

Report



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Deliverable D3.1 Report on the comparative systematic review of the literature from key scientific, medical, social science and bioethics journals.

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Executive Summary.

A review of the scientific, legal, sociological and ethics literatures concerning the use of human embryonic or foetal tissue in research was conducted. Scientific publications were identified that dealt with anatomy, biochemistry and physiology as well as gene expression and these papers were scrutinised for descriptions of the source of tissue and the governance arrangements within which the scientists worked.

It appears that most research that uses post-implantation embryonic tissue uses material gathered in an *ad hoc* manner, and there is little evidence of current systematic collection of tissue. The science literature identified some common aspects of research, such as the requirement to obtain prior ethics review board approval for studies, across Europe. However, it was notable that descriptions of the acquisition of tissue were rather cursory. The justification for the use of human embryonic and foetal tissue, rather than model animals such as mouse, was made by several authors. The major reasons given were the differences between animal and human brain development and the different consequences of the same pattern of gene expression in animal and human studies.

The legal and social scientific literature identified some key issues for *DGEMap* to consider when drawing up a governance framework. The regulation of research using early human material was found to be variable across Europe, although where research on such tissue was permitted, regulation tended to be based on that of the UK. However, a consistent theme that emerged was the contradiction and complexity in law where the aborted human embryo was concerned. Much of the literature relating to professional guidelines on the use of post-implantation embryonic and foetal tissue was concerned with the uses of such tissue in transplant medicine, and the ethical framework developed by a pan-European transplant research group is presented as a supplement to this report. Another feature of the legal landscape is the current fluidity of the situation, the result of the recent introduction of the EU human tissues and cells directive and the changing regulatory regimes in the UK and France.

The ethics literature revealed an ongoing debate around the differences in views of continental European and North American ethicists; although there seems to be no consensus as to whether or not there is a particularly European approach to ethics. There is some consensus on the view that early human developmental tissue is in some way different from other donated or cadaveric tissue.

Further exploration of the findings of the literature review will be undertaken following interviews with senior scientists and the conclusions reached will be presented in the DS3 summative report.



1. Introduction.

This report of the review of literature on the ethical, social and legal aspects of the Developmental Gene Expression Map (*DGEMap*) design study presents the strategy used and a description of the results obtained. The aim is to offer the reader a general understanding of the issues that the work of *DGEMap* raises and the potential impact these may have on the proposed infrastructure. The details of the search strategy are presented as Supplement 1.

1.1 The project.

The *DGEMap* project did not begin in a vacuum, but rather grew out of pre-existing research within the Institute of Human Genetics (IHG) in Newcastle University. This provided the starting point for the literature review; in particular publications by the *DGEMap* project coordinator, and two senior members of staff at the IHG.

In essence, the science under consideration is concerned with the study of the expression of particular genes during the early stages of human development.

1.2 The tissue.

Studies such as *DGEMap* cannot be conducted without access to the developing embryo and this is only made possible by using model animals or following donation of suitable tissue by women who have undergone elective termination of pregnancy. Clearly, the ethically contentious nature of this tissue makes it important for a detailed study of the legal, ethical and social considerations of the *DGEMap* project to be conducted.

Burn and Strachan (1995) made the case for the study of human development despite the ethical concerns that arise from the nature of the tissue that is required and Strachan et al (1997) called for a database of gene expression involved in human development to be created. Bullen, Robson and Strachan (1998) published a comparison of the efficacy of surgical and medical techniques for the collection of post-implantation embryos suitable for use in developmental research. The molecular genetics of human development were explored in detail by Strachan, Lindsay and Wilson (1997).

The human tissue samples required for the research and development of the molecular genetics component (DS4) of the *DGEMap* project are currently acquired from the Human Developmental Biology Resource (HDBR) which is a UK based joint venture of the Medical Research Council (MRC) and the Wellcome Trust (Lindsay and Copp 2005).

This resource is a collection of human embryonic and foetal tissue (hereafter hEFT) donated for research by women undergoing termination of pregnancy at two centres in



the UK; the Royal Victoria Infirmary, in Newcastle upon Tyne and University College Hospital, London (Gerrelli, personal communication).

The design of the *DGEMap* project, the above publications and discussion with the project coordinator defined the subject area for consideration in this review. The *DGEMap* project, and this review, begin from the premise that abortion is legal in the UK and that suitable guidelines are in place, the Polkinghorne guidelines of 1989, governing the donation and research on human embryonic and foetal tissue resulting from elective termination of pregnancy. The review thus does not engage directly in detail with the social, legal and ethical aspects of abortion. The focus is rather on the issues that arise from scientific research that uses tissue from dead, post-implantation, embryos and fetuses.

Two other areas of interest with regard to developmental gene expression are also excluded from this review; the use of animals in scientific research and the storage and use of personal genetic data.

2. Data sources and methods.

Literature searches of six computer databases accessible through the Newcastle University library were conducted, with the emphasis on four categories of literature decided *a priori*: namely, Scientific, Legal, Sociological and Ethical.

When the terms used in these searches were specific to the subject of *DGEMap*, gene expression in early human development, few relevant results for any category other than scientific were found, and those that were found had been written by the Newcastle based scientists noted in the introduction.

From an ethical, legal and social aspects (ELSA) perspective it is a reasonable assumption that the concerns regarding developmental gene expression research are the same as the concerns raised by any research that uses human embryonic or foetal tissue. Therefore, the search terms were widened and the results then refined as detailed in Supplement 1. In summary, these searches aimed to uncover literature relating to terms such as

- ‘embryo’
- ‘foetus’ (or ‘fetus’)

in areas such as

- biochemistry
- anatomy
- bioethics
- philosophy
- law
- social sciences

but excluding scientific publications relating to human embryonic stem cells.

Only references with abstracts available in English were reviewed but no limit was placed on the date of publication.



Once references were identified, these were subjected to a selection process whereby papers were examined, manually, against particular exclusion criteria. These criteria are noted, in Supplement 1, within the description of the results obtained from the different sources. Furthermore, specific journals were identified in the course of these searches that contained frequently cited authors or that published many papers concerned with the subjects of interest. The contents pages of these journals were reviewed manually and relevant material extracted.

3. Results.

The literature identified from the searches contained original research, reviews and commentary. Two sets of professional guidelines were also found which have some relevance to the *DGEMap* project.

All the papers or book chapters identified by the searches were gathered together in electronic (PDF) format where possible, or as hard copy when necessary. The references were entered onto an Endnote database which was made available to all *DGEMap* project members via the project's shared computer drive space. The finished database contained 232 references.

The vast literature on the scientific aspects of the project could not be reviewed systematically, but filtered as detailed in Supplement 1 and bearing in mind that related components of the project (DS2; D2.1 and DS3; D3.3) were to identify research groups and potential users of the research infrastructure being designed.

Analysis of the material obtained showed that there is significant subject overlap in the social, ethical and legal literatures and so in the description of the analysis that follows, these subjects will be interwoven. Several different subject areas were found to be relevant to the wider aims of this report and these will be detailed. However, the analysis begins with the findings from the particular reading applied to the science papers uncovered.



4. Analysis.

4.1 Scientific literature.

Of necessity, the number of science papers reviewed was very small (60 papers) in relation to the total production relating to work using the human embryo or foetus (over 19,000 hits searching Medline). However, from a qualitative analysis perspective this offers a representative sample of work through the 1980s to 2006 from which inferences can be made and useful data extracted. It was thus possible to build a wide picture of how scientists obtain, use and view human embryonic and foetal tissue.

It was observed that science papers usually offered little or no acknowledgement of the source of the tissue with which scientists work. Descriptions of the procedures by which human embryonic or foetal tissue (hEFT) are obtained were found to be limited and often rather cursory in nature. A typical example being:

Human embryos were collected from legally terminated pregnancies in agreement with the French law and ethics committee recommendations. (Odent et al, 1999: 1688).

No further mention of the source of the tissue is made at any point. From the perspective of the scientist there is no need.

There is an agreement amongst a group of journal editors that authors must make some reference to the research governance arrangements they work within. The “Uniform requirements for manuscripts submitted to biomedical journals” was established by the International Committee of Medical Journal Editors (ICMJE) and these state,

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach, and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study. (ICMJE, available online 20/04/07)

The resulting reports of these aspects by authors in these journals tends to be rather formulaic, meeting the requirements but not often going beyond them. The requirements mean, however, that some indication of governance arrangements is made clear.

4.1.1 Gene expression mapping.

Gene expression mapping in early human development concerns the identification of the locations of particular genes that are active at particular times during the



development of a human being from conception through to birth. However, the very earliest stages of development are not available for research as, for practical purposes, only embryos that are at least midway through the third week of development are collected. This is the earliest point at which tissue is likely to be available following termination of pregnancy. While technical matters do not prevent study of foetal tissue of up to full term, the particular material available to *DGEMap* will be in the range of 4 to 14 weeks, the range of tissue held by the HDBR (Lisgo, personal communication).

For the purposes of this report it is not necessary to detail the means by which gene expression is located or quantified, these technicalities are dealt with in the report from DS4 and found elsewhere. It is sufficient to note that once collected, embryos must be preserved in such a way that the products of gene expression are accessible for analysis. This analysis involves cutting the embryo into sections and then visualising the products of gene expression (ribonucleic acid or protein) in some way.

4.1.2 Justification for research using human tissue.

Burn and Strachan (1995) note that a strong driver for their research on human development is the prevalence of malformation amongst newborns. These authors further note that genetic predisposition to malformations have long been known and they believed that the human genome project would identify potential candidates. However, to link malformation with candidate genes requires an understanding of the action of genes in normal development.

Bullen et al (1998) have similar reasons for human developmental biology research being undertaken,

Our knowledge of the genetic mechanisms underlying early human development and maldevelopment remains rudimentary. The fact that one in 30 newborns has a major malformation underscores the clinical importance of developmental research. (Bullen et al 1998: 220)

The authors are clearly concerned with clinical applications of research, and they provide a figure for the incidence of malformation that justifies research in this field. This rate of maldevelopment has been uncovered by the ongoing reporting to a service within the UK's National Health Service (NHS), by hospitals and midwives, of all birth defects in particular geographic regions. For a description of the service and the prevalence of congenital anomalies throughout the UK, see Rankin et al (2005).

