

SaBTO

**Advisory Committee on the
Safety of Blood, Tissues and Organs**

Donation of Starting Material for Cell-Based Advanced Therapies: a SaBTO Review

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Dr Kevin Brown, Public Health England

Professor Kate Gould, Newcastle upon Tyne Hospitals NHSFT

Dr Lyn Healy, UK Stem Cell Bank, National Institute for Biological Standards and Control, a centre of the MHRA

Dr Charles Hunt, UK Stem Cell Bank, National Institute for Biological Standards and Control, a centre of the MHRA

Dr Graham Jackson, Medical Research Council Prion Unit

Professor Paul Kellam, Wellcome Trust Sanger Institute

Professor Richard Knight, UK National CJD Research and Surveillance Unit

Dr Simon Mead, Medical Research Council Prion Unit

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Attendees at the SaBTO Open Meeting on 28th April 2014, on the topic of Cell-based advanced therapies, also raised and discussed a number of points which SaBTO took into account when finalising the report.

2 Executive summary

Cell-based advanced therapies span the donor selection and screening, procurement, processing, immunological matching and clinical transplantation seen in blood transfusion, cell, tissue and organ transplantation and the level of manufacturing seen in the pharmaceutical and biotechnological industries. These therapies vary from minimally manipulated autologous products through to potentially large scale allogeneic products derived from pluripotent stem cells of considerable complexity. They are rightly subject to stringent regulatory control which, depending on their classification, may be under one or more of the blood, tissue and cells or medicines pieces of legislation and their approved guidance documents. However there are a number of open issues beyond mandatory requirements, some of which, in the UK, fall into the remit of SaBTO (the Advisory Committee on the Safety of Blood, Tissues and Organs), including the extent of donor screening for infectious agents and genetic abnormalities, the nature and extent of informed consent and the duty of care to the donor should findings arise which are of relevance to his or her health, family or public health. There are also risks associated with the manufacturing process itself, the characterisation of the cellular product and its behaviour in the recipient post-transplant, but these exogenous risks were considered to be out-with the remit of SaBTO. The Working Group was therefore established to review the endogenous risks associated with cellular therapies, particularly with respect to donor selection, consenting and testing, and to make recommendations to SaBTO on how these can be optimised in order to support the development of cellular therapies in the UK whilst maximising donor and patient safety.

The possibility of infection from transplanted cell therapies remains one of the greatest risks to potential recipients. Whereas the majority of infectious agents will have a cytopathic effect on the cell line and be detected by mandatory product (Quality Control) testing so that their existence will be recognised and the cells discarded before use, there are some potential, and possibly some as yet unknown pathogens, which may be able to incorporate themselves into cells and establish persistent yet non-evident infection. These infective agents may originate from the donor cells themselves, contamination at the time of harvesting, or during the propagation process.

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The Working Group recommends that the selection and testing of blood and tissue donors for cellular therapies should follow existing SaBTO guidance on the selection and assessment of donors, and on risk assessment for infection; abide by legal requirements, and follow the best available professional guidance. Consideration should be given to infectious agents that may not be cytopathic and may not be detected by mandatory tests but could replicate in *in vitro* culture systems or precipitate cellular transformation. Vigilance should be maintained for new and emerging infections, and consideration given to the potential for their transmission through a cell line. Consideration of the short term follow up of the donor is also deemed important, for which baseline legislative requirements exist. When considering the safety of a product, account needs to be taken of the effect of inactivation/decontamination strategies undertaken during processing, and their effect on the infection potential of the final product. For live donors, a risk assessment should be done to mitigate risk at the point of donation, for infections and for agents that could replicate *in vitro* and cause cell replication or transformation. An assessment of the risk to the potential recipient should be performed, for example whether they are immunosuppressed or not. Existing SaBTO guidance on donor testing should be followed, but also testing of the end product for bacteria and fungi using assays such as the existing 16S and 18S PCRs¹ should be considered, and these and other tests required for use on cell lines or products should be appropriately validated.

The genetic risks that might be associated with cellular therapies are as yet unknown. Whilst it is clear that there must be some risk either to the function of a cellular therapy or to the recipient(s), this cannot be quantified with certainty and with the exception of a few specific cases, there is uncertainty about the relationship between genetics and disease. Thus the assessment of risk is based on previous information about the genetic selection procedures for blood, cell, tissue and organs including gametes and an understanding of the underlying scientific knowledge, including its limitations.

The Working Group recommends that no routine genetic screening should be carried out on donors, but that relevant genetic tests may be done on the stem cell lines / derived product. The reason for this is that there is a significant genetic distance

¹ 16S and 18S PCRs: polymerase chain reaction (PCR) is a laboratory testing technique which uses amplification of a genetic sequence, including of 16S or 18S ribosomal RNA, to detect microbial pathogens.

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between the donor and the cellular product. Thus routine donor selection or screening (by history or testing) for genetic variation is unlikely to be relevant. Genetic tests are recommended on the cellular product that would be determined by its required function and the indications for its use and, if the product is classified as medicinal, may be required as a result of assessment during either clinical trial or marketing authorisation application assessment. Given the complexity of the options, this would have to be individually risk assessed during the assessment process of medicinal products or, for those regulated under blood or tissues directives, by the producer and by the clinician / patient.

The Working Group recommends that the nature and extent of any genetic testing should be individually risk assessed by the producer, regulatory authority and clinician.

Some of the most challenging aspects of cellular therapies concern informed consent and traceability. The rapid pace of progress and increasing variety and complexity of technologies and products are testing both the regulatory environment and established practice. In such a rapidly evolving field, there will always be a delicate balance between three factors: the duty of care owed to donors; the duty of care owed to recipients, and the development and regulation of the technologies themselves.

In the meantime a number of open issues remain, including those relating to traceability; the implications for the donor in the event of identification of known or novel infectious or genetic disease markers, either at the time of donation or at any time in the future; the implications for potential previous recipients of the development of post-donation disease in the donor which may have an infectious or genetic basis; the extent to which the development of clinical problems in recipients may have implications for the donor and/or his/her family; and the nature of informed consent from a donor's perspective, and whether or to what extent they should be able to waive feedback.

The Working Group makes two important background points: that it is essential that the subject of cell-based advanced therapies is discussed openly and transparently, in order to build growing and informed public awareness, and that consent should be regarded as a process not an event. The main themes and principles pertinent to issues of consent and traceability in cellular products include assessment of the donor's capacity to consent and the provision of sufficient clear information in order for donors to make an informed decision. The information can be communicated in

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different ways – verbally or written or both – but the fact that the information has been given and explained needs to be recorded. Consideration needs to be given to provision of sufficient staff training and time for the consenting process, explaining the limits of certainty and the scope of consent including the testing that may be carried out and the circumstances in which the donor could choose whether to receive feedback (when the information has a direct consequence for their or their immediate family's health, for example, but not when there are implications for public health). Donors also need to understand the need for and duration of traceability, the potential retention of samples for future testing, and the implications thereof. Donors need to understand that their donations may be used to develop therapeutic products by commercial manufacturers, potentially for widespread use in the UK and overseas, but that their donation is a gift and they cannot themselves expect to benefit financially if this occurs. The Working Group suggests that consideration should be given to Cell Therapy History Files, documenting the development of a cellular product, and to ensuring that consent remains valid at all stages of the process.

3 Background and process

3.1 Introduction

Cell-based advanced therapies comprise a spectrum of complex cellular products manufactured from donated human tissues and cells or blood components and transplanted into, or administered as medicinal products to, patients for therapeutic purposes. Whilst the field is usually thought of as a sub-set of Regenerative Medicine, it overlaps with other developing fields of adoptive immunotherapy, gene therapy and tissue engineering and may involve the use or co-administration of novel devices. In addition it combines the donor selection, consenting, screening and procurement challenges seen in blood transfusion and cell, tissue and organ transplantation with, for those classified as medicinal products, the need for good manufacturing practice, quality control and regulatory compliance. Finally, from the patient's perspective, issues of immunological matching, the transplantation or administration procedure and potential long term clinical impact need to be considered. It is important to understand that cellular therapies are not homogenous stable chemical entities, they are complex heterogeneous biological systems in their own right; they vary and change according to their biological heritage and their *in vitro* and *in vivo* microenvironment. In the patient they may exert a complex mixture of immunological, morphological and metabolic effects with long term impact including chimerism.

Significant investment is now being made both in the UK and internationally in the development of cellular therapeutics and regenerative medicine, partly as a reflection of advances in our understanding of stem cell and developmental biology and partly as a reflection of increasing awareness of the impact an ageing demography and increasing prevalence of chronic degenerative conditions is likely to have on the health and economies of most developed and emerging economies in the decades to come. For those classified as medicinal products, increasing numbers of novel cellular therapies are entering clinical trial and, at the time of writing, four have achieved European Marketing Authorisation, but the challenges remain formidable, not least the importance of balancing the need for rapid development of the field with assurance of the quality, safety and effectiveness of this new class of therapeutic

agent. Whilst the overarching EU regulatory framework is in place, and the detailed regulatory requirements and the formally approved guidance beneath this framework are evolving rapidly in response to this emergent technology, there remain a number of open issues, some of which overlap with SaBTO's remit.

3.2 Categories of cellular therapies

From a clinical perspective (rather than legal classification) cellular therapies can be categorised according to the extent of cell manipulation involved during manufacture:

- **Category 1: minimally manipulated cell therapies:** the most relevant paradigm for which is the established field of haematopoietic stem cell (HSC) transplantation where HSC procured from autologous or allogeneic bone marrow, mobilised peripheral blood or umbilical cord blood are transplanted fresh or cryopreserved as a mononuclear cell preparation and thawed just prior to transplantation. Preparation of enriched cell populations on the basis of immunophenotypic markers such as CD34 or CD133, either for haematopoietic transplantation (homologous use) or in heterologous use (where they are classified as medicinal products) for other indications - for example to improve post-myocardial infarction perfusion (heterologous use), also falls into this category. As another example, the production of islet cells through digestion, centrifugation and washing, for the treatment of type-2 diabetes mellitus, from pancreata donated by deceased allogeneic organ donors, also falls into this category. Issues of donor selection, screening and consent are similar to those seen in standard cell, tissue and organ transplantation, and the majority of such therapies involve a one to one relationship between the donor and recipient.
- **Category 2: somatic cell therapies:** in which autologous or allogeneic cells, donated by living or deceased donors, are isolated and cultured for a limited period of time *in vitro* (usually for a matter of days, up to a week or two) prior to transplantation into one, or a handful of, recipient(s). Examples include corneal limbal stem cell transplantation for the treatment of ocular surface disorders and dendritic cells for the treatment of certain forms of cancer. Some somatic cells are cultured for a prolonged period of time *in vitro* (usually for several weeks) prior to transplantation potentially into a large number of

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recipients. Examples include mesenchymal stromal cells (MSC) for the treatment of autoimmune diseases or to ameliorate graft versus host disease, and virus-specific cytotoxic T lymphocytes (CTL) to treat disseminated infection or cancer in immunosuppressed patients. Some category 2 products may be genetically modified, for example by transduction of T cells with modified T cell receptors or chimeric antigen receptors in order to alter specificity. Whilst there is considerable overlap with Category 1 cellular therapies in terms of donor selection and microbiological screening (for example: corneal epithelial stem cell with corneal transplantation; MSC with HSC transplantation and CTL with donor lymphocyte infusions respectively), the cell culture process includes 'substantial' manipulation of the cells and introduces complexity in terms of (*inter alia*) the risk of in-process contamination, genetic or epigenetic instability and the character and function of the final product.

- **Category 3: stem cell lines:** are derived either from *in vitro* blastocysts (human embryonic stem cells [hESC]) or genetic reprogramming of adult cells (induced pluripotent stem cells [iPS]). Such cell lines will proliferate indefinitely in culture and can also differentiate into most if not all of the cell types present in an adult. They therefore open the possibility of indefinite scalability and of a single (allogeneic) donor contributing multiple cell or tissue products to multiple recipients over an extended period of time. Examples include hESC-derived retinal pigment epithelium cells for Stargardt's Macular Dystrophy (advanced cell therapies), neural stem cells for patients disabled by ischaemic stroke (ReNeuron) or iPS-derived red cells or platelets. Some cell lines may undergo genetic modification to alter differentiation or augment potency. The donor selection, microbiological screening and genetic stability risks are amplified in this context by the potentially high number of recipients of each donation, as are the risks during manufacture (for example a pluripotent stem cell line may go through several passages followed by a complex multi-step differentiation protocol, amounting to several months in culture).
- **Category 4: tissue engineered products and organoids:** human tissues do not consist of single cell suspensions but of complex three dimensional structures involving a variety of cell types and extracellular matrix components. Some early progress has been made in this space through, for

example, the use of decellularised cadaveric human trachea to provide a scaffold which is then recellularised with autologous MSC and epithelial cells and can be used for treatment of tracheal stenosis². Moreover there is accumulating evidence that human pluripotent stem cells can give rise to complex self organising 3D organoids with many of the structural features of human liver or neural tissue³.

3.3 Open issues

3.3.1 Donor screening for infectious agents

Whilst there is mandatory screening of almost all donors for some known pathogens (for example human immunodeficiency virus [HIV], hepatitis B [HBV], hepatitis C [HCV], human T-lymphotropic virus 1 [HTLV1] and syphilis), some are screened for selectively, only in certain 'at risk' donor subpopulations (malaria or West Nile Virus in potentially exposed travellers), or when products are to be administered to 'at risk' patient groups (such as cytomegalovirus [CMV]). Moreover, there are many potential pathogens in the human population which are not currently screened for at all – some are undetectable (such as prion diseases); some are pathogenic in some recipients, such as patients who are immunosuppressed, but not in healthy individuals (such as hepatitis E or human herpesvirus 8 [HHV8]); some are of uncertain pathogenicity (such as transfusion-transmitted virus [TTV]); some are probably as yet unknown. There are open questions as to which of this extended range of microbiological agents could and should be screened for, the impact of screening with new assays which may be introduced during the lifetime of the product, and the advisability and interpretation of emerging whole genome sequencing (WGS) approaches to the detection of hitherto unknown microbiological agents. The extent to which the results of such screening need to be communicated to the donor and/or recipients of products needs to be given consideration.

3.3.2 Donor screening for genetic abnormalities

² Macchiarini P, Jungebluth P, Go T, Asnaghi MA, Rees LE, Cogan TA et al. [Clinical transplantation of a tissue-engineered airway](#). Lancet 2008; 372: 2023-2030.

³ Takebe T, Sekine K, Enomura M, Koike H, Kimura M, Ogaeri T et al. [Vascularised and functional human liver from an iPSC-derived organ bud transplant](#). Nature 2013; 499: 481-4.

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Similarly, whilst little or no genetic screening of donors is carried out currently, our developing understanding of human genetics suggests that it will become increasingly possible to screen individuals for propensity to development of disease. Consideration needs to be given to the consequences of WGS, and to the implications for the donor and his / her family if genetic or other abnormalities are discovered during the life history of the cell line – perhaps years or decades after the original donation – and the extent to which the donor or his / her family need to be informed of such emergent findings.

3.3.3 Informed consent and traceability

Most of the donor selection and informed consent issues relating to Category 1 and 2 cell therapeutics have been well worked through in the context of the tissues from which they have been derived. However there are a number of issues which assume greater importance in the context of Category 3 and 4 cell therapeutics. In particular, given that full traceability must be maintained for 30 years after the last clinical use of the product, it is possible that development of positive test results or of clinical disease in the donor or recipients may have consequences for the donor and / or other recipients many years after the initial donation.

Scalable cell populations such as those of MSC, which can be derived from one or a handful of donors, may be transplanted into a large number of recipients over an extended period of time. A 'one to many' risk therefore exists of a large number of recipients being affected by amplification of an infection, propensity to neoplasia or functional abnormality present in the donor or introduced or amplified during the manufacturing process. These risks are increased in the context of pluripotent (hESC and iPSC) lines, cellular therapy products derived from which could be administered to very large number of individuals with many different kinds of medical conditions over a long period of time.

In the majority of instances hESC lines are derived from supernumerary morula / blastocysts generated during routine clinical *in vitro* fertilisation (IVF), often some months or years after the original procurement of the gametes. The donor selection and screening procedures for IVF are quite different from those involved in a routine blood or tissue donation. In addition only a minority of IVF-generated embryos will be used to generate clinical grade hESC lines. Open issues include the extent to which it is necessary and appropriate to re-approach the embryo donors to ascertain further medical history, if possible, or perform further microbiological screening; and the

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extent to which testing of the hESC line itself can be considered a suitable alternative strategy.

For iPS cell lines, the donor of the skin or blood sample can be more easily subject to a donor selection / screening process – but there are open issues around whether current donor selection criteria are sufficient: for example would a more detailed medical history and / or inspection of the donor's medical notes be appropriate? Is a family propensity to disease of importance, for example of early onset cardiovascular disease if endothelial cells are to be derived? Is the post-donation medical history of the donor of relevance?

Consideration also needs to be given to the selection and screening criteria used for donors of supporting material including cells or cell lines used in co-culture. The consent and traceability issues discussed may apply in the same way to these donors.

3.3.4 Risks introduced during the manufacturing process

A number of risks may be introduced during the manufacturing process including infectious agents – particularly bacteria, mycoplasma or fungal infections which may arise from the reagents or environment; other adventitious agents such as contaminants of toxic materials in reagents and equipment; and inherent genetic and epigenetic instability of cell lines themselves particular under high passage culture which may give rise to an increased risk of neoplasia.

3.3.5 The characterisation of the process and product

In the context of cellular therapies, the manufacturing process and indeed the microenvironment in which the cell product is maintained post manufacture and prior to transplantation have a critical impact on the nature of the product itself. The heterogeneity of the cell population during culture; the persistence of or reversion to pluripotency; the risk of generation of or differentiation into alternative lineages, and the phenotypic and functional characterisation of the final product are all key issues which as yet have not yet been fully worked out for the new generation of cellular therapeutics.

3.3.6 The behaviour of the cellular therapy in the recipient

As noted above, cellular therapies are complex living systems which will be subject to dynamic change in response to the *in vivo* environment once transplanted, raising

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the possibility if not likelihood that the therapeutic will evolve in its structure, function and/or dispersion during the life-time of the recipient. Key issues include the risk of immunological rejection of the product, a risk of lack of integration into the appropriate microenvironment, and the risk of dissemination of the cellular therapy leading to ectopic tissue formation. The tracking of cells and of their local and systemic impact over potentially long periods of time remain under-developed fields.

These risks are among those which the developer should consider during development and the Competent Authority will assess as part of the overall assessment for approval of a Medicinal Product dossier (Clinical Trial Authorisation or Marketing Authorisation Application).

3.4 The regulatory environment

In the UK, procurement and testing of blood components for human use are regulated under the EU Blood Directive (2002/98/EC)⁴, transposed into UK law as the Blood Safety and Quality Regulations (SI 2005:50)⁵, the competent body for which is the Medicines and Healthcare products Regulatory Agency (MHRA). Procurement and testing of tissues and cells (other than gametes and embryos) for human use are regulated under the EU Tissues and Cells Directive (2004/23/EC)⁶, transposed into UK law as the Human Tissues (Quality and Safety for Human Application) Regulations⁷ (SI 2007:1523), the competent body for which is the Human Tissue Authority (HTA). The creation and use of embryos for hESC derivation are subject to regulation under the Human Fertilisation and Embryology Act (2008)⁸, which incorporates the elements of the EU Tissues and Cells Directive relating to gametes and embryos, the competent body for which is the Human Fertilisation and Embryology Authority (HFEA). Category 1 cellular therapies used in homologous indications are regulated under the Human Tissues (Quality and Safety for Human Application) Regulations (SI 2007:1523) by the HTA. Category 1 cellular therapies used in heterologous indications and all higher categories of cellular therapies are

⁴ EU Blood Directives 2002/98/EC, 2004/33/EC, 2005/62/EC and 2005/61/EC. See

http://europa.eu/legislation_summaries/public_health/threats_to_health/c11565_en.htm

⁵ Blood Safety and Quality regulations. See <http://www.mhra.gov.uk/Howweregulate/Blood/>

⁶ EU Tissues and Cells Directives 2004/23/EC, 2006/17/EC and 2006/86/EC. See

http://europa.eu/legislation_summaries/public_health/threats_to_health/c11573_en.htm

⁷ Human Tissues (Quality and Safety for Human Application) Regulations 2007. See

<http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/legislation/eutissueandcellsdirectives.cfm>

⁸ Human Fertilisation and Embryology Act 2008. See <http://www.hfea.gov.uk/134.html>

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regulated under the Medicines Directive (2001/83/EC)⁹ with a large proportion fulfilling the Advanced Therapy Medicinal Products (ATMP) regulations (EC Regulation 1394/2007)¹⁰, the competent body for which is the MHRA (for manufacturing and clinical trial authorisations) in the UK. However Marketing Authorisation for ATMPs is granted under a centralised procedure and is therefore under the remit of the European Medicines Agency under Regulation 726/2004.

All medicinal products including ATMPs need to be manufactured, tested and released in compliance with EU Good Manufacturing Practices (Eudralex Volume 4)¹¹ and tested in the clinical setting in line with the EU Clinical Trial Directive (2001/20/EC)¹² and in accordance with Good Clinical Practice (2005/28/EC¹³ and Eudralex Volume 10¹⁴).

Appendix 1 provides more detail on the legal and regulatory environment.

3.5 The scope and remit of the working group

The Working Group was established to review the endogenous risks associated with cellular therapies, particularly with respect to donor selection, consenting and testing, and to make recommendations to SaBTO on how these can be optimised in order to support the development of cellular therapies in the UK whilst maximising donor and patient safety (see Appendix 2).

3.5.1 Remit of the Working Group

⁹ Amended EU Medicines Directive 2001/83/EC, see http://ec.europa.eu/health/documents/eudralex/vol-1/index_en.htm; Regulation (EC) 726/2004, see http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l22149_en.htm

¹⁰ Regulation (EC) 1394/2007 of the European Parliament and of the Council of 13. See http://ec.europa.eu/health/human-use/advanced-therapies/index_en.htm.

¹¹ Volume 4 of *The rules governing medicinal products in the European Union* contains guidance for the interpretation of the principles and guidelines of good manufacturing practice for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC and 91/412/EEC respectively. Published at http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

¹² EU Clinical Trial Directive 2001/20/EC. See http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm

¹³ EU Good Clinical Practice Directive 2005/28/EC. See http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm

¹⁴ Volume 10 contains guidance documents applying to clinical trials. Published at http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm

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- To examine the extent to which donor selection procedures used for blood, tissue, haematopoietic stem cell and solid organ transplant donation are applicable in the context of cellular therapies and related Advanced Therapy Medicinal Products (ATMPs). Particular attention will be given to donors of stem cell lines (human embryonic stem cells, induced pluripotent stem cells, induced somatic stem cell lines) in view of the increased risk of a single donor contributing to potentially large numbers of recipients over a long period.
- To define the potentially infectious agents of interest, both those currently screened for and other infectious agents of potential relevance including but not limited to endogenous retroviruses, prion diseases and infections which are of low pathogenicity in a healthy host but may be pathogenic in a host with a specific disease or immune suppression.
- To review the extent to which it is possible to screen the donation or product thereof rather than the donor for infectious disease.
- To assess the potential risk of genetic abnormality in the donor giving rise to a product which may give rise to disease in the recipients.
- To establish the extent to which genetic screening or indeed whole genome sequencing of a cell line may be appropriate.
- To consider the issues relating to traceability between the donor and recipient(s) and the duration for which reference materials and documentation will need to be retained.
- To consider the implications for the donor in the event of identification of known or novel infectious or genetic disease markers either at the time of donation or at any time in the future.
- To consider the implication for potential previous recipients of the development of post-donation disease in the donor which may have an infectious or genetic basis.
- To consider the extent to which the development of clinical problems in recipients may have an implication for the donor and / or his / her family.
- To consider the nature of informed consent from a donor's perspective and whether they should be able to waive feedback.

3.5.2 Scope of the working group

Endogenous risks were considered to be *in scope* i.e. those associated with the starting cellular material which could be of an infectious, neoplastic or genetic nature:

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- Minimally manipulated cellular therapies
- *In vitro* somatic cultured cells
- Cell therapies derived from stem cell line including :
 - Human embryonic stem cells
 - Induced pluripotent stem cells
 - Induced oligopotent stem cells
- Tissue Engineered products which include living cells
- Genetically engineered cellular therapies.

Exogenous risks were considered to be *out of scope* i.e. the risk of damage or contamination relating to the manufacturing process itself:

- Persistence or reversion to pluripotency leading to risk of teratoma
- Neoplasia induced by genetic or epigenetic abnormalities in the cell line
- Contamination with microbiological agents
- Contamination by other agents in the manufacturing process.

Issues related to the clinical use of the product were also considered *out of scope*:

- Acute toxicity
- Immunological rejection of the allogeneic cellular tissue
- Dissemination of the cellular therapy leading to ectopic tissue formation
- Generation of alternative lineages leading to inappropriate tissue.

It was acknowledged by the Working Group that the areas considered *out of scope* for this piece of work are still of the utmost importance to the quality and safety of the cellular therapy product, and that in many cases the differentiation between endogenous and exogenous risks is artificial. For example a bacterial contamination of the cell therapy is of serious importance whether it is derived from the donor or the culture environment. Cross-reference has been made to these issues where appropriate.

3.6 The process and membership of the Working Group

The Working Group was set up in autumn 2012 following a series of meetings and discussions. A group of SaBTO members met with representatives of the regulatory bodies - the HTA, the HFEA and the MHRA - in February 2012. A number of issues

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were explored, such as whether the current regulatory framework seamlessly covered the whole process from initial donation to authorisation of stem-cell derived medicinal products; and the regulatory requirements, and the support available for developers of such ATMPs in meeting them.

In March 2012, members of the UK National Clinical Human Embryonic Stem Cell Forum (NChESF), who were involved with derivation and banking of hESC from IVF embryos, met with experts in prion disease and tissue banking, to explore the possibilities and implications of prion infection in stem cells (and other tissues) intended for clinical use. As no risk assessment had been undertaken, the group requested advice from SaBTO.

At its meeting in September 2012, SaBTO discussed this request, together with information on a proposal from the HTA to put forward amendments to the EU Tissues and Cells directive 2006/17/EC which were designed to resolve difficulties arising from the application of the current donor testing requirements to human embryonic stem cell derivation.

In October 2012, SaBTO members met with regulators and relevant policy leads from the Department of Health to establish the scope of SaBTO's task. It was agreed that while risks arising from the manufacture of ATMPs were fully covered by HTA and MHRA regulation, advice from SaBTO would be helpful on the donation of starter material and patient management, such as a range of microbial risks including but not limited to prion disease; donor selection and testing, and informed consent; and the implications of diseases identified in the future.

