The Working Group on Regenerative Medicine and Research Report

and Recommendations 2011

Executive Summary

Approved by the UCD Research Ethics Committee (REC) for submission to the UCD Academic Council
(22/09/11)

Summary of Findings and Recommendations

- The REC Working Group reaffirms that the use of human adult stem cells in research should be permitted and encouraged, providing that the current established legal and ethical safeguards in relation to use of human tissues are observed.

- The Group recognises the growing importance of induced pluripotential stem cells (IPSC). IPSC can play a significant role and are likely to have a prominent position in future research. The REC Working Group encouraged the use of these IPSC where possible. The Group recognises, however, that there may be some limitations preventing IPSC completely replacing embryonic stem cells in research. In particular, IPSC may not be able to provide information about the mechanisms of early human embryogenesis. There is continuing scientific debate on whether IPSC have similar attributes to embryonic stem cells with regard to their potential for use in regenerative medicine and also whether they can induce similar immune responses.

- The Group reiterates the recommendations already contained in its 2005 report, which oppose the creation of human embryos for research purposes. It notes that the creation of human embryos for research purposes is also prohibited by the current Irish Medical Council Guidelines and by Article 18 of the Council of Europe Convention on Human Rights and Biomedicine.

- The Group recognises that under current Irish law there is no legal constraint on the importation and use of human embryonic stem cells (hERC) in research. The Group recognizes that European Union Tissues and Cell Directives set common safety and quality standards for human tissues and cells across the EU, including human eggs and sperm. These Directives have been set into Irish law. These Directives do not cover “research using human tissues and cells, such as when used for purposes other than application to the human body e.g. in vitro research or in animal models.”
• The Group recognises, however, that the issue of the use of embryonic stem cells in research is a matter on which there is deep controversy and sincere disagreement. The Group is not in a position to formulate policy for UCD on the ethical use of human embryonic stem cells. The Group recommends that this issue be discussed widely by the University before a policy is agreed.

• The Group understands that the Governing Authority wishes to consult widely in the university on this policy document. In particular, the Group recommends that the Academic Council be consulted on the issue of research involving human embryonic stem cells (hESC) or stem cell lines derived therefrom.

• The issue of UCD employees and students (as part of their academic programme) working in other institutions abroad on human embryonic stem cells was discussed by the Working Group. UCD employees are bound by the policies of UCD regardless of wherever they are working. Medical doctors are bound by the Medical Council Regulations in the country where the stem cell research is being carried out.

• The Working Group is of the view that the REC should recommend that the Academic Council promote discussion of the issue of human embryonic stem cell research throughout the University with a view to considering one of the following options:

1) Prohibit any research involving human embryonic stem cells and/or human embryonic stem cell lines.

2) Permit research on human embryonic stem cell lines under strict regulation by the University.

• The Group recommends that, in the event that UCD does formulate a policy, including strict regulation, permitting the use of human embryonic stem cells or human embryonic stem cell lines in accordance with option 2), applications for such research should be reviewed by the HREC –Sciences Committee, which would seek the additional specific expertise required to carry out such a review.
The Working Group on Regenerative Medicine Report and Recommendations 2011

Chairperson
Professor Dermot Moran

Final Draft Thursday, September 22\textsuperscript{nd} 2011
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2011

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Membership

The members of the Working Group were:

- Professor Dermot Moran, UCD School of Philosophy, Chair of the Working Group
- Mr John Coman, UCD Corporate and Legal Affairs Secretary.
- Professor David Brayden, UCD School of Veterinary Medicine, and Fellow, UCD Conway Institute.
- Professor Dervilla Donnelly, Emeritus Professor of Organic Chemistry, UCD,
- Professor Andrew Green, Professor of Medical Genetics, UCD School of Medicine and Medical Science, and Director of the National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin 12.
- Professor Suzanne Quin, UCD School of Applied Social Science
- Professor William Watson, UCD School of Medicine & Medical Science, and Fellow, UCD Conway Institute
- Dr Peter Wilson, Chair, UCD Research Ethics Committee (REC)

Executive Assistance was provided by

- Ms. Janette Stokes, Research Ethics Administrator, UCD Office of Research Ethics

Terms of Reference

The Working Group on Regenerative Medicine was asked in November 2008 [Minutes of the REC meeting 4 November 2008] by the REC to reconvene to review recent changes (specifically the situation in University College Cork (UCC) and to revise and update the original document of 2005 (revised 2006). See http://www.ucd.ie/researchethics/pdf/ucd_rec_working_group_on_regenerative_medicine_report_2006.pdf

Meetings Held

Work of Working Group

The working Group reviewed a number of recent developments and publications:

A. The International Situation
   1. The United Nations Declaration on Human Cloning.
   3. The Current Legal Situation in the USA.

B. The Situation in Europe and the European Union
   1. The Council of Europe Convention on Human Rights and Biomedicine
   2. The Charter of Fundamental Rights of the European Union
   3. The European Human Embryonic Stem Cell Registry
   4. European Science Foundation Science Policy Briefing 38 – Human Stem Cell Research and Regenerative Medicine – May 2010
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   7. Trinity College Dublin Policy on Good Research Practice (May 2009)
A. The International Situation

1. The United Nations Declaration on Human Cloning

*Solemly declares* the following:

(a) Member States are called upon to adopt all measures necessary to protect adequately human life in the application of life sciences;

(b) Member States are called upon to prohibit all forms of human cloning inasmuch as they are incompatible with human dignity and the protection of human life;

(c) Member States are further called upon to adopt the measures necessary to prohibit the application of genetic engineering techniques that may be contrary to human dignity;

(d) Member States are called upon to take measures to prevent the exploitation of women in the application of life sciences;

(e) Member States are also called upon to adopt and implement without delay national legislation to bring into effect paragraphs (a) to (d);

(f) Member States are further called upon, in their financing of medical research, including of life sciences, to take into account the pressing global issues such as HIV/AIDS, tuberculosis and malaria, which affect in particular the developing countries.