Fougerousse et al (2000) present a scientific case for the study of gene expression using human tissue rather than model organisms, such as the mouse. They described research in which comparisons were made between expression of particular genes in mouse and the corresponding gene in human. They found that,

Wnt7a, a very highly conserved gene known to be important in early development, shows significant differences in spatial and temporal expression



patterns in the developing brain (midbrain, telencephalon) of man and mice. CAPN3, the locus for LGMD2A limb girdle muscular dystrophy, and its mouse orthologue differ extensively in expression in embryonic heart, lens and smooth muscle. (Fougerousse et al 2000: 165)

They conclude that although mouse models will continue to be important research tools, the differences in developmental gene expression between the two species can be so profound that research on human tissue is essential. They note that,

Already, there are numerous examples where inactivation of a mouse orthologue results in a phenotype that is substantially different from the human disease that it was intended to model.” (Fougerousse et al 2000: 171)

In addition to an explanation for the need to use human tissue for research which is similar to those noted above, Lindsay and Copp (2005) note another reason for this area of research;

Many disorders are evident at birth and, even for disorders that appear later in life, it is now clear that many have their origins during foetal development ... Determining the expression patterns during embryonic and foetal development of genes that underlie such disorders is, therefore, a crucial step towards revealing gene function. Clearly, it is also important to define the expression patterns of genes that regulate normal human development because this will help to reveal possible disease mechanisms, and might highlight potential direct or indirect targets for therapeutic interventions. (Lindsay and Copp 2005: 587)

For these authors, the fundamental work of understanding human development is focused on the potential clinical application of this knowledge.

The range of science papers reviewed revealed a number of aims and aspirations, and these are summarised in Table 1.



Table 1. Summary of the aims and aspirations of science papers.

First author	Aims	Aspirations
Akbar et al (1998)	Study particular enzyme expression	Understand role in fertilization, implantation and development.
Almqvist et al (1996) Gordon et al (2004)	Characterise morphology and chemical characters of developing brain Efficacy of embryonic cell implantation	Treatment of Parkinson's disease by transplant
Anderson et al (1999) Durand et al (2002) Fougerousse et al (2000) Beckmann	Characterise expression of proteins and genes related to muscular dystrophies	Understand the development and relatedness of different muscular dystrophies
Bertossi et al (1999) Virgintino et al (1998) Bibas et al (2000) Tuori et al (1999) Dame and Juul (2000) Juul et al (1998) Davidson et al (1983) Lu et al (2005) Marin-Garcia et al (2000) Sola et al (1999) Herlenius and Lagerkrantz (2001) Itoh and Onishi (2000) Robertson Kanazir et al (1997) Meyer Kappelmayer et al (1995) Kerwin et al (2004) Kurjak et al (2004)	Study development of blood brain barrier. Development of auditory and other sensory systems. Characterise function of interleukin receptors and other biologically active compounds and receptors. Characterise expression of isoenzymes. Study distribution of neurotransmitters in fetal brain. Foetal liver metabolism. Neo cortical development Gene expression, measurement and visualisation. Anatomical study of human vomeronasal organ.	Fundamental understanding of systems during human development



Lindsay and Copp (2005) Luton et al (1997) Nebot-Cegarra Quere et al (1999) Sano et al (2000) Sobrier et al (2004) Terzic and Saraga-Babic (1999) Sherwood		
Edstrom et al (2000) Koenig et al (2001) Yang and Pace (2001)	Study expression of factor involved in coagulation Study development of blood system from foetus to neonate	Understanding normal expression for insight into specific foetal and neonatal disease
Braybrook et al (2002)	Expression of genes involved in cleft palate conditions in human and mouse model	Development of mouse model for studying role of gene in craniofacial development
Brizot et al (1996)	Measure protein and mRNA expression in foetal liver	Develop maternal blood test to identify trisomy in foetus
Buraczynska et al (1995) Gou et al (2001) Jay et al (1997)	Construct human cDNA library cDNA library from a single embryo Construct cDNA library	Create a resource for the study of developmental gene expression Efficiency of use of tissue Find candidate genes for disease
Chen et al (2005)	Expression of growth factors in foetal skin	Understand scarless healing of foetal skin for application to wound healing.
Dizon-Townson et al (2000) Yamada et al (2005)	Development and role of placenta in first trimester Anatomical study of fused umbilical arteries	Understanding of normal reproduction and obstetric disease
Espinosa-Parrilla et al (2002) Odent et al (1999) Gottlieb et al (1998)	Characterise expression of a gene associated with malformations. Characterise protein and gene expression associated with complex disease in human and mouse. Expression of gene linked to severe disease and	Understand foetal malformation, including facial clefts, and the potential links to later onset disease



<p>Guimot (2004)</p> <p>Suzuki (2001)</p> <p>Hedborg (1994)</p> <p>Mah (2004)</p> <p>Del Santo (1998)</p>	<p>malformation.</p> <p>Anatomical study of development of the tempromandibular joint</p>	
<p>Fougerousse (2000)</p>	<p>Characterise differences in gene expression in mouse and human</p>	<p>Understanding of evolution through differences in expression of conserved sequences</p>
<p>Oey (2005)</p> <p>Quinton (1997)</p>	<p>Measure long-chain fatty acid metabolism in neonates and foetal tissue</p>	<p>Understanding of neonatal and childhood or adult metabolic disorders</p>



4.1.3 History.

The relatively recent advent of developmental gene expression research is clearly not the first time scientists have made use of human embryonic or foetal tissue. Three particular other areas of research effort were identified in the literature. Firstly, detailed anatomical studies of human development were conducted from the earliest times, such as Galen and Aristotle in Ancient Greece and detailed drawings were made by Da Vinci (Yoxen 1990, Verklan 1993). Ostrer et al (2006) also cite the work of von Beer in the early 19th century. With the advent of new imaging technologies, anatomical studies continued throughout the 20th century and are still ongoing, for example Bertossi et al (1999), Bibas et al (2000), Del Santo et al (1998), Mah (2004), Nebot-Cegarra et al (1999).

Secondly, biochemical studies have been undertaken, both in fundamental research and in that concerned with particular diseases.

Thirdly, the 1980s saw the development of treatments for certain neurological conditions, such as Parkinson's disease, by grafting cells or tissue fragments from foetuses into adults afflicted by these conditions.

4.1.4 Anatomical studies.

At the beginning of the 20th century biologists began systematic collection for anatomical studies, the most famous of which is now known as the Carnegie collection. The study of this large bank of human developmental samples has given its name to the classification of the human embryo during the early phases of development; Carnegie Stages (Morgan 2004).

Despite the detailed work undertaken on this collection, some gaps in knowledge remain; in particular, gene expression in the very earliest stages of development. Gastrulation takes place in the second week of gestation and organogenesis at three to four weeks. Embryos of this developmental age are, for practical reasons, rarely available today. They cannot be grown *in vitro*, for legal and technical reasons. In the UK the Human Fertilisation and Embryology Act (1990) makes it illegal to grow a human embryo *in vitro* for more than 14 days, and most countries in Europe which have any law have based their regulation on the same time scale (EGE 200?). The third week of development is generally too early to be accessed through elective termination, however, historically some embryos of this age have been obtained.

Yoxen (1990), in a summary of the history of research involving human embryos, notes that "morally significant" (Yoxen 1990: 27) research involving human embryos did not begin with IVF (his major concern when writing) but rather went back at least a century. By the 1930s research had advanced in the USA to the point where two pioneers, Rock and Hertig, were searching for early embryos in the fallopian tubes of women who had presented for sterilization by hysterectomy. Such operations were;

timed to be slightly later than their estimated date of ovulation, in the hope that they might have had intercourse before coming into hospital and,



unbeknown to them, have conceived. In a very small number of cases this was indeed so, and from their organs Hertig removed both fertilized and unfertilized ova, which were then sectioned, examined and made part of the Baltimore collection. (Yoxen 1990:36)

In these cases it is unclear whether or not the women, who had consented to surgery, were aware of the subsequent use of the removed tissue or the motives for the research. Furthermore, it was later admitted by a nursing assistant of Rock's that, without explanation, she encouraged women who were to have sterilization procedures to engage in intercourse prior to hospital admission, in order to increase the chances of finding an embryo. It was also the case that the women were observed for many months prior to surgery, in order to more accurately calculate when they would ovulate.

Such practices may have gone on unquestioned since at the time there was a more paternalistic approach taken by physicians, and accepted by patients. This was also before the second world war, and the medical research abuses that happened at that time and which were the major drivers in the development of requirements for consent procedures.

Yoxen (1990) also noted the then current practice of asking women about to undergo hysterectomy to “undergo superovulation so as to allow ova to be removed from their ovaries for subsequent in vitro fertilization” (Yoxen 1990:38), which he describes as a modern revision of Rock's questionable practices 50 years earlier. He noted anecdotal evidence suggesting that women were offered earlier operations if they agreed to such donation; which of course would not benefit them. For Yoxen, this,

simply underlines the historical conclusion that in evaluating embryo research we should attend primarily to the rights and feelings of the women who would make it possible, rather than to the characteristics of the potentiated cluster of cells we call an embryo” (Yoxen 1990: 38)

This observation will obviously have significance for the stem cell debate, but discussions around the use of tissue obtained from abortion can also be informed by such a suggestion.