The Working Group was recruited in late 2012. The Chair, Professor Marc Turner, had in-depth expertise in cellular therapies, being Professor of Cellular Therapy at the University of Edinburgh; long experience of donor selection and testing, as Medical Director of the Scottish National Blood Transfusion Service; and extensive knowledge of prion disease, being Chair of both the UK Blood Services' Prion Working Group and SaBTO's Prion Sub Group. The Working Group first met in March 2013.

The Working Group agreed to focus particularly on therapies developed from pluripotent stem cell lines, as these were likely to be given to large numbers of recipients over a long period of time so that any risks were magnified. The Group considered its work fell into three areas – infectious risks, genetic risks, and issues relating to consent and traceability – and divided into three sub-groups to address

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them. Membership of the Working Group and the sub groups is shown below. The sub group considering infectious risks collaborated on some issues with the group at the National Institute for Biological Standards and Control reviewing risks associated with adventitious agents, and is grateful for their contribution. The sub groups worked via email and telephone conference, and the Working Group as a whole met in March, July and September 2013 and January 2014. An advanced draft of the Working Group's report was sent to key stakeholders for their response and comment in February 2014.

This work formed the subject of SaBTO's Open Meeting in April 2014, allowing wider discussion of some of the issues considered and of the Working Group's conclusions. The Working Group's report and recommendations were submitted to SaBTO at its committee meeting in April in 2014, when points raised at the Open Meeting were also reported.

Membership of the Cell-Based Advanced Therapies Working Group

Name	Position and Role on Working Group	Sub group
Professor Marc Turner	SaBTO Member: Chair and expert in cellular therapy	
Dr Paul De Sousa	SaBTO Member: Expert in regenerative medicine	Genetic risks
Dr Rob Elles	Clinical Director and Director of Business Development and External Affairs, Genetic Medicine, Manchester Academic Health Sciences Centre: Clinical genetics expert	Genetic risks
Professor Bobbie Farsides	Professor of Clinical and Biomedical Ethics at Brighton and Sussex Medical School: Bioethicist	Joint lead, Consent & traceability
Dr George Galea	SaBTO Member: Tissues and cells expert	Consent & traceability
Professor Kate Gould	SaBTO Member: Infection expert	Lead, Infectious risks
Mrs Gill Hollis	SaBTO Member: Patient representative	Joint lead, Consent & traceability
Professor Richard Knight	SaBTO Member: Prion disease expert	Infectious risks

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Professor Alison Murdoch	SaBTO Member: <i>In vitro</i> fertilisation / human embryonic stem cell expert	Lead, Genetic risks
Professor Tom Solomon	SaBTO Member: Infection expert	Infectious risks
Dr Glyn Stacey	Director, UK Stem Cell Bank, and Chair, UK National Clinical Human Embryonic Stem Cell Forum: Human stem cell banking expert	Infectious risks
Professor Richard Tedder	SaBTO Member: Infection expert (scoping stage)	Infectious risks
Dr Ludovic Vallier	Director of the hIPSC (human induced Pluripotent Stem Cells) Core Facility and Reader in Stem Cells and Regenerative Medicine at the University of Cambridge: iPS expert	Genetic risks
Mrs Laura Witjens	Chief Executive, National Gamete Donation Trust: Donor expert	Consent & traceability
Dr Robin Buckle	Director of Science Programmes & Director, UK Regenerative Medicine Platform, Medical Research Council: Observer, Medical Research Council	
Professor Johan Hyllner	Chief Scientific Officer, Cell Therapy Catapult: Observer, Cell Therapy Catapult	
Dr Sarah Moyle	Head of the Clinical BioManufacturing Facility, the Jenner Institute, Oxford: Observer, BioIndustry Association	Consent & traceability
Dr Chris O'Toole	Head of Research Regulation, Human Fertilisation & Embryology Authority: Observer, Human Fertilisation & Embryology Authority	
Dr Amy Thomas	Regulation Manager, Human Tissue Authority: Observer, Human Tissue Authority	
Mr Emyr Harries	Senior Scientific Officer, Dept. of Health Genetics & Advanced Therapies Team: Policy support	

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The possibility of infection from transplanted cell lines remains one of the greatest risks to potential recipients.

Whereas the majority of infectious agents will have a cytopathic effect on the cell line, and their existence will be recognised and the cells discarded before use, there are some potential, and possibly some as yet unknown pathogens, which may be able to incorporate themselves into cells and establish persistent yet non-evident infection.

These infective agents may originate from the donor cells themselves, contamination at the time of harvesting, or during the propagation process.

Previous SaBTO publications have addressed the risk of infections in other situations and we agree that these recommendations are applicable in general terms to cells.

This section specifically addresses situations which are over and above those cited in those documents and focuses on hazards that may arise from cells donated for therapy.

4.1 Relevant documents considered

The subgroup reviewed the following documents:

- SaBTO Guidance on the Microbiological Safety of Human Organs, Tissues and Cells Used in Transplantation, published February 2011¹⁵
- SaBTO Tissues and Cells; MSM* Donor Selection Review, July 2013. (*MSM: men who have had sex with men)¹⁶
- National Institute for Biological Standards and Control Adventitious Agents Working Group Meeting reports from 30th September 2013 and 26th November 2013

¹⁵ Published at <https://www.gov.uk/government/publications/guidance-on-the-microbiological-safety-of-human-organs-tissues-and-cells-used-in-transplantation>.

¹⁶ Published at <https://www.gov.uk/government/publications/donor-selection-criteria-for-men-who-have-had-sex-with-men>.

- A Risk Assessment Tool Powerpoint on: “Viral Risk Assessment of Animal derived Raw Materials” produced by one of the major pharmaceutical companies
- WHO 2010 evaluation of cell substrates for the manufacture of vaccines and biotherapeutics¹⁷
- The report of a National Clinical Human Embryonic Stem Cell Forum meeting on prion disease contamination in human embryonic stem cell lines, in Edinburgh in March 2012 (see Appendix 4).

It was concluded that whilst SaBTO documents provide a good basis for the identification, reduction and mitigation of risk, and that additional testing of the donor may not be required, there may be special issues to address for the preparation of cell therapies.

4.2 General principles

4.2.1 Risk assessment

It is recommended that the risk assessment process should follow the principles of ICH Q9¹⁸ as enshrined in Eudralex Volume 4 Part III. Guidance on the use of a risk-based approach in the development of ATMPs, and the methodology to be followed, is also provided by the European Medicines Agency (EMA) Committee for Advanced Therapies (CAT).¹⁹

A number of issues are particularly important for the assessment of potential microbial contamination in cell therapy products.

A wide range of bacterial and fungal, parasitic and viral organisms occur in the environment and as normal body flora in humans. These vary widely in their ability to

¹⁷ WHO (2010) Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks. Proposed replacement of TRS 878, Annex 1. WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Published at

http://www.who.int/biologicals/Cell_Substrates_clean_version_18_April.pdf

¹⁸ ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Quality Guideline 9. Published at

<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>

¹⁹ The guidance is published at

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139748.pdf

cause infections in patients receiving cell therapy, from being overtly pathogenic to having no known adverse impact on human health.

Some groups of organisms are known to be opportunist pathogens causing disease in compromised patients and it would be expected that patients undergoing cell therapy, especially where the patient is immunocompromised, would fall into this risk group. In such cases those organisms known to commonly cause infection in immunocompromised patients should be considered in the development of regimes for donor screening and/or testing of starting cells as appropriate, to reduce the risk of infection to levels acceptable for the specific therapy²⁰.

Whilst cell therapy patients would be subject to clinical surveillance and any potential infection managed according to best clinical practice, those infections which lack an effective clinical response may need to be prioritised in testing regimes for sourced cells and tissues.

All microbial detection methods applied to cell therapies would need appropriate validation and control to give assurance on reliability, particularly in respect of sensitivity, specificity and robustness of the methods used for each product.

4.2.2 Microbiological contamination of the donated tissue

Risk assessment should focus on those organisms most likely to be present as contaminants in the original tissue and, where cell culture processes are used, those that may persist in cultured cells and/or transform them.

Typically medicinal product cell therapies are subjected, via Good Manufacturing Practice (GMP), to manufacturing practices and controlled environmental conditions whose purpose is to protect the product from the environment and so help assure the integrity and sterility of the final product. In addition sterility testing is required as one of the finished product release tests which evaluates the integrity of the overall processing of the cell therapy product and thus will alert the manufacturer to an elevated risk of endogenous or exogenous contamination with bacteria and/or fungi.

²⁰ For reviews of infections that may arise in immunocompromised patients see: (1) Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H, Ljungman P. Fourth European Conference on Infections in Leukaemia (ECIL-4): [guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus](#). Clin Infect Dis. 2013 Jan;56(2):258-66; (2) Cunha BA. [Central nervous system infections in the compromised host: a diagnostic approach](#). Infect Dis Clin North Am. 2001 Jun;15(2):567-90. Review; (3) Englund J, Feuchtinger T, Ljungman P. [Viral infections in immunocompromised patients](#). Biol Blood Marrow Transplant. 2011 Jan;17(1 Suppl):S2-5. doi: 10.1016/j.bbmt.2010.11.008; (4) Mueller NJ, Fishman JA. [How should we evaluate organ donors with active or prior infections?](#) J Hepatol. 2006 Oct;45(4):507-13.

Mycoplasma and Acholeplasma are known to replicate effectively in cell culture, and thus testing for these organisms by Pharmacopoeia methods will typically form part of the routine screening of cell banks and cell-based products should there be a realistic risk of contamination with these organisms. In addition, manufacturing risks are considered during clinical and marketing authorisation assessments under the Quality and Safety aspects of the product.

However, other bacteria are known to be capable of replication to significant levels in cell culture without being evident from standard sterility test results (e.g. leptospira, mycobacteria). Whilst methods for comprehensive screening of cell therapy products for bacteria and fungi using a single test are not currently available (though see section 5.4 on Whole Genome Sequencing), molecular tests for screening, such as nucleic acid testing for the presence of evolutionary conserved 16S ribosomal DNA sequence common to all pathogenic and non-pathogenic bacteria and fungi, may be considered, subject to validation for each product. Molecular testing may be more sensitive and is often more rapid than conventional culture and will pick up microorganisms which will not grow on conventional media. Regular inspection of cell cultures by microscopy as part of good cell culture practice²¹ is also recommended to assist in the detection of such contaminants and should be part of routine safety screening throughout the processing of cell therapy products involving cell culture.

4.2.3 Latent viral infections

Viruses which can cause latent infection in humans are not uncommon and under certain circumstances they may become reactivated (e.g. human CMV, Varicella-Zoster, herpes simplex virus [HSV]) and cause infection in recipients of affected cell therapies. To address this issue the cell therapy developer / manufacturer will need firstly to ensure that donor selection would identify any special circumstances which may indicate risk factors associated with such infections and secondly, implement screening of donor material or cell lines as they consider appropriate for the particular clinical application.

²¹ For example, Coecke S, Balls M, Bowe G, Davis J, Gstraunthaler G, Hartung T et al; Second ECVAM Task Force on Good Cell Culture Practice. [Guidance on good cell culture practice. a report of the second ECVAM task force on good cell culture practice](#). Altern Lab Anim. 2005 Jun;33(3):261-87.

4.3 Supplementary points to consider

It is recommended that the risk assessment process should include the key elements set out below.

4.3.1 Compliance with donor selection criteria

UK Blood Services use SaBTO and Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) guidelines for the selection and screening of donors (SaBTO, 2011 – 2013²²; Guidelines for the Blood Transfusion Services in the UK²³). If it should be found that not all donor selection criteria were assessed or microbiological assays undertaken (for example in embryo donors where considerable time may have passed between the original donation and the release for hESC line development), consideration should be given to risk assessment and / or a derogation from the relevant regulatory authority. If validated tests are available it may be possible to test the cell line rather than re-test the donor(s).

4.3.2 Living versus cadaveric donors

Cadaveric donations are generally considered to be suboptimal for the purposes of cell therapy due to the higher risk of microbial contamination, potentially poorer cell viability and quality, and raised potential for the presence of inhibitors of nucleic acid amplification tests. Living donors are therefore preferred as a tissue source for the preparation of cell therapies where possible.

For living donors, the risk of organisms causing acute infection can be minimised where there is a follow up with the donor 14 to 21 days after donation²⁴. This would aim to establish sustained symptom-free status and would mitigate against the large majority of acute microbial infections. However, there may need to be microbiological screening for infections that would remain asymptomatic in the donor after that time.

²² (1) SaBTO Guidance on the Microbiological Safety of Human Organs, Tissues and Cells Used in Transplantation, published February 2011 at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215959/dh_130515.pdf;
(2) Donor Selection Criteria Review, published September 2011 at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216109/dh_129909.pdf;
(3) Tissues and Cells: MSM Donor Selection Review, published October 2013 at <https://www.gov.uk/government/publications/donor-selection-criteria-for-men-who-have-had-sex-with-men>.

²³ Guidelines for the Blood Transfusion Services in the UK, published at <http://www.transfusionguidelines.org.uk/index.asp?Publication=RB>.

²⁴ If the results of any initial tests are positive, there may be mandatory follow up requirements.

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Under these circumstances, the residual risk from live donors is most likely to arise from subacute viral infections that could be present in the source tissue, such as persistent viruses; and where cells from the tissue are cultured, consideration of risk would focus on those organisms that might replicate in the cell or tissue processing (most likely cell culture) or cause cell transformation (exemplars are given in the list of tissues in Appendix 3).

Where cadaveric donors are proposed, measures will be needed to ensure avoidance of likely contamination arising following death and to address the likelihood of acute infections that cannot be mitigated by post donation review of the donor, as well as consideration of those subacute infections to be addressed for live donors as already discussed.

4.3.3 Microbial hazards specific to the selected tissue

Each tissue source needs to be considered at three stages, 1) primary tissue, 2) cultivated cells at limited passage and 3) undifferentiated iPSC and hESC or other cell lines. Organisms likely to persist and potentially replicate *in vitro* or cause cell transformation would need to be considered for any cell therapy product involving a cell culture process.

In any proposed risk assessment process, patient treatment options to combat infection will also need to be considered, ranging from situations where there is standard effective treatment to those where there is no effective treatment.

Where tissues are sourced from outside the UK or where there is evidence that the donor had a history of extensive or recent foreign travel, additional potential contaminants may need to be considered including a range of parasitic infections due to organisms such as Plasmodium, Histoplasma, Filaria *etc.* For imported human tissues, manufacturers should also assure compliance with the relevant HTA Guidance²⁵.

4.3.4 Microbial hazards potentially occurring in all tissues

Organisms such as mycoplasma, other bacteria, fungi and persistent viruses could be present in any tissue and may require the application of screening tests. Such testing may include specific polymerase chain reaction (PCR) and European

²⁵ HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment, November 2010. Published at http://www.hta.gov.uk/db/documents/Annex_-_Guide_to_Quality_and_Safety_Assurance_for_Tissues_and_Cells_for_Patient_Treatment.pdf

Pharmacopoeia testing for mycoplasma, 16S ribosomal RNA amplification for bacteria, and molecular tests for fungi and the most likely persistent viruses.

4.4 Whole genome sequencing (WGS)

A number of viruses could or are known to arise in source materials (reagents and cells for cell therapies) by contamination of cell culture reagents of animal origin, and some are capable of infecting human cells or could adapt to cell culture or interact with other viruses creating new hazards. Cell therapy patients may often be immunocompromised and more susceptible to viruses which might not normally cause infection, or could establish non-cytopathic, yet significant, biological effects. Although the likelihood of these hazards may be low, they need to be addressed in risk assessment. However, standard techniques have demonstrably failed to provide a comprehensive safety screen against virological contamination in cells used to manufacture vaccines, which has subsequently been identified through the application of WGS of raw materials and/or cell cultures. This technology has enabled identification of numerous new and unexpected contaminants, including previously unknown agents and genetic variants of an original virus missed by the established PCR screen for that virus target.

This clear evidence that WGS provides a screening method that can enhance product safety has led to its rapid uptake in industry to screen cell lines used in manufacture.

WGS could potentially drive a completely new approach to safety testing of cell therapies, capable of detecting any microbial contamination, known or unknown. However, in the absence of commonly available reference materials and recommendations on approaches to test control, there remain significant scientific issues relating to its use for safety testing. Key challenges are:

- The veracity of a “negative” result
- Optimisation of sample preparation (to identify any bias in isolation of different agents)
- The potential bias in sensitivity of detection for the range of potential contaminants.

These issues need to be addressed if this powerful technology is to be used with confidence to assure the acceptability of cell therapies.

4.5 Special considerations for human stem cell lines

Issues for hESCs could be developed as an extension of considerations for reproductive tissue (for hESCs) and hiPSCs from the tissue of origin (cord blood, skin and epidermal fibroblasts). The propensity for contamination and propagation of virus in differentiated cultures from stem cell lines may be different to that in undifferentiated lines. It is possible that undifferentiated cells may be more resistant to certain infections, as they do not express a mature tissue phenotype: this may need to be assessed, and possibly addressed with additional testing, depending on the assessment of risk of contamination in the context of the overall manufacturing process and sourcing of raw materials.

The practice of culturing stem cell lines on a layer of human feeder cells is likely to continue for some time in early hESC derived products. The use of non-human feeder cells is not considered desirable, primarily due to the risks of severe patient immune reactions to non-human glycoproteins and the potential presence of animal viruses. Human feeder cells would need to be risk assessed in much the same way as the cells to be used in therapy.

4.6 Additional considerations

The excipients and raw materials used in the cell therapies may need special consideration from a microbiological risk perspective²⁶, but whilst not specifically the subject of this group's consideration, a draft for risk assessment of certain high risk reagents, consisting of three stages (based on ICH Q9), is proposed as follows.

4.6.1 Risk identification

Identify groups of adventitious viruses potentially present in the material. In addition, monitor reports and publications for new viruses, for example those discovered

²⁶ WHO (2010) [Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks](#). Proposed replacement of TRS 878, Annex 1. WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland

through WGS. The likelihood of the presence of such agents should be evaluated; if considered necessary, include them in the risk assessment process.

4.6.2 Risk reduction

The risk of contamination can be reduced by using various established measures. Ongoing collection of inactivation data from viral clearance experiments (e.g. γ -irradiation, low pH) is important, in order that treatment regimes can be implemented that are effective for a broad range of potential contaminants.

4.6.3 Risk mitigation

Such measures will enable the residual risk to be defined, for which a control strategy can be developed. For example, the geographic source of materials can be controlled to reduce the risk of contamination with significant agents that may be prevalent in particular regions, while testing may be extended to viruses highlighted in the risk assessment through liaison with the suppliers of the material.

4.7 Prions and prion infectivity

Prion infectivity is generally associated with abnormal prion protein. Although the molecular basis of infectivity is not finally established, the generally accepted view is that an abnormal form of prion protein (of which there are several) is either the infectious agent (the 'prion') or the principal component of it.

Until the prion is fully characterised, there will be no definitive detection method for the infective agent itself. Detection of infectivity therefore depends on either the detection of a form of abnormal prion protein as a correlate of infectivity, or the demonstration of infectivity via animal transmission experiments. Some protein detection methods (eg PMCA, RT-QuIC²⁷) may distinguish abnormal and normal prion protein forms, but many do not and, therefore, require the removal of normal prion protein before testing (relying on the generally different physico-chemical characteristics of the protein forms). It should be restated that there are potentially several species of abnormal prion protein with different sensitivities and uncertainty

²⁷ Two amplification technologies used in testing for abnormal prion protein: Protein Misfolding Cyclic Amplification (PMCA) and real-time quaking-induced conversion (RT-QuIC).

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as to the key infective species. In addition, the amount of abnormal prion protein present in biological fluids or tissues may be below the sensitivity of standard detection methods, requiring concentrating or amplification processes as a preliminary step to detection. There are different forms of human prion disease: sporadic, variant or iatrogenic Creutzfeldt-Jakob disease (CJD) and genetic prion disease. Sporadic and iatrogenic CJD and genetic prion disease occur worldwide and therefore the potential for contamination of cellular products should be considered a global problem.

Possible sources of prion infectivity in cell-lines and cell-based products are:

- Donors
- Accidental introduction of infectivity during growth and processing
- Gene / protein changes in cells in culture.

4.7.1. Donors

It is assumed that clinically ill individuals are readily identified and do not act as donors.

Sporadic CJD (sCJD)

This is rare and typically affects the middle-aged and elderly. There is no known significant pre-clinical infectivity phase in non-central nervous system tissue; infection appears to start centrally and spread centrifugally only in later disease stages.

Genetic Prion Disease (gPD)

If a potential donor has a family history of gPD, they should either be excluded or accepted only if *PRNP*²⁸ mutation testing is negative. The chance that a well donor, without a known family history of gPD, would be a prion mutation carrier is extremely small.

²⁸ *PRNP*: the gene that encodes prion protein in humans.

Iatrogenic CJD

Individuals 'at risk' (from blood, human growth hormone etc) are identifiable in general and have been notified of their status, so can be eliminated in donor selection.

Variant CJD (vCJD)

Subclinical variant CJD (vCJD), originally arising from infection with bovine spongiform encephalopathy (BSE), is the major concern within the UK.

There is agreement that, for the purposes of public health considerations and policy, approximately 1:2000 of the UK general population should be considered as subclinically infected (and potentially infective) with BSE/vCJD. This is based on the study of surgical appendix specimens, and further studies are planned to attempt to clarify whether this figure is a true index of the frequency of subclinical infection in the population. There are no published prevalence studies of subclinical infection outside of the UK population on which to base comparable risk estimations for non-UK countries. The level of past dietary BSE exposure in non-UK populations is uncertain, although it is highly likely to have been significantly lower in many countries. Although there are published tables of BSE risk, surveillance for BSE is very limited in some countries. International cattle BSE and human vCJD data suggest a lower risk in some countries (such as France) and an arguably negligible risk for some countries but, for a variety of reasons, it is not valid to simply extrapolate from cattle BSE figures to human infection prevalence. It is possible that tissue donors may originate from outside the UK and it is very difficult to accurately evaluate the level of risk from these donors.²⁹

The risk of dietary infection in the UK is age-related. The first dietary precautions were established in 1989 and clinical vCJD has not been identified in the UK in an individual born after 1989. Further measures were put into place in 1996 and dietary BSE exposure is considered very unlikely in those born after this year. They, and UK cord blood donors (see below), are therefore likely to be at very low risk of subclinical

²⁹ (1) Sanchez-Juan P, Cousens SN, Will RG, van Duijn CM. [Source of variant Creutzfeldt-Jakob disease outside United Kingdom](#). Emerg Infect Dis. 2007 Aug;13(8):1166-9 and (2) Brandel JP, Heath CA, Head MW, Levavasseur E, Knight R, Laplanche JL et al. (2) [Variant Creutzfeldt-Jakob disease in France and the United Kingdom: Evidence for the same agent strain](#). Ann Neurol. 2009 Mar;65(3):249-56. doi: 10.1002/ana.21583.

CJD infection. Other routes (non-dietary) of potentially relevant exposure are: certain types of surgery, blood / blood product treatments, dentistry, and maternal. To date, only blood and blood products have been implicated in actual instances of transmission. The others remain theoretical, and maternal transmission in human prion disease has never been reported despite known pregnancies in affected mothers. It also seems unlikely that a hESC line could be infected from the parental donors during the IVF process.

The tissue distribution of infectivity in clinical cases of vCJD has been published.³⁰ The distribution of infectivity in subclinical cases is not clear but there is evidence for infectivity being present in blood, tonsil, spleen, appendix and lymph nodes. While it is reasonable to assume, as a precaution, that all tissues could carry a risk of transmitting disease, the risk of infection of an iPSC line may be related to the presence or level of infectivity in the tissue from which it is derived. Thus one may expect a greater risk of any form of CJD from neural tissue than from, say, skin or blood. Similarly, there are potentially different considerations depending on the eventual use of a product. For example, cells or products destined for central nervous system use would probably carry a greater risk of transmission of prion disease if infectivity were present, and with a shorter incubation period.

In relation to possible donor testing, there are vCJD tests in development, or being assessed, in clinically symptomatic patients, that may, or may not, be useful in subclinical infection as well. Tests for prion protein / infectivity in development need to be considered but need to be assessed for sensitivity and reliability in this context.

Current UK donor selection policies mean that individuals with a family history of genetic prion disease are excluded from donating blood, cells, tissues or organs. Similarly, those who have received a blood transfusion are excluded from being blood donors, because of the potential for blood exposure to vCJD from the donor.

4.7.2 Special considerations for cell lines proposed for use in human therapy

It is probable that all cell lines express some prion protein and may thus be susceptible to amplification of abnormal prion protein. Certain variants of the native protein are known to be more susceptible to conversion to the abnormal prion state, and cell therapy developers / manufacturers may wish to consider this when

³⁰ WHO 2010 Report No WHO/EMP/QSM/2010.1
(www.who.int/bloodproducts/tablestissueinfectivity.pdf)

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selecting cell lines for therapy. Appropriate spiking experiments simulating the cell banking and production processes, analysed by a quantitative or semi-quantitative assay for abnormal prion protein, may be useful in providing an indication whether prion protein amplification in the selected cell culture system would, or would not, occur.

Raw materials used to derive and culture cell lines need to be assessed and selected to minimise the risk of prion disease contamination. The donors of human feeder cells also need to be subject to the same considerations of selection and screening as those of the manufacturing cell line.

4.7.3 Accidental introduction of infectivity during growth and processing

This is not considered here, but is part of the regulatory assessment process for medicinal products during Clinical Trial and Marketing Authorisation Applications.

4.7.4 Gene / Protein changes in cells in culture

There are two theoretical possibilities: the development of *de novo* PRNP mutations during cell growth and division, and the spontaneous development of abnormal prion protein during normal cell protein production. Both are considered highly unlikely phenomena.

4.7.5 Other comments

As has been noted above, the potential for CJD contamination of cellular products is a global issue. In comparison to the risks arising from the general uncertainties about certain therapies (especially for central nervous system disease), the nature of the diseases being treated and the other potential risks of treatment, it might be argued that the small and possibly long term risks from prion infection are relatively insignificant. While difficult to accurately quantify, the risk posed by prion disease in this context is likely to be significantly less than many of the other risks considered in this report.

