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Code of Practice for the use of Human Stem Cell Lines

Foreword

This Code provides guidance on best practice for those working with stem cell lines and specifies oversight mechanisms for research involving human embryonic stem cell lines. It also sets out the requirements for the activities of the UK Stem Cell Bank in relation to procuring, storing and distributing human stem cell lines in order to support research that will help improve understanding of human development and disease and aid the generation of strategies to treat serious disease.

The UK Stem Cell Bank was established in 2003 in response to Government recommendations to facilitate the sharing and use of quality controlled human stem cell lines by the clinical and research communities. The Bank is overseen by an independent Steering Committee (the Steering Committee for the UK Stem Cell Bank and for the Use of Stem Cell Lines – hereafter called the Steering Committee), which has developed this Code of Practice to explain the role of the Steering Committee and to provide guidance and assistance on best practice to those working with stem cell lines.

In the UK, research involving human embryos, including the generation of human embryonic stem cell lines, is under statutory control by the Human Fertilisation and Embryology Authority (HFEA). Embryonic stem cell lines once established are not embryos and the Government has passed legislation that establishes that research involving such cell lines does not need the same level of regulation to which embryo research is subject to by the HFEA. However, as the generation of embryonic stem cell lines involves the destruction of human embryos, oversight in the form of a Steering Committee was recommended to ensure that research is conducted within an ethical framework that is transparent to the public and is in keeping with HFEA regulations. The oversight mechanisms governing research involving established human embryonic stem cell lines and this Code of Practice are voluntary. However, adherence is a HFEA licensing requirement in the UK and there is an expectation by Government that they are adhered to. In addition scientists have a desire for there to be ethical oversight of all work involving human embryonic stem cells. Other pluripotent stem cell lines, whether fetal, adult or those generated through induced pluripotency, are not subject to the same level of oversight by the Steering Committee, although the ethical considerations in relation to their derivation and use are covered within this Code of Practice.

This Code of Practice should be regarded as an evolving document which will be revised and updated in line with both practice and the requirements arising from relevant UK and EU legislation such as the Human Tissue Act and the EU Tissue and Cells Directive.

Contents

1. Purpose of the Code of Practice

This Code was drawn up by the Steering Committee for the UK Stem Cell Bank and for the Use of Stem Cell Lines and benefited from input by a wide range of stakeholders. It provides guidance on best practice for those working with stem cell lines and specifies oversight mechanisms for research involving human embryonic stem cell lines. The Code should provide confidence and reassurance to professionals and the public alike that stem cell research in the UK is performed to best practice and is conducted within a transparent and ethical framework. The main emphasis of the Code is on human embryonic stem cell lines. However, references to stem cell lines derived from other human tissues are included as the UK Stem Cell Bank will curate and distribute human cell lines from all sources. For ease of reference text referring specifically to embryonic stem cells has been italicised.

This Code also sets out the requirements for the activities of the UK Stem Cell Bank in relation to procuring, processing, testing and storing human stem cell lines, and providing those for basic and clinical research leading to the development of therapeutic interventions. These principles, outlined in section 4, will ensure that the UK Stem Cell Bank operates within a transparent, regulated and ethical framework.

2. Definition of stem cells

2.1 Stem cells

Stem cells have the capacity to divide to generate "daughter" cells that retain the properties of the stem cell, or to produce daughters that begin to "differentiate" into a more specialised cell type, or to produce one daughter cell of each type. Stem cells are thus central to normal human growth and development, and are also a potential source of new cells for the regeneration of diseased or damaged tissue. Stem cells are present at all stages of development, and in many (possibly most) tissues of the adult. At present, stem cells are impossible to identify by their physical characteristics alone, although they can be enriched in a population of cells. Stem cells from different tissues, and from different stages of development, vary in terms of the number and types of cells to which they normally give rise. For the purposes of this Code of Practice, the Steering Committee has defined four classes of stem cells: embryonic stem cells, somatic stem cells, embryonic germ cells and induced pluripotent stem cells (see below).

Until it is known which stem cells have the greatest potential in terms of developing human therapies, the Steering Committee endorses research on all types of stem cells.

2.1.1 Embryonic Stem Cells

At the earliest stages after fertilisation (up to about the eight cell stage) all the cells of the embryo are "totipotent" (i.e. they have the capacity to develop into

every type of cell needed for full development, including extra-embryonic tissues such as the placenta and umbilical cord). After about five days the blastocyst stage is reached. Within this ball of 50 to 100 cells lies the inner cell mass, which will develop into the embryo proper. The inner cell mass comprises about a quarter of the cells at this stage of development and a unique class of stem cells, referred to as embryonic stem (ES) cells, can be derived from it. Embryonic stem cells derived from the mouse have the innate capacity ("potential") to differentiate into each of the 200 or so cell types which make up the body, and are described as "pluripotent" (see also glossary of terms). The capacity of human embryonic stem cells to contribute to all tissue types in development has not yet been fully established, though this potential has been demonstrated in "teratoma assays" whereby such cells can give rise to multiple tissue types after transplantation into mice. Both human and mouse embryonic stem cells can, to the best of our knowledge, be grown over long periods of time in culture and expanded in number without changing their cellular phenotypes or genotypes. In the case of mouse stem cells they are also known to maintain their pluripotent state under these culture conditions.

2.1.2 Embryonic Germ Cells

In mammals, egg and sperm cells (gametes) are derived from a founder population of primordial germ cells set aside early in embryogenesis. Embryonic germ cells are a special class of stem cells that can be derived from primordial germ cells, and in mice such cells have been shown to be pluripotent. However, the situation for human embryonic germ cells is not yet clear. Other germ-line stem cells, notably spermatogonia, can also be derived from children or adults and maintained in culture. While these stem cells are usually "unipotent", in that they would naturally only give rise to sperm, it has been found that these too can be manipulated in the laboratory to provide a subpopulation of cells that demonstrate aspects of pluripotency. These cells may be equivalent to embryonic germ cell lines, but are likely to have lost their genetic imprinting.

2.1.3 Somatic Stem Cells

As development proceeds beyond the blastocyst, stem cells comprise a progressively decreasing proportion of cells in the embryo, fetus and body after birth. However, many, if not most tissues in the fetus and human body contain stem cells which, in their normal location, have the potential to differentiate into a limited number of specific cell types in order to regenerate the tissue in which they normally reside. These stem cells are described as "multipotent". Extra-embryonic tissues such as the placenta, amniotic fluid and umbilical cord also contain stem cells with the same genetic makeup as the cells of the embryo, and under special laboratory conditions these cells can demonstrate a broader potential to differentiate, although whether these truly represent pluripotent cells remains controversial.

Increasingly common is the use of mesenchymal stem/stromal cells (MSC's) for regenerative medicine. MSC's are ubiquitously distributed in the body, but are usually harvested from either the bone marrow or adipose tissue. They classically show adipogenic, chondrogenic and osteogenic differentiation potential in line with their normal developmental role, but may elicit subtle

beneficial effects in many healing tissues through the release of paracrine-acting growth factors.

2.1.4 Induced Pluripotent Stem Cells

Induced pluripotent stem (iPS) cells are a type of pluripotent stem cell derived from a non-pluripotent cell, for example fully differentiated cells from adult skin. It has been established that numerous different cell types can be used to produce iPS cells, which are believed to be like embryonic stem cells in many respects. For example they express certain "stem cell" genes and show the same ability to differentiate; they can also form teratomas in mice (a tumour made of multiple tissue types). iPS cells were first produced in mouse cells in 2006 by introducing retroviruses containing key genes whose expression was known to give rise to pluripotency in embryonic stem cells. This approach was successfully repeated in human cells in 2007. Many different techniques have now been used to produce iPS cells, including the introduction of exogenous genes on non-integrating viral vectors and plasmids, and use of small molecules that can substitute for the products of "stem cell" genes. The reprogramming factors used to generate iPS cells may vary and the absolute requirements are not yet fully understood.

The full extent of iPS cells' relationship to natural pluripotent stem cells such as embryonic stem cells is still being assessed. Nevertheless, the discovery of iPS cells provides a route to obtain pluripotent stem cells from patients to develop cell-based models of disease and future therapeutic options.

2.1.5 The relationship between embryonic stem cells and other stem cells derived from embryonic or fetal tissue.

Embryonic stem cells are a very specific class of stem cell which can be derived from the blastocyst and are considered to be pluripotent. Confusingly, stem cells derived from the early embryo after the blastocyst stage and from the fetus are sometimes also referred to as 'embryonic' stem cells in the literature; however, such cells are not known to be pluripotent and (along with extra-embryonic stem cells) are more akin to adult stem cells which have a more restricted ability to differentiate into different cell types. They are therefore referred to in this Code of Practice as "somatic" stem cells.

2.2 Stem cell lines

A stem cell line comprises cells that can be expanded for prolonged periods in appropriate culture conditions without any change in genotype or phenotype. Embryonic stem cells can be maintained in this way, and a "normal, diploid" cell line would not include cells which have been immortalised following any acquired or induced alteration in genotype, such as those routinely used in biomedical research. Stem cells can also be derived from many adult tissues, although in the vast majority of cases it has not proved possible to maintain them as stem cell lines in the laboratory. However, in some instances genetic manipulation has been used to "conditionally" immortalise adult stem cells to allow them to be maintained as (clonally-derived) cell lines; the immortalisation gene can then be inactivated to allow the stem cells to differentiate.

Importantly, phenotypically indistinguishable stem cell lines might have different differentiation capacities; the basis for this is not yet understood. Ideally cell lines should be clonal, that is derived from a single cell. In practice, however, this criterion cannot always be satisfied.

2.3 The relationship of the Code of Practice to different types of stem cell

This Code applies to all research involving established human embryonic stem (ES) cell lines, since their generation involves the destruction of human embryos. Other pluripotent stem cell lines, whether fetal, somatic or those generated through induced pluripotency, fall outside this Code of Practice, although ethical considerations remain in relation to their derivation and use. For example, these cells may be used extensively in research resulting in a lot of information becoming available about the cells, and potentially about the person from whom they were derived. If the cells were eventually used in therapy the donor's genetic make up could be transplanted into potentially thousands of people. Researchers working with these cells should therefore consider that many of the issues and regulations that apply for ES cells have relevance (for more detail see sections 3 and 9.2).