4.1.5 Tissue collections.

The tissue for most recent anatomical studies reviewed appears to be collected *ad hoc* by individual researchers. While the sample of science papers reviewed here is limited as noted above, very few referred to obtaining samples from central collections, the majority merely noting that samples were ‘obtained’. In some cases collections of particular tissues are maintained, such as that in London relating to the development of hearing discussed by Bibas et al (2000). A further example of a developmental tissue collection is noted by Nebot-Cegarra et al (1999) based near Barcelona: the Bellaterra Collection of Prof. Domenech Mateu. Sherwood also reports work using the Walmsley Collection, located in the School of Biomedical Sciences, University of St Andrews (Sherwood et al 1999: 414). There is nothing more said about the origins of the material, the conditions under which it was



obtained or the regulation of the use of it. Finally, outside Europe Yamada et al (2005) report,

Since 1961, 40,000 human conceptuses have been placed in the Kyoto Collection of Human Embryos, in a collaborative effort of several hundred obstetricians. In most of the cases, pregnancies were terminated for social reasons, mostly in healthy women during the first trimester of pregnancy (Maternity Protection Law of Japan). The terminations of pregnancy were performed mainly by curettage procedures. (Yamada et al 2005: 1710-12)

Many of the papers reviewed for this report focused on biochemical analysis of various systems of the developing human embryo. As shown in Table 1, these studies cover a range of issues and aspirations ranging from fundamental understanding of development, through study of particular maldevelopments to producing specific clinical tests for conditions.

The locations of researchers around the world using hEFT is of significant interest to *DGEMap* and is the subject of a separate analysis and report; D3.2.

4.1.6 The source of human tissue in research papers.

In general, the source of tissue is described in the materials and methods sections of the scientific papers. This tends to be rather cursory, in keeping with the observations of Yoxen (1990). A typical example is Odent et al;

In situ hybridization.

Human embryos were collected from legally terminated pregnancies in agreement with the French law and the Ethics Committee recommendations. (Odent et al 1999:1688)

Nothing further is said in this particular paper, although the work reported involved DNA samples from living family members in the research as well as hEFT, and so some acknowledgement of gratitude is made. Most other papers reviewed simply report that embryos were obtained from legal termination of pregnancy; see Buraczynska et al (1995), Espinosa-Parilla et al (2002), Fougousse et al (2000), Sobrier et al (2004), Akbar et al (1998), Almqvist et al (1999) and others.

An interesting example of how scientists describe the acquisition of the human tissue for their research is found in Brizot et al, who state,

Specimens of liver were collected from 13 trisomy 21 fetuses, five trisomy 18 fetuses and 24 normal fetuses after surgical termination of pregnancy at 12- 15 weeks of gestation. The diagnosis of trisomy was made by chorion villus sampling in singleton pregnancies referred to our centre because of increased fetal nuchal translucency thickness detected at routine ultrasound examination. ... The study was approved by the hospital Research Ethics Committee and tissue collection was made in accordance with the Polkinghorne guidelines on the research use of fetal material. (Brizot et al 1996, p156)



This study, conducted in the UK, thus makes use of material from termination of pregnancy following the discovery of foetal abnormality. The authors are explicit in their naming of the ethical approval and guidelines to which they work. However, the manner in which the normal foetal material was obtained is not immediately clear in the section quoted above or elsewhere in the paper. Whether these normal foetuses were obtained from terminations carried out for other reasons, or the result of misdiagnosis of trisomy, remains unknown. The authors appear not to consider this ambiguity important; the focus of the paper is on the clinical benefits arising from the results of their research.

In the papers under consideration, it was noticeable that all those using hEFT and published by researchers based in Italy made use of embryos or foetuses that had spontaneously aborted; Bertossi et al (1998), Virgintino et al (1998), (2000), (2001).

Also typical of the scientific papers reviewed is that the materials and methods section is the only time the source of the tissue is mentioned, if at all. For example, Akbar et al state,

Decidua, chorionic villus and fetal tissues were obtained with the consent of the subjects immediately after termination of pregnancy under section 2 of the 1967 Abortion Act at 8 – 12 weeks of gestation. (Akbar et al 1998 :206)

In this case there is the reduction of the women providing the foetuses to “subjects”, and also, common to all papers reviewed, is the absence of any acknowledgement of gratitude. It is striking that in none of the science papers reviewed did anyone acknowledge or thank, anonymously, the women who gave their consent for their foetal tissue to be used in the research. The only type of study that does acknowledge the contribution of those who donate tissue samples is that which traces an altered gene through families. One such example is Odent et al who note, “We are very grateful to the families and for the support of clinical geneticists, obstetricians and paediatricians who sent us the blood samples.” (Odent et al 1999: 1688)

Finally, in relation to the source of tissue, some papers mention consent. For example, Braybrook et al (2002) who say, “Informed consent was obtained from all of the patients or their parents documented in this study.” (Braybrook et al 2002, p2802). This of course, referring to the living tissue donors. The authors continue,

The collection and use of human embryos was carried out with ethical permission from the Joint Ethics Committee of the Newcastle Health Authority and with appropriate consent. Following either surgical or medically induced termination of pregnancy embryos were staged, fixed in 4% paraformaldehyde in phosphate-buffered saline and then wax-embedded. (Braybrook et al 2002: 2802)

The general note of the governance arrangements under which the work was conducted is typical of many papers. Another example, in the materials and methods section, the authors state,



Aborted human embryos timed post-conception were isolated and appropriate organs were dissected and frozen at -80C at the University of Washington. ... The embryos were obtained with appropriate human subject safeguards under guidelines approved by the human subjects committees at the Universities of Washington and Michigan. (Buracinska et al 1995: 198)

Again, it is interesting to note the reduction of women to ‘subjects’ and the rather generalised way in which the governance arrangements are noted. However, this and other papers are concerned with the science and so there is no need to be more detailed so long as the editorial requirements of the particular journal are met. It is also worth again noting that in none of these cases above is there any indication that the tissues collected have been a part of any systematic collection, but rather *ad hoc* for the research to be undertaken.

In all the research papers reviewed for this report, the developmental age of hEFT used ranges from 3.5 weeks to full term. The papers reviewed study all the major organs and overall development, however, without a full content analysis on the many thousands of references obtained on the most broad search strategy, it is not possible to identify any particular focus of research.

It is not the purpose of this review to detail the specifics of the scientific research that has been, and is being, undertaken but rather to explore the ethical, legal and social aspects of this research area, and this is the subject of the remainder of this report.

4.2 Ethical, legal and social aspects of research using early human tissue.

As noted above, while there is variability in its reporting, all published research using hEFT is regulated by both legislation and voluntary codes of practice or guidelines. The details of the regulatory frameworks in place forms the subject of another report to be presented later in the project. However, it is appropriate to report some of the findings here, as these form the context within which the ethical and social literature is situated.

4.2.1 Regulation and guidelines.

A number of guidelines and regulations were published and enacted during the 1980s, for example in France, Australia, the USA and the UK (Verklan 1993) (Boer 1994). Boer notes that many of the then existing regulations were contradictory and so an organization was formed to produce guidelines for one particular group of researchers using hEFT. These will be described in more detail in section 4.2.2, below. However, from a *DGEMap* perspective, the guidelines in the UK are of the most pressing relevance.

The Polkinghorne guidelines (Polkinghorne 1989) were established in the UK in 1989 by a committee under the leadership of the Reverend John Polkinghorne, a respected theologian and former scientist. These were published in the form of a Government Command Paper (Cm 762) and were the result of a review of the guidelines on the use



of foetal tissue in research that were in place at that time (Peel 1972). The driver behind the review of the Peel guidelines was the increasing interest by scientists and clinicians in transplanting foetal neural tissue into patients with degenerative neurological disorders. Pfeffer and Kent (2006) summarise the report of Polkinghorne's committee,

The committee took the view that only tissue from the dead fetus *ex utero* is ethically available for use; the 'supply' of fetal tissue must be separated from the practice of research and therapy – in other words, the investigator must not be involved in the procedure (the 'separation principle'); the method of terminating the pregnancy must not be influenced by research requirements and consent for research should be general, not specific (that is, details of the research which might use the material should not be specified to the woman). The committee had been persuaded that women might be influenced in their decision to have an abortion by the possibility of the fetus being used in a particular way; for example, they might conceive a pregnancy deliberately to provide neural tissue for transplantation into a relative with Parkinson's disease. (Pfeffer and Kent 2006: 216)

There is a suggestion by Polkinghorne that tight regulation is not the best way to govern research in this area, as it is less flexible and able to respond to new developments as professional guidelines such as those of the Peel report, or his own.

Finally, it is only permissible to use the embryo or foetus after death; which in this case is defined in the Polkinghorne guidelines as the irreversible cessation of respiration and heart beat. This definition differs from that used in determining death in any already born human being, which is irreversible loss of function of the brain stem (Brown 1986). The reasons behind this relate to the difficulty of determining activity in the brain stem of an embryo or foetus and the likely trauma that would be caused by attempting to do so.

4.2.2 Findings from literature searches.

As noted in section 2, the literature searches were broad enough in scope to find social scientific and ethics literatures on biological research that uses early human tissue. The areas of work that yielded the most pertinent findings were;

- Foetal tissue grafting
- Tissue banking: 'Biobanking'
- Human Stem cell science

Foetal tissue grafting.

The starting point for the discussion of the literature on foetal tissue grafting is a review by Verklan (1993) of the history of ethical concern relating to the use of human embryonic and foetal tissue (hEFT) to that point. She notes, from an American perspective, three phases of ethical concern;



- (1) the response to liberalised abortion laws (1970 – 78);
- (2) Prenatal diagnosis (1978 to early 1980s);
- (3) transplantation of hEFT (1983 onwards).

Discussions on hEFT transplantation in the USA were influenced by a series of reports from around the world. The first was by the Australian National Health and Medical Research Council in 1983 and was followed by a publication on the same subject in 1984 by the French National Ethics Committee. 1986 saw the adoption of Recommendation 1046 by the European Union, formulating rules on the therapeutic uses of tissue from the dead, including foetal tissue.

Verklan (1993) notes that

there is no doubt that that the product of human reproduction is not human; this is based on biology. It is the term *person* that raises controversy. Genetic distinctness can be delineated from the moment of conception; however, the moment that personhood exists continues to be debated.
(Verklan 1993: 1173).

The notion of ‘personhood’ is one to which this review will turn later.

