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KETUA PENGARAH KESIHATAN MALAYSIA
DIRECTOR GENERAL OF HEALTH MALAYSIA

Kementerian Kesihatan Malaysia,
Aras 12, Blok E7, Parcel E,
Pusat Pentadbiran Kerajaan Persekutuan,
62590 Putrajaya.

Tel : 603-88832545
Faks : 603-88895542
E-mail : ismailmerican@moh.gov.my

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5 Disember 2006

Pengarah Kesihatan Negeri
Jabatan Kesihatan Negeri .....

Pengarah
Institut Penyelidikan Perubatan
Jalan Pahang
50588 Kuala Lumpur.

Dekan
Fakulti Perubatan .....

Presiden
Persatuan Hospital-Hospital Swasta Malaysia.

Y.Bhg. Datuk/Tuan/Puan,

GUIDELINES ON STEM CELL RESEARCH MINISTRY OF HEALTH

Dengan hormatnya saya merujuk kepada perkara di atas.

2. Bersama-sama ini disertakan buku ***"Guidelines On Stem Cell Research, Ministry of Health"*** yang telah disediakan oleh Bahagian Perkembangan Perubatan, Kementerian Kesihatan Malaysia.

3. Garispanduan ini disediakan supaya dapat dijadikan panduan kepada pengamal-pengamal perubatan di hospital-hospital kerajaan dan juga swasta, agar penyelidikan *stem cell* ini dapat dijalankan secara beretika dan mengikut perundangan yang telah ditetapkan. Dengan penyediaan garispanduan ini, Kementerian Kesihatan Malaysia berharap akan dapat meningkatkan mutu penyelidikan dalam bidang *stem cell* dan membantu penyelidik-penyelidik menggunakan kemudahan-kemudahan yang tersedia ada melalui peraturan-peraturan digariskan agar hasil penyelidikan tersebut dapat memberi manfaat kepada orang ramai dan kepada pesakit-pesakit khususnya.

Sekian, terima kasih.

' BERKHIDMAT UNTUK NEGARA '

TAN SRI DATUK DR. HJ. MOHD ISMAIL MERICAN
Ketua Pengarah Kesihatan Malaysia.

What is Stem Cell?

1 Introduction

In the recent years, stem cell biology and stem cell research has captured both the scientific and international news headlines. It is universally agreed that there is an enormous potential in this area with the numerous clinical applications. Simultaneously, discussions and debates regarding the ethical issues have also been widespread.

The Ministry of Health of Malaysia has realized that despite the current controversies surrounding stem cell research, it is also crucial for the local scientists and clinicians to be involved in stem cell research at least within the existing ethical guidelines that have to be agreed upon. It is also vital for us to keep abreast of current advances in science, especially so when there's an enormous potential of revolutionizing therapy in the form of cell replacement therapy. Hence, the MOH has decided to setup a task force to address vital issues in stem cell research and come up with a consensus on this area.

1.1 What is a stem cell?

A stem cell is a cell that has the ability to divide *(self-replicate)* for indefinite periods often throughout the life of the organism. Under the right conditions, given the right signals and growth factors, stem cells can give rise *(differentiate)* to the many different cell types that make up the organism. Hence, stem cells have the potential to develop into mature cells that have characteristic shapes and specialized functions, such as heart cells, skin cells, or nerve cells.

1.2 The status of stem cell research in Malaysia

Stem cell research is relatively new in Malaysia. Most of the work thus far has involved haemopoietic stem cells *(bone marrow, peripheral blood and cord blood)*. As these are from adult tissues, the ethical concerns are minimal as they are being used in the setting of haemopoietic stem cell transplantation. As these are already standard therapies, there are very little ethical concerns. The use of sources of stem cells other than the adult stem cells e.g. cell lines or fertilized embryos is a major concern as it is likely that our local researchers would soon be conducting research in this area.

