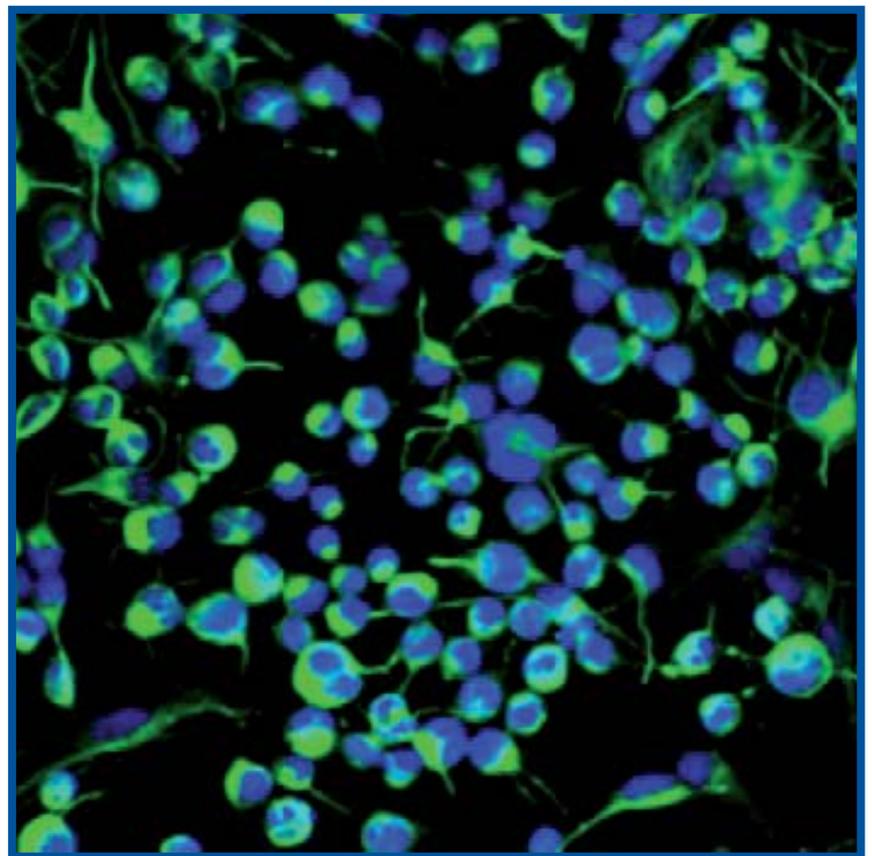


Ethical legal and social issues in stem cell research and therapy

A briefing paper from Cambridge Genetics Knowledge Park



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I. Introduction

Stem cell research is an important new domain of biomedical research that has the potential to offer viable therapeutic options for debilitating disease and injury. However, stem cell research has proved something of a political, ethical, social and legal minefield, creating challenges for regulatory bodies, policy makers and scientists as they traverse their way through a tangled web of regulations and moral proselytising.

I.1 Scientific background

Stem cells are cells that have the potential both for self-renewal and to differentiate into specialised cell types. Stem cells found in the early mammalian embryo, at around 5-7 days after fertilisation, are able to give rise to all the different cell types of the organism. These embryonic stem (ES) cells are said to be 'pluripotent'. Stem cells are also found in the fetus, in umbilical cord blood, and in tissues of the adult organism, where they provide a pool of progenitor cells for the development and renewal of specific tissues such as the blood and the nervous system. There is evidence that some non-embryonic stem cells are able, under appropriate conditions, to differentiate into cell types other than those of the tissue from which they are isolated, but the degree of their developmental plasticity is not yet clear.

Stem cell researchers hope that it might be possible to use stem cells, or specialised cell types differentiated from them, to repair organs and tissues damaged by injury or by degenerative or auto-immune diseases including Parkinson's disease, multiple sclerosis and type I diabetes. Stem cell-derived transplants could be autologous (derived from the patient – only applicable in the case of adult and possibly cord blood stem cells) or allogeneic (derived from an unrelated but immunologically matched donor).

Other applications for stem cells are also being investigated, for example as sources of differentiated cell types for drug screening and toxicity testing, or as vehicles for drug delivery. Research on stem cells also promises to yield new insights into the molecular control of cell differentiation.

Any stem cells, or cell types derived from them, that are transplanted into an unrelated recipient run the risk of causing a serious immune reaction and may be rejected. The process of cell nuclear replacement, or 'therapeutic cloning', has been suggested as a way of avoiding this problem by making it possible to derive ES cells that are genetically (and therefore immunologically) identical to the recipient. Cell nuclear replacement involves injecting the nucleus from a normal body cell into an oocyte (egg) from which the nucleus has been removed, creating a construct that can be induced to behave as if it were a fertilised egg, dividing and developing into an embryo. This is the same process that was used to create the first cloned mammal, Dolly the sheep. The difference is that in 'therapeutic cloning' the aim is to use the cloned embryo to derive ES cells, not to implant it in a woman's uterus with the purpose of producing a cloned human being.

In February 2004, Dr Hwang Woo-suk and his colleagues in South Korea reported that they had successfully cloned 30 human embryos, from which they had extracted stem cell lines.¹ In May 2005, Hwang and his team published a paper claiming they had made 11 patient-specific cell lines using donated eggs and the DNA from people suffering from diseases such as juvenile diabetes and spinal cord injury.² However, both of these papers have now been shown to contain fraudulent data and have been retracted by the publisher, Science magazine.^{3,4} Ethical issues have been raised by this scandal and these will be discussed more fully throughout this paper.

While these revelations of research misconduct have shocked the scientific community, they have not deterred researchers from continuing work to create cloned human ES cells. Researchers from Newcastle have created cloned blastocysts but they only survived a short number of days.⁵ Researchers believe that therapeutic applications of the approach are likely but are still many years away. Not all cell nuclear replacement research is aimed at developing transplantation therapies. For example, studies using cloned ES cells from patients suffering from genetic or other diseases may yield valuable information about the way in which these diseases develop. There is strong Government and charitable sector support in the UK for funding stem cell science. Besides increased funding for

research activities, the Government launched in 2005 the UK Stem Cell Initiative 'to safeguard the UK's long-term excellence in the field of stem cell research and to shape the transformation of research into patient benefit and commercial opportunities.' A MORI poll has also shown that there is public support in the UK for the use of embryos for research into finding treatment for serious diseases and fertility research.⁶

Research programmes are underway using both ES cells and various types of non-embryonic stem cells; most scientists agree that all types of stem cells should be studied to maximise the chances that successful therapies can be developed. There is no significant controversy surrounding research on adult stem cells. ES cell research, however, has aroused vigorous debate.

Less public attention has been paid to the issues surrounding the therapeutic use of stem cells and cellular products derived from them. By way of shorthand, we refer to this clinical use of stem cells as 'stem cell therapy'. This new branch of medicine represents a subset of the wider field of cell and tissue therapy. Many of the issues that have to be addressed in developing a safe and robust regulatory regime for stem cell therapy are common to both ES- and adult stem cell-derived therapies. Other clinical uses of stem cells are foreseen that we do not address in specific detail because they represent a standard variation of existing medical technology and therefore raise no new issues. For example, biomolecules isolated from stem cells might be used therapeutically to stimulate a patient's own endogenous stem cells.

1.2 Aims of this paper

This second edition updates the material presented in the first edition. As before this paper has two main aims:

- to present a critical summary of the major debates and policy responses relating to ES cell *research*, drawing attention to some of the challenges posed by conflicting moral values in an era of global scientific endeavour
- to provide an analysis of the key ethical and regulatory implications for stem cell *therapy*

Our discussion focuses primarily on the current position in the United Kingdom, and on the issues arising from research on ES cells and their potential medical applications. Selected references are cited as examples of where further information and discussion may be found, but we have not attempted to compile a comprehensive bibliography.

We do not discuss in this paper the issues raised by the use of fetal or cord blood cells. A detailed discussion of cord blood banking in both the public and private sectors has been published.⁷

2. Embryonic stem cell research

Any society grappling with the question of whether to allow embryo research, and under what conditions, must first resolve its stance on the issue of the moral status of the human embryo. In this part of the paper, we begin by outlining the major arguments that have been put forward on this question. We move on to summarise the current legal and policy stance on embryo research in the UK, then highlight some further issues raised by such research, including the sourcing of embryos and oocytes and the consent of donors, and the different values placed on embryos by different groups in society.