In the context of the transplantation of foetal tissue, Verklan notes that there is a requirement to use cells that are living, even though the organism as a whole is dead. She notes the various definitions of death given in the reports mentioned above, and that all of them include cessation of blood circulation. This is the same criterion as in the Polkinghorne guidelines.

In the USA, the National Institutes of Health (NIH) panel that considered foetal transplantation included in its rationale the observation that elective terminations are legal and would happen anyway and the researcher using the resulting foetal tissue had no decision-making role in the abortion. Thus researchers should be free to use the tissue without being regarded as complicit in any ‘moral evil’ and that, indeed, the utilitarian position that,

the potential good that may be achieved through transplantation or research outweighs the harm that is possibly inflicted by an elective abortion. One may argue that a truly pro-life position favours the affirmation of life that transplantation entails. (Verklan 1993: 1175)

With the development of this area of transplant medicine came an increased interest in, and debate on, the ethics of using human embryonic or foetal tissue. The subject areas covered in this literature include, the link between human embryonic and foetal tissue in research and abortion issues, the philosophical basis of personhood, the safety and efficacy of such treatments, the moral status of the embryo and foetus, the potential for medical use of human embryonic and foetal tissue to increase the rate of abortion, consent, and the attitudes of women to the use of such tissue in research.

Boer (1994), on behalf of the Network of European CNS Transplantation And Restoration (NECTAR), described the guidelines that were laid down for all European



organisations who wish to conduct research and experimental treatments using foetal tissue grafts to treat diseases of the brain, such as Parkinson's disease. These guidelines describe the requirements and working practices to which groups must adhere to become members.

Boer (1994) states that the first meeting that led to the formation of this network took place near Paris in 1991 and comprised 13 groups from 11 European countries. The identities of these groups are not revealed in the paper. In discussing the deliberations of this group, Boer states,

An important aspect in neural transplantation in humans is the fact that it touches upon relatively new ethical questions in biomedical research concerning the retrieval and use of human embryonal and fetal material. ... In principle, the possible use of embryonal and fetal organs or tissue would be analogous to the use of organs and tissue from deceased persons ... However, since the decision on therapeutic abortion might be influenced by the donation of tissue for a given therapy and conception might even be brought about with the sole purpose of obtaining organs or tissue from embryonal or fetal origin, additional regulation is called for. If, moreover, transplantation were to become a standard therapy for certain common diseases, this could create a demand for human fetuses or embryos, with the chance that they would then be debased to the status of organ or tissue sources. (Boer 1994: 2)

Boer concludes that the ethical and legal ramifications of foetal tissue grafting cannot be completely isolated from the ethical and legal aspects of abortion.

In a short review of the political and legal debate at the time of writing (early 1990s) Boer notes that there are diverse views between and within countries as to the moral judgement on abortion. Criticism of research using embryos has been advanced from a pro-life perspective and also by pointing out that questions about the use of aborted tissue is often approached from;

a scientific and technological perspective with the rationale that scientific research is important and beneficial to mankind ... consequently ... norms have been established that impede research as little as possible. (Boer 1994: 2).

However, this latter objection is dismissed by Boer, evidenced by the large and growing body of ethics literature on the subject, noting,

A full ethical judgement, however, generally lags behind scientific developments: indeed, ethical issues are often raised through scientific achievements. Therefore, ethical issues on the use of human embryos or fetuses will remain continuously open and under discussion. (Boer 1994: 2)

Boer's paper details the ten guideline statements that were adopted by NECTAR. The detail of these is provided in Supplement 2, however, it is sufficient to note here that the guidelines are strikingly similar to the Polkinghorne guidelines introduced in the



UK the year before the first meeting of NECTAR; these in turn are close to the guidelines produced by the majority of the NIH panel, as discussed below.

Boer (1994) notes that NECTAR was established partly in order to “formulate self-imposed ethical guidelines for the use of human embryonic and fetal tissue for scientific and therapeutical purposes, including their rationale.” (Boer 1994, p2). The guidelines the organization produced were designed to ensure a uniform code amongst the members and to support applications to medico-ethical committees. It was also suggested that the NECTAR guidelines might form the basis for future European level legislation on the issue.

The principles on which the NECTAR guidelines are based are described.

Four general moral principles served as the basis for these discussions: (1) human beings and their autonomy should be respected, (2) what is good should be done (“beneficence”), (3) what is bad should be avoided (“non-maleficence”), and (4) what is just should be based on the fair distribution of the available means, on respect for human rights and on morally acceptable legislation. (Boer 1994, p2)

These are clearly the four principles of medical ethics developed in the USA by Beauchamp and Childress in the late 1970s. The Four Principles are general guides that leave considerable room for judgement in specific cases. These are,

Respect for autonomy: respecting the decision-making capacities of autonomous persons; enabling individuals to make reasoned informed choices.

Beneficence: this considers the balancing of benefits of treatment against the risks and costs; the healthcare professional should act in a way that benefits the patient

Non maleficence: avoiding the causation of harm; the healthcare professional should not harm the patient. All treatment involves some harm, even if minimal, but the harm should not be disproportionate to the benefits of treatment.

Justice: distributing benefits, risks and costs fairly; the notion that patients in similar positions should be treated in a similar manner.

(<http://www.ethox.org.uk/framework/framework.htm>)

Further discussion of this basis for research ethics will follow in a later section.

de Wert et al (2003) follow p on the work of NECTAR and present a review of ethical and professional guidelines for the transplantation of human embryonic and foetal tissue (EFTT) into adults or children and notes;

Currently, just one of the participating countries has a specific law on EFTT, namely Spain (Law on the donation and use of human embryos and fetuses, 1988). (de Wert et al 2003: 80)

The Netherlands, then as now, was considering the introduction of a bill on foetal tissue, and France and the UK were noted as having guidelines developed by national



ethics committees. The authors note that the Polkinghorne guidelines have a *de facto* authoritative status.

All the eight countries analysed permit foetal transplantation, and thus have reached a consensus on abortion and the uses to which foetal tissue can be used. By implication this will also include research. The countries are - Belgium (B), Denmark (DK), France (F), Italy (I), The Netherlands (NL), Portugal (P), Spain (E), and the United Kingdom (UK). All include approaches to the separation of the decision to abort and the subsequent move to obtain consent for use of the abortus, however, there are differences in the strength of this. Polkinghorne is the strongest statement of the separation. Overall, these countries share a general consensus that research on aborted foetuses is acceptable and there are only small variations in the approaches they take.

The relationship between research and abortion.

Boer noted above that foetal tissue transplantation cannot be divorced from considerations of the abortion issue. This is not the view that was taken by the National Institutes of Health (NIH) in the USA a few years previously. As described by Strong (1991), the NIH set up a panel to review issues in foetal tissue research and transplantation in 1988 following the announcement of a moratorium on funding this area of research by federal government. The findings of the review was that the majority of the panel found that there was no link between the issues of foetal tissue research and issues of abortion. However, a minority view on the panel opposed this view.

Opposition to the use of foetal tissue took three main strands.

- (1) Use of tissue is wrong because abortion is wrong;
- (2) Use in research may increase the number of abortions;
- (3) Scientists are morally complicit in abortion, which is a moral wrong.

Strong notes that two of the NIH panel members, Burtachaell and Bopp were in the forefront of opposition and they argued that informed consent for the use of the foetal remains cannot be given rightfully. Strong notes,

[Burtachaell] claims that informed consent for use of tissue is important because of our views concerning respectful treatment of human cadavers. He points out that when we remove body parts to further our own purposes respect for the dead requires consent, either by the donor prior to death or by one who has moral authority to serve as guardian of the deceased's remains. (Strong 1991: 71)

Since Burtachaell holds the view that the foetus has the moral status of a person, then there is no-one in a position to give consent on the use of the foetal tissue. By making a decision that resulted in the death of the foetus, this argument holds that the mother forfeits her moral authority to donate the foetal remains. If the father concurs with the decision to terminate the pregnancy, then he too, in Burtachaell's view, has no right to consent to the use of the tissue.



The second argument made against permitting the use of foetal tissue in research by Burtachaell and others, was that an increase in the number of abortions would follow as a woman who was ambivalent about proceeding with a termination may be persuaded to go ahead if she knows the tissue could be used in medical therapies or research. Such use of this tissue would also, it is argued, make abortion more acceptable to society in general, also affecting the number of abortions performed.

The third opposition argument was that to use foetal remains made available through elective abortion rendered the scientists morally complicit in the abortion; which the dissenters viewed as a moral wrong. Indeed, Burtachaell and Bopp made the rather inflammatory comment that foetal tissue research was comparable with Nazi atrocities.

Strong (1991) describes the counter arguments made by the majority of the NIH panel to the three opposition positions and states that in his view each fails to adequately address the arguments. With respect to the first of these, the majority view was that by setting particular guidelines on the timing of consent and the separation of researchers and the woman's medical carers, then the use of the tissue could be ethically isolated from the practice of abortion. This, of course, requires the viewpoint that the foetus does not have the moral status of a person. Strong regards this as failing to refute Burtachaell's argument, concluding,

if human fetal cadavers deserve the same respect as adult cadavers, then consent for the use of fetal remains by one morally authorised to give it is required, and this requirement may be lifted only if there are overriding ethical considerations. (Strong 1991: 73)

With regard to the second argument of the dissenting panel members, the majority noted that the potential for increasing numbers of abortions was speculative, and furthermore that even if there was a small increase in numbers of foetal deaths caused by abortion, other issues in society are acceptable despite the likelihood of increased numbers of deaths; the examples given being construction of new roads and firearms sales.

Again Strong regards the counter-argument as failing in its objective to refute the argument that foetal tissue research is morally isolated from abortion.

the response to the entrenchment argument [societal acceptance of abortion] is itself speculative, as almost any prediction about these matters is bound to be. ... Robertson's reply to the argument concerning individual abortion decisions seems implicitly to acknowledge that the issues are not morally isolated. He suggests that the deaths associated with an activity like highway engineering are an evil that is sometimes outweighed, in part, by the worthy goals of the activity. (Strong 1991: 73)

Even the response to the third, controversial, strand of opposition is deemed inadequate by Strong. The panel made the case that researchers were not complicit in abortion as they were merely making use of tissue that would otherwise be discarded.