The Working Group examined the ISSCR Guidelines. According to its own mission statement:

*The International Society for Stem Cell Research is an independent, nonprofit organization established to promote and foster the exchange and dissemination of information and ideas relating to stem cells, to encourage the general field of research involving stem cells and to promote professional and public education in all areas of stem cell research and application.*

([http://www.isscr.org/Mission_Statement/2810.htm](http://www.isscr.org/Mission_Statement/2810.htm))

The Working Group noted that the ISSCR is a voluntary group of stem cell researchers and that the ISSCR guidelines, which date from 2006, have no legal standing.

Given that the ISSCR document recommends forms of research (Category 2) that would extend beyond what University College Cork or the Irish Council for Bioethics would approve, the Working Group would caution against using the ISSCR document, or selected excerpts from it, as a basis for UCD’s policy on embryonic stem cell research.
3. The Current Legal Situation in the USA

Under the Bush administration, federal funding was restricted to the 21 hES cell lines already in existence. In March 2009 President Obama overturned the constraints put in place by his predecessor. In August 2010, US District Judge Royce Lamberth blocked President Obama’s executive order, claiming that the funding violates a 1996 law prohibiting the use of federal funds for any research which involves the destruction of human embryos. The judge temporarily blocked all federal funding for hESC research. Research using private funding is not blocked. On 29th April 2011 the U.S. Court of Appeals of the DC Circuit ruled to overturn the preliminary injunction in the case Sherley v. Sebelius that prohibited the funding of human embryonic stem cell research by the U.S. National Institutes of Health (NIH). The court has now ruled that the NIH can use federal money to fund research involving hESC. The legal situation in the USA is evolving. The states of Minnesota and Oklahoma (as of April 2011) are in the process of passing legislation which will criminalise certain embryonic stem cell research procedures. The Minnesota Bill, which has passed Committee readings in the House of Representatives and the Senate, seeks to ban somatic cell nuclear transfer. The Oklahoma Bill (The Destructive Human Embryo Research Act), which has passed through the House with a majority of 86 votes to 8, is currently going through the State Senate. If passed it would make it illegal to conduct embryonic stem cell research, which results in the destruction of the embryo and prohibits the buying, selling and transferring of embryos for research. Concern has been expressed over the commercial impact of this Bill.
B. The Situation in Europe and in the European Union

1. The Council of Europe Convention on Human Rights and Biomedicine


Article 18 of this Convention states:

**Article 18 – Research on embryos in vitro**

1. Where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo.
2. The creation of human embryos for research purposes is prohibited.

The Working Group notes that Ireland has not ratified this Convention.

2. The Charter of Fundamental Rights of the European Union (2010/C 83/02)

The Charter of Fundamental Rights of the European Union which, by virtue of the Lisbon Treaty, is now applicable in Ireland.

Articles 1, 2 and 3 are worthy of note

**Article 1**

Human dignity is inviolable. It must be respected and protected

**Article 2**

1. Everyone has the right to life.
2. No one shall be condemned to the death penalty, or executed

**Article 3**

1. Everyone has the right to respect for his or her physical and mental integrity.
2. In the fields of medicine and biology, the following must be respected in particular:

(a) the free and informed consent of the person concerned, according to the procedures laid down by law;
(b) the prohibition of eugenic practices, in particular those aiming at the selection of persons;

(c) the prohibition on making the human body and its parts as such a source of financial gain;

(d) the prohibition of the reproductive cloning of human beings


3. The European Human Embryonic Stem Cell Registry

The European Human Embryonic Stem Cell Registry was set up to coordinate information across the EU on stem cell research. It is funded through a Specific Support Action within the ‘Life Sciences, Genomics, and Biotechnology for Human Health’ Priority of the Sixth Framework Research Programme of the European Union.

The European regulatory situation is very varied. According to the website of the European Human Embryonic Stem Cell Registry (http://www.hescreg.eu/index.php?id=15)

The regulatory situation is as follows:

Belgium, UK and Sweden allow therapeutic cloning, which is expressly excluded from FP6.

Czech Republic, Denmark, Finland, France, Greece, Netherlands, Portugal (the law has not yet entered into force) and Spain have regulations allowing the derivation of new hESC from embryos created as a result of medically-assisted in vitro fertilization to induce pregnancy, and no longer to be used for that purpose (supernumerary embryos).

Estonia, Hungary, Latvia and Slovenia have no specific regulations on hESC, but allow some research on supernumerary embryos.

Germany and Italy have regulations which restrict hESC research. These regulations mean that scientists in these countries cannot derive new hESC, but can import them. In Germany, these cells have to have been derived before 1 January 2002.