2 Background on stem cells

During normal human embryogenesis, the totipotent fertilized egg differentiates into a wide variety of cell types that form the adult organs. Many mature organs, including the bone marrow, skin, and small intestine, maintain a pool of undifferentiated stem cells, which are capable of both self-renewal and of differentiating into at least 1 or more mature cell types. It is hence possible to regenerate damage or senescent cells throughout life.

The pluripotent stem cell was first recognized in teratocarcinomas. These are bizarre gonadal cancers containing a wide array of tissues derived from the three primary germ cell layers that constitute the embryo i.e. the endoderm, mesoderm and ectoderm. Hence, these tumors may contain a large assortment of tissues including cartilage, muscle, bones, hairs, teeth or even an eye. The differentiated cells of the tumour are formed from pluripotent EC cells present in the tumour. Cultured EC cell lines are derived by isolating EC cells from tumours and growing them *in vitro.*

Stem cells have been exploited for therapeutic purposes for more than 40 years. One such application is the use of haemopoietic stem cell transplantation for the treatment of certain haemopoietic and non-haemopoietic malignancies. The application and usefulness of stem cell transplantation has been limited by the fact that many other organs *(brain, spinal cord, heart, kidney, pancreas)* were thought to lack detectable stem cells. It was also believed that cells from one organ could not be reprogrammed to differentiate into different cell lineages during adulthood.

The premise of utilizing stem cells as a form of cell replacement therapy is an attractive one. A simplistic vision is of course to be able to culture the stem cells, induce them to differentiate into specific lineage (brain cells, pancreatic cells, kidney cells, etc) and eventually perhaps into a fully functioning organ which can replace a defective organ or degenerative cells.

Recent discoveries have revolutionized stem cell biology and have demonstrated the clinical potential of these cells in a wide range of human diseases:-

1. Stem cells have been detected in organs such as brain and muscle, which previously was thought to lack stem cells and regenerative potential.

2. Organ specific adult stem cells appear to display much more plasticity than originally thought meaning that stem cells isolated from one tissue are able to differentiate into a variety of unrelated cell types and tissues. For example, it has been shown in animal experiments that neural stem cells can differentiate into haemopoietic lineages.

   Similarly, haemopoietic stem cells can differentiate into several non-haemopoietic cell types including skeletal muscle. Studies in post transplant patients have shown the presence of donor's cells in the heart and liver of the recipient, implying that the haemopoietic stem cells not only regenerate or repopulate the marrow but also play a role in the regeneration of non-haemopoietic tissues.

3. Human embryonic stem cells can be isolated from early fetuses and made to differentiate in vitro into a wide variety of cell types. Embryonic stem cells are totipotent cells derived from the inner cell mass oan early stage fertilized embryo. Under appropriate tissue culture conditions, embryonic stem cells have the capacity for unlimited replication while maintaining totipotency, and when reimplanted into a blastocyst, such cultured stem cells can contribute to all the organs of the resulting adult animal.

3 Potential Applications

3.1 Cell replacement therapy

As the pluripotent stem cells can be expanded indefinitely in culture, maintain a normal karyotype and have the potential to generate into any cell type in the body, they provide an incredible and invaluable resource for the repair of diseased or damaged tissues in our bodies.

Pluripotent stem cell differentiation has been typically been directed by manipulating their environment by trial and error. This is achieved by growing stem cells at high density, growing them on different types of feeder cells and by addition of growth factors.

For example, pancreatic cells for use in patients with insulin-dependent diabetes mellitus, liver cells for those with liver failure, or even neural cells for those with degenerative disease of the brain including Parkinson's disease, multiple sclerosis and stroke.

3.2 Gene therapy of stem cells

Gene therapy for stem cells can be used to correct genetic disorders. For example, gene therapy for patients with severe combined immunodeficiency (SCID) has already been shown to be successful albeit in a small group of patients. Certain genes, for example the gene for multi-drug resistance, may also be inserted into stem cells to make them less susceptible to cytotoxic agents.