The majority of the panel felt that provided their guidelines on consent were followed complicity was avoided. Strong (1991) suggests that while this argument may be satisfactory, the panel went too far in their judgement; goaded perhaps by the links to Nazi atrocities made by the opponents.

Despite suggesting that the NIH panel majority failed to adequately demonstrate that foetal tissue research and abortion are not morally linked, Strong (1991) contends that there is a case to be made in favour of foetal tissue research. He says,

It is not plausible to maintain that there is nothing morally problematic about abortion. At the very least, one can argue that the potential of the fetus to become a person gives *some* moral significance. However, it can be argued that whatever wrong might be involved in the use of fetal tissue obtained from induced abortions is outweighed by the potential benefits to patients. This moral balancing involves two basic factors: the degree of wrongness in using the tissue; and the degree of potential likelihood of potential benefits to patients resulting from the tissue use. The less the wrongness and the greater and more likely the benefits, the stronger is the argument that fetal tissue transplantation is ethically justifiable. (Strong 1991: 74)

He then demonstrates that the degree of wrongness is relatively low; arguing that foetuses do not have the same rights as post-natal individuals and therefore are not considered fully to be persons. This is based, in part, on the lack of development of the areas of the brain involved in cognition and pain perception. Thus foetal tissue of 8 – 11 weeks development, as would be required for neuronal transplant, is not being derived from a person. Further, since the early foetus is not a person, then there is no requirement for exactly the same consideration of respectful treatment that is afforded adult cadavers. He states,

Consent for the use of fetal tissue seems to be required, rather, in order to protect the interests of the woman having the abortion. (Strong 2001, p74)

It is noted in the report on the DS3 symposium (D3.5) that presently consent is technically not required in law in the UK, under the provisions of the Human Tissue Act (2004). However, Human Tissue Authority (HTA) guidelines suggest that given the sensitive nature of the tissue then consent should be sought (HTA 2006) though there are no detailed requirements. The HDBR still seeks consent from women, applying the Polkinghorne guidelines while awaiting further clarification from the HTA on the details of what they consider adequate information on which to base consent.

Ethical principles.

Williams (2005) notes that the ethical principles enumerated above in the discussion of the NECTAR guidelines, are “predominantly individualised concepts, containing little capacity or authority to balance the competing needs of patients.” (Williams 2005: 2087). However, there is a strand of literature that suggests that these principles may not be the best approach for ethics in Europe (Campbell 2005).



Hayry asks “Are there distinctly European values in bioethics?” (Hayry 2003: 408) and observes that some philosophers suggest that dignity, precaution and solidarity are perhaps more European than the four ‘Georgetown Principles’ of Beuchamp and Childress. Hayry, however, argues that the suggested principles comprise terms that can be read, and thus interpreted, in different ways and so one cannot assume there is a popular European consensus on values.

The Georgetown principles are “founded both on the duty-based moral philosophy of Immanuel Kant, and on the outcome-based ethics of Jeremy Bentham and John Stuart Mill.” (Hayry 2003, p200) These are “deontological” and “consequentialist”. This approach has been criticised by many, and Hayry summarises the arguments, noting,

Some of [the] concerns have included that the four concepts have too little content (that they can mean anything, depending on the person using them); that they have too much content (that people using them are forced to buy into an exclusively American system of values); that there are too many principles (that, for instance, nonmaleficence and beneficence should be fused together as a principle of utility); and that there are too few of them (that, for instance, the virtues of care, friendliness and charity, crucially important in good health care provision, are not addressed of all, or at least they are not included in the list). (Hayry 2003, p200)

Hayry (2003) believes that while Beuchamp and Childress did well in combining these two approaches to ethics, they missed one other avenue: Virtue Ethics. This is a “teleological approach” that has its basis in Aristotle, and re-emerged in Europe in the 1980s, becoming popular among Continental philosophers. It was also transposed into Catholic ethics by Thomas Aquinas in the 13th century. Hayry (2003) defines the terms that have been associated with such an approach thus;

Solidarity is often portrayed as the European counterpart of justice. It is related to, but should not be confused with, the liberal and utilitarian accounts of fairness and equality. ... Solidarity... is in European debates linked with communities rather than official state functions, voluntary rather than enforced activities, spontaneous rather than organized events, and reciprocal rather than contractual exchanges. (Hayry 2003: 206)

Dignity is a term that is frequently used in connection with medical ethics, however, Hayry points out that this term is problematic to define as there are at least five “conflicting interpretations for the concept of dignity” (Hayry 2003: 203) that can give different answers to the same ethical questions. He concludes that the variety of meanings of each of these terms means that there is much theoretical work remaining,

If we take seriously the idea that European values should be as far removed from *hedonism*, *individualism*, and *nihilism* as possible, the actual ideals we are after might simply be *prudence*, *communality*, and a *deep sense of values*. It is possible that a level-headed combination of these could offer the alternative to the Georgetown principles European ethicists are so determined to find. But here, too, a lot of work is required in the future. (Hayry 2003: 208)



Until the theoretical and conceptual work is done to develop these notions of prudence, communality and a deep sense of values, Hayry believes it is difficult to see how a specifically European approach can be developed. However, he suggests that it is irrelevant where ideas come from, so long as they encourage further debate and discussion.

In other discussions on virtue ethics, Gardiner (2003) believes that it has a number of advantages over the more established four principles;

- It recognises that emotions are an integral and important part of our moral perception.
- It considers the motivation of the agent to be of crucial importance. Decisions are anchored in the characteristic virtuous disposition of the moral agent who typically wants to behave well.
- As there are no rigid rules to be obeyed, it allows any choices to be adapted to the particulars of a situation and the people involved. Two people might both behave well when resolving the same situation in different ways.
- This flexibility encourages the pursuit of creative solutions to tragic dilemmas.
- Virtue ethicists recognise that tragic dilemmas can rarely be resolved to the complete satisfaction of all parties and that any conclusion is likely to leave some remainder of pain and regret.

(Gardiner 2003: 301)

Gardiner (2003) does point out that virtue was not ignored by Beauchamp and Childress, and that they considered five virtues applicable to the medical practitioner: trustworthiness, integrity, discernment, compassion, and conscientiousness. Furthermore,

For centuries moral philosophers have approached ethical dilemmas by stripping away emotional responses and trying to reason out a solution, but our feelings are fundamental to our human experience. ...

The virtuous person perceives a situation, judges what is right, and wants to act accordingly because it is in her disposition to act well.

It is not sufficient to follow rules irrespective of internal attitudes, feelings, and reason. The virtuous moral agent has a deep desire to behave well. This contrasts with Kant's view: he believed it was more virtuous to act well from duty even if one is not disposed to do so. (Gardiner 2003: 298)

Gardiner concludes that virtue ethics is not a simple replacement for deontology or consequentialism, but rather an additional tool to enhance deliberation on difficult questions.

Dyer (1997), writing from an American perspective, presents some reflections on the ethics of genetic science in the 'postmodern' world. He suggests that there has been a shift in the emphasis on different ethical principles through the 'modern' to the 'postmodern' eras.



Evolution of ethical priorities

1950s-60s	1970s-80s	1990s
Beneficence	Autonomy	Social justice
Autonomy	Beneficence	Autonomy
Social justice	Social justice	Beneficence

(Dyer 1997: 169)

These principles are described by Dyer as being recognizably ‘modern’ in character, and based on the relationship of the individual to the collective. Dyer sees ethics in the ‘modern’ age being focussed on the autonomy of the individual but believes there is a move towards emphasis on the health of the population.

Dyer’s argument is that the rise of medical techniques such as transplantation, life support, and genetic engineering, led to a focus on the individual and,

It could no longer be assumed that a patient would necessarily want what the doctor had to offer. Explicit informed consent was required as opposed to the implicit consent that might accompany the treatment of infections” (p169).

He notes that this shift mirrored the rise of the consumer and civil rights movements. The new developments in genetic technologies thus mean that while the individual will continue to benefit, the population as a whole may also benefit on economic grounds. He says,

For example, genetic alteration might be given strong economic incentive if the cost of treating a genetic anomaly (let us imagine addictive propensities) outweighed the cost to society of altering such traits genetically.
(Dyer 1997: 172)

Dyer’s observations on the importance of individualism in the period up to the 1990s coincides with the observation of Hayry (2003) that the dominant medical ethics model in the USA can be accused of “excessive individualism” (Dyer 1997: 201).

Discussing stem cell science, Hauskeller (2004) argues that the institutional structures and traditions of policy-making and ethical reasoning in the UK were instrumental in the successful creation of a stem cell research industry in this country. She says,

Equally important in ethical tradition and practiced most clearly in the health sector is a general orientation towards the common good. Health care provision by the National Health Service (NHS) is organized around the social idea of providing universally available comprehensive health care based on equality and fair financing. The NHS was set up this way in 1948...(Hauskeller 2004: 510)



This contrasts with Dyer (1997) who argued that there has only been a shift towards social justice in the last decade where there had been a previous focus on the individual.

Moral status and respect for the developing embryo.

There is a large and significant literature on the moral status of the embryo, ranging from the utilitarian, such as Singer's view that since an embryo has no experience of happiness, then its loss can be compensated for by creating a new embryo (see Bunning 1997), to the views of the Catholic Church which views the embryo as a person from 'the moment of conception', (see Fenton 2006).

In much of the above the discussion on whether or not embryonic or foetal tissue should be used for transplantation or research, a recurring theme in the literature is that of personhood. This concept is explored further in the literatures on in vitro fertilisation (IVF) and human embryonic stem cells. These areas of literature, of course, discuss pre-implantation human embryos of only a few days development and, crucially, which are still alive and capable of further development. Despite the nature of the material being radically different from that which the *DGEMap* project engages with, the fundamental concepts of personhood are of relevance and will be explored from this perspective.

