

Guidelines on Using Cells from Established Human Embryonic Stem Cell Lines for Research

Discussion document

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How to Have your Say

Your feedback is important in helping to develop *Guidelines on Using Cells from Established Human Embryonic Stem Cell Lines for Research*. Please take this opportunity to have your say. You can provide comment by making a submission on your own behalf or as a member of an organisation. A summary of submissions will be released following completion of the consultation process.

The Ministry welcomes all feedback. There are some key questions we would like you to think about and comment on. These questions are found on detachable pages at the back of this document.

There are three different ways you can make a submission.

1. Write down your comments on the detachable form at the back of this document and post them to:
Tanith Robb
Sector Policy
Ministry of Health
PO Box 5013
Wellington.
2. Download the submission form in Word format from <http://www.moh.govt.nz/publications>, save it to your computer, fill it in and email it to: tanith_robb@moh.govt.nz
3. Email your comments to: tanith_robb@moh.govt.nz

All submissions are due by 5 pm Friday 3 March 2006.

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All submissions will be analysed before the draft guidelines are finalised and sent to the Minister of Health for final approval.

If there is sufficient demand, the Ministry will organise meetings to hear oral submissions on the draft guidelines. Please contact Tanith Robb before 3 March 2006 if you wish to make an oral submission.

Executive Summary

The purpose of this discussion document is to seek your views on proposed guidelines for using cells from established human embryonic stem cell lines for research. Established human embryonic stem cell lines are stable populations of undifferentiated cells, obtained from human embryos, that can self-replicate and remain undifferentiated for long periods of time in culture outside of the body. Proposed guidelines on the research use of such cells are to be found at the end of this discussion document. Once finalised, these guidelines will be used by researchers and by ethics committees that consider research using human embryonic stem cells.

In New Zealand, research involving human embryos, including the generation of human embryonic stem cell lines, is under the statutory control of committees established under the Human Assisted Reproductive Technology (HART) Act 2004. Once established, human embryonic stem cells are not embryos, and their use does not require the same level or type of regulation. However, the generation of embryonic stem cell lines involves the destruction of human embryos, which raises a number of ethical issues. These issues are discussed in the chapter on ethics (chapter 4).

Human embryonic stem cell research is carried out in most jurisdictions in the developed world, under a variety of regulatory systems. Although legislation and regulations relevant to human embryonic stem cell research already exist in New Zealand, there is no guidance specific to this research, and no such research takes place in this country. Guidelines are needed to clarify the issues that this research raises, to place appropriate restrictions on such research and to provide certainty for researchers, ethics committees and members of the public.

The Ministry of Health (the Ministry) is aware that delays in clarifying the regulation of human embryonic stem cell research have created difficulties for researchers in planning research programmes and that further delays may mean that opportunities to develop capability and capacity in this type of research may be lost. The Ministry has undertaken to develop final guidelines on research using established embryonic stem cell lines as soon as possible.

Structure of the discussion document

The discussion document is set out in six chapters.

Chapter 1 contains the basic facts about human embryonic stem cells. It explains where human embryonic stem cells are found, the properties that make them interesting to researchers and how they differ from other types of stem cells. This chapter also identifies possible sources of embryos for deriving embryonic stem cell lines.

Chapter 2 focuses on what researchers hope to achieve by using human embryonic stem cells in research. The main goal of stem cell research, regenerative medicine, is explained, and specific possible applications are summarised. The types of research that could be carried out on human embryonic stem cells are identified, including basic biological research and intervention research. Finally, this chapter contains a short summary of what has been achieved so far in research using human embryonic stem cells and the challenges that must be overcome if the benefits of this research are to be realised.

Chapter 3 discusses existing regulatory instruments that are of some relevance to the use of cells from established human embryonic stem cell lines for research. These instruments include legislation and regulations as well as documents that have legal force by less direct means. The

HART Act 2004 is explained in detail as it provides guidance on matters closely related to the research use of established human embryonic stem cells.

Chapter 4 discusses the specific ethical issues raised by using cells from established human embryonic stem cell lines for research. These include issues around the destruction of embryos, consent, respect for human tissue, the commodification of the body and accountability and transparency for the public. Because research using established human embryonic stem cells requires the destruction of human embryos, the chapter outlines four possible policy positions with respect to the use of embryos in research. These positions differ in the types of embryos that can be used to derive human embryonic stem cells.

Chapter 5 summarises the policies of a number of other countries with respect to research using human embryos and embryonic stem cells. These countries are grouped in terms of the four policy positions identified previously in chapter 4.

Proposed guidelines for using cells from established human embryonic stem cell lines for research are included as a chapter at the end of this discussion document. The proposed guidelines draw on the ethical issues discussed earlier in chapter 4, with provisions designed to address those issues. The proposed guidelines are also drawn with an eye to existing regulatory instruments, some of which address to varying degrees some of the ethical issues associated with human embryonic stem cell research.

1 What are Embryonic Stem Cells?

1.1 Embryonic stem cells are found in early embryos

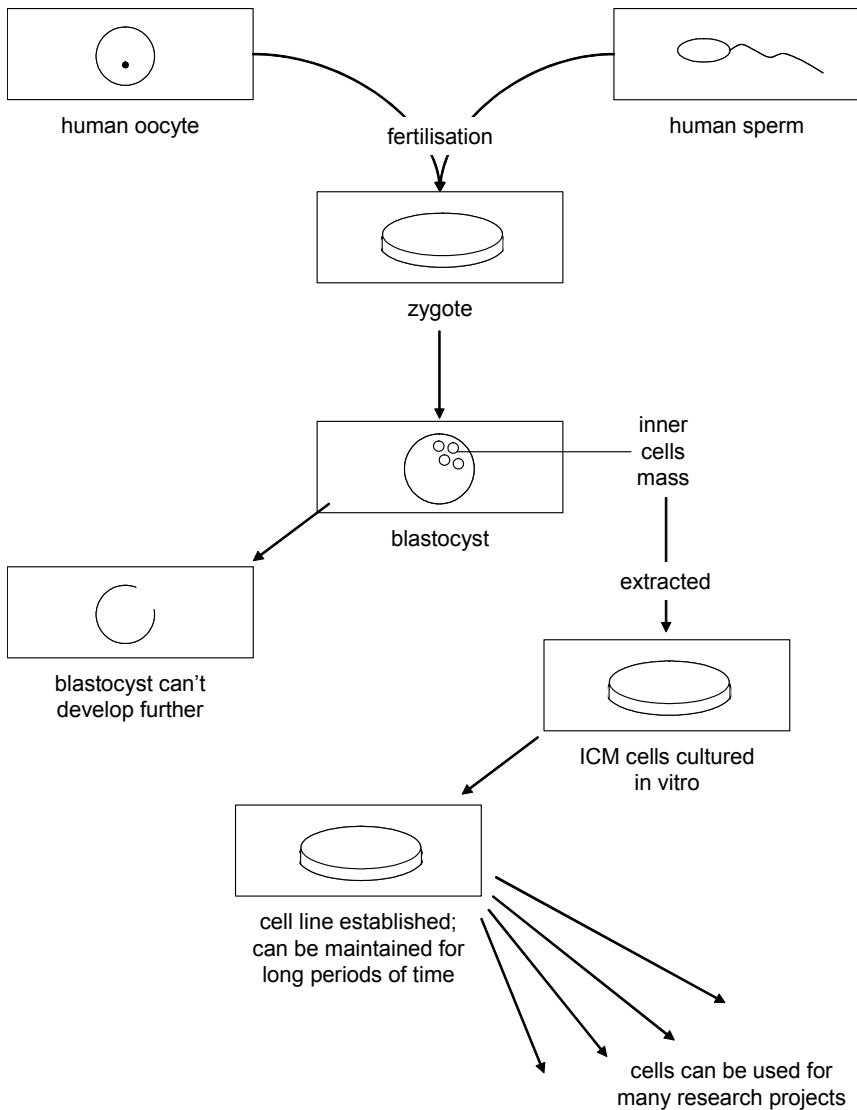
Human beings begin as a single cell, called a zygote, formed by the fusion of a female's egg cell with a male's sperm cell in a process called fertilisation. The zygote then divides to form two daughter cells, each of which then divides, and so on. Four or five days after fertilisation, the embryo forms a hollow mass of cells called a blastocyst. Blastocysts consist of two groups of cells – an outer layer of cells called the trophectoderm, inside which there is a fluid-filled cavity (called a blastocoel) and a small inner cell mass. Cells from the trophectoderm give rise to the placenta and other extra-embryonic tissues, while the embryo itself develops from the inner cell mass. This is an example of cell differentiation, the process whereby less specialised cells divide and give rise to cells with a more specialised function in the body.

Human embryonic stem cell lines are derived from cells from the inner cell mass of the blastocyst. Once isolated, such cells can be grown in culture in the laboratory and used for research purposes. However, isolating and maintaining human embryonic stem cell lines is not a straightforward matter even for experienced researchers as the underlying mechanisms of cell differentiation are not yet well understood.

1.2. Embryonic stem cell lines are not embryos

Embryonic stem cell lines are derived from embryos, but they are not themselves embryos. Embryonic stem cells cannot give rise to human beings. This is because the cells of both the inner cell mass, which are embryonic stem cells, and the trophectoderm, which gives rise to extra-embryonic tissues such as the placenta, are needed to allow an embryo to implant in the womb and grow to term.

The inability of human embryonic stem cells to give rise to human beings means that they are not totipotent. Totipotent cells are cells that, under the right conditions, have the ability to develop into an entire person. An example of a totipotent cell is the zygote. Cells in the embryo lose their totipotency at around the eight-cell stage of development.



1.3 Embryonic stem cell lines can give rise to cells from a large range of cell types

Cells divide many times very quickly in the embryonic and early fetal stages of development. As they divide, they differentiate into the vast array of different cell types that are found in adult humans. Some cells become skin cells, others become nerve cells and others blood cells and so on. The process of differentiation begins very early in development.

Many cells continue to divide after they have differentiated. Skin cells, for example, are constantly dying and being shed and so must be continually replaced through cell division. Once differentiated, cells generally cannot divide to form cells of a type other than their own. Skin cells may divide to form more skin cells and liver cells to form more liver cells, but neither of these cell types can give rise to a line of cells from any other part of the body. However, some cells of the adult body remain unspecialised to a certain degree.

Human embryonic stem cells are relatively undifferentiated and have been shown to be able to give rise to a large number of cell types. Importantly, the cell types so far derived have come from all three of the body's basic germ layers, suggesting that human embryonic stem cells may have the potential to give rise to every cell type in culture. This ability to give rise to such a large and diverse range of cell types means that human embryonic stem cells are pluripotent stem cells. Combined with the human embryonic stem cell's ability to be cultured for long periods of time, this pluripotency is the main reason why many researchers believe such cells are crucial to our understanding of human development and disease.

1.4 Embryonic stem cell lines can be cultured for very long periods of time without differentiating

Researchers have discovered that under certain conditions human embryonic stem cell lines can be maintained in an undifferentiated state in the laboratory for months or even years. Other types of stem cells are not so easy to culture. For example, adult stem cells tend to differentiate spontaneously after a relatively short time. The ease with which human embryonic stem cell lines can be maintained gives them considerable promise as a research tool because one line can be used for a number of research projects throughout its existence.

1.5 Other stem cells do not have the same properties as embryonic stem cells

There are a number of non-embryonic sources of human stem cells. However, stem cells from these sources are not able to give rise to as many types of cells as human embryonic stem cells and are generally more difficult to culture. Each non-embryonic source of human stem cells is discussed below.

1.5.1 Adult (somatic) stem cells

Stem cells have been found in many tissues of the adult human body, including the brain, the lining of the blood vessels, cornea, retina, dental pulp, spinal cord, skeletal muscle, pancreas and liver among others. Adult stem cells exist in small numbers, are frequently difficult to extract and exist to replace cells in the tissue where they are found. For example, the haematopoietic stem cells found in bone marrow can give rise to a range of cell types found in the blood (National Institutes of Health 2001).

Because of this limited ability to give rise to different cells, adult stem cells are considered to be multipotent rather than pluripotent. Researchers have so far been unable to demonstrate convincingly that stem cells found in any part of the adult body are pluripotent, although some studies have demonstrated a limited degree of plasticity. While some adult stem cells have been shown to be able to give rise to unrelated cell types – for example, neural cells have been derived from blood stem cells – this plasticity appears to be very restricted (Wagers and Weissman 2004). It is of course possible that further research on adult stem cells will reveal methods of deriving as many types of cell from them as is currently possible with human embryonic stem cells.

Adult stem cells do not behave in culture in as predictable and stable way as do embryonic stem cells. They are more difficult to culture and maintain, and tend to spontaneously differentiate after a relatively short period of time. Because of these limitations, most researchers consider that adult stem cell research should be undertaken as well as, not in place of, research using human embryonic stem cells.

1.5.2 Umbilical cord blood stem cells

Stem cells are also found in the umbilical cord, which supplies blood and nutrients to the growing fetus during pregnancy. Umbilical cord blood is relatively rich in haematopoietic stem cells, which can give rise to a number of different types of blood cells. This blood has not yet developed immune characteristics to the same degree as adult blood and is therefore less likely to cause an immune reaction when used in transplants. Researchers are hopeful that umbilical cord blood stem cells could be used to develop therapies for a range of diseases.

Umbilical cords also contain other types of stem cells that can give rise to nerve tissue and may therefore hold promise for treating degenerative conditions of the nervous system, such as Parkinson's disease. However, these umbilical cord blood stem cells have not been shown to differentiate as readily into other types of cell. While researchers are optimistic about the therapeutic potential of stem cells from the umbilical cord blood, these cells are not considered to be an alternative to embryonic stem cells.

1.5.3 Fetal stem cells

The other developmental stage at which stem cells have so far been found is in the fetus, where precursors of sex cells have been shown to be differentiable into cell types from each of the three basic body layers, a key test of pluripotentiality. However, these pluripotent fetal cells are inferior to embryonic stem cells in terms of their ability to survive undifferentiated in culture for long periods of time. The use of cells from aborted fetuses also raises ethical issues that many people consider to be at least as complex as those raised by using human embryonic stem cells for research.

1.6 When embryonic stem cells are obtained from an embryo, that embryo cannot go on to develop into a fetus

When embryonic stem cells are obtained from the inner cell mass of a blastocyst, that blastocyst cannot develop into a human being and is therefore destroyed. The process of obtaining cells from the inner cell mass of the blastocyst destroys the trophoblast, meaning the placenta and other extra-embryonic tissues cannot develop. In the future, it may be possible to obtain embryonic stem cells in such a way that the blastocyst can continue to develop normally, but this is not currently scientifically possible. The process by which embryonic stem cells are obtained raises a number of ethical issues for many people. These ethical issues are explored in chapter 4 of this discussion document.

1.7 Embryonic stem cells must be obtained from embryos *in vitro*

Blastocysts are very small, making them virtually impossible to find and extract from a woman's body. For this reason, all research embryos must be created *in vitro* in laboratories and fertility clinics. The types of *in vitro* embryos that could be used to create human embryonic stem cell lines are detailed below.

1.7.1 Surplus *in vitro* fertilisation embryos

The most obvious source of embryos is from the quantities left over after fertility treatment. When a single woman or a couple attempts to conceive using *in vitro* fertilisation, more embryos are created than are usually necessary. This is done to minimise the chances that eggs will have to be extracted

from the woman multiple times as this procedure is invasive, unpleasant and carries a small but significant risk of harmful side effects.

There are approximately 5000–7000 of these ‘surplus’ embryos frozen in New Zealand fertility clinics and millions more frozen in other fertility clinics around the world. Currently, the woman or couple can use these embryos to try to have another child, donate them to other infertile couples, or choose to destroy them by allowing them to be thawed out. The HART Act advisory committee will develop guidelines on the donation of embryos for research.

If no decision is made on the use of frozen *in vitro* fertilisation embryos, there is still a legislative 10-year time limit on the storage of surplus embryos. The vast majority of these surplus embryos will be allowed to develop no further and will be destroyed by being allowed to thaw out after the 10-year storage limit runs out. A 2003 survey in the United States found that there were nearly 400,000 surplus *in vitro* fertilisation embryos in fertility centres in that country, of which only 11,000 were available for research. Given that the highest quality embryos are implanted, not stored, and given the technical difficulties inherent in deriving embryonic stem cells, it is estimated that these surplus *in vitro* fertilisation embryos could be used to create 275 embryonic stem cell lines (Hoffman et al 2003).

There are obvious advantages in using surplus *in vitro* fertilisation embryos to derive embryonic stem cell lines. There are enough of these embryos to represent an adequate supply for basic stem cell research, even allowing for a very low rate of consent to donate. Some people believe that since most surplus *in vitro* fertilisation embryos will be destroyed anyway, we should maximise their use in potentially beneficial research.

1.7.2 *In vitro* fertilisation embryos created specifically for research

Another possible source of embryos for embryonic stem cell research is those that are created specifically for research. There are a number of ways in which such embryos could be created. The first is by the *in vitro* fertilisation of a donated egg by donated sperm, as occurs in *in vitro* fertilisation therapy. This source of embryos raises extra ethical issues since it involves creating human life in order to destroy it. In addition, the creation of *in vitro* fertilisation embryos for research would currently require large numbers of egg cells from the ovaries of female donors, given the high (but falling) rates of failure in establishing human embryonic stem cell lines from embryos created for research. There is concern that large-scale egg collection for this purpose would cross a line in the commodification of the human body, and concern about a heightened risk of breast cancer in women who undergo hormone treatment to donate egg cells (Burkman et al 2003).

However, some researchers consider that there may be significant advantages to creating embryos for research through *in vitro* fertilisation. This technique would allow researchers to study embryonic stem cell lines with known genetic profiles. For example, it would be useful to study a line with a susceptibility gene for a given condition in order to develop therapies for that condition. As surplus *in vitro* fertilisation embryos generally do not have known genetic profiles, they could not be used for such research.

1.7.3 Somatic cell nuclear transfer (SCNT)

Another way of creating embryos is by placing the nucleus of an adult cell in an egg cell whose nucleus has been removed. This cell, which is practically genetically identical to the person from whom its nucleus was obtained, can be induced to develop in exactly the same way as a zygote. This process is called somatic cell nuclear transfer (SCNT) or, more simply, cloning.

Cloned embryos can be used in two ways. Research and therapeutic cloning, which involve producing cloned embryos for the purposes of research and treating disease, are distinct from reproductive cloning, which would involve producing cloned embryos to implant into the womb. Reproductive cloning raises a host of ethical issues for many people and is banned in most developed countries, including New Zealand. Some people are concerned about research and therapeutic cloning on the grounds that they could lead to reproductive cloning and a loss of respect for individual human life. The need to obtain egg cells on a large scale for SCNT creates another set of ethical issues to work through (Magnus and Cho 2005).

However, due to recent advances in the creation of embryos by SCNT, many researchers are hopeful that embryonic stem cells derived from such embryos could be used to develop therapies that are ideally suited for use in one specific person, or a specific group of people (Hwang et al 2004, 2005). Because they are genetically identical to the nucleus donor, any cells or tissues developed from an SCNT embryo would be perfectly compatible for transplantation into that person. No immunosuppressant drugs would be required. This would be a major advantage in terms of both cost and health outcomes as immunosuppressants are expensive and cause a host of side effects. However, person-specific therapies using SCNT embryos will almost certainly not be developed for a number of years.

It is important to note that the HART Act 2004 prohibits the cloning of humans for reproductive purposes. There is also a strong global consensus that reproductive cloning of humans is not ethically acceptable at this time, and all developed nations who have legislated around embryo research have banned this activity.

The HART Act advisory committee will develop guidance on the use of SCNT for therapeutic purposes.

1.7.4 Other currently experimental methods

A number of other possible ways of creating embryos for use in embryonic stem cell research exist. These include:

- parthenogenesis and androgenesis, in which the egg or sperm respectively is induced to develop into an embryo without fertilisation
- embryo splitting, in which one embryo is effectively cut in half before the blastocyst stage
- ‘stembrid’ cells, in which established embryonic cell lines are fused with adult cells to create a line genetically identical to the adult cells.

To date, embryonic stem cell lines have not been created using such experimental approaches.

1.8 It may one day be possible to create human pluripotent stem cell lines without using human embryos

Because of the ethical issues associated with using human embryonic stem cells for research, efforts to create cells with the same properties as human embryonic stem cells in ways that do not require the destruction of human embryos have been taken very seriously. In the United States, the President’s Council on Bioethics has recently reported on four such potential alternative sources of human pluripotent stem cells (President’s Council on Bioethics 2005). These sources are:

- frozen embryos that fail to thrive after thawing and may therefore already be dead
- cells obtained as part of embryo biopsy
- ‘biological artifacts’ similar to embryos
- dedifferentiated somatic cells.

All of these alternative sources are currently considered to be highly experimental by most researchers. In addition, they raise their own ethical issues. While further research may allow these cells to be used in place of human embryonic stem cells, this research should occur at the same time as, not in place of, research using human embryonic stem cells.

2 Research Using Cells from Established Human Embryonic Stem Cell Lines

This chapter contains a broad overview of:

- the potential benefits researchers hope to acquire by using cells from established human embryonic stem cell lines for research
- the types of research that will be required to obtain these benefits
- the current state of our knowledge of human embryonic stem cells.

2.1 The potential benefits of human embryonic stem cell research

Research on human embryonic stem cells is at an early stage. At the moment, most such research is basic biological research whose aims include learning how to control the differentiation of embryonic stem cells into different cell types and investigating the effects of embryonic stem cells in animal models of disease. It is important to be clear that therapies to treat disease and relieve human suffering will not be developed from human embryonic stem cells for a number of years. An appropriate degree of caution is necessary in discussing the potential benefits of this research. Nevertheless, the fact that human embryonic stem cell research may one day lead to improvements in human health and the alleviation of suffering is an important justification for such research.

The three main reasons why research on established human embryonic stem cell lines is likely to be carried out – developing the discipline of regenerative medicine, understanding cell growth, proliferation and differentiation, and understanding the causes of developmental abnormalities – are described below.

2.1.1 Regenerative medicine

Most researchers see the main goal of human embryonic stem cell research to be the development of new therapies through the discipline of regenerative medicine. Because human embryonic stem cells are able to give rise to any type of cell, they may be able to be used to replace cells lost through injury or disease. Some specific potential focuses of regenerative medicine are outlined below.

2.1.1.1 Heart muscle cells

Heart muscle cells, or cardiomyocytes, do not readily replace themselves following a heart attack. Instead of having functional contracting heart muscle cells, a person who has suffered a heart attack develops scar tissue on their heart that seriously affects the organ's ability to pump blood. The goal of one possible line of embryonic stem cell research would be to develop therapies to regenerate healthy heart muscle tissue in people who have had heart attacks. People who have congenital heart defects could also benefit from such therapies.

2.1.1.2 Diabetes

Juvenile-onset diabetes is caused by a lack of functioning insulin-producing cells in the pancreas. Insulin controls how much of the sugar in food is broken down and used by the body and how much stays in the bloodstream. Because their bodies do not produce insulin, type one diabetics rely on injections to stop their blood sugar level from fluctuating wildly. It may one day be possible to use embryonic stem cells to create replacement pancreatic cells for use in people with this type of

diabetes. Although successes have been achieved in this area using other stem cells, human embryonic stem cells would have an advantage due to their immunological properties.

2.1.1.3 Neurological conditions

Many neurological conditions are caused by degeneration of the tissue of the central nervous system. Examples of such conditions include stroke, Parkinson's disease, Alzheimer's disease and multiple sclerosis. As brain tissue does not regenerate to any significant extent, human embryonic stem cells could one day be grown into replacement neurons or neural support cells for the treatment of these conditions (Kerr et al 2001). People who sustain spinal cord damage in accidents could also benefit from therapies developed from human embryonic stem cell research.

2.1.1.4 Autoimmune diseases

There is a range of diseases in which the body's immune system attacks itself instead of foreign cells. Examples of these autoimmune diseases include lupus, rheumatoid arthritis and Crohn's disease. Researchers and medical professionals believe that stem cells could one day be used to assist in the treatment of sufferers of autoimmune diseases. Such treatment could involve destroying the malfunctioning immune system and introducing stem cells capable of regenerating a new immune system that does not attack body cells. A significant degree of success has been achieved in this area already using adult haematopoietic stem cells, but human embryonic stem cell research may assist in the development of further therapies.

2.1.1.5 Other conditions

The list of conditions that could be treated using such a regenerative approach is long. For example, human embryonic stem cells could also be used in the treatment of burns, wounds, coronary heart disease or cancer, by manipulating the stem cells to create different cell types that are involved in the development of these diseases and conditions.

2.1.2 Understanding cell growth, proliferation and differentiation

Cancers are caused by abnormalities in these processes. Knowing more about how normal cell processes are regulated in the human body would assist in the development of therapies for cancer sufferers, as well as suggesting ways of preventing cancers from forming. Research on established human embryonic stem cells has the potential to contribute much knowledge in this area.

2.1.3 Understanding the causes of developmental abnormalities

Using cells from established human embryonic stem cell lines for research could help us to understand the complex process by which human bodies are built out of a single zygote. Knowledge of the developmental pathways that lead to the birth of normal, healthy human beings will help doctors and scientists understand the causes of fetal developmental abnormalities, which lead either to miscarriages or to the birth of children affected by developmental disorders.

This knowledge would benefit two groups of people. It would help those at risk of having children with genetically based developmental abnormalities as tests could be developed to detect faults in the genes that control development. Knowledge about human development obtained from research on human embryonic stem cells could also help people who have fertility problems, such as recurrent miscarriages, since many developmental abnormalities are fatal to the embryo or fetus. A large

number of New Zealanders are estimated to have fertility problems that could be treated with the help of such knowledge of human development.

2.2 Types of human embryonic stem cell research

The discussion above outlines the understanding and knowledge that researchers believe they could acquire, and the therapies they believe they could develop, by using cells from established human embryonic stem cell lines for research. However, such research will take a number of forms. As is explained further in the chapter on existing regulation (chapter 3), some of these forms of research will require greater regulatory oversight. These forms of research are explained below.

2.2.1 Basic biological research

Most current research on established human embryonic stem cells is basic biological research. This type of research aims to discover basic facts about human embryonic stem cells in culture in the laboratory. Examples of research objectives that would be met through basic biological research include directing the differentiation of human embryonic stem cells, testing the effects of human embryonic stem cells in animal models of disease and developing more effective culture media on which to grow human embryonic stem cell lines in future.

Although many aspects of basic biological research require ethical oversight due to the need to destroy embryos for research purposes, the fact that this research does not involve human subjects means that oversight may not need to be as comprehensive in other ways as is the case for intervention research.

2.2.2 Innovative practice

Innovative practice is not research, but it is very closely related to research. An innovative practice involves providing a clinical intervention – such as the use of a medicine, a medical device or a clinical procedure such as an operation – whose efficacy is unproven or untested or which is not in common use. The overall goal of any innovative practice is either to provide some immediate treatment to a person or to a group of people or to create new efficiencies in practice that will benefit consumers on a more general level.

Unlike intervention research, innovative practice does not involve systematic comparison between one group of people and another. However, innovative treatment does involve human subjects, meaning that issues associated with the safety of the innovative practice will need to be considered as part of any ethical oversight. All of the reasons for which basic biological research involving human embryonic stem cells requires ethical oversight also apply to innovative treatment using these cells.

2.2.3 Intervention research

This type of research involves giving similar groups of people different treatment and studying whether or not outcomes between the groups are different in order to determine if there is a causal relationship between the intervention and study variables. An example of intervention research involving cells from established human embryonic stem cells would be comparing the effectiveness of these cells with the effectiveness of injected insulin in the treatment of diabetes. Another example might be research to determine whether treatment with heart muscle cells derived from human embryonic stem cell lines improves health outcomes among people who have suffered a heart attack. Clinical trials, a type of intervention research, will be required in order to determine whether each type of regenerative medical therapy is effective.

In general, there is a higher standard of oversight for intervention research than for other types of research given the safety issues involved. For example, clinical trials of pre-registration medicines must be reviewed by the Health Research Council of New Zealand's Standing Committee on Therapeutic Trials, as well as by an ethics committee.

2.2.4 Observational studies

In health research, observational studies are distinguished from intervention research by the fact that no intervention other than recording, classifying or analysing data takes place. In an observational study, the investigator has no control over study variables and merely observes outcomes.

This type of research is unlikely to be carried out to any significant degree with respect to human embryonic stem cells. In addition, it is not clear that observational studies raise extra ethical issues where they involve human embryonic stem cells.

2.3 The current state of knowledge of human embryonic stem cells

Human embryonic stem cell research is in its early stages. With respect to the types of research outlined above, most researchers are still focusing on basic biological research. It is clear that intervention studies will not be justifiable until a number of technical challenges, described below, are overcome. These challenges are not expected to be overcome for many years.

This section does not cover every aspect of the research that has been done using cells from established human embryonic stem cell lines; rather, it focuses on what is known about key aspects of these cells. The evidence that these cells may one day be able to be used to develop regenerative medical therapies is presented as are the limitations of most established human embryonic stem cell lines and the challenges that must be overcome before therapies can be developed and subjected to intervention research.

2.3.1 Mouse embryonic stem cells

Mouse embryonic stem cells have been much more extensively studied than human embryonic stem cells, having been first derived from mouse blastocysts in 1981 (Martin 1981; Evans and Kaufman 1981). There are examples of mouse embryonic stem cell lines that have been cultured for nearly 20 years. Much of the research suggesting that human embryonic stem cells could lead to new therapies was done using mouse cells, and the same culture base – mouse fibroblasts – has been used to culture cells from both species. However, there are many differences between mouse and human embryonic stem cells, including differences in their required culture medium (Pera and Trounson 2004). These differences complicate the inferences that are made from the success of studies on mouse embryonic stem cells to the potential of human embryonic stem cell research to lead to therapies.

2.3.2 Human embryonic stem cells

The successful isolation and culture of human embryonic stem cells was first described in 1994 (Bongso et al 1994), while the first stable human embryonic stem cell line was created in 1998 by James Thomson of the University of Wisconsin (Thomson et al 1998). Research on embryonic stem cells is therefore still in its early stages, although there are a relatively large number of centres worldwide conducting research in this area. Leading centres in human embryonic stem cell research include South Korea and the United Kingdom, where relatively permissive regulatory regimes support human embryonic stem cell researchers.

In spite of the short period of time that has elapsed since the creation of the first human embryonic stem cell line, a reasonable amount of evidence has been obtained to support the belief that human embryonic stem cells may be able to be used to replace cells and tissue damaged or destroyed by injury or disease. Some of the evidence is presented below.

Human adult cells are often genetically modified for research purposes, and it is likely that some research on human embryonic stem cell lines will involve genetic modification of the stem cells. For example, cells could be genetically modified to express various human genes to assess the role of these genetic factors in cell differentiation. It is not clear whether the genetic modification of human embryonic stem cells raises extra safety or ethical issues than the genetic modification of human adult cells. However, where human embryonic stem cell research involves importing or developing genetically modified cells, the law requires approval from the Environmental Risk Management Authority (ERMA New Zealand). ERMA New Zealand approval is additional to other forms of approval or review that may be required.

2.3.2.1 Heart muscle cells

Some researchers have shown that human embryonic stem cells can develop into functional heart muscle cells, and others have performed transplants of embryonic stem cells into the hearts of mice with encouraging results (Kehat et al 2001; Rienecke et al 1999). There is also indirect evidence that embryonic stem cells may act as a catalyst to the development of other tissues (Heng et al 2005).

2.3.2.2 Diabetes

Research on mice has shown that embryonic stem cells can produce insulin-secreting cells that have a therapeutic effect in diabetic mice, while other researchers have demonstrated that embryonic stem cells can be induced to express genes to control the production of insulin (Lumelsky et al 2001; Assady et al 2001; Segev et al 2004). Other studies on mice have highlighted the risk of tumours forming when embryonic stem cells are transplanted (Fujikawa et al 2005).

2.3.2.3 Neurological conditions

Many experiments in mice have demonstrated the promising ability of embryonic stem cells to regenerate brain tissue (for example, Chiba et al 2004). When transplanted into chicken embryos, neural precursors developed from mouse embryonic stem cells developed into motor neurons (Wichterle et al 2002). In addition, clinical trials in the United States and Sweden on Parkinson's disease patients have shown that transplanting neural cells derived from fetal stem cells can have a limited therapeutic effect (Sonntag et al 2005). Recent research on rats has suggested that human embryonic stem cells could be useful in assisting recovery after stroke (Wei et al 2005). Other researchers have recently shown that embryonic stem cells can have a therapeutic effect in primate models of Parkinson's disease (Takagi et al 2005).

2.3.2.4 Autoimmune disease

Because adult haematopoietic stem cells are relatively easy to obtain, they may hold more promise for developing therapies for autoimmune disease than human embryonic stem cells. However, cells derived from human embryonic stem cells have recently been shown to prevent the onset of an autoimmune disease called encephalomyelitis in mice (Hirata et al 2005). Other researchers have demonstrated that human embryonic stem cells can give rise to haematopoietic cells and that these cells give rise to lineages of functional blood cells in the body (Kyba et al 2002).

2.3.3 Limitations of current established human embryonic stem cell lines

Although embryonic stem cell lines can be cultured for long periods of time, new lines will be continually required if research is to have any chance of giving rise to regenerative medical therapies. This is because the older a cell line is, the more likely it is for mistakes to occur at the genetic level when cell division takes place. This leads to an accumulation of tumour-causing genetic mutations within the stem cell line. These mutations reduce the safety of the cell line and make it less suitable for use in intervention research on human subjects as transplants are more likely to cause tumours to develop in the person receiving the cells. In addition, there have been problems with some human embryonic stem cell lines not retaining their potential through extended periods of culture in the lab (National Academy of Sciences 2005).

Moreover, the fact that human embryonic stem cell lines have been grown on mouse fibroblasts as a nutrient source means that many established lines are unsuitable for transplantation into humans, as will be required to develop therapies from such cells. The feeder cells, and other factors introduced to the cell lines, may be contaminated with bacteria or viruses that are harmless to mice but may cause disease in humans. In addition, the presence of molecules produced by animals but not by humans will cause an immune reaction if transplanted into the human body (Martin et al 2005). Researchers have only very recently discovered techniques of maintaining human embryonic stem cell lines in culture without relying heavily on products derived from mice to support their growth (Pera and Trounson 2004; Klimanskaya et al 2005).

Many researchers consider that there is insufficient genetic diversity among established human embryonic stem cell lines to allow the development of therapies that are immunologically compatible with a significant number of people and population groups. Many researchers also consider that genetically defined lines should be created to help research into specific diseases and conditions (National Academy of Sciences 2005).

The conclusion to be drawn from the existence of these limitations is that effective therapies will not be able to be developed from research using cells from human embryonic stem cell lines that have already been established. New cell lines will almost certainly be required.

2.3.4 Therapeutic cloning

Therapeutic cloning is a relatively new technology, and the use of embryonic stem cells created from SCNT embryos is less well studied than those created from surplus *in vitro* fertilisation embryos. Since the first successful reproductive cloning of a mammal in 1996 (Campbell et al 1996), several groups of researchers have used SCNT mouse embryos to derive mouse embryonic stem cells, although there is a low rate of success associated with producing stem cell lines from SCNT embryos (National Academy of Sciences 2005).

Embryonic stem cells were first successfully derived from human SCNT embryos in South Korea in 2004 (Hwang et al 2004). Obtaining a single line required nearly 250 attempts. However, in May 2005, a team lead by the same scientist, Hwang Woo-suk, announced that it had created person-specific embryonic stem cell lines from 11 people of a variety of ages and sexes (Hwang et al 2005), thereby proving that it is generally possible to use SCNT embryos to create individualised cell lines. The stem cell research community has hailed this research as a significant breakthrough.

2.3.5 Challenges for the future

A number of significant challenges must be solved before any therapies can be developed from research on established human embryonic stem cell lines. There must be more research using a greater number of cell lines of greater genetic diversity, including lines with known genetic backgrounds, such as susceptibility genes. To achieve this, it may be necessary to create cell lines with known genetic profiles by *in vitro* fertilisation, SCNT or some other method.

So far, established human embryonic stem cell lines have been created using multiple cells from the same or many embryos. One technical challenge will be to develop monoclonal cell lines, which originate from a single blastocyst cell. As mentioned above, alternatives must also be found to using animal-derived products in the culture of human embryonic stem cell lines as their presence poses risks of cross-species infection. Recent advances in the design of growth media suggests that it may be possible to culture human embryonic stem cells in a medium that is free of animal products (Xu et al 2005).

Researchers do not currently have extensive knowledge of the processes involved in cell differentiation and are therefore unable reliably to direct embryonic stem cells to give rise to cells of a given type. Although researchers have experienced some success in directing embryonic stem cells to give rise to a number of different cell types, a great deal of uncertainty remains in this area. In a related area, techniques must also be developed to improve the maintenance of human embryonic stem cell lines in an undifferentiated state in culture.

The ability of human embryonic stem cells to give rise to different cell types must be tightly controlled and directed before such cells can be used in humans. Uncontrolled differentiation could lead to the growth of tumours in people who receive embryonic stem cells. Much more needs to be known about the mechanisms involved in cell differentiation before this risk can be minimised to a level where trials could begin on humans.

The use of SCNT embryos for research would raise extra technical challenges, including finding a reliable and ethical source of egg cells with which to make embryos.

Overall, the state of research using cells from established human embryonic stem cell lines holds immense promise but also faces immense technical and scientific challenges. It is important to be realistic about the chances that some or all of these challenges will not be surmountable, or if they are, to recognise the timeframe involved in developing therapies. What can be said with a fair degree of certainty, however, is that a great deal of further research will be required on stem cells of all different types if there is to be a chance of gaining significant health benefits from established human embryonic stem cell lines.

3 Existing Regulation in New Zealand

There are a number of laws in New Zealand that are relevant to the question of how research using cells from established human embryonic stem cell lines should be regulated. Regardless of the content of guidelines on using cells from established human embryonic stem cell lines for research, stem cell researchers are required to meet their obligations under these laws.

These laws include:

- the Human Assisted Reproductive Technology (HART) Act 2004
- the Human Tissue Act 1964, and associated review
- the Hazardous Substances and New Organisms (HSNO) Act 1996
- the New Zealand Public Health and Disability Act 2000
- the Medicines Act 1981, and associated review.

The relevance of each of these laws to research using established human embryonic stem cells is explained below.

3.1 The Human Assisted Reproductive Technology (HART) Act 2004

The Human Assisted Reproductive Technology (HART) Act 2004 establishes a clear legal framework for assisted reproductive technology and human reproductive research, which is defined as ‘research that uses or creates a human gamete, a human embryo, or a hybrid embryo’. Substantial penalties can be imposed where human reproductive research is carried out without the approval of an ethics committee set up under the HART Act. This law is therefore relevant to the use of embryos to derive embryonic stem cells but is not relevant to the use of cells from established human embryonic stem cell lines.¹

The advisory committee set up under the HART Act will consider guidance on the research use of human embryos in New Zealand, including their use to derive stem cell lines. An appropriate degree of consistency must be ensured between regulating research that uses established embryonic stem cells and regulating human reproductive research. For this reason, it may be appropriate for the guidelines on research use of cells from established human embryonic stem cell lines to be reviewed in light of the HART Act advisory committee’s work.

3.2 The Human Tissue Act 1964, and associated review

Another piece of legislation relevant to human embryonic stem cells is the Human Tissue Act 1964. Due to its age, this Act is currently under review, with new legislation expected to be introduced in 2006.

New legislation to replace the Human Tissue Act will address, among other things, the use of all human tissue in research, including issues of consent, safety, storage and disposal.² Human embryonic stem cells are human tissue. It may therefore be appropriate for guidelines on using cells

¹ The only possible exception would be where an established human embryonic stem cell line was used to create a human gamete, a human embryo or a hybrid embryo.

² This new legislation will not regulate the use of human tissue covered by the HART Act, namely gametes and embryos.

from established human embryonic stem cell lines for research to assume the status of regulations under any new legislation.

3.3 The Hazardous Substances and New Organisms (HSNO) Act 1996

The Hazardous Substances and New Organisms (HSNO) Act 1996 exists to protect the environment and the health and safety of people and communities by preventing or managing the adverse effects of hazardous substances and new organisms. The definition of a ‘new organism’ includes genetically modified human cells. The HSNO Act is therefore relevant to research using human embryonic stem cells where those cells have been genetically modified or where the research involves genetic modification.

Where human embryonic stem cell research involves importing or developing genetically modified cells, the law requires approval from the Environmental Risk Management Authority (ERMA New Zealand). ERMA New Zealand approval is additional to other forms of approval or review that may be required. Failure to gain ERMA New Zealand approval where it is required is a serious offence, punishable by a fine of up to \$500,000 and up to three months imprisonment.

3.4 The New Zealand Public Health and Disability Act 2000

In general, health and disability research is ethically reviewed in New Zealand by seven health and disability ethics committees established under the New Zealand Public Health and Disability Act 2000.³ Although these committees focus on ensuring the protection of human participants in research, they also have the authority to review research that ‘seeks to further scientific or professional knowledge by means of questionnaires, interviews or other techniques of information gathering, or by means of laboratory analysis of human blood, tissues, etc, of living people, cadavers or discarded body tissues (for example, placenta)’ (Ministry of Health 2002).

This definition covers basic biological research using established human embryonic stem cells. The seven health and disability ethics committees could therefore ethically review such research.

These seven health and disability ethics committees are required to operate in accordance with their terms of reference, which contain requirements around membership, approval, meetings and decisions, as well as stating that health and disability ethics committees must comply with the *Operational Standard for Ethics Committees* (Ministry of Health 2002). This document sets out the main principles that ethics committees must use in deciding whether to approve an application. The main principles are:

- respect for persons
- informed consent
- privacy and confidentiality
- validity of the research proposal
- justice
- cultural and social responsibility
- compensation for research participants.

³ A number of institutional ethics committees, based mainly at universities, also exist. These committees are not established in law.

There is no legislative mechanism that requires researchers to submit their research to a health and disability ethics committee. However, ethical review is required in order to obtain funding from many sources, such as the Health Research Council of New Zealand, and in order for the study to be published in a scientific journal.

3.5 The Medicines Act 1981, and associated review

The Medicines Act 1981 ensures that medicines are safe to use in New Zealand by establishing a regulatory regime for medicines, medical products and related products. Under this Act, a medicine is defined as an article administered to one or more human beings for a therapeutic purpose. Where human embryonic stem cells or products derived from them are administered for a therapeutic purpose, they will be subject to the provisions of the Medicines Act. All medicines must go through a registration process before they can be sold or distributed.

This Act contains provisions around the use of pre-registration medicines in clinical trials. Under these provisions, clinical trials involving human embryonic stem cells or products derived from them will require the approval of the Director-General of Health on the recommendation of the Health Research Council of New Zealand.

Legislation to establish a trans-Tasman regulator is currently being negotiated by officials and Ministers in New Zealand and Australia. This legislation will replace the Medicines Act in New Zealand. Researchers who wish to carry out clinical trials, including clinical trials involving human embryonic stem cells, will be required to comply with the provisions of this new legislation.

4 Ethical Issues Associated with Research Using Established Human Embryonic Stem Cells

Research using cells from established human embryonic stem cells raises a number of ethical issues, some of which are not raised by other types of research. These issues can be divided into two main sets: firstly, there are those associated with the way in which the cell line was established; secondly, there are those associated with the use to which the established human embryonic stem cell line is to be put. These two sets of issues will be dealt with in turn in this chapter, as will the question of how to ensure that the identified ethical issues are appropriately addressed. The policy implications of these ethical issues are also discussed.

4.1 Ethical issues associated with the way in which human embryonic stem cell lines were established

This set of issues relates to what has already happened in the process of deriving and establishing a human embryonic stem cell line that is to be used for research. If the process by which a cell line is established is unethical, then further uses of that cell line will also be unethical, as such uses would imply an acceptance of an unethical process. Two main ethical issues are discussed in this section: donor consent and embryo destruction. These ethical issues are dealt with in parts two and three respectively of the proposed guidelines at the end of this document.

4.1.1 Embryo destruction

4.1.1.1 Embryos and moral persons

Although embryonic stem cells are not embryos, the debate around human embryonic stem cell research has focused primarily on whether it is defensible to destroy embryos in order to collect stem cells for use in research. The answer to this question depends on the moral status of the embryo. Very broadly, three schools of thought can be identified on this issue.

First, many people believe that even the earliest embryos have the same moral status as other people – in other words, embryos are moral persons, capable of being harmed and benefited just like us. Those who hold this view consider that destroying embryos counts as murder, and is ethically commensurate with killing a person. On this view, the promise human embryonic stem cell research holds in terms of developing new therapies is irrelevant to whether we should do such research – after all, we would not be justified in murdering adults to achieve the same goal. If embryos are moral persons, their destruction in order to further medical research would be extremely difficult – possibly impossible – to justify.

Second, many people see the embryo at its blastocyst stage as a mere collection of cells that should not be considered as a moral person, and do not have any of the rights of other humans. On such a view, embryos are not capable of being harmed or benefited. Their use for any purpose whatsoever is ethically defensible, so long as other issues such as consent are adequately addressed. If this view of the moral status of embryos is correct, it might be unethical *not* to use surplus *in vitro* fertilisation embryos, at least, for research that aims to alleviate human suffering.

Third, many other people adopt a stance somewhere between these two extremes, considering that embryos have rights and are owed protections, perhaps due to their potential to become moral persons that can be harmed and benefited or due to shared genetic heritage, but that these rights and protections exist to a lesser degree than those of full moral persons. On this view, an embryo's rights

and protections must be weighed against the potential benefits of using the embryo for research. Each research project using human embryonic stem cells will therefore be ethically defensible to a different degree, depending on the research's potential benefits.

The question of when a developing human becomes a moral person is not a scientific one and cannot be answered by science. On the first view above, moral personhood is acquired very early in development, perhaps at fertilisation. People who hold the second view believe that moral personhood comes much later – perhaps once the developing individual is viable, can feel pain or is born. The intermediate stance outlined above assumes that moral personhood is acquired gradually throughout the process of development. As an individual develops from a zygote to an adult human, it acquires a more extensive range of rights and is owed a greater number of duties. For example, some people refer to the appearance in embryos of the 'primitive streak', which appears around 14 days after fertilisation, as a morally relevant developmental stage. The primitive streak may be morally relevant in two ways. First, it marks the beginnings of a nervous system in the embryo and thereby is relevant to questions of when the developing individual acquires the capacity to be harmed. Secondly, twinning cannot occur after the primitive streak has appeared. If the embryo develops after this point, it can only give rise to a single individual. The point at which the developing embryo implants into the wall of the uterus may also be a morally relevant developmental stage, as may the time of appearance of all major body organs.

Although dialogue on the question of the moral status of the human embryo is important, it must be accepted that the chances of consensus are very slim. As such questions are usually unable to be answered definitively, there may be no right or wrong answer. Instead, it may be more appropriate to aim for consistency with existing policies.

4.1.1.2 Consistency with existing policies

Rather than argue from first principles about whether the early embryo is a moral person, it is possible to look at relevant policies in place in New Zealand and thereby determine the value that our society places on embryos at different stages of development. A number of provisions in New Zealand law suggest that our society does not consider developing humans, particularly early embryos, to have the same rights and protections as children or adult humans. These provisions include the following examples.

- The Human Assisted Reproductive Technology (HART) Act 2004 places much greater restrictions on what may be done with an embryo after it has passed the 14-day stage of development. Before this stage, embryos may be used in human reproductive research, imported and exported, and developed outside the womb, subject in all cases to guidelines and comprehensive ethical oversight. These activities may not be carried out using embryos that have developed past 14 days. In addition, the HART Act states that embryos may not be stored for longer than 10 years in the absence of an ethics committee approving a longer storage period. As it is extremely unlikely that all stored embryos will be implanted and given a chance to develop past the 14-day stage, this provision of the HART Act practically requires the large-scale destruction of human embryos in New Zealand.
- In the case of fetuses, the Contraception, Sterilisation and Abortion Act 1977 and the Crimes Act 1961 allow for the termination of a pregnancy in a number of cases, including where the continuation of the pregnancy would result in serious danger to the life of the mother. In these cases, the competing interests of the mother and the fetus are weighed, and the mother's interests are found to be more significant even where the fetus must be destroyed to protect them. Most developed nations, including those that outlaw destructive embryo research, take a similar view. Ireland is an exception.

- A child becomes a human being within the meaning of the Crimes Act ‘when it has completely proceeded in a living state from the body of its mother, whether it has breathed or not, whether it has an independent circulation or not, and whether the navel string is severed or not’ (s159). Developing fetuses and embryos therefore do not enjoy the same rights and protections as infants – for example, a fetus cannot be murdered. However, the Crimes Act does make it a criminal offence to cause ‘the death of any child that has not become a human being in such a manner that he would have been guilty of murder if the child had become a human being’, although the penalty for this crime is less than that prescribed for murder (s182).
- New Zealand allows the use of preimplantation genetic diagnosis (PGD), a method by which embryos are tested for serious genetic disorders. PGD is an established procedure under the HART Act, meaning that it can be carried out without specific ethics committee approval in some cases.⁴ PGD is carried out on embryos that have developed for around three days, before they have reached the blastocyst stage from which human embryonic stem cells can be derived. Where an embryo with a serious genetic condition, such as cystic fibrosis or haemophilia, is detected, it is not considered for transfer to the womb. The use of PGD suggests that its benefits can outweigh the harms associated with the destruction of affected embryos.

There is a strong argument on the grounds of consistency with existing policies that suggests that in New Zealand it can be ethically acceptable to destroy embryos for research purposes, including creating embryonic stem cell lines. New Zealand society, as expressed in the law, does not appear to support the view that early embryos are moral persons that we can never use for research that could benefit others. There are some ends – including to facilitate the birth of an *in vitro* fertilisation child and to protect the health of the mother – that already justify the destruction of embryos and fetuses in New Zealand law.

4.1.1.3 Implications for policy

Given the points discussed above, what are the possible policy positions that New Zealand could take with regard to using embryos to derive established human embryonic stem cell lines? Very broadly, there are four such possible policy positions, each of which is adopted by at least one other developed country. The policies of many countries are discussed in detail in chapter 5.

The four possible policy positions are:

1. banning the use of embryos in research, and banning the use of established human embryonic stem cells in research
2. banning the use of embryos in research, but allowing the use of established human embryonic stem cells in research
3. allowing surplus *in vitro* fertilisation embryos to be used in research, and allowing the use of established human embryonic stem cells in research
4. allowing surplus *in vitro* fertilisation embryos and embryos created specifically for research to be used in research, and allowing the use of established human embryonic stem cells in research (Towns and Jones 2004).

New Zealand policy on the use of embryos for research is to be developed by the advisory committee set up under the HART Act. Until such a policy is developed, New Zealand will effectively adopt position 2, allowing the use of cells from established human embryonic stem cells in research under guidelines, but not allowing embryos to be used in research. However, the question of whether

⁴ The Human Assisted Reproductive Technology Order 2005 lists all such established procedures.

researchers may use established human embryonic cell lines derived from surplus *in vitro* fertilisation embryos or both surplus *in vitro* fertilisation embryos and embryos created for research must still be answered.

The HART Act advisory committee is working to produce a more definitive answer on whether the creation of human embryos specifically for research is acceptable to New Zealanders. In the meantime, a more conservative position could be adopted, allowing cells derived from surplus *in vitro* fertilisation embryos, but not embryos created specifically for research, to be used. It is unlikely that such a policy would adversely impact on researchers in New Zealand in the short to medium term. This position is reflected in the proposed guidelines set out at the end of this document.

4.1.2 Consent to the use of embryos for research

All research using human tissue raises consent issues. In general, the requirement to obtain informed consent recognises the need for researchers to show respect for persons. Although human embryonic stem cell lines established overseas do not have to meet the requirements of New Zealand law, these consent issues must still be addressed if the use of such cell lines is to be ethical in this country.

In New Zealand, the situation with regard to consent to use embryos in research is clear. The HART Act ethics committee must impose conditions on researchers to ensure that the informed consent of any person is obtained before their embryos or gametes are used (HART Act, s19(4)(b)). The requirement to obtain consent in such circumstances is entirely consistent with the importance placed on consent by both the Code of Health and Disability Services Consumer' Rights 1996 (Health and Disability Commissioner 1996), which requires informed consent for the research use of tissue in general, and the *Operational Standard for Ethics Committees* (Ministry of Health 2002), which lists informed consent as one of the main principles to be used by health and disability ethics committees in considering the applications they receive.

The nature of human embryonic stem cell lines means that additional requirements may be made for obtaining consent from the embryo donor. Human embryonic stem cell lines may be cultured for long periods of time and used in a number of different research projects, some of which will not be able to be envisaged when consent is sought. The consent obtained from the embryo donors should indicate an understanding and acceptance of this fact. The embryo donors should also be made aware that once a cell line is created using their embryo, they will have no control over the research uses to which the cell line is put and will thereafter be unable to withdraw their consent for the use of their embryo. Finally, donors should understand that products with a commercial value may be created using cell lines derived from their embryo and should accept that they will not receive any compensation for profits made from these products.

The HART Act also bans the giving and receiving of valuable consideration for the supply of human embryos and gametes. This provision is an expression of New Zealanders' values and beliefs about the commodification of early forms of human life. It is important to ensure that researchers in New Zealand do not obtain and use imported human embryonic stem cell lines where payment or similar valuable consideration is made in exchange for the embryos. The consent obtained from overseas embryo donors should show that no valuable consideration has been given or received.

Issues of consent to participate in research are also relevant to many types of research using human embryonic stem cells. Human subjects involved in innovative practice, intervention research (including clinical trials) and observational studies using human embryonic stem cells must give their informed consent to participate in such research. However, the issues in regard to where these cells

are used do not appear to be significantly different from those raised by other types of research on human subjects. Ethics committees regularly deal with these issues in line with the *Operational Standard for Ethics Committees* (Ministry of Health 2002) and other guidance. No further provisions appear to be necessary.

4.1.3 Compliance with regulations in the country of origin

Even if a human embryonic stem cell line created overseas meets the ethical standards of New Zealand law, it would be inappropriate to allow cells from that line to be used here in research if the line's derivation was not in accordance with the laws and regulations of the country in which it was created. Further, if the cell line was processed in any way in a third country, this processing must have been carried out in a way that accords with the laws and regulations of that third country.

4.2 Ethical issues associated with the proposed research use of cells from established human embryonic stem cell lines

This set of issues relates to what is intended to be done with the human embryonic stem cell line once it has been established. As the section above indicated, the ethical defensibility of a research project that uses human embryonic stem cells will depend on the benefits that are expected to accrue from such research. Ensuring that human embryonic stem cell research will have significant benefits is therefore an ethical issue.

4.2.1 Justification for the research use of human embryonic stem cells

There are two questions relevant to deciding whether a research project using human embryonic stem cells is justified. The first question is, Can the research objective be met by using other approaches that do not involve human embryonic stem cells? Examples of possible alternative approaches include using animal embryonic stem cells or adult stem cells. If the research objective can be met by other means, then approval should not be given to using human embryonic stem cells for that purpose.

In spite of this safeguard against unnecessary use of embryonic stem cells for research, it is important to recognise that a huge amount of basic research will be necessary in order to obtain sufficient knowledge of human developmental pathways to allow therapies to be designed. This basic research will need to involve as many different types of stem cells as possible, including human embryonic stem cells. It is important that the need to ensure that human embryonic stem cells are used appropriately is balanced with the need to ensure that this basic research can go ahead.

If the research objective cannot be met by using other approaches, then the second relevant question – Are the benefits of this research likely to justify the use of human embryonic stem cells? – must be asked. It would clearly be inappropriate to allow research that was expected to provide trivial or insignificant benefits to be carried out using human embryonic stem cells. Virtually all jurisdictions restrict the use of human embryonic stem cells to research that, to quote Germany's Stem Cell Act 2002, serves 'eminent research aims' in basic research or for the development of medical procedures to be applied to humans. It is proposed that guidelines on the research use of established human embryonic stem cells should include similar restrictions.

4.2.2 Research design

Scientific studies that are poorly designed are not likely to yield useful data and are therefore unlikely to lead to benefits. Such research is always unethical where carrying out the research entails

potential harm, as is the case with, for example, research on human subjects and research using human embryonic stem cells. Research on human subjects is not presently required to be peer reviewed for methodology and design quality, although there is a presumption that peer review will be obtained. Given the need for research using human embryonic stem cells to realise benefits in order to be ethical, it may be appropriate to require that such research be peer reviewed by an independent expert person or committee in every instance. The proposed guidelines set out at the end of this document require peer review of this nature.

4.2.3 Leftover human embryonic stem cells

Given that established human embryonic stem cell lines can be cultured for very long periods of time, it is important to consider issues relating to cells that are not used in their approved research project. A requirement for researchers to destroy any leftover cells is not proposed, but Part Three of the proposed guidelines asks researchers to provide details of how such cells will be stored or disposed of.

4.3 Ensuring that the ethical issues are dealt with appropriately

The proposed guidelines set out at the end of this discussion document would ensure that the ethical issues identified are dealt with by requiring all research proposals involving established human embryonic stem cells to be approved by an ethics committee established under the New Zealand Public Health and Disability Act 2000. As discussed in chapter 3, these health and disability ethics committees are able to consider research that ‘seeks to further scientific or professional knowledge by means of questionnaires, interviews or other techniques of information gathering, or by means of laboratory analysis of human blood, tissues, etc, of living people, cadavers or discarded body tissues (for example, placenta)’ (Ministry of Health 2002). This definition covers basic biological research using established human embryonic stem cells. Other types of research using human embryonic stem cells, such as intervention studies, are human subjects research and must also obtain ethical approval from these committees.

Most jurisdictions that allow human embryonic stem cell research require that proposals be ethically reviewed in some way. Some countries, such as Germany, have created dedicated ethics committees that consider only proposals for research that uses human embryonic stem cells. However, it is likely that a small amount of human embryonic stem cell research will be carried out in New Zealand compared to other jurisdictions. It may therefore be difficult to justify a separate system of ethical review in this country. Many other countries, like Switzerland and the Netherlands, use existing ethics committees to review research involving human embryonic stem cells.

In all cases, the onus will be on researchers who apply for ethical approval to demonstrate that their research meets the requirements of the guidelines, as well as the requirements of ethical research in general as expressed in the *Operational Standard for Ethics Committees* (Ministry of Health 2002) and other related documents.

4.3.1 The wider role of ethics committees

The role of ethics committees is not limited to ensuring that unethical research does not take place – they should also ensure that research that clearly meets ethical standards is allowed to go ahead with a minimum of further intervention. As part of this duty to allow good research to proceed, ethics committees should avoid the unnecessary consideration of matters that have already been decided. For example, once a human embryonic stem cell line has been approved for use in a research project, issues relating to the origin of that cell line should not be reconsidered in future applications for

research using that cell line. It is proposed that guidelines include a section on ‘approved human embryonic stem cell lines’ to make such applications easier for researchers.

Ethics committees exist to protect the public, and are accountable to the public. Given the level of concern around human embryonic stem cell research, ethics committees should work to ensure that the process by which such research is considered and approved is transparent. In addition, it is proposed that ethics committees establish a publicly available electronic register of approved human embryonic stem cell research projects. This register would contain information on which institutions are carrying out human embryonic stem cell research, what the research objective is, which cell lines are being used in the research and any restriction on what may be done with the cell lines due to the nature of the consent obtained, legislation in the country of origin or any other reason. This register would also serve to inform researchers of which cell lines are approved human embryonic stem cell lines.

5 Overview of International Regulations of Research Using Human Embryos and Human Embryonic Stem Cells

In the previous chapter, four possible positions were identified with respect to using embryos to derive human embryonic stem cell lines. These positions were:

1. banning the use of embryos in research, and banning the use of established human embryonic stem cells in research
2. banning the use of embryos in research, but allowing the use of established human embryonic stem cells in research
3. allowing surplus *in vitro* fertilisation embryos to be used in research, and allowing the use of established human embryonic stem cells in research
4. allowing surplus *in vitro* fertilisation embryos and embryos created specifically for research to be used in research, and allowing the use of established human embryonic stem cells in research (Towns and Jones 2004).

The regulatory systems of a number of countries are organised in terms of these positions in this chapter, starting with the more restrictive regimes and moving to the more permissive. Details of the regulation of research using established human embryonic stem cells are included where available.

5.1 Italy (position 1)

Law 40, 2003

Passed in December 2003, Law 40 is one of the most restrictive laws in the world on assisted reproduction and embryo research. Essentially, Law 40 means that *in vitro* fertilisation embryos may only be created and implanted three at a time. Although an estimated 30,000 surplus *in vitro* fertilisation embryos were frozen in Italy before this law was passed, no surplus *in vitro* fertilisation embryos can now be created, and Law 40 bans the research use of the existing frozen embryos. No embryonic stem cells can be created or used for research in Italy.

5.2 Germany (position 2)

Embryo Protection Act 1990
Stem Cell Act 2002

5.2.1 What sorts of embryos can be used for embryonic stem cell research?

Any use of an embryo ‘not suiting its own preservation’ is banned in Germany under the Embryo Protection Act 1990. However, embryonic stem cells do not count as embryos for the purposes of the Embryo Protection Act. Specific legislation on research of imported human embryonic stem cells exists in Germany. The Stem Cell Act 2002 bans, as a matter of principle, the importation and utilisation of embryonic stem cells but provides for exceptions to this ban under certain circumstances (Stem Cell Act, s1).

Only embryonic stem cells that were derived from surplus *in vitro* fertilisation embryos before 1 January 2002 may be imported and used for research in Germany. In addition, the derivation of the

embryonic stem cells must not have been obviously contrary to major principles of the German legal system (Stem Cell Act, s4).

5.2.2 What types of research are allowed?

Embryonic stem cell research may only be carried out where:

- the research serves ‘eminent research aims’ in basic research or for the development of medical procedures to be applied to humans
- according to the state of the art in biomedical science, the questions studied by the research have been examined as far as possible using animals
- the research cannot be carried out using any other type of cell (Stem Cell Act, s5).

5.2.3 What oversight regime is in place for embryonic stem cell research?

There are two parts to the oversight of embryonic stem cell research in Germany – the ‘competent agency’ and the Central Ethics Commission on Stem Cell Research (ZES). The competent agency can approve the importation and utilisation of embryonic stem cells if it is satisfied that the criteria described above have been met. The competent agency must also store basic information about approved research using embryonic stem cells in a publicly accessible registry (Stem Cell Act, s11).

The competent agency must consider the opinion of the ZES when deciding whether or not to approve an application to import and use embryonic stem cells (Stem Cell Act, s6, s7). The ZES consists of nine members with backgrounds in biology, ethics, theology and medicine who are appointed by the federal government (Stem Cell Act, s8). So far, the competent agency, the Robert Köch Institute, has granted nine licenses under the Stem Cell Act. As at March 2005, one application for approval was being considered.⁵

The German government is also required by the Stem Cell Act to submit a report to the lower house of the German parliament detailing the results of approved research using embryonic stem cells (Stem Cell Act, s15).

5.2.4 What are the consent requirements?

The Stem Cell Act does not contain detailed consent requirements, as it only addresses imported embryonic stem cells. However, the Act does require that the embryonic stem cells be derived in accordance with relevant legislation in the country of origin and that no compensation or financial benefit be given in exchange for the embryos used (Stem Cell Act, s4).

5.3 Australia (position 3)

Research Involving Human Embryos Act 2002

Prohibition of Human Cloning Act 2002

5.3.1 What sorts of embryos can be used for embryonic stem cell research?

The Research Involving Human Embryos Act 2002 originally restricted embryo research to surplus *in vitro* fertilisation embryos that were created before 5 April 2002 (Research Involving Human

⁵ Dr Peter Löser. Geschäftsstelle der Zentralen Ethik-Kommission für Stammzellenforschung (ZES), personal communication, 15 March 2004.

Embryos Act, s24). However, this provision expired in April 2005. Research may now be carried out on any embryonic stem cell line derived from a surplus *in vitro* fertilisation embryo (Research Involving Human Embryos Act, s46). Research and therapeutic cloning is banned, as is reproductive cloning, under the Prohibition of Human Cloning Act (s9).

5.3.2 What types of research are allowed?

Decisions about whether or not to allow an embryo research project to proceed in Australia are made with regard to ‘the likelihood of significant advances in knowledge or improvement in technologies for treatment as a result of excess [*in vitro* fertilisation] embryos proposed in the application, which could not be reasonably achieved by other means’ (Research Involving Human Embryos Act, s21(4)). All research uses of embryos, including embryonic stem cell research, require the researcher to obtain a licence from the licensing committee of the National Health and Medical Research Council (NHMRC) (Research Involving Human Embryos Act, ss20–28).

5.3.3 What oversight regime is in place for embryonic stem cell research?

An information sheet has been produced by the NHMRC for research ethics committees that review applications for research using cells from established human embryonic stem cell lines (National Health and Medical Research Council 2001). The main points of this information sheet are that:

- research using human embryonic stem cell lines should be considered in the same way as other research on human products, such as blood and tissue
- research using human embryonic stem cell lines should be presented to an ethics committee for consideration
- the ethics committee should consider whether the human embryonic cell lines were derived in an appropriate manner, in accordance with relevant guidelines in Australia
- the embryo used to derive the human embryonic stem cell line must have been a surplus *in vitro* fertilisation embryo, and informed consent must have been obtained from the donors
- where doubt exists as to the origin of a human embryonic stem cell line or requirements of Australian standards cannot be met, the ethics committee should not permit the research to proceed.

5.3.4 What are the consent requirements?

The woman for whom an embryo was created, and if applicable, her spouse at the time the embryo was created, must have given written authority for the research use of the embryo or have determined in writing that the embryo was excess to her/their needs (Research Involving Human Embryos Act, s9). In addition, the licensing committee and ethics committee must have regard to guidelines issued by the NHMRC on relevant matters in deciding on applications for licences. The *Ethical Guidelines on the Use of Assisted Reproductive Technology in Clinical Practice and Research* (National Health and Medical Research Council, 2004) contain a more detailed discussion of the consent requirements for research involving excess *in vitro* fertilisation embryos, including embryonic stem cell research.

5.4 France (position 3)

Bioethics Law 2004⁶

⁶ Loi no.2004–800 du 6 août 2004 relatif à la bioethique.

5.4.1 What sorts of embryos can be used for embryonic stem cell research?

France adopted a new Bioethics Law on 6 August 2004, replacing previous legislation prohibiting all embryo research. Under the new law, embryo research is still banned in principle. However, a five-year moratorium is placed on this prohibition where a number of conditions are met. Only embryos that were created as part of assisted reproductive treatment and are no longer required for that treatment may be used for research. French law specifically prohibits the creation of embryos for research (Bioethics Law, 2151–2).

5.4.2 What types of research are allowed?

Research on embryos, including research to derive human embryonic stem cell lines, may only be carried out where it is:

- likely to result in major therapeutic advances
- unable to be carried out in any other way, according to the state of scientific knowledge (Bioethics Law, 2151–5).

5.4.3 What oversight regime is in place for embryonic stem cell research?

All research using human embryos must be authorised by the Agence de la Biomedicine (Agency for Biomedicine), whose decisions are communicated to the Ministers of Health and Research. These Ministers retain the power to stop this research for a number of reasons (Bioethics Law, 2151–5).

5.4.4 What are the consent requirements?

The written informed consent of the couple involved in creating the embryo is required for research to take place using that embryo. After consent is given, the couple must be given three months in which to change their mind before research begins using their embryos.

5.4.5 Are there other specific provisions around importation?

The Bioethics Law has a specific clause relating to the importation of fetal and embryonic cells and tissue. Importation requires the prior authorisation of the Agency for Biomedicine, which reports to the Ministers of Health and Research. This authorisation can only be given if the cells or tissue were obtained in accordance with the principles on respect for the human body enshrined in the French Civil Code (Bioethics Law, 2151–6).

5.5 Switzerland (position 3)

Embryonic Stem Cell Research Act 2003⁷

Embryonic Stem Cell Research Regulations 2005⁸

5.5.1 What sorts of embryos can be used for embryonic stem cell research?

Swiss law specifically prohibits the creation of embryos for research purposes. This prohibition extends to the creation of embryos by somatic cell nuclear transfer (Embryonic Stem Cell Research Act, s3(1)(a)). Research is therefore only possible on excess *in vitro* fertilisation embryos.

⁷ Loi fédérale relative à la recherche sur les cellules souches embryonnaires.

⁸ Ordonnance relative à la recherche sur les cellules souches embryonnaires.

5.5.2 What types of research are allowed?

The only way human embryos can be used for research in Switzerland is to produce embryonic stem cells; all other uses are prohibited by the Embryonic Stem Cell Research Act (s3(2)(a)). Stem cell research and production is only possible on embryos that have not passed their seventh day of development (Embryonic Stem Cell Research Act, s3(2)(c)).

5.5.3 What oversight regime is in place for embryonic stem cell research?

The production of embryonic stem cells from human embryos must be authorised by the Swiss Federal Office of Public Health and must be approved by an ethics committee (Embryonic Stem Cell Research Act, s7(1), s11). An ethics committee must approve all embryonic stem cell research.

5.5.4 What are the consent requirements?

Under the Embryonic Stem Cell Research Act, research is only possible with the written informed consent of the couple concerned, and this consent can only be given after the embryo is established as surplus to the couple's requirements. The couple must be informed of the use to which their embryo will be put and may retract their consent at any stage (Embryonic Stem Cell Research Act, s5). More specific requirements on consent are included in regulations under the Act (Embryonic Stem Cell Research Act Regulations, ss1–4).

5.5.5 Are there other specific provisions around importation?

The importation of embryonic stem cells is covered in both primary legislation and in regulations in Switzerland. Under primary legislation, authorisation from the Federal Office of Public Health is required to import embryonic stem cells. Importation is only possible if the stem cells are to be used for a specific research project and were obtained from an excess *in vitro* fertilisation embryo with the informed consent of the couple concerned (Embryonic Stem Cell Research Act, s15).

Under regulations that sit under the Embryonic Stem Cell Research Act, an applicant who wishes to import embryonic stem cells must provide the Federal Office of Public Health with:

- the research protocol
- the favourable opinion of the competent ethics committee
- a description of the cell lines to be imported
- an affidavit from the responsible body in the country of origin, showing that the cells were derived from excess *in vitro* fertilisation embryos with the informed consent of the couple concerned, who were not remunerated (Embryonic Stem Cell Research Act, s13).

5.6 United Kingdom (position 4)

Human Fertilisation and Embryology Act 1990

Human Fertilisation and Embryology (Research Purposes) Regulations 2001

5.6.1 What sorts of embryos can be used for embryonic stem cell research?

There is no prohibition on the creation of embryos for research in British law. The first licence to create embryos for research was issued in August 2004. However, most embryo research involves surplus *in vitro* fertilisation embryos.

5.6.2 What types of research are allowed?

Under the original Human Fertilisation and Embryology Act 1990, embryo research was permitted to:

- promote advances in the treatment of infertility
- increase knowledge about the causes of congenital disease
- increase knowledge about causes of miscarriage
- develop more effective techniques of contraception
- develop methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation (Human Fertilisation and Embryology Act, schedule 2, s3(2)).

In January 2001, the Human Fertilisation and Embryology (Research Purposes) Regulations were passed, adding three new purposes for which embryo research could be undertaken, which were to:

- increase knowledge about the development of embryos
- increase knowledge about serious disease
- enable any such knowledge to be applied in developing treatments for serious disease (Human Fertilisation and Embryology (Research Purposes) Regulations, s2(2)).

The use of embryos to produce stem cells has been legal in the United Kingdom since these regulations were passed.

5.6.3 What oversight regime is in place for embryonic stem cell research?

The Human Fertilisation and Embryology Authority (HFEA) licenses and monitors clinics that carry out research on human embryos. The HFEA considers applications for research licences for research involving human embryos, including the use of embryos to extract human embryonic stem cells. Approval by a properly constituted external research ethics committee is a necessary condition for considering any application. All applicants must also:

- justify the use of human embryonic stem cells rather than adult stem cells
- provide detailed information about the fate of the stem cells throughout the process
- place a sample of all cell lines in the United Kingdom Stem Cell Bank (HFEA, date unknown).

The HFEA is not directly involved in the use of established embryonic stem cell lines. Oversight of the United Kingdom Stem Cell Bank is through the United Kingdom's Medical Research Council, which has consulted on a draft code of practice for the use of all human stem cells, including those derived from embryos, those that are imported and those that have not been deposited at the Bank.

This draft code of practice states that the steering committee of the Bank 'expects that human embryonic stem cell lines are only used by bona fide research groups for justified and valuable purposes that reflect the requirements of HFEA regulations. This is:

- research that increases the knowledge about the development of embryos or has the long-term goal of helping to increase knowledge about serious diseases and their treatment
- basic cell research that underpins these aims
- development of cell based therapies for clinical trials in respect of serious human diseases.' (Medical Research Council 2005, s8.1.1)

The draft code of practice expects but does not require scientific peer review of research using established human embryonic stem cell lines, and research ethics committee approval is not required for this research.

5.6.4 What are the consent requirements?

The HFEA has requirements in regard to the consent that must be obtained from those who donate embryos for research. In particular, donors must be informed:

- of the details of the specific research project
- that any stem cell lines created may continue indefinitely and be used in many different research projects
- that the decision to donate will not affect their treatment in any way
- whether the embryos will be made anonymous
- whether information will be fed back to the donors
- that donors can vary or withdraw the terms of their consent until the point where the embryos are used
- that once a researcher has established a line using embryonic stem cells, the donors have no control over the future use of the cells
- that stem cells derived will be deposited in the United Kingdom Stem Cell Bank and may be used for other projects
- that cell lines and discoveries made using those cell lines may be patented, and the donor will not benefit financially
- of how the research is funded, including the benefits that will accrue to researchers and their departments.

5.7 Belgium (position 4)

Law on Embryo Research 2003⁹

5.7.1 What sorts of embryos can be used for embryonic stem cell research?

The Law on Embryo Research allows for embryos to be created specifically for research purposes where the research cannot be carried out on excess *in vitro* fertilisation embryos and meets the criteria above (Law on Embryo Research, s4(1)). As with the United Kingdom, which also allows embryo creation for research purposes, most embryo research is carried out on surplus *in vitro* fertilisation embryos.

5.7.2 What types of research are allowed?

Belgium's Law on Embryo Research 2003 states that research on embryos is legal provided the research is:

- carried out for therapeutic purposes
- based on the most up-to-date scientific knowledge
- unable to be done using alternative methods
- carried out on embryos of less than 14 days of development
- carried out by qualified professionals in a suitable institution

⁹ Loi relatif à la recherche sur les embryons *in vitro*.

- approved by an ethics committee (Law on Embryo Research, s3).

5.7.3 What oversight regime is in place for embryonic stem cell research?

The Law on Embryo Research created a federal commission for scientific and medical research on embryos *in vitro*, which is responsible for overseeing the administration of the Law and has powers to stop embryo research (Law on Embryo Research, s9, s10).

5.7.4 What are the consent requirements?

Embryo donors must give written informed consent to the use of their embryos for research purposes (Law on Embryo Research, s8).

5.8 The Netherlands (position 4)

Embryo Act 2002¹⁰

5.8.1 What sorts of embryos can be used for embryonic stem cell research?

In the Netherlands, the Embryo Act 2002 allows the use of excess *in vitro* fertilisation embryos for research purposes, including obtaining embryonic stem cells for research (s8). The creation of embryos specifically for research is generally prohibited, but the prohibition does not apply to some research whose aims can only be met by using such embryos (Embryo Act, s11).

5.8.2 What types of research are allowed?

Non-reproductive embryo research can only be approved where:

- it can be reasonably assumed the research will lead to new insights in medical science
- no alternative method to achieve these insights exists
- the research is robustly designed and carried out by qualified professionals (Embryo Act, s10).

5.8.3 What oversight regime is in place for embryonic stem cell research?

All embryo research must first be reviewed and approved by the Central Committee on Research Involving Human Subjects (CCMO) (Embryo Act, s3(2)). The CCMO must report annually to the Minister of Health, who in turn sends this report to both Houses of the Dutch Parliament.

5.8.4 What are the consent requirements?

Embryos can be donated with written informed consent from the couple that created them, and no financial consideration can be given to the couple (Embryo Act, s8). The following conditions must also be met.

- Information must be supplied in such a way as to be reasonably certain the person concerned has understood it, and sufficient time must be given to allow a considered decision.
- The purposes for which the embryos may be used and the period for which they will be kept must be put in writing.
- The embryo donors may require that they be informed about the research uses to which their embryo is intended be put and that research will not go ahead without their specific consent.

¹⁰ Embryowet.

5.9 United States (various positions)

No specific federal legislation

5.9.1 What sorts of embryos can be used for embryonic stem cell research?

No federal law in the United States prohibits the creation of embryos for research. However, federal funds may only be used for embryonic stem cell research where the cells were derived from surplus *in vitro* fertilisation embryos on or before 9 August 2001. Many states (including California, New Jersey and Massachusetts) have passed their own more permissive legislation to make state funds available to human embryonic stem cell researchers. However, most states have no legislation that specifically addresses the regulation of human embryonic stem cell research (National Academy of Sciences 2005).

5.9.2 What types of research are allowed?

As there is no federal legislation on embryonic stem cell research, no specific restrictions exist around the uses to which embryonic stem cells may be put in the private sector.

5.9.3 What oversight regime is in place for embryonic stem cell research?

There is no dedicated oversight regime for embryonic stem cell research in the United States. There are, however, a number of sources of unofficial guidance including the National Institutes of Health (2001) and the National Academy of Sciences, which released comprehensive guidelines for researchers and the ethics community in April 2005. While these guidelines carry considerable weight, they do not have any legal status. The primary recommendations of the guidelines were that an oversight committee be set up in each institution where embryonic stem cell research takes place and that a national ethical oversight system be set up to track developments in the field (National Academy of Sciences 2005).

5.10 Summary table

A summary table of the policies of these and other countries is provided below.

Position 1 The use of embryos in research is banned. The use of established human embryonic stem cells in research is banned.	Position 2 The use of embryos in research is banned. The use of established human embryonic stem cells in research is not banned.	Position 3 The use of surplus IVF embryos in research is not banned. The use of established human embryonic stem cells derived from such embryos in research is not banned.	Position 4 The use of embryos created for research and surplus IVF embryos in research is not banned. The use of established human embryonic stem cells derived from such embryos in research is not banned.
Austria Ireland Italy Norway Poland (United States: at least eight states)	Germany New Zealand (until guidance is developed by the HART Act advisory committee) (United States: federal funding)	Australia Canada Czech Republic Denmark Finland France Greece Hungary Russia Spain Switzerland Taiwan	Belgium China India Israel Netherlands Singapore South Korea Sweden United Kingdom (United States: at least three states)

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Legislation and Regulations

New Zealand	Human Assisted Reproductive Technology (HART) Act 2004 Hazardous Substances and New Organisms (HSNO) Act 1996 Human Tissue Act 1964 New Zealand Public Health and Disability Act 2000 Contraception, Sterilisation and Abortion Act 1977 Medicines Act 1981 Crimes Act 1961
Australia	Research Involving Human Embryos Act 2002 Prohibition of Human Cloning Act 2002
Belgium	Law on Embryo Research 2003
France	Bioethics Law 2004
Germany	Embryo Protection Act 1990 Stem Cell Act 2002
Italy	Law 40, 2003
The Netherlands	Embryo Act 2002
Switzerland	Embryonic Stem Cell Research Act 2003 Embryonic Stem Cell Research Regulations 2005
United Kingdom	Human Fertilisation and Embryology Act 1990 Human Fertilisation and Embryology (Research Purposes) Regulations 2001

Glossary

adult stem cell	An undifferentiated, multipotent cell found in differentiated tissue in the body.
blastocoel	The fluid-filled cavity of a blastocyst.
blastocyst	A 4–5 day old embryo. Blastocysts consist of two groups of cells – a spherical outer layer of cells called the trophectoderm, inside which there is a fluid-filled cavity, called a blastocoel, and a small inner cell mass. Cells from the inner cell mass are embryonic stem cells.
cloning	The production of an organism that is genetically identical to another organism.
consent	Agreement to health care procedures made by a person with the capacity and legal competence to make such decisions.
culture	The growth of cells in a culture medium in a laboratory.
degenerative	A condition marked by gradual deterioration of organs and cells along with loss of function.
differentiation	The process whereby relatively unspecialised cells give rise to cells with a specific structure and function in the body.
duty	A requirement arising from the need to observe the rights of others.
embryo	The product of fertilisation until the eighth week of development. After the eighth week, the developing entity is called a fetus.
embryonic germ layer	One of the three types of differentiated cell layer – endoderm, mesoderm, and ectoderm – present in the embryo shortly after the blastocyst stage of development. The three layers are examples of differentiated cells.
embryonic stem cell	An undifferentiated, pluripotent cell found in the early embryo.
established human embryonic stem cell line	A stable population of embryonic stem cells obtained from human embryos, that can self-replicate and remain undifferentiated for long periods of time in culture outside of the body.
ethics committee	A body established to consider the ethical issues associated with a particular activity. Seven ethics committees are established under the New Zealand Public Health and Disability Act 2000 to consider health and disability research.
fertilisation	The process whereby an egg cell fuses with part of a sperm cell to produce a zygote.
fetus	The stage of development lasting from the eighth week after fertilisation until birth.
haematopoietic stem cell	A type of adult stem cell found in the bone marrow that can give rise to a number of different types of blood cells.

immunosuppressant	A drug that impairs the function of the immune system. Immunosuppressants are used following transplants of foreign cells or tissues to avoid rejection.
implantation	The process whereby an embryo is implanted into the uterine wall.
<i>in utero</i>	In the womb.
<i>in vitro</i>	'In glass'; in a laboratory dish or test tube or some other artificial environment.
<i>in vitro</i> fertilisation	An assisted reproductive technique whereby an egg cell is fertilised by a sperm cell in the laboratory.
inner cell mass	The group of cells in the inside of a blastocyst, from which develops an embryo proper.
monoclonal	Relating to a single clone. A monoclonal cell line is derived from a single cell.
moral person	An entity that is the subject of rights and duties.
mouse fibroblasts	Cells that give rise to connective tissue in mice; the culture medium used to maintain human embryonic stem cells in their undifferentiated state.
multipotent	Able to give rise to cells from a limited number of related cell types.
oocyte	An egg cell.
PGD	Pre-implantation genetic diagnosis; a technique whereby three-day-old <i>in vitro</i> embryos are tested for serious genetic disorders before being transferred to the womb.
plasticity	The limited ability of some adult stem cells to give rise to cells from unrelated cell types.
pluripotent	Able to give rise to cells from all or most of the cell types found in a mature individual, but not able to give rise to a complete individual organism.
regenerative medicine	A branch of medicine that aims to create new cells and tissue to treat disease and damage.
right	An entitlement; a claim specifying acts that are forbidden, permitted or required to be done to the holder of the right.
SCNT	Somatic cell nuclear transfer; a cloning technique whereby the nucleus of a somatic (body) cell is transferred into an oocyte whose nucleus has been removed.
somatic stem cells	Another name for adult stem cells.
surplus IVF embryo	An embryo created during IVF but no longer required for implantation.
totipotent	Able to give rise to a complete individual organism.

trophectoderm	The outer layer of cells of a blastocyst, which give rise to extra-embryonic tissue such as the placenta.
tumour	An abnormal mass of tissue with no useful bodily function.
zygote	The product of fertilisation; the cell formed by the fusion of an egg cell and part of a sperm cell.

Proposed Guidelines for Using Cells from Established Human Embryonic Stem Cells Lines for Research

Part One – Ethical review and other requirements

Research to be approved by an ethics committee prior to commencement of research

1. All research using established human embryonic stem cells must be ethically reviewed and approved by an appropriate ethics committee before the research is started. Except where legislation requires otherwise, the appropriate ethics committee will be a health and disability ethics committee established under the New Zealand Public Health and Disability Act 2000.¹¹
2. Research on embryonic stem cells must comply with all other standards of ethical research in New Zealand as expressed in the *Operational Standard for Ethics Committees* and other guidance for researchers and ethics committees.

Part Two – Provisions associated with the way in which the human embryonic stem cell lines have been established

Embryo(s) to have been created for the purpose of fertility treatment

3. The principal researcher must provide the ethics committee with evidence that the embryo(s) used to create the stem cell line in question were created for the purpose of fertility treatment and are no longer required for that purpose.

Consent

4. The principal researcher must provide adequate evidence that the people whose gametes were used in creating the embryo gave free and informed consent to the use of that embryo to derive embryonic stem cell lines. Adequate evidence may include copies of the original donor consent forms, a suitably witnessed declaration from the supplier of the consent obtained, details of the requirements of ethical review and other regulations in the country of origin, or other suitable documentation.
5. The principal researcher must provide evidence that consent to derive embryonic stem cell lines was requested after the embryo(s) in question were determined to be surplus to the requirements of the consenting people.
6. The evidence provided should show that the people who gave consent to the use of the embryo in research were adequately informed that:
 - (i) their decision on donation would not affect any aspect of their future treatment in any way
 - (ii) they could withdraw or amend their consent up until the time when the embryos were used
 - (iii) they would have no control over the use of cells from embryonic stem cell lines derived from the embryo

¹¹ For research using human embryonic stem cells that fits the definition of human reproductive research under the Human Assisted Reproductive Technology (HART) Act 2004, the appropriate ethics committee will be the HART Act ethics committee.

- (iv) any stem cells created may be able to be cultured indefinitely and used in multiple research projects
 - (v) they would not benefit financially from any profits made from embryonic stem cell lines or products derived from such lines.
7. The principal researcher must provide evidence to the ethics committee that the consent of the people whose gametes were used in creating the embryo was not given in exchange for any payment or consideration.

Regulation in the country of origin and third countries

8. The principal researcher must provide evidence that the human embryonic stem cells were obtained in accordance with the laws and regulations of the country of origin and any third country in which they were processed.

Part Three – Provisions relating to proposed use of the established human embryonic stem cell lines

Justification for research

9. The principal researcher must demonstrate to the ethics committee that the application relates to research that has the long-term goal of helping to increase knowledge about either serious diseases and their treatment or the processes of human development. Such research may include basic biological research, innovative practice and intervention research, including clinical trials.
10. The principal researcher must clearly explain and demonstrate to the ethics committee why this objective cannot be addressed through other types of research, including research on other stem cells (such as adult stem cells or animal embryonic stem cells).

Research design and quality

11. The principal researcher must provide evidence to the ethics committee that their research protocol has been favourably peer reviewed in every instance by a suitable qualified and experienced independent person or committee.

Excess human embryonic stem cells

12. The principal researcher must describe to the ethics committee how any embryonic stem cells left over after the completion of the research project will be securely stored or disposed of.

Part Four – Duties of ethics committees

Research using approved human embryonic stem cell lines

13. Where an application involves the use of established human embryonic stem cells from a line that has already been approved for another research project in New Zealand, the ethics committee shall not reconsider issues relating to the origin of that stem cell line. These issues are addressed in Part Two of these guidelines.

Publicity

14. Ethics committees shall co-operate to establish a register of publicly available information on approved human embryonic stem cell research and recognised sources of human embryonic stem cells. This register shall include:
 - (i) the short title of the research project
 - (ii) an explanation of the goals and methodology of the research project in layman's terms
 - (iii) the full name of the institution at which the research is to be carried out
 - (iv) the name or identifying code of the cell line from which the human embryonic stem cells were obtained
 - (v) the name and address of the supplier of the cells
 - (vi) any restrictions on the uses to which human embryonic stem cells from the cell line may be put due to the nature of the consent obtained from the donors of the embryos used to derive the cell line or any other reason.
15. This register should be publicly available in electronic form.

Submission Booklet

This discussion document asks for your feedback on proposed guidelines on the research use of established human embryonic stem cells. These proposed guidelines are set out on pages 41–43.

The Ministry of Health is interested in any comment you may have on any aspect of the discussion document and proposed guidelines but is particularly interested in whether you think the proposed guidelines adequately address the ethical issues identified. The questions below follow the content of the proposed guidelines. There are also general questions and issues that you may want to comment on.

Please return only one copy of your submission no later than **5 pm, Friday 3 March 2006** to:

Tanith Robb
Sector Policy
Ministry of Health
PO Box 5013
Wellington

Phone: (04) 470 0676
Fax: (04) 496 2340
Email: tanith_robbs@moh.govt.nz

Please indicate which sector(s) your submission represents

(You may tick as many boxes as apply)

Academic/research

Māori

Pacific

Education/training

Non-government agency

Health sector (personal)

Health sector (public)

Industry

Other *(please specify)*

All submissions will be acknowledged by the Ministry and a summary of submissions will be sent to all those who request a copy. The summary will include the names of all those who made a submission. In the case of those who withhold permission to release personal details, the name of the organisation will be given if supplied.

Do you wish to receive a copy of the summary of submissions?

Yes

No

Your submission may be requested under the Official Information Act 1982. If this happens, the Ministry of Health will release your submission to the person who requested it. However, if you are an individual as opposed to an organisation, the Ministry will remove your personal details from the submission if you check the following box.

I **do not** give permission for my personal details to be released to persons under the Official Information Act 1982.

Part One

1. Is it appropriate for guidelines to require ethics committees to review all research using established human embryonic stem cell lines, including basic biological research? If not, why not and should some other form of oversight be put in place?

Yes

No

Comment:

2. If yes, do you agree that the health and disability ethics committees established under the New Zealand Public Health and Disability Act 2000 are the appropriate ethics committees to consider applications for such research?

Yes

No

Comment:

Part Two

3. Given that the Human Assisted Reproductive Technology (HART) Act 2004 advisory committee will produce guidance on the use of embryos for research in New Zealand, do you agree that it is appropriate for guidelines on the research use of established human embryonic stem cell lines to restrict researchers to only using lines derived from surplus *in vitro* fertilisation embryos?

Yes

No

Comment:

4. Are the proposed provisions around consent adequate to address the consent issues raised by human embryonic stem cell research? If not, why not?

Yes

No

Comment:

5. Are the requirements on the evidence that researchers must provide around the level of consent obtained reasonable? Are there instances in which researchers may not be able to meet these requirements?

Yes

No

Comment:

Part Three

6. Do you agree that human embryonic stem cell research should be limited to research that 'has the long-term goal of helping to increase human knowledge about either serious diseases and their treatment or the processes of human development'? If not, what boundaries should be placed on such research?

Yes

No

Comment:

7. Is the requirement for researchers to demonstrate that the research objective cannot be addressed through other types of research reasonable?

Yes

No

Comment:

8. Does a requirement that research using human embryonic stem cell lines be peer reviewed in every instance by a suitable independent person or committee adequately address the need for such research to be soundly designed?

Yes

No

Comment:

9. Do the guidelines deal with the issue of leftover human embryonic stem cells adequately? Is it appropriate for researchers to store such leftover cells, or should they be disposed of once the approved research project has finished?

Yes

No

Comment:

Part Four

10. Do you agree that once a human embryonic stem cell line has been approved for use in a research project in New Zealand, that cell line should be considered as an 'approved human embryonic stem cell line' by ethics committees that consider later applications to use the cell line? If not, why not?

Yes

No

Comment:

11. Does establishing a publicly available register of approved human embryonic stem cell lines and approved research projects adequately address the transparency and accountability issues involved in this research?

Yes

No

Comment:

12. Is it appropriate for ethics committees to establish such a register? If not, who should be responsible for its establishment?

Yes

No

Comment:

13. Are the details that the proposed guidelines specify should be available from the register reasonable? If not, why not?

Yes

No

Comment:

General questions

14. Do the proposed guidelines identify all relevant ethical issues that are specific to human embryonic stem cell research?

Yes

No

Comment:

15. If not, what extra issues should be identified?

Comment:

16. How should these issues be addressed in guidelines?

Comment:

Further comments