3.3 Whole organ replacement

Cells can now be differentiated into various tissues. Researchers are now optimizing the process of proliferation and differentiation of these cells. In addition, the use of 3-dimensional cell culture technology will allow cells to form a 3-dimensional formation for the creation of specific organs.

4 Sources of stem cells

4.1 Adult stem cells

These somatic stem cells are derived from bone marrow, peripheral blood or placental cord blood. Such cells have several advantages including avoidance of ethical and religious implications.

4.2 Embryonic stem cells

These are derived from 3 sources

(i) *Embryonic carcinoma (EC) cells*
As mentioned above, these are derived from germ cell tumours where EC cells are isolated from the tumours and are then grown in medium containing serum.

(ii) Embryonic stem (ES) cells derived from pre-implantation embryos
These are obtained from the pluripotent inner cell mass (ICM) cells of pre-implantation, blastocyst stage embryo. Couples undergoing IVF treatment often have embryos that they longer need. These embryos can either be allowed to die, donated to another couple or donating them for research.

(iii) Embryonic germ (EG) cells derived from primordial germ cells of the post-implantation embryo.

These are derived from primordial germ cells (PGCs) of the post-implantation embryo.

Although EC, ES and EG cell lines have been isolated from mice and primates, only ES cells have been isolated from non-human primates.

5

Ethical considerations

Stem cell therapies raise many difficult and important ethical issues and concerns. These are expected for any new approaches or new therapies involving human experimentation. In addition stem cell research involves unique and specific genetic and cellular methods for manipulation as well as applications. There are still ongoing debates on this and whilst consensus has been reached in some areas, others are still controversial. The following are some of the issues raised :-

1. The source of stem cell is a major ethical concern. The use of embryos is generally not agreed upon especially when fertilization is performed for the sole use of stem cell research. However, the use of leftover embryos from in vitro fertilization techniques is still being debated.

2. For those who believe that the human embryo, even at the one-cell stage, having absolute moral value, equal to that of a newborn baby or and adult, any embryo research is ethically unacceptable, as it tantamount to murder.

3. The early embryo could be regarded as having a symbolic moral value, as a potential human being, and therefore worthy of respect, but in judging whether or not embryo research is ethical or not, the stage of development and the objective of the research must be taken into consideration. From the Islamic point of view, the stage of ensoulment has to be taken into account as well. For this, there are two schools of thought i.e. most of the jurists have agreed that ensoulment takes place at 120 days whilst some believe this to occur at 40 days.

4. Despite the approval by US President to provide funding on research on the 64 stem cell lines already in storage, there are still opponents raising strong objections and ethical campaigns. It should be noted that 70 members of the Congress signed a statement of objection to the use of human ES cells in research considering that as an unethical disregard of this early stage of human life.

5. Countries with laws that allow human embryo research set a time limit for research *(usually 14 days i.e. just before the fetus begins to form).* Laws should also specify purposes of clinical relevance.

6. Stem cell research even at its most fundamental must eventually aim at therapy for serious and intractable disease.

5.1 The Islamic Point of View

The issues relating to stem cell research, freezing of embryos and gene therapy was discussed in a series of seminars held by the Jordan Society of Islamic Studies and Medical Studies and published in a book in September 2000. The following consensus was agreed upon by the participating Muslim jurists :

1. Culture of human cell lines in the laboratory and experimentation on them for the purpose of organ transplantation to save human life is permissible.

2. Scientists may use human cells derived from aborted fetuses, deemed not to be viable, or from tissues removed in the process of surgeries to cure diseases, as sources for cells to be used for research aiming at organ transplantation.

3. It is not permissible to induce fertilization of human sperm and ova, in any way or form, with the purpose of using the fertilized ova for research.

4. Freezing and maintenance of sperms, ova and embryos should be supervised by a reliable central authority, that adopts and follows reliable procedures which guarantee no mixing of lineages. Such authority should be administered and managed by Muslim workers reliable in their faith and knowledge. Such central authority shall not function for financial profit.

5. It is permissible to use cloning technology and genetic engineering to produce and introduce human genetic material into a human being aiming at curing illnesses provided that Syari'ah guidelines are not violated, and among those and among those is the rule of 'no harm'. Such procedures should reach a level of perfection whereby they significantly produce more benefit than harm.

6. The same technology could be used to introduce healthy genetic material into ova, fertilized ova or fetuses, aiming at prevention or curing diseases. Provided that the rule of 'no harm' is applied and that the procedure is not used to interfere with the general *(non-pathological)* human characteristics e.g. color of skin, eyes etc. or to change the composition of the heritable characters of the cells.

5.2 The non-Muslim point of view and status of regulation worldwide

The basis for the regulation of stem cell research follows along similar facts and arguments. Source of the stem cells, objective of research, and the symbolic moral right of the embryo are the major reference points. Table 1 and Table 2 show the current status of regulation of human embryo research worldwide.

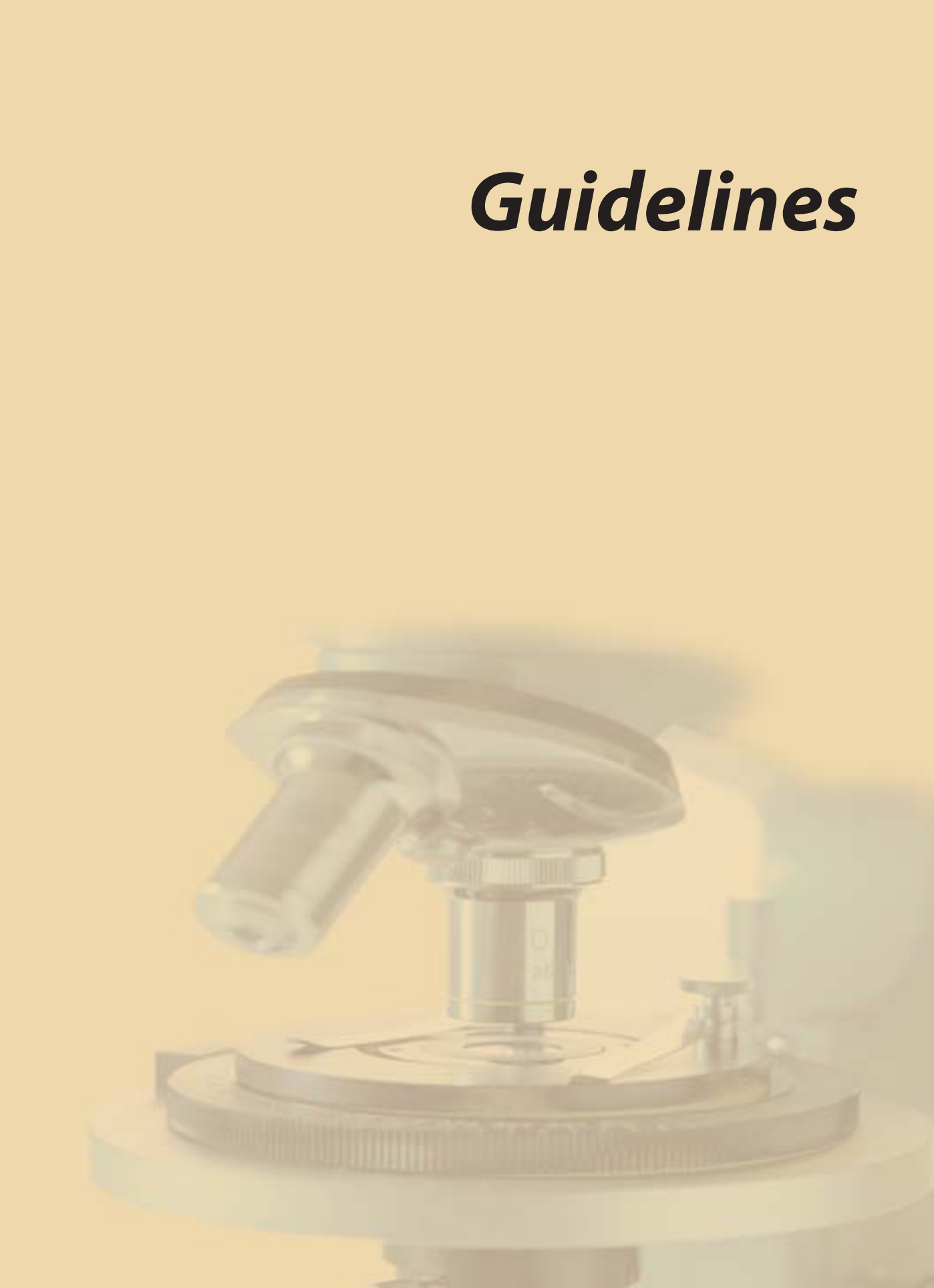
Table 1 : Status of regulation of human embryo research in Europe

Status of regulation	Countries
Regulated by law	Denmark, Finland, Hungary, Spain, United Kingdom
Law in preparation	France, Netherlands, Protugal
Prohibited	Austria, France, Germany, Ireland, Norway
No law yet	Belgium, Czech Republic, Greece, Italy, Poland, Slovenia, Switzerland, Turkey

Table 2 : Status of regulation of human embryo research in Europe

Countries	Status
Australia	Victoria prohibits human embryo research and ES cell derivation, but allows research on imported cell lines
Israel	Derivation of human ES cell lines from 'spare' IVF embryos is permitted
Japan	Human ES derivation is to be regulated. Reproductive cloning is prohibited. Other forms of assisted reproductive technology and human embryo research will be regulated
United States	A few states have law prohibiting any human embryo reseacrh. However there is no regulation of privately funded research. Congress prohibits federal funding of human embryo research including ES cell derivation. NIH is funding research on the 64 human ES cell lines already in existence but not on any derived after 9 August 2001
Korea	Evidence of pluripotent embryonic stem cell derived from a cloned blastocyst. Human cloning still prohibited.

Guidelines



6

Guidelines for stem cell research in Malaysia

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

2. All stem cell research must passed through an institutional review board and a institutional ethics committee to prevent unethical research and unethical use of stem cells

3. 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

4. Research on stem cells derived from adult stem cells is allowed in accordance to existing guidelines

5. Use of fetal tissues from legally performed termination of pregnancy is also allowed in accordance to existing guidelines

6. Use of non-human stem cell lines are also allowed *(mice and primates)*

7. Use of embryonic stem cell lines *(from 64 cell lines)* for research and therapeutic purposes should be allowed

8. The creation of embryos either from Assisted Reproductive Techniques / Somatic Cell Nuclear Transfer (SCNT) specifically for the purpose of scientific research is presently prohibited

9. Use of sample or excess embryos either from assisted reproductive techniques requires further deliberations and guidance from the various religious authorities, although from the Islamic point of view this is allowed specifically for research cloning *(refer to 'Keputusan Muzakarah Jawatankuasa Fatwa Majlis Kebangsaan Bagi Hal Ehwal Agama Islam Malaysia Berkaitan Pengklonan Dan ART' dated 22 February 2005 on page 11)*

Fatwa

KEPUTUSAN MUZAKARAH JAWATANKUASA FATWA MAJLIS KEBANGSAAN BAGI HAL EHWAL AGAMA ISLAM MALAYSIA BERKAITAN PENGKLONAN DAN ART (ASSISTED REPRODUCTIVE TECHNOLOGY)

7

HUKUM PENGKLONAN TERAPEUTIK DAN PENYELIDIKAN SEL STEM *(STEM CELL)*
Bil : MFK Kali Ke-66
Tarikh : 22 Februari 2005
Keputusan :

7.1 Pengklonan terapeutik untuk tujuan rawatan perubatan seperti mencipta sel-sel tertentuatau menggantikan organ yang telah rosak dengan mengambil kira langkah-langkah sempadan yang dibenarkan oleh syarak adalah **diharuskan.**

7.2 Harus menggunakan embrio yang disimpanbeku atau lebihan embrio dari proses persenyawaan di luar rahim (IVF) untuk tujuan penyelidikan dengan syarat mendapat persetujuan pasangan suami isteri yang menerima rawatan dan kajian tersebut dilakukan sebelum mencapai tahap 'alaqah' **(***blastocyst).*

7.3 Penyelidikan ke atas pra-embrio selain dari untuk tujuan terapeutik hendaklah mendapat kebenaran daripada pasangan suami isteri dan pra-embrio hasil penyelidikan ini, tidak boleh sama sekali ditanam dalam rahim isteri atau mana-mana wanita yang lain.

7.4 Harus melakukan penyelidikan ke atas pra-embrio untuk mengetahui penyakit genetik bagi pasangan yang berisiko tinggi dan hanya embrio yang dikenalpasti bebas dari penyakit sahaja boleh ditanam dalam rahim ibunya dalam tempoh perkahwinan yang sah.

7.5 Rawatan kejuruteraan genetik ke atas pra-embrio yang melibatkan pengubahsuaian sifat semulajadi seperti rambut, warna rambut, kebijaksanaan, ketinggian dsb termasuk memilih jantina adalah haram. Bagaimanapun pemilihan jantina diharuskan sekiranya factor jantina menatijahkan suatu penyakit genetik yang serius yang boleh membawa kematian.

7.6 Sebarang penyelidikan yang berunsurkan komersial atau yang tiada kaitan dengan kesihatan ibu atau janin adalah **tidak dibenarkan.**

7.7 Penyelidikan hendaklah dijalankan **secara sah** dan proposal penyelidikan mestilah jelas, saintifik dan dikendalikan oleh penyelidik yang benar-benar mempunyai kemahiran, amanah dan bertanggungjawab.

7.8 Sel stem daripada sumber-sumber berikut adalah **harus** digunakan untuk tujuan rawatan perubatan dan kaji selidik :

i. Daripada seorang dewasa (sel stem dewasa) dengan izin dan prosedurnya tidak mengakibatkan mudarat;

ii. Daripada seorang kanak-kanak dengan keizinan ibu bapanya dan prosedurnya tidak mengakibatkan mudarat;

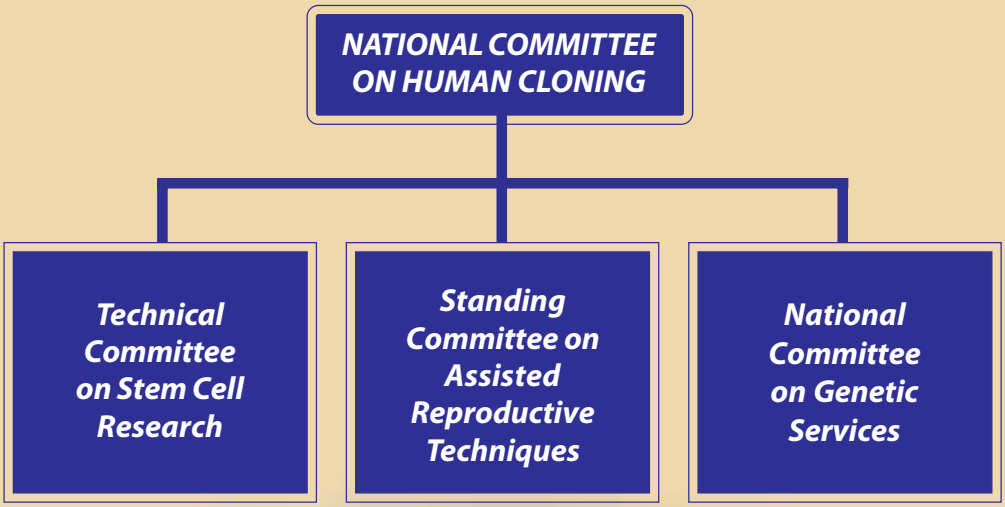
iii. Daripada uri dan darah tali pusat bayi dengan keizinan ibubapanya;

iv. Daripada janin yang gugur secara spontan atau keguguran akibat daripada rawatan perubatan yang dibenarkan syarak dengan syarat mendapat keizinan ibubapanya, bukan janin yang digugurkan secara sengaja atau digugurkan tanpa sebab-sebab perubatan yang dibenarkan oleh syarak;

v. Daripada lebihan embrio (excess embryos) yang disimpan beku daripada teknologi bantuan kesuburan IVF dengan syarat mendapat keizinan daripada ibubapanya. Sel stem daripada embrio yang dihasilkan secara sengaja *(created embryo)* dengan teknologi *Somatic Cell Nuclear Transfer (SCNT)* adalah tidak dibenarkan berdasarkan kaedah sad al-zaraie' (menutup pintu keburukan).

Committees

Various Subcommittees Under National Committee On Human Cloning



Secretariat
O & G / Pediatric Services Unit
Medical Development Services Section
Medical Development Division
Ministry of Health
Aras 5 - 7, Block E1, Parcel E,
Government Office Complex
62590 Putrajaya
Tel : 03-88831153 / 03-88831161
Fax : 03-88831155

Technical Committee on Stem Cell Research

Advisor	:	**Tan Sri Datuk Dr. Hj. Mohd Ismail Merican** *Director General of Health, MOH*
Chairperson	:	**Prof. Dr. A Rahman A Jamal** *Faculty of Medicine, UKM*
Co-chairperson	:	**Dr. Zubaidah Zakaria** *Institute of Medical Research*
Members	:	**Dato' Dr. N.Sivalingam** *International Medical University*
		Dato' Dr. Yasmin Ayob *National Blood Services Centre*
		Dr. Hj. Mohd Farouk Abdullah *Dept. of O&G, HTAR, Klang*
		Dr. Roshida Hassan *Dept. of Pathology, HKL*
		Dr. Hishamshah Ibrahim *Dept. Of Paediatrics, HKL*
		Dr. Chang Kian Meng *Dept. Of Medicine, HKL*
		Dr. Puteri J Noor M Baharuddin *(Secretary) IMR*
		Dr. Fuzina Noor Hussein *Institute of Medical Research*
		Prof. Dr. Cheong Soon Keng *Faculty of Medicine, UKM*
		Prod. Madya Dr. Saifulaman Said *Faculty of Applied Science, UiTM*
		Dr. Rozita Rosli *Faculty of Medical Sciences, UPM*
		Puan Aliza Yaacob *Institute of Medical Research*

Drafting Committee For The Guidelines On Stem Cell Research

Chairman : **Y.Bhg Dato' Dr. Noorimi binti Hj Morad**
Deputy Director General of Health (Medical)
Ministry Of Health

Members : **YBhg Dato' Dr Azmi bin Shafie**
Director, Medical Development Division

Dr. Teng Seng Chong
Senior Deputy Director
Medical Development Division

Dr. Hishamsah bin Mohd Ibrahim
Consultant Paediatrician, HKL

Dr. K. Mukudan
Head of O&G Department
Hospital Ipoh and National Adviser to the O&G Services, MOH

Dr. Puteri J Noor Megat Baharuddin
Research Officer
Institute Medical Research

Professor A. Rahman bin A. Jamal
Director,
Institut Perubatan Molekul (UMBI)
HUKM

Dr. Musa bin Nordin
Presiden, Persatuan Perubatan Islam Malaysia

Secretariat : **Dr. Noor Aziah Zainal Abidin**
Senior Principal Assistant Director
Medical Development Division

Dr. Jafanita Jamaludin
Assistant Director
Medical Development Division

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