There has been an ongoing debate on the stem cell issue since 1998 when James A. Thomson first reported the successful derivation of stem cell lines from a human embryo. Even before this there was a debate on the nature and status of the embryo resulting from the developments in IVF techniques. This was not confined to the UK, where the world's first 'test tube baby' had been born. Germany in particular had a high profile public debate on the issue, resulting in 1990 in the Embryo Protection Act (August 2000, Beckmann 2004). The UK response to the issue was the Warnock committee report which gave rise to the Human Fertilisation and Embryology Act (1990) and the creation of the HFEA (Kirejczyk 1999, Warnock 2000).

Baldwin (2005) discusses the Warnock committee and their deliberations on research using human embryos, in the context of IVF. He notes that the committee had a minority view that research on embryos should be treated in the same way as research on infants. This suggests that the minority view, of opposition to research, was based on a belief that the embryo is fully human; that is a 'person'. However, the majority of committee took a gradualist view of the developing human being, with the embryo being viewed more like a person the closer it gets to viability. Since the embryo has the potential to develop into a human being the committee majority agreed that there should be an "added measure of respect" in dealing with this entity. This respect was to be manifest in two ways; firstly, the 14 day limit on research; secondly, that embryos could only be used for certain specified types of research. Baldwin also notes,

the moral status of the embryo was thoroughly debated in the course of the public debates in 2000 – 2002 about stem cell research, and I shall not attempt



to review those arguments here, although I think that we still lack an altogether satisfactory statement of the case for embryo research.
(Baldwin 2005: 85)

Gomez-Lobo (2004) notes that arguments calling for respect for embryos are generally based on the potentiality of the embryo; its potential to become an adult. While Gomez-Lobo concludes that embryos are ‘persons’, Mahowald (2004) argues against this, saying that;

Recognition that an entity is a human being is sufficient for some of us to construe the entity as deserving of respect, but this does not commit us to view all human beings as actual persons, or as deserving of the same respect we tender to actual persons. ... actual persons have a *prima facie* legal and moral right to self-preservation” (Mahowald 2004: 212)

So a case can be made for the destruction of potential persons, in the form of blastocysts for producing stem cells, though only under conditions which include the aim being to preserve the life of existing persons.

Harris, (1990) notes that there is a feminist approach that does not view the embryo as a separate human entity, but rather puts women and the social context at the centre of debate. Harris takes a view that if a society permits abortion there can be no justification for not permitting research on embryos. He suggests that there is no difference between using the tissue from abortions and from cadavers. In a paper that argues in favour of embryonic stem cell research, and was part of the Eurostem project, Harris notes,

The European Group on Ethics, which advises the European Parliament, is one of the few to have highlighted the women’s rights issues that arise here.
(Harris 2003: 354)

He further states,

In most E.U. countries, there is a parallel between the permissibility of embryo research and the permissibility of abortion. Ireland is the only E.U. country whose constitution affirms the right to life of the unborn, where this right is equal to that of the mother (Harris 2003: p357)

To this must now be added Malta, which has even more restrictive legislation than Ireland (EGE2005).

Harris (2003) also introduces an ethical principle that will be of interest to *DGEMap*,

The ethical principle that I believe we all share and that applies to the use of embryos in stem cell research is the Principle of Waste Avoidance.” (Harris 2003: 361)

This concerns the “powerful moral reasons to avoid waste and do good instead.” (Harris 2003: 362) and thus suggests that there is a moral obligation to use



supernumary embryos and aborted embryonic or foetal tissue for research that may lead to therapies which treat or prevent disease.

Savalescu (2002) discusses the notion of personhood in relation to the issue of abortion. Although large parts of his argument fall outside the scope of this review, it is apposite to note his view that the beginning of personhood can be ascertained by noting when personhood ends. In Western culture the end of a person is taken to be brain death. Thus the beginning of a person should be the beginning of consciousness. There is general agreement that the relevant degree of brain development to permit consciousness has not been completed before about 20 weeks. In this argument, Savalescu notes that it can thus not be considered wrong to abort a foetus before about the 20th week of development. It is not killing a person, but rather preventing a person from coming into being. In this regard, he argues, it is analogous to contraception.

Schmidt et al (2004) observe that Hausekeller (2004) describes the UK as being characterized by the high value placed on certain individualistic principles, such as autonomy and choice. She notes the UK's desire to be a leader of embryonic stem cell research, both in science and in influencing international regulation. Schmidt et al state,

Hauskeller, however, is eager to point out that this project is doomed to fail since, in European standards (EU), there is not agreement as to the ontological and moral status of the embryo and the principles or concepts (i.e. respect, dignity, right to life, sanctity, etc.) that should guide bioethical reflections.” (Schmidt Jotterand and Foppa 2004: 503)

Mauron and Baertschi (2004) report a particular position has been taken on the embryo in the Swiss debate on stem cells. They note that it has the same basis as elsewhere in Europe.

The *Respect Model* ... assigns to the embryo some form of intrinsic value that commands respect without preventing all forms of killing of early embryos.” (Mauron and Baertschi 2004: 503)

Notions of respect and human dignity are at the core of this and Mauron and Baertschi find the roots of this in Kant. They suggest that oversimplification of argument has led to *embryological Kantianism*, common in official pronouncements. The authors find problems with this approach, in particular over the ambiguity of what is meant by respect. Maio (2004) finds that the same problem of multiple meanings assigned to respect and dignity affect the debate in France. The legal position in France is described as ambiguous, with no definition of the embryo, and yet the embryo is accorded respect. The national ethics commission proposed in 2000 that research on stem cells should be liberalised. This position was reached based on a concept of “virtual solidarity” where patients who might benefit from research are given a higher moral status than the embryos that would be destroyed.



The common theme emerging from all the stem cell literature was the contested nature of the human embryo and the confusion and complexity attendant on all debates and regulation concerning it.

Biobanks and human tissue.

The literature on the collection and retention of human tissue, biobanking, also provides some themes and issues of relevance to *DGEMap*. In relation to collections of any human tissue, Ashcroft (2000) raises the questions,

Is surgical 'waste' discarded material, or something which the patient still has rights over? Who owns a sample or an archive? Do we always need consent? For example, do we need to get consent for a specific use, or is generic consent for 'research purposes' acceptable? Can we reuse or reanalyse a sample without going back to get patients' authorization? Is anonymization essential, or can linked archives be used, and under what conditions? (Ashcroft 2000: 408)

He observes that these issues are unlikely to be resolved in the near future and that when they are, the resulting guidelines will be more, rather than less, stringent. Ashcroft also explores the issue of trust,

one can argue that a 'high' standard of ethics has other benefits - careful attention to ethics often goes hand in hand with other factors of good clinical practice, and with a higher degree of public trust and acceptance of clinical research. (Ashcroft 2000: 410)

He concludes that two ethical principles are in tension with regard to retaining biological samples. "the public interest in research and the moral rights to autonomy and respect for the person." (Ashcroft 2000, p410) The balance between these conflicting positions should be made,

through a process of social choice about which should take priority 'all things considered'. This process of social choice is not free of costs, and it is part of the duty of the research community to make us aware of these costs, so that if we choose to pay them, at least we will do so with our eyes open. (Ashcroft 2000: 410)

Bauer et al (2004) say, in relation to tissue banking, that there is a general trend to more commercialisation, but that there continues to be a great deal of collaboration between the for-profit and not-for-profit sectors. Ethical issues can arise from this, especially with regard to the potential for financial incentives to academic researchers compromising the quality of the research done, or reporting on its findings. They say,

For example, financial incentives to academic researchers (e.g., stock options and royalties) could undermine scientific standards of integrity by promoting secrecy, data hoarding, and even the manipulation of research outcomes. (Bauer et al 2004: 16)



Tissue banking raises issues of how the human body is viewed and how it is treated in life, and in death. In describing the prevailing view that tissue donation is usually seen as a gift, Bauer et al note,

the buying and selling of human biological samples debases the value of human life, is antithetical to the gift paradigm of tissue transfer, can lead to further oppression of the disenfranchised and the poor, and is an affront to the dignity of donors and their families. (Bauer et al 2004, p16)

They note, however, that the commodification of human tissue is not new, giving as examples; blood, sperm, hair and corneas. However, there are many more potential uses of tissue and data now than previously and these raise additional ethical concerns.

Some research has been conducted on attitudes of women to donating foetal tissue for research. This was conducted in the wake of the Polkinghorne guidelines and was particularly focussed on foetal tissue transplantation. Anderson et al (1994) report significant support from all women (94%) for donations, with the respondents about to undergo a termination especially supportive of research using foetal tissue. No specific mention was made by the researchers about the potential commercial exploitation of the tissue. Stegmayr et al (2003) found little difference in attitudes to donation of tissue from cadavers when requests were differentiated between academic research and commercial research. The question of whether such findings would apply to foetal tissue remains unresolved.

On the issue of commercialization,

the policies developed by the European Commission (EC), the Medical Research Council (MRC), and France are explicit in their rejection of financial compensation and profit sharing with donors/families. (Bauer et al 2004: 17)

This position is taken for two reasons. One, that financial benefits could lead to exploitation, the other that tissues are 'gifts' and as such should receive no financial recompense. These points do not, however, lead any of the three bodies to reject collaboration with commercial companies. The MRC even notes that commercial partners should be given exclusive rights over data for a period of time, to allow them some benefit, in order to encourage private sector companies. The French position is that the private sector may have more resources to develop treatments that will benefit public health in the long run.

The American Medical Association now have a policy that potential donors to tissue banks are told in advance of consent the level of confidentiality that will be possible, that is, whether their tissue will be anonymous or traceable. The EU requires traceability and confidentiality for tissue that will be used in applications involving patients, but does not place this requirement on tissue used only in research.

Bauer et al (2004) note that if commercial concerns are involved in the banking or supply of banked tissue, then there is always a possibility of conflict of interest when prioritising the allocation of tissue to the researchers who request it. There should be



no possibility that personal, or institutional financial gain subverts the allocation of tissue since the donors will have given consent on the presumption that the overriding concern will be the quality of the research to be undertaken.