The other EU countries have no specific regulation on this issue but Austria, Lithuania, Malta, Slovakia and Poland have clearly indicated that they are against hESC research.
4. European Science Foundation Science Policy Briefing 38 – Human Stem Cell Research and Regenerative Medicine – May 2010

The Working Group considered the European Science Foundation (ESF) Policy Document on hESC (May 2010) which can be found at http://www.esf.org/publications/science-policy-briefings.html. This document states

Continued research on all types of SCs derived from embryos, foetal tissues and adults remains necessary as it is too early to predict their value in a specific field. Research using embryonic and iPS cells is required, as the knowledge derived from both is complementary and for the moment the benefits and risks are not sufficiently known.

5. European Court of Justice Preliminary Ruling 10th March 2011; Opinion of the Advocate General, delivered on 10th March 2011 on case C_34/10 Oliver Brüstle V Greenpeace.

The Working Group considered the reported ‘preliminary ruling’ of 10th March 2011 by the Advocate General in the case Oliver Brüstle v Greenpeace. The Court has been asked to define embryo for European patenting law purposes. The decision of the Advocate General is as follows:

In view of all the foregoing considerations, I propose that the Court give the following answers to the questions asked by the Bundesgerichtshof: ‘Article 6(2)(c) of Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions must be interpreted as follows:

– The concept of a human embryo applies from the fertilization stage to the initial totipotent cells and to the entire ensuing process of the development and formation of the human body. That includes the blastocyst.
– Unfertilised ova into which a cell nucleus from a mature human cell has been transplanted or whose division and further development have been stimulated by parthenogenesis are also included in the concept of a human embryo in so far as the use of such techniques would result in totipotent cells being obtained.
– Taken individually, pluripotent embryonic stem cells are not included in that concept because they do not in themselves have the capacity to develop into a human being.
– An invention must be excluded from patentability where the application of the technical process for which the patent is filed necessitates the prior destruction of human embryos or their use as base material, even if the description of that process does not contain any reference to the use of human embryos.
– The exception to the non-patentability of uses of human embryos for industrial or commercial purposes concerns only inventions for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it.’
It is clear that this preliminary ruling proposes to interpret the Directive 98/44/EC (which is in force in Ireland) as prohibiting the patenting of any research that involved—at some prior stage—the destruction of the human embryo. This ruling may have implications for international investment in stem cell associated Biotech research in the European Union.

In relation to the European Court of Justice decision of the 10th March 2011 in the case of Brüstle it should be borne in mind that this decision is for the purposes of patenting law only. Notwithstanding, judicial notice would probably be taken of it.
C. The Situation in Ireland

1. Absence of National Policy on Stem Cell Research

In Ireland there is no national policy on human embryonic stem cell (hESC) research. In April 2005, the Report of the Government-appointed Commission on Assisted Human Reproduction was presented to the Government. The Working Group noted that the Programme for Government 2011 includes the following paragraph:

**Bioethics**
We will legislate to clarify the law surrounding assisted human reproduction including
the law relating parental relationships arising from assisted human reproduction.

We will legislate to regulate stem cell research.


2. European Union Tissues and Cell Directives

The European Union Tissues and Cell Directives introduced common safety and quality standard for human tissues and cells across the EU and includes human eggs and sperm.

The first Directive **2004/23/EC** concerns standards for donation, procurement and testing, processing, preservation, storage and distribution.

The second Directive **2006/17 EC** covers donation, procurement and testing.

The third Directive **2006/86 EC** covers standards of traceability, notification of serious outbursts, reactions, events, etc.

The first and second Directives were transposed into Irish law under and by virtue of **SI 158 of 2006**. These regulations came into effect in 2006.

The third Directive was transposed by **SI 598 of 2007**.

The regulations apply to all prescribed activities for human applications. Human applications is defined as the use of tissues or cells on or in a human recipient and extra corporals applications.
The regulations also apply to tissues and cells that are applied to the human body in clinical trials.

The general accepted view is that the Directives do not apply to tissues and cells used in research.

Paragraph 11 of the preamble to Directive 2004/23/EC provides as follows:-

“This Directive does not cover research using human tissues and cells, such as when used for purposes other than application to the human body eg in vitro research or in animal models. Only those cells and tissues that in clinical trials are applied to the human body should comply with the quality and safety standards laid down in this Directive.”

It would seem therefore from the above that if the stem cells are imported purely and simply for research purposes and are not intended for human application, that the specific legislation referred to above does not apply.

Under Regulation 25 any person who knowingly supplies tissue or cells which are not labeled in accordance with the requirements of Regulation 14 shall be guilty of an offence. Regulation 26 makes it an offence to import below standard tissues and cells.

3. Supreme Court Ruling 15 December 2009 in the case Mary Roche (Applicant/Appellant) and Thomas Roche, Anthony Walsh, David Walsh and Sims Clinic Ltd (Defendants/Respondents) and Attorney General.

An important and relevant Supreme Court Judgment was issued on 15th December 2009. The full text of the individual judges’ judgments is available on the Courts website, see link (http://www.courts.ie/Judgments.nsf/Webpages/HomePage).

The case was between Mary Roche (Plaintiff/Appellant) and Thomas Roche, Anthony Walsh, David Walsh and Sims Clinic Ltd (Defendants/Respondents) and Attorney General (notice party). The case concerns the fate and constitutional position of three frozen embryos which the plaintiff wished to have released to her and used for implantation in her against the wishes of her estranged husband, Thomas Roche. The embryos were created after the Roches underwent IVF treatment in 2002. Mrs Roche, who already had one child, became pregnant and had a child as a result of the IVF. Shortly afterwards the couple separated. In November 2006 the High Court rejected Mrs Roche’s argument that the embryos are protected by Article 40.3.3 of the Constitution. The High Court ruled that the embryos are not ‘unborn’ within the meaning of the Constitution.
All five Supreme Court Judges dismissed the Appeal on all fronts. The Supreme Court ruled that the term ‘unborn’ only applies after implantation in the womb and does not apply to frozen or invitro embryos, and therefore that unimplanted embryos are not afforded the legal protection guaranteed by Article 40.3.3 of the Constitution.

On the basis of this judgement it now appears to be established law that the term “unborn” within the meaning of the Irish Constitution does not refer to an unimplanted embryo, and therefore the protection afforded to the unborn in the Constitution does not apply to the three surplus frozen embryos involved in this dispute, and which had been stored in the Sims Clinic, nor indeed to any embryos in a test tube.

Generally, the Judges of the Supreme Court were of the view that despite the fact that the an in vitro embryo does not come within the meaning of “unborn” and therefore Article 40.3.3 of the Constitution does not afford it any protection, that it is generally accepted that the human embryo does have moral qualities and a moral status and that its creation and use cannot be divorced from our concept of human dignity. Additionally the spare embryos were described as “lives” or at least “potential lives” and that accordingly they needed to be treated with respect.”

Several of the Supreme Court judges, including Judges Hardiman and Fennelly criticized the legislature for not having taken any positive steps to regulate the area of assisted reproduction.


The Seventh revised edition (2009) of the Guide to Professional Conduct and Ethics for Registered Medical Practitioners was considered by the Working Group. With regard to the issue of assisted human reproduction the new text differs substantially from the earlier Sixth Edition.

The original Section F entitled ‘GENETIC TESTING AND REPRODUCTIVE MEDICINE’ which was present in the Sixth Edition has been expunged.

Section 24.1 and section 24.5 require consideration

24.1. In a rapidly evolving and complex area, doctors are reminded of their obligation to preserve life and to promote health. The creation of new forms of life for experimental purposes or the deliberate and intentional destruction of in-vitro human life already formed is professional misconduct.

24.5 Techniques such as I.V.F. should only be used after thorough investigation has failed to reveal a treatable cause for the infertility. Prior to fertilization of an ovum, extensive discussion and counselling is essential. Any fertilised ovum
must be used for normal implantation and must not be deliberately destroyed.

If couples have validly decided they do not wish to make use of their own fertilised ova, the potential for voluntary donation to other recipients may be considered.

This entire section has now been removed.

In the revised Seventh Edition a new paragraph (Paragraph 20 in Section B on page 20) has been inserted, which reads:

20.4 You should not participate in creating new forms of life solely for experimental purposes. You should not engage in human reproductive cloning.

It is important to note the word “solely” here. The Guidelines clearly rule out the creation of embryos solely for experimental purposes. One unstated implication is that the use of embryos originally created for other purposes in scientific research is not explicitly prohibited. It appears not to rule out the use of embryos created for other purposes (e.g. in-vitro human fertilization treatments) but which are surplus to requirement and may then be used for research and experimentation.

However, the Medical Council recognizes that, in the absence of legislation in this area, there is a need for further guidelines on assisted human reproduction. The Medical Council did announce plans to begin work on drafting these guidelines. None are available to date.

The Working Group notes that these Guidelines apply only to medical clinicians.

5. Policy of Science Foundation Ireland (SFI) re Research using Human Embryonic Stem Cells

The Working Group considered the current policy of the SFI regarding hESC research. The SFI statement reads:

Pending legislation from the Department of Health and Children governing assisted human reproduction and related practices, and in line with a current directive from the Department of Enterprise, Trade and Innovation, SFI is not in a position to fund research using human embryonic stem cells.

This statement is taken from the SFI website (17/06/2011) (http://www.sfi.ie/funding/grant-policies/research-using-human-embryonic-stem-cells/).
6. University College Cork University Research Ethics Board Document

The Working Group considered the policy in University College Cork (UCC) regarding research involving hESC [see Appendix III]. In UCC, the University Research Ethics Board (UREB) has responsibility to formulate and monitor the University’s policy on research ethics. The UREB produced a consultative document outlining various options. Opinion was canvassed widely in the university and eventually a policy was decided on the basis of a vote by the UCC Academic Council. The agreed policy document states:

UREB considers it preferable that researchers who seek to carry out research using hESC should apply to do so using hESC lines imported from approved sources in other jurisdictions. This policy will be reviewed in light of any judicial or legislative changes that impact on the legal situation pertaining to the use of hESC in Ireland.

The UREB established a subcommittee: the human embryonic stem cell advisory committee (HESCAC) with 5 external and 2 internal members, initially chaired by Professor Dolores Dooley.

The Working Group considered the UCC Terms of Reference document in which four policy options were laid out for discussion by the university. One option presented in the UCC document was to permit the creation of human embryonic stem cell lines for research from excess human embryos specifically donated for that purpose from IVF clinics where they are no longer needed for reproductive purposes.

The Working Group noted that IVF clinics in Ireland are currently unregulated, although some claim to operate according to ‘best practice’ and the issue of donor consent may not have been clearly defined. Notwithstanding, there are in these clinics surplus embryos which will never be used for the purpose for which they were created and may in the circumstances be allowed to perish. It is hard to make the case that research involving the creation of new stem cell lines from unregulated sources would constitute best practice and the Group does not recommend this option being put to the university for its consideration. The Working Group does not support research involving human embryonic stem cells from these sources due to lack of regulation in the area.

Having regard to the preliminary ruling concerning Directive 98/44/EC which prohibits the patenting of any research that involves—at some prior stage—the destruction of the human embryos, it would appear that any research undertaken using excess embryos donated from IVF clinics would also not be patentable.

The Group does not recommend the fourth option set out in the UCC document: the creation of embryonic stem cells for research.
7. Trinity College Dublin Policy on Good Research Practice (May 2009)

The Working Group studied the document *Policy on Good Research Practice* produced by Trinity College Dublin (May 2009). The document comes to the following conclusions regarding research involving human embryonic stem cells:

In the area of utility of stem cells derived from human embryos in research, in the absence of a national framework or legislation on this matter, TCD subscribes to an ethical code of practice on the use of established human embryonic stem cell lines (hES cells) in research compliant with that detailed in the published opinion of the Irish Council for Bioethics, and to the guidelines of the Irish Medical Council. Any transfer of established human embryonic derived cell lines to TCD for use in research must be accompanied by a full materials transfer agreement, including details of the ethical compliance of the transferring institution for the derivation of the line in accordance with ISSCR guidelines. Researchers wishing to employ stem cells derived from human embryos in their research in Trinity College Dublin are required to have their proposed use of such materials reviewed by a College ethics subcommittee in the context of compliance with international ISSCR ethical guidelines. TCD formally limits the permitted range of experimentation involving on hES cells, to those defined as category 1 and category 2 section (10.2e) in Section 10 of the ISSCR Guidelines (see Appendix).

For clarity, this policy serves to:

- restrict hES research in TCD to the use of pre-existing hES cell lines, with such research being “confined to cell culture or involve(s) routine and standard research practice”. (ISSCR Category 1);

- facilitate under ISSCR Category 2 (10.2e) the use of hES cell lines to generate chimaeric models in animals such as mice and rats;

- exclude the generation or study of chimaeric non-human primates;

- prevent any research in areas classified as ISSCR Category 3 (including therefore the use of hESC in humans or non-human primates);

- prevent any research in which chimaeric animals containing hES cells are bred.

- prevent any research on human embryos so precluding the generation of any new hES cell lines at TCD;

This policy position is deemed pragmatic insofar as it underpins TCD’s enshrined principles of academic research freedom through facilitating qualified and responsible researchers who wish to import and study established hES cell lines within an ethical framework of use. Such researchers, with requisite internal ethical approval, will be able to carry out a wide range of studies on these cells in vitro and in routine animal models. This policy makes a clear distinction between the study of non-human primates and common laboratory animals such as mice and
rats. TCD researchers will not be able to create new hES cell lines under this policy.

In all cases where research is carried out under the Auspices of Trinity College Dublin, within or without the defined campus properties, the College expects compliance with the policies as set out in this document and additional compliance with the policies of the relevant body of the organization wherein any external research is conducted.”

The Working Group noted that the ISSCR guidelines are referred to in the TCD policy document, which makes statements about what is or is not permitted according to the ISSCR categories. It was noted that the TCD document makes selective use of these guidelines. For instance, TCD permits the use of existing hES cell lines in cell culture (ISSCR category 1) but requires a special committee to review such use, whereas the ISSCR document states that such use does not need any special ethical review. Furthermore, ISSCR Category 2, which the ISSCR recommends should be permitted subject to special ethical review, contains a number of types of research which would not be permitted under Irish Council of Bioethics or UCC guidelines. These include:

10.2a) Forms of research that involve the derivation of new human pluripotent cell lines by any means.
10.2b) Forms of research in which the identity of the donors of blastocysts, gametes, or somatic cells from which totipotent or pluripotent cells are derived, is readily ascertainable or might become known to the investigator.
10.2c) Forms of research in which human totipotent cells or pluripotent stem cells are mixed with pre-implantation human embryos. In no case shall such experiments be allowed to progress for more than 14 days of development in vitro, or past the point of primitive streak formation, whichever is first.
10.2d) Clinical research in which cells of totipotent or pluripotent human origin are transplanted into living human subjects.

The fifth ISSCR category in 10.2(e) is the only one which TCD would approve. This permits making chimeric hES/animal cells, but avoiding the use in primates or cerebral cortex or germline tissue, a condition which is not set out in the ISSCR document.

10.2e) Forms of research that generate chimeric animals using human cells. Examples of such forms of research include, but are not limited to introducing totipotent or pluripotent human stem cells into non-human animals at any stage of post-fertilization, fetal, or postnatal development. The final category 3 from ISSCR effectively is research that ISSCR feels should not be permitted, because of the risk of producing an organism or gametes from ES cells.
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2011

Summary of Findings and Recommendations

• The REC Working Group reaffirms that the use of human adult stem cells in research should be permitted and encouraged, providing that the current established legal and ethical safeguards in relation to use of human tissues are observed.

• The Group recognises the growing importance of induced pluripotential stem cells (IPSC). IPSC are likely to have a prominent position in future research. The Group encouraged the use of IPSC where possible. The Group recognises, however, that there are significant arguments that IPSC cannot fully substitute for embryonic stem cells in regenerative medicine research. In particular, IPSC may not be able to provide information about the mechanisms of early human embryogenesis. There is continuing scientific debate on whether IPSC have similar attributes to embryonic stem cells with regard to their potential for use in regenerative medicine and also recent suggestion that they may both induce similar toxic immune responses.

• The Group reiterates the recommendations already contained in its 2005 report, which oppose the creation of human embryos for research purposes. It notes that the creation of human embryos for research purposes is also prohibited by the current Irish Medical Council Guidelines and by Article 18 of the Council of Europe Convention on Human Rights and Biomedicine.

• The Group recognises that under current Irish law there is no legal constraint on the importation and use of human embryonic stem cells (hERC) in research. The Group recognized that European Union Tissues and Cell Directives set common safety and quality standards for human tissues and cells across the EU, including human eggs and sperm. These Directives have been set into Irish law. These Directives do not cover “research using human tissues and cells, such as when used for purposes other than application to the human body e.g. in vitro research or in animal models”.

• The Group recognises, however, that the issue of the use of embryonic stem cells in research is a matter on which there is deep controversy and sincere disagreement. The Group is not in a position to formulate policy for UCD on the ethical use of human embryonic stem cells. The Group recommends that this issue be discussed widely by the University before a policy is agreed.
• The Group understands that the Governing Authority wishes to consult widely in the university on this policy document. In particular, the Group recommends that the Academic Council be consulted on the issue of research involving human embryonic stem cells (hESC) or stem cell lines derived therefrom.

• The issue of UCD employees and students (as part of their academic programme) working in other institutions abroad on human embryonic stem cells was discussed by the Working Group. UCD employees are bound by the policies of UCD regardless of wherever they are working. Medical doctors are bound by the Medical Council Regulations in the country where the stem cell research is being carried out.

• The Working Group is of the view that the REC should recommend that the Academic Council promote discussion of the issue of human embryonic stem cell research throughout the University with a view to considering one of the following options:

  1. Prohibit any research involving human embryonic stem cells and/or human embryonic stem cell lines.

  2. Permit research on human embryonic stem cell lines under strict regulation by the University.

• The Group recommends that, in the event that UCD does formulate a policy, including strict regulation, permitting the use of human embryonic stem cells or human embryonic stem cell lines in accordance with option 2), applications for such research should be reviewed by the HREC –Sciences Committee, which would seek the additional specific expertise required to carry out such a review.
Appendix I

Report from Professor Andrew Green on Induced Pluripotential Stem Cells.

In 2006, Takahashi and Yamanaka showed that differentiated ‘adult’ skin cells (fibroblasts) from mice could be reprogrammed into stem cells. These stem cells, even though derived from a differentiated cell type, could then form any of the three embryonic cell types, endoderm, mesoderm, or ectoderm. The cells were called induced pluripotent stem cells, or IPSC. The transformation process, also called de-differentiation required the forced over expression of 4 critical genes OCT4, SOX2, Kif4 and c-myc. The technique has been taken up by many laboratories worldwide and human IPSC have been produced successfully, and transformed into many different cell types.

IPSC show many of the characteristics seen in embryonic stem cells, either produced from fertilized embryos or from somatic cell nuclear transfer. These similarities are found in both mouse derived and human IPSC.

IPSC technology has been proposed as a method of producing cells suitable for tissue regeneration, to treat a wide variety of human disease. However, to date, as is the case for ESC, this potential has yet to be fully realized. Cellular models of human disease, matched to a specific patient, have been produced using IPSC technology, for conditions such as motor neuron disease, Fanconi’s anaemia, and Long QT syndrome. Skin cells have been taken from a patient, transformed into IPSC, and then those cells are then differentiated into the specific affected tissue. For instance, IPSC from patients with motor neuron disease have been transformed into nerve cells, skin cells from patients with Fanconi’s anaemia have been transformed into blood cells, and skin cells from patients with Long QT heart disease have been transformed into heart muscle cells. These cells can be studied to understand the disease process, and to study the response to potential treatments. In mice, the genetic condition sickle cell disease was successfully corrected by skin IPSC, which had been genetically engineered to produce normal haemoglobin.

IPSC are still a considerable distance away from being used in clinical treatments. This is in part due to significant safety concerns. Two of the 4 genes used to make IPSC cells are genes that have critical roles in cancer development, and IPSC therefore could have the potential to become cancerous, in a specific cellular environment. There are also recent concerns that IPSC, similar to ESC, may surprisingly induce immune responses even though they are sourced from the same patient.

IPSC technology produces cells that are pluripotential, without any need for the use of human embryos or embryonic stem cell lines. IPSC technology has been put forward as a replacement for embryonic stem cell technology, making the use of ESC redundant.

However, there has been a great deal of scientific debate as to whether IPSC and ESC are identical. The common features, such as the ability to self renew, the expression of pluripotency cell markers, the ability to form tumors called teratomas, and in mice the ability to generate chimaeras, are similar for both cell types. However, there are
significant differences in the regulation of gene expression (epigenetics) between IPSC and ESC, and there is evidence that IPSC retain some of the genetic imprint of the skin fibroblast cells from which they came.

In addition, IPSC will not be able to provide information about the mechanisms of early human embryogenesis, whereas ESC can give much more information about early human development.

A recent review from 4 of the leading IPSC scientists in Nature Genetic Reviews indicates that all 4 are very clear that research using embryonic stem cells should continue, and that developments in ESC technology are currently significantly further ahead than those in IPSC technology.

Therefore, even though there have been great strides in the development of IPSC technology, the weight of scientific opinion is that IPSC cells will not replace, but will in fact complement ESC technology.
Appendix II

Ms Fiona Duffy

Review of Legal Position Post 2005 to Include the High and Supreme Court Decisions in Roche v Roche

The 2004 Guide to Ethical Conduct and Behaviour published by the Medical Council at paragraph 24.5 provides

“any fertilised ovum must be used for normal implantation and must not be deliberately destroyed.”