Similarly, the requirement to deposit human stem cell lines in the UK Stem cell Bank only applies to ES cells, as required under HFEA licence. There is no such requirement to deposit iPS cells, fetal or somatic stem cell lines within the UK Stem Cell Bank, although the Steering Committee will consider applications to bank such lines where these are likely to provide a valuable resource for research (see Section 6).

3. Legislation governing the establishment and use of human stem cell lines

3.1 The Human Tissue Act (2004) - (See page 44 for full web link)

The removal, storage and use of human material (organs, tissues and cells) in England, Wales and Northern Ireland is governed by the Human Tissue Act (2004) (HT Act). In Scotland, the Human Tissue (Scotland) Act 2006 applies, in addition to certain sections of the 2004 Act, including those relating to storage of tissue for DNA analysis.

The HT Act makes donor consent a fundamental principle underpinning the lawful storage and use of human material and makes it an offence to use tissue for certain purposes without appropriate consent. It also provides for the establishment of the Human Tissue Authority (HTA), which holds responsibility for licensing activities within its remit, and issues codes of practice giving practical guidance on the conduct of these activities. In Scotland the basic approach is consistent but the legislation only applies to tissue from the deceased and the HTA does not licence premises or activities in relation to the HT Act.

The Human Tissue Act 2004 applies to any material from a human body consisting of, or including human cells, with exception of hair and nail of a living person, and gametes and embryos, which are separately regulated by the Human Fertilisation and Embryology Act 1990). Established cell lines as well as any other human material created outside the human body are excluded from the Act. However, it should be noted that cell lines that are intended for use in human application are regulated under the Human Tissue (Quality and Safety for Human Application) Regulations 2007.

Human tissue that is stored with the intention of deriving iPS cells for research needs to be stored under an HTA research licence and the relevant consent requirements complied with. These are discussed further in section 9.2.3. Once an iPSC line has been derived it falls outside of the remit of the HT Act.

3.2 The European Union Tissue and Cells Directives and The Human Tissue (Quality and Safety for Human Application) Regulations 2007 - (See page 44 for full web link)

These Directives apply to tissues and cells (including cell lines) for human application. The Directives were transposed into UK law via the Human Tissue (Quality and Safety for Human Application) Regulations 2007 and became law on 5 July 2007. Under these Regulations the Human Tissue Authority is responsible for regulating establishments across the whole of the UK. It licences and inspects establishments involved in the procurement, testing, processing, storage, distribution and import/export of tissues or cells for use in human application.

3.3 The Human Fertilisation and Embryology (HFE) Act (1990, 2001 and 2008) - (See page 44 for full web link)

The special regulations which govern the creation and use of human embryonic stem cells reflect the fact that the human embryo has a special moral status. The position adopted by Parliament in this legislation is that the embryo, unlike an infant, does not have the full rights of a person. However, its human potential gives it an intrinsic value which implies that neither its creation nor its destruction are to be treated casually. Regulation of research on human embryos in the UK is governed by the Human Fertilisation and Embryology Act 1990, which was amended in 2001 to accommodate advances in human stem cell research, and further revised in 2008.

The Human Fertilisation and Embryology Authority (HFEA) was established under the HFE Act 1991. This HFEA subjects all embryo research in both the private and public sector to a robust system of case-by-case review before any license to permit research is issued. No research is allowed on embryos over 14 days old. At the time of the 1991 Act, embryo research was restricted to the study of infertility, miscarriage and congenital disease. In 2000, the Chief Medical Officer published *Stem Cell Research: Medical Progress with Responsibility,* to take account of contemporary developments in embryonic stem cell research. Following this report and widespread debate in both houses of Parliament, the HFE legislation was amended in 2001 to allow the use of

embryos for stem cell research. The HFEA can license the derivation of stem cells from embryos that are: (i) surplus to IVF requirements, or (ii) created by IVF specifically for research purposes, or (iii) created by therapeutic cloning or somatic cell nuclear transfer (SCNT).

Further amendments were introduced in the HFE Act 2008 to allow for generation and use of defined categories of interspecies embryos, referred to as human admixed embryos (HAE) for research, subject to the same conditions that apply to human embryos.

The categories of HAE authorised in the Act are:

a. '*Cytoplasmic hybrid'*: replacing the nucleus of an animal egg or cell with a human nucleus, cell, gamete or two pronuclei,

b. '*True hybrid'*: created from human and animal gametes or pronuclei,

c. '*Transgenic human embryo'*: a human embryo with animal nuclear or mitochondrial DNA inserted into any cell,

d. '*Chimeric human embryo'*: a human embryo that has been altered by the introduction of one or more animal cells,

e. any embryo not falling within (a) to (d) which contains both nuclear or mitochondrial DNA of a human and nuclear or mitochondrial DNA of an animal ("animal DNA") but in which the animal DNA is not predominant.

The Human Fertilisation and Embryology Authority (HFEA) is the regulatory authority empowered to issue licences for research that involves the creation or use of human or human admixed embryos. It is an offence to carry out any such research without a licence from the HFEA. A research licence will not be granted unless the HFEA is satisfied that any proposed use of human or human admixed embryos is necessary for the research and that the research is necessary or desirable for the purposes specified in the amended Act, namely:

a. increasing knowledge about serious disease or other serious medical conditions,

b. developing treatments for serious disease or other serious medical conditions,

c. increasing knowledge about the causes of any congenital disease or congenital medical condition that does not fall within paragraph (a),

d. promoting advances in the treatment of infertility,

e. increasing knowledge about the causes of miscarriage,

f. developing more effective techniques of contraception,

g. developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation, or

h. increasing knowledge about the development of embryos.

Human or human admixed embryos created for research purposes may not be implanted into a woman and must not be kept for longer than 14 days or the appearance of the primitive streak, whichever occurs first.

Licences issued by the HFEA are subject to conditions. Importantly, HFEA licences for projects involving the derivation of human embryonic stem cell lines require licencees to deposit a sample of each cell line generated in the UK Stem Cell Bank. Licencees are not permitted by the HFEA to carry out secondary research projects on ES cells or to transfer ES cell lines to third parties without the approval of the Steering Committee.

The HFEA's regulatory responsibility is for research using human embryos. Stem cells taken from an embryo are no longer the subject of regulation by HFEA with the exception of the requirement to fulfil conditions of the licence as described above. The conservation and use of human embryonic stem cells and stem cell lines is the responsibility of the Steering Committee (see Section 5).

The amended Act makes it an offence, punishable by up to 10 years imprisonment and an unlimited fine on conviction, to implant into a woman an embryo other than those "permitted" by legislation. In brief, "permitted'" embryos are created from human eggs and sperm and have not had alterations to their DNA other than to prevent serious mitochondrial disease.

3.4 Medicines for Human Use (Clinical Trials) Regulations 2004 - (See page 44 for full web link)

Stem-cell (gamete-derived) cell based products that involve the destruction of a human embryo in their formulation are initially licensed by the HFEA. At the point where the embryo has been destroyed and cells are harvested these human cells would fall under the remit of the HTA. The development of a product using these cells is under the remit of the HTA until such time as the MHRA classifies the product as an Investigational Medicinal Product (IMP) or the product is classified as an Advanced Therapy Medicinal Product (ATMP). Once this classification has been confirmed the Manufacture, Clinical Trial Approval and Marketing approval (for IMPs) are under the remit of the MHRA and not the HTA.

Trials of IMPs in the UK are authorised and regulated by the Medicines and Healthcare products Regulatory Agency (MHRA). Stem cell lines that fall within the EU definition of medicinal product which are used in clinical trials to assess safety or efficacy in humans will be IMPs and such trials must be authorised by the MHRA.

3.5 EC Regulation on advanced therapy medicinal products 2007 - (See page 44 for full web link)

It is obligatory under the Regulation that all advanced therapy medicinal products (ATMPs) which may include stem cells therapies (regardless of derivation) are subject to the European centralised marketing authorisation procedure which is co-ordinated on behalf of the European Commission by the

European Medicines Agency (EMEA). Such submissions can be discussed with the MHRA[1].

3.6 Clinical trials involving the use of human stem cell lines - the role of the Gene Therapy Advisory Committee (GTAC) - (See page 44 for full web link)

GTAC has UK-wide responsibility for the ethical oversight of proposals to conduct clinical trials involving gene therapy or stem cell therapies derived from stem cell lines. It is both a Government Scientific Advisory Committee and a Research Ethics Committee formally recognised in statute. Its terms of reference are:

- To consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks.
- To consider and advise on the acceptability of proposals for research on human subjects using cells derived from stem cell lines, based on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks.
- To provide ethical advice on the use of unlicensed gene therapy and stem cell line derived therapies in humans.
- To work with other agencies which have responsibilities in this field, including research ethics committees, and agencies with statutory responsibilities - the Medicines and Healthcare products Regulatory Agency, the Human Tissue Authority, the Health and Safety Executive and the Department for Environment Food and Rural Affairs.
- To provide advice to United Kingdom Health Ministers on the above matters.

Researchers wishing to conduct clinical trials using products derived from stem cell lines should contact the GTAC Secretariat for initial discussions (gtac@dh.gsi.gov.uk).

3.7 Overview of regulatory requirements

Research involving human stem cells, and in particular the development of stem cell therapies, may involve many regulatory approvals. This is due to the nature of UK and EU legislation by which embryos, cells, tissue, clinical trials and licensing of therapies fall under separate legislation. An interactive resource explaining all the UK regulatory requirements, information and points of contact within the relevant organisations is provided through the Department of Health / Medical Research Council (MRC) "UK Stem Cell Tool Kit" – (See page 44 for full web link). This resource allows researchers to build a customised 'map' outlining all of the regulatory steps necessary to undertake research involving human stem cells and to translate ideas for a new treatment from the laboratory to patients.

[1] http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/index.htm

4. The UK Stem Cell Bank and its Principles of Operation

The House of Lords Select Committee on Stem Cell Research recommended in 2002 that a national stem cell bank should be established to prepare and store stocks of frozen stem cell lines. The UK Stem Cell Bank was established at the National Institute for Biological Standards and Control (NIBSC), a centre for the UK Health Protection Agency, in January 2003, with funding from the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC), to store ethically sourced, quality controlled, human stem cell lines from all sources (adult, fetal and embryonic) on a single site. The preparation of cryopreserved stocks of a cell line comprising multiple aliquots, each of which can be used to regenerate a culture representative of the original cell line. This is a fundamental element of good practice in the management of cell lines for laboratory use and for the delivery of cells for use in clinical application or product manufacture (Coecke et al., 2005; UKCCCR, 1999; WHO, 1998).

The UK Stem Cell Bank facilitates the sharing of quality controlled stem cell lines by the clinical and research communities. In so doing supports research that will help to better understand human development and disease and aid the development of strategies to treat serious diseases. It will also reduce the need for individual research teams to generate their own stem cell lines, minimise the use of human tissues, and enable different researchers to work on identical material so that direct comparisons may be made between studies.

In order to avoid conflicts of interest, the UK Stem Cell Bank has been located in an independent national institution. The Bank does not receive or store human embryos; neither does it conduct discovery research on the banked stem cell lines nor carry out research into stem cell biology. With the approval of the Steering Committee, the UK Stem Cell Bank may pursue research aimed at improving banking, characterisation, safety testing and preservation of stem cell lines and it must also obtain permission from the MRC and the Steering Committee before applying for any supplementary funding. All staff working for the UK Stem Cell Bank are required to refrain from activities that might represent a conflict of interest with the operation of the UK Stem Cell Bank as an independent organisation within the stem cell field and are required to submit information to the NIBSC register of conflicts of interest.

The UK Stem Cell Bank will store and distribute stem cell lines, but ownership of any Intellectual Property embodied in the these lines remains with the originator. To obtain stem cell lines deposited after April 2010 the requestor will be required to sign a Research Use Licence which will set out the terms of use for that line. Stem cell lines deposited before April 2010 will only be released by the Bank to requestors when an appropriate agreement or (licence), between the requestor and the originator, is in place to cover intellectual property aspects of line ownership.

Significant progress in stem cell research can only be made through international collaboration and it has therefore been agreed that the UK Stem Cell Bank can be accessed by researchers from academia and industry in the UK

and abroad. Overseas researchers have to undergo the same review procedures as researchers in the UK (see Section 7 and 8).

This section, along with sections 5 & 6, describes the standards of best practice that the UK Stem Cell Bank adopts in the procurement, processing, testing, preservation and supply of stem cell lines. It also specifies the criteria against which the UK Stem Cell Bank will be audited by the Steering Committee and sponsors. The diligent application and verification of the principles of operation laid down for the Bank should provide confidence and reassurance to professionals and the public that the UK Stem Cell Bank is adhering to best practice and complies with these principles.

4.1 Ethical Principles

The UK Stem Cell Bank has been charged with providing ethically sourced and quality controlled adult, fetal and embryonic human stem cell lines for research and the development of therapies. *All UK researchers deriving human embryonic stem cell lines are required, as a condition of their HFEA licence, to lodge samples of their embryonic stem cell lines in the UK Stem Cell Bank.* This is not a requirement for iPSC and somatic cell lines, although appropriately derived lines may also be deposited in the UK Stem Cell Bank.

Embryonic stem cell lines derived in the UK are thus subject to the donor consent requirements of the HFEA, including those relating to donor anonymity. The Steering Committee (section 5.1) has responsibility for ensuring that essential donor consents, ethical approvals, licences and authorisations are in place for all stem cell lines deposited in the UK Stem Cell Bank, and for all projects receiving cell lines from it. For traceability purposes, copies of the signed donor consent forms relating to cell lines accepted for deposit in the UK Stem Cell Bank are lodged with the Secretary to the Steering Committee who maintains these records in strictest confidence. Information relating to the identity of the donors is neither revealed to the Steering Committee members nor, importantly, to staff of the UK Stem Cell Bank. Thus Bank staff have no contact whatsoever with the donors of the embryos from which the stem cell lines are derived, are not involved in the consenting process nor do they know the identities of the donors.

4.2 Quality Assurance

4.2.1 The UK Stem Cell Bank Quality Management System

In order to comply with the Human Tissues (Quality and Safety for Human Applications) Regulations (2007), which deliver the requirements of the EU Tissues and Cells Directive (2004/23/EC, 2006/17/EC and 2006/86/EC), the Bank has put in place a Quality Management System which covers all licensable activities as set out in HTA Directions. This Quality Management System, described in the UK Stem Cell Bank's Quality Manual, ensures the safety and quality of the stem cell lines prepared by the Bank.

An effective document management system has been established so that all relevant documents (policies, procedures, sample/user records, quality control

records, training records etc.) relating to the processes carried out in the Bank are properly recorded. Documents are version controlled and archived to ensure that obsolete versions cannot be used.

Each cell line and the cell banks prepared from it must be correctly identified at all times. This is achieved by using unique identifiers traceable to the respective cell line's accession number. This is linked to the Steering Committee's unique application number. This system of unique identifiers maintains donor anonymity but still allows for traceability from donor to recipient or vice-versa in the event of a discovery which might significantly affect the health of the donor.

Records are maintained for each cell line. These provide evidence that the cell line has been procured, processed, tested, stored and released according to the procedures described in the Quality Management System. This information is held, together with the original application form, Materials Deposit Agreement and information on the cell line supplied by the depositor, in a Cell Line Master File. Once information including all test data has been received and the file completed it is independently reviewed and authorised by the Bank's Operations and Quality Managers or their designees.

Any deviations, errors, or anomalies in procedures as well as complaints from users are also managed within the Quality Management System. These are documented and reviewed and reported annually in the Bank's Annual Report. Resolution of such events is linked to a programme of preventative actions to assure continuous improvement in the Bank's operation.

In addition to the compliance reporting required by the HTA, the Bank operates a system of internal quality audits to monitor compliance with the HTA Directions, and identify areas for improvement in its quality system. These audits are planned and conducted by appropriately qualified individuals who are independent of the Bank's operational management. Inspections are performed by the Competent Authority, the HTA, which licences the Bank for the purposes of processing, testing, storage and distribution (including import and export) of cell lines intended for clinical use.

4.2.2 Role of Staff and External Advisors

The UK Stem Cell Bank operates under a licence from the Human Tissue Authority. Under the Human Tissue Act (2004) and The Human Tissues (Quality and Safety for Human Applications) Regulations (2007), the Bank's Licence Holder (LH) and Designated Individual (DI) have primary (legal) responsibility for, and play a key role in implementing the requirements of the licence.

Responsibility for the operation of the Bank, as set out in HTA Directives, and for ensuring that staff comply with the Quality Management System lies with the Bank's Operations Manager. The Operations Manager reports directly to the Designated Individual in all matters relating to processing, testing, storage, distribution, import and export of stem cell lines. The Quality Manager for the Bank is responsible for quality assurance as defined in the HTA Directions and provides advice and support on quality matters. The Quality Manager is independent of the Bank and reports directly to the Licence Holder. Jointly, the Operations Manager and Quality Manager are responsible for authorising the

release of stem cell lines. Deputies for each of the key post within the quality management system have been identified and all members of staff, working under the HTA licence, have documented job descriptions which detail their responsibilities.

The quality of the cell banks prepared by the Bank is the responsibility of all members of staff working under the HTA licence and all staff are expected to take personal responsibility for the quality of their work and maintain an up-to-date record of training which includes annual statements of competency.

The Bank maintains access to expert medical and microbiological advice through a Medical Advisor and a Microbiological Advisor. These advisors must be appropriately trained in order to discharge their responsibilities to the Bank. Their roles and responsibilities are documented in formal job description.

4.2.3 Facilities and Procedures

All facilities, process and critical equipment used in the processing, testing, storage and supply of cell lines have been qualified and validated and are maintained to meet the requirements of the Human Tissue (Quality and Safety for Human Application) Regulations (2007) as set out in HTA Directions. The cell culture procedures adopted by the UK Stem Cell Bank meet current best practice.

4.3 Operation of the Stem Cell Bank

In order to effectively manage procurement, processing, testing, storage and distribution, all stem cell lines regardless of their designation as either "Laboratory" or "Clinical" Grade are banked in facilities by processes that comply with the UK Stem Cell Bank's Quality Management System. Cell lines for clinical research or therapy in humans ("Clinical Grade") must undergo additional levels of testing commensurate with risk (see also section 6.5).

4.3.1 Deposit of Stem Cell Lines

The UK Stem Cell Bank ensures that for each cell line accessioned by the Bank, there is evidence of approval for deposit by the Steering Committee; that there is traceability to a Steering Committee References Number (the SCSC number) and that any constraints on the use or release of the cell line, either made by the depositor or by the original donor are clearly documented and available to researchers. The Bank also seeks documented evidence from the Steering Committee that donor consent (as set out in section 9) complies with HFEA and HTA requirements.

Depositors are required to provide a minimum number of aliquots of their cell line from the earliest passage level that is consistent with proven viability. The samples provided must be viable and free from contamination or otherwise compromised such that its scientific value cannot be recovered. Non-viable or contaminated samples will be reported to the depositor and repeated failure to

supply samples of an approved line shall be reported to the Steering Committee for appropriate action.

Following notification by the Steering Committee that a cell line has been approved for deposit the bank will contact the depositor to begin the process of accessioning the cell line into the Bank. This will involve personnel from the Bank and the depositor's laboratory who will together identify a suitable stock of cells for transfer and also gather the requisite information and available test data that will allow the Bank to culture the cell line.

Each cell line deposited must meet the UK Stem Cell Bank's specification which details the requirements for deposit in terms of viability, safety and characterisation. Additional requirements for 'clinical grade' cell lines will need to be met in order for the UK Stem Cell Bank to comply with the Directions of the Human Tissue Authority.

Each cell line deposited in the Bank receives a unique UK Stem Cell Bank accession number and any replacement samples of a cell line provided by the depositor for whatever reason will receive a new accession number.

4.3.2 Banking of Stem Cell Lines

Before culturing, the Bank carries out an evaluation of each cell line in consultation with the depositor to determine the method of culture and the types of characterisation that may be required. The banking procedures followed by the bank will normally include the establishment of a 'Pre-master' stock of cells prepared from material supplied by the depositor. This comprises a number of aliquots from a single pooled culture of cells. This, early passage stock of cells, provides material for initial testing and archival material for disaster recovery or confirmation of adverse discoveries affecting the cell line.

A sample of the 'Pre-master' cell bank is expanded to provide a 'Master' cell bank that will, once established, provide the bank from which will be derived all future distributed material. Samples of the Master bank are used to produce a 'Distribution' cell bank from which cells are released to users. This stock, once exhausted, is replenished by further culture of samples from the Master cell bank. Each cell bank is quality controlled and characterised appropriately. In general each cell line is cultured and preserved according to methods provided by the depositor up to the level of the first 'Distribution' cell bank. Generic procedures being developed by the Bank will be applied to subsequent 'Distribution' cell banks; however the 'Master' cell bank will be as representative as possible of the original cells provided by the depositor. All cell banks whether at the Pre-master, Master or Distribution levels, are assigned a unique cell bank number. Each aliquot of cells within a cell bank is also assigned its own identifier.

4.3.3 Qualification and Testing of Stem Cell Lines

Each cell bank is tested for viability, mycoplasma contamination, sterility, mandatory viral markers and identity as a minimum. The cell lines are maintained under quarantine conditions until the first mycoplasma and sterility tests are completed. In addition to the quality control and characterisation

tests, phenotypic and genotypic stability will eventually be determined using techniques appropriate for each cell line. This process will assure consistency of cells in the banking process and ultimately the minimum population doublings or passages recommended for the use of each cell line. Once completed the test data and other information is used to prepare a certificate of analysis for each cell line released.

Any genetic testing undertaken on the stem cell lines by the UK Stem Cell Bank is kept in strict confidence by the Bank unless otherwise approved by the Steering Committee. Any adverse discoveries of a genetic or infectious nature are discussed with the microbiological and medical advisors and where necessary the Steering Committee before appropriate action is taken.

On completion of the banking process the depositor is offered a sample of the UK Stem Cell Bank's stocks to evaluate. Any significant deviations between bank test data and that of the depositor's laboratory are discussed with the depositor and an appropriate course of action, or appropriate annotation in the cell line entry in the UK Stem Cell Bank inventory of stem cell lines, agreed.

All information pertaining to the deposit, processing, testing, storage and distribution of each cell is held in its Cell Line Master File. Once banking and testing of the cell line has been completed, this file is reviewed by both the Operation Manager and Quality Managers. The Cell Line Master File must be reviewed and approved by them before the cell line is released for use.

Where testing is carried out by third parties, whether internally through other NIBSC divisions or with external agencies, written agreements defining the relationship and specifying the services required will be put in place. These agreements will comply with HTA Directions.

4.3.4 Storage and Distribution of Stem Cell Lines

The UK Stem Cell Bank defines and documents the conditions under which the stem cell lines are stored. Cell lines are stored under conditions that as far as possible prevent both the deterioration of the material and possible cross-contamination. A proportion of each bank is stored in a secure off-site location. All storage equipment is validated, monitored and alarmed.

Cell lines are transported to and from the UK Stem Cell Bank in validated containers that ensure the cells are maintained at an appropriate temperature. Appropriate transportation times and temperatures are defined and documented by the Bank. It is the Bank's policy only to ship frozen or vitrified material. The UK Stem Cell Bank does not supply growing cultures of stem cells to third parties.

The Bank has put in place documented procedures for sales order processing and dispatch of stem cell lines to customers. Dispatch of cells is carried out under ISO9001 through the NIBSC dispatch department. This includes the tracking of shipped samples and the maintenance of records of shipment. The Bank charges the full cost of shipment including where appropriate the return of Bank's transportation containers.

The Bank's requirements, both for off-site storage and dispatch services, are the subject of written agreements which will comply with HTA Directions.

4.3.5 Recall and Disposal of Stem Cell Lines

The UK Stem Cell Bank requires all depositors and users of stem cell lines and other third party service providers to have in place a procedure for adverse event and adverse incident reporting. The Bank has a documented procedure for the recall of lines in the event of an adverse incident or event and for reporting such events to the HTA. This procedure complies with the Human Tissues (Quality and Safety for Human Applications) Regulations (2007) and provides for:

- prevention of distribution of affected cell lines,
- communication of recall notices to all relevant parties,
- reconciliation of returned lines,
- storage quarantine and disposal of returned samples and
- assuring appropriate action in relation to adverse event reporting in compliance with the above mentioned regulation.

Disposal procedures for material are documented in the UK Stem Cell Bank quality management system and are compliant with local policy, the Human Tissue Act (2004) and the Human Tissue (Quality and Safety for Human Application) Regulations 2007.

The Steering Committee requires that embryonic stem cell lines considered unsuitable for release are quarantined and archived rather than discarded. In the case of cell banks, where there are multiple samples in storage, only a limited number of units are retained with the remainder being disposed of as clinical waste under NIBSC documented procedures. In the case of material found to be derived from Transmissible Spongiform Encephalopathy (TSE, also known as prion diseases or CJD) - affected donors, the Steering Committee will be engaged in the decision on storage and disposal. The process for disposal must be suitable for the inactivation of any infectious agents known or suspected to be involved.

4.3.6 Inventory of Stem Cell Lines

A list of all stem cell lines approved by the Steering Committee for deposit in the Bank is maintained on the UK Stem Cell Bank website. The stem cell 'catalogue' includes general information on the depositor, the cell line and any ethical or consent constraints imposed by the depositor or donor. Once a cell line has been banked, tested and approved for release to researchers, its listing in the stem cell catalogue is amended to include scientific information and test data as well as any other pertinent information. The Bank's catalogue is different to the Steering Committee UK Stem Cell Lines Registry which lists all the lines that have been approved by the Steering Committee for use in the UK, regardless of whether they are available from the Bank (see section 7.2).

4.3.7 Assessment of Risk and Contingency Planning

The UK Stem Cell Bank has put in place a high-level risk assessment, managed through the NIBSC risk register and reviewed annually. This register of risk is

reported to the Management Committee and included in the Bank's Annual Report to the Steering Committee. In addition to this general risk register each cell line is risk assessed against a number of criteria. The Bank will put in place an extended risk based assessment for "Clinical Grade" cell lines based on the HTA Directions.

The Bank has put in place policies and procedures to ensure continuity in the supply of stem cell lines under adverse circumstances, which includes back-up for critical systems and an off-site stock for disaster recovery. It includes a policy for securing the Bank's stock of cell lines in the event of closure of the Bank.

NIBSC ensures that all stored data is secure and regularly backed-up to secure storage. Access to the site and to the Bank is strictly controlled.

4.3.8 Health and Safety

NIBSC operates a comprehensive health and safety policy in line with statutory requirements, including the appointment of a full-time safety adviser, and occupational health staff. A comprehensive safety training programme is provided to all members of staff on commencement of their employment and staff undergo mandatory refresher course at the NIBSC proscribed interval.

5. Governance of research involving established human embryonic stem cell lines

Unlike human embryos, embryonic stem cells do not have the potential to become a human person and do not therefore have the moral status of human embryos. Accordingly the Government has passed legislation that establishes that research involving established stem cell lines does not need the same regulation to which embryo research is subject to by the HFEA. However, as the generation of embryonic stem cell lines involves the destruction of human embryos, oversight in the form of a Steering Committee was recommended to ensure that research performed is in keeping with HFEA Regulations. The oversight mechanisms governing research involving established embryonic stem cell lines are voluntary. However, they are a condition of the statutory regulation in the UK and there is an expectation by Government that these are adhered to.

Induced pluripotent stem (iPS) cells have similar properties to human embryonic stem cells but are derived from adult cells and are not subject to such considerations. The only exception to this would be under circumstances where iPS cells might be used to generate reproductive cells such as oocytes or spermatozoa – any use of such derivatives for reproductive purposes would fall under the remit of the HFEA. Broad ethical considerations in relation to the derivation and use of iPS cells are discussed in section 9.

5.1 Steering Committee for the UK Stem Cell Bank and for the Use of Stem Cell Lines

The Steering Committee was established in December 2002 as an independent national committee overseeing the UK Stem Cell Bank and research involving established human embryonic stem cell lines, whether obtained from the Bank or from elsewhere. All applications to deposit stem cell lines in the UK Stem Cell Bank or to access banked stem cell lines are evaluated by the Steering Committee. The Steering Committee is a non-statutory body that reports annually to the MRC, works closely with the DH, the HFEA, HTA and the MHRA, and briefs Ministers as necessary. It is the role of the Steering Committee to support stem cell research and to ensure that this is conducted within an ethical framework that is transparent to the public. The membership of the Committee includes expertise in science, medicine, ethics and theology as well as lay members and representatives from regulatory and funding agencies. The membership and terms of reference are available on the MRC web site. (Steering Committee) – (See page 43 for full web link)

5.2 UK Stem Cell Bank Management Committee

A Management Committee for the UK Stem Cell Bank has been established by NIBSC to deal with operational issues. Its terms of reference and membership, which includes in-house and external scientific experts, stem cell scientists, lay members, representatives from the commercial sector and the funding agencies, are published on the MRC website (Bank Management Committee) – (See page 43 for full web link). The Management Committee reviews the processes, systems and standards that must be followed by the UK Stem Cell Bank. In partnership with the Bank, it develops and reviews the Bank's strategic objectives which it presents to the Steering Committee. Implementation of these objectives is the responsibility of the relevant Manager for the Bank under the supervision of the Bank's Director. The Management Committee reports formally to the Steering Committee through the Director of the Bank and provides to it a full written report on an annual basis.

5.3 Audit

The funders of the UK Stem Cell Bank may, with reasonable notice to NIBSC, inspect documents, practices and other information (and take away copies considered necessary) about management of the Bank and to examine the financial records relating to the operation of the Bank, in order to assure themselves about compliance with high standards of internal management and financial control, and with guidelines established by the Steering Committee.

The Steering Committee reserves the right to seek periodic independent audit of the research carried out by both UK and overseas researchers with stem cell lines deposited in, or obtained from the UK Stem Cell Bank, in order to assure compliance with relevant regulations and permissions. Immediate action will be taken if there is evidence of non-compliance with, or deviation from, appropriate licences, authorisations and formal procedures (e.g. withdrawal of the line from the Bank, exclusion of a researcher from future use of the Bank, reporting non-compliances to the researcher's host Institution, funders and national regulators.

5.4 Annual Reports

The UK Stem Cell Bank reports on a regular basis to its Management Committee and the Steering Committee and an annual report, approved by Management Committee, is submitted to the Steering Committee and published on the Bank's website. This report should include reviews of bank activity, including cell banking and distribution, changes in staff, research and development, quality assurance audits and their outcomes, risk management and finance.

5.5 Engagement with the Stem Cell Community and the Public

The Bank has established an independent website (www.ukstemcellbank.org.uk) which includes a catalogue of stem cell lines held by the Bank, information on depositing and accessing cell lines and other useful information for users including links to other relevant websites. It has also established an enquiries email line (enquiries@ukstemcellbank.org.uk). A documented process for handling general enquiries and complaints has been established under the Quality Management System and targets for response times have been set. Customers can expect a formal response to enquiries within five working days.

Periodically, the Bank will contact researchers and other customers who have used the Bank's cell lines to obtain summaries of their work and compile these reports for presentation to users of the Bank. In this way users may be able to benefit from responses on use of the cell lines (both positive and negative data) obtained directly on cells provided by the UK Stem Cell Bank.

The UK Stem Cell Bank will also establish relationships with other national stem cell banking resource centres to share knowledge and best practice. It will continue to interact with national and international research initiatives, contributing on those aspects of research in which it is permitted to engage by the Steering Committee.

The UK Stem Cell Bank will continue to engage with all those interested in stem cells and their application through its ongoing programme of external activities including contributions to training courses, attendance at exhibitions and presentations at scientific meetings. This engagement will include periodic questionnaires to recipients of lines and communications via the UK National Stem Cell Network and its annual conference. The bank also supports activities that explain the rationale for stem cell research and banking, including the provision of suitable information to the general public.

6. Deposit and Withdrawal of Stem Cell Lines from the UK Stem Cell Bank

This section deals with the processes and requirements for depositing stem cell lines in and accessing stem cell lines from the UK Stem Cell Bank. General principles underlying the use of human embryonic stem cell lines in the UK and for obtaining stem cell lines from sources other than the UK Stem Cell Bank can be found in sections 7 and 8.

The UK Stem Cell Bank stores and makes available human embryonic and somatic stem cell lines. The UK Stem Cell Bank does not store heterogeneous

pools of stem cells that contain or are merely enriched for stem cells (e.g. bone marrow, peripheral blood or cord blood).

It is a condition of an HFEA licence that a representative proportion of the cell line(s) derived from each embryo donated altruistically must be made available for research use via the UK Stem Cell Bank. This can be satisfied by one of the following:

A. Deriving research grade stem cell lines for distribution from master cell banks, that themselves can be laboratory or clinical grade, so that all clinical grade cell lines have research grade counterparts available for distribution.

B. Banking a subset from the separate cell lines that are sometimes obtained during the derivation process from a single embryo, provided each daughter cell line had appropriate ES cell characteristics.

C. Other approaches may be possible that would lead to the desired end and these could be proposed by the depositor and discussed by the Steering Committee.

Consent procedures for these cell lines are audited by the HFEA. The Steering Committee also encourages the deposition of human embryonic stem cell lines derived outside the UK as well as somatic stem cell lines derived in the UK or abroad as long as these fulfil the criteria of informed consent and are of value to the research community.

Derivatives of banked human embryonic stem cell lines, including genetically modified, abnormal or differentiated cells, do not need to be deposited in the Bank (unless this is a requirement of the funding agreement under which such lines were generated, for example funding from the UK Research Councils [2]). However the Steering Committee would welcome deposit of such lines that would be scientifically useful to the research community.

6.1 Depositing Stem Cell Lines in the UK Stem Cell Bank

All applications to deposit embryonic stem cell lines in the Bank are made to the Steering Committee and not to the Bank. Before accepting stem cell lines for deposition in the Bank, the Steering Committee has to satisfy itself that these have been ethically sourced, with fully informed donor consent, and that the cell lines present a valuable resource for the biomedical research community. In order to provide the Steering Committee with the information needed to make an informed decision about the deposition of cell lines in the Bank, researchers are requested to complete an application form. This can be found on the Bank's website together with information on the application process. Information on the application procedure is also provided in section 8.

Before stem cell lines approved for deposit by the Steering Committee can be released for use, a Material Deposition Agreement (MDA) has to be signed between the owner of the cell lines (normally the employer of the researcher who has derived the stem cell line) and the Bank. This agreement sets out the

[2] http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC001898

terms under which the cell line is deposited and includes the terms under which the cell line is made available to accessors. *When ES cell lines are deposited the MDA should incorporate a statement on existing Intellectual Property Rights (IPR).*

Research grade lines deposited after 01 April 2010 can be distributed by the UK Stem Cell Bank under its own terms of use including a Research Use Licence (RUL). This licence will be available for laboratory use (excluding research in humans) of stem cell lines without an individually negotiated Material Use Licence (MUL). The RUL is designed to protect the depositor's rights to intellectual property and standardize the process of accessing lines from the Bank. The RUL is available on the UK Stem Cell Bank website.

The Material Deposition Agreement is available on the UK Stem Cell Bank website. This is negotiated between the owner of the stem cell lines and the Bank on a case by case basis. It is recommended that the depositor's technology transfer staff are alerted to the MDA at an early stage to avoid unnecessary delays.

The UK Stem Cell Bank will provide Depositors with information on request as to who has accessed their cell lines, and information on their use as described in the abstract provided on the relevant application to the Steering Committee.

6.2 Examples of stem cell lines that can be deposited in the UK Stem Cell Bank

- *human embryonic stem cell lines*
- human stem cell lines from extra-embryonic tissues (trophoblast and yolk sac endoderm)
- human embryonic germ cell lines
- human mesenchymal stem cell lines and other somatic stem cell lines from any stage of development, if available
- human fetal / progenitor stem cell lines (N.B. fetal stem cells are neither clonal nor immortal, though some progenitors such as neural stem cell lines can be)
- induced pluripotent stem cell lines
- haematopoietic stem cell lines from cord blood or bone marrow (N.B. these might be propagated using genetic manipulations, new culture conditions, or growth factors)
- stable, human somatic stem cell lines derived from embryonic stem cells
- conditionally immortalised human progenitor/stem cell lines (N.B. these can only be deposited in the Bank if depositors can make a persuasive case to the Steering Committee that the lines are of outstanding research value to the scientific community).

In addition the Bank will curate cells used to facilitate the growth of embryonic stem cell lines in culture (e.g. standardised feeder cells).

6.3 Curation Policy

For each cell line approved by the Steering Committee the Bank will apply its Banking and Curation Policy, established by its Management Committee and approved by the Steering Committee. This determines the level to which each deposit is progressed in terms of banking and testing. This policy is based on the duty of the bank to provide safe storage of a sample of each cell line approved by the Steering Committee, and also on the need to develop the scientific value of the UK Stem Cell Bank holdings.

The UK Stem Cell Bank recognises two forms of deposit: banking and curation. Banking is defined as the expansion of a stem cell line to form one or more stem cell banks for eventual release for research or therapeutic applications. Curation is defined as the custodianship of a limited stock of a stem cell line for storage or archival purposes only.

In order to facilitate transparency the Bank applies published criteria. These criteria will be subject to periodic review and the status of all cell lines held by the UK Stem Cell Bank is reviewed on an annual basis. Any changes to the designation of the cell line shall be notified to the Depositor and published on the Bank's website.

6.4 Accessing Stem Cell Lines from the UK Stem Cell Bank

All applications to access embryonic stem cell lines from the Bank are made to the Steering Committee and not to the Bank. In order to provide the Steering Committee with the information needed to oversee research involving stem lines, researchers are required to complete the relevant application form following the guidance set out in Section 7 and provided on the Bank's website. For access to lines other than embryonic stem cell lines, applications may be made directly to the Bank.

For access to lines deposited after 01 April 2010 all accessors of stem cell lines only for laboratory use will be required to sign a standard Research Use Licence (RUL). The RUL is designed to protect the depositor's rights to intellectual property. If an accessor plans to use a stem cell line for commercial or clinical purposes they will need to negotiate a specific licence for "commercial manufacture and sale" or for "clinical use" with the depositor. These licences will set out the terms for exploitation of the stem cell line. IP holders will not be obliged to issue a Clinical Use Licence as a research grade component for each line would be available for research use. The Commercial Manufacture and Sale Licence should be subject to standard commercial negotiation between IP holder and any potential user and will not have any restrictions imposed by the Steering Committee.

For lines deposited prior to 31 March 2010, where the terms of deposit require the accessor to agree a Material Use Licence (MUL), the accessors will still have to negotiate the terms for that licence with the depositor. In addition they will have to sign the Material Access Agreement (MAA) supplied by the Bank.

Whilst agreements can be negotiated before Steering Committee approval has been given, the agreements can only be executed following Steering Committee approval. Once the UK Stem Cell Bank receives confirmation approval to access a banked cell line and signed copies of appropriate agreements are in place the Bank will despatch the cell line(s). It is recommended that the accessor's technology transfer staff are alerted to the need for these access agreements to avoid unnecessary delay.

The Bank can be accessed by researchers from academia and industry in the UK and abroad. All applications must be approved by the host institution (academia or companies) and for overseas applicants the same review procedures by the Steering Committee apply. Researchers accessing stem cell lines from the Bank must comply with legislation in the UK and the country where the research is to be performed and are expected to comply with this Code of Practice. Any change to the terms of the application approved by the Steering Committee should be discussed with the secretariat to the Steering Committee and may require a fresh application as approvals are given by the Steering Committee on a project by project basis. Where approval is given by the Steering Committee for use of a line in a consortium project or where there are multiple named collaborators, it is the responsibility of the lead applicant to ensure that the Code of Practice is adhered to by all the partners. Third party transfer of lines supplied by the Bank is not permitted save where specified in the MAA or RUL.

Researchers should notify the UK Stem Cell Bank if cell lines accessed from the Bank fail to exhibit expected properties. Complaints will be documented and investigated under the Bank's Quality Management System (see section 4.2.1).

Stem cell lines accessed from the UK Stem Cell Bank will have been allocated a unique Bank accession number; this should be quoted by accessors in all publications.

The UK Stem Cell Bank will supply both 'laboratory' grade stem cell lines that cannot be used in human application, and 'clinical' grade lines which have been derived and processed in facilities approved by the appropriate regulatory agency which may eventually be used in research involving human participation, clinical trials or human therapy. The Bank may also supply 'laboratory' grade subsets of 'clinical' grade cell lines specifically for non-clinical research (see section 6.5). It will be important therefore for accessors to specify in their application to the Steering Committee whether 'laboratory' or 'clinical' grade stem cell lines are requested. All stem cell lines available from the Bank in the early phase will be 'laboratory' grade.

6.5 Clinical Grade Cell Lines for Laboratory Research Purposes

The UK Stem Cell Bank may bank cultures of 'clinical' grade cell lines and supply a 'laboratory' grade component of those lines for research purposes that do not involve human participation under the terms of the research use licence. Such 'laboratory' grade samples must not be developed for clinical use, and where the intent for use of the cells in humans becomes a reality it is expected that the researcher would obtain a sample of the 'clinical' grade stock of the respective

cell line. At such a time a separate clinical research or commercial licence would need to be negotiated with the depositor of the line.

It is possible that a 'laboratory' grade cell line may prove to have unique properties that justify its development for use in humans. Any such cell line could in principle be re-derived to 'clinical' grade standard, though all cell lines intended for human application must be procured, tested, processed, stored, distributed and imported/exported at an HTA licensed establishment under The Human Tissue (Quality and Safety for Human Application) Regulations 2007.

6.6 Charges levied by the UK Stem Cell Bank

The contract between the funders and the UK Stem Cell Bank makes provision for a schedule of charges for the provision of stem cell lines to users. The Steering Committee has indicated that the charges levied will be different for academic researchers and commercial users of the Bank with commercial users expected to pay the full economic costs. It is also expected that charging for services provided by the UK Stem Cell Bank will be in line with general principles applied by funding bodies and will allow for recovery of some of the operating costs of the Bank over time.

A schedule of charges has been established by the Bank, but as of December 2009, no charges other than third party shipping fees, have been levied for research grade cell lines. This situation will be kept under review. An up to date schedule of charges (including shipment charges) as well as notification of any change to the Bank's policy is available on the UK Stem Cell Bank website.

6.7 Liability

NIBSC is responsible for all aspects of operation of the UK Stem Cell Bank and for any breaches in Bank operating standards, procedures or quality control arrangements that are not in compliance with prevailing practices. However, the MRC is responsible for the operation of the Steering Committee, the application process and the decisions emanating from it.

Stem cell lines stored in the UK Stem Cell Bank will be supplied to users without warranty of merchantability or fitness for a particular purpose or any other warranty, express or implied, and without any representation or warranty that they are free of extraneous agents or that the use or supply of the cell lines will not infringe any patent, copyright, trademark or other right of any third party. Therefore to the fullest extent permitted by Law, NIBSC will not accept liability for any claims resulting from the research conducted on the stem cells and stem cell lines obtained from the Bank by a user. Liability in such claims will be in accordance with the end user, user and depositor agreements for the relevant cell lines to the extent that users will indemnify NIBSC from any issues arising out of usage.

Researchers accessing banked stem cell lines will be required to agree a Research Use Licence or a Materials Access Agreement (where lines were

deposited before March 2010 the depositor may require a Materials Use Licence to be in place between depositor and accessor before their cells are released).

All depositors will be required to sign a Materials Deposition Agreement and will be invited to disclose any known pre-existing conditions of the cell lines being deposited, either at the time of deposition, or at the first time that the pre-existing condition becomes known to the depositor. Depositors will be invited to indemnify NIBSC against issues arising from pre-existing conditions that the depositor could have reasonably foreseen.

7. Accessing stem cell lines from the UK Stem Cell Bank and using human embryonic stem cell lines from sources other than the UK Stem Cell Bank

7.1 General principles

7.1.1 Research projects in which human embryonic stem cell lines may be used

The use of embryonic stem cells in research was debated at length in both Houses of Parliament during the passage of the Human Fertilisation and Embryology Act and its amendments in 1990, 2001 and 2008. Parliament made it clear that human embryonic stem cell lines should not be used for trivial purposes.

The Steering Committee 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 the law relating to this area. This is:

a) research which 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 (as set out in the 1990 Act as amended by the 2008 HFE Bill);
b) basic cell research which underpins these aims (as recommended in the House of Lords Report 2002);
c) development of cell based therapies for clinical trials in respect of serious human diseases.

The Steering Committee further recognises the importance of training of staff using human embryonic stem cell lines and therefore the requirement on occasion to use stem cell lines for training purposes.

7.1.2 Peer Review

It is normally expected that the research projects for which human embryonic stem cell lines are used have been subjected to independent scientific peer review. However, peer review is not a pre-condition for Steering Committee approval. For instance researchers should have the opportunity to access human embryonic stem cell lines in order to generate preliminary data for grant applications, while development projects in the commercial sector are not usually subject to independent peer review.

7.1.3 Research Ethics Committee approval

Research Ethics Committees are concerned that patient care and diagnostic needs are not compromised by the diversion of material for research purposes and protect the dignity, rights, safety and well being of all research participants. Research Ethics Committee approval must be obtained:

- *as part of the application procedure for an HFEA research licence*,
- for research involving human tissues and
- for clinical trials of all stem cell derived therapeutic products.

The Steering Committee has agreed that Research Ethics Committee approval is not required for laboratory-based research involving established human embryonic stem cell lines.

7.2. Using human embryonic stem cell lines from sources other than the UK Stem Cell Bank

The Steering Committee oversees all research involving human embryonic stem cell lines in the UK, whether these are accessed from the UK Stem Cell Bank or from elsewhere.

It is expected that the UK Stem Cell Bank will become the first port of call for researchers wishing to work with human embryonic stem cell lines. The Bank will make available standardised, quality controlled aliquots of stem cell lines and will allow researchers to work with well defined material so that direct comparisons can be made between studies.

Although the Steering Committee expects the UK Stem Cell Bank to be the preferred source of stem cell lines, it is not a requirement that lines are exclusively accessed from the Bank. It is anticipated that there will be occasions when researchers wish to access human embryonic stem cell lines from other sources (e.g. international cell lines not deposited in the Bank or cell lines not yet ready for distribution by the Bank). However, all researchers wishing to work with human embryonic stem cell lines within the UK (whether accessed from the Bank, from other sources in the UK or oversees) must inform the Steering Committee through the application procedure detailed in Section 8.

The Steering Committee needs to satisfy itself that the research fulfils the criteria in section 7.1.1 and that the human embryonic stem cell lines have been ethically sourced with fully informed and free donor consent. Information in relation to the ethical sourcing of human embryonic stem cell lines does not need to be provided for human embryonic stem cell lines that a) were created in the UK (as consent procedures have been approved by the HFEA), or b) have previously been approved by the Steering Committee for import or banking.

7.2.1 UK Stem Cell Lines Registry

A register of Steering Committee approved human embryonic stem cell lines is available on the MRC web site (UK Stem Cell Lines Registry) – (See page 44 for full web link). *This registry lists all the hES cell lines that have been approved by*

the Steering Committee for use in the UK, irrespective of whether they are available through the UK Stem Cell Bank or not. The UK Stem Cell Bank catalogue provides details on the subset of these lines that are deposited in the UK Stem Cell Bank.

UK researchers wishing to transfer human embryonic stem cell lines to collaborators for a project that has been approved by the HFEA as part of the licence for the derivation of human ES cell lines do not need to apply to the Steering Committee, although subsequent research uses for different projects would require approval.

7.3 Export of stem cell lines

Researchers wishing to export human embryonic stem cell lines to research establishments outside the UK should apply to the Steering Committee as outlined in Section 8. Research performed oversees should:

- *fulfil the criteria in Section 7.1.1;*
- *comply with legislation in the UK and in the country where the research is performed and*
- *comply with this Code of Practice.*

8. Application Procedure

The Steering Committee convenes four times per year to consider applications, with two of these meetings held virtually. Applications can be submitted at any time and will be reviewed at the first available decision point.

Applications that fit specific criteria and therefore do not raise any significant issues can be fast tracked for approval by the secretariat under delegated authority. For this procedure to occur, *all* of the following criteria must be met:

- the cell line(s) requested has been previously approved by the Steering Committee and is listed in the UK Stem Cell Lines Registry;
- the project has been subject to independent peer-review;
- the cell lines requested are only to be used for in vitro research;
- no animals are involved in the research, except for teratoma assays in small mammals with the appropriate Home Office licence;
- no hybrids/chimeras are involved; and
- the research will be undertaken only at site(s) in the UK

Under these circumstances this procedure typically takes 2 weeks. The Secretariat can also amend existing approvals to incorporate additional hES cell lines without referral to the Steering Committee, provided the lines in question are listed in the UK Stem Cell Registry.

The UK Stem Cell Bank website has an on-line application process for all applications to the Steering Committee for:

a) the deposition of stem cell lines in the Bank,
b) for access to stem cell lines from the Bank,

c) to import human embryonic stem cell lines from sources other than the Bank
d) to export human embryonic stem cell lines from sources other than the Bank and,
e) to use human embryonic stem cell lines from sources other than the Bank.

9. Donor Consent

9.1 Donor Consent for the use of embryos in research

Free and informed consent are key principles of the Human Tissue Act (2004) and the HFE Act (1990). Comprehensive information must be given in a form that is readily accessible and allows a free and informed decision to be made by potential donors. All written information provided and consent forms have to be approved by Local Ethics Committees and for research involving embryos also by the HFEA. The HFEA requires that the donor couple must have given in principle consent for the use of embryos in research. In addition, the Steering Committee has in collaboration with the HFEA drawn up a list of criteria that must be addressed in information leaflets and consent forms provided by IVF clinics for the donation of embryos for stem cell research. Donors should be approached as early as possible, usually before ovary stimulation, to allow sufficient time to think issues over.

Information Leaflet and Consent Forms:

Before patients give consent to donation of their embryos for use in research projects to derive stem cell lines, they must be given oral information supported by relevant written material. Details of the supporting information that HFEA requires is available to donors and the written consent that must be provided can be found at http://www.hfea.gov.uk/3468.html#guidanceSection5018

Further guidance on consenting arrangements has been published by the UK national network of 'human embryonic stem cell coordinators' (HESCCO) - see hESCCO: development of good practice models for human ES cell derivation (Franklin et al Regen Med (2008) 3(1), 105-116).

9.2 Deriving stem cells from non-embryonic tissues

9.2.1 Fetal Tissue

Fetal tissue is subject to the Human Tissue Act 2004. Researchers should ensure consent is obtained in accordance with the Human Tissue Authority Code of Practice on Consent. All such work will need Research Ethics Committee (REC) approvals.

9.2.2 Tissues used to create human admixed embryos.

The HFE Act 2008 contains provisions relating to consent for the use of gametes or cells to create human admixed embryos (see section 3.3). There are different requirements depending upon the source of the cells used and when they were collected.

i) **Existing Holdings of Tissue (held before the commencement date of the 2008 Act [3]).** These cells can be used without specific consent providing that they were already being lawfully stored for research purposes (which includes compliance with the Human Tissue Act 2004) and that the research is conducted under an HFEA licence and with appropriate REC approval.

ii) **Gametes or cells from children (under 18 years)**
Such material can be used to create embryos for research subject to strict safeguards and under licence from the HFEA. This provision was included to ensure that disorders which are lethal in childhood are not excluded from embryo research, and in particular stem cell research. The requirements are that:

- the child suffers from, or is likely to develop, a serious disease, a serious physical or mental disability or any other serious medical condition,
- the child is not competent to deal with the issue of consent to the use of its cells to bring about the creation in vitro of an embryo or human admixed embryo for use for the purposes of a project of research[4],
- any embryo or human admixed embryo to be created in vitro is to be used for the purposes of a project of research which is intended to increase knowledge about:
  a) the disease, disability or medical condition that the child suffers from as above or any similar disease, disability or medical condition, or
  b) the treatment of, or care of persons affected by, that disease, disability or medical condition or any similar disease, disability or medical condition,
- there are reasonable grounds for believing that research of comparable effectiveness cannot be carried out using cells from persons who have capacity to consent to such research.

iii) **Gametes or cells from adults who lack capacity to consent**
Provision is also made for material from adults who lack capacity to consent to be used to create embryos or admixed embryos for research purposes. Such research must be conducted under licence from the HFEA who will require assurance on the points below. Researchers must justify why the research cannot be done using cells from adults with capacity. For many diseases, even neurodegenerative disorders, there will be a group of patients who retain capacity from whom consent could be sought. The conditions for using material from those who cannot consent are:

[3] This date was not available at time of publication
[4] There is an assumption that children over 16 will have capacity to consent unless shown otherwise. In Scotland there is legislation defining this – see MRC Guidance on research involving children for further details

- The patient suffers from, or is likely to develop, a serious disease, a serious physical or mental disability or any other serious medical condition,
- They lack capacity to consent to the use of human cells to bring about the creation in vitro of an embryo or human admixed embryo for use for the purposes of a project of research,
- The person responsible under the licence has no reason to believe that the patient had refused such consent at a time when s/he had that capacity,
- it appears unlikely that the patient will at some time have that capacity,
- any embryo or human admixed embryo to be created in vitro is to be used for the purposes of a project of research which is intended to increase knowledge about:
  a) the disease, disability or medical condition mentioned above or any similar disease, disability or medical condition, or
  b) the treatment of, or care of persons affected by, that disease, disability or medical condition or any similar disease, disability or medical condition,
- there are reasonable grounds for believing that research of comparable effectiveness cannot be carried out if the only human cells that can be used to bring about the creation in vitro of embryos or human admixed embryos for use for the purposes of the project are the human cells of persons who have capacity to consent to this.

In order to use such cells the researcher must identify a person engaged in caring for the patient or interested in their welfare other than in a professional capacity or for remuneration, and who is prepared to be consulted about the proposed research. If the researcher cannot identify such a person the researcher must nominate a person who is prepared to be consulted by the researcher and who has no connection with the project. The person identified by the researcher must then be asked their opinion as to what the patient's wishes and feelings about the use of their human cells for this purpose would be likely to be if they had capacity in relation to the matter.

iv) **Any other adult gametes or cells**.
There must be effective consent in place for the use of any other cells to create, store or use an admixed embryo for research. This includes consent from donors of cells used directly to create an admixed embryo or donors of cells used to create an embryo from which an admixed embryo is then derived.

9.2.3 Tissues used to create induced pluripotent stem cells

The donation of tissue for the production of iPS cells must be in accordance with the requirements for tissue use for research. The consent provided by the donor would need to be based on appropriate information about the intention of the research and creation of iPS cells and will fall under the HT Act 2004 and the HTA CoP on consent. All research involving human tissue should have Research

Ethics Committee (REC) approval but this is not a legal requirement. The Human Tissue Act 2004 applies to the UK; most of it is not applicable in Scotland which has separate Human Tissue (Scotland) Act 2006. Under the 2004 HT Act consent is required to store or use tissue with the following exceptions:

- **tissue is from a living person and**
- **the tissue is anonymised (the researcher is not in possession, and not likely to come into possession of information that identifies the person from which it has come;) and**
- **the material is used for a specific research project approved by a recognised research ethics committee (e.g. NHS REC).**

Tissue from children who lack capacity to consent can only be used with consent from a person with parental responsibility or, if no such person exists, someone of a defined 'qualifying relationship'. Tissue from adults who lack capacity can only be used subject to the requirements of the relevant legislation. These requirements are broadly similar to those described above in section 9.1 and are described in detail in MRC Guidance on Adults who Lack Capacity to Consent.

Consent to use tissue to create iPS cells should be explicit about the nature of such research. Depending on the specific project researchers should consider ensuring specific consent is sought for areas that may be of particular interest to donors. These include:

- Potential commercial applications of cell lines,
- Genetic analysis of derived cells,
- Use in animal research, and
- Potential use in clinical transplantation.

10. Derivation and use of Stem Cell Lines

10.1 Quality and safety standards in fundamental stem cell research

Careful recording of procedures and results is essential for the verification of quality and integrity of research and can prove invaluable in resolving problems.

Those working with stem cell lines are expected to follow the general principles of Good Research Practice – (See page 43 for full web link) (Medical Research Council, 2000) as well as best practice for cell culture procedures (UK Coordinating Committee on Cancer Research,1999) – (See page 45 for full web link)

10.2 Regulation governing the derivation and processing of clinical grade stem cell lines

All tissues and cells intended for human application are governed by the EU Directive on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Storage and Distribution of Human Tissues and Cells – transposed into the UK as the Human Tissue (Quality and Safety for Human Application) regulation 2007. The Directive covers haematopoietic, umbilical cord and bone marrow stem cells, reproductive cells (eggs, sperm),

fetal tissues and cells and adult and embryonic stem cells. The Directive does not cover research for purposes other than application to the human body, e.g. in vitro research or in animal models. The aim of the Directive is to lay down standards of quality in order to ensure a high level of protection of human health.

A key principle of the EU Tissue Directive is the requirement of traceability of human tissues and cells from donor to recipient and vice versa in order to make it possible to verify the compliance with quality and safety standards. A cell line developed *de novo* should be given a unique and unambiguous identifying number that must preserve donor anonymity and be used in all procedures and publications. Researchers must ensure that it is possible to trace cryopreserved stem cell lines to the primary cells and the donated human tissue, and must ensure that an anonymised link can be put in place with the UK Stem Cell Bank for the purposes of traceability

Stem cells and stem cell lines intended for human use must be derived and processed in facilities that meet the statutory requirements of for the HTA Directions, as a minimum, the stages of donation procurement and testing. The requirements of good (pharmaceutical) manufacturing practice (GMP) should be applied to subsequent activities where the stem cell and stem cell lines in question have a reasonable expectation of clinical utility. The good practice standards applicable under these circumstances should be discussed with the HTA and GMP standards with the MHRA.

11. Intellectual Property

11.1 Patentability of stem cells

A notice setting out the UK Patent Office's general practice on the patentability of inventions involving human stem cells, published in February 2009 may be found at http://www.ipo.gov.uk/pro-types/pro-patent/p-law/p-pn/p-pn-stemcells-20090203.htm**;** this states that each case will be treated on its own merits in the light of all relevant circumstances, and stresses that the Office's practice is subject to any future guidance from the UK courts. In summary, the Patent Office:

- will not grant patents for processes of obtaining stem cells from human embryos,
- will not grant patents for human totipotent stem cells and
- will grant patents for inventions involving human pluripotent stem cells provided they satisfy the normal requirements for patentability.

11.2 Intellectual property generated by the UK Stem Cell Bank

Subject to the approval of the Steering Committee, the staff of the UK Stem Cell Bank will perform validation and other tests on newly deposited cell lines, as well as research aimed at improving Banking processes and procedures (e.g.

relating to storage, reproducibility and quality). Bank staff must not however, conduct discovery research on Banked cell lines.

During the period of MRC/BBSRC funding, any intellectual property arising from research and development activities carried out pursuant to the UK Stem Cell Bank's operation will be assigned to MRC for the purposes of protection and exploitation. Net revenues generated from exploitation of such intellectual property will be used solely for supporting the operation of the UK Stem Cell Bank. When an invention is dependent on a specific cell line, the owners of any Banked stem cell lines used by the UK Stem Cell Bank in generating such intellectual property, shall have the royalty-free, non-exclusive right, without the right to sub-licence, to such intellectual property for use only with the specific cell line(s) involved in generating such intellectual property. In the event the depositor wishes to use the intellectual property other than solely with the specific stem cell line then a further licence or permission will be required from MRC.

Other than as set out above, the UK Stem Cell Bank will not take any direct interest in intellectual property embodied in deposited cell lines, and any legal agreements involving the Bank will incorporate this principle. Furthermore, the UK Stem Cell Bank must not transfer, transmit or in any other way disclose commercially confidential information about banked cell lines to any third party, without prior permission from the depositor.

12. Glossary of terms and abbreviations

Accessor
A researcher who withdraws a stem cell line from the UK Stem Cell Bank for use in an approved research project.
(Note: applications to the Steering Committee to access a stem cell line from the UK Stem Cell Bank must be made by the host institution rather than the researcher).

Aliquot
A defined amount of something e.g. cells.

Anonymisation
The process of removing personal names and data from documents that would reveal the identity of a person.

Archived
Data or samples that have been preserved against future need.

Auditing
A systematic, independent and documented process for obtaining evidence to determine the extent to which the Quality Management System requirements are fulfilled.
(Note: Guidance on auditing quality and environmental management systems is provided in ISO 19011).

Autologous
From the same individual.

BBSRC
Biotechnology and Biological Sciences Research Council

Blastocyst
A hollow ball of 50-100 cells reached after about five days' embryonic development just prior to implantation in the uterus.

Cell culture
Cells maintained in the laboratory by repeated passage in a sterile container.

Cell line
A well characterised cell culture, normally derived from a single cell, that has been demonstrated to be phenotypically and genotypically consistent over a specified number of population doublings.

Clinical grade
A stem cell line appropriate for use in clinical research and application, i.e. it has been derived under conditions of Good Manufacturing Practice (GMP) and has passed rigorous safety testing to allow it to be used in studies involving human-participation.

Clinical trial
A rigorously controlled test on human subjects of a new drug, or other treatment, or a new invasive medical device.

Clonal
Derived from a single cell.

Confidentiality
Prevention of disclosure, other than to authorised individuals, of a participant's identity.

Consent
The voluntary consent given by a patient (or next of kin) to participate in a study (which may include donating tissue) after being informed of its purpose, method of treatment, procedure for assignment to treatment, benefits and risks associated with participation, and required data collection procedures and schedule.

Curation
Long term preservation of material or data, sometimes in an archive.

Deposit
A representative proportion of the cell line(s) derived from each embryo donated altruistically that is made available for laboratory research use via the UK Stem Cell Bank.

Depositor
A researcher who deposits a stem cell line in the UK Stem Cell Bank
(Note: applications to the Steering Committee to deposit a stem cell line in the UK Stem Cell Bank must be made by the host institution rather than the researcher).

DH
Department of Health

Differentiation
The process by which a cell becomes specialised to its final function.

Diploid
Containing two sets of chromosomes.

Documented procedures
Procedures that have been tested and optimised and written up in an operating manual for others to use.

Donor
A person who gifts embryos, cells or tissues.

Embryo
The first stage in the development of a human being, usually the result of fertilising an egg with a sperm; from the eighth week of fertilisation the embryo is referred to as a fetus.

Embryonic germ cells
Stem cells derived from primordial germ cells.

EMA
European Medicines Agency

Exogenous
Originating outside of the body.

Exploitation
The process of turning a patented invention into a commercial success.

Fetus
A developing human from eight weeks after conception to birth.

Full economic costs
The all inclusive cost of an activity, i.e. producing a finished cell line.

Gamete
A male sperm or female egg.

Gene
A functional unit of heredity that is a segment of DNA located in a specific site on a chromosome. A gene directs the formation of an enzyme or other protein.

Genotype
The genetic constitution of an organism. This information is used as a "blueprint" or set of instructions for building and maintaining the organism. The instructions are located within the DNA of cells and are written in a coded language (the genetic code); they are copied at the time of cell division or reproduction and are passed from one generation to the next.

GTAC
Gene Therapy Advisory Committee

HFEA
Human Fertilisation and Embryology Authority

HTA
Human Tissue Authority

Human Admixed Embryos
Embryos which contain both human and animal material. The most common type is a cytoplasmic hybrid embryo, which is created by adding the nucleus from a mature human cell (such as a skin cell) to an animal egg cell emptied of its nucleus, via a process called somatic cell nuclear transfer. Cytoplasmic hybrid embryos are 99.9 per cent human.

Immortalized
Made immortal. An immortalized cell line has the ability to grow through an indefinite number of divisions in culture, normally as a result of genetic manipulation.

Induced pluripotent stem cell (iPS cells), are a type of pluripotent stem cell derived from a non-pluripotent cell, such as a differnetiated skin cell.

Informed consent
The voluntary consent given by a patient to participate in a study after being informed of its purpose, method of treatment, procedure for assignment to treatment, benefits and risks associated with participation, and required data collection procedures and schedule.

Intellectual Property
Intellectual Property is any product of the human intellect that is unique, novel and unobvious and has some value in the market place.
(Note: the employer of a researcher who derives a stem cell line is normally the owner of any intellectual property relating to that cell line)

IVF
In vitro fertilisation; the fertilisation of an egg by a sperm outside of the body.

Laboratory grade
A stem cell line appropriate for use in laboratory-based research but not for clinical application, i.e. it has not been derived under conditions of Good Manufacturing Practice (GMP).

Liability
The state of being legally obliged and responsible.

Marginal costs
The amount by which production costs are increased as a result of generating one additional unit of output.

Mesenchymal stem cells
Rare stem cells present in human bone marrow that have been shown to differentiate into a variety of different cell types in culture.

MHRA
Medicines and Healthcare products Regulatory Agency

MRC
Medical Research Council

mRNA
Messenger ribonucleic acid is the molecule that carries the information from DNA to acts as a template for protein synthesis.

Multipotent stem cells
Stem cells that have the potential to differentiate into a limited number of specific cell types in order to regenerate the tissue in which they normally reside.

Mycoplasma
A type of bacterium which commonly infects cells grown in culture.

Passage
Transfer of cells from one culture environment to another.

Patent
A patent for an invention is granted by government to the inventor, giving the inventor the right for a limited period to stop others from making, using or selling the invention without the permission of the inventor. When a patent is granted, the invention becomes the property of the inventor, which - like any other form of property or business asset - can be bought, sold, rented or hired.

Phenotype
The "outward, physical manifestation" of the organism; i.e. the sum of the atoms, molecules, macromolecules, cells, structures, metabolism, energy utilization, tissues, organs, reflexes and behaviours. The phenotype is the product of the genotype.

Pluripotent stem cell
A single pluripotent stem cell has the ability to give rise to types of cells that develop from the three germ layers (mesoderm, endoderm and ectoderm) from which all the cells in the body arise. Pluripotent cells thus have the potential to develop into every cell type in the human body, but cannot develop into an embryo on their own.

Population doubling
A measured doubling of cell numbers.

Primary cells
Cells derived from an in vivo or ex vivo source.

Primordial Germ Cells
Precursors of reproductive cells within the embryo that give rise to eggs and sperm.

Processing
All operations involved in the preparation of the stem cell line, from receipt through preparation and packaging to its completion as a finished therapy.

Quality management systems
The set of interrelated or interacting elements that is implemented by an organisation to direct and control its activities in order to fulfil stated, implied or obligatory needs or expectations.
(Note: fundamental principles of Quality Management Systems are described in ISO 9000)

Reproductive cloning
The implantation of an embryo produced by cell nucleus replacement / somatic cell nuclear transfer (therapeutic cloning) into the womb of a woman for the purposes of generating a pregnancy therefrom.
(Note: this procedure is illegal in the UK and in many other countries in the world.)

Requestor
A researcher seeking approval from the Steering Committee to withdraw a stem cell line from the UK Stem Cell Bank for use in an approved research project.
(Note: applications to the Steering Committee to access a stem cell line from the UK Stem Cell Bank must be made by the host institution rather than the researcher.)

Risk
Combination of the probability of occurrence of harm and the severity of that harm.

Risk/benefit assessment
Weighing of the potential benefits of a treatment against the harm that the recipient might experience.

Somatic stem cells
Stem cells derived from the adult body or fetus.

Somatic Cell Nuclear Transfer (SCNT)
The transfer of an adult cell nucleus into an egg that has had its nucleus removed to asexually create an embryonic clone without the fusion of sperm and egg.

Stakeholders
Parties or individuals with an interest in an issue or question.

Stem cells
Cells capable of self replication, proliferation and differentiation.

Stem Cell Bank
A facility that is responsible for accessioning, processing, packaging, labelling, storage and delivery of a finished stem cell line issued under its name.

Sterile
Condition of a product that is free from contaminating organisms.

Tissue engineering
The application of principles and methods of engineering and life sciences to the design, specification and fabrication of cells, biomaterials or biomolecules to restore or modify the biological functions of tissues.

Third party
Someone other than the principals who are involved in a transaction

Totipotent stem cell
At two to three days after fertilisation an embryo consists of identical cells which are totipotent; that is to say, each could give rise to an embryo on its own. Such cells are totally unspecialised and have the capacity to differentiate into any of the cells which constitute the fetus including the placenta and membranes around the fetus.

Toxicology
Study of the potential of materials to give rise to harm to health by virtue of their effect on biological systems.

Traceability
Tracking an individual through their medical history.

Trademark
A formally registered symbol identifying the manufacturer or distributor of a product.

Validation
Establishment of documented evidence which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes.

Verification
Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

13. Full Website Links:

3.1 The Human Tissue Act (2004):
http://www.legislation.hmso.gov.uk/acts/acts2004/20040030.htm

3.2 European Tissue and Cells Directive:
http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/legislation/eutissueandcellsdirectives.cfm

3.3. The Human Fertilisation and Embryology (HFE) Act (1990 and 2008) -
http://www.opsi.gov.uk/acts/acts1990/Ukpga_19900037_en_1.htm

3.4 Medicines for Human Use (Clinical Trials) Regulations 2004
http://www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm

3.5 EC Regulations on Advanced Therapy Medicinal Products 2007

http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/index.htm

3.6 The Role of the Gene Therapy Advisory Committee (GTAC) and the Regulatory Route Map:
http://www.dh.gov.uk/ab/GTAC/index.htm

3.7 The UK Stem Cell Tool Kit
http://www.sc-toolkit.ac.uk

4. The UK Stem Cell Bank:

http://www.ukstemcellbank.co.uk/

5.1 Steering Committee:
http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Stemcellbank/Steeringcommittee/index.htm

5.2 Bank Management Committee:
http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Stemcellbank/Managementcommittee/index.htm

7.2 UK Stem Cell Lines Registry
http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Stemcellbank/Usingthestemcellbank/MRC003079#P19_725

9.2 Donor Consent for the use of embryos in research
http://www.hfea.gov.uk/3468.html#guidanceSection5018

10.1 Good Research Practice:

http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Researchpractice/MRC002539
UK Coordinating Committee on Cancer Research, 1999:
http://www.nature.com/bjc/journal/v82/n9/pdf/6691169a.pdf

10.2 EU Directive on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, processing, Storage and Distribution of Human Tissues and Cells
http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=en&numdoc=32004L0023&model=guichett

11.1 Patentability of stem cells
http://www.ipo.gov.uk/pro-types/pro-patent/p-law/p-pn/p-pn-stemcells-20090203.htm