Another conflict of interest issue arises when the curators of the bank engage in research themselves, and receive a request from a competing laboratory. This is different from the situation where a bank has been established for a particular cause, Alzheimer's is given as an example, when the curators may reasonably turn down requests for tissue for other areas of research.

Transparency in allocation procedures, and the checks and balances in the process, are suggested as the means to reassure donors. However, Bauer et al (2004) note that few of the policy documents of tissue banks that they surveyed mentioned this issue and most of those were rather vague in their treatment of the subject.

Confidentiality was found to be an important issue in all the countries the authors surveyed. Bauer et al note that,

if researchers may access the donor's medical records [then] safeguards must be put into place to protect the donor's (or donor's family's) confidentiality, even prior to the informed consent process. (Bauer et al 2004: 21)

A range of policies were found in different organisations, but all provided for confidentiality by anonymising or coding tissue samples. However, when discussing anonymity, Hansson (2004) observed the potential for no donated tissue to remain anonymous in a situation where genetic sequence data becomes a part of a citizen's medical records.

There is a discussion of the 'gold standard' of informed consent; going back to donors to seek consent for research on tissue donated previously for other work, and the authors say,

Unless donors (or their families) understand the specific nature of a research protocol in which they are enrolling, they neither can assess adequately whether participation in the overall investigation is consistent with their values, nor freely and deliberately refuse participation in certain aspects of a study. (Bauer et al 2004: 22)

Their research found a wide range of national views on issues of consent, and although not directly concerned with banking of foetal material, these may be of interest to *DGEMap*. Belgium, France, Spain and the European Commission adopted a position of presumed consent for organ and tissue retrieval from the dead, whereas the UK and USA were engaging in processes to obtain consent, though based on varying degrees of detail.

There is an argument presented by Hansson (2004) that it is unethical to 'disturb' donors by going back to them to seek consent for different use of the tissue they donated for one particular purpose, in contrast to the 'gold standard' described by Bauer et al (2004).



Bauer et al (2004) conclude that from their review there appears to be little consistency in the ethical issues that policy documents address, or the definitions and uses of similar terms when they are used. They suggest that the four key issues they identify (commercialization, confidentiality, informed consent and quality of research) should form the basis of discussions on the harmonization of guiding principles for tissue banks at local and international level. International as no tissue should be exported to regimes that do not meet the same criteria as the originating source.

However, Maschke and Murray (2004) note;

Bauer, Taub, and Parsi's review of an international sample of standards on informed consent, confidentiality, commercialization, and quality of research in tissue banking reveals that no clear national or international consensus exists for these issues. The authors' response to the lack of uniformity in the meaning, scope, and ethical significance of the policies they examined is to call for the creation of uniform ethical guidelines. (Maschke and Murray 2004, p1)

However, Maschke and Murray suggest that the potential for binding international guidelines to be set requires further exploration. Maschke and Murray say that there is currently little incentive for nation-states to initiate policy-making at the global, or even international, level given the variation of seemingly irreconcilable views on issues such as consent and confidentiality. Furthermore, the recent international attempts to regulate cloning have shown that many nations use global policy-making as a means of promoting particular domestic agendas.

Godard et al (2003a, 2003b) write on a range of social and ethical issues with regard to DNA banking and Genetic services. They say,

Regulations pertaining to the storage of human biological materials and genetic data are at their beginning stage in most European countries but the multiplicity of actors and of rules that regulate them (public versus private, hospitals, research centers, laboratories) make the situation increasingly difficult to comprehend. (Godard et al 2003a: S89)

The aim of the authors is,

to formulate a professional and scientific view on the social, ethical, and legal issues that impact on data storage and human DNA banking practices for biomedical research in Europe. (Godard et al 2003a, p S89)

However, they then place a limit on their aim, by stating that they do not intend to cover forensic databases or human embryos in their discussion. This is a result of the 'special' ethical considerations of these types of database and tissue. It is not made clear whether the 'embryos' to which they refer are living or dead. Once again, this highlights the complexity and constantly changing nature of governance in this area of human tissue collection.



Hansson (2004) found the same three main areas of concern as Bauer et al (2004); namely,

- Informed consent.
- Anonymity.
- Commercialization.

In relation to consent, Hansson notes that a British study has shown that parents often want to be asked to consent to their child's organs being used in research,

not because they wanted to say 'no' but because they wanted to say 'yes,' thereby contributing to the care of future generations of children.
(Hansson 2004: 321)

Hansson (2004) found that Iceland has an 'opt out' system for consent and that Denmark is considering the same. Tissue removed during surgery will be banked and used in research unless the person from whom it was taken has specifically opted out of the system; consent is presumed. However, it is not clear whether or not this would include an embryo or foetus following abortion.

Sweden has, from 2004, introduced legislation that requires both academic and industrial research proposals to be scrutinised by the same ethics committees. This differs from other countries such as the USA where, Hansson notes, industrial research is often not subjected to the same level of scrutiny.

In relation to international trade and collaboration Hansson notes,

There is also a need to harmonize the ethical requirements in order to prevent countries from competing for research by underbidding in terms of consent procedures, privacy requirements, or security arrangements.
(Hansson 2004: 324)

Hansson does not, however, suggest how such harmonization could be achieved, especially in the light of the differences of views throughout Europe, let alone in the wider international community. As an example of this issue, Cambon-Thomsen et al (2003) conducted an empirical study on biobanking of human genetic material and data in six EU countries as part of a larger study studying collections of material across many species and genera. Their work focused on France, Germany, the Netherlands, Portugal, Spain, and the UK, and data was collected in 1999-2000.

Surveys of organisations holding banks of tissue were conducted, postal questionnaires mostly, and content analysis of documentary material was conducted. The questionnaire comprised 60 questions covering 10 areas of interest and responses were obtained from public and not-for-profit organisations only, no commercial responses.

Of the organisations responding, those in the Netherlands had little interest in harmonizing practices throughout the EU. All other countries saw benefits in harmonization, though French respondents thought ethical problems might prevent it.



The authors report extreme variability in working practices and oversight or regulation throughout the institutions responding. They also note that while there was a commonality of understanding of ethical issues,

ethical issues were generally known and those reported were related to information and consent, data confidentiality, exchange and management. Consent forms have gradually been applied ...[but] Their content is variable and heterogeneous. (Cambon-Thomsen 2003: 148)

The authors also note, “The perception that a strict framework of specific ethical issues was necessary was strongest in large banks with lots of exchanges.” (Cambon-Thomsen 2003, p149) It is noted that many banks finance their existence by charging fees for services or licences.

Research ethics: a neglected perspective.

There is an argument presented by Bunning (1997) that is applicable to all types of research, but particularly of the type *DGEMap* engage in;

An ethical problem of a different kind emerges when the principal researcher tries to pass on his own emotional problems to a hierarchically lower placed assistant. As part of their training programs, students are often instructed to prepare the foetuses. Sometimes such instructions resemble a kind of initiation rite into the privileged world of scientific research. The students are not in a position to decline. The same might be true for the professional biotechnician who managed to get employment from the research institute: refusal might result in discharge. The ethical moment of reflection here should be whether it is acceptable for the responsible researcher to delegate an emotionally loaded action to another person. (Bunning 1997: 269)

Similarly,

when the goal of the experiment is based upon personal experiences of the principal researcher, e.g. the suffering of human patients in the clinic, it would appear difficult to pass this motivation on to an assistant who never leaves the basic labs. (Bunning 1997: 269)

Bunning also notes that in religiously inspired views on abortion, the woman is denied authority over the unborn. He closes by observing,

society expects someone to take up the challenge to exterminate one of the congenital spells that inflict severe suffering in patients and their families. Therefore, someone has to do the job, and society should accept the responsibility to protect that person who is sensitive to the moral aspects and at the same time tough enough to resist the emotional burden of his profession. That is a person who is humane, with respect to humans and animals. (Bunning 1997: 271)

There is, however, no indication of the form such protection should take.



5. Discussion.

The foregoing report on the findings of the search of the literature has identified a number of key issues for *DGEMap* and leaves many questions open. Its purpose was to identify key themes and concerns in the different literatures relating to the use of human embryonic and foetal tissue. These findings will now inform the design of the semi-structured interviews with senior scientists. Detailed discussion of the implications for *DGEMap* of the literature findings, interviews and other activities will be left to the final, summative report for DS3, however, some initial discussion of the forgoing report on the literature is appropriate.

The review of the science papers led to the observation that while many different classifications could be made, based on nationality, region, organ or disease studied, the most fundamental classification of the reported work appears to be the three major categories outlined below.

- Category one. Papers where the authors clearly set the work they discuss in terms of immediate clinical value, relating to both foetal development and maintenance of pregnancy, or contributing knowledge to improve clinical practice in the near term.
- Category two. Papers whose authors set their work in the context of understanding the fundamentals of specific disease or malformation by studying normal, and/or abnormal, development.
- Category three. Papers where the work is of basic science; studying and reporting on normal human development.

Regardless of category, it appears that there is little work, other than anatomy, that draws on existing systematic collections of tissue. Rather, tissue seems to be collected in an ad hoc manner when required. The conditions of collection are not usually specified but all authors note that the work was conducted following review by an ethic committee of some type. For the UK, this will mean, in general, that the Polkinghorne guidelines are followed.

It is not possible to tell from the science papers whether or not tissue is held anonymously, but it can be inferred from Bibas et al (2000) that this is not always the case.

The science papers were also used to provide information for a report on the location of research groups in Europe that use human developmental tissue (D3.3) and so details will be found in that document. It is enough to note here that research using such tissue is carried out in a number of locations throughout the EU and other European states.

The biobanking literature contained several recurring themes: consent to donate tissue, confidentiality and anonymisation of tissue and data, and the possibilities for



commercial exploitation of tissue. These themes and their potential impact on *DGEMap* were explored in the symposium that was organised by DS3, and which is the subject of report D3.5. The implications for *DGEMap* must, however, await a more detailed design for the research infrastructure. For example, discussions on the anonymisation of tissue collections will only be of relevance should DGEMap become more formally linked with the HDBR.



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Supplement 1.

Strategy and Results from a search of literature databases.