Given the dietary protective measures in place in the UK combined with the currently very low level of BSE in UK cattle, there is good reason to consider that the risk of prion infection is very low in the UK general population born after 1996. To date, no case of vCJD has been reported in the UK in anyone born after 1989 (when the main dietary protective measures were put in place) and further dietary protective

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measures were introduced in 1996. Although it cannot be stated that those born after 1996 have no risk of BSE/vCJD infection, the risk is likely to be extremely low.

The above considerations do not significantly conflict with, or add to, the SaBTO 2011 *Guidance on the Microbiological Safety of Human Organs, Tissues and Cells Used in Transplantation*. They do not necessarily provide more specific information than the summary of the NChESF meeting in Edinburgh in March 2012 (see Appendix 4). Human medicinal products must comply with the 'Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products' (EMA/410/01 rev.3)³¹.

³¹ Published at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf.

5 Genetic risks associated with cellular therapies

The genetic risks that might be associated with cellular therapies are as yet unknown. Whilst it is clear that there must be some theoretical risk, this cannot be quantified with certainty. Thus the assessment of risk is based on previous information about similar procedures and an understanding of the underlying scientific knowledge, including its limitations.

Therefore we addressed the following questions.

In relation to the genetic risks, we started by reviewing current practice in similar fields. Specifically we have addressed the following questions.

1. What are the genetic selection procedures for blood, bone marrow and organs including gametes (international)?
2. Why are the genetic selection procedures done for blood donors?
3. Why are genetic selection procedures done for gamete donors?
4. What is the relevance of these screening processes for stem cell lines?
5. What is the relationship between genetics and function of the stem cells donated?

In recognition that there are genetic differences between populations, we considered the effect this would have on international collaborations and commercial implications.

There is a potential risk that a genetic abnormality in the donor will give rise to a product which may cause disease or donated cell malfunction in the recipients. Since this is only theoretical at present, we reviewed evidence from previous practice of donation of cells, tissues and organs. Specifically, we addressed the following questions.

1. What is the evidence of a disease other than infection being passed from donor to recipient?
2. Does this have a genetic basis and would screening of the donor alter potential risk?

Finally, we looked at the new techniques e.g. WGS for genetic analysis, to address their relevance to the screening and selection of donors.

5.1 Review of current practice

5.1.1 What are the genetic selection procedures for blood, cells, tissues and organs including gametes (international)?

The regulatory procedures for the genetic selection of blood, tissue and organs are long standing and have been subject to considerable review over many years. There is international consensus about these procedures which enables the transfer of donations across international boundaries. The current regulations for genetic screening of donors of blood, cells, tissue and organs are listed in Appendix 5 and of gamete donors in Appendix 6.

There are no current regulations related to genetic analysis for the accreditation of cell lines for therapeutic use.

5.1.2 Why are the genetic selection procedures done for blood / cell / tissue / organ donors?

The primary aim of the current regulatory screening tests is to identify the risk to the donor of the donation process; e.g. someone with a bleeding disorder would be a high risk living organ donor but not a high risk *post mortem* donor. Medical history of the donor is taken primarily to assess the risk of transmissible disease (infection).

There is evidence that other professional groups are discussing the genetic screening of donors. The American Association of Blood Banks (AABB) provides the following recommendation.

“Screening for Family Medical and Genetic History

Cord blood collection facilities should consider screening their cord blood donors for genetic disease risk. Adult cellular therapy donors would have the knowledge of a diagnosis of a genetic disease that can be transmitted, however in the case of cord blood donors the baby may not yet manifest disease characteristics and cannot be tested for the presence of every genetic disease. Therefore, the mother, father, baby’s siblings, baby’s grandparents, and baby’s mother’s or father’s siblings’ history must be obtained to evaluate for genetic disease risks. Some suggested disease categories to include when performing genetic screening are: Cancer or leukemia,

Genetic risks associated with cellular therapies

Red Blood Cell Diseases, White Blood Cell Diseases, Immune Deficiencies, Platelet Diseases, Other Blood Diseases, Hemoglobin Problems, Metabolic/Storage Diseases, Acquired Immune System Disorders, or other serious or life-threatening diseases. Several sources, including the transplant center physicians, should be consulted in the process of creating a Family Medical and Genetic History Questionnaire.”

ABO (blood group) and HLA ([human leucocyte antigen] tissue) typing of the donor is carried out to assess the rejection potential and will be relevant to the selection of allogeneic donors for cellular therapy for the same reason.

Genetic tests for specific abnormalities are carried out and it could be relevant to consider testing of donors of cells for cellular therapy if the final use were restricted to specific predictable functions.

5.1.3 Why are genetic selection procedures done for gamete donors?

The risk that a child will be born with a congenital abnormality after spontaneous conception is about 2-3%. The majority (around 80%) of these are sporadic or multifactorial including both genetic and environmental factors. Of the remainder most relate to *de novo* genetic variations in the conceptus, whilst a very small minority relate to a genetic variation in the parents.

The Regulations and current practice for genetic screening of gamete donors place emphasis totally on the risk to the potential child. Screening is done by question and testing.

It is relevant to note that the screening results are reviewed by professionals and there are no absolute exclusion criteria given. In practice there is flexibility for clinical judgment, risk assessment and patient choice.

5.1.4 What is the relevance of these screening processes for stem cell lines?

Karyotype

In vivo created embryos have a high rate of genetic (chromosome) abnormality (more than 50%).³² The implantation potential (baby per transferred embryo) in routine IVF

³² Fragouli E, Alfarawati S, Spath K, Jaroudi S, Sarasa J, Enciso M et al. [The origin and impact of embryonic aneuploidy](#). Hum Genet. 2013 Sep;132(9):1001-13. doi: 10.1007/s00439-013-1309-0. Epub 2013 Apr 26.

Genetic risks associated with cellular therapies

is about 20%. Most of those embryos donated for the derivation of hESCs will not develop and it is likely that many will have genetic abnormalities. The successful derivation of hESC lines probably selects those of relatively normal genetic composition. Of the 24 hESC lines in the UK Stem Cell Bank, 23 have a normal karyotype and one was selected to have a cystic fibrosis mutation. Detailed genome analysis of the lines is not routinely carried out. Anecdotally, the differences in culture requirements and differentiation potential suggest that there are probably similar genetic variations between these lines as are seen in the general population.

Most donors of embryos (despite representing the infertile population) for hESC derivation will be healthy thus genetically normal, and since the rate of abnormality in the embryos is so high, the relative value of karyotype screening of the donor is limited.

Genome analysis

Selected or whole genome screening of the cell lines may be relevant for both hESC and iPS cells or other stem cell products because of the high rate of *de novo* genetic variation in hESC as described above.

There is evidence of a high rate of genetic and epigenetic abnormality in pluripotent stem cell lines. Whilst the detection of a genome variation in a donor is likely to mean that this variation is present in the stem cell line, the presence of a normal genome in the donor does not indicate that the cell line will be normal. The genetic risk to the line will mainly relate to the derivation and culture process, not the genetic normality of the donor.

5.1.5 What is the relationship between genetics and function of the stem cells donated?

There is a relationship between the molecular basis of the maintenance of stem cell function (pluripotency), the ageing process and the origin of some cancers. This is linked to mitotic errors in cell growth and division and so has a genetic basis.

It is likely that mitotic errors will influence the function of the stem cells (and derived therapeutic products) but this is still an area of uncertainty.

5.2 Genetic variation in different populations

It is accepted that there are genetic variations between geographically separated populations that have health implications. In the context of this paper, the relevance is that, if selection by screening or testing is recommended, then the specific tests will need to be modified for different populations.

It is noted that the differences in infection risk geographically (e.g. prion risk) already have had an impact on the commercial potential of health products. This is less likely to be an issue for genetic risk because specific genetic tests are likely to be available if there is a known clinical association.

5.3 Risk posed by genetic abnormality in the donor

5.3.1 What is the evidence of a disease other than infection being passed from donor to recipient?

The use of stem cell therapies and ATMPs (i.e. to multiple recipients) is not yet widespread thus the risk of transmission of pathology of genetic origin is unclear. But cell, tissue and organ transplants have a long history and there is information about the risk of such donations.

A review was carried out to ask the following questions:

- Under what circumstances is 'foreign' DNA found in a recipient?
- Are there any reports that this causes problems?
- What are the long term outcomes / complications (e.g. cancer) of (i) solid organ transplant (ii) bone marrow transplant?
- Have any of the problems been associated with genetic problems in the donor cells?

The result of this review is in Appendix 7. The summary conclusions are that the co-existence of donor cells within a recipient on a long term basis (chimerism) has not been considered to be a pathological state. Conversely there is evidence that it might confer benefit in the transplant situation.

There is an increased risk of cancer in recipients of donated cells, tissues or organs. Most of this risk relates to recurrence of primary tumours in the recipients or is

presumed to be related to immunosuppression therapy. The risk of donor origin cancer, derived or transmitted, is 0.06%.³³).

5.3.2 Does a transmitted pathology as above have a genetic basis and would screening of the donor alter potential risk?

Whilst the evidence available does not indicate that there is a significant risk to the recipient from a genetic variation in the donor, this evidence has come mainly from individual donors to individual recipients. Furthermore, there is little evidence that this has been specifically investigated as a potential risk factor. The use of ATMP to multiple recipients may give the evidence required in the future.

There is not a clear separation between transmission of disease by a specific organism (e.g. virus) and transmission by genetic abnormality e.g. protein misfolding diseases³⁴. In some cases the genetic test is specific and the related risk well defined, whilst in others they are uncertain at present.

5.4 What is the relevance of whole genome sequencing (WGS) to current or future pathology?

The context of this review must be within an understanding of the relationship between the genome and health. This is beyond the scope of this paper but relevant points are given in Appendix 8. In summary, the relevance of WGS for individuals is still highly debatable, with environmental factors probably playing a more important role in health. The same argument may apply to stem cell lines, i.e. the culture environment and the transplant niche may be more relevant to the outcome than the genome of the donor.

5.5 Other points for consideration in the formulation of recommendations

³³ Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. [Cancer transmission from organ donors - unavoidable but low risk](#). *Transplantation*. 2012;94(12):1200-7.

³⁴ Reynaud E. [Protein Misfolding and Degenerative Diseases](#). *Nature Education* 2010; 3(9):28

It is not possible to make sense of genetics unless there is a specific clinical question to ask. In relation to ATMPs, the question relates to the function and safety of the therapeutic product and how this relates to the risk / benefit for the recipient.

The number of genetic variations is infinite and each has a different clinical implication.

There is the possibility that the genetic basis of pathology will be better understood in the future.

It is likely that the interpretation of genetic variations on cell function will acquire better significance in the future.

There are practical implications for donor screening because of the time distance between the donation and the potential use of the cells. Also not only will the final use of the cells be uncertain for a long time period, but the use may vary over time. If any genetic tests are recommended, then consent for retrospective WGS will be needed.

Should recommendations be made about the genetic testing of the final ATMP, i.e. the differentiated cells before use on each treatment or each batch? This would be similar to the testing of drugs. There is no information yet about the genetic testing criteria for differentiated products (rather than stem cells).

Since these are new treatments, long term follow up studies are required.

5.6 Recommendations

5.6.1 Possible options for recommendation for potential regulation are (individually or in combination):

- Whole genome screening for donors
- Whole genome screening for some donors e.g. where donated cells may be dispersed throughout the body and settle in different niches rather than be in a distinct site
- Genetic history for all donors
- Genetic history for some donors
- Specific genetic test for some donors

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- No genetic screening for donors and relevant genetic tests would be done on the stem cell lines/derived product.

5.6.2 The recommendation is that no genetic screening should be carried out on donors and that relevant genetic tests should be done on the stem cell lines/derived product, for the following reasons:

- There is a significant genetic distance between the donor and the ATMP. Thus routine donor selection or screening (by history or testing) for genetic variation is unlikely to be relevant.
- It would be commercially prudent to undertake selection and screening of the donor to avoid unnecessary expense in the production of a product that may subsequently have a limited market. This would be a commercial decision not a regulatory requirement.
- Tests are recommended on the ATMP that would be determined by the required function of the product and the indications for use. Given the complexity of the options, this would have to be individually risk assessed by the producer and by the clinician / patient.

With the exception of a few specific cases, there is uncertainty about the relationship between genetics and disease and if a decision was taken in principle to regulate genetic testing, the recommendations would be likely to become outdated / challenged in a rapidly moving complex field. There is therefore a risk that premature regulation in this uncertain area may stifle a new technology that has significant therapeutic potential.

6 Informed consent and traceability

Some of the most challenging aspects of cellular therapies concern informed consent and traceability. The rapid pace of progress and increasing variety and complexity of technologies and products are testing both the regulatory environment and established practice. Clearly, the duty of care owed to donors and recipients must be upheld, which means that safety and quality remain paramount, but this needs to be done in such a way that it does not stifle development. In such a rapidly evolving field, there will always be a delicate balance between these three factors: the duty of care owed to donors; the duty of care owed to recipients; and the development and regulation of the technologies.

In the meantime, a number of open issues remain, including: those relating to traceability; the implications for the donor in the event of identification of known or novel infectious or genetic disease markers, either at the time of donation or at any time in the future; the implications for potential previous recipients of the development of post-donation disease in the donor which may have an infectious or genetic basis; the extent to which the development of clinical problems in recipients may have implications for the donor and/or his/her family; and the nature of informed consent from a donor's perspective, and whether or to what extent they should be able to waive feedback.

In order to consider these open issues, our approach was to:

1. prepare worked examples, which illustrate the characteristics of products - current and potential – with increasing levels of complexity and numbers of recipients exposed to them;
2. plot these examples on a matrix, to show the extent to which each example raises concerns in relation to regulation, traceability and ethics / consent; and
3. through analysis of the matrix, identify common themes or overarching principles which might help address the open issues, in addition to providing guidance to cover future products or situations.

This approach necessarily included a review of current relevant regulations, existing consent and traceability processes, and current industry practice. We have tried to avoid being overly prescriptive, instead drawing out general principles. Although

cellular therapies initially appear disparate, use of the matrix as a framework helped identify common topics which should have relevance well into the future.

6.1 Worked Examples

The spectrum of cellular therapies is wide-ranging, from minimally manipulated cells to complex biological systems, with the different EU directive requirements that may apply as described in section 3.4. To illustrate some of the characteristics of these products, we prepared worked examples, with increasing levels of complexity and numbers of recipients exposed to them. They are also at different stages of clinical use. We started with some examples which are already established procedures, as they illustrate the current approach to issues of consent and traceability in cellular therapies. These are, generally, most straightforward; there is usually a donor:recipient relationship of 1:1 – and often the donor is also the recipient of the therapy. We then worked through examples which are increasingly complex, either because of the amount of cell manipulation, and/or the length of the storage time, and/or the number of potential recipients. Some of these examples are entering clinical trial, while others are still at research stage. But given the accelerating pace of development, it may not be long before the more complex, currently theoretical examples pose practical questions.

Summaries of the examples follow, but a detailed narrative and full discussion of the consent and traceability issues of each can be found in Appendices 9 and 10, and a summary in Appendix 11.

Category 1: minimally manipulated cell therapies

- *Example 1A – Autologous haematopoietic stem cells, for donor's own treatment*

HSCs are removed from the mobilised peripheral blood of a multiple myeloma patient as part of standard treatment. They are stored while she receives large doses of chemotherapy, in an attempt to cure the disease, after which she receives her own cells back in an infusion.

- *Example 1B – Allogeneic haematopoietic stem cells from a matched donor*

A man with acute myeloblastic leukaemia requires a transplant of healthy cells as part of his therapy. There are no appropriately matched siblings. He is therefore matched with a donor on the registry of people willing to donate

HSCs. Cells are collected from the donor through their mobilised peripheral blood and transplanted to the patient.

- *Example 1C – Allogeneic cord blood from an altruistic donor*

A pregnant woman is under the medical care of a hospital which offers women the opportunity to donate cord blood after the birth of their babies. This will be an altruistic donation, held in the public cord blood bank, and transplanted into matched patients when required.

- *Example 1D – Autologous cord blood for potential use by the family of the donor*

Pregnant women can arrange to have their cord blood collected and stored by a private cord blood bank. In this case, it is being stored for possible autologous use in the future should the child develop a condition treatable with their own cord blood.

- *Example 1E – Autologous immature gametes*

A 10 year old girl is about to embark on treatment for Hodgkin lymphoma which may leave her infertile. Immature gametes are collected from her, in the form of ovarian cortical slices. These are frozen and stored until such time that she decides to use them – possibly many years later. If they are transplanted, they are completely unmodified. They are thawed and given back to the same person who donated them.

Category 2 – Somatic cell therapies

- *Example 2A – Corneal limbal stem cells (autologous)*

A man has received chemical burns to one eye in an industrial accident. In an attempt to restore the sight of this eye, he undergoes a transplant of his own corneal epithelial stem cells taken from the limbal region of his undamaged eye. Between collection and transplant, the cells are isolated and cultured for a limited period of time *in vitro*.

- *Example 2B – Mesenchymal stromal cells*

A man suffering from life-threatening graft versus host disease receives injections of MSCs from an unrelated donor. The MSCs collected from the donor will have been isolated and cultured for a prolonged period of time *in vitro* prior to transplantation into potentially a large number of recipients.

Category 3 – Stem cell lines

- *Examples 3A & 3B – Induced pluripotent cells and human embryonic stem cells*

The final examples have been considered together, as many of their characteristics are shared: such cell lines will proliferate indefinitely in culture and can differentiate into most, if not all, of the cell types present in an adult. They therefore present the possibility of indefinite scalability and of a single donor contributing multiple cell or tissue products to multiple recipients over an extended period of time.

6.2 Examples plotted onto the consent and traceability matrix

After preparing the worked examples, we plotted them on a matrix, to illustrate where each product sits in relation to the others with respect to two key areas:

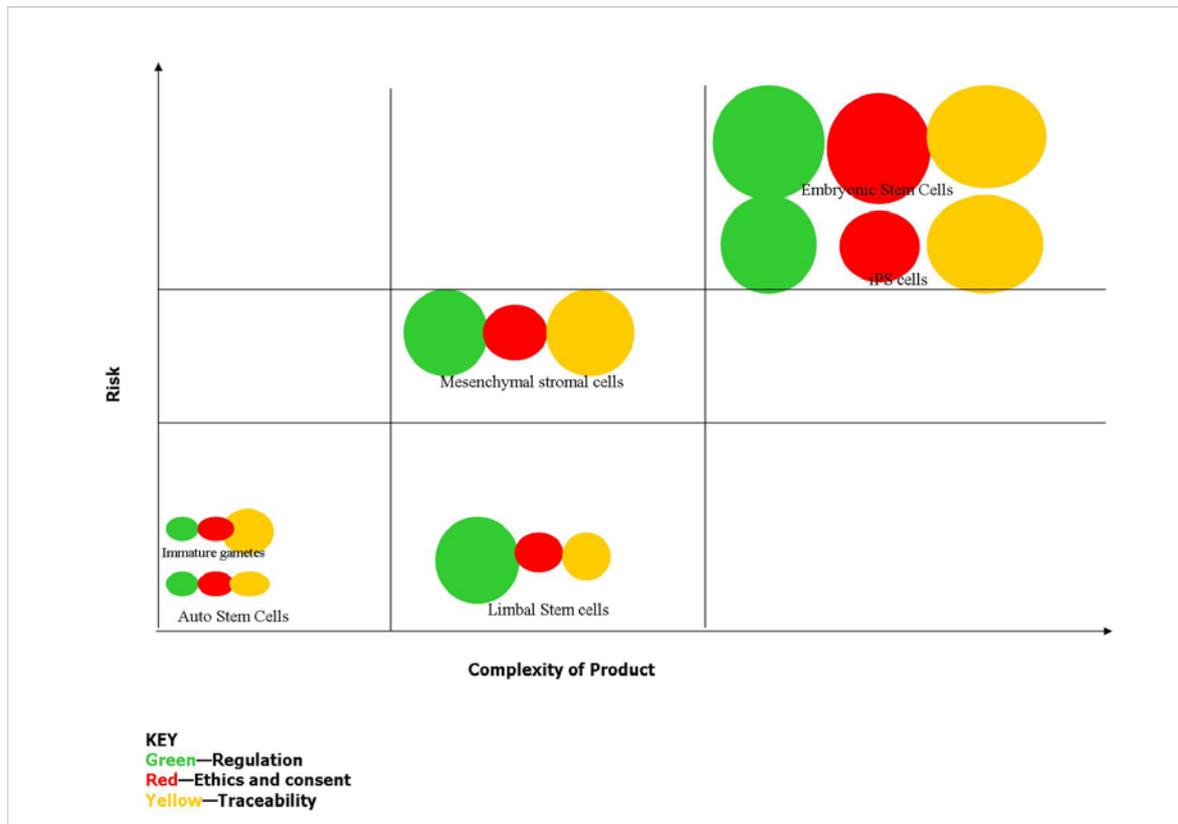
- the complexity of the product, and
- the potential risks of the product.

Generally speaking, as the complexity of each product increases, the number of recipients who might benefit from the product also increases. This relationship is a correlation rather than a causal one and is a broad generalisation. It can be assumed that in the current state of technology, simple (or relatively simple) products are usually given to one or very few patients. As the biological culture systems become more complex, the number of patients that could potentially be exposed increases significantly and it is envisaged that the number of patients that could be exposed to a product derived from a single biological system may reach thousands, or possibly even hundreds of thousands. Clearly, there are exceptions to this and some simple products can be given to large numbers of people.

Further, in an attempt to compare the issues involved within the different products, three key issues have been chosen:

- the *regulations* that govern each product (shown in green)
- the *ethical and consenting issues* surrounding each product (shown in red)
- *traceability* issues (shown in yellow).

Figure 1 – Consent & Traceability Matrix



The size of each coloured sphere is intended to reflect the complexity of each key issue considered. These are shown in the matrix above. Cellular therapies have been grouped in boxes and those that are in the same box are generally considered to have approximately equivalent levels of risk / complexity.

It is important to note that the chart above is an oversimplification since there is a considerable degree of overlap between the various products / categories. However, it helps to tease out the various complex issues involved.

6.3 Main themes and principles

As described above, we have analysed the worked examples thoroughly, and although consent can appear to be quite different in different circumstances, we have identified some common themes and overarching principles which might help address the open issues, in addition to providing guidance to cover future products or situations. These themes and principles are summarised below.

Some of our background work informing these principles is contained in the following documents:

- Appendix 9 – Worked Examples: Detailed Narrative
- Appendix 10 – Worked Examples: Donation Journey
- Appendix 11 – Worked Examples: a Summary.

However, before listing the main themes and principles, there are *two important background points* that should be noted:

6.3.1 It is essential that the subject of cell-based advanced therapies is discussed openly and transparently, in order to build growing and informed public awareness.

A basic way of complementing any consent process is to ensure that people have a sound, up-to-date and realistic understanding of the underlying subject. Early public education and engagement may help build a societal attitude that is open to the issues, and dispel some of the unease which may surround it. Commercial aspects of the subject are also regarded by the public with some suspicion, and education needs to stress the potential benefits of well regulated, innovative science to public patients in the UK. Open and transparent discussion would also reflect general trends towards increasing patient and public involvement in trials, which would suggest speaking to patients early on in trial design, and the growing momentum behind making scientific papers widely available irrespective of findings.³⁵

6.3.2 Consent is always a process, not an event

It is particularly important to stress this point when dealing with the donation and subsequent use of materials which could be separated by some considerable time and possibly place. For some cellular therapies, the consent process may be long and may involve a number of separate events or actions. For example, the provision of information to the donor is one of these actions, and the taking of consent is another, each part of the whole process.

³⁵ The Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, last amended in 2013, is an international policy initially accepted by the World Medical Association General Assembly in 1964. Paragraph 36 says: ‘Researchers have a duty to make publicly available the results of their research on human subjects . . . Negative and inconclusive as well as positive results should be published or otherwise made publicly available.’ It is published at <http://www.wma.net/en/30publications/10policies/b3/>

It is also important to appreciate the complications introduced by novel treatments which may mix research with therapeutic treatments. The terms of the research may dictate the information flows between a clinician and a patient, limiting the clinician's freedom to determine what, when and how information is given. In a 1993 article in the British Medical Journal entitled "Fully informed consent can be needlessly cruel"³⁶, the authors, cancer specialists, argued that giving all the information required by a patient to consent to participate in a clinical trial meant telling them too much about their poor prognosis and was "needlessly cruel". This tension between managing the information flows in order to allow a patient to make informed decisions to consent both to treatment and participation in a trial is challenging, because the information given in respect of each may vary. By extension, similar tensions can also be seen in situations where the initial donation of material may be for a completely different purpose; the couple undergoing fertility treatment, for example, where "spare" embryos might be available which could theoretically be used in cellular therapies in the future. In this case it is particularly important to ensure that the consent to donate is consistent with the choices the donors wish to make in relation to their on-going treatment and primary goal of having a child.

The main themes and principles pertinent to issues of consent and traceability in cellular products follow below.

6.3.3 Capacity to consent

We made the assumption throughout that we were dealing with adults with capacity to consent. In the case of children the legal position is less clear cut but we support the principle that children and young people who have the capacity to consent should be asked to do so. Where a parent is asked to consent on behalf of a young child who clearly does not have the capacity to do so, the parents need to be well informed about the present and future implications for their child, and be assisted in thinking through the issues raised by donation. It will be the parents' and the clinicians' responsibility to consider the donor child's best interests alongside those of any possible recipient. In some cases, the potential donor will be deceased and in such cases consent will be sought from family members. Current legislation, precedent and guidance covers capacity to consent, and is no different for donation of cellular material than it is for other forms of donation.

³⁶ Tobias JS, Souhami RL, Fully informed consent can be needlessly cruel. Meyerstein Institute of Clinical Oncology, Middlesex Hospital, London. BMJ. 1993 November 6; 307(6913): 1199-201.

6.3.4 Recording of consent

As with other forms of donation, the consent must be recorded, together with the fact that clear, sufficient information has been given and explained. In addition, for donations of cells which have potential use in cellular therapies, it may be appropriate to establish a Cell Therapy History File (CTHF) (see section 6.4.3) at this time; if so, then the detailed consent would be recorded in the CTHF.

6.3.5 Clear, sufficient information

It is essential that the people being asked to consent are given enough information on which to make their decision, and that the information is clearly presented and understood.³⁷ Written information needs to be presented in standard English, avoiding jargon and technical terms as far as possible. In line with a commitment to patient and public involvement, ideally potential donors would be involved in the production of Donor Information. The information may need to be communicated in both verbal and written form, and the fact that the information has been given and explained needs to be recorded. Due consideration must be given to the needs of those for whom English is not their first language, and in line with the requirements of the Mental Capacity Act the onus is upon those seeking consent to ensure that an individual donor's decision-making capacity is maximised.

In the provision of information, two particular factors to consider are:

- **Staff training** – Not only do the public need to be educated about the field of cellular therapies, but staff giving the information to potential donors and recipients need both to possess thorough knowledge of that information and to have 'bought in' to the programme. Staff need to be adequately trained and regularly updated. (There is a close parallel here with the importance of staff training to the recent progress made in increasing the numbers of organ donors.)
- **Time** – Whether in a research or a therapeutic setting, enough time needs to be given to donors and recipients to allow them to make an informed decision; this includes ensuring that teams are sufficiently resourced and that the entire process is well-supported.

³⁷ An example of the information centres should give donors before they consent to research and stem cell derivation is provided by the HFEA Code of Practice, Guidance note 22, including the additional requirements for stem cell research, published at <http://www.hfea.gov.uk/3468.html>.

6.3.6 Limits of certainty

As an emerging technology that is developing rapidly, uncertainty is inherent in many aspects of cellular therapies, including the exact therapeutic advantages that may follow; at any one time, there will be limits to the extent to which the risks and benefits can be identified and quantified. When people are being given information on which to make a decision, whether it is as a donor of cells or as a recipient of treatment with a cellular therapy, these limits of certainty should be communicated to them, as part of the consent process; and it is important to manage the expectations of those coming forward to donate, particularly if they are motivated by concern for their own health or that of their family.

6.3.7 The scope of consent

The scope of the consent needs to be reasonably explicit, although a balance needs to be struck. A blanket, generic consent may mean that the person giving consent does not know or understand the implications of what they are consenting to, and yet if the initial consent form is too detailed, it may be too restrictive and exclude the possibility of future (non-controversial) use. (This illustrates the importance of consent being thought of as a process, rather than an event.)

The scope of the consent must take into account the following:

- **Testing and screening** – Another area to be considered as part of the consent process is that of testing and screening donors and their donations for safety and quality.
 - Donors need to understand that they will be consenting to health and background checks, data on which will be stored with any sample.
 - Donors also need to understand that their consent will be sought so that any stem cell line or product derived from it could be tested for the presence of viruses or other diseases that may affect the safety of the products derived.
 - The regulations concerning the testing requirements for infectious diseases could potentially be amended. The HTA is working on a proposed amendment of the European Tissues and Cells Directive donor testing requirements to allow testing of the cell line rather than the donor. In the meantime, donors should consent to give a blood

sample which can be tested for infectious diseases should a stem cell line be derived.

- As per 5.6.2, it is recommended that genetic tests should be done on the stem cell lines / derived products, rather than genetic screening being carried out on donors.
- In each case, the consent needs to cover not only the tests available today, but also tests that may be available in the future. It is always a challenging ethical issue asking people to consent to possible future actions as yet unspecified. In the interests of assisting decision making, it would be helpful for donors to be provided with examples of the type of tests that may come on line and the implications of them.

Testing and screening raise the possibility of significant or incidental findings for the donor. Whether it is the donor or the resultant stem cell line / derived product that is tested, because traceability is retained, it will always be possible to trace back findings to the donor. This raises the questions of the circumstances in which results would be fed back to the donor, and whether such feedback could be waived by the donor. Whoever is giving consent needs to be told the circumstances in which they would receive feedback (information which has a direct consequence for the donor's health, their immediate family's health, or public health, for example). They would benefit from being prepared to receive such information and ideally the institution arranging the donation should be prepared to provide or arrange appropriate support when such information is communicated. Where there is no public health need for a donor to be told of such a result (for example a risk they might pass on infection to others), they might choose to be given feedback only if the condition concerned has consequences for the donor's health and can be treated. There is a growing literature relating to the issue of incidental findings and the lessons learnt will be of particular importance in this context.

- **Traceability** – The need for robust traceability systems is one of the operational and practical consequences detailed in 6.4.1 below, but aspects of traceability also need to be considered as part of the consent process. Those giving consent need to understand the need for traceability, and the implications of it. They should be told that regulations dictate the minimum lengths of time for which traceability is required. It is also important for people to understand the limitations of traceability and the circumstances in which

they may or may not be alerted to an issue arising in relation to their traceable donation. For example they should be contacted if findings have important implications for themselves, their families or public health, but they may choose whether or not they wish to be informed of findings of no or uncertain import. As supply lines lengthen, and as cellular therapies become more complex, involve more intermediaries and have potentially global reach, the practical ability to trace back donations becomes significantly more difficult. However, note that *tracing back donations* and *contacting donors* are two separate actions, and consent also needs to differentiate them. The EU regulations concern traceability; there must be systems in place to ensure that all tissues and cells procured, processed, stored or distributed are traceable from donor to recipient and vice versa. The same regulations also require data allowing full traceability to be kept for at least 30 years.³⁸

- **Duration** – Consent can be given for a limited period of time, or can be enduring. It is especially important to be explicit about duration when dealing with advanced cellular therapies because periods between donation and subsequent therapeutic use can be extremely long: in some cases, several decades. In most cases of cellular therapies, it would not be appropriate for consent to be time-limited – but again, the donor needs to be aware of the consequences of this. Given the lengthy and potentially complex existence of some donated material, it is particularly important to be clear about the ability to withdraw consent, and the stages at which this can be done / the point at which it becomes impossible.
- **Retention of samples** – It is also pertinent to recognise that both commercial enterprises and public organisations may want to retain samples of the donated material, for a number of reasons, most of which are related to the safety and quality of the donated material (though this is not a regulatory requirement). Such samples can also prove valuable in the context of lookback either to confirm or exclude the possibility that a recipient has been infected by a product; however the maintenance of a long term sample archive is not a trivial undertaking. Retention of samples must comply with regulatory and legal requirements and professional guidance and there needs

³⁸ *European Union Tissues and Cells Directive 2004/23/EC*, as implemented into UK law via the *Human Safety (Quality and Safety for Human Application) Regulations 2007*, detailed in the HTA's *Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment (The Guide)*, paragraphs 163 and 89, published at http://www.hta.gov.uk/db/documents/Annex_-_Guide_to_Quality_and_Safety_Assurance_for_Tissues_and_Cells_for_Patient_Treatment.pdf.

to be robust ethical governance of any banking systems. It may be necessary to review the periods for which such blood / tissue samples need to be retained. Once again the donor should be asked explicitly to consent to such retention, and the organisation responsible for retention needs to be identified. It is worth repeating that the donor needs to understand 'why' as well as 'how' their donation will be stored as both are relevant to a decision to donate.

6.3.8 Commercial involvement or implications should be openly disclosed, and explicitly covered by the consent

While UK research in cellular therapies is currently spread across academia, the public sector and private enterprises, it is likely that translational work in the future will be led by commercial enterprises. Indeed, commercial involvement may be the only way, in most cases, that developments will take place and the potential benefits of such therapies be realised. Therefore, in obtaining consent from donors in respect of any type of starting material, any commercial involvement needs to be explained upfront and be explicitly covered. If commercial involvement is possible or likely, donors may need to be given an option to consent to their cells and tissues being used for non-commercial purposes but excluded for use by commercial organisations, though in some instances this might mean the donation would not be taken. Donors will also need details of where additional information can be obtained, particularly in situations where treatments containing or expanded from the donated material may be given to many recipients. The level of commercialisation involved in the development of cellular therapies is likely to be a step change from that seen in relation to most current types of donation (such as blood or organs), and consideration should be given to the impact this may have on donors' perceptions of the donation itself.

Donors should be aware that it is a legal and regulatory requirement that donation is non-remunerated so while there might be some potential for financial reimbursement (in relation to reasonable costs incurred, for example), the consent should explicitly state that they will receive no financial benefit from their donation, and that they waive any rights to any registered patent now or in the future, should their donation lead to a commercial product.

6.3.9 Overseas domains

As detailed in 6.4.5 below, cellular therapies are being developed around the globe, with starting material and products moved between different domains. It is important that donors understand this, and consent to their donation being used anywhere in the world; it is unrealistic to get consent for the donation only to be used in the UK. However, while consent can allow for use in domains outside the UK, it is the responsibility of those obtaining a donation within the UK to ensure that the countries with which they share materials conduct their work in a manner consistent with their own. Only then would it be appropriate to assume that no further information was required from the donor.

With regard to materials sourced from overseas, HTA guidance³⁹ provides a useful precedent. It states that the importers should satisfy themselves that, in the countries from which they seek to import tissue, the gaining of consent for the purpose to which the tissue is subsequently put is part of the process by which the tissue is obtained. Compliance with the EU Blood and Tissues and Cells Directives should be sought and any non-compliance discussed with the regulators.

6.3.10 Ensuring that the consent remains valid for all stages

The maxim that consent is a process, not an event, is particularly pertinent to advanced cellular therapies, where the material donated may have a long and complex existence. It is essential that consent remains valid for all stages of the consent process, from donation through research and clinical trials and to established treatment. The validity of consent is especially relevant in instances where the intended use of the donated material changes over time.

It is of key importance therefore to ensure that the initial consent is right, because if new or further consent is required it may not be desirable or practical to contact the donor. The group believes that it is possible to take enduring consent at the time of donation provided sufficient thought has been given to the potential future uses of the material and sufficient information and time given to the donor to make an informed decision; it may also be necessary to emphasise the limits of certainty. We believe this is preferable to trying to seek new consent.

³⁹ See the section on Import and Export, in particular paragraph 206, of HTA Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment, published at [http://www.hta.gov.uk/db/documents/Annex -
Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment.pdf](http://www.hta.gov.uk/db/documents/Annex-_Guide_to_Quality_and_Safety_Assurance_for_Tissues_and_Cells_for_Patient_Treatment.pdf)

Informed consent and traceability

In many current examples of cell and tissue donation, the consent granted may include use for research purposes. However, generic consent granted for research purposes does not also imply consent for use in therapeutic products. Moreover, any cell or tissue procurement for clinical cell therapy manufacture will have to meet GMP standards from the outset. In practice, this means that it is not possible to procure cells or tissues at research grade and then convert that consent to GMP grade at a later stage. Therefore, even if it is the same donor, any cell or tissue donation which might lead to use in advanced cellular therapies should undergo a separate consent and procurement process.

6.3.11 Some areas are particularly controversial, due to ethical concerns being layered upon ethical concerns

Consent to donation of embryos for use in cellular therapies falls into this category. The issues relating to the creation and use of human embryos are seen by many as complex and contested. It is therefore important that appropriate sensitivity is shown when requesting and pursuing such a donation.

6.4 Operational and practical consequences

In the course of our work we also identified some areas of important operational or practical consequence should the field of cellular therapies develop as predicted. Although outside the direct scope and remit of this paper, they are key to any consideration of traceability and consent in connection with cellular therapies.

6.4.1 Robust systems of traceability

An important practical implication leading from the development of cellular therapies is the need to build and maintain a robust system or systems of traceability. As explained above, current EU regulations require the maintenance of traceability data (but not samples) for 30 years after clinical use or discard (see Appendix 1). Meeting these traceability requirements, particularly for products of which there may be many recipients and/or long time periods between the initial donation, receipt of the product and development of any symptoms in the donor or recipient, will demand a significant investment in record-keeping. The logistics of such a system and the storage of the associated paperwork and potentially samples may provide considerable challenges,

given the long storage periods, large volumes of products and numbers of donors and recipients involved.

Such traceability systems will need to be robust, properly governed, and flexible enough to allow for the necessary anonymisation of products, should traceability be required either for the donor's benefit (or that of his/her family) or if public health issues arise. In addition, it will be necessary to be able to keep track of donors to particular products (see 6.4.2 below). It is also essential that such systems are all-encompassing, including all the parties involved in such work – blood establishments, universities, hospitals and others, both in the public and private sector. Numerous IT-based systems already exist in the UK, and it may be useful to examine some of them in detail, to determine the best solution. This is clearly a substantial piece of work which, although it is outside the scope of our remit, we believe is crucial to the future quality and safety of cellular products.

In addition to extended supply lines, another feature of the evolving industry is the existence of many small companies, which can be the subject of merger and acquisition activity, or which can fail. The EU regulations require each company to be responsible for having a contingency plan to maintain traceability records in such cases, and the regulators work with establishments to ensure that the records are kept appropriately for the required period. For example, if an establishment licensed under the EU Tissues and Cells Directive revoked its licence, the HTA would require information on the transfer of records, preferably to another UK licensed establishment. In the case of bankruptcy, the European Medicines Agency would be responsible for holding the traceability data relating to centrally authorised ATMPs; while for ATMPs made and used under the hospital exemption, it would be a condition of operating under the scheme that the manufacturer and hospital should have arrangements in place for the data to be transferred to the MHRA in the event of operations ceasing.⁴⁰

6.4.2 Practicalities of tracing donations to recipient and vice versa

As detailed above, EU regulations require that there are systems in place to ensure the traceability of all tissues and cells procured, processed, stored or distributed, from donor to recipient and vice versa, and of all product-contacting materials which

⁴⁰ See paragraph 15 in the MHRA guidance on the UK hospital exemption scheme, published at <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>.

could impact the safety of the product. However, even with robust traceability systems in place, in practice it could be very difficult to keep track of donors, and to link any disease a donor might develop which had a genetic or longstanding infectious cause (which would have implications for the recipients of the cellular therapy) to a donation they had made in the past. We believe that in many cases it would not be practicable to do more than check the donor's health one month after donation (the rationale for this is set out in section 4.3, 'Living versus cadaveric donors'). It is also important to consider long term follow up of recipients and in particular to consider mechanisms for the linkage of information across therapies developed from an individual donor or cell line by different companies. Universal use of a donor's and recipient's NHS number instead of, or as well as, a hospital number could help to facilitate such long term traceability.

6.4.3 Cell Therapy History Files

To reach the point of conducting a clinical trial in human subjects with a cell therapy medicinal product, researchers in the UK may have been regulated by up to three separate regulatory authorities (the HFEA, HTA and MHRA).

A concern for researchers is that each authority will have different requirements for quality and record keeping. Without a good understanding of the regulatory environment, organisations wishing to conduct clinical trials of cell therapy products may overlook the recording of information from an early stage in the process which is necessary at a later stage.

Researchers are advised to prepare appropriate documentation for any cells lines with the possibility of future clinical potential. This documentation could be used to form the basis of a Cell Therapy History File (CTHF). A CTHF is intended for establishments and companies involved in the procurement, testing, processing, storage and distribution of human cells and tissues for human application and/or therapeutic use. A CTHF aims to gather the requisite traceability data; key details of processing and testing of the human starting material; information on the raw materials / reagents, production process, testing performed, storage and distribution of a human master cell bank / cell line, and any relevant information on downstream processing of a Master Cell Bank. This document would be a living (regularly updated) document to be passed in full, or in part, from one laboratory or organisation to the next.

There is no statutory requirement for a CTHF, but if a recognised template were to be developed, this could provide a recommended structure for information gathering. It could be used to facilitate regulatory submissions and could aid innovation. Future partner organisations wishing to obtain, or work with, the original group on a cell line could use it to perform due diligence exercises; alignment with American, Japanese and other regulatory bodies' requirements would provide international applicability to this document for global innovation.

6.4.4 International aspects

Any discussion of UK guidelines and regulations needs to recognise that the field of advanced cellular therapies is global. According to the European Science Foundation, in terms of hESC research, the UK is one of three countries in Europe with a policy and regulatory framework assessed as “very permissive” (the others are Sweden and Belgium).⁴¹ This factor has contributed to the UK's position as one of the leading countries in the field worldwide. The challenge is to ensure that the UK can respond to research and technological developments and maintain its global competitive advantage, while simultaneously ensuring that the quality and safety of its cellular products remain paramount.

As discussed elsewhere in this document, much of the guidance in this field is provided by EU Directives, which have been transposed into UK law. In addition, there are formally adopted guidance documents which interpret medicinal products legislation and which are used by assessors and inspectors. We recognise that although some of the EU Directives and guidance documents may benefit from a review, the UK cannot make unilateral decisions to stray from harmonised European policy, and some of the suggestions above would have to be followed up with the appropriate European authorities. However, it is also pertinent to note that member states differ in how they interpret and implement EU Directives; in practice, this suggests that the UK may be less fettered by some aspects of EU policy than it first seems.

Nevertheless, there is a risk that where researchers or companies feel that European or UK regulations restrict their activity, they may move some of their processes, or even their entire operations, to a jurisdiction where treatment is, in their eyes, more

⁴¹ Human Stem Cell Research and Regenerative Medicine - Focus on European policy and scientific contributions, European Science Foundation, October 2013. Published at: http://www.esf.org/fileadmin/Public_documents/Publications/HumanStemCellResearch.pdf

Informed consent and traceability

favourable. For example, the EU Directive dictates that traceability in relation to starting material must be maintained for at least 30 years, whereas for starting material sourced from the US, traceability need only be maintained for 10 years. For UK researchers, sourcing starting material from the US becomes increasingly more attractive.

Consequently, when considering guidelines or making recommendations in the field of cellular therapies, it is impossible to look at the UK in a vacuum; the whole international background needs to be considered, along with the safety and quality issues.

7 Summary of recommendations

Infectious risks

Risk assessment

1. Follow existing SaBTO guidance on the selection and assessment of donors, and on risk assessment for infection, and apply it to tissues and cells; abide by legal requirements, and follow the best available professional guidance.
2. For live donors, risk assess to mitigate risk at the point of donation, and consider infections or agents that may not be cytopathic but could replicate *in vitro* or precipitate cell replication or transformation.
3. Maintain vigilance for new and emerging infections, and consider the potential for their transmission through a cell line.
4. Consider follow up of the donor.
5. When considering the safety of a product, take into account the effect of inactivation / decontamination strategies undertaken during processing, and their effect on the infection potential.
6. Consider assessment of the risk to the potential recipient, for example whether they are immunosuppressed or not.

Testing

7. Follow existing SaBTO guidance on donor testing.
8. Test the end product for bacteria and fungi using assays such as the existing 16S and 18S PCRs.
9. Validate appropriately these and other tests required, including new tests, for use on each cell line or product.

Genetic risks

The recommendation is that no genetic screening should be carried out on donors and that relevant genetic tests should be done on the stem cell lines / derived product. These recommendations are based on the following considerations:

Summary of recommendations

1. There is a significant genetic distance between the donor and the ATMP. Thus routine donor selection or screening (by history or testing) for genetic variation is unlikely to be relevant.
2. It would be commercially prudent to undertake selection and screening of the donor to avoid unnecessary expense in the production of a product that may subsequently have a limited market. This would be a commercial decision not a regulatory requirement.
3. Tests are recommended on the ATMP that would be determined by the required function of the product and the indications for use. Given the complexity of the options, this would have to be individually risk assessed by the producer and by the clinician / patient.
4. With the exception of a few specific cases, there is uncertainty about the relationship between genetics and disease.
5. If a decision is taken to regulate genetic testing prematurely, the recommendations are likely to become outdated / challenged in a rapidly moving complex field.
6. There is a further risk that over-regulation in this uncertain area may stifle a new technology that has significant therapeutic potential.

Informed Consent and Traceability

Background points:

1. The subject of cell-based advanced therapies should be discussed openly and transparently, in order to build growing and informed public awareness.
2. Consent should always be considered as a process, not an event.

Guiding principles:

1. *Capacity to consent* – the donation of cellular material should be assessed in the same way that it is for other forms of donation.
2. *Recording of consent*
 - The consent must be recorded, together with the fact that clear, sufficient information has been given and explained.
 - For donations of cells with potential for use in cellular therapies, consideration should be given to the establishment of a Cell Therapy History File.

Summary of recommendations

3. *Communication of information*

- People being asked to consent should be given enough information on which to make an informed decision, and that information should be clearly presented – verbally or in written form or both – and understood.
- Staff giving the information should be adequately trained, and enough time should be allowed for the consenting process.
- In cellular therapies, there are limits to the extent to which risks and benefits can be identified and quantified; these limits of certainty should be communicated to the person consenting to donation or treatment.

4. *Scope of consent* – should be explicit, and take into account:

- Testing and screening – Donors need to understand that they will be consenting to various tests including: health and background checks; tests on their donation, or stem cell lines or products derived from it, for the presence of viruses or other diseases that may affect the safety of the products derived; and the provision of a blood sample which can be tested for infectious diseases should a stem cell line be derived. Consent should cover not only the tests available today, but also tests that may be available in the future. Donors should also be told the circumstances in which they could choose whether to receive feedback (e.g. information which has a direct consequence for their or their immediate family's health) and when they could not (e.g. information affecting public health).
- Traceability – Donors need to understand the need for traceability, and the implications of it, together with the circumstances in which they may or may not be alerted to an issue arising in relation to their traceable donation.
- Duration – In most cases of cellular therapies, consent should not be time-limited, but donors need to be aware of the consequences of this. It is important to be clear about the ability to withdraw consent, and the stages at which this can be done to the point at which it becomes impossible.
- Retention of samples – The donor should be asked explicitly to consent to this.

5. *Commercial involvement and overseas domains* – Commercial involvement or implications should be openly disclosed, and explicitly covered by the consent; donors need to understand that their donations may be used to develop therapeutic products by commercial manufacturers, potentially for widespread

Summary of recommendations

use in the UK and overseas, but that their donation is a gift and they cannot themselves expect to benefit financially if this occurs.

6. *Validity of consent* – Consent must remain valid at all stages of the development process. To avoid having to seek new consent, which might be impractical or undesirable, consideration should be given to the possibility of taking enduring consent at the time of donation, provided sufficient thought has been given to the potential future uses of the material and sufficient information and time given to the donor to make an informed decision.

8 Appendices

Appendix 1: The regulatory context of the development and manufacture of cell-based advanced therapies

The development of cell-based advanced therapies is a rapidly evolving field in both scientific and regulatory terms. This appendix describes the key regulatory requirements for the sourcing, manufacture and licensing of cell-based advanced therapies.

1 Regulatory requirements with regard to starting material in the UK

The starting material for human cell-based therapeutic products will be either donated blood, tissues or cells. In the UK the creation and use of embryos for hESC derivation are subject to regulation under the Human Fertilisation and Embryology Act (2008)¹, which incorporates the elements of the EU Tissues and Cells Directive relating to gametes and embryos, the competent body for which is the HFEA. The collection and testing of blood components for human use are regulated under the EU Blood Directive (2002/98/EC)², which is transposed into UK law as the Blood Safety and Quality Regulations (SI 2005:50)³, the competent body for which is the MHRA. The procurement and testing of tissues and cells (other than gametes and embryos) for human use are regulated under the EU Tissues and Cells Directive (2004/23/EC)⁴ which is transposed into UK law as the Human Tissues (Quality and Safety for Human Application) Regulations⁵ (SI 2007:1523), the competent body for which is the HTA. The Blood and Tissue Directives similarly set quality and safety standards for the collection or procurement of the human source material and subsequent testing, processing, traceability and surveillance requirements; these are summarised below.

1.1 Donor Selection

Mandatory donor selection criteria are set by all Blood and Tissue Services in the UK order to maintain a safe and adequate supply for patients, avoid any harm to donors and ensure compliance with the EU Blood Directive (2002/98/EC)² or the EU Tissues and Cells Directive 2004/23/EC⁴. Manufacturers should however consider any

additional donor selection issues that may be product specific as part of their overall risk assessment and subsequent procedure.

1.2 Blood as a starting material

In the UK the collection and testing of blood components for human use is regulated under the EU Blood Directive (2002/98/EC)² and its commissioning Directives 2004/33/EC⁶ (technical requirements), 2005/61/EC⁷ (traceability requirements and notification of serious adverse reactions and events) and 2005/62/EC⁸ (Quality System requirements). These are transposed into UK law as the Blood Safety and Quality Regulations (SI 2005:50) and subsequent amendments⁹.

The Blood Directive applies to the collection and testing of human blood and blood components, *whatever their intended purpose*, and to their processing, storage, and distribution *when intended for transfusion*. That is to say, if the blood or blood component is to be used as the starting material in a medicinal product, only the collection and testing of the product fall under the Blood Directive. Any material sourced from outside the EU must comply with the Blood Directive and its commissioning directives. This Directive does not apply to blood stem cells.

These legislative documents require the collection and testing and the subsequent processing, storage and distribution of the blood and blood components, when intended for transfusion, to be performed in a Blood Establishment authorised by the MHRA as the national competent authority for blood. Blood establishments are required to have a Responsible Person who has overall responsibility to ensure there are appropriate quality systems in place which ensure the following: appropriate donor eligibility assessment and consenting procedures; adherence to the mandatory testing requirements (ABO/Rh^a and testing against a minimum panel of HIV-1, HIV-2, Hepatitis B, Hepatitis C, Syphilis with others required in certain circumstances); processing, storage and distribution in accordance with Good (manufacturing) Practice¹⁰; collection and notification to the MHRA of any serious adverse events or reactions associated with the use of blood/blood components, and the maintenance of traceability from donor to recipient and vice versa for a period of not less than 30 years.

^a ABO/RH: blood is grouped according to inherited antigens. The two most common systems group blood into type A, B, AB or O; and according to the presence/absence of the Rhesus antigens.

1.3 Tissues and cells as starting materials

The procurement and testing of tissues and cells (other than gametes and embryos) for human use are regulated under the EU Tissues and Cells Directive (2004/23/EC)⁴ and its implementing Directives 2006/17/EC¹¹ (technical requirements for the donation, procurement and testing, as amended¹²) and 2006/86/EC¹³ (traceability requirements, notification of serious adverse reactions and events, and certain technical requirements for coding, processing, preservation, storage and distribution). These are transposed into UK law as the Human Tissues (Quality and Safety for Human Application) Regulations, when intended for human application (SI 2007:1523)¹⁴. Additional aspects of the collection, use and storage of human cells and tissues fall under the Human Tissue Act, 2004¹⁵. Further guidance on both the Human Tissue Act and the Human Tissues (Quality and Safety for Human Application) Regulations is provided in the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment¹⁶ and HTA Codes of Practice¹⁷.

The EU Tissues and Cells Directive applies to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications. As with the Blood Directive, where cells and tissues are used to manufacture medicinal products, only the donation, procurement and testing of the cells or tissues fall under the Tissues and Cells Directive. The Directive does not apply to tissues and cells used as an autologous graft within the same surgical procedure, blood and blood components as defined by Directive 2002/98/EC, or organs or parts of organs if it is their function to be used for the same purpose as the entire organ in the human body. Any material sourced from outside the EU must comply with the Tissue and Cells Directive and its commissioning directives.

These legislative documents require the collection and testing and the subsequent processing, storage and distribution of the tissues and cells to be performed in a Tissue Establishment licensed by the HTA as national competent authority for tissues and cells. Tissue Establishments are required to have a Designated Individual who has overall responsibility to ensure there are appropriate quality systems in place which ensure the following: appropriate donor eligibility assessment and consenting procedures (for living and deceased donors); adherence to the mandatory testing requirements (testing against a minimum panel of HIV-1, HIV-2, Hepatitis B, Hepatitis C and syphilis with others required in certain circumstances); processing, storage

and distribution in accordance with Good Practice; collection and notification to the HTA of any serious adverse events or reactions associated with the use of the tissue or cell, and the maintenance of traceability from donor to recipient and vice versa for a period of not less than 30 years.

Blood and blood components used for transfusion^a and tissues and cells for transplantation remain regulated under their respective Blood and Tissues and Cell Directives. However if these are used in the manufacture of medicinal products their downstream manufacture, product testing, storage and distribution are regulated under the Medicines Directive 2001/83/EC¹⁷. In the UK, for products incorporating a Cell Banking step, then all processing following the creating and storage of the Master Cell bank is regulated under the medicines legislation.

2 Medicines Legislation

2.1 Medicines Directive and Medicines Regulations

All medicinal products for human use in the EU are regulated under the Medicines Directive 2001/83/EC¹⁸, as amended¹⁹, this includes Advanced Therapy Medicinal Products (ATMPs) and are therefore subject to the same regulatory requirements. This Directive details the requirements for: the sourcing of starting and raw materials and excipients used in the manufacture of the product; the sourcing, manufacture and certification of active substances used in the manufacture of the product; the manufacture, testing, labelling, storage, distribution and advertisement of the medicinal product; pharmacovigilance, and the importation of medicinal products in the EU. In addition it details the requirements for the licensing of premises used in the manufacture of medicinal products. This Directive and its subsequent amendments have been transposed into UK law as the Human Medicines Regulations 2012 (SI 2012/1916)²⁰. For cell banked products, the Master Cell Bank is seen as the starting material for the subsequent medicinal product and is regulated under the Medicines Directive¹⁷.

The Medicines Directive defines a medicinal product as:

- Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

^a Without an industrial processing method.

- Any substance or combination of substances which may be used in or administered to human beings with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

2.2 Advanced Therapy Medicinal Products

EU medicines legislation sets out three types of ATMPs – Somatic Cell Therapy, Tissue Engineered Products (Cell-based products) and Gene Therapy and form a subset of medicinal products. These are defined in EC ATMP Regulation 1394/2007²¹ which was transposed in the UK as the Advanced Therapy Medicinal Products Regulations (2010)²². Somatic Cell Therapy and Gene Therapy products had been part of medicines legislation since 2003 but the ATMP Regulations extended the definition to include Tissue Engineered Products.

Definition

The ATMP regulation²⁰ extended the definition of medicinal products to include a definition of a tissue engineered product. A Cell or Tissue derived medicinal product can be considered 'engineered' according to the following definition:

- it contains or consists of cells or tissues that have either been subject to '*substantial manipulation*'* or that are *not intended to be used for the same essential function(s)* in the recipient as in the donor
- is presented as *having properties for treating or preventing disease* in patients.

This includes the following groups of product:

- (a) a gene therapy medicinal product
- (b) a somatic cell therapy medicinal product
- (c) a tissue engineered medicinal product
- (d) a combination product (cell or tissue with an integrated Medicinal Device).

*Non-substantial Manipulation

- cutting
- grinding
- shaping
- centrifugation
- soaking in antibiotic or antimicrobial solutions
- sterilisation
- irradiation
- cell separation, concentration or purification
- filtering
- lyophilisation
- freezing
- cryopreservation
- vitrification

Traceability

The ATMP regulation stipulates the licence holder should have a traceability system that ensures that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be

traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used. Practically this requires all licence holders or manufacturers of ATMPs to retain records for all materials which could have an effect on the safety and/or quality of the product – starting materials (including non-human), raw materials and all materials coming into contact with the product – for a period of not less than 30 years.

This responsibility for the traceability of human-derived material is shared between the parties involved in the sourcing of human material, processing and clinical use of the product:

- **Blood and Tissue Establishments:**
- Blood and Tissue Establishments must ensure a link from donor to recipient and vice versa
- **Companies/groups making the cell-based medicinal products:**
- Companies/groups making the therapies are responsible for tracing products from where they are manufactured to the hospitals where they are delivered to patients. To ensure compliance for the human donor starting material, manufacturers and licence holders will need to have a traceability system that is compatible with that used by the Blood or Tissue Establishment from which they sourced their human starting material. For other materials it is recommended that appropriate information is retained in the Batch Manufacturing Records, and that these are retained for a minimum of 30 years after the final release of the product
- **Hospitals:**
- The responsibility to trace all the patients that receive the product then falls to the hospital delivering the product.

Post-authorisation follow up of efficacy and adverse reactions and risk management²³

Due to the novelty and complexity of some ATMPs, and the possibility for long-term effects and/or failure of the products, the ATMP regulation further extended the post-marketing obligations of licence holders. It requires licence holders to follow up not only safety but also efficacy post-marketing, and this should be planned and submitted to the European Medicines Agency (EMA) as part of the Marketing Authorisation (Licence) Application (MAA), detailed both in Risk Management and

Pharmacovigilance plans for the product. The applicant or holder of a marketing authorisation may request advice from the Agency on pharmacovigilance and on the risk management system.

Incentives

In addition, the regulation provides incentives to companies and groups involved in developing ATMPs, including offering scientific support to companies to help them design pharmacovigilance and risk-management systems (systems used to monitor the safety of medicinal products); fee reductions for scientific advice and MAA submissions; scientific recommendations on ATMP classification, and evaluation and certification of quality and non-clinical data. In addition, companies developing ATMPs receive scientific support from the EMA in the design of pharmacovigilance and risk-management systems.

2.3 Orphan designation

Many cellular therapies are for the treatment of rare diseases, many of which fulfil the criteria of an *Orphan Medicine* for which there are very small markets, making it unlikely that the developers will recoup the cost of research and development. To provide incentives to such developers the EMA released Regulation No 141/2000 Orphan medicinal products. The purpose of this Regulation is to introduce incentives to develop and market medicinal products for the prevention, diagnosis and treatment of rare conditions ('orphan medicinal products'). A medicinal product must be designated an orphan medicinal product if it is intended for the diagnosis, prevention or treatment of a condition affecting no more than five per ten thousand persons in the EU or if it is intended for treating a serious or debilitating disease and it is unlikely that without incentives marketing it would generate sufficient return to justify the necessary investment.

A number of incentives exist for the developers of orphan medicinal products; exclusive marketing rights for a ten-year period, reduced clinical and preclinical packages and access to reduced fees and requirements for scientific advice and licensing.

3 Licensing of the medicinal products

3.1 Manufacturing Authorisation

In the EU all medicinal products need to be manufactured in a licensed facility. In the UK manufacturing licences are issued by the MHRA as national competent authority. There are four types of manufacturing licences in the UK:

Manufacturer's/importer's licence (MIA)

Allows the holder to manufacture and/or assemble (package) medicinal products that hold a Marketing Authorisation and distribute (wholesale deal) licensed medicinal products imported from countries outside the EEA.

Manufacturer investigational medicinal products (MIAIMP)

Allows the holder to manufacture investigational medicinal products used in clinical trials.

Manufacturer 'specials' licence (MS)

Allows the holder to manufacture unlicensed medicinal products (commonly referred to as 'specials') and import unlicensed medicinal products from outside the EEA. Discussed in Section 3.3 below.

Hospital exemption licence: Manufacturer's Licence – Exempt Advanced Therapy Medicinal Products (MeAT)

Allows the holder to manufacture exempt Advanced Therapy Medicinal Products on a non-routine basis for use in hospitals in the UK. Discussed in Section 3.3 below.

3.2 Quality considerations

All medicinal products must be manufactured, tested, stored and distributed in accordance with Good Manufacturing Practice²⁴ as detailed in Eudralex; The rules governing human medicinal products Volume 4²⁵ (transposed in the UK to the 'Orange Guide'). Additional EU guidance on the quality requirements for Cell-Based Medicinal Products can be found at the EMA site and should be considered by developers of such products: of particular relevance are the guideline on human cell-based medicinal products²⁶ and the reflection paper on stem cell-based medicinal products²⁷.

Appendix 1

An almost unique consideration (other than for radiopharmaceuticals) for cell-based medicinal products is the often very short shelf life of the product following release, which has the secondary effect that the product will often be released and used before all final release tests are available. It is important that these risks are mitigated extensively e.g. facilities fully qualified, processes validated, operators fully trained, rapid access to Qualified Person certification (required for the release of any medicinal product for clinical use in the EU, see Annex 2 of Eudralex Volume 4 for the two stage QP certification process), post-transplant notification and risk management plans.

As detailed in Section 1 above the collection, procurement and testing of human-derived materials must be in compliance with the EU Tissues and Cell Directive⁴ or EU Blood Directive². Other considerations for the sourcing of human and animal ingredients must also be considered in the development of human cell-based medicinal products; specifically, for prion-related risk reduction measures for human-derived material and animal-derived materials which may be used in the manufacture of the product, see the joint position statement by the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Advanced Therapies (CAT) on Creutzfeldt-Jakob disease and ATMPs²⁸ and others^{29,30}.

A Cell Therapy History File (CTHF) could be used by establishments and companies to gather the requisite traceability and other key processing information. Although not a regulatory requirement, this document could facilitate regulatory submissions and/or due diligence exercises.

3.3 Clinical Trial

The trial of all medicinal products in the EU must be in compliance with the EU Clinical Trial Directive³¹ and in accordance with EU Good Clinical Practice (GCP)^{32,33}, transposed in the UK in the Medicines for Human Use (Clinical Trials) Regulations 2004³⁴. These require all investigational medicinal products used in a clinical trial to be manufactured in a licensed facility (MIA(IMP)) and in accordance with the national competent authority and Ethics Committee approvals, Clinical Trial Authorisation and associated documentation.

As detailed above there are a number of considerations for the clinical trial of ATMPs. Guidance on the application of GCP in relation to cell-based medical products is given in Detailed Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products, released by the European Commission in

2009³⁵. Furthermore, since many of the products will be used to treat orphan or rare diseases and so there are restricted numbers of patients available for recruitment onto a clinical trial of the product, the EMA guidance on clinical trials in small populations should be considered³⁶.

It should be noted that the Clinical Trial Directive will be replaced by the EU Clinical Trial Regulation. The proposed Regulation introduces a single, streamlined authorisation procedure for all clinical trials and greater transparency on conduct and results of clinical trials. It is anticipated the Clinical Trial Regulation will be introduced in 2016/2017.

3.4 Marketing Authorisation (Product Licence)

Centralised Authorisation

Due to the potential novelty and complexity of ATMPs, all advanced therapy products come under the Centralised Marketing Authorisation Application (MAA) procedure which, if successful, means the product is licensed throughout Europe. This is designed to make it easier for companies to market their products and for patients in the different Member States to gain access to these products.

Following submission of a MAA, the CAT (a committee of experts drawn from all Member States established to support the assessment of ATMP products in Europe) prepares a draft opinion on the quality, safety and efficacy of the product. This opinion is then sent to the CHMP, the committee responsible for human medicines at the Agency. Based on the CAT opinion, the CHMP adopts a recommendation to the European Commission on the granting, variation, suspension or revocation of a marketing authorisation.

Risk-based approach

The clinical use of ATMPs may be associated with specific risks, which may be related to the quality, biological activity and application of the ATMP. Since ATMPs are very diverse in nature, each product/product type will bring a specific consideration or challenges. The ATMP Regulation introduced a risk-based approach³⁷ to determine the extent of quality, non-clinical and clinical data for inclusion in a MAA submitted to the EMA.

The risk analysis aims to allow a flexible approach to the development and use of such products and should cover the entire development including (but not limited to)

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the origin of cells; ability to proliferate and/or differentiate and to initiate an immune response; level of cell manipulation; combination products; nature of gene therapy medicinal products; extent of replication competence of viruses or micro-organisms; level of integration; long term functionality; risk of oncogenicity; mode and frequency of administration or use; distribution chain, and risk/benefit analysis of the therapy. Other relevant data (quality, non-clinical and clinical data etc) may also be considered in the risk analysis.

The application of the risk-based approach in the preparation of a MAA dossier is optional. However, in cases where the risk-based approach is being applied, the applicant is advised to follow the methodology laid down in the guideline³⁶.

As detailed above, once the products are authorised and marketed in the European Union, the Agency carries out further assessment of their safety and effectiveness²². Safety and efficacy follow-up systems form part of the risk management system and should be planned in the EU-Risk management plan. Both follow up systems are defined as any systematic collection and collation of data that is designed in a way that enables learning about safety and/or efficacy of an ATMP.

Exemption schemes

All medicinal products to be supplied within the EU must either be used in part of an authorised clinical trial or hold a valid Marketing Authorisation. Certain exemptions from these requirements allow the manufacture and supply of an unlicensed medicinal product. These schemes are incorporated into the Human Medicines Regulations 2012 Part 10, and are summarised below.

'Specials' supply

Article 5.1 of Directive 2001/83/EC¹⁷ provides for each Member State to introduce legislation allowing the supply of an unlicensed medicinal product to meet the specialist needs of an individual patient and in response to a *bona fide* unsolicited order. The healthcare professional has direct personal responsibility for prescribing the unlicensed product. If a 'special' is manufactured in the UK, the manufacturer must hold a manufacturer's (specials) licence (Section 3.1 above). A 'special' may not be advertised and may not be supplied if an equivalent licensed product is available which could meet the patient's needs. Essential records must be kept and serious adverse

drug reactions reported to the MHRA. A 'specials' product may be imported into the UK or exported from the UK to other EU Member States if their national law allows.

The MHRA Guidance Note 14³⁸, 'The supply of unlicensed relevant medicinal products for individual patients', provides guidance to manufacturers about the conditions under which they may manufacture and supply 'specials', and their legal obligations.

Hospital Exemption Supply

Article 28.2 of the ATMP Regulation 1394/2007 applies to ATMPs which are prepared on a ***non-routine*** basis and used within the same Member State in a hospital in accordance with a medical prescription for an individual patient. The exemption was included in the Regulation in recognition of the small scale and developmental nature of activity carried out in some hospitals. In the UK, the manufacture of ATMPs under the hospital exemption must take place in a facility authorised by the MHRA (MeAT (Hospital Exemption)). In addition, traceability, quality and pharmacovigilance standards for ATMPs made under the exemption must be equivalent to those for ATMPs for which a centralised market authorisation would be granted by the EMA. As with 'specials' in the UK the supply of a product manufactured under the Hospital Exemption allowance must be manufactured to meet the needs of an individual patient and the healthcare professional has direct personal responsibility for prescribing the unlicensed product. The product manufactured under this scheme may not be advertised and may not be supplied if an equivalent licensed product is available which could meet the patient's needs. Products manufactured and supplied under the Hospital exemption scheme, unlike under a 'specials' licence, may only be used in a hospital within the same Member State. A summary comparative table of the two schemes is below.

Table 1. THE RELATIONSHIP BETWEEN ‘SPECIALS’ AND HOSPITAL EXEMPTION SCHEMES IN THE UK

Hospital exemption	The ‘specials’ scheme
The ATMP must be prepared and used in the same EU Member State	Products meeting the requirements of the scheme can be manufactured in the UK or imported to the UK
The ATMP must be commissioned by a medical practitioner	Products can be prescribed by doctors, dentists and supplementary prescribers
The ATMP must be custom made to meet an individual prescription and preparation must be on a “non-routine basis”	There is a special needs test (interpreted to mean the absence of a pharmaceutically equivalent and available licensed product)
The product may not be supplied if a licensed alternative is available which meets the needs of the patient	The product may not be supplied if a licensed alternative is available which meets the needs of the patient
The ATMP must be used in a hospital	There is no stipulation as to location
Qualified Person certification not required	Qualified Person certification not required

Relevant legislation

¹ Human Fertilisation and Embryology Act 2008.

² EU Blood Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC.

³ SI 2005:50 Blood Safety and Quality regulations.

⁴ EU Tissues and Cells Directives 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

⁵ Human Tissues (Quality and Safety for Human Application) Regulations 2007.

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⁶ Commission Directive 2004/33/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.

⁷ Commission Directive 2005/61/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events.

⁸ Commission Directive 2005/62/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments.

⁹ Blood Safety and Quality Regulations and subsequent amendments:

- The Blood Safety and Quality Regulations -SI 2005/50
- The Blood Safety and Quality (Amendment) (No. 2) Regulations 2005 - SI 2005/2898
- The Blood Safety and Quality (Amendment) Regulations 2006 No.2013
- The Blood Safety and Quality (Amendment) Regulations 2007 No. 604
- The Blood Safety and Quality (Amendment) Regulations 2007 No.604: Explanatory Memorandum
- The Blood Safety and Quality (Fees Amendment) Regulations 2008 No. 525
- The Blood Safety and Quality (Fees Amendments) Regulations 2009 - SI 2009 No 372
- The Blood Safety and Quality (Fees Amendment) Regulations 2010 - SI 2010 No 554.

¹⁰ Good Practice Guidelines for Blood Establishments and Hospital Blood Banks Required to Comply with EU Directive 2005/62/EC.

¹¹ Commission Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

¹² Commission Directive 2012/39/EU amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells.

¹³ Commission Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

¹⁴ Human Tissues (Quality and Safety) for Human Application Regulations 2007.

¹⁵ Human Tissue Act 2004.

¹⁶ HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment

¹⁷ HTA Codes of Practice:

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- Code of practice 1 - Consent
- Code of practice 2 - Donation of solid organs for transplantation
- Code of practice 3 - Post-mortem examination
- Code of practice 4 - Anatomical examination
- Code of practice 5 - Disposal of human tissue
- Code of practice 6 - Donation of allogeneic bone marrow and peripheral blood stem cells for transplantation
- Code of practice 7 - Public display
- Code of practice 8 - Import and export of human bodies, body parts and tissue
- Code of practice 9 – Research.

¹⁸ Directive 2001/83/EC on the Community code relating to medicinal products for human use

¹⁹ 2001/83/EC subsequently amended by ; Directive 2002/98/EC, Directive 2003/63/EC, Directive 2004/24/EC, Directive 2004/27/EC, Regulation No 1901/2006, Regulation No 1394/2007, Directive 2008/29/EC, Directive 2009/53/EC, Directive 2010/84/EU, Directive 2011/62/EU

²⁰ Human Medicines Regulations 2012 SI 2012/1916

²¹ Regulation (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

²² The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010 no 1882

²³ Article 14 of Regulation 1394/2007, detailed guidance available in Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products EMEA/149995/2008

²⁴ Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

²⁵ Eudralex Volume 4 of "The rules governing medicinal products in the European Union" Good manufacturing practices for medicinal products for human and veterinary use.

²⁶ Guideline on human cell-based medicinal products EMEA/CHMP/410869/2006

²⁷ Reflection paper on Stem Cell Based Medicinal Products EMA/CAT/571134/2009

²⁸ CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products

²⁹ WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies 2010 see www.who.int/bloodproducts/tablestissueinfectivity.pdf

³⁰ Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) (2011/C 73/01)

Appendix 1

- ³¹ Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
- ³² Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- ³³ Eudralex Volume 10 of "The rules governing medicinal products in the European Union" Clinical Trial Guideline
- ³⁴ The Medicines for Human Use (Clinical Trials) Regulations 2004 - SI 2004/1031 amended by The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 - SI 2006/1928, The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 – SI 2006/2984, The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 – SI 2008/941
- ³⁵ Detailed guidelines on good clinical practice specific to advanced therapy medicinal products ENTR/F/2/SF/dn D(2009) 35810
- ³⁶ Clinical Trials in Small Populations; CHMP/EWP/83561/05
- ³⁷ Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products EMA/CAT/CPWP/686637/2011.

Appendix 2: The remit and terms of reference of the working group

SABTO

ADVISORY COMMITTEE ON THE SAFETY OF BLOOD, TISSUES AND ORGANS

CELL-BASED ADVANCED THERAPIES WORKING GROUP

REMIT AND TERMS OF REFERENCE

Background

1. The Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) reviewed issues relating to the microbiological and other risks related to different types of human cell therapies at its meeting on 11th September 2012.

2. In the light of these considerations a meeting was held to discuss and scope SaBTO work on microbiological risk related to human stem cell therapy. Several issues were considered including:
 - What are the issues around human embryonic stem cell use and microbiological risks that need to be addressed?
 - What are the questions SaBTO is being asked to find an answer for, in collaboration with other Advisory Committees if appropriate?
 - What should / could be done, the boundaries and what realistically could be achieved?
 - What should the output be?
 - Who should be in the working group? Who else should be involved?
 - How should the work be approached?

- How much time will be needed for the work?

The outcome of that meeting is reflected in this document.

Remit

3. The Working Group will review the endogenous risks⁴⁴ associated with Cellular Therapies particularly with respect to donor selection, consenting and testing, and make recommendations to SaBTO on how these can be optimised in order to support the development of Cellular Therapies in the UK whilst maximising donor and patient safety.
4. Its remit includes:-
 - To examine the extent to which donor selection procedures used for blood, tissue, haematopoietic stem cell⁴⁵ and solid organ transplant donation are applicable in the context of cellular therapies and related Advance Therapy Medicinal Products. Particular attention will be given to donors of stem cell lines (human embryonic stem cells, induced pluripotent stem cells⁴⁶, induced somatic stem cell lines⁴⁷) in view of the increased risk of a single donor contributing to potentially large numbers of recipients over a long period of time.
 - To define the potentially infectious agents of interest, both those currently screened for and other infectious agents of potential relevance including but not limited to endogenous retroviruses⁴⁸, prion diseases and infections which are of low pathogenicity in a healthy host but may be pathogenic in a host with a specific disease or immune suppression.
 - To examine the applicability of existing and new testing strategies including those of prion diseases to cellular therapies and the extent to

⁴⁴ Endogenous risks: those originating in the starting donor material (eg infection, genetic abnormality), as opposed to the manufacturing process.

⁴⁵ Haematopoietic stem cells are cells that can divide and differentiate to give rise to all the various types of blood and immune cells.

⁴⁶ Pluripotent stem cells can give rise to any foetal or adult cell type. Induced pluripotent stem cells are (usually adult) cells genetically reprogrammed to make them pluripotent.

⁴⁷ Induced somatic stem cells are undifferentiated cells that have been genetically reprogrammed so they can multiply to regenerate tissue, giving rise to all the cell types needed for a particular organ.

⁴⁸ An endogenous retrovirus carries its genetic blueprint in RNA. When it infects a host cell it uses an enzyme to create DNA from its RNA. This becomes integrated into the host's genome and is inherited by subsequent generations.

which it is possible to screen the donation or product thereof rather than the donor.

- To consider the potential differential risk associated with tissues derived from different geographical populations.
- To assess the potential risk of genetic abnormality in the donor giving rise to a product which may give rise to disease in the recipients.
- To establish the extent to which genetic screening or indeed whole genome sequencing of a cell line may be appropriate.
- To consider the issues relating to traceability between the donor and recipient(s) and the duration for which reference materials and documentation will need to be retained.
- To consider the implications for the donor in the event of identification of known or novel infectious or genetic disease markers either at the time of donation or at any time in the future.
- To consider the implication for potential previous recipients of the development of post-donation disease in the donor which may have an infectious or genetic basis.
- To consider the extent to which the development of clinical problems in recipients may have an implication for the donor and/or his/her family.
- To consider the nature of informed consent from a donor's perspective and whether they should be able to waive feedback.
- Recommendations for disseminating the outcome of the work.

5. In scope:

- Endogenous risks i.e. those associated with the starting cellular material which could be of an infectious, neoplastic or genetic nature, including zoonotic disease in the donor, and opportunistic contamination of the donated tissue by infection of plant or animal origin
- Non-homologous (heterologous) use of CD34 cells
- In vitro somatic cultured cells
- Cell therapies derived from stem cell line including :
 - Human embryonic stem cells
 - Induced pluripotent stem cells
 - Induced oligopotent stem cells
- Tissue engineered products which include living cells
- Genetically engineered cellular therapies.

6. Out of scope:

- Haematopoietic stem cell transplantation and donor lymphocyte infusions⁴⁹
- Minimally manipulated cellular therapies including CD34 selection⁵⁰ and T cell depletion⁵¹ for haematopoietic stem cell transplantation
- Exogenous risks *i.e.* the risk of damage or contamination relating to the manufacturing process itself. These include:-
 - Persistence or reversion to pluripotency leading to risk of teratoma⁵²
 - Neoplasia induced by genetic or epigenetic⁵³ abnormalities in the cell line
 - Contamination with microbiological agents including potential zoonotic agents in animal derived products
 - Contamination by other agents in the manufacturing process.

These risks are addressed by Good Manufacturing Practice principles and are subject to inspection by the regulatory authorities.

- Issues related to the clinical use of the product including:
 - Acute toxicity
 - Immunological rejection of the allogeneic⁵⁴ cellular tissue
 - Dissemination of the cellular therapy leading to ectopic⁵⁵ tissue formation
 - Generation of alternative lineages leading to inappropriate tissue.

These risks are addressed as part of the clinical trial authorisation process.

- Acellular materials or scaffolds used in tissue engineering

⁴⁹ A donor lymphocyte infusion is given to improve the success of a haematopoietic stem cell transplant or to boost an anti-tumour immune response.

⁵⁰ CD34 is a protein found on the surface of some bone marrow and blood cells. In CD34 selection, it is identified as the tissue is run through a machine to select out CD34 positive cells.

⁵¹ Reducing T cells may reduce the chance of the recipient having an immune response against the donor's cells.

⁵² Teratoma: a tumour containing one or more of the 3 layers of cells found in an embryo.

⁵³ Epigenetic: relating to change in gene expression caused by external factors rather than change in the gene itself.

⁵⁴ Allogeneic: from a donor, not genetically identical.

⁵⁵ Ectopic: out of its right place.

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- Genetic constructs in and of themselves
- Gametes donated between co-habiting couples, where the consent given limits their use to treatment/use of the co-habiting couple only.

Terms of Reference

7. In formulating its advice, the working group will:
- Take account of the scientific evidence currently available, including the nature of uncertainties and assumptions used to reach conclusions
 - Take account of the infectivity risk associated with different tissue sources
 - Take account of the differences in risk/benefit for different types of tissue and cellular products
 - Identify specific areas of research where further work is required to manage uncertainty
 - Take account of the impact of cell therapy donation on the donor
 - Consider the impact of cellular therapies on recipients
 - Take care of the need to maintain the safety of cell therapies and remit of the precautionary principle
 - Take account of any legal requirements
 - Take account of any other SaBTO recommendations
 - Be ultimately accountable to SaBTO
 - Consider the impact of its advice on the development of the cellular therapy field both in the United Kingdom and internationally.

Members will:

- Observe the confidentiality of the working group's proceedings, and the information acquired in the course of the work, both during the life of the working group and afterwards
- Refrain from expressing views or giving information about the working group's work, as a member of the working group, without the prior approval of the working group Chair, the SaBTO Chair or the secretariat.

Membership

8. *The membership of the Working Group is set out in section 3.6 above.*

Work Programme

9. The work of the group is expected to be initiated in spring 2013 and completed in spring 2014 according to the following schedule:-

Sub group meeting	Milestone	SaBTO Meeting
March 2013	Agreement of Terms of Reference Review of existing papers Identification of specific work required	Update SaBTO at meeting on 24 th June 2013
July 2013	Review of section outlines and draft scope/content Identification of any additional information required Formulation of further work required	Update SaBTO at meeting on 17 th September 2013
September 2013	Review of progress to date and emerging issues Sections drafted	Update SaBTO at meeting on 3 rd December 2013
January 2014	Review of draft Report Agreement of recommendations Report sent out for consultation in February / March 2014	
April 2014	Review of feedback and agreement of final draft	
	Report to SaBTO	SaBTO Open meeting 28 th April 2014 Report presented to SaBTO meeting 29 th April 2014

10. The working group may meet in person or by telecom.
11. Administrative issued will pass to the SaBTO Secretariat who will also maintain the document library.
12. Members of the Working Group are asked to claim expenses from their employing organisation. Where this is not possible, they can be claimed from DH. Expenses in relation to travel and subsistence necessarily incurred in carrying out the work of the Group are payable in line with the DH rates for individuals who serve on committees. This is standard class for rail travel and economy class for air travel. Members of the Working Group are asked to make every effort to use public transport where possible rather than taxis although these may be used for local journeys (under 5 miles). Receipts must be submitted with claims.
13. Papers will be circulated no later than 7 days prior to any ordinary meeting.

Communications

14. The establishment of the working group will be recorded in the minutes of the SaBTO meeting of 10th December 2012.
15. The Working Group will include stakeholders as detailed in section 8, and will consult with other stakeholders including the UK regulatory authorities (*inter alia* the Medicines Healthcare products Regulatory Agency, Human Tissue Authority, Human Fertilisation and Embryology Authority, Gene Therapy Advisory Committee, European Medicines Agency) as required. It will consider whether it is appropriate to conduct any further consultation when formulating its recommendations, although it is expected that sufficient expertise will be included in the group. Unless specifically stated members of the Working Group are not considered to be representatives of the organisations listed.

Appendix 2

16. The recommendations of the Working Group will be published in a report and recommendation to SaBTO, with discussions and outcomes recorded in the public minutes of the meeting.

17. This document will be appended to the report, so that the membership of the group is made public.

18. The Working Group will draw up a list of stakeholders that should be informed of SaBTO's recommendations and/or any decisions by ministers. This will include:
 - UK Department of Health
 - Human Tissue Authority
 - Medicines and Healthcare products Regulatory Agency
 - Human Fertilisation and Embryology Authority
 - Human Stem Cell Bank
 - UK Blood Services
 - European Medicines Agency
 - Medical Research Council
 - Health Professional organisations
 - Patient groups
 - Groups representing cellular therapy developers.

Appendix 3: Tissues under consideration for use in cell therapies

The table of tissue sources below represents those which are considered most likely to be used for the isolation of cells for therapy. The table also shows for each tissue source exemplars of contaminants that could potentially give rise to malignant transformation in donor or recipient patient cells and could result in persistent infection of cells cultured in vitro, or are known to give rise to infection in immune-compromised patients.

A wider range of tissues including examples from the intestinal and genito-urinary tracts are now being used in “regenerative surgery” procedures including use of sections of intestine for oesophageal repair. These should be considered under guidance for transplantation and have therefore been excluded from consideration here.

Table of likely tissue sources utilised for cell therapy and exemplar contaminants

Tissue source	Example of potential cell therapy	Exemplars of agents which could cause potentially malignant transformation in the donor cells or recipient patients	Exemplars of agents that could establish persistent infection during culture of cells and cause infection in immune-compromised recipients
Reproductive cells: sperm/testicular, egg, embryo	Applications arising from use of stem cell lines	Human papillomavirus (HPV)	Human herpes viruses (notably HHV8)
Bone	Bone precursors	-	Parvovirus B19, Brucella spp

Appendix 3

Tendon and other cartilage structures	Chondrocyte precursors	-	-
Adipose tissue	Mesenchymal stromal cells	-	Adenovirus
Skin	Keratinocyte precursors for skin engraftment. Also cells reprogrammed to create hiPSC lines in turn differentiated to generate cells of diverse tissues	HPV	Adeno-associated virus
Cornea and limbal tissue	Limbal stem cells for corneal repair	Herpes simplex virus 1 (HSV-1)	Adenovirus, chlamydia
Upper respiratory tract: mouth buccal and gingival oral surfaces, teeth etc	Buccal epithelium for corneal repair, mesenchymal stromal cells (milk teeth)	Epstein-Barr virus (EBV)	EBV
Lower respiratory tract (trachea, bronchus and lung)	-	-	<i>Chlamydia psittaci</i>
Liver (e.g. hepatocytes, Kupffer cells and reticular endothelial cells)	-	EBV, HSV	Hepatitis viruses A-E, adenoviruses; parvovirus B19, human herpesvirus 6, human herpesvirus 7
Pancreatic islets	Islets in use for cell therapy, pancreatic stem cells	HSV	Enteroviruses, mumps, Varicella-Zoster virus
Spleen	Immune cells	-	Parvovirus B19, measles

Appendix 3

Vasculature and placenta	Endothelial cells, MSCs	-	Parvovirus B19, human herpes virus 7
Blood and bone marrow	Sources of C34+ stem cells that may be 'mobilised' and/or otherwise cultured or reprogramed to create hiPSC lines in turn differentiated to generate cells of diverse tissues	EBV	Parvovirus B19, <i>Coxiella burneti</i> , <i>Brucella spp</i>
Brain and central nervous system including neural stem cells, subventricular zone (SVZ) & subependymal zone (SEZ), astrocytes/oligodendrocytes	Fetal neural transplants, neural cell lines	HSV	Varicella-Zoster, enteroviruses (echovirus, coxsackie A and B viruses), mumps, <i>Brucella spp</i> , measles

Appendix 4: Report of the NChESF meeting of 28 March 2012

**Report to SaBTO of the
National Clinical Human Embryonic Stem Cell Forum
consultation meeting on
TSE infection risk in Human Embryonic Stem Cells for clinical use
in Edinburgh on 28th March 2012**

Members of the UK National Clinical Human Embryonic Stem Cell Forum (NChESF) who are involved with derivation and banking of human embryonic stem cells from IVF embryos, met in with experts in TSE (transmissible spongiform encephalopathies, ie prion disease) and tissue banking, to explore the possibilities and implications of TSE infection in stem cells (and other tissues) intended for clinical use. As noted in the report of the meeting with the regulators re ATMPs (advanced therapy medicinal products) held in Feb 2012, the perception that human tissue products emanating from the UK are at particular risk of TSE contamination could adversely affect marketing of stem cells derived in the UK. TSE contamination and testing was not considered specifically as part of the EU Tissue and Cells Directive, and so far no formal risk assessment has been undertaken.

The meeting was chaired by Dr Glyn Stacey (UK Stem Cell Bank) and short presentations to initiate discussions given by:

- Professor Richard Knight (National CJD Research & Surveillance Unit)
- Professor Jean Manson (Roslin Institute)
- Professor Marc Turner (Scottish National Blood Transfusion Service)
- Professor Peter Braude (SaBTO).

Issues addressed were:

- What are prions and why do they matter?
- Trends in risk of TSE in cattle and humans in the UK and elsewhere
- Non-bovine and non-human sources of TSE – emerging issues
- The risk of, and steps taken to avoid, TSE contamination of donated human blood, organ and tissue
- Risks of TSE contamination in gametes and embryos in the general

population and amongst IVF patients and donors

- Recommendations on current best practice for testing for vCJD contamination
- Constructing a risk assessment process for TSE contamination in human embryonic stem cell lines.

Following wide ranging discussion the group agreed 13 key conclusions and recommendations that addressed TSE risk (items 2-7) and diagnostic testing (items 8-13).

1. The risk of TSE in clinical grade stem cells is a global issue and should be considered from that perspective; only then should the outcome be applied to a UK position.⁵⁶
2. Maternal transmission (sheep), patient to patient, and transmission between single cells is known although the precise nature of the infectious agent and pathogenesis of the disease are still largely unknown.
3. An asymptomatic BSE/vCJD infection rate of ~1:4000 in the UK population is currently accepted based on existing knowledge.
4. There is an ongoing need for a review of risk from tissues, including in UK stem cell lines. This risk needs to be put in context against other tissues and in other countries.
5. The route of exposure is likely to be a key factor in pathogenesis as the risk and incubation period for iatrogenic CJD shortens the closer the target is to the central nervous system.
6. Risks of transmission could be associated with gamete donors, and with gamete processing and its components.
7. Questions still remain about zoonotic potential of new and newly recognised animal TSE since different strains of animal disease can behave very differently.
8. A validated prion screening test is not yet available but a practical position is testing for abnormal prion protein.
9. Tests for prions/TSE are in development (3 current lead candidates) but are still in the academic domain and are oriented primarily towards blood

⁵⁶ <http://www.guardian.co.uk/science/2012/apr/25/mad-cow-disease-us-mutation>;
<http://weddelswift.com/2012/04/25/bse-case-confirmed-in-usa/>

screening applications. The group recognised a need to promote exchange and evaluation of samples between groups, including cells and their derivatives as test substrates.

10. There is a need to evaluate test criteria and for closer identification of the infectious agent being tested.
11. Testing of cell banks (product testing) is a more relevant approach than donor screening; an alternative would be testing of startup cells whose provenance should be traceable to low risk inputs/starting materials.
12. Criteria will need to be established for how / whether results should be interpreted with respect to public risk and feedback to the cell donor(s).
13. Banks for generic clinical use should be regarded very differently in terms of testing requirements when compared to banks producing cells for specific indications/products.

General Conclusions and actions suggested:

- The group concluded that there was significant new data on CJD infection.
- The group agreed that a narrative with its recommendations should be drafted for SaBTO.
- The group recommended that SaBTO should be asked to formally examine this issue and provide guidance. This guidance should be specific to the 'clinical grade' hESC (human embryonic stem cell) lines now being established, but SaBTO should be encouraged to recognise that there are aspects generic to human application of other cell and tissue products.
- Regarding testing of cell banks of hESC lines: the group agreed that the testing of lines in those centres/banks involved directly in product manufacture would probably need to be more extensive than requirements for those in centres established solely as derivation centres with the intention of providing starting materials for a potentially broad range of human applications.

Participant List

Kevin Bruce	Roslin Cells
Stephano Codognotto	Kings College

Appendix 4

Bertie Craig	Newcastle
Heather Da Costa	Sheffield
Janet Downie	Roslin Cells
Michael Fenster	Pfizer UK
Lyn Healy	UKSCB
Zoe Hewitt	Sheffield
Charles Hunt	UKSCB
Dusko Ilic	Kings College
Sebastian Sethe	NChESCF Secretary
Jill Shepherd	HTA
Jinpei Ye	Manchester
Peter Braude	SaBTO
Jillian Cooper	NIBSC
Paul DeSousa	University of Edinburgh
George Galea	SNBTS
Mark Head	National CJD Surveillance Unit
Richard Knight	National CJD Research & Surveillance Unit
Jean Manson	Roslin Institute
Glyn Stacey	UKSCB
Marc Turner	SNBTS
Graham Jackson	MRC Prion Unit

Professor Peter Braude

SaBTO

Appendix 5: Current regulations for genetic screening of donors of blood, cells, tissues and organs

Blood

- UK - MHRA regulatory oversight
- UK Blood Safety and Quality Regulations (BSQR) (SI 2005: 50)
- UK BSQR transpose into UK law European Directives (2002/98/EC, 2004/33/EC, 2005/61/EC and 2005/62/EC)
- “Red Book” = Guidelines for the Blood Transfusion Services in the UK (9th ed. 2013). Guidelines reflect:
 - Best practice
 - Standards to be met by products
 - Technical details of processes involved
 - Legally binding requirements of UK BSQR
- Guidelines compiled by a group of experts involving many from outside blood transfusion services, called the Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC)
- JPAC has standing advisory committees (SACs) focused on:
 - Blood components
 - Care and selection of donors
 - Clinical transfusion medicine
 - Immunohaematology
 - Information technology
 - Plasma for fractionation
 - Stem cells
 - Tissues
 - Transfusion transmitted infection.
- Key institutions involved in developing UK guidelines & regulations:
 - World Health Organisation (www.who.int)
 - Council of Europe (www.coe.int; 47 member states, population 820 million, recommendations not legally binding) and the European Union (http://europa.eu/index_en.htm; subset of 28 member states, population 503 million, issues directives transposed into law by member states)

Appendix 5

- European Pharmacopoeia (<http://www.pheur.org>) = collections of standardised specifications that define the quality of pharmaceutical preparations – binding on EU member states
- UK government (<https://www.gov.uk/government/organisations/cabinet-office>).

Organs, Tissues and (non-reproductive) Cells

- UK HTA regulatory authority
- Human Tissue Act 2004 England, Wales and Northern Ireland
- Human Tissue Act Scotland
- UK Human Tissue (Quality and Safety for Human Application) Regulations 2007 (SI 2007: 1523)
- UK Human Tissues (Quality and Safety for Human Application) Regulations, 2007 transpose European Tissue and Cells Directives (2004/23/EC, 2006/17/EC 2006/86/EC) – authorised by HTA/HFEA
- UK Quality and Safety of Human Organs Intended for Transplant Regulations 2012 (SI 2012: 1501)
- UK Quality and Safety of Human Organs Intended for Transplant Regulations transpose into UK law The European Union Organ Donation Directive (2010/53/EU)
- Red Book Chapter 22 – Tissue banking: selection of donors
- Red Book Chapter 24 – Haematopoietic progenitor cells.

Professional advice

- *American Association of Blood Banks (AABB)* (www.aabb.org) is comprised of representation from the AABB, a US FDA liaison, an ethicist, the American Association of Tissue Banks, American Society for Blood and Marrow Transplantation, American Society for Apheresis, Foundation for the Accreditation of Cellular Therapy (FACT), International Society for Cellular Therapy and National Marrow Donor Program.

Appendix 6: Current regulations for genetic screening of gamete donors

UK regulators

The HFEA requirements for screening of gamete donors in relation to their genetic history are as follow (HFEA Code of Practice T52)⁵⁷.

“a. Donors must be selected on the basis of their age, health and medical history, provided on a questionnaire and through a personal interview performed by a qualified and trained healthcare professional. This assessment must include relevant factors that may assist in identifying and screening out persons whose donations could present a health risk to others, such as the possibility of transmitting diseases, (such as sexually transmitted infections) or health risks to themselves (e.g. superovulation, sedation or the risks associated with the egg collection procedure or the psychological consequences of being a donor).”

Professional advice

The consensus recommendations from the learned societies in the UK (British Fertility Society, Royal College of Obstetricians and Gynaecologists, Association of Clinical Embryologists, British Andrology Society) for the genetic screening of gamete donors is given below⁵⁸.

“Genetic history

The donor should not have any significant heritable condition; this being defined as one that has a major adverse effect on lifestyle or life prognosis. When taking the medical history, enquiries should be made to establish that the potential donor does not have familial disease with a major genetic component, such as cleft lip or palate, congenital hip dislocation, neural tube defects, congenital heart malformation, clubfoot or (in the male) hypospadias. These have an increased chance of occurring

⁵⁷ <http://www.hfea.gov.uk/498.html>

⁵⁸ Association of Biomedical Andrologists; Association of Clinical Embryologists; British Andrology Society; British Fertility Society; Royal College of Obstetricians and Gynaecologists. UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors (2008). Hum Fertil (Camb). 2008 Dec;11(4):201-10. doi: 10.1080/14647270802563816.

Appendix 6

in the offspring of an affected individual; any significant Mendelian disorders, such as (but not exclusively) albinism, haemophilia, haemoglobin disorders, hereditary hypercholesterolemia, neurofibromatosis or tuberous sclerosis; familial disease with a known or reliably indicated major genetic component, such as debilitating asthma, juvenile diabetes mellitus, epileptic disorder, severe hypertension, a psychosis, rheumatoid arthritis or a severe refractive disorder; a chromosomal rearrangement that may result in unbalanced gametes. Furthermore, the potential donor should ordinarily not be heterozygous for an autosomal recessive gene known to be prevalent in the donor's ethnic background. This includes cystic fibrosis in Caucasian populations, glucose-6-phosphate dehydrogenase deficiency or α^0 or β -Thalassaemia in Mediterranean populations, sickle cell disease in African & Afro-Caribbean populations and Tay-Sachs disease in Jews of Eastern European descent. But in exceptional circumstances (e.g. in cases of known donation where the donor is known to the recipient) the presence of a recessive gene disorder may not necessarily be a contraindication to donation provided that when the donation is used, all parties are fully informed and the view of an appropriately qualified clinical geneticist is obtained.

This should take into account the type of treatment being offered as well as the genetic profile of the donor and recipient couple.

Family genetic history

Enquiries should also be made to establish that the potential donor's genetic parents, siblings and offspring are free of: any of the major malformations outlined in the first bullet point above; non-trivial disorders showing Mendelian inheritance in the following categories: autosomal dominant or X-linked disorders, such as Huntington's disease; autosomal recessive disease particularly if it has a high frequency in the population such as, for example, cystic fibrosis; a chromosomal abnormality (unless the donor has a normal karyotype); a history of any mitochondrial disorders (egg and embryo donors only). If there is any evidence of the above, then an appropriately qualified clinical geneticist should evaluate the risk and the donor be offered any relevant screening."

European practice⁵⁹

UK practice is based on EU regulations although the interpretation varies in different EU countries. The European Sperm Bank operates throughout Europe (and the USA, Canada, South America, Australia) and their screening includes tests for the following:

- 3-4 generation family medical history, which is reviewed by a trained genetic specialist or medical doctor
- Cystic fibrosis screening for 32-86 mutations in the cystic fibrosis gene (all Caucasian donors)
- Chromosome analysis
- Thalassaemia (all donors). An HPLC (high performance liquid chromatography) analysis is done to detect this indirectly.
- Tay-Sachs disease (donors with Ashkenazi Jewish or French Canadian ancestry)
- Canavan disease (donors with Ashkenazi Jewish ancestry)
- Familial dysautonomia (donors with Ashkenazi Jewish ancestry)
- Fanconi anemia type C (donors with Ashkenazi Jewish ancestry)
- Gaucher disease (donors with Ashkenazi Jewish ancestry)
- Niemann-Pick type A disease (donors with Ashkenazi Jewish ancestry)
- Sickle cell disease (donors with African ancestry are genetically screened).

US practice

This is largely unregulated within States but sperm banks are subject to professional regulation that is similar to that in Europe. Sperm banks are regulated at the national level by the AATB.

⁵⁹ <http://www.europeanspermbank.co.uk/>

Appendix 7: Risks of genetic based variations from existing transplant procedures

Questions asked in search

- Under what circumstances are 'foreign' DNA found in a recipient? This would be a potential precedent for evidence of subsequent problems in a recipient.
- Are there any reports of that causing problems?
- What are the long term outcomes/complications (e.g. cancer) of (i) solid organ transplant (ii) bone marrow transplant?
- Have any of the problems been associated with genetic problems in the donor cells?

The implications of Chimerism

Chimerism is a common phenomenon. It is a normal occurrence during pregnancy and can exist in the long term after parturition⁶⁰. Fetomaternal microchimerism may be beneficial during the implantation process and there is no evidence that there are long term consequences for the mother.

Similar benefit for the recipient may be seen in the development of a stable chimerism after transplant as the requirement for immunosuppressants may be reduced or removed entirely. This understanding has led to the practice of giving donor leukocytes as part of stem cell therapy to promote stable chimerism.^{61,62,63}

⁶⁰ Dawe GS, Tan XW, Xiao ZC. [Cell migration from baby to mother](#). Cell Adh Migr. 2007 Jan-Mar;1(1):19-27. Epub 2007 Jan 28.

⁶¹ For chimerism, see <http://www.4transplant.com/en/chimerism.htm>

⁶² Scandling JD, Busque S, Dejbakhsh-Jones S, Benike C, Millan MT, Shizuru JA et al. [Tolerance and Chimerism after Renal and Hematopoietic-Cell Transplantation](#). N Engl J Med 2008; 358:362-368. January 24, 2008. DOI: 10.1056/NEJMoa074191

⁶³ Baron F, Sandmaier BM. [Chimerism and outcomes after allogeneic hematopoietic cell transplantation following nonmyeloablative conditioning](#). Leukemia (2006) **20**, 1690–1700. doi:10.1038/sj.leu.2404335; published online 27 July 2006

Do donor cells cause an unwanted problem in recipients?

As yet there are no long term follow up studies of recipients of the advanced cell therapy products that are the subject of this review. This review is therefore of outcome for the recipients of solid organ transplants and bone marrow transplant.

Organ donation

There is a risk of an undiagnosed tumour in a donor at the time of donation which may be passed on to the recipient. In one case, 3 recipients developed a melanoma from a donor⁶⁴. The same study found that '8 deaths, in a cohort of 108,062 recipients, represent an overall donor related tumor death rate of 0.007% or 1 donor related tumor death for every 13,508 recipients' i.e. a very small risk. Since the risk of this occurring may be higher in older donors, it has been suggested that the donor age should be considered⁶⁵. This relates to tumours in the donor at the time of donation and that risk would be higher in those who have an increased genetic risk of cancer.

A more recent study reviewed the outcome of 30,765 transplants from 14,986 donors and found that the risks of donor origin cancer was 0.06%, donor derived cancer 0.01% and donor transmitted cancer 0.05%.⁶⁶ This study concluded that the risks are rare, cannot be eliminated and that this information should be the basis of taking informed consent.

There has also been a long term follow up of transplant survivors⁶⁷. Unfortunately the cause of death of many recipients was not given in that study so it is not helpful for this review. A recent review of the cancer risk for solid organ transplant survivors has been reported⁶⁸. This found that the cancer rate was double that of the population. There was considerable variety of tumour type and it was assumed that the

⁶⁴ Myron Kauffman H, McBride MA, Cherikh WS, Spain PC, Marks WH, Roza AM. [Transplant tumor registry: donor related malignancies](#). Transplantation. 2002 Aug 15;74(3):358-62.

⁶⁵ Niederwieser D, Gentilini C, Hegenbart U, Lange T, Moosmann P, Pönisch W et al. [Transmission of donor illness by stem cell transplantation: should screening be different in older donors?](#) Bone Marrow Transplant. 2004 Oct;34(8):657-65.

⁶⁶ Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. [Cancer transmission from organ donors-unavoidable but low risk](#). Transplantation. 2012;94(12):1200-7.

⁶⁷ Ramcharan T, Matas AJ. [Long-term \(20-37 years\) follow-up of living kidney donors](#). Am J Transplant. 2002 Nov;2(10):959-64.

⁶⁸ Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ et al. [Spectrum of cancer risk among US solid organ transplant recipients](#). JAMA. 2011 Nov 2;306(17):1891-901. doi: 10.1001/jama.2011.1592.

pathologies were largely related to associated therapy and original pathology. There was no discussion about a potential genetic origin of the tumour.

A further long term study (20 to 37 years) of living kidney donors revealed too many unknown causes of death to be helpful⁶⁹.

Bone marrow transplantation

There is an increased risk of cancer in survivors of BMT. In one study it was found to be 3.8 times higher⁷⁰ and the cause was thought to be related to the immunosuppressant therapy. In another study the rate was 4.5 times higher⁷¹. In that report, all the tumour DNA was of recipient origin. A case report of squamous cell carcinoma after BMT found donor cells within the tumour but the tumour was not thought to be of donor origin⁷².

Tests related to risk to donor

There are recommendations that relate to the screening of donors for conditions that include genetic based pathology but these all relate to the risk to the donor of the donation process^{73,74}.

⁶⁹ Ramcharan T, Matas AJ. [Long-term \(20-37 years\) follow-up of living kidney donors](#). Am J Transplant. 2002 Nov;2(10):959-64.

⁷⁰ Kolb HJ, Socié G, Duell T, Van Lint MT, Tichelli A et al. [Malignant Neoplasms in Long-Term Survivors of Bone Marrow Transplantation](#). Ann Intern Med. 1999;131(10):738-744. doi:10.7326/0003-4819-131-10-199911160-00004

⁷¹ Au WY, Chan EC, Pang A, Lie AK, Liang R, Yuen AP et al. [Nonhematologic malignancies after allogeneic hematopoietic stem cell transplantation: incidence and molecular monitoring](#). Bone Marrow Transplant 2004;34:981–5.

⁷² Miyawaki Y, Imoto I, Tokairin Y, Kawada K, Nakajima Y, Nishikage T et al. [Esophageal squamous cell carcinoma developed 11 years after allogeneic bone marrow transplantation for acute lymphatic leukemia](#). Jpn J Clin Oncol. 2013 Jan;43(1):69-73. doi: 10.1093/jjco/hys184. Epub 2012 Dec 4.

⁷³ Halter JP, van Walraven SM, Worel N, Bengtsson M, Hägglund H, Nicoloso de Faveri G et al. [Allogeneic hematopoietic stem cell donation-standardized assessment of donor outcome data: a consensus statement from the Worldwide Network for Blood and Marrow Transplantation \(WBMT\)](#). Bone Marrow Transplant. 2013 Feb;48(2):220-5. doi: 10.1038/bmt.2012.119. Epub 2012 Jul 9.

⁷⁴ Ljungman P, Bregni M, Brune M, Cornelissen J, de Witte T, Dini G et al. [Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe 2009](#). Bone Marrow Transplant. 2010 Feb;45(2):219-34. doi: 10.1038/bmt.2009.141. Epub 2009 Jul 6.

Appendix 8: The genetic basis of disease and screening healthy individuals

The genetic basis of disease

Genetic variations in the DNA of different individuals and between the various cells and tissues of the body are the primary cause of most rare diseases. In addition they may interact with environmental factors to influence a person's susceptibility to, or the course of, common conditions.

Variation in constitutional DNA

Variants in the DNA carried on chromosomes in the nucleus exert their influence on the cell and the body by determining the quantity of proteins and how effectively they function in metabolism and in forming the structure of tissues. Individuals differ in appearance and other characteristics because of normal genetic variation, which is also reflected in different susceptibility to disease-causing environmental factors including smoking, elements of the diet and exposure to infectious agents.

More dramatically a simple genetic variant may be sufficient to trigger a monogenic disease. This may be inherited from one parent (dominant diseases and recessive conditions carried on the X-chromosome) or from both parents (autosomal recessive conditions). The risk to an individual of being affected by this type of disease or of passing it to a child is often indicated by a family history of the condition.

Single gene disorders may also be the result of a spontaneous new mutation occurring in the formation of a gamete or an error occurring in the first few cell divisions in the developing embryo. In this circumstance the resulting genetic disease appears sporadically and in the absence of any family history.

Similarly large scale chromosomal imbalances which may extend to the loss or gain of a whole chromosome can develop in gamete formation or early embryo development, resulting in multisystem developmental conditions such as Down syndrome.

- **Mutations in mitochondrial DNA**

Most of the DNA in the cell is carried in the nucleus but some is carried in thousands of mitochondria in the cytoplasm. Mitochondrial DNA (mtDNA) codes for genes essential for the energy-generating function of these cell organelles. Mutations in mtDNA are inherited through the female line (in the cytoplasm of the unfertilised egg). Eggs can contain all normal or all abnormal mtDNA or both normal and abnormal mtDNA. Mitochondrial diseases are often multisystem disorders; symptoms can include neurological problems, seizures, developmental delay, visual and/or hearing impairment, heart and/or liver failure. The severity of symptoms usually relates to the proportion of normal to abnormal mitochondria.

- **Acquired somatic mutations**

Errors in DNA replication in cell divisions occurring after birth and at any life stage from childhood to old age may result in a mutation which is carried stably in a set of daughter cells in a particular tissue. This is most frequently seen where the mutation triggers a chain of events leading to loss of control of cell proliferation and the formation of a cancerous tumour.

- **Epigenetic effects**

Embryonic tissues form as a result of specific and stable patterns of gene expression. The cells forming these tissues retain this differentiated state mostly by retaining and passing on to daughter cells a chemical modification of particular DNA bases forming a fixed imprint. An imbalance of this system can cause some childhood developmental genetic conditions, and its disruption in some somatic cells can be a cause of tumour development.

In a healthy individual can a medical and family history predict the risk of a genetic related pathology?

Many healthy individuals have one or two family members who share a medical condition but the predictive value of this information for the subject and their blood relatives is usually limited. A prediction of an enhanced risk of disease is possible if

the family history is more extensive, the inheritance pattern is obvious and symptoms clearly indicate a genetic disease.

Healthy patients are often referred from primary to secondary care and then to specialist clinical genetic services because of a concern raised by a family history. The example used here is familial breast cancer. In a triaging process the family history is first formally recorded and assessed, often with the aid of a computer algorithm. A woman may be reassured at this stage that her chance of breast cancer is not elevated over the population risk and advised to take advantage of the standard age-related cancer screening and advice on personal monitoring. A small number of patients at high risk are referred to a tertiary level service for a more detailed assessment of the pedigree which may involve confirming diagnoses using, for example, medical notes of affected relatives. In these cases an elevated risk of breast cancer in a healthy woman on the basis of her validated family history is used to offer to look for mutations in pre-disposition genes in an affected relative. Women from families with a known pathogenic genetic variant in one of the breast and ovarian cancer predisposition genes (BRCA1 or BRCA2) are offered a pre-symptomatic test.

In summary an expert assessment of family history is often used in clinical practice to modify a patient's risk of developing a genetic disorder.^{75,76,77}

To what extent can the risk of a genetic related pathology be identified by genome analysis?

In the illustration above, a healthy woman with a family history can be given an evidence based life-time risk of developing breast cancer based on an accurate genetic test for a family-specific genetic variant judged to be pathogenic.

⁷⁵ Biswas S, Atienza P, Chipman J, Hughes K, Barrera AM, Amos CI et al. [Simplifying clinical use of the genetic risk prediction model BRCAPRO](#). Breast Cancer Res Treat. 2013 Jun;139(2):571-9. doi: 10.1007/s10549-013-2564-4. Epub 2013 May 21.

⁷⁶ Turati F, Edefonti V, Bosetti C, Ferraroni M, Malvezzi M, Franceschi S et al. [Family history of cancer and the risk of cancer: a network of case-control studies](#). Ann Oncol. 2013 Oct;24(10):2651-6. doi: 10.1093/annonc/mdt280. Epub 2013 Jul 24.

⁷⁷ Kashani M, Eliasson A, Vernalis M, Costa L, Terhaar M. [Improving assessment of cardiovascular disease risk by using family history: an integrative literature review](#). J Cardiovasc Nurs. 2013 Nov-Dec;28(6):E18-27. doi: 10.1097/JCN.0b013e318294b206.

Appendix 8

In the absence of a family history or a sign or symptom related to a medical condition, genetic tests on healthy individuals in the NHS setting are not carried out. However a current large scale National Institute for Health Research study is assessing the utility of combining standard mammography screening with the utility of a medical and family history plus an analysis of a number of genetic biomarkers to personalise the optimum interval for further breast screening.

In the direct-to-consumer genetic testing market, a screen of a panel of single nucleotide polymorphism biomarkers indicative of raised or lowered risks relative to the population risk of common conditions is offered to healthy persons. These tests probably have a low absolute predictive value of disease risk in any one individual. For example the US Evaluation of Genomic Applications in Practice and Prevention (EGAPP) programme evaluated a test of 28 genetic variants claimed to predict the risk of type 2 diabetes in the general population. EGAPP concluded that the net health benefit from this test 'is close to zero' and discouraged clinical use without further evidence^{78,79}.

⁷⁸ Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. [Recommendations from the EGAPP Working Group: genomic profiling to assess cardiovascular risk to improve cardiovascular health](#). Genet Med. 2010 Dec;12(12):839-43. doi: 10.1097/GIM.0b013e3181f872c0.

⁷⁹ Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. [Recommendations from the EGAPP Working Group: does genomic profiling to assess type 2 diabetes risk improve health outcomes?](#) Genet Med. 2013 Aug;15(8):612-7. doi: 10.1038/gim.2013.9. Epub 2013 Mar 14.

Appendix 9: Worked examples – consent and traceability

CATEGORY 1 - Minimally manipulated cell therapies

- 1A Autologous haematopoietic cells (HSC)
- 1B Allogeneic haematopoietic cells
- 1C Allogeneic cord blood
- 1D Autologous cord blood
- 1E Autologous immature gametes

CATEGORY 2 - Somatic cell therapies

- 2A Corneal limbal stem cells
- 2B Mesenchymal stromal cells (MSC)

CATEGORY 3 – Stem cell lines

- 3A Induced pluripotent cells (iPS cells)
- 3B Human embryonic stem cells (hESC)

CATEGORY 1 – MINIMALLY MANIPULATED CELL THERAPIES

EXAMPLE 1A – Autologous haematopoietic stem cells

Background

Anne is a 52 year old woman with multiple myeloma. As she is fairly young and otherwise in good health, her doctors believe she is a good candidate for a HSC transplant, using her own stem cells, as part of her treatment. First she is given medication to stimulate her body to produce HSCs, which are removed and stored. In the following week, Anne receives large doses of chemotherapy to kill the cancer cells. She then receives her own stem cells back through an infusion; this should help the bone marrow to start producing healthy cells again.

Complexity of product – Low: no manipulation and storage time is usually quite short.

Risk to/exposure of recipients – Low: usually the single donor is also the single recipient.

a) Regulation

Established procedure, governed by:

- EU Tissues & Cells Directive (2004/23/EC), transposed into UK law as the Human Tissue (Quality & Safety for Human Applications) Regulations 2007 (SI 2007: 1523)
- NHSBT MPD 565.

b) Ethics and consent

Generally extremely straightforward, as long as the underlying condition merits the risk of the procedure. The donor consents to the stem cells being harvested and used for their own treatment.

Increasingly, though, the stimulation of the bone marrow to increase the peripheral blood HSCs is so effective that excess stem cells are produced. This primarily allows for additional autologous transplants to take place in the future if the first one fails. The patient consents to the cells being frozen and stored, and discarded when they are no longer required (if patient is cured or dies) or if they prove unsafe or unsuitable for use.

c) Traceability

Very straightforward, due to donor and recipient being same. There may be a period of up to 10 years between collection and use of material.

d) Consent form

Example - Scottish National Blood Transfusion Services NATF 087 02 (Relates to SOP No. NATS CLS 025) - *Consent for Autologous HPC-A Collection and Storage (adult donor)*.

EXAMPLE 1B - Allogeneic haematopoietic stem cells

Background

John is 25 years old, and has been diagnosed with acute myeloid leukaemia, a blood cancer. After he did not respond to chemotherapy, his medical team decided to treat his condition with a transplant of healthy HSCs from a suitable donor. John's sister and brother both were willing to be donors, and they were tested, but were found to be unsuitable – neither had the same tissue type as John. The doctors then approached the registry of people willing to donate stem cells or bone marrow. They found a match for John in Alan, a 22 year old student. The registry contacted Alan, and arranged for him to travel to London to have peripheral HSCs collected. These were then transplanted into John.

Complexity of product – Low: no manipulation and storage time is usually short.

Risk to/exposure of recipients - Low: usually there is a single donor and a single recipient. There is rigorous medical screening of the donor.

a) Regulation

Established procedure, governed by:

- Human Tissue Authority's Code of Practice 1 on *Consent* and Code of Practice 6 on *Donation of Allogeneic Bone Marrow and Peripheral Blood Stem Cells for Transplantation*
- EU Tissues & Cells Directive (2004/23/EC), transposed into UK law as the Human Tissue (Quality & Safety for Human Applications) Regulations 2007 (SI 2007: 1523)
- NHSBT MPD 565.

b) Ethics and consent

Generally straightforward. The BBMR (British Bone Marrow Registry) maintains details of potential altruistic donors, who will only be called upon to make a donation if there is a match. Expenses are paid. The main issues concern consent where the matched donor is a relative, particularly a child, but this is covered in depth by the HTA. Note that some of the searches are global; there are various registries that are/can be searched to find an identical match. HTA insists that the collection/consent/screening needs to be equivalent to UK standards, and this is covered by guidance from the Bone Marrow Donors Worldwide and individual registries.

c) Traceability

Few potential difficulties, because of the recruitment of donor through the family or registry; single donor and single recipient; and the short time frame between collection and use of material.

d) Consent form

Example - NHSBT Form 1365/2 *Information for Stem Cell Donors/Consent*.

EXAMPLE 1C – Allogeneic cord blood

Background

Lucy is pregnant, and under the medical care of a hospital which offers women the opportunity to donate cord blood after the birth of her baby to the public cord blood bank. (There are currently 6 such hospitals in England and 1 in Scotland: the cord blood is collected, processed, stored and supplied by the NHS Cord Blood Bank in England and the Scottish National Cord Blood Bank.) Lucy decides to donate her cord blood. This will be held in the public cord blood bank, and transplanted into matched patients when required. Cord blood is rich in stem cells, and can be used to treat patients with a wide range of blood disorders and cancers. Only 3-4% of stored cord blood is released on an annual basis. There is therefore a large reservoir of cells - many of which will never be released for clinical use, due to quality of the product collected. There is increasing demand to release these cells for research, which raises consent issues that need to be covered at the time of collection.

Complexity of product – Low: no manipulation. Storage time can vary from very short to long.

Risk to/exposure of recipients – Low: usually there is a single donor and a single recipient. There is rigorous medical screening of the mother.

a) Regulation

Established procedure, governed by:

- EU Tissues & Cells Directive (2004/23/EC), transposed into UK law as the Human Tissue (Quality & Safety for Human Applications) Regulations 2007
- Facilities must have HTA licence.

b) Ethics and consent

Donation to a public cord blood bank is an altruistic act. However, the first priority of a medical team is the safe delivery of the baby. Consent in England is currently being updated; it currently allows wide interpretation of use of stem cells donated in this way.

c) Traceability

Straightforward if the transplant happens soon after cord blood is banked, but becomes more problematic when cord blood is used overseas (allowable by consent form) or after long storage times (which is routine).

d) Consent forms

Examples - NHSBT Form 2794/3 *Consent for Cord Blood Donation, Testing, Storage & Use* (currently being updated) and Scottish National Blood Transfusion Service Cord Blood Bank Form GLAF CBB 001 05 *Consent for Cord Blood Donation, Testing, Storage & Use*.

The following website, relating to public banks in the US, gives a very good account of the 'process' that would ideally be followed -

<http://bloodcell.transplant.hrsa.gov/cord/options/donating/index.html>.

EXAMPLE 1D – Autologous cord blood

Background

Another option open to Lucy, who is pregnant, is to arrange to have her cord blood collected and stored by a private cord blood bank. A number of such private cord blood banks have been established recently, and are marketing their services actively. The motivation behind collection by a private cord blood bank is entirely different from altruistic, allogeneic donation. Cord blood being collected and stored for possible autologous use in the future provides families with an “insurance policy” should their child develop a condition treatable with their own cord blood. This topic is currently subject to much debate. Quite apart from commercial aspects concerning the fees charged by such organisations for their services and the slim chances of the stem cells ever being required, uncertainty remains over the efficacy of such treatments after the cord blood has been stored for long periods.

Complexity of product – Uncertain - Some manipulation might take place in the future, and storage times are usually long.

Risk to/exposure of recipients – Uncertain – Although the donation is hypothecated for use of the donor and his or her family, uncertainty surrounds the clinical utility of such materials.

They may also be used allogeneically if they are not used autologously: some banks propose this e.g. Virgin Health Bank has partnered with the NHS. If this is done, appropriate consent is sought up-front.

a) Regulation

This is covered by the HTA in the UK. (Currently, in some countries it is illegal and many potential donors travel to give birth in countries where it is allowed, to enable them to take part in this programme).

b) Ethics and consent

There are several issues to consider in this context. Public cord banks in the UK do not usually offer an autologous service, so commercial companies will provide the main option to those wishing to bank their baby's umbilical cord for their own use. The Council of Europe, concerned by the proliferation of private cord blood banks, has issued recommendations (at <https://www.edqm.eu/en/autologous-cord-blood-banks-1520.html>). Their concern has been shared by relevant Medical and Nursing bodies, for example the Royal College of Obstetrics and Gynaecology⁸⁰, who have considered the potential for a conflict of interest during a baby's delivery. The key issue is the need for proper consent based on sound and accurate information (no hyperbole about the cell utility, no emotional coercion), and the consent form signed by the donor should be quite separate from any storage or contractual agreement. Attention must also be paid to the need for Good Manufacturing Practice of the products.

c) Traceability

Although the family donating should be sufficiently motivated to keep a record of where the cord blood is stored, long storage periods and dependence on the record-keeping of private companies could cause traceability problems. Any traceability system needs to be all-encompassing to include all involved parties, commercial or otherwise.

d) Consent forms

Consent forms are hard to access and probably vary too much to offer a single example of good practice.

EXAMPLE 1E – Autologous immature gametes

Background

Sarah is a 10-year-old girl newly diagnosed with Hodgkin lymphoma. She is about to start chemotherapy, and she and her parents have been told that a side-effect of the treatment may be to leave her infertile. They are discussing whether she should have her own immature gametes collected and frozen for potential use some time in the future. This would involve ovarian slices being collected through a laparoscopic surgical procedure, and then frozen, until such time that Sarah, in conjunction with her clinician, decides to use them, or until they will not be required e.g. following a spontaneous pregnancy. It is possible that the eggs would have to be stored for a period in excess of 20 years. Professional guidelines exist as to when it is appropriate to use these cells.

⁸⁰ The Royal College of Obstetrics and Gynaecology advice is published at <http://www.rcog.org.uk/womens-health/clinical-guidance/umbilical-cord-blood-banking>.

If a decision is made not to use them for Sarah, such eggs are increasingly being used for research. Currently, when the gametes are collected, the donor is given an option to consent to be approached in the future about them being used for research; Sarah would have to give specific consent for each research project in which her gametes were used.

Complexity of product – Low: no manipulation. Storage time can vary.

Risk to/exposure of recipients – Low: they are the patient's own gametes.

a) Regulation

This is a relatively established procedure, governed by:

- EU Tissues & Cells Directive (2004/23/EC), transposed into UK law as the Human Tissue (Quality & Safety for Human Applications) Regulations 2007 (SI 2007: 1523)
- Human Fertilisation and Embryology Act (2008) (competent body HFEA).

b) Ethics and consent

Relatively straightforward, as the immature gametes are being collected to be used in the donor's own treatment. But because consent is being obtained in respect of a child, the parents will need to be involved. (Note the laws on capacity to consent, including on the basis of age, are different in Scotland from the rest of the UK). Also these cells may be used for research purposes if they are no longer needed.

c) Traceability

Length of time between collection and storage causes traceability problems, even with small and simple programmes. Note that traceability data are EU requirement for 30 years after the product has been used or discarded.

d) Consent form

There are HFEA forms for this specific purpose.

CATEGORY 2 – SOMATIC CELL THERAPIES

EXAMPLE 2A – Corneal epithelial stem cells

Background

In a work accident, Peter suffered a chemical burn to his right eye. In an attempt to restore the sight of this eye, he is going to undergo a transplant of corneal epithelial stem cells from the limbal region (at the rim of his cornea). The cells will be taken from his left eye, which was undamaged (although it would also be possible to use such cells donated by living or deceased donors). The cells are isolated and cultured for a limited period of time *in vitro*, before being transplanted onto the cornea of Peter's right eye, on a bed of donated amniotic membrane (placenta).

Complexity of product – Medium: although the storage time is short, the cell culture process, with its substantial manipulation of the cells, introduces additional risks.

Risk to/exposure of recipients – Low: either autologous, or one donor for one or two recipients at most.

a) Regulation

Original cell retrieval governed by:

- EU Tissues & Cells Directive (2004/23/EC), transposed into UK law as the Human Tissue (Quality & Safety for Human Applications) Regulations 2007. After donation, procurement and testing, it becomes an ATMP and is governed by:

- EC Reg 1394 2007 & Medicines Directive 2001/83/EC (competent body MHRA)
- European Medicines Agency (re marketing)
- EU Good Manufacturing Practices (Eudralex Volume 4) (re manufacturing, testing and release)
- EU Clinical Trial Directive (2001/20/EC) & Good Clinical Practice (2005/28/EC and Eudralex Volume 10) (re testing in the clinical setting).

b) Ethics and consent

For autologous donors, the ethical and consent issues are reasonably straightforward, as long as the underlying condition merits the risks of the procedure. The donor consents to the cells being harvested and used for a specific purpose, which should result in therapeutic benefit. However, the manipulation of the cells introduces complexity in terms of the character and function of the final product.

c) Traceability

Straightforward, due to donor and recipient being the same, or the therapy being used for a limited number of patients (2 at most), and because the material is used following only a few days of storage in culture.

d) Consent form

Routine tissue donor consent forms are used for both autologous and allogeneic donations.

EXAMPLE 2B - Mesenchymal stromal cells

1 donor- potentially many recipients - ATMP

- Starting material - autologous or allogeneic -from bone marrow, adipose tissues or tissues of mesenchymal origin
- Transplanted into patient after a period (sometimes prolonged) of culture
- Many other potential recipients may be exposed to this material.

Background

Peter is a middle aged man who suffered from acute myeloblastic leukaemia. He received a bone marrow transplant from an unrelated donor where the match was only 4/6. The graft took and the patient was recovering well, but after a few weeks Peter developed severe graft versus host disease, which did not respond well to conventional therapy. This is a well recognized complication after such a transplant. Graft versus host disease varies in severity from Grades I to IV, becoming progressively more severe. In Peter's case the severity was such (Grade III) that Peter was in danger of losing his life from this complication. Peter had not responded to standard second line treatment for this condition.

It is known that MSCs are useful in ameliorating graft versus host disease and the consultant in charge discussed the option with Peter of enrolling him in a clinical trial of MSC injections from an unrelated donor. The consultant explained to Peter that experience with such cells is rather limited, but trials done to date indicate that MSCs are indeed beneficial in such a situation. Such therapy is not a standard form of therapy and can only be done in the context of a clinical trial. Peter agreed to this, having understood that this is experimental treatment, but with the expectation that some improvement may occur. The consultant gave Peter a detailed information leaflet and a full consent sheet was signed by both parties.

Side effects of MSC infusions are not usually severe and in many cases the infusions are completely uneventful.

Complexity of product – High

Risk to/exposure of recipients – High: the cultures derived from one donation may be passaged and purified a number of times and given to numerous recipients.

a) Regulation

The cell collection is governed by the EU Tissues and Cells Directive (2004/23/EC) **and after culture MSCs are considered as ATMPs and are governed by EC Reg 1394 2007** and the Medicines Directive (2001/83/EC), EU Good Manufacturing Practices (Eudralex Volume 4) with respect to manufacturing, testing and release and EU Clinical Trial Directive (2001/20/EC) and Good Clinical Practice (2005/28/EC and Eudralex Volume 10) with respect to testing in the clinical setting.

Their use in a clinical trial is governed by the Clinical Trial Regulations, while Marketing Authorisation is through the centralised procedure.

b) Ethics and consent

MSCs may be derived from

identical or haplo-identical donors or unrelated third party donors.

Donor selection is usually straightforward and follows that for other stem cell donations of which there are many worked examples. It is essential that there is no coercion on siblings to donate.

All MSCs in use to date are used in the context of a clinical trial, and detailed explanatory documents must be discussed with the recipients to ensure informed consent is extant.

c) Safety and traceability

Donors of MSCs, particularly unrelated ones, need to be aware that their cells may be stored for a significant period of time and that the products derived from their cells may be used for many patients, possibly in a variety of clinical situations. It is important that consent is as explicit as possible and should include the use of their cells for therapeutic purposes, and if not so used, whether the cells can be used for research, including (and specifically) commercial research, and/or for training purposes. It is also important that the donors are aware that if the cells cannot be used (for any reason), they will be discarded using appropriate and safe methods.

The donors also need to be aware that their donated cells may be stored for prolonged periods of time and that it is highly likely that newer microbiological markers may be discovered in the time after the cells were donated. To ensure the safety of the products such new markers will be tested for. It is essential that potential donors are fully aware of this.

Current protocols in the context of tissues and cells dictate, that should a microbiological marker be found at any time which may have implications for the donor or their family, the donor will be informed, even when these tests are performed a significant period of time after their donations. Past experience has shown that this duty of care prevails. It may be that donors who do not wish this to happen should not be enrolled in such procedures.

Appendix 9

If such procedures are followed it clearly becomes very important to be able to maintain a robust system of traceability to enable contact to be made with the donors for a prolonged period of time. (Current EU regulations require the maintenance of traceability data for 30 years after clinical use or discard, from the ATMP Regulation Article 15 - “a minimum of 30 years after the expiry date of the product”). Numerous IT based systems already exist and it may be useful to examine some of them in some detail. It will be important that such traceability systems are properly governed, are robust and flexible enough to allow for the necessary anonymisation of products while still allowing the necessary traceability, either for the donor’s benefit (or his/her family’s) or if public health issues arise. It is also essential that such systems are all-encompassing, including all the parties involved in this work - blood establishments, universities, hospitals and others.

CATEGORY 3 – STEM CELL LINES

EXAMPLES 3A and 3B - Induced pluripotent cells and human embryonic stem cells

1 donor-potentially very many recipients (potentially limitless). Classed as ATMPs

- Collection of originating cells governed differently- iPS cells are governed by HTA under the EUTCD for donation, procurement and testing (but derivation may be under medicines legislation in the future) and hESC are governed by HFEA.
- These products are not in general use at the moment and although potential in the future is potentially limitless, current use is very restricted. To put their use in context, there are currently four ATMP licensed in the EU. In the UK there is one clinical trial using hESC derived retinal pigment epithelial cells for Stargardt's macular dystrophy.

Both types of cells may be kept for prolonged periods of time and therefore the issues described under example 2B are all very relevant. Safety of the products becomes even more critical in view of the potential exposure to them of a very high number of recipients. It is likely that the products in question will be tested very rigorously with the most sensitive tests available at the time of release. (Current methodology would at least be NAT testing for a range of microbiological agents). As has been described earlier, in the case of hESC, there are specific and significant issues surrounding the testing of the cell donors. Testing of the product using validated methodology would be a very useful way forward. This is currently not lawful and changes in EU regulation are already being sought to allow it to happen.

The issues of consent, particularly in the case of hESC, also deserve special consideration. Whilst the issues mentioned previously (example 2B) are all very relevant, there are some different issues that merit particular thought. Current practice surrounding the donation of gametes to form embryos is primarily done to treat infertility - not for reasons of research or future therapies. Strict regulations surround the process of gamete donation and the uses of embryos resulting from such donations. They vary according to whether the purpose of the gamete donation is to form embryos to treat infertility or purely for research, but in both cases fully informed, written, signed consent of the gamete donors is essential. In particular, gamete donors being asked to consent to the formation of embryos for research purposes must understand what the research is about, so that they can qualify their consent if appropriate. We believe that the creation of hESC lines should be grounded in these ethical principles and regulation.

Finally it is important to mention that particularly in this context (i.e. examples 3A and 3B) it is likely that depending on the envisaged therapeutic clinical intervention being contemplated, specific tests will be done on the cell line in question, to ensure that it is satisfactory for the condition it is being used for. It may also be tested for specific genes e.g. as would be the case if the cells are

being used to treat Huntington's disease. This knowledge may have significant implications for the donors or their family. Because the use of these products is so protean, it is not known at the time of collection which genes / specific markers one would test for in the future. Donors need to understand this at the time of donation to grasp the potential implications. Therefore consent should be as clear and as explicit as possible.

Issues of traceability are similar to those described above (Article 15 of the ATMP Regulation). It is important that traceability mechanisms allow for the tracing of potentially a large cohort of recipients (as is likely). It is also essential to be able to keep track of the donors to a particular product.

The British Society for Human Genetics, The Royal College of Physicians and The Royal College of Pathologists has recently issued a joint report on Consent and Confidentiality in Clinical Genetic Practice which provides very useful guidance in this regard.⁸¹

⁸¹ Royal College of Physicians, Royal College of Pathologists and British Society for Human Genetics. [Consent and confidentiality in clinical genetic practice: guidance on genetic testing and sharing genetic information, 2nd edn. Report of the Joint Committee on Medical Genetics](#). London: RCP, RCPATH, 2011.

Appendix 10: The donation journey – potential hotspots

Issues of consent and traceability to consider

Starter material - what material are we talking about?

Recruitment of donors - how do we attract donors, what might count as a reasonable incentive, what might count as coercion or exploitation? How does this form of donation differ in terms of what people need to know / can know up front?

Availability of material - how do we decide that something is reasonably available for donation e.g. when is an embryo genuinely 'spare', what if the material comes from a baby or deceased individual? Is there a difference between 'waste products' such as a circumcised foreskin and other forms of material which could be of use to the donor e.g. blood? What is the primary intention of the procedure?

Consent to donation - how, when and by whom is consent sought? How do we guard against conflicts of interest e.g. in the Assisted Reproductive context where embryos might be sought for research purposes from people who want them to become babies? What do people need to know in order to consent and how do we deal with the inherent uncertainty in this context? Should consent be fettered or unfettered?

Consent to testing of material/donor - to ensure the safety of donated products, do we need to test the donor and/or the product and how do we feed back information to anyone deemed unsuitable to donate? What if new tests develop over time and are applied to stored material, do we give people the results?

Consent to potential uses - sometimes we argue that ends justify means but would it ever be safe to think that way in this context? Having said that, do we have to think in terms of making morally relevant distinctions between different kinds of use e.g. major or relatively minor uses, life-enhancing, life-creating and life-saving etc? To what extent should we be defining or limiting future possible uses?

Consent to storage and discard - time periods, when can it be discarded?

Traceability - how easy and practical is it to maintain traceability?

Duty to inform - how, if at all, does an individual (or their family) remain tied to a donation in terms of entitlement to information about what was done with it, what was achieved (or not)? This is slightly different to the clinically relevant information that might be discussed under traceability.

Operational Issues (though out-of-scope of this group's remit)

Collection of material - how will the material be collected, and will this be disruptive of normal practices if it is in a therapeutic setting e.g. umbilical cord? How burdensome is it? Are there any risks involved?

Storage of material - what sort of storage system do we feed into, is it possible / important to offer anonymity / confidentiality to people? What can we learn (good and bad) from existing biobanks and repositories?

Access to materials - how do we set up governance structures for access to stored material etc (consider international perspective, private enterprise etc)?

	EXAMPLE 1A
Starter Material	Autologous haematopoietic stem cells (to be used in donor's own treatment)
Recruitment of donors	Donors motivated to donate, as best treatment for self.
Availability of material	Specific aim of procedure is to obtain stem cells.
Consent to donation	Straightforward. As per other medical procedures, risks of procedure will be balanced by therapeutic benefits, and fully explained to patient.
Consent to testing of material/donor	Tests for infectious agents including HIV, HBV, HCV, syphilis and HTLV, and possible further tests in future. Will be informed of results, and if an abnormal test is found, will be asked to attend for further tests and advice.
Consent to potential uses	Obtaining consent for specific collection of stem cells for own treatment is straightforward. Increasingly, though, excess stem cells are collected, primarily to allow for additional autologous transplants to take place in the future.
Consent to storage and discard	The patient consents to the cells being frozen and stored, and discarded when they are no longer required (if patient is cured or dies) or if they prove unsafe or unsuitable for use.
Traceability	Very straightforward, due to donor and recipient being same. There may be a period of up to 10 years between collection and use of material.
Duty to inform	
OPERATIONAL ISSUES	
Collection of material	Specific aim of procedure is to collect stem cells.
Storage of material	Straightforward.
Access to materials	

	EXAMPLE 1B
Starter material	Allogeneic haematopoietic stem cells – generally haematopoietic stem cells from mobilised peripheral blood taken from a living, matched donor
Recruitment of donors	Donors motivated by altruism. Donor will either be someone matched from the combined Anthony Nolan / British Bone Marrow Registry (who is only paid reasonable expenses) or a relative of the patient requiring a stem cell transplant.
Availability of material	The material is only obtained after a match is ascertained, so has specific use in the treatment of one individual. The specific aim of the donation procedure is to collect stem cells.
Consent to donation	Freely given. Potential conflict of interest arises when a relative – particularly a child – is the donor.
Consent to testing of material/donor	Donors consent to testing for “important biological markers ” – some are listed but it is not an exhaustive list.
Consent to potential uses	Consent is for one donation to provide stem cells for one stem cell transplant for one matched patient. A further collection might possibly be required from the same donor for the same patient, but in such a case, separate consent would be obtained. The original consent also permits storage of T cells to be given after the same transplant. Consent allows “waste products” to be used anonymously for research, service development or education.
Consent to storage and discard	Agrees to storage and freezing of this single donation if required. Agrees to disposal of donation when no longer required or found to be unsuitable for clinical use.
Traceability	Few potential difficulties, because of the recruitment of donor through the family or registry; single donor and single recipient; and the short time frame between collection and use of material.
Duty to inform	
OPERATIONAL ISSUES	
Collection of material	Donation only occurs when match is found.
Storage of material	Generally donation used immediately, but in a few cases material will be stored for a very short time.
Access to materials	

	EXAMPLE 1C
Starter material	Allogeneic cord blood from altruistic donors who donate cord blood to the public cord blood bank after the birth of their babies
Recruitment of donors	Donors are largely motivated by altruism. There is no financial incentive to donors; the costs of donation and storage of the cord blood are borne by the cord blood bank.
Availability of material	Collection of material is secondary to safe delivery of baby; first priority of medical team is health of mother and baby. Birth has to take place in one of (currently) 7 NHS hospitals in UK with licence, trained staff and facilities.
Consent to donation	English consent form currently very general – but being updated. Scottish version very detailed.
Consent to testing of material/donor	Done by cord bank staff. Tested for routine microbiological markers and others specifically as required e.g. CMV.
Consent to potential uses	Altruistic donation.
Consent to storage and discard	Cord blood is stored for prolonged periods of time and the majority of the units collected are not released. Increasing pressure to use these cells for research purposes.
Traceability	Significant issues with maintaining traceability after such a long period of storage, particularly if the cord cells are used to produce ATMPs etc. Will also depend on the consent obtained.
Duty to inform	
OPERATIONAL ISSUES	
Collection of material	Few hospitals currently have licence, trained staff and facilities. Cord blood collection secondary to health of mother and baby.
Storage of material	Central public cord blood banks covering England and Scotland.
Access to materials	

	EXAMPLE 1D
Starter material	Autologous cord blood, usually collected, processed and stored in a private cord blood bank
Recruitment of donors	Commercial activity, marketed to pregnant women.
Availability of material	Collection of material is secondary to safe delivery of baby; first priority of medical team is health of mother and baby. Company collecting must be HTA registered.
Consent to donation	Important that there is no coercion and that all the facts about these cells and their potential uses are fully explained.
Consent to testing of material/donor	Maternal consent is always sought.
Consent to potential uses	Needs to be explained at the beginning of the process - depends on the approach of each particular bank; availability for allogeneic use; use for research etc.
Consent to storage and discard	Long term storage.
Traceability	Although the family donating should be sufficiently motivated to keep a record of where the cord blood is stored, long storage periods could result in traceability problems.
Duty to inform	
OPERATIONAL ISSUES	
Collection of material	
Storage of material	Company must be HTA registered. Important for companies to maintain their traceability even if they move, are sold or merge etc.
Access to materials	

	EXAMPLE 1E
Starter material	Autologous immature gametes
Recruitment of donors	Donor motivated to donate, although need to involve parents if under age of consent.
Availability of material	Specific procedure to collect gametes. In the future, some gametes may become “spare”.
Consent to donation	Donor is child, so special rules apply. HFEA covers this aspect.
Consent to testing of material/donor	Material is tested for routine markers.
Consent to potential uses	Initial consent will be for own treatment of infertility in future or suppression of premature menopausal symptoms. However, may consent to be approached to use unwanted gametes in research – would still need to consent to each specific research project.
Consent to storage and discard	Initial consent will include storage. A decision to discard will be made in the future jointly between the patient and her clinician according to current professional guidance.
Traceability	Length of time between collection and storage causes traceability problems, even with small and simple programmes. Note that traceability data for 30 years after the product has been used or discarded are an EU requirement. (This applies to all tissues and cells).
Duty to inform	
OPERATIONAL ISSUES	
Collection of material	Laparoscopic surgical procedure required. Essential that risks/benefits are properly explained.
Storage of material	Long term.
Access to materials	

	EXAMPLE 2A
Starter material	Autologous corneal epithelial stem cells from limbal region
Recruitment of donors	Donors motivated to donate, as best treatment for self.
Availability of material	Specific aim of procedure is to obtain corneal epithelial stem cells.
Consent to donation	Straightforward. As per other medical procedures, risks of procedure will be balanced by therapeutic benefits, and fully explained to patient.
Consent to testing of material/donor	Consent obtained as per routine autologous cell / tissue collected.
Consent to potential uses	Obtaining consent for specific collection of stem cells for own treatment is straightforward.
Consent to storage and discard	Normally stored for a short period of time – a few weeks.
Traceability	Very straightforward, due to donor and recipient being same, (or one donor for one or two recipients at most), and generally a short time between collection and use of material.
Duty to inform	
OPERATIONAL ISSUES	
Collection of material	Specific aim of procedure is to collect stem cells.
Storage of material	Straightforward – short period.
Access to materials	

	EXAMPLE 2B
Starter material	Mesenchymal stromal cells (MSCs) from bone marrow, adipose tissues or tissues of mesenchymal origin. Donation may be autologous or allogeneic.
Recruitment of donors	Allogeneic donors motivated by altruism. Selection will usually follow the same procedures as for other stem cell donations. Essential that there is no coercion of relatives to donate.
Availability of material	To date, most donations of MCSs have been in the context of clinical trials, some of which are quite advanced.
Consent to donation	Detailed consent required by donor and recipient. Use of MSCs is still confined to clinical trials; this must be explained to the donor and the recipient. The risks of the procedure must also be fully explained.
Consent to testing of material/donor	Consent of the donor needs to be as explicit as possible and include testing of the donation and cells. Because there is a possibility of prolonged storage (see below), it is also possible that new tests may become available during the storage period, and consent needs to cover such new tests.
Consent to potential uses	Consent of the donor needs explicitly to cover the possibility of their cells, or products derived from their cells, being used: in many patients; for a variety of therapeutic purposes; for research purposes (including, specifically, in commercial research); and for training purposes.
Consent to storage and discard	Donors need to be made aware that their donated cells may be stored for a prolonged periods of time, and that if their cells cannot be used, for any reason, they will be discarded using appropriate and safe methods.
Traceability	If allogeneic, traceability may be complicated, because of the possibility of the cells or products derived from them being used in many patients, and potentially long periods between collection and use of material.
Duty to inform	Current protocols require that the donor be told of any test or marker which has implications for the donor or their family.
OPERATIONAL ISSUES	
Collection of material	Currently, the specific aim of the procedure is to collect MSCs.
Storage of material	Potentially prolonged. Requires a robust traceability system.
Access to materials	Current examples are in the context of clinical trials; no central infrastructure in place.

Appendix 11: Consent and traceability, summary of worked examples

	EXAMPLE 1A Autologous haematopoietic stem cells	EXAMPLE 1B Allogeneic haematopoietic stem cells	EXAMPLE 1C Allogeneic cord blood	EXAMPLE 1D Autologous stem cells	EXAMPLE 1E Autologous immature gametes	EXAMPLE 2A Corneal epithelial stem cells	EXAMPLE 2B Mesenchymal stromal cells
1. INFORMED CONSENT OF DONOR							
1.1. Is consent required?	Y	Y	Y	Y	Y	Y	Y
1.2. Who may give consent to donation?							
1.2.1. Living donors	Y	Y	Y	Y	Y	Y	Y
1.2.2. Deceased donors	N	N	N	N	N	Y	N
1.2.3. Children/mentally incapacitated	Y	Y	N	Y	Y +parents	N	N
1.3. Has sufficient written or verbal information been provided for the person giving consent to make a properly considered decision?							
1.3.1. Use of documentation	Y - HPA-C leaflet	Y - 6-page info sheet	Y - Patient info sheet	Y	Y	Y	Y
1.3.2. Communication	Y	Y	Y	Y	Y	Y	Y
1.4. Format of consent:							
1.4.1. How is consent being given and recorded?	Paper	Paper	Paper	Paper	Paper	Paper / telephone	Paper

Appendix 11

Continued...	EXAMPLE 1A Autologous haematopoietic stem cells	EXAMPLE 1B Allogeneic haematopoietic stem cells	EXAMPLE 1C Allogeneic cord blood	EXAMPLE 1D Autologous stem cells	EXAMPLE 1E Autologous immature gametes	EXAMPLE 2A Corneal epithelial stem cells	EXAMPLE 2B Mesenchymal stromal cells
1.4.2. Does the consent have to be in writing?	Y	Y	Y	Informed consent does NOT have to be in writing in the UK to be valid	Y	N	Y
1.5. Scope of consent							
1.5.1. Collection	Y	Y	Y	Y	Y	Y	Y
1.5.2. Testing							
1.5.2.1. Testing for infection	Y	Y	Y -Mother and baby		Y	Y	Y
1.5.2.2. Testing for safety & quality	Y	Y	Y - Mother and baby		Y	Y	Y
1.5.2.3. Consent for donor/relatives/medical professionals to be informed if certain test results are abnormal now or in the future (also consider i) how unexpected findings are handled, ii) ability of donor to waive this feedback and iii) practical issues re contacting relatives, especially if long time has elapsed from original donation)	Y	Y	Y		Y	Y	Y

Appendix 11

Continued...	EXAMPLE 1A Autologous haematopoietic stem cells	EXAMPLE 1B Allogeneic haematopoietic stem cells	EXAMPLE 1C Allogeneic cord blood	EXAMPLE 1D Autologous stem cells	EXAMPLE 1E Autologous immature gametes	EXAMPLE 2A Corneal epithelial stem cells	EXAMPLE 2B Mesenchymal stromal cells
1.5.3. Usage of donation							
1.5.3.1. General or specific?	Specific	Specific	General	Specific	Specific	General	Specific
1.5.3.2. Research use of waste or surplus material?	Y - optional	Y - optional	Y - optional	Optional	Y - optional	Y optional	Y optional
1.5.3.3. Other therapeutic?	Not covered	Not covered	Y optional	Optional	N	Y optional	Y optional
1.5.4. Storage & Discard of donation							
1.5.4.1. Storage – duration of storage	Y - unspecified	Y - unspecified	Y - unspecified	Unspecified	Y HFEA specifies	Y short term	Y – unspecified
1.5.4.2. Further tests now and in future (including some not currently known, and some which may involve DNA analysis)	Y - without limit	Not covered	Y - without limit	Without limit	?	Y short term	Y – without limit
1.5.4.3. Discard of donation unsuitable for use	Y	Y	Y				Y
1.5.5. Personal information							
1.5.5.1. Storage of personal information (anonymised?)	Y	Not covered	Y	Y non anonymised	Y non anonymised	Y	Y

Appendix 11

Continued...	EXAMPLE 1A Autologous haematopoietic stem cells	EXAMPLE 1B Allogeneic haematopoietic stem cells	EXAMPLE 1C Allogeneic cord blood	EXAMPLE 1D Autologous stem cells	EXAMPLE 1E Autologous immature gametes	EXAMPLE 2A Corneal epithelial stem cells	EXAMPLE 2B Mesenchymal stromal cells
1.5.5.2. Sharing of personal information amongst health profs	Not covered	GP	Y			Y	
1.5.6. Commercial/financial							Y optional
1.5.6.1. Consents to the donor receiving no financial benefit from donation, including waiving rights to any registered patent now or in future	Not covered	Y	Should be	Should be		Y should be	Y
1.6. Duration of consent							
1.6.1. Time-limited or enduring?	Enduring	Enduring	Enduring	May be either	Time limited	Time limited	Enduring
1.6.2. Withdrawal of consent permitted?	Y - any time	Y (but not unreasonable) Only permitted until the conditioning of the patient starts	Not covered	Y for specific issues	Y	Y (N in Scotland)	Y (but not unreasonable) Only permitted until the primary material enters manufacturing
1.7. Responsibility of donor – future contact							

Appendix 11

Continued...	EXAMPLE 1A Autologous haematopoietic stem cells	EXAMPLE 1B Allogeneic haematopoietic stem cells	EXAMPLE 1C Allogeneic cord blood	EXAMPLE 1D Autologous stem cells	EXAMPLE 1E Autologous immature gametes	EXAMPLE 2A Corneal epithelial stem cells	EXAMPLE 2B Mesenchymal stromal cells
1.7.1. Consent to centre holding contact details:							
1.7.1.1 Of donor	Not covered	Not covered	Y		Y	Y	Y
1.7.1.2 Of relatives	Not covered	Not covered		Either	Y	Y	Y
1.7.2. Donor agrees to inform centre if develops medical condition	Not covered	Not covered	Y - re baby	Y	Y	N	Y
1.8 Export to other domains	Not covered	Not covered	Y - worldwide	N/A	N/A	N/A	Y if part of a multicentre clinical trial
3. TRACEABILITY							
3.1. What material needs to be stored?							
3.1.1. Documentation	Y		Y	Y	Y	Y	Y
3.1.2. Physical samples	y		Y	Y but for a limited time	Y	Y	Y
3.2. Storage location?			Public cord blood bank			Bank that took the donation	Institution that took the donation

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Continued...	EXAMPLE 1A Autologous haematopoietic stem cells	EXAMPLE 1B Allogeneic haematopoietic stem cells	EXAMPLE 1C Allogeneic cord blood	EXAMPLE 1D Autologous stem cells	EXAMPLE 1E Autologous immature gametes	EXAMPLE 2A Corneal epithelial stem cells	EXAMPLE 2B Mesenchymal stromal cells
3.3. Duration?			Without limit	30 years	30 years after use or discard	30 years after use or discard	30 years after use or discard
3.4. Responsibilities for updating				Clinical Governance of the bank		Bank that took the donation	Institution that took the donation
3.5. Practical difficulties				May be significant		Limited	May be significant

Appendix12: Glossary and abbreviations

AABB	The American Association of Blood Banks
Adventitious agent	A foreign substance (e.g. virus or other toxin) that is introduced accidentally or inadvertently
Allogeneic	From a donor, not genetically identical.
ATMP	Advanced therapy medicinal product, comprising Somatic Cell Therapy, Gene Therapy and Tissue Engineered Products.
Autologous	From an individual's own body.
Autosomal recessive disorder	An individual will have an autosomal recessive disorder only if they inherit a copy of the recessive gene (on an autosomal, i.e. non-sex, chromosome) from both parents. If they have one copy they will be a carrier, and can pass the gene to their children.
Blastocyst / morula	Very early stages of embryonic development. In the first few days, division of the fertilised egg forms a cell mass resembling a mulberry (a morula); these cells compact into a fluid filled ball (a blastocyst).
BSE	Bovine spongiform encephalopathy. A prion disease of cattle.
Cell-based advanced therapy	Therapy that uses cells which have been manipulated or cultured, to treat a disease, condition or injury.
Cellular therapy	Therapy that uses whole cells to treat a disease, condition or injury.
Chimerism	When an individual is composed of two or more populations of genetically different cells (from birth or e.g. as a result of transplanting an organ/cells from another individual).
Chromosome	Thread-like structure containing DNA, found in the nucleus of every cell. Humans have 23 pairs of chromosomes. When a cell divides (mitosis), a copy of each pair is passed to each daughter cell, so it has a full set. When gametes divide (meiosis), half the chromosomes are passed to the daughter cell(s), as it will combine with another gamete, in fertilisation, containing half the other parent's chromosomes.
CJD	Creutzfeldt-Jakob disease. A prion disease affecting humans.
CMV	Cytomegalovirus.
Corneal epithelium	Epithelial cells cover the surface of the cornea (and the other structures in the body).
Corneal limbal area	The outer edge of the cornea.
CTHF	Cell Therapy History File. A record of traceability and quality data that is compiled early on in the development of a cellular therapy and kept updated. This can be transferred with the cell line from one laboratory / organisation to the next.
CTL	Cytotoxic T lymphocyte. (See T lymphocyte.)
Cytopathic effect	Damage to host cells resulting from viral infection.
Cytotoxic	Able to cause cell death.
<i>De novo</i>	From the beginning, anew. <i>De novo</i> mutation: a genetic mutation that did not originate from either parent.
Differentiation of cells	The process by which a specialised cell type develops from a less specialised cell type.
DNA	Deoxyribonucleic acid. DNA contains the encoded instructions to cells that direct development, function etc. The nucleus of each cell contains DNA, packed into chromosomes. These are passed to

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	daughter cells when cells multiply.
Donor lymphocyte infusion	A donor lymphocyte infusion is given to improve the success of a haematopoietic stem cell transplant or to boost an anti-tumour immune response.
EBV	Epstein Barr virus.
Ectopic	Out of its right place.
Endogenous	Produced, originating or growing from within.
Epigenetic	Relating to change in gene expression caused by external factors rather than change in the gene itself.
Excipient	Any constituent of a medicinal product other than the active substance (and the packaging material).
Exogenous	Having an external cause or origin.
Gamete	A male or female germ cell (sperm or ovum) that unites in sexual reproduction to form a zygote.
Gene	Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring. Each gene contains a particular set of instructions, usually coding for a particular protein or function.
Genome	The whole of an organism's hereditary information.
Graft versus host disease	Transplanted immune cells attack the host's body cells.
Haematopoietic stem cell	Haematopoietic stem cells can divide and differentiate to give rise to all the various types of blood and immune cells.
HBV	Hepatitis B.
HCV	Hepatitis C.
hESC	Human embryonic stem cell. (See that definition.)
Heterologous	Derived from a different organism.
Heterozygous	Humans carry two copies of each gene, one from each parent. If a mutation occurs in one copy, the individual's genotype is heterozygous; if both copies are mutated, it is homozygous.
HFEA	Human Fertilisation & Embryology Authority.
HHV	Human herpes virus.
HIV	Human immunodeficiency virus.
HLA	Human leucocyte antigen. (See that definition.)
Homologous	Showing a degree of similarity (e.g. in position, structure, function or characteristics) that may indicate a common origin.
HSC	Haematopoietic stem cell.
HSV	Herpes simplex virus.
HTA	Human Tissue Authority.
Human embryonic stem cell (hESC)	A cell that can replicate indefinitely and generate all cell types in the body. Found in the inner cell mass of an embryo 4-5 days after fertilisation.
Human leucocyte antigen (HLA)	Protein controlled by the major histocompatibility complex. HLAs play a key role in determining compatibility between a transplant donor and recipient.
Immunocompromised	Unable to develop a normal immune response, because of disease, or treatment e.g. to suppress the immune system to prevent rejection

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	following a transplant.
Immunophenotypic marker	Antigen expressed by cells, used as a marker to identify and sort one type of cell from another, or healthy from diseased cells, in immunophenotyping.
<i>In vitro</i>	Procedure performed outside the living organism. (It may involve cells or tissue from the organism.)
<i>In vivo</i>	Procedure performed in the living organism.
Induced pluripotent stem cells	Induced pluripotent stem cells are (usually adult) cells genetically reprogrammed to make them pluripotent.
Induced somatic stem cells	Induced somatic stem cells are undifferentiated cells that have been genetically reprogrammed so they can multiply to regenerate tissue, giving rise to all the cell types needed for a particular organ.
iPS	Induced pluripotent stem cell. (See that definition.)
IVF	<i>In vitro</i> fertilisation: a treatment for infertility.
Karyotype	The number and appearance of a complete set of chromosomes in a species or individual.
Lineage	The developmental sequence by which embryonic stem cells develop into mature adult somatic cell types via temporary intermediate progenitor cell types.
Lymphocyte	A type of white blood cell that can destroy infected or cancerous cells and direct an immune response.
Mendelian disorder	A monogenic disorder, caused by mutation in a single gene.
Mesenchymal stromal cells	These cells have anti-inflammatory properties, promote the repair of damaged tissues and modify immune responses, making them suitable to treat conditions including graft-versus-host disease.
MHRA	Medicines and Healthcare products Regulatory Agency.
Mitochondrial disorder	Disease resulting from failure of the mitochondria, energy-generating organelles found in all cells except red blood cells. A small amount of DNA is found in mitochondria (most is in the cell nucleus).
Mitotic errors	Chromosomes split into two identical sets during mitosis, the process by which a cell duplicates, but may become damaged, misplaced, inverted etc.
Mobilised peripheral blood	Mobilised blood has an increased number of haematopoietic progenitor cells in the peripheral (circulating) blood, so is used to enrich for these cell types.
MSC	Mesenchymal stromal cell. (See that definition.)
NChESF	National Clinical Human Embryonic Stem Cell Forum.
Neoplasia	Formation of tissue by abnormal growth or cell division.
Oligopotent stem cells	Cells with the ability to differentiate into just a few types of cells.
Oocyte	A cell from which an ovum (egg) develops.
PCR	Polymerase chain reaction. A technique to amplify a DNA sequence; used in a variety of applications including DNA cloning for sequencing, and the detection and diagnosis of infectious disease.
Peripheral blood	Blood in the circulatory system.
Pharmacopoeia	A publication setting regulatory standards for ingredients, dosage forms and analysis methods for medicines.
Phenotype	The observable expression of a particular trait (e.g. stature) based on

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	genetic and environmental influences.
Pluripotent stem cells	Pluripotent stem cells can give rise to any foetal or adult cell type.
<i>Post mortem</i>	After death.
Primary tumour	The original tumour, not one growing from abnormal cells that have spread from elsewhere in the body.
<i>PRNP</i>	The gene that encodes for prion protein in humans.
Recessive gene	A gene that is not expressed unless an individual has two of them, one from each parent. (See autosomal recessive disorder definition.)
Regenerative medicine	The process of replacing or regenerating human cells, tissues or organs to restore or establish normal function lost due to age, disease, damage, or congenital defects.
Retrovirus	A retrovirus carries its genetic blueprint in RNA. When it infects a host cell it uses an enzyme to create DNA from its RNA. This becomes integrated into the host's genome and is inherited by subsequent generations.
Somatic cells	Cells other than the germ cells. (Germ cells are those that give rise to sperm or egg cells in humans.)
Stem cell	A cell that can reproduce indefinitely and is capable of differentiating into different types of specialised cells. Each major tissue system is thought to have its own type of stem cell.
Subclinical infection	Infection causing no signs or symptoms, that cannot be detected without testing for a specific infectious agent.
T lymphocytes	A type of lymphocyte. (See that definition.)
Teratoma	A tumour containing one or more of the 3 layers of cells found in an embryo.
Transduction	A process by which foreign DNA is introduced into a cell using a viral carrier.
TSE	Transmissible spongiform encephalopathy. Prion disease. A group of progressive neurodegenerative disorders.
TTV	Transfusion-transmitted virus.
vCJD	Variant Creutzfeldt-Jakob disease. A human prion disease.
Whole genome sequencing (WGS)	The process to determine the sequence of nucleotides on a DNA molecule, which encodes the inherited instructions to cells.