2.1 The moral status of the embryo

In order to derive ES cells, the embryo must be destroyed at around 5-7 days after fertilisation (the blastocyst stage) by harvesting the cells from the part of the embryo called the inner cell mass. The question is whether it is right to do this.

2.1.1 The embryo, the 'pre-embryo' and the concept of personhood

At one end of the spectrum of views on this issue is the belief that the embryo, from the moment of conception, is created by God and is a person in its own right with the same moral status as an adult human. Those who hold this view, such as Catholic Bishop Richard Doerflinger, say that it is wrong to destroy embryos of any gestational age, for any purpose.⁸

This absolutist view is not shared by all those with religious beliefs. An alternative stance is that the embryo acquires full personhood, and the moral rights that go with this status, by gradual stages during the process of development between conception and birth. It follows that it might be ethically acceptable, under certain circumstances, to use embryos for research. This view has been defended by some theologians from other faiths, including Protestant Christians, Jews, Muslims and Buddhists, and is also held by many people who do not have a religious faith.⁹

In the debate about embryo research, the formation of the primitive streak has been suggested as a key cut-off point. This event, the appearance of a surface thickening that marks the first visible organisation of the embryo, occurs at around 14 days after fertilisation. The term 'pre-embryo' was introduced in 1985 to describe the early embryo up to this point. One argument that was used to justify drawing a distinction between the pre-embryo and the embryo proper was that it is possible for the pre-embryo to split into two, or twin. It followed, according to this argument, that the pre-embryo was not a 'person', given that the concept of personhood is often taken to imply indivisibility or individuality.

Others have argued that the concept of the pre-embryo is a rhetorical device invented to justify embryo research and that it creates an artificial division in what is, in reality, a continuous developmental process.^{10,11} Nevertheless, the 14-day limit is viewed in the UK as commanding broad social acceptance and has been adopted in this country as the cut-off point for allowing embryo research.

2.1.2 The embryo's 'right to be born'

Further protagonists in the debate, such as Glenn McGee and Arthur Caplan¹², argue that those who would seek to ban ES cell research need to show more than just that embryos have the moral status of persons. They say it must also be shown that the embryo has a positive right to be born. Many reproductive biologists argue that it is difficult to assert that such a right exists, given the high level of natural wastage of embryos. In addition, some long-accepted methods of artificial contraception, such as the intrauterine device, work not by preventing conception but by preventing implantation of the early embryo. It seems inconsistent for society to condone such methods (or indeed to allow abortion for any reason) while condemning the use of embryos for research.

2.1.3 The use of embryos that would otherwise die or be destroyed

Gene Outka¹³ defends a more conservative but still a permissive position. From his perspective embryos do have intrinsic moral value but it might be permissible to use embryos that are surplus to *in vitro* fertilisation (IVF). The idea here is that if embryos are definitely not going to be implanted then 'nothing is lost' by their being used for ES cell research. Such claims imply that it might be acceptable to use spare embryos for ES cell research even if it is the case that they have the moral status of persons.

This argument has found favour in some countries which sanction the use of surplus IVF embryos for research but not the creation of embryos specifically for that purpose. The distinction here is between using, for an important medical purpose, embryos that have been created by a couple who are trying to have a child but which have to be destroyed because they cannot be implanted, and deliberately creating an embryo with the aim of destroying it. The latter, it is argued, is immoral because it treats the embryo as a mere commodity.¹⁴

Another suggested solution to the problem of destroying viable embryos is to create embryos that cannot develop to term. This can be done, for example, by inducing unfertilised eggs to develop as if fertilisation had occurred, producing 'parthenogenetic' embryos that can go through the early cleavage divisions to the blastocyst stage but cannot develop into a fetus.¹⁵ Other techniques for creating 'ethical embryos' have also been suggested.¹⁶ Unfortunately, however, these ideas run the risk of trying to please everyone but pleasing no-one. Those with absolutist religious views are likely to regard the creation of such 'embryos' as unnatural and immoral, while scientists object that ES cells created in this way are likely to have abnormalities that will seriously limit their usefulness.

2.1.4 'Respect' for embryos

Meyer and Nelson¹⁷ defend a liberal ethical position that is shared by many scientific researchers in the stem cell field and has been largely adopted by policy makers in the UK. They refute the notion that it is appropriate to think of embryos as having the full status of persons but propose that we might have other reasons to 'respect' them. They use Mary Anne Warren's¹⁸ taxonomy of kinds of moral respect to argue that embryos deserve respect because of the mere fact that they are alive and because people do ascribe value to them. In this view the 'respect' accorded to embryos can take the form of needing an important justification for destroying them. The alleviation of the suffering of people afflicted by serious diseases can be regarded as providing such a justification.

2.1.5 Competing ethical principles

In the debate about embryo research, including stem cell research, it has been pointed out that the moral status of the embryo is not the sole ethical consideration: there is also an obligation to do everything possible to alleviate the suffering of existing human beings and, if ES cell research has the potential to achieve that end, there is a moral duty to pursue it.¹⁹ The question, then, becomes one of achieving a balance between competing ethical principles.

In deciding where this balance should lie, it has been suggested that various considerations should be taken into account, including the likelihood that the research will be successful, and the possibility of achieving the same goal (that is, better treatments for serious diseases) by other means. Some people who oppose ES cell research suggest that it is unjustified because better prospects are offered by adult stem cell therapy. The difficulty with this position, however, is that it is not possible to know whether it is true unless the research is done, and if other lines of research prove unsuccessful, valuable time will have been lost and many people will have suffered and died in the meantime. Policy makers in the UK have accepted the view, held by most scientists in the field, that research on both embryonic and adult stem cells should be pursued.

2.1.6 Cell nuclear replacement

A further ethical debate surrounds the use of cell nuclear replacement ('therapeutic cloning') to create embryos for the derivation of stem cells. Some people feel an instinctive distaste for what they regard as an 'unnatural' process. It is difficult, however, to find a logical defence for this view, as many long-accepted technological developments are similarly 'unnatural'.

Another frequently heard argument is that of the 'slippery slope': that perfecting techniques for cell nuclear replacement will make it more likely that reproductive cloning will eventually happen.⁹ Some scientists have sought to separate the two issues by rejecting the use of the word 'cloning' in the context of stem cell research.²⁰ Others, however, say that it would be misleading to deny that an embryo produced by cell nuclear replacement is a 'cloned' embryo. Instead, they prefer to counter the slippery slope argument by maintaining that society does have the ability to impose limits on the uses of technology and that all that is needed is a clear legal ban on *reproductive* cloning.

A further criticism of cell nuclear replacement research is that it is, as some have claimed for ES cell research in general, unnecessary and unlikely to lead to successful therapies for disease. Again, this cannot be resolved unless the research is done, but some have argued that the low chance of success does constitute an ethical reason for giving priority to other types of ES cell research.²¹

2.2 Regulation of embryo research and embryonic stem cell research in the UK

In the United Kingdom, vigorous debate throughout the 1980s on the ethics of embryo research was spurred by the development of IVF technology. Although it was not possible to reconcile the many and diverse views on embryo experimentation, Parliament eventually passed the 1990 Human Fertilisation and Embryology (HFE) Act, which has remained the cornerstone of the UK's regulatory framework in this area. The basic principles underlying the legislation were those set out in the Warnock report on human fertilisation and embryology.²² The UK is regarded as in the 'advance guard' among countries attempting to develop regulatory approaches to stem cell research.

2.2.1 The Human Fertilisation and Embryology Act and Regulations

Under the HFE Act it is legal to carry out research on human embryos up to 14 days after fertilisation. The 1990 Act enabled research to be licensed for certain specific purposes mostly related to improving the understanding and treatment of infertility or miscarriages, or to the development of new methods of contraception. Controversially, the Act also made it legal to create embryos specifically for research.

A statutory authority, the Human Fertilisation and Embryology Authority (HFEA), was set up to oversee compliance with the Act and to license laboratories wishing to carry out embryo research. Investigators applying for licences must comply with various conditions: for example, embryos must not be used or kept outside the human body at a stage of development beyond 14 days, and it must be shown that it is 'necessary or desirable' to use embryos to achieve the aims of the research.

The legislative framework for embryo research was amended, extended and judicially reviewed between 2001 and 2003. Most significantly, the government introduced the HFE (Research Purposes) Regulations 2001 following recommendations from a working party chaired by the Chief Medical Officer and a separate inquiry by the Nuffield Council on Bioethics.^{23,24} These regulations extended the list of purposes for which embryo research could be licensed by the HFEA to include research aimed at understanding the development of embryos, or understanding or treating serious disease. The main reason for the introduction of these regulations was to enable ES cell research, and its regulation by the HFEA.

The House of Lords conditioned its approval of the Regulations with a requirement that the government consider the results of an inquiry into stem cell research by a specially constituted committee of the House of Lords. That inquiry subsequently supported the terms and principles of the Regulations.⁹

The government is currently considering amendments to the HFE Act.³⁷ A public consultation was held in 2005 to solicit comments on proposed changes. The government sought views on updating the law to take into account changes in the science. For example, stakeholders were asked their opinion on whether the creation of human-animal chimeras, now seen as potential research tools, should be legislated for in the Act. The Act will also need to be amended in order to implement

requirements of the EU Tissue Directive and its related technical directives. The draft amendments are expected sometime in 2006.

2.2.2 Legal challenges to cell nuclear replacement

While Parliament was considering the 2001 Research Purposes Regulations, the political party Pro-Life Alliance instituted court proceedings challenging the HFEA's declaration that it could, if it received an application, grant a licence for research involving embryos created by cell nuclear replacement. The Alliance's principal argument was that embryos created in this way were not the result of 'fertilisation' and therefore were not covered by the HFE Act. If this was correct, the HFEA had no power to approve or reject research proposals; moreover, scientists were not even required to submit licence applications. Research with embryos created by cell nuclear replacement (a cloning technology) was unrestricted, or so it was argued.

Although initially successful in the High Court, the Alliance's argument was rejected by the Court of Appeal and the House of Lords.²⁵ The difference was that the senior courts were willing to give the relevant provision a purposive and liberal (rather than literal) construction.²⁶ This conclusion was reached even though the prospect of cloning by cell nuclear replacement technology was not contemplated by MPs at the time the Parliament passed the legislation, and the MPs had prohibited the only known method of cloning (embryo splitting). The House of Lord's decision was unanimous (5:0). It implicitly indicated that senior judges find cell nuclear replacement to be a promising field of medical research which raises the same ethical concerns as embryo experimentation (no more, and no less).

2.2.3 Ban on reproductive cloning

In the hiatus between the High Court's decision and the appeal court hearings the government faced a difficult predicament. It appeared that the judiciary might agree that the HFE Act was too narrowly worded to cover embryos cloned through the cell nuclear replacement process. Parliament felt bound therefore to pass swiftly the Human Reproductive Cloning Act 2002. This Act prohibits anyone placing an embryo in a woman if it has been created in anyway other than by fertilisation.

2.2.4 Management of stem cell resources: the UK Stem Cell Bank

The House of Lords' report on stem cells recommended the setting up of a national Stem Cell Bank to manage these resources under an ethical governance framework. The first of its kind in the world, the UK Stem Cell Bank (hosted by the National Institute of Biological Standards and Control) has two functions: as a repository for all stem cell types (adult, fetal and embryonic) and as a supplier of cell lines for basic research and clinical applications. The Bank accepts both stem cell lines developed in the UK and appropriately accredited lines created in other countries.

The first ES cell lines to be derived in the UK, developed at King's College London and the University of Newcastle, were deposited in May 2004 at the official opening of the Bank. These were both research-grade lines. No lines that can be used in clinical research have yet been deposited; the first are expected in 2007.²⁷ The Medical Research Council (MRC) maintains a register of stem cells lines that have been deposited.²⁸ By virtue of the European Medicinal Products Directive²⁹ and the European Commission Directive on Good Manufacturing Practice (GMP)³⁰, all medicinal products for human use must be manufactured according to GMP requirements to ensure quality and safety. Sheffield University has built one of the UK's first GMP-quality laboratories for creating clinical grade ES cell lines.³¹

An independent Steering Committee evaluates all applications to deposit and to access cell lines. Requests for deposits or access must show that all ethical approvals, licences and authorisations are in place. A Management Committee oversees the operation of the Bank itself. The Bank's Code of Practice for the Use of Human Stem Cell Lines broadly outlines the criteria that should be observed when deriving and using human stem cell lines.³²

Sections of the Code set rules concerning information to be given to potential donors and consent requirements. The central idea is that donors are asked to gift their stem cells, relinquishing all future control, after comprehensive information is provided to them about the implications of doing so. The

Code will be updated to take into account requirements arising from the implementation of the Human Tissue Act 2004 and the EU Tissue Directive. These requirements will address, for example, the selection and testing of donors and the procurement and processing of tissues and cells. The implications of these provisions are discussed further in later sections of this paper.

The HFEA has made compliance with the Code a condition of a licence for ES cell research, and requires a sample of all ES cell lines be deposited with the Bank. One justification for this requirement is that mandatory banking will minimize the numbers of embryos that are used, which some say is a mark of 'respect'. Strictly speaking, it is questionable whether the HFEA has legal power to make the Code binding on those who apply for its licences, since its statutory powers apply to the creation and storage of embryos and the storage of gametes. Stem cell lines are neither embryos nor gametes. The HFEA is relying on a broad interpretation of its power to license embryo research. It asserts it has the power to limit how the *results* of that research can be used.

2.2.5 Areas of ambiguity in the current regulatory framework for research

Notwithstanding some clarification from the courts and Parliament, there remain some ambiguities in the governance of embryo research. As noted above, the HFEA may only grant a licence if the research is 'necessary or desirable'. This phrase is not defined. The HFEA granted its first licence to create embryos by cell nuclear replacement in August 2004 to researchers at the Newcastle Fertility Centre at Life³³; a second in January 2005 to the Roslin Institute in Edinburgh.³⁴ An employee of a special interest group decided to challenge the HFEA's decision to grant the first licence.³⁵ He asked that the grant of the licence be quashed and for a declaration that the HFEA had acted unlawfully in granting it. However, he withdrew his challenge prior to the High Court deciding whether to grant leave to commence procedures for judicial review.

The 2001 Research Purposes Regulations allow research to be licensed where it is likely to increase knowledge about 'serious disease'. The point at which one differentiates serious disease from less serious disease is unclear. One issue is whether this line is to be judged from the perspective of an individual or society.^{36,9} The government seems to have had the former in mind, but regulators might be persuaded to adopt a broader public-health definition in relevant situations. There is also an element of doubt about the legitimacy of basic cellular research that uses embryos but has no direct therapeutic application. It might be permitted if it can be shown to be a necessary precursor to the development of therapies for serious diseases. It is less clear whether ES cell research aimed at improved drug discovery or drug safety-tests could be licensed.

The role of the HFEA in embryo research may be modified in the future. In 2008 the HFEA is due to merge with the Human Tissue Authority, a statutory body to be set up under the provisions of the Human Tissue Act 2004, to create a new authority called the Regulatory Authority for Tissue and Embryos (RATE).³⁷

2.2.6 Approaches to regulation in other countries

A full discussion of regulatory approaches in other countries is beyond the scope of this paper but a few broad comparisons can be made. The HFEA's licensing system has been used as a template for governance by some other jurisdictions that permit IVF and embryo research, though several of these countries stipulate that researchers may only use embryos that are surplus from IVF programmes and may not create embryos specifically for research. Comparative legal research suggests that national policies reflect each country's historical experience, philosophical and religious traditions.

Although no firm generalisations can be made, countries with a strong Catholic tradition tend to be more restrictive.³⁸ Some nations, such as Australia and Canada, take the view that, at this point in time, new embryos are not required to advance research. Supernumerary embryos from IVF treatments are thought to suffice, especially when combined with the possibility that adult stem cell therapies might succeed. This position may change in Australia, as an independent review committee has recently recommended to the Australian government that the ban on therapeutic cloning should be lifted and a stem cell bank should be established.³⁹ Their government will be considering the recommendations.

In the United States, a Presidential order restricts federal funding for ES cell research to a small number of cell lines that were already in existence at the time of the order, in August 2001.⁴⁰ There has been, however, growing support in the US Congress for ES research. In May 2005, the US House of Representatives passed the Stem Cell Research Enhancement Act 2005 that would allow research on ES cells using donor IVF embryos.⁴¹ The legislation still needs to be approved by the US Senate. If the Senate does approve the legislation, President Bush has said he will veto it. Whether there are enough votes in Congress to override the veto (two-thirds of the members in each house) remains to be seen. In the absence of any federal legislation, however, individual states are free to go their own way, and several – most notably California – have pledged large sums of money for ES cell research. Private funding for ES cell research is also unaffected by the Presidential order. Many commentators have criticised the current lack of a coherent regulatory framework in the United States.³⁸

2.2.7 European regulation

Some member states of the European Union (EU) have pressed for harmonisation of European legal standards. Not surprisingly the proposals have been considerably stricter than UK law, since many European nations prohibit the deliberate creation of embryos for research purposes while supporting other types of stem cell research. For example, the Council of Europe's Convention on Human Rights and Biomedicine prohibits the creation of human embryos for research purposes⁴², thereby also prohibiting therapeutic cloning research, but not ES cell research based on supernumerary IVF embryos.

Conventions of the Council of Europe (not to be confused with Directives of the European Union) are binding only on countries that have signed and ratified them; the UK has not ratified the Convention on Human Rights and Biomedicine. In a push for binding legal standards, the European Parliament proposed amendments⁴³ to the draft EU Tissue Directive.⁴⁴ If accepted, the amendments would have prohibited therapeutic cloning and ES cell research. However, as it turned out, the European Council rejected the amendments and the EU Parliament did not pursue the issue further.

There has also been protracted wrangling within the EU over the issue of EU funding for ES cell research. Again, no consensus stance was reached. The current situation is that applications can be made for funding from countries where such research is legal, and they are considered on a case-by-case basis. Conservative members of the EU Parliament have again called for a ban on funding for ES cell research in the upcoming Seventh Research Framework Programme (FP7)⁴⁵ but the details of the budget have not as yet been finalised.

2.2.8 International regulation of stem cell research

In a further push for a harmonised regulatory position, in 2001 France and Germany proposed the negotiation, at the level of the United Nations, of an international convention against the reproductive cloning of human beings. Premised on the distinction between cloning of human embryos for reproductive purposes and cloning for other purposes, including research, the proposed treaty would have imposed a global ban on the former while leaving the latter for regulation at the national level.

A competing proposal was subsequently made by a group of States (including the United States of America and Costa Rica), which rejected this distinction and instead called for an international convention prohibiting human cloning, regardless of its purpose. This proposal had the support of over 60 nations but was highly contentious as it sought to prohibit all forms of human cloning, including that used for ES cell research. It was, in turn, opposed by a group of States supporting a revised version of the original Franco-German text (now spearheaded by Belgium). The revised text established a basic prohibition on cloning for reproductive purposes, but gave States the choice of either banning, imposing a moratorium on, or strictly regulating human cloning for other purposes.

The American/Costa Rican proposal was also opposed by a group of predominantly Islamic States which were concerned about its underlying premise, namely that the human embryo in its earliest stages constitutes life – an essentially Christian perspective. Since 2002, efforts at finding a consensus solution have proved fruitless. In 2003, an attempt by the supporters of the total ban to break the deadlock by submitting it to a vote was thwarted by a procedural motion (to postpone the matter) in the Legal Committee of the General Assembly, which was carried by 80 votes to 79. In the face of a continued stalemate in 2004, the Italian delegation proposed a compromise draft resolution that

would drop the idea of an international treaty and replace it with a draft declaration seeking to preserve the position of both sides. The Legal Committee voted in February 2005 to approve a non-binding declaration banning human cloning.⁴⁶ As the wording can be interpreted to include therapeutic cloning, the UK voted against the declaration and will not recognise it.

2.3 Ethical sourcing of embryos and oocytes

Those societies that decide to allow research on human embryos must ensure that the rights and values of the donor couple or individuals (in the case of gamete donation) are respected. Their embryos, 'left over' from IVF treatments or specifically created, are managed in various ways: they can be maintained in a frozen state for up to five years (which may be extended under certain conditions), they can be donated to other infertile couples, they can be made available for research purposes, or they can be destroyed.

2.3.1 Informed consent for embryo donation

At a legal level, donors are protected by requirements for informed consent. The HFE Act 1990 stipulates that UK donors of embryos for research should be given appropriate counselling and 'such relevant information as is proper' to make a decision whether to donate. They should also be informed that prior to the embryo being used in research, they may vary or withdraw the terms on which they gave consent. The HFEA's Code of Practice for IVF clinics states, in addition, that where consent is sought for the use of embryos in stem cell research, donors must be given 'thorough and appropriate information, including that any stem cell lines may continue indefinitely and may be used in different research projects'.⁴⁷

There are, however, more subtle social and psychological issues that must be considered. HFEA guidelines recommend that IVF clinics ask couples to designate in advance how they want their extra embryos to be managed. However, couples undergoing the physically and psychologically stressful process of infertility treatment⁴⁸ may not be in the best environment to assess carefully the implications of donating their embryos or gametes for research purposes. There is a danger that, despite being told they are under no obligation to consent they may nevertheless feel under pressure to do so, or be overwhelmed by the extra burden that informed decision-making entails. (By contrast, the American Society for Reproductive Medicine recommends that consent for donation of embryos for research should only be sought once IVF treatment has ceased for whatever reason.⁴⁹) UK stem cell research coordinators, who give information to potential donors about stem cell research and take consent if agreed, have formed a national group, human embryonic stem cell coordinators organization (hESCCO), and are looking at developing a uniform process of giving information to potential donors. They are creating a core set of information sheets and consent forms for stem cell research.⁵⁰

Couples may have strong views about the types of research for which they would allow their spare embryos to be used. Research by Sarah Franklin and colleagues⁵⁰ has pointed at some of the reasons people give for their willingness (or lack of) to donate their spare embryos. Positive reasons include wanting to help others suffering from infertility and to help research in general. Some of those who would not donate said they considered their embryo to be a potential life and therefore would not sacrifice it for research purposes; others would not donate because they did not understand what the research might entail. Some of those unsure wondered if the research was being done for the 'right' reasons. The hESCCO group has conducted a multi-centre national pilot study into patient attitudes towards donating embryos for stem cell research.⁵⁰

Social science research shows, too, that when questions about research are approached in the context of treatment, the boundaries between treatment and research tend to become blurred. In this situation, couples may not sufficiently understand the aims of the research or the psychological risks and benefits of donation, casting doubt on the validity of any 'informed consent' they may give.

2.3.2 The 'value' of embryos: waste material or valuable commodity?

The transformation of discarded embryos into stem cells has been referred to by one scientist as the process of turning 'garbage into gold'.⁵¹ For donor couples, the transformation of embryos from intended babies, to 'waste' or 'leftover' material and then finally to a source of precious stem cells is a complex and value laden process.⁵²

The justification for using materials that would otherwise be considered waste becomes a little less obvious when those materials are understood to have an economic value, especially when their initial creation incurred substantial financial (not to forget emotional and physical) cost to the donors. It has to be borne in mind that in the vast majority of cases, couples having made such an enormous emotional, financial and physical investment are unlikely to have reaped the benefit in terms of a successful pregnancy. On average, almost 80% of couples undergoing a single cycle of IVF treatment will be unsuccessful. Nevertheless it is illegal under the HFE Act for them to incur any financial reward for donating their embryos and they have no financial stake in any materials or procedures developed from their donation.

Most commentators support a ban on the 'sale' of embryos. For example, the European Group on Ethics in Science and New Technologies, which advises the European Commission, has stated that 'embryos as well as cadaveric tissues and fetal tissues must not be bought or sold...Measures should be taken to prevent such commercialisation'.²¹ The argument is similar to that used in connection with organ donation: financial incentives may induce people to act in a way that is not in their best interests.

2.3.3 Sourcing of oocytes for the creation of embryos or cell nuclear replacement

The creation of embryos for research or (eventually) therapy, either by fertilisation of an egg by sperm or by cell nuclear replacement requires a supply of oocytes. Oocyte donation entails hyperstimulation of the ovaries by hormone injection, followed by surgery to harvest the oocytes. It therefore carries significant medical risk for the donor.