S 1.1 Strategy and results from ECO, WorldCat and ArticleFirst.

The Online Computer Library Centre (OCLC) FirstSearch portal was used to search these databases. Search terms are shown in *italics* and Boolean operators are in capitals.

OCLC Search 1. *ethics AND embryo AND research* in Public affairs and law.

From the **207** records found **49** were academic papers. Of these, **24** records were selected as having some relevance (to...). However, the majority concerned stem cells. Exclusion criteria were; specifically relevant to USA or other nations only, outdated legislation or practice, subject irrelevant, eg welfare of the child arguments relating to IVF. Finally, papers concerned solely with abortion were excluded.

OCLC Search 2. *human AND embryo AND gene WITH expression* in Life Sciences

From the **13** records found, **7** were academic papers. Of these **4** concerned IVF and pre-implantation embryos.

OCLC Search 3. *“human foetus” AND “gene expression”* in Life sciences.

No records were returned.

OCLC Search 4. *early AND human AND development* in all areas.

The **19000** records found were refined using additional terms,

((early AND human AND development) AND embryo OR foetus OR fetus) and abstract in English)
resulting in **3976** records returned.

Further refinements:

NOT “stem cells” AND “gene expression”
reduced this to **42** records.

After excluding papers which did not deal with human tissue, these papers formed the basis for the analysis of scientific publications.



To these were added papers from searching the 3976 records for; “*Carnegie stage*” which returned **13** records and which was designed to identify papers dealing with the same tissue samples as the *DGEMap* project scientists. Papers not dealing with human tissue were excluded .

Searches 1 to 4 resulted in a total of **55** science papers for review, all of which specifically reported research using human embryonic or foetal tissue.

OCLC Search 5. (“*human embryo*” AND *ethics*) NOT “*stem cell*” NOT *preimplantation*

Search area Social Sciences (Public Affairs and Law produced the same results.)

90 records were found, the majority of which were books or internet resources related to IVF, despite using exclusion criteria in the search terms that were chosen to avoid such references.

OCLC Search 6. “*human fetus*” OR “*human foetus*” AND *ethics* In area Social Sciences.

Returned **10** records, of these all but one were books which could be excluded as being outdated or of no real relevance to the project.

OCLC Search 7. (*bioethics* AND *human*) AND *fetus* OR *foetus* In search area Bioethics.

Returned no records.

Replacing *foetus* OR *fetus* with *embryo* returned **17** records. The majority of these were American and concerned the moral status of the embryo in IVF.

OCLC Search 8. (((“*early human development*” AND (*embryo* OR *foetus* OR *fetus*)) AND *bioethics* In all search areas.

No records were returned.



S 1.2 Strategy and results from MEDLINE database.

MEDLINE Search 1. (“early human development” AND (embryo OR foetus OR fetus)) AND bioethics

Returned **343** records.

Changing the search to exclude the term *bioethics* but search within the Record Type “Bioethics” resulted in **746** records.

These were refined using the following exclusion criteria:

- papers specifically relevant to USA or other nations only
- outdated legislation or practice
- subject irrelevant, e.g. welfare of the child arguments relating to IVF or mental illness in pregnancy
- papers concerned solely with abortion.

MEDLINE Search 2. *ethics AND (foetus OR fetus)*

Returned **265** records of which **61** were academic papers. These were refined using the same exclusion criteria as MEDLINE search 1.

S 1.3 Strategy and results from the ISI Web of Science. (WoS)

A series of searches were performed using the Web of Science portal. Based on the experience gained from the FirstSearch and MEDLINE searches, a refinement of the same search terms outlined above was used and this identified a similar body of literature, with no new branches of literature identified.. Additional searches to broaden the scope of the data are detailed below.

WoS Search 1. *ethics AND “human tissue”*

With the language restricted to English, this search returned **18** records, the majority of which had already been identified.

WoS Search 2. *(medical AND ethics AND human) AND (embryo OR foetus OR fetus)*

Restricted to English language publications, this search returned **34** records. Again the results were refined using the same exclusion categories as MEDLINE search 1.

Those references not previously found were added to the database.



S 1.4 Strategy and results from SCOPUS database.

Scopus Search 1. *(ethics AND research AND “human tissue”)*

The subject areas included in the search were mult, agri, bioc, immu, neur, phar, medi, nurs, vete, dent, heal, soci, atrs, busi, econ and psyc.

Of the **51** references returned, the **2** not already identified were added to the database. This suggests that the Scopus database contained the same literature as other databases previously searched.

In an effort to identify ethics literature on the use of ‘waste’ tissues SCOPUS was searched using the following terms,

Scopus Search 2. *ethics AND surgical AND waste*

When restricted to those references relating to the use of human tissue, **3** references were returned.

Scopus Search 3. *ethics AND discarded AND tissue*

Returned **4** references, two of which were new and relevant.

Scopus Search 4. *“clinical waste”*

Returned **3** references after refinement only one of which was relevant.

Scopus Search 5. *ethics AND use AND clinical AND waste*

Returned **11** results, none of which were relevant.

The SCOPUS database was also checked against the most successful of the previous searches.

Scopus Search 6. *ethics AND embryo AND NOT preimplantation*

This returned **1065** records which were then refined.

(“human embryo” OR “human foetus” OR “human fetus”) AND ethics AND research

This returned **87** records of which **12** were previously known and **2** new relevant references found. The remainder were not relevant as they concerned the specific situation in the USA or elsewhere, they were concerned with voting patterns in a Canadian election, they related specifically to living embryos in IVF or cloning or they concerned theological issues about living embryos. Others were excluded since they detailed outdated legislation or science.



Supplement 2. NECTAR Guidelines.

NECTAR ethical guidelines for the retrieval and use of human embryonic or fetal donor tissue for experimental and clinical neurotransplantation and research

Clinical and experimental groups or institutions that are members of NECTAR will obey the present ethical guidelines, irrespective of the fact that national legislation may permit them to deviate from these guidelines and provided national legislation allows them to follow these guidelines.

- 1) Tissue for transplantation or research may be obtained from dead embryos or fetuses, their death resulting from legally induced or spontaneous abortion. Death of an intact embryo or fetus is defined as absence of respiration and heart beats.
- 2) It is not allowed to keep intact embryos or fetuses alive artificially for the purpose of removing usable material.
- 3) The decision to terminate pregnancy must under no circumstances be influenced by the possible or desired subsequent use of the embryo or fetus and must therefore precede any introduction of the possible use of the embryonic or fetal tissue. There should be no link between the donor and the recipient, nor designation of the recipient by the donor.
- 4) The procedure of abortion, or the timing, must not be influenced by the requirements of the transplantation activity when this would be in conflict with the woman's interests or would increase embryonic or fetal distress.
- 5) No material can be used without informed consent of the woman involved. This informed consent should, whenever possible, be obtained prior to abortion.
- 6) Screening of the woman for transmissible diseases requires informed consent.
- 7) Nervous tissue may be used for transplantation as suspended cell preparations or tissue fragments.
- 8) All members of the hospital or research staff directly involved in any of the procedures must be fully informed.



9) The procurement of embryos, fetuses or their tissue must not involve profit or remuneration.

10) Every transplantation or research project involving the use of embryonic or fetal tissue must be approved by the local ethical committee.

EXPLANATORY NOTES

Status of guidelines

NECTAR has been initiated to stimulate collaboration of research groups with a mutual interest in the development of neurotrans-plantation as a possible therapy in brain diseases. The idea behind this collaboration is not that if there are ethical objections against experimental transplantation studies in one country, these studies should be carried out in another country where obtaining permission will not cause any problems. The ethical issue concerning the use of human embryos and fetuses available from legally induced abortions as well as from spontaneous abortions is considered to be universal. Therefore all NECTAR group members should adhere to the present guide-lines in order to make NECTAR a credible network within the European communities.

In Europe, legislation on elective abortion, in particular, differs widely from country to country [7,18,70] and can even change rapidly within one country as a result of dramatic political changes, as was the case in, e.g. Poland (J. Dymecki, personal communication). Moreover, there is always constant pressure on the prevailing views on elective abortion, since moral judgements differ among people, for instance on religious grounds [72]. The ethical views on the use of embryonal and fetal organs and tissue are less controversial within and among European nations, but are, as stated above, influenced by the views on elective abortion. It is the aspect of the use of legally obtained human embryonal or fetal material that is covered by the present NECTAR guidelines.

The NECTAR guidelines will obtain the status of a solid standard and a useful reference in any application for the use of embryonic and fetal tissue if each member group fully agrees with the directives given and adopts them as common practice. In that case they might also serve as a background for formal legislation on the issue in the various countries or even at the European level in the Council of Europe and the EU. The presently formulated self-adopted guidelines must not be seen as the final or definitive statement of NECTAR. Ethical aspects will remain under continuous evaluation as a result of both practical experience and further discussions with those outside the field of (neuro)transplantation.

The present ethical guidelines cannot be followed in countries where their application will lead to prosecution, but NECTAR groups from countries where legislation is more liberal than the NECTAR guidelines should still comply with the latter.

Definitions



Embryonic state is defined as between 15 days and 8 weeks post-conception of a pregnancy. In the absence of more precise information (i.e. menstrual cycle length), conception is presumed to have taken place two weeks after the beginning of the woman's last menstrual period. At 8 weeks the rudiments of nearly all the main structures have been laid down and there is a general appearance of a mammal-to-be with four limbs and a head. However, the 8-week dividing line is still arbitrary, since a firm scientific basis for the transition to the fetal stage is lacking [56]. The *fetal stage* is taken to be the subsequent period between 8 weeks and the time the baby is born, at approximately 38 weeks post-conception (40 weeks post-last menstrual period). The distinction of the 15-day stage as the beginning of the embryonic stage is not arbitrary: the pre-embryo is not isomorphic with the later developmental stages, since cells cannot yet be defined as contributing to the embryo or to the extra-embryonic tissue [30], and complete implantation has not yet been accomplished [56]. The possible use of *pre-embryos* or cells thereof (as well as of fertilized human egg cