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OPEN ACCESS AND THE REGULATION OF COMMERCIALISATION OF HUMAN STEM CELL LINES IN THE UKSCB

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Abstract

Although the United Kingdom is well regarded internationally for its initiative with the UKSCB, its regulatory framework poses significant issues for the realisation of therapies from human stem cell lines. A reassessment of the operations of the Bank in the wider context of stem cell line governance provides an opportunity to examine the relationship between the considerations that shaped HFEA policy on embryo research and their impact on the subsequent use of stem cell lines.

The proposal of this paper is that governance of the use of stem cell lines is not an integral part of the UK regulatory framework for embryo research and that commercial considerations are not necessarily subordinated to this regime. On the contrary, commercial considerations are highly relevant and should be given close attention by policymakers and the Steering Committee of the Bank in the process of development of an open access production system for stem cell lines in the United Kingdom.

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1. Background

The tremendous therapeutic potential of human stem cells¹ has, in recent years, generated huge interest in the scientific and medical communities, as well as with politicians, ethicists, lawyers and the public. The policy focus in the United Kingdom has so far rested largely on basic or primary research, and the derivation of human embryonic stem (ES) cells, with less attention being paid to downstream or secondary research utilising subsequently propagated ES cell lines and the development of emerging therapeutic treatments. Given that the aim of most ES cell research is to produce tangible and validated therapies, there is a need to consider more closely what sort of regulatory arrangements, if any, should govern the use of established ES cell lines for treatment and the commercial production of clinical applications.

The House of Lords Select Committee of the United Kingdom, in its 2002 Report on Stem Cell Research,² concluded that – despite sensitivities attached to the use of certain types of tissue – ES cells, once established as a line, are not embryos, and there is no need for special regulatory arrangements for their use beyond those, such as informed consent, applying to the use of other human material.³ Commercial interests, it said, play a key role in the development and dissemination of therapies and treatments, and are to be encouraged, but should be subject to a regulatory regime for research on early human embryos that is based on ethical, social and scientific considerations without regard to future commercial benefits.⁴ The continuation of a history of fruitful collaboration between industry and research institutes in the United Kingdom was strongly endorsed.

These recommendations raise key questions about the interface between governance of stem cell lines and the regime governing embryo research in the UK. What are the essential concerns on which the regulation of embryo research is based? Do they necessarily dominate the governance of downstream research use and commercial development of established stem cell lines? Can they be satisfied outside of the scheme for governance of stem cell lines?

At the end of the day, the HL Select Committee supported the proposals of the Department of Health “to establish a stem cell bank overseen by a steering committee, responsible for the custody of stem cell lines, ensuring their purity and provenance and monitoring their use”. It suggested that “[a]s a condition of granting a research licence, the HFEA should require that any ES cell line generated in the United Kingdom in the course of that research is deposited in the bank. Before granting any new licence to establish human ES cell lines, the HFEA should satisfy itself that there are no existing ES cell lines in the bank suitable for the proposed research”.⁵ The recommendation was strongly influenced by a desire to minimise the need to generate

¹ F Watt and R Driskell, “The Therapeutic Potential of Stem Cells” (2010) 365 *Philosophical Transactions of the Royal Society B* 155-163.

² House of Lords’ Select Committee on Stem Cells, “Report on Stem Cell Research” (2002) available at <http://www.parliament.the-stationery-office.co.uk/pa/ld200102/ldselect/ldstem/83/8309.htm> (accessed 21 Apr 2010).

³ *Ibid.*, paras 8.23 and 8.25.

⁴ *Ibid.*, para 6.10.

⁵ *Ibid.*, para 8.29.

new ES cell lines (and consequently minimise the use of embryos for research) while not impeding scientific and medical progress.⁶

Such a bank was in fact established, and a standard condition is applied to all embryo research licences as proposed. The question that this raises for the production of cell-based therapies in the UK is the extent to which limitations on the commercial use of established stem cell lines can be justified by reference to ethical, social and scientific considerations that influence the regulation of embryo research. How does the regulatory framework in the UK manage the relationship between these considerations and the commercialisation of established stem cell lines once they have been derived?

This paper proposes that there are reasons to rethink the regulation of the use of human stem cell lines as a mechanism that is interrelated with, but not subordinate to, the regime governing embryo research. Such a mechanism must take into account all considerations relevant to the development of the technology – research, development of applications and commercialisation – if cell-based therapies are to be realised. No commercial considerations should be disregarded in the development of this mechanism, either by the founders of the bank, or through legislative means, for the management of stem cell lines in the United Kingdom.

2. The Bank in Context

The UK Stem Cell Bank (UKSCB, or Bank), set up by the Medical Research Council (MRC) in 2003, is overseen by the Stem Cell Steering Committee (Steering Committee) and sits at the interface of three existing legislative regimes and their respective statutory authorities: the Human Fertilisation and Embryology Authority (HFEA) overseeing reproductive treatment and embryo research; the Human Tissue Authority (HTA) governing human tissue and transplantation; and the Medicines and Healthcare products Regulatory Agency (MHRA) regarding clinical product testing.