Donated oocytes are used in infertility treatment, to help women who are unable to produce their own eggs. It is illegal for gametes (sperm or eggs) to be bought or sold; where any money is paid, it is understood to be payment not for the material itself but as financial compensation for the inconvenience, discomfort and expenses incurred. In the UK the HFEA have recently consulted the public about their views on a number of issues related to infertility treatment, including whether women undergoing IVF should be financially compensated for eggs that they wish to donate.⁵³ As a result of the consultation, the HFEA has decided that, in addition to reimbursement of out-of-pocket expenses, donors may receive compensation for loss of earnings up to a limit of £250.⁵⁴

Donation of oocytes to help infertile couples is generally regarded as an altruistic act though there has been controversy over the question of whether women who donate 'spare' eggs created during their own IVF treatment should be rewarded by discounts on the cost of their treatment. It is also debatable whether donation of oocytes for the creation of embryos for stem cell research should be regarded as altruistic, given the commercial profits that may eventually flow from this work. An increasing number of biotech and pharmaceutical companies are gathering an array of 'valuable' bodily materials including DNA samples and umbilical cord blood (also used for stem cell research) from various corners of the globe for scientific and commercial exploitation. Nevertheless, the issue of making payments for gametes remains ethically controversial as many see this as leading to the 'commodification of the body'⁵⁵ and furthering the exploitation of women's bodies in particular.

Research on therapeutic cloning exacerbates the problems associated with oocyte donation because of the extremely low efficiency of the process. Hwang and colleagues, in their two discredited papers claimed that they required the use of 427 eggs to derive a cloned blastocyst but in reality they used many hundreds more than they reported. It has also emerged that many of the women have suffered from ovarian hyperstimulation syndrome as a result of donating.⁵⁶ When the European Group on Ethics in Science and New Technologies recommended in 2002 that therapeutic cloning research should not be pursued at present, its principal reason was the ethical problem involved in sourcing oocytes for such research.²¹

The discredited Korean work has also raised important questions about informed consent for oocyte donation. Controversy first broke out over the work when it emerged that some of the eggs used in the research had apparently been donated by a female scientist who was part of the research team. It has now been determined that a number of Hwang's team had donated eggs.³ Bioethicists have pointed out that this was at the very least a breach of good practice:

donors and researchers should be kept at arm's length, so that investigators cannot influence donors either consciously or inadvertently.⁵⁷ It has also been argued that recruitment of students or junior employees as egg donors might lead to a perception of coercion by senior investigators. The Korean National Bioethics Committee is considering tightening their ethical guidelines in the wake of the Hwang scandal, to include limiting the number of times a woman might donate her eggs in her lifetime to two and banning junior researchers from donating their eggs.⁵⁸

In light of the controversy surrounding this subject, the HFEA is reviewing its policy for donors of eggs, sperm and embryos for research purposes.⁵⁹ Currently in the UK, the majority of eggs and embryos used in licensed research projects are obtained from women undergoing fertility treatment. The HFEA is now considering the evidence for permitting other categories of donors, such as altruistic donors, 'known donors' (eg employees of fertility clinics or friends or relatives of patients with serious disease), and egg sharers. The rules for importation of gametes for licensed research are also being reviewed. A revised policy is expected later in 2006.

3. Other issues raised by stem cell research

The issues we have discussed so far are, for the most part, ones that relate either to embryo research in general, or to ES cell research in particular. There are, however, other issues that arise in stem cell research. While these issues – which include the sourcing of non-embryonic tissues, the challenges caused by differing ethical values in an era of global science, and the problems to be addressed when research reaches the stage of clinical experimentation – are not unique to the field of stem cell research, they must nevertheless be taken into account by scientists and policy makers if the field is to progress in a socially acceptable way.

3.1 Sourcing other tissues for stem cell research and transplant: legal issues

Donations of tissue other than gametes and embryos, such as stem cells from adults, are not generally thought to be problematic in ethical terms, provided tissue is taken in accordance with prevailing laws including laws on consent. Broadly speaking, the legal standards differ depending on a donor's capacity to consent (eg whether the donor is a fetus, young child, mature child, adult or deceased person), and the associated risks and sensitivities (eg whether the donation concerns regenerative tissue, non-regenerative tissue, or an organ).

Until the Human Tissue Act 2004 takes effect in 2006, donations for stem cell research and transplant (other than embryos and gametes) will be largely governed by the common law. Even once the Human Tissue Act is implemented, the common law will continue to regulate the removal of tissue from the living and use of material 'created outside the body', both of which are excluded from the scope of the Act. However, the Human Tissue Act alters the current law in relation to use and storage of material from the living and removal, use and storage of material from the dead in significant ways.⁶⁰ Most notably a researcher is required, subject to some exceptions, to obtain 'appropriate consent' before using or storing a tissue sample for the purposes of research or transplant. ('Appropriate consent' is not required for research where the tissue comes from a living person whose identity is and is likely to remain anonymous, and the research has been ethically approved in accordance with regulations made by the Secretary of State). A researcher who fails to obtain 'appropriate consent' could be prosecuted for a criminal offence for which the penalty is 3 years imprisonment, a fine or both. This is regardless of the sample's size or from whom it came, although the precise steps required for 'appropriate consent' may vary in different circumstances. These are not described by the Act, but the Human Tissue Authority has published draft codes of

practice that include guidance on consent.⁶¹ Final versions of the codes will be published in Spring 2006.

3.2 Embryo and stem cell research in an age of global science

Increasingly, biomedical research is a global enterprise. Collaborations, both academic and commercial, often cross national boundaries, and both biological material and data are transferred among scientists and institutions in different parts of the world. Differences in moral values and cultural attitudes can have an impact on the practice of global science. In South East Asia for example, where there is a great deal of biotech activity, such research seems to be subject to more relaxed ethical restraints than those that apply in western countries. It would be a mistake to conclude from this that this research lacks any ethical sensitivity⁶² but it would be fair to say that these countries do not share the importance placed on informed consent by western countries.

Such differences raise a dilemma when scientists have the option of importing material for stem cell research. The central question is whether it is ethical or legal to use imported material where the consent process meets the rules of the country of collection but not the standards of ethical sourcing that apply in the country of destination.

Legal standards in the UK try to avoid the worst risks of exploitation whilst recognising that valuable imports will be stopped if European standards are strictly insisted upon. Under the HFE Act, import of embryos or gametes is regulated through the licensing arrangements for embryo research: a licensee who wishes to import embryos or gametes must apply for and receive authorisation from the HFEA.

Other tissue imports are regulated by the Human Tissue Act 2004, which relaxes the rules ordinarily applying to non-imported material. The rule that tissue may only be used in accordance with appropriate consent is specifically abrogated. Nonetheless, the Human Tissue Authority is preparing some guidance on good practice and scientists importing ES cell lines should seek the approval of the Steering Committee of the UK Stem Cell Bank.

The regulatory system has thus provided a skeleton framework for monitoring the acceptability of using imported bodily material in stem cell research and therapy. But more detailed guidance remains to be developed. Given the continuing ethical doubts and controversy, this will not be straightforward. Just as difficult as setting appropriate standards is the question of rule design. This needs to guard against an international black market developing in embryos, gametes, tissues and cell lines, which is an all too familiar problem with kidney transplants.

3.3 Clinical studies

Some approaches to stem cell therapy, mostly involving autologous transplants or transplants derived from fetal tissue, have already reached the stage of clinical studies in patients. Clinical studies are subject to detailed governance procedures, including approval by research ethics committees and, in some circumstances (gene therapy is an example) by other regulatory bodies. In the EU, member states must govern clinical trials that involve investigational medicinal products in accordance with the EU Clinical Trials Directive.⁶³ The provisions of this Directive have been incorporated into UK law as the Clinical Trials Regulations 2004. The Directive includes certain rules about the acceptable level of risk, the operation of ethics committees, the responsibilities of researchers and research sponsors, and consent.

However, once again, there are more subtle issues to consider.