The 2009 (Seventh Edition) Guide to Ethical Conduct and behaviour makes no reference to how fertilised ovum should be cared for. Section 20.4 provides:-

“You should not participate in creating new forms of life solely for experimental purposes. You should not engage in human reproductive cloning.”

Mr Justice McGovern in his Judgement in the case of Roche -v- Roche delivered on the 15th November 2006 states, in relation to the Medical Council Guidelines:-

“These ethical guidelines do not have the force of law and offer only such limited protection as derives from the fear on the part of a Doctor that he might be found guilty of professional misconduct with all the professional consequences that might follow. The fact that something is not prohibited by the law does not of itself means that it is morally acceptable to carry out that act.........”

The Commission on Assisted Human Reproduction reported in 2005. In relation to IVF it recommended, with one dissenting voice:-

“If frozen embryos still remain after the couple have completed their treatment, the available options include:-

Donation to another couple

Donation for research

Being allowed to perish.”

The legislative position remains unchanged. It is however important to review these provisions purely because the reason for the Constitutional amendment which brought in Article 40.3.3 into the Constitution was to enshrine in the Constitution the protection of the unborn and its right to life and in particular to preclude the legislator from repealing Section 58 of the Offences Against the Person Act 1861 in so doing legalise abortion.

Sections 58 and 59 of the Offences Against the Person Act 1861 in effect make abortion in this country a crime.
These provisions are confirmed in Section 58 of the Civil Liability Act 1961 which provides that:-

“The law relating to wrongs shall apply to an unborn child for his protection in like manner as if the child were born, provided the child is subsequently born alive.”

They are further confirmed in Section 10 of the Health (Family Planning) Act 1979 as follows:-

“Nothing in this Act shall be construed as authorising –

(a) The procurement of abortion,

(b) The doing of any other thing the doing of which is prohibited by Section 58 and 59 of the Offences Against the Person Act 1861 (which sections prohibit the administering of drugs or the use of any instrument to procure abortion)…….”

The constitutional position, and in particular the interpretation of Article 40.3.3 and the meaning of “the unborn” as contained therein has been clarified not only by the High Court in the Judgement of Mr Justice McGovern in the case of Roche V Roche delivered on the 15th November 2006 but also by the Supreme Court and its Judgements on the Appeal from the High Court delivered on the 15th December 2009.

In the High Court the learned Judge held that it was a matter for the Oireachtas to decide what steps should be taken to establish the legal status of embryos in vitro.

After lengthy analysis the High Court concluded that there was no evidence that it was ever in the mind of the people voting on the eighth amendment to the constitution that “unborn” meant anything other than a foetus or child within the womb, and on that basis it could not be concluded that embryos outside the womb or in vitro fell within the scope of Article 40.3.3.

The Attorney General in its submission to the Supreme Court on the constitutional issue submitted that the frozen embryos do not constitute the “unborn” within the meaning of Article 40.3.3 of the Constitution with the consequences that the State is not obliged to facilitate their implantation.

The Attorney General further submitted that defining the unborn so as to include pre-implantation embryos, would contravene the text, purpose and spirit of Article 40.3.3 which it was submitted was inserted into the Constitution for the purposes of prohibiting the termination of pregnancies.

All five Judges in the Supreme Court dismissed the Plaintiff’s Appeal. It was generally accepted that the purpose of Article 40.3.3 was to address the issue of miscarriage and abortion, and that it was drafted having regard to the special relationship which exists between the mother and the child which she carries. Article 40.3.3 addresses the position of the unborn in relation to and juxtaposed to the life of the mother. It was generally accepted that it would never have been in the contemplation of the Irish
people voting in relation to the constitutional amendment that life outside the womb was also to be protected.

The Chief Justice dismissed the Appeal to the Supreme Court on constitutional grounds for the reason that the frozen embryos were not “the unborn life” within the meaning of Article 40.3.3. Notwithstanding he did make certain observations, in particular that such a finding does not mean that such embryos should not be treated with respect as entities having the potential to become a life in being.

The Chief Justice is the only Judge in the Supreme Court who touched on the question of when life begins, at the same time acknowledging that there is no clear view or consensus on this question. Notwithstanding he does state “I think it can be said that the human embryo is generally accepted as having moral qualities and a moral status. Its creation and use cannot be divorced from our concepts of human dignity.”

He refers to the report of the Constitutional Review Group of the Oireachtas published in July 1996, in particular the following:-

“Definition is needed as to when the “unborn” acquires the protection of the law. Philosophers and scientists may continue to debate when human life begins but the law must define what it intends to protect.”

“In my view the provision of the Constitution was intended to embrace human life before birth without exception and to extend to it, in express positive terms, the constitutional protections available to life after birth already provided for in Article 40.3.1.”

The Chief Justice expresses the view that the protection of the mother’s rights in certain circumstances cannot be interpreted as intending to remove protection from human life because it is outside the womb, or to devalue the equal right to life of the unborn because it is outside the womb. On that basis the Chief Justice was not prepared to accept the argument that merely because the embryo is outside of the womb that it is precluded from the protection of Article 40.3.

The Chief Justice further went on to state that embryos outside the womb have the same qualities as they would have in the womb. Notwithstanding in his conclusion on the issue he stated:-

“Accordingly in my view it has not been established by the applicant, and it is not a justifiable issue for this Court to decide, that the frozen embryos constitute “life of the unborn” within the meaning of Article 40.3.3.”

Mr Justice Geoghegan in his Judgement indicated that he was in agreement “that spare embryos, being lives or at least potential lives, ought to be treated with respect.” He goes on to note how this area is constantly changing:-

“hardly a day passes now when some new alleged medical use of an embryos is signposted in the media, one of the latest being a cure for total blindness. The moral and ethical problems in this area are legion. There is no common agreement on their resolution. Since most of these problems are of an ultra
modern nature, I rather doubt that there is a constitutional solution to them, that does not mean that there cannot and indeed should not be regulation by the Oireachtas.”

Mr Justice Fennelly in his judgement states:-

“Counsel for the Attorney General argued before us that there is no law or public policy regarding the protection of frozen embryos. In short that they have no legal status.”

Article 18 of the Council of Europe Convention on Human Rights and Biomedicine prohibits the creation of human embryos for research purposes.

The Charter of Fundamental Rights of the European Union which is now, by virtue of the Lisbon Treaty, applicable in this country, prohibits the use of embryos for the cloning of human beings.

The United Nations Declaration on Human Cloning also prohibits the use of embryos for the cloning of human beings.
Appendix III

University College Cork Policy on Human Embryonic Stem Cell Research (Feb 2008)

University Research Ethics Board (UREB)

It is the responsibility of scientific researchers who seek to conduct research using human embryonic stem cells (hESC) to ensure that such research is carried out according to rigorous and transparent standards of research ethics.

There is a current legislative vacuum in Ireland regarding the research use of embryos created for purposes of reproduction or the creation of embryos for research purposes.

UREB considers it preferable that researchers who seek to carry out research using hESC should apply to do so using hESC lines imported from approved sources in other jurisdictions. This policy will be reviewed in light of any judicial or legislative changes that impact on the legal situation pertaining to the use of hESC in Ireland.

UREB also recommends that

1. Every research project involving the use of hESC must be submitted to UREB for ethical review before the start of the project.

2. To facilitate review and monitoring UREB will establish a subcommittee with appropriate expertise to advise UREB in relation to the following:

   - the scientific merit of the research aims of the project
   
   - the repository from which it is proposed that the hESC lines will be imported including its protocols for deposit, storage and distribution of hESC lines
   
   - the source of the cells used in the production of the cell lines and in particular the procedures used in the procurement of the cells to ensure voluntary informed consent of donors, privacy, and absence of any payment or other inducements to donors
   
   - adherence to bio-safety and quality assurance measures
   
   - the relevant expertise of the investigator to undertake the research
the scientific justification for the use of hESC lines, including the feasibility of using alternative research methods (such as animal or in vitro models) that do not require the use of hESC lines.

3. Approval of all research projects shall be by a majority of UREB members after consideration of the scientific and ethical issues.

4. UREB will also decide the frequency and timing of ongoing monitoring of approved projects to ensure that the conditions of the ethical approval are complied with throughout the project.

5. An appeal from UREB’s decision may be made to the Academic Council Research Committee.
Appendix IV Court of Justice of the European Union

According to Advocate General M. Yves Bot, ifipotent cells carrying within them the capacity to evolve into a complete human being must be legally classified as human embryos and must therefore be excluded from patentability.

Nor can a procedure using other embryonic stem cells, known as pluripotent cells, be patented where it first requires the destruction or modification of the embryo.

Mr Olivier Brustelo holds a patent, filed in December 1997, which concerns isolated and purified neural 1 precursor 2 cells, produced from human embryonic stem cells used for the treatment of neural defects. According to information provided by Mr Brustelo, the first clinical applications have already been developed, in particular for patients suffering from Parkinson's disease.

On the application of Greenpeace eV, the Bundespatentgericht (Federal Patent Court, Germany) declared Mr Brustelo's patent invalid, in so far as it related to procedures allowing precursor cells to be obtained from human embryonic stem cells.

The Bundesgerichtshof (Federal Court of Justice, Germany), to which Mr Brustelo had appealed, decided to stay proceedings and refer questions to the Court of Justice on the interpretation, in particular, of the term "human embryo", which is left undefined by European Parliament and Council Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions. 3 The questions concern, essentially, whether the exclusion of the human embryo from patentability concerns all stages of life from the fertilisation of the ovum or whether other conditions must be satisfied, such as the attainment of a certain stage of development.

As a preliminary, the Advocate General, Mr Yves Bot, makes the point that the Court is being called upon for the first time to consider the concept of use of embryos for industrial or commercial purposes contained in Directive 98/44. Having stated at the outset his awareness of the extreme sensitivity of that question and the importance of the philosophical, moral, human, economic and financial issues at stake, the Advocate General begins his legal analysis by stating that, since the directive pursues the objective of establishing effective and harmonised legal protection of biotechnological inventions, the embryo needs to be given an autonomous definition in EU law. That analysis is supported by the first interpretations by the Court in its case-law concerning that directive.

After pointing out the major divergences existing between the legislation of the Member States and the impossibility, in the current state of scientific knowledge, of using a criterion of that nature capable of being recognised by all the Member States, the Advocate General bases upon the wording of the directive, which, in Article 5(1), protects "the human body, at the various stages of its formation and development".

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1 Neural cells are defined as immature cells which are capable of forming mature nervous system cells, such as neurons.
2 i.e., immature body cells which are still able to multiply. These precursor cells have the capacity to develop and differentiate into specific mature cells.

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