The only legal link between the HFEA regime over embryo research (including the derivation of ES cell lines) and the Bank is the standard HFEA licensing condition that requires the deposit of ES cell lines in the Bank and compliance with the Code of Practice.⁷ According to the Code:

Licences issued by the HFEA are subject to conditions. Importantly, HFEA licences for projects involving the derivation of human embryonic stem cell lines require licencees to deposit a sample of each cell line generated in the UK Stem Cell Bank. Licencees are not permitted by the HFEA to carry out secondary research projects on ES cells or to transfer ES cell lines to third parties without the approval of the Steering Committee.⁸

The condition mandates that a sample of all ES cell lines derived under HFEA licences for embryo research must be deposited in the Bank, in order for them to be

⁶ *Ibid.*, para 8.24.

⁷ There are questions about whether the jurisdiction of the HFEA extends beyond its embryo research remit to impose licensing conditions related to the ongoing use of the derived stem cell lines. See R Morgan, “A Lack of Foresight? Jurisdictional Uncertainties in the Regulatory Interface between the HFEA, the UK Stem Cell Bank and Beyond” (2007) 27 *Legal Studies* 511-513.

⁸ UKSCB, *Code of Practice Version 5* (draft – Nov 2009) para 3.3.

curated and disseminated freely to other researchers. It also requires cell developers to comply with the Code of Practice for the use of Human Stem Cell Lines (Code of Practice or Code) - prepared by the Steering Committee – that governs operations of the Bank. The Code shapes the “open access” policy by requiring participants in the banking scheme to “voluntarily” enter into standard contractual arrangements with the Bank: a Materials Deposition Agreement (MDA) by cell line depositor and a Research Use Licence (RUL) defining terms of subsequent use by third parties upon withdrawal. If the user anticipates that ongoing research on the cell lines may result in a commercial outcome, a separate contract must be negotiated between user and depositor in order to address the allocation between them of intellectual property rights in any products that might potentially result.

It is important to note that the condition impacts only on those developers whose ES cell lines are derived under HFEA embryo research licence in the UK. Users of stem cell lines that are of non-embryonic derivation or created outside of the UK (irrespective of derivation) have no legal obligation to follow the rules set out in the Code of Practice for their deposit and withdrawal from the Bank or subsequent use - although the Code tries to impose an expectation that they will, and there may be good political and funding reasons for doing so. The Stem Cell Steering Committee itself has no formal powers: it was set up without statutory basis or legislative mandate, on the premise that there was an urgent need and no other structure in place to oversee the ongoing use of the products of embryonic research. The *Human Tissue Act 2004* had not yet been passed, and, when it did come into force, stem cell lines were exempt from its licensing requirements because they are not material “taken from a human body”.⁹ As of 2007, however, research must be licensed under the *Human Tissue (Quality and Safety for Human Application) Regulations 2007* if it involves human tissue or cells, including cell lines, which may be transplanted into humans.¹⁰ These Regulations govern quality and safety in the processing, storage and distribution of stem cell lines for human application,¹¹ but do not address concerns pertaining to stem cell derivation, nor impose limitations on commercial activities related to stem cell lines.

3. Commercial Constraints

Although the UK is well regarded internationally for its initiative with the Bank, its regulatory framework poses significant issues for the realisation of therapies from human stem cell lines. To start with, fundamental uncertainties in the constitution and operations of the Bank may prevent corporations from satisfactorily assessing the risk of investment in therapeutic development. The fifth major revision of the Code of Practice has been pending for eighteen months, and the precise form and substance of the Deposit and Research Use agreements have yet to be finalised. Technology has advanced to the point that the Stem Cell Steering Committee recognises that the commercialisation of ES cell-based products may not be far away and is considering how this will impact on the operation and governance of the UKSCB.

⁹ *Human Tissue Act 2004* (ch 30) s 16. But query whether adult somatic cells removed for purposes of industrial cell line development would require licensing.

¹⁰ *HTA Code of Practice 9: Research*, first edition, provided for under section 26 of the *Human Tissue Act 2004*, in force 15 September 2009 pursuant to HTA Directions 002/2009.

¹¹ Human Tissue Authority, *Position Statement on regulating human embryonic stem cell lines for human application*, joint statement of the HTA, HFEA and MHRA, 3 May 2007 (updated May 2008).

The HFEA licensing condition and the Code of Practice impose significant constraints on activities and interests in regard to ES cell lines. An early version of the Code¹² expressly prohibited out and out sales by requiring that depositors under the Materials Deposit Agreement (MDA) and users under the Materials Access Agreement (MAA) agree that cell lines would not be sold “for financial gain”.

In subsequent versions of the Code, the Steering Committee began to address how the arrangements for deposit and access could be made more commercially friendly without relinquishing control over stem cell lines deposited in the Bank. In the July 2009 draft revision,¹³ it retained the MDA (prohibiting depositors to sell their cell lines), but replaced the Materials Access Agreement with a Research Use Licence (RUL) for access to research-grade stem cell lines only, and abandoned the MUL directly between depositor and user.

Only the Bank and the applicant user are parties to the Research Use Licence, which is nevertheless designed to protect the intellectual property rights of the depositor. Users requesting access warrant that banked cell lines will be used only for purposes pre-approved by the Steering Committee, and agree to notify any modification of the approved research to the Bank. Transfers of banked or derivative materials from the user to subsequent (third) parties require the user to obtain an assignment of any intellectual property rights created by such a third party during subsequent research. This draft reiterates that “for the avoidance of any doubt”, third party transfers must comply with UK law and the Steering Committee’s Code of Practice.

The same version¹⁴ contemplates negotiation of a separate commercial use agreement (CUA) directly between depositor and user. The use of banked material for research in humans and “any commercial purpose whatsoever” will require user and depositor to negotiate a specific licence for “commercial manufacture and sale” or for “clinical use” defining the terms for exploitation of the stem cell line. This is to be “subject to standard commercial negotiation” between the depositor or the holder of intellectual property and any potential user and is not to be subject to any restrictions imposed by the Steering Committee.¹⁵

The latest revision of the Code¹⁶ is pending, subject to the finalisation of the RUL. As a number of depositors expressed concern about being reliant on the Bank for enforcement of their legal rights under the RUL, it is presently being redrafted as a three way agreement between the depositor, the Bank and the user.

Despite the evolution of the Code towards greater commercial freedom for development of cell therapies for human application, the policy of open access to cell lines essentially prevents any one party from securing exclusive control over any particular cell line deposited with the Bank. Exclusivity over those lines with significant commercial potential could be very important to large-scale developers seeking patentable products, and the ability to attract this sort of investment may be a primary consideration of cell laboratories, should public funds become scarce. Nevertheless, non-proprietary business models based on the success of open source in

¹² UKSCB, *Code of Practice for the Use of Human Stem Cell Lines, Version 3* (Aug 2006).

¹³ *Code of Practice for the use of Human Stem Cell Lines, Version 4, Draft Revision* (July 2009).

¹⁴ *Ibid.*

¹⁵ *Ibid.*, para 6.4.

¹⁶ UKSCB, *Code of Practice for the use of Human Stem Cell Lines, Version 5, Draft Revision* (Nov 2009).

the computer software industry are being explored for use in the development of biotechnologies in hopes of promoting innovation without undermining commercial viability. I discuss this idea further in the last section of the paper.

4. A Separate Regime for Stem Cell Lines

These developments present an opportunity for reassessment of the structure of the Bank in the wider context of stem cell line governance. It is also a chance to examine the relationship between the considerations that shaped HFEA policy on embryo research and their impact on the subsequent use of stem cell lines.

It is necessary first to define the scope of the regime governing embryo research in the UK, and ask what considerations have informed it. The HL Select Committee suggested that commercial interests in the development of stem cell lines should be subject to a regulatory regime governing research in early human embryos – one based on ethical, social and scientific considerations without regard to future commercial benefits. It is relevant to ask, then, whether the UK regime for regulation of embryo research extends to and includes the UKSCB scheme for banking and disseminating of stem cell lines. If so, subordination of commercial interests to scientific and ethical/social considerations would, according to the Select Committee, be justified. If not – that is, if the management of established stem cell lines is an essentially separate undertaking in which the Bank has a particular function – then the design of that undertaking must be informed by all considerations relevant to the use of stem cell lines, including commercial factors and the public interest in the realisation of cell-based therapies. Only if this mechanism comes into direct conflict with the ethical or scientific informants of the embryo research regime should the ethical considerations be prioritised so that they dominate or exclude the development of commercial outcomes and interests.

The proposal of this paper is that the mechanism for regulation of the use of stem cell lines - for research, development and treatment - is not an integral part of the UK regime governing embryo research and therefore commercial considerations need not be disregarded in its development. On the contrary, the governance of stem cell lines interfaces with, but is not subordinated to the regime for regulation of embryo research. Commercial considerations are therefore highly relevant and should be given close attention by the Steering Committee and legislators in the management of stem cell lines in the United Kingdom.

4.1 A Distinction Between Embryo and Stem Cell Line

4.1.1 Ontological Shift

This proposal rests on the premise that a human stem cell line is not an embryo. Even an ES cell line that is derived from an embryo is not just a different form of the same thing, but an ontologically different entity, cultivated from bodily “fragments that are derived from a particular person, but no longer constitutive of human identity”.¹⁷ The debate as to whether the ES cell line is imbued with moral significance by reason of its origin is outside the scope of this paper, except to say that if it has a special status

¹⁷ P Rabinow, *French DNA: Trouble in Purgatory*, (Chicago and London: Chicago University Press, 1999).

after derivation, this is qualitatively different than the special status attributable to the embryo. As compared to the embryo, which is defined by attributes rendering it capable of becoming a living human being, the ES cell line never has such capacity.

For all practical intents and purposes, the embryonic stem cell line is a biomaterial. This perspective is in keeping with the law of the UK that has sanctioned stem cell derivation for the public good of treatment of serious disease, and with the view of the House of Lords when it said in 2002 that “embryonic stem cells once established as a line are not embryos, and should not therefore be subject to the same regulatory arrangements that currently apply to embryo research”.¹⁸

Not only are ES cell lines not embryos, but they can be aligned, for regulatory purposes, with stem cell lines derived from any source of primary tissue. All established human stem cell lines are biomaterials of human origin. The Code of Practice contemplates that in addition to ES cell lines, the Bank will curate lines originating from multipotent adult somatic cells¹⁹ and induced pluripotent stem cells.²⁰ The technology itself makes it difficult to differentiate between stem cell lines from different sources. For example, scientists anticipate the possibility of enabling pluripotency in adult cells in order to differentiate germ cells that may be fertilised to produce embryos from which stem cells may be derived. Is the resulting stem cell line of adult somatic origin or embryonic?

Further, the Steering Committee purports to oversee all UK research involving human stem cell lines of whatever origin and whether accessed from the UKSCB or elsewhere. The problem is that not all stem cell lines are treated equally: originators of ES cell lines are obliged to deposit their lines in the Bank and abide by the Code, while developers of non-ES cell lines are not. If the regulatory enterprise is to take full advantage of the potential benefits of the technology – as it must – then its policy objectives should promote the optimal use of all human stem cell lines equally. The question as to whether equal treatment means the same treatment is a different one that will not be addressed here, but the regulation of downstream research on stem cell lines in the wider context must reflect equal concern for the effective utilisation of all types of stem cell lines.

4.1.2 Regulatory Demarcation

The distinction between embryos and stem cell lines has already been recognised in their different legislative treatment under the HFEA and HTA, and affirmed by the Steering Committee of the Bank in its Code of Practice:

The HFEA’s regulatory responsibility is for research using human embryos. Stem cells taken from an embryo are no longer the subject of regulation by HFEA with the exception of the requirement to fulfil the conditions of the licence.²¹...The conservation and use of human embryonic stem cells and stem cell lines is the responsibility of the Steering Committee.²²

¹⁸ House of Lords’ Select Committee on Stem Cells, see note 2 above.

¹⁹ UKSB, see note 16 above, para 2.1.3.

²⁰ *Ibid*, para 2.1.4.

²¹ *Ibid*, para 3.3.

²² *Ibid*.

If the governance of stem cell lines is distinct from the oversight of embryo research, how do the two regimes interface? How does it relate to the HFEA regime and the objectives for setting up the Bank? What are the essential concerns on which the HFEA regime governing embryo research is based? Do they necessarily dominate the governance of downstream research use and commercial development of established stem cell lines? Can they be satisfied outside of the scheme for governance of stem cell lines?

Put differently, do the ethical and scientific considerations informing the regime for embryo research necessitate the banking of the resulting ES cell lines in such a way that the realisation of their commercial potential is limited? More broadly, does the regime for regulating embryo research necessarily, and so legitimately, have anything to say about the commercialisation of ES cell lines?

4.2 Ethical and Social Considerations: Minimisation and Monitoring

The founders of the Bank, and subsequently the Steering Committee, sought to minimise the need to generate new ES cell lines, thus limiting wider embryo destruction,²³ and agreed on the need to monitor the ongoing use of stem cell lines²⁴ to ensure compliance with HFEA purposes²⁵ and donor consent.²⁶ The policy concern common to these objectives is that the public should have confidence in the whole of the stem cell endeavour through a system characterised by ethical propriety and transparency. It is open to question, however, whether minimising and monitoring are the ways to achieve this, and whether these functions can only be carried out through the banking of cell lines.

If minimisation of embryo destruction is an important consideration in the governance of embryo research and can only be achieved by a system that compromises commercial interests, then it will take priority. Likewise, if the monitoring of ongoing research – for compliance with approved purposes and donor consent - is an essential feature of the regulatory regime governing embryo research and cannot be extricated from the structure of the Bank, then commercial interests will remain a secondary concern. It is proposed though, that neither of these scenarios holds true. I argue below that overall embryo death is not reduced by the Bank, and the embryonic origin of ES cell lines does not necessitate that they be monitored any differently than cell lines of non-embryonic origin. There are no legislative purposes specific to ES cell lines with which research must conform, and the HFEA prevents embryo donors from imposing any restrictions on downstream research. Management systems under the HTA and the UKSCB Code of Practice apply to all types of stem cell lines in the Bank and aim at traceability rather than at enforcing compliance. Are these ethical and social factors essential to the regime governing embryo research, and if so are they necessarily implemented through the operations of the Bank in a way that restricts commercial use of stem cell lines? I suggest not.

²³ House of Lords' Select Committee on Stem Cells, see note 2 above, para 8.24.

²⁴ *Ibid*, paras 8.24, 8.28 and 8.29.

²⁵ UKSB, see note 16 above, para 5.

²⁶ From conversation of the author with a member of the UKSCB Steering Committee, Nov 2009.

4.2.1 *Minimising Ethical Impact*

First, the concept of minimisation of embryo destruction through the sharing of ES cell lines for downstream research is, when seen in perspective, a fiction. In the UK, the embryos or blastocysts from which the ES cell lines are derived are usually obtained from a fertility clinic, and would otherwise be discarded after *in vitro* fertilisation (IVF) treatment. Although sharing may serve to minimise the need for derivation of new ES cell lines, it will only reduce the already small proportion of unused IVF embryos that are donated to research.

The number of embryos that will actually perish is determined not by research needs but by the assisted fertility practice of creating more embryos than necessary; those that are superfluous may be frozen, donated to research or discarded. One report²⁷ cites Department of Health statistics indicating that over 50% of IVF embryos created in the UK are unused: a total of 1.2 million of over 2 million (2,137,924) created from 1991 to 2005. Of the 1.2 million destined for discard, only 6.9% (82,955) were salvaged for research, of which stem cell derivation is but a small part. In this light, it is difficult to support the notion that the status of the embryo will be undermined if more HFEA licences are granted, or that it is a sign of respect to restrict them. On the contrary, it would be responsible to encourage as much research as possible in order to use surplus embryos that are otherwise going to waste. Despite its strengths as a repository and curator of stem cell lines, to portray the Bank as an important vehicle for minimising the destruction of embryos is misleading. It is possible that there are other types of public engagement available that are equally effective in demonstrating the credibility of HFEA research in the UK and the relationship of embryo research to fertility treatments as the primary source of donated embryos.

4.2.2 *Monitoring Compliance with Permitted Purposes*

Monitoring the compliance of downstream research with permitted purposes is equally problematic. First, the fact that there is no real necessity for oversight specific to research on ES cell lines is acknowledged by the Steering Committee itself. Secondly, the application of the HFEA purposes designed for research on embryos to ongoing research on ES cell lines is a pure innovation of the Steering Committee. The HFEA rules do not apply to ES cell lines and no such criteria are applied to cells for human application under the HTA Regulations. Nevertheless, the Committee goes out of its way to create a regulatory divide between embryonic and non-embryonic stem cell lines where there is no need to do so. Neither the oversight of ES cell line research, nor the embryo research standards with which they are asked to comply, are required by law.

The Steering Committee, in the UKSCB Code of Practice asserts that:

Unlike human embryos, embryonic stem cells do not have the potential to become a human person and do not therefore have the moral status of

²⁷ BioNews London, "UK Parliament Alarmed by 1.2 Million Leftover IVF Embryos" (2009) available at http://www.ivf.net/ivf/uk_parliament_alarmed_by_1_2_million_leftover_ivf_embryos-o3162.html (accessed 7 Mar 2010). Lord Alton in Jan 2008 requested the data provided by the Department of Health's minister whilst challenging the permitted creation and uses of unwanted embryos particularly for research during recent parliamentary debates on the *Human Fertilisation and Embryology (HFE) Bill 2007*.

human embryos. Accordingly the Government has passed legislation that establishes that research involving established stem cell lines does not need the same regulation to which embryo research is subject to by the HFEA. However, *as the generation of embryonic stem cell lines involves the destruction of human embryos, oversight in the form of a Steering Committee was recommended to ensure that research performed is in keeping with HFEA Regulations.* The oversight mechanisms governing research involving established embryonic stem cell lines are voluntary. However, they are a condition of the statutory regulation in the UK and there is an expectation by Government that these are adhered to [emphasis added].²⁸

The fact that the need for ongoing oversight is attributed to the destruction of embryos implies a concern to ensure public confidence that may or may not involve special measures for validating compliance of research with approved objectives. Public confidence that embryos are not being treated in a casual or trivial fashion is achieved through strict legal and ethical criteria for disaggregation, which will have been met by the time the resulting ES cell lines are deposited in the Bank. Once they have been generated, nothing further can be done to ensure compliance with rules of ethical conduct in the derivation of stem cell lines.

Transparency regarding the provenance and handling of the resulting ES cell lines is important for public confidence in research at all stages, but in the context of the Bank it has more to do with traceability and the demonstration of quality and safety than with the establishment of any further ethical safeguards. In accordance with the *Human Tissue (Quality and Safety for Human Applications) Regulations 2007* and the *EU Tissues and Cells Directives*, the Bank ensures traceability through a quality management system, including records for each cell line. While “oversight” was only recommended for ES cell lines, these systems rightfully apply to all deposited stem cell lines, without special relevance for those of embryonic origin.

The Steering Committee again fails to distinguish stem cell lines from embryos when it determines that research in ES cell lines should comply with the HFEA regulations governing permitted purposes for embryo research. UK legislation does not define the purposes to which stem cell lines may be put following their withdrawal from the Bank. The HFEA regulations apply only to research involving embryos, and despite extended debate about the use of stem cell lines during the passage of the HFEA and its amendments in 1990, 2001 and 2008,²⁹ Parliament declined to regulate the matter further, concluding only that human ES cell lines should not be used for “trivial purposes”. Stem cell lines are exempt from the HTA 2004, and the HTA Regulations 2007³⁰ regarding cells for human application are concerned with quality and safety rather than criteria for use. Approval by an Ethics Committee is required for research projects that need an HTA licence, but this applies only to clinical grade stem cell lines intended for human application and not to research grade lines that will stay in the laboratory.³¹

²⁸ UKSB, see note 16 above, para 5.

²⁹ *Ibid*, at, para 7.1.1.

³⁰ *Human Tissue (Quality and Safety for Human Application) Regulations*, 2007 No. 1523.

³¹ UKSB, see note 16 above, para 7.1.

Nevertheless, the Steering Committee has taken it upon itself, without any statutory mandate, to apply the purposes intended for *embryo* research to all subsequent research on ES cell lines. It says that:

The Steering Committee expects that human embryonic stem cell lines are only used by *bona fide* research groups for justified and valuable purposes that reflect the requirements of the law relating to this area. This is:

- a. research which increases the knowledge about the development of embryos or has the long term goal of helping to increase knowledge about serious diseases and their treatment (as set out in the 1990 Act as amended by the 2008 HFE Bill)
- b. basic cell research which underpins these aims (as recommended in the House of Lords Report 2002)
- c. development of cell based therapies for clinical trials in respect of serious human diseases.³²

While the earlier versions of the Code adopted by reference the purposes defined in the HFEA Regulations 2001, the current draft refers to “justified and valuable purposes”, supported with hard but inapplicable law and soft guidance.

The point here is not to assess the legitimacy of the purposes that might apply to research in ES cell lines, but to emphasise that this is a unilateral attempt by the Steering Committee to regulate, where there is no need for special oversight of ES cell lines on the basis of their origin. Research on stem cell lines does not operate in a regulatory vacuum, but under the framework governing the use of human tissue. The measures taken by the Steering Committee are unjustifiable as they create confusion and do not contribute in the intended way to the founding of public confidence in the management of stem cell research. As a result, the monitoring of downstream research in stem cell lines for compliance with permitted purposes cannot be said to be an essential consideration shaping the regulation of embryo research.

4.2.3 Monitoring Compliance with Donor Consent

What about the monitoring of compliance with uses imposed by tissue donors? Free and informed consent is considered the “lynchpin to ethically acceptable research.”³³ and its necessity for the protection of tissue donors is underscored by legal controls in relation to specialised regimes, such as embryo research. The *Human Fertilisation and Embryology Act 1990* requires that donor consent to the use of embryos must specify at least one of several purposes, including research,³⁴ which must increase knowledge about the development of embryos, or about serious disease, or apply such knowledge to the development of treatments for serious disease.³⁵ Although the act contemplates the application of conditions to modify the consent,³⁶ which theoretically permits the donor to impose limitations on downstream research, it does not specify any parameters for those limitations. The problem for enforcement is the

³² *Ibid*, para 7.1.1.

³³ JK Mason and GT Laurie, *Mason & McCall Smith's Law and Medical Ethics*, 7th ed (Oxford: Oxford University Press, 2006) 655.

³⁴ *Human Fertilisation and Embryology Act 1990* (ch 37), Sch 3, s 2(1).

³⁵ *Human Fertilisation and Embryology (Research Purposes) Regulations 2001*, No. 188, s 2(2).

³⁶ *Human Fertilisation and Embryology Act* see note 34 above, s 2(1).

lack of clarity in the law regarding the extent to which a donor of primary material may control or affect the nature of secondary research, which can be particularly important when it involves the acquisition of property, intellectual property rights and the dissemination of products on a commercial basis.

UK legislation does not stipulate that users of cell lines, including those withdrawn from the Bank, must respect the restrictions imposed by a donor's consent.³⁷ Consequently, it is unlikely that liability will accrue where, for example, a developer contravenes the wishes of a donor who has stated that no pharmaceutical company is to have access to stem cells derived from his tissue. Downstream researchers might choose to decline the donation if they think the conditions of consent are too restrictive, but if not, and the consent is contravened, then the donor has only the common law and the non-statutory powers of the Steering Committee of the UKSCB to rely upon.

As in other types of tissue donation, the question as to what exactly donors consent to, and whether their wishes will be respected, is a difficult one, because the research intentions for the tissue may not be determinable from the outset. This is especially true of stem cell lines, which, once stabilised, will replicate indefinitely, making it impossible to predict all downstream uses to which they might be put. Adhering to a strict standard of informed consent would necessitate that researchers go back to the donor repetitively to validate consent for each future project. The appropriateness here of a blanket or "in principle" consent to all subsequent research is itself an interesting idea, as the identity of the object of the proposed research changes irrevocably in mid-stream. Although donor consent to research on the embryo is governed by the HFEA, the ES cell lines generated thereby come under a separate regime regulating tissue, with different consent requirements.

The human tissue rules are not much help. Stem cell lines fall outside the ambit of the *Human Tissue Act 2004*,³⁸ and the *HTA Regulations 2007*, governing cells intended for human application, ensure traceability through procedures including verification of records of consent and donor identification,³⁹ but do not specify the nature of the conditions that may be imposed on research through donor consent.

In practice, donors are expected to make an unconditional gift of their tissue. The House of Lords Select Committee in 2002 anticipated this situation and recommended that "to prevent future restrictions in using ES cell lines...the HFEA should not permit ES cell lines to be generated from donated embryos unless informed consent places no specific constraint on their future use".⁴⁰ The Act does not strictly support this position, leaving open the possibility of limitations on downstream research and the question of their enforcement. Nevertheless, there are sound policy reasons for it,

³⁷ K Liddell and S Wallace, "Emerging Regulatory Issues for Human Stem Cell Medicine" (2005) 1 *Genomics, Society and Policy* 54, 66.

³⁸ HTA consent is required for the removal, storage and use of "relevant material" from dead bodies or the living: *Human Tissue Act Code of Practice on Consent 2009*, ss 24-25.

³⁹ Requirements imposed by the HTA implement EU Directives: *Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004*; *Commission Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and of the Council of 8 February 2006*; and *Commission Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council of 24 October 2006*.

⁴⁰ House of Lords' Select Committee on Stem Cells, see note 2 above, para 8.33.

and informally the Authority does require parents to provide consent “in principle”⁴¹ through standardised forms of consent, including a waiver of potential benefits. The HFEA and the Steering Committee have collaborated to draw up a list of criteria that must be addressed in information leaflets and consent forms provided by IVF clinics for the donation of embryos for stem cell research.

4.2.4 Monitoring Mechanisms

Failure to discuss how the system will ensure compliance was observed as a shortcoming of the Bank soon after it was set up.⁴² The powers of the Steering Committee are limited. It cannot force compliance by privately-funded corporations who are working with cell lines of non-embryonic origin, or those who have imported their cell lines from outside of the country. The Steering Committee does however have responsibility for ensuring that essential donor consents and ethical approvals are in place for all stem cell lines deposited with the Bank and projects receiving cell lines from it.⁴³ Any constraints on the use or release of a cell line, made either by the depositor or the original donor, must be clearly documented and available to researchers. Furthermore, the Steering Committee must supply documented evidence that the donor consent complies with the HFEA and HTA requirements. Reflecting the HTA Regulations 2007 and European Directives, the Code emphasises traceability for purposes of safety and quality, and confidentiality of the donor consent forms, rather than compliance, and asserts strongly that neither Steering Committee members nor UKSCB staff have any contact with the consenting process, the consent records, or donors themselves.⁴⁴

Despite stringent systems to ensure traceability, there is no procedure in the Code for positive enforcement: the inspection of research premises to ensure compliance of users with the terms of the donor’s consent following release of the cell lines from the Bank. The MRC, in its Supplementary Terms and Conditions to be applied to new and extant MRC grants, reserves the right to audit, at any time and without prior notice, compliance of MRC-funded research with the consent obtained from the donor(s), but it is not apparent whether this is done in practice.

From these observations, it is possible to conclude that the goal of monitoring compliance - both with proposed uses for ongoing research and with donor consent - has not been facilitated in any formal way through the Bank and that no special enforcement mechanism will be lost if the regulation of stem cell lines is reconsidered and developed in order to take into account all relevant factors including commercialisation of the development of stem cell lines. Monitoring of compliance with donor consent is not a consideration so essential to the shape of the regulatory regime for embryo research that it ought to trump commercial interests in stem cell lines. Instead, in developing the regime for ongoing use of biomaterials there should be an assessment of the need for further legislative clarity regarding donor consent and its enforcement as a means of better protecting donors and providing certainty to downstream developers.

⁴¹ UKSB, see note 16 above, para 9.1.

⁴² Liddell and Wallace, see note 37 above.

⁴³ UKSB, see note 16 above, para 9.1.

⁴⁴ Liddell and Wallace, see note 37 above.

If ethical motivators for the Bank are not substantial enough components of the regime for regulation of embryo research to warrant commercially restrictive governance of stem cell lines, can the same be said of the promotion of innovation?

4.3 Science, Innovation and Open Access

4.3.1 Scientific Considerations and Embryo Research

The fact that the Steering Committee requires the deposit of cell lines, in order to make them freely available to researchers, raises the question as to whether the “open access” approach is compatible with the generation of sustainable business models for production of cell-based products. If governance of stem cell lines is distinct from and not subordinate to the regulation of embryo research then there is scope for innovative thinking in the design of an effective system for encouraging both innovation and commercialisation of stem cell lines. Such thinking requires an analysis of the way in which the access policies of the Bank interact with strategies for commercialisation of emerging therapies. If the regulation of stem cell lines is seen as an extension of the embryo research regime, rather than distinct from it, then commercial interests must, according to the House of Lords Select Committee, be disregarded, and there is limited scope for remodelling the Bank in a way that encourages industry to take a strong role in the development of commercially viable therapies.

This paper again asserts that stem cell lines, of whatever origin, are entities distinct from embryos and demand regulation as biomaterials. The question under this heading is whether the *scientific* implications of the open access requirements of the Bank are essential to the regulation of embryo research, to the exclusion of commercial considerations.

When the HL Select Committee endorsed the Department of Health proposal for establishment of a stem cell bank, an increase in scientific innovation or efficiency in the delivery of clinically proven therapies did not feature anywhere in its 2002 Report. In its view, the urgent motivation for the bank was, in the absence of any responsible regulatory authority, the need for a body that would have custody and oversight of the use of human embryonic stem cell lines. The goal was to reduce the need to use early human embryos in research. The Select Committee said:

Stem cell “lines” derived from a single early human embryo can be maintained in culture, in principle indefinitely. As more of these lines are developed it is important that a stem cell bank should be set up for research purposes as a matter of urgency to ensure that there is a single body responsible for the custody of stem cell lines, ensuring their provenance and purity and monitoring their use. In that way stem cell lines can be made widely available to reputable researchers and an overview maintained of their use. Over time this will reduce the need for research on early human embryos.⁴⁵

Motivation for the Bank is based primarily in the ethical concerns discussed in the previous section, rather than in any express intention to use the Bank to drive innovation or promote speedy production of clinically-based treatments. The Steering Committee viewed the scientific benefits of sharing stem cell lines as a positive by-

⁴⁵ House of Lords’ Select Committee on Stem Cells, see note 2 above, para 14.

product of the oversight mechanism and emphasised the role of the Bank as a repository for the curation and quality control of stem cell lines. The possibility of “wider availability of stem cell lines to researchers” through the bank was welcomed, not for promotion of innovation in its own right, but as a way of purportedly minimising the use of human embryos.

The scientific benefit of making quality-controlled stem cell lines accessible is that more researchers are able to use identical material, enabling them to make direct comparisons between studies. The assumption is that this will increase innovation, and presumably result in more efficient production of cell-based therapies. These benefits are not an essential informant of the HFEA regime for research on *embryos*, but they are a major consideration in the design of a regulatory model for subsequent research in regard to *stem cell lines*, informing ongoing research and their commercial outcomes and facilitating the ongoing translation of stem cell lines into medical treatments for human application. The possibility that research on stem cell lines might turn up information that could obviate the need for destruction of embryos in the future does not render the scheme for stem cell lines an integral part of the regime that governs embryo research. The Bank curates and disseminates stem cell lines, but it does not handle embryos.⁴⁶ The HFEA licensing condition mandating the deposit of ES cell lines – which links the embryo research regime to the Bank - is the only factor in the equation that affects embryo research, and that condition is not determinative of the structure and operations of the Bank.

Like the alleged ethical and social motivators for the Bank, the scientific benefits associated with an open access repository for the curation of stem cell lines are not key to the regulation of embryo research, to the exclusion of commercial interests. Commercial factors affecting the development of stem cell lines are not subject to the framework for regulation of embryo research on scientific grounds. The developers of the Bank are therefore unrestricted as to the range of concerns that they may consider in the design of an open production system.

4.3.2 *Open Access Production System*

If the regulatory framework for stem cell lines is an extension of the embryo research regime to the point of disregarding commercial interests, then there is limited scope for encouraging industry to take a strong role in the development of commercially viable therapies. Affirmation of the stem cell regime as an independent enterprise frees up opportunities for creativity in the design of a system that will encourage both innovation and commercialisation. A successful open source production system needs to be based on a feasible business model with appropriate incentives for all participants. The contractually constructed system under the Code of Practice does not at present serve all participants in the Bank equally well. The commercial reality confronting producers of ES cell lines – whether research or clinical grade – is the lengthy, expensive and risky production process, requiring up front capital investment. Although it is beyond the scope of this paper, an exploration of the origins of open access in the open source software movement and its potential application to biotechnology might assist with the development of non-proprietary commercial models or a model with a combination of proprietary and non-proprietary components.

⁴⁶ UKSB, see note 16 above, para 4.

Further development of the system will require an analysis of the way in which the access policies of the Bank interact with strategies for commercialisation of emerging therapies. Part of the process will be a closer examination of the commodification of stem cell lines – its ethical, technical and commercial implications - and the commercialisation of cell-based products. The commercial use of the human body and its parts has always been contentious, as reflected in the complexity of the law and policy that informs this area. The devaluation, in human terms, of primary tissue by its transformation into an economically valuable commodity is traditionally considered problematic. On the other hand, basic stem cell science is insufficient for the purposes of producing clinically useful outcomes, and its direction toward applications with therapeutic benefit necessarily entails commodification that confronts traditional ethical views. While this is not the place to explore these issues, it is clear that a serious review of the current regime will be required in order to ensure that they are addressed in any adequate way.

5. Conclusion

The regulation of the downstream use of human stem cell lines in the United Kingdom is in need of serious reconsideration. Now that the policy decision has been taken to permit the derivation of embryonic stem cell lines, it is incumbent upon regulators to structure an environment that is conducive to the commercial production of cell-based therapies, so that established stem cell lines are put to the best possible use. The current framework is problematic for commercial production, because the contractually constructed parameters of the UKSCB prevent cell line developers from maintaining control over their lines, and define and limit the nature of the transactions that they may enter into.

Commercial interests have been minimised in part because the Bank was originally designed to assure the public of the ethical credibility of embryo research, with the possible side benefit of promoting further innovation. Commercial interests were seen as important, but were subjected to the ethical, social and scientific considerations informing the regulation of embryo research, without regard to commercial outcomes. More recently, however, the Steering Committee has recognised the need to facilitate commercialisation and is making more overt attempts to adapt the open access policies of the Bank to the needs of potential developers.

It is submitted here that the proper approach to the regulation of human stem cell lines in the UK requires consideration of all factors relevant to the production of commercially viable clinical treatments. There is no legitimate basis for policymakers to deny or subordinate commercial interests in established stem cell lines on the basis of public concerns arising out of embryo research that are either unsubstantiated or may be addressed through means such as public engagement outside of the regulatory regime.

The premise that the sharing of stem cell lines through the Bank will minimise the number of embryos destroyed is misleading and an insufficient reason to disregard commercial interests in development. The idea that the Bank is necessary for monitoring the compliance of ES cell lines – with permitted uses or donor consent – is also ill-founded. Once established, cell lines of embryonic derivation need not be treated any differently than any other human tissue; in practice “monitoring” in the Bank applies equally to all stem cell lines, and is little more than a documentation system to assure traceability for purposes of quality and safety.

The way forward for the development of an open access production system is through a better understanding of what commercialisation entails and an analysis of the interaction of access policies with strategies for commercialisation. Validation of the distinction between the regulatory mechanisms for human stem cell lines and embryo research also permits greater creativity in the design of business models that are compatible with innovation, including non-proprietary “open” alternatives. The objective is to foster innovation, without discouraging the downstream use of cell lines, in ways that will result in sustainable commercial production of therapies. Although there is a need to address public sensitivities about the use of products of embryo derivation, the way to do this is not through disregard for the needs of commercial enterprise, but by public education about the due diligence that characterises every stage of the process of stem cell research, development and commercialisation.