigen-specific T- cells and dendritic cells shall be done in research settings.

e. Gene therapy to correct genetic disorder e.g. subacute combined immune deficiency disorders (SCID) and thalassaemia is still in developmental phase.

f. All other All other indications not listed in as standard or established shall be considered experimental and must first be approved by the institutional review board (IRB) and/or institutional ethics committee. Copies of the proposal must also be submitted to the NSCRE sub-committee.

g. The use of human Embryonic Stem Cell (hESC) for therapy shall be considered experimental.

4. Xenotransplantation

a. Xenotransplantation involving stem cells/cells e.g. islet cells for tissue repair and regeneration shall not be performed until more scientific and clinical evidence is obtained.
b. Rejection and the risks of transmission of infectious diseases have not been adequately dealt with.
c. Clinical trials shall occur only when there are preclinical data indicating a high probability of benefit to the recipients and data on safety.
d. Xenotransplantation or therapy involving the use of animal stem cells or animal cells is currently prohibited.
e. Any clinical xenotransplantation shall only be approved by the NSCRE sub-committee.

5. Patient evaluation

The National Guidelines for Haemopoietic Stem Cell Therapy lists out the steps which shall be followed for patient evaluation.

6. Regulation and Standards

a. Registered medical practitioners intending to perform or performing stem cell or cell based therapies may also do so in Private healthcare facilities and services which shall be licensed under the Private Healthcare Facilities and Services Act 1998 for such purposes.

b. It is recommended that these centres perform internal and external audits to ensure quality, viability, purity, safety, reproducibility and efficacy of the end-products.

c. The procurement and processing of stem cells shall comply with the National Standards of Procurement and Processing of stem cells.

d. Laboratories performing gene therapy research involving the use of viral vectors shall comply with Biosafety Level 3 (Medical laboratories).

e. Personnel performing stem cell transplants shall be adequately trained and proficient and shall acquire privileging status from the respective institutions.