3.3.1 Unrealistic expectations and 'hype'

ES cell research in particular has been subject to a great deal of media and scientific hype.⁶⁴ The campaign headed by the late actor Christopher Reeve, who was paralysed by a spinal injury sustained in a riding accident, was targeted primarily at the US Federal Government to lobby for the removal of

restrictions on ES cell research in the US, but this campaign has reached a much larger and more general audience. Reeve, the actor who played the movie role of Superman prior to his injury, has helped to create 'heroic' images and ideas about the possibility of stem cell medicine. His campaign and those of others, while helping to alert public attention and enlist support for stem cell research, have contributed to public perceptions that such cures are not only likely but 'just around the corner'.

These unrealistic perceptions have been exacerbated by media coverage. In relation to the media coverage of news-breaking medical research more generally, Rebecca Dresser, for example, has shown that journalists often use extravagant language, deploying terms such as 'breakthrough' to dramatise a story, and complicated research indications are often over-simplified, creating unrealistic expectations of cures. In her study of patient advocacy, Dresser has shown that the media can play a significant role in contributing to 'therapeutic misconception'.⁶⁵

The phenomenon of 'therapeutic misconception' is relatively common in clinical trials (as Appelbaum et al note).⁶⁶ For example, despite explanations to the contrary, patients offered the opportunity to participate in clinical trials frequently believe that research protocols are designed to benefit them directly rather than to test or compare treatment methods. Even potential subjects who demonstrate an understanding of randomization, double-blinded studies, and the use of placebos, often persist in a belief that they will receive the treatment most likely to benefit them.

In the context of clinical studies on stem cell therapies, attempts will need to be made to dampen any unrealistic expectations in prospective participants. Awareness of the problem by researchers is a starting point.

3.3.2 The design of clinical studies

Careful consideration will also need to be given to the design of clinical studies. Although the randomized controlled trial is the preferred methodology insofar as it is the scientific gold standard, from an ethical perspective it may be problematic for early-stage studies. For example, a great deal of criticism has been levelled at double blind, placebo-controlled fetal neural cell transplant trials that were conducted in patients with advanced Parkinson's disease in the US.⁶⁷ Patients in the placebo arm were subjected to sham neurosurgery that involved drilling holes into their skulls. Many bioethicists and clinicians have expressed concern about exposing patients to such risks where there is no possibility of benefit⁶⁸. They argue that where the experimental treatment involves invasive surgery – as it will in many applications of stem cell medicine – the control treatment should not be sham surgery but the current clinically approved treatment and standard of care. The fetal tissues transplant surgery has also been criticised on methodological grounds: it is claimed that the inclusion of the sham surgery control group did not make the trials more scientifically valid than had they simply included a control group who had received medical treatment as indicated.

Bioethicist Renee Fox⁶⁹ also advocates a more patient-oriented approach for early clinical studies and regrets what she sees as a shift away from a patient centred approach of the past, where such studies moved between the laboratory and the bedside and where the design of the study was such that alterations could easily be made to accommodate patients. These debates raise questions about whether the clinical trial model is the most suitable model for early studies or whether there may be alternative models that satisfy both ethical and methodological concerns. Yet again, such issues are complex and hotly contested but they will need to be undertaken by those wishing to embark on stem cell research involving patients, not least given that the eyes of the media and the public at large are likely to be firmly fixed on this research.

3.3.3 Balancing risks and benefits in clinical studies

Many devastating diseases have been suggested as possible candidates for stem cell therapy. New therapies can carry considerable risks, and the potential complications and dangers of stem cell therapy are serious, including tumour formation, infection and immunological complications. It could be argued, therefore, that the priority for stem cell transplantation studies should be terminal diseases of older people, such as late-stage Parkinson's disease or Alzheimer's disease.

On the other hand, a greater number of life-years would be gained from successful treatment of younger people suffering from autoimmune diseases such as Type I diabetes or multiple sclerosis, or from brain injury. Where no other treatment is available, high-risk experimental treatments are easily justified but if, as in the case of Type I diabetes, relatively effective therapies are available, the decision to enrol children or young adults in clinical trials of stem cell therapies is a serious one.

Many people suffering from terminal or debilitating diseases, fearing that the time available to them for treatment is limited, have been travelling to other countries, such as Russia, India or China, to take advantage of untested stem cell therapies.^{70,71} There are no regulatory bodies to monitor these treatments; no data is published in peer-reviewed journals to enable others to replicate any results. These procedures cost large amounts of money but have no proven scientific efficacy and may cause harm. The failure of these 'rogue' treatments may damage public faith in any future proven treatments. In order to maintain public trust, stem cell therapies must be safe and efficacious. Producing the scientific data necessary to prove therapeutic benefit, through properly conducted clinical trials, is a process that will take many years. But some believe that this position is delaying therapies from being developed and ways of reducing the time necessary to test new therapies should be considered. Scientist Ian Wilmut advocates enlisting the terminally ill to test potential treatments.⁷² A balance may need to be struck between gathering sufficient evidence to ensure a treatment is ready to test on patients (thus protecting patients' confidence in science) and speeding the clinical process in some way to prevent people from falling victim to unproven and potentially unsafe 'snake oil' treatments.

4. Issues raised by stem cell therapy

While the regulation of stem cell research has dominated the literature to date, a number of regulatory issues are emerging that relate more specifically to stem cell therapy.⁷³ In the UK, the UK Stem Cell Bank and the Medicines and Healthcare products Regulatory Agency (MHRA) are developing policies which seek to ensure that clinical grade tissues from embryo and adult stem cells are safe, high-quality, ethically sourced, traceable and commercially viable.

4.1 Regulation of product development

The safety of human tissue product development has, up until now, been regulated by codes rather than law. The three principal codes in this regard were written by the Medical Devices Agency (MDA, now part of the MHRA),⁷⁴ and the Department of Health (DH).^{75,76} The MDA's code includes rules on characterizing quality, batch control, infection controls, risk minimization, certificates of raw material analysis, scaffolds, donor screening, cell culture preparation, and full passage data. Other rules recommend procedures to prevent contamination, tampering and deterioration, and labels that advise on handling and hazards.

The DH's guidance documents on tissue banks and safety issues related to transplantation are equally technical and detailed. In conjunction with these codes, the DH has encouraged therapeutic tissue banks to apply for voluntary accreditation with the MHRA.⁷⁷ In a related action, the Human Tissue Authority has piloted a self-assessment licensing scheme which is to be the basis for the formal licensing of therapeutic tissue banks commencing in April 2006 as is required under the EU Tissue Directive.⁷⁸ Their licensing requirements will be updated when all the Technical Standards supporting the EU Tissue Directive are finalised.

The DH and MDA Codes, published in 2000 and 2002 respectively, will need to be brought up-to-date for the purposes of stem cell therapy, in light of European and UK tissue-related legislation. This will be particularly important in order to ensure these various pieces of legislation are being properly implemented in practice and to clarify any potential areas of confusion (eg the possible overlap of the HTA licensing scheme and the MHRA accreditation scheme in regulating tissue establishments). It will also be important when considering the future development of stem cell products that combine

nanotechnology, tissue engineering and genetic technology to develop 'intelligent' regenerative structures.⁷⁹

4.2 The EU Tissue Directive

The UK regulatory framework applicable to stem cell therapy is required to incorporate the provisions of a European Union Directive 'on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells' (generally known as the 'EU Tissue Directive'). The Directive applies, amongst other things, to cellular stem-cell-derived materials that are intended for human application, but not to the preceding *in vitro* research. The Directive was agreed in March 2004 and member states, including the UK, are obliged to implement it by April 2006.

Safety and quality are addressed in a set of rules on product recall, preservation, storage, labelling, packaging and adverse incident reporting. To ensure that the rules are adhered to and that premises are suitable for the development of clinical-grade tissue therapies, each member state is responsible for seeing that establishments that handle relevant tissue are licensed and follow a quality assurance system. Strict rules on the traceability of product development will also apply to achieve rigorous accountability.

These general rules will be supplemented by two European Commission Directives detailing technical requirements. The first, Commission Directive 2006/17/EC, contains standards for donation, procurement and testing of human tissues and cells. The second, containing standards for processing, preservation, storage and distribution, is still being finalised by the European Commission. In broad terms, these propose that donated and processed tissue must be tested for infection (e.g. HIV, hepatitis and syphilis) and characterized. Living donors of tissue are required to undergo a prior medical examination and interview.

The Directive also recommends that member states 'endeavour' to ensure that donations are voluntary and unpaid but it does not make this a strict requirement. The recommendation against payment is made largely for reasons of safety, on the grounds that the availability of payment could be an incentive for a donor to withhold information about their health that could cast doubt on the quality of the tissue for human application. The Human Tissue Act prohibits the sale of tissue intended for transplantation.

The EU Tissue Directive also requires that member states should ensure that imports of human tissue intended for human application from non-EU countries come from establishments that are accredited or licensed for that purpose by the competent authority (the MHRA in the UK). Imports must also meet standards of quality and safety equivalent to European standards. It is not entirely clear whether the requirement that donations be voluntary and unpaid applies to imported tissue.

While the Directive roughly indicates the information to be provided to donors, largely it leaves standards of consent to national laws. This and other issues that were judged to be essentially ethical, rather than relevant to safety or public health, were downplayed on the basis that the European Union was not competent to legislate on these issues.⁸⁰

4.3 Obtaining market approval

The more general regulatory regime for market approval will also be relevant to stem cell therapies. This field of regulation exists to ensure that the safety of a medicine, medical device or other medical technology is satisfactorily established before it is released to the public. A key question is whether transplantable material from stem cells or associated derivatives have been appropriately dealt with according to the Medicinal Products Directive.^{81,82} One difficulty is that this Directive stereotypically deals with pharmaceutical drugs rather than transplanted tissue. Hence, some commentators and European countries have perceived problems with slotting stem cell therapies neatly under its provisions.

This confusion as to where a 'border-line' product might fall has been addressed by the European Commission. Firstly, directives have come into force amending the Medicinal Products Directive. Commission Directive 2003/63/EC provides definitions for gene therapy medicinal products and somatic cell therapy medicinal products. Directive 2004/27/EC modifies the definitions of medicinal products so it will be clearer where border-line products should be categorised. When in doubt, according to this Directive, if a product 'may' fall under the category of a medicinal product, the Directive will apply to it.

In addition, there is the draft Regulation on advanced therapy medicinal products⁸³, which will further impact bringing a stem cell based therapy to market. The products that fall under the draft Regulation are gene therapy and somatic cell therapy medicinal products (as defined in Commission Directive 2003/63/EC) and tissue-engineered products (defined in the draft Regulation). Previously tissue-engineered products had not been covered by legislation, leaving them to be regulated differently in different member states to the detriment of the industry. This draft Regulation provides consistent marketing authorisation requirements for all three categories of products. These products were grouped together, according to the European Commission, because they are expected to have a major impact on medical practice. The finalised Regulation will harmonise standards across the European Union, minimising regulatory hurdles and enhancing Europe's competitiveness in these potentially profitable fields.

The draft Regulation, which still needs to be considered by the European Parliament and the Council, will be relevant to stem cells or their derivatives that are combined with a non-biological matrix, capsule or scaffold to aid transplantation or integration into the host tissue. It covers both autologous and allogeneic human products. Research activities are excluded as the draft Regulation focuses on bringing down-stream products to market.

Once the draft Regulation is finalised, it will be binding on the member states and UK legislation will no doubt need to be amended. In the meantime, the former UK Medicines Control Agency and the MDA (now both part of the MHRA) have both set some indicative standards,^{74, 84, 85} but there are ambiguities and gaps. Both the MDA and the UK Stem Cell Bank recommend that 'regulatory guidance should be obtained from the medicinal authorities on cell lines/tissues arising from stem cell technologies'.^{74, 32}

4.4 Securing the trust of donors

Securing the trust of members of the public who are the source of the precursor tissue for the stem cell lines used in stem cell therapy may be a challenging task.

Earlier in this paper we discussed some of the issues for donors who are asked to donate material for use in stem cell research. Many of these issues are likely also to be relevant to donors of tissues destined for clinical use. Additional issues arise when stem cells are prepared for human application.

4.4.1 Tissue traceability and donor confidentiality

Under the EU Tissue Directive, member states are required to take steps to ensure that all tissues and cells procured, processed, stored or distributed on their territory can be traced from the donor to the recipient and vice versa for a period of 30 years. These rules apply only when it is intended that the tissue (or cell lines derived from it) will be used in clinical transplants.

Although there are sound public health reasons for this policy, it has implications for donor privacy. Individuals may be concerned that information arising from their donation is kept private. Medical testing is part of the process of donating tissue for stem cell therapy in order to assess the safety and quality of the tissue before it is used for transplantation. This involves screening for certain infectious diseases and genetic traits, and blood typing, and may produce sensitive information that must be kept confidential.

The traceability requirements imposed by the EU Tissue Directive may also have a significant effect on the rate at which embryos and other materials needed for stem cell therapy are donated. Couples

may be reluctant to donate embryos unless their connection as 'parents' is severed by irreversible donor anonymity and the prospect of reversible anonymisation could be unappealing. The full implications of tissue traceability for donation are as yet unclear. However it is likely that information given to prospective donors will inevitably become more complex and the process of informed consent correspondingly arduous.

4.4.2 Feedback of medical information to donors

There is also the question of whether donors wish to know this information themselves, or be informed about anything of medical importance that is subsequently discovered through use of their donated material. The Code of Practice for the Use of Human Stem Cell Lines recommends "...that donors are informed that no individual feedback will be given on tests performed by the UK Stem Cell Bank or research results of subsequent studies..."³². The Bank's Steering Committee will only pass information to donors if it believes a special case should be made.

4.5 Securing the trust of patients offered stem cell therapies

Many steps have been taken to ensure that the regulatory system promotes safe and high quality stem cell therapies, and addresses tumorigenicity, stability, adventitious agents, antibiotics use, freezing and the like. These criteria apply to tissue generally and stem cell therapy specifically. Whilst the issues of safety and quality have been thoroughly and openly addressed, other factors relevant to reassuring prospective patients have been neglected in comparison.

4.5.1 Compensation and liability for injury

One oversight has been the failure to discuss how the system will ensure compliance. There is also a question whether the system does enough to ensure manufacturers are sufficiently accountable to *patients* injured by stem cell therapies, as opposed to the official regulators.

The EU Tissue Directive makes no specific provision about compensation where a patient is harmed by a tissue therapy. It seems likely that such claims would have to be made through product liability laws (e.g. the law of negligence and consumer protection legislation). A successful action under the Consumer Protection Act 1987 might be made difficult by the controversial 'development risks defence', under which it is a defence for the producer to show that, at the relevant time, the state of scientific and technical knowledge was not such that he could be expected to discover the defect.

4.5.2 Information about origins of stem cell therapy

Governance documents also fail to discuss end-users' interest in knowing that a stem cell therapy they are offered is derived from destructive research with embryos. The draft Commission Directive on coding, processing, preservation, storage and distribution of human tissues and cells requires that the label on the primary tissue/cell container (or its accompanying documentation) includes information on the morphology of the tissues and cells contained within.⁸⁶ Similarly, the Advanced Therapies draft Regulation⁸³ states that the label for the product will include "...where the product contains cells or tissues, the statement 'This product contains cells of human/animal [*as appropriate*] origin' together with a short description of these cells or tissues and of their specific origin." Likewise, a description of the origin of the cells or tissues used in the product is required on the package leaflet. In this way, it may be possible to ascertain whether or not embryonic stem cells were used in the process of creating the product.

4.6 Intellectual property rights

It is important for businesses that invest large sums of money in stem cell research that the regulatory system includes mechanisms for clear and secure chains of title, allows them to recoup investment through intellectual property rights, and keeps regulatory burdens minimal.

Generally, an invention that is sufficiently disclosed and demonstrates novelty, inventiveness and potential for industrial application can be the subject of a valid patent. However, some inventions are excluded from patentability on the grounds that the granting of a patent would be contrary to public policy or morality. Stem cell research is particularly contentious at present.

4.6.1 Intellectual property rights in the UK

The UK Patent Office is willing to grant patents for adult stem cell lines. It will also grant patents claiming pluripotent cell lines from embryos, provided the claims do not expressly claim rights over the use of human embryos. (Inventions whose commercial exploitation involves the use of human embryos are an excluded category of invention under the Patents Act 1977.) Processes for obtaining stem cells from human embryos are not patentable because such inventions are said to involve 'uses of human embryos' and thus fall within the prohibited category.

The UK Stem Cell Bank has specified conditions that attach to the use of cell lines deposited in the Bank. Property rights in the cell lines will remain with the depositor. Depositors will then negotiate Materials Use Licenses with each would-be accessor to their line to protect their proprietary interests.³² Intellectual property rights can be asserted in these licences. Some 'reach-through claims' could be expected (patent claims or licence terms asserting a right to a share of revenue generated from downstream products, methods and protocols), but these are unlikely to be as controversial as reach-through claims stemming from gene patents, which cannot be invented around.

4.6.2 European position

Although the rules under the European Patent Convention (EPC) are worded in a similar way to the 1977 Patent Act (both adopting the wording of Articles 5 and 6 of the EU Directive on the legal protection of biotechnological inventions), the European Patent Office's Opposition Division has interpreted the morality exclusions differently from the UK Patent Office. For example, in 1999 the University of Edinburgh was granted a European patent related to animal transgenic stem cells. Many groups objected strongly to the patent, claiming that it could be interpreted to extend to humans and potentially to human cloning.⁸⁷ The patent also raised questions regarding the morality of using human embryos to derive stem cells. The Opposition Division decided that stem cell lines isolated from embryos are *not* patentable because the invention was developed through the use of human embryos and would involve the use of embryos to repeat it.⁸⁸ Unless the ruling is reversed on appeal, the implication is that applicants seeking a patent over a stem cell line isolated from human embryos will need to apply to the national patent offices in each of the European countries in which they seek protection. They will not be able to apply to the European Patent Office for a patent valid in EPC countries.

Another case that is shaping this area of European patent law is the Wisconsin Alumni Research Foundation (WARF) patent, which protects techniques for isolating and culturing primate embryonic stem cells. The patent includes a description of the method of manufacture that requires the destruction of the embryo that produced the stem cells. While this patent is valid in several jurisdictions, including the United States, the patent was rejected by the European Patent Office on the grounds of morality. This is a broad interpretation of Rule 23(d)(c) of the European Patent Convention that states that European patents will not be granted for biotechnological inventions using human embryos for industrial or commercial purposes. The case has now been sent to the European Patent Office Enlarged Board of Appeal.

The European Commission has launched a study into the ethical and legal aspects of stem cell patenting. The European Parliament has shown a strong objection to the patenting of embryonic stem cells and has called for '...the rejection of interventions in the human germ line, the rejection of cloning of the human being in all phases of its development and the rejection of research on human embryos, which destroys the embryo.'⁸⁹ It has asked the Commission to examine whether this can be achieved through amending the Directive on the legal protection of biotechnological inventions.⁹⁰

Despite the controversies, according to one report patent activity worldwide has increased, with over 3,000 applications related to adult and embryonic stem cell technologies filed worldwide since 2000.⁹¹

4.7 Gaps and problem areas in the regulatory framework

The scientific progress associated with stem cell therapy does not enter a regulatory vacuum, and social policy is designed to adapt to changing social circumstance. Nevertheless, as we have pointed out in section 4, there are several ethical, social and legal issues that deserve closer scrutiny. These include the creation of a stem cell bank with regulatory powers but no statutory standing, regulating early clinical trials that involve unfamiliar scientific risks associated with new types of tissue transplants, uncertainties about patentability, and cultural differences about the moral significance of informed consent and cloning.

In addition, a number of issues have been discussed here that arise in other fields of biolaw. These include highly variable standards of consent nationally and internationally, doubts about the appropriateness of holding out financial rewards or incentives for tissue donation, insufficient attention to methods of enforcement and compliance, difficulties with sharing information without unduly interfering with individuals' privacy, and methods of compensating patients for defects with experimental treatments.

These difficulties raise the question of whether the existing regulatory framework is adequate. Perhaps, it could be argued, a special regulatory regime is needed for stem cell research or therapy or both in order to maintain public confidence. This was the recommendation made by the UK Stem Cell Initiative (UKSCI) in their 2005 report.⁹² They suggested that a special body should be created, on the model of the Gene Therapy Advisory Committee (GTAC), to oversee the scientific and ethical review process for proposed clinical trials involving stem cell therapies. The government did not agree with this suggestion. Instead, as they expected only a small number of clinical trial applications over the next few years, they decided that GTAC should review those proposals as well as those for gene therapy trials. But this decision will be kept under review. There is always a danger that another regulatory body will only add another layer of bureaucracy onto an already difficult research process. But the UKSCI report did make the point that with a controversial field such as embryonic stem cell research, such a committee could 'act to maintain public confidence in this area as the field matures into an established branch of medicine.'⁹²

4.8 Opportunity costs, resource allocation and equity

Despite their promise, stem cell based therapies are likely to remain, at least for many years, both expensive and technologically demanding. There will inevitably be opportunity costs for cash-limited healthcare systems considering making such treatments available. If, on the other hand, taxation-funded healthcare services such as the UK's National Health Service were to decide not to fund stem cell therapies, these therapies would be available only to individuals wealthy enough to pay for their own treatment. The ethical questions raised by expensive new therapies are not unique to stem cells but nevertheless merit consideration.

Other questions of social justice may arise. It has been suggested, for example, that the UK Stem Cell Bank should seek to build up a collection of clinical-grade stem cell lines representing a range of different tissue types, with the aim of being able to provide immunologically-matched lines for as many patients as possible. It is possible, however, that despite good intentions such repositories may fail to include the less common tissue types⁹³, thus potentially disadvantaging minority racial and ethnic groups.

Researchers have reported that the actual number of ES cell lines needed by the UK Stem Cell Bank to provide treatment to the UK population is fewer than expected.⁹⁴ Craig Taylor and colleagues predict that only 150 individual cell lines would provide a full blood and tissue match to 20% of the population, a beneficial match to 38% and a tissue match to 84%. Only 10 donors with the most common tissue types would be required to provide full matches to 38% of the population or a beneficial match for 68%. The authors recognised however that these predictions exclude some ethnic groups and this raises ethical and policy questions. Commentators suggest that now is the time for the UK Stem Cell Bank to consider a national policy that will make best use of its resources.⁹⁵

4.9 Longevity, 'immortality' and individual identity

The aim of all medical treatments is to extend healthy life. The opportunity offered by stem cell therapies may be different in kind, however. If tissues that normally degenerate, either as a result of disease or during the ageing process, can be successfully regenerated by stem cell therapy (perhaps even through serial treatments), it might be possible to extend the recipient's lifespan by a significant margin. It has even been suggested that stem cell medicine might offer the prospect of 'immortality', that is, the indefinite prolongation of life.

The social consequences of a significant increase in longevity are unknown. Once again, issues of social justice and equity arise if the opportunity to live longer is available only to those who can afford access to an expensive treatment. Nevertheless, John Harris has argued that it would be wrong not to pursue cures for terrible diseases 'even if the price we have to pay for those cures is increasing life expectancy and even creating immortals'.⁹⁶ He suggests that a more rational approach would be to ensure 'commensurate work in ethics and social policy' to devise ways of coping with the new challenges.

Many scientists regard the idea that stem cell therapy will markedly increase lifespan – and particularly that it will enable humans to aspire to anything like 'immortality' – as fanciful.⁹⁷ Equally remote is the possibility that transplants of stem cells into the brain could result in the recipient losing his individual identity and essentially becoming another person; this has been suggested in the past as a possible consequence of transplanting tissue into the brain.⁹⁸ While such scenarios provide useful ideas for science fiction novels and speculation in the popular press, it seems unlikely that society will have to grapple with them for any practical purposes in the foreseeable future.

5. Concluding remarks

There is understandable excitement in the world of biomedical research about the potential of stem cells to offer therapies for some of the most intractable diseases suffered by humans. Like new genetic technologies, however, stem cell research and technology arouse deep-seated fears and worries in many people, particularly with respect to the issues of embryo research and cell nuclear replacement.

In this paper we have highlighted these and other controversies, and have drawn attention to some of the less thoroughly studied issues to be faced 'further down the line', if and when stem cell-derived therapies become a reality. The importance of these issues should not be underestimated and many are deserving of further social science and legal research. It is to be hoped, however, that the approach to policy development for stem cell research and therapy in the UK – broadly permissive but with provision for rigorous ethical and legal oversight – will enable policy to evolve in a way that is rational and commands broad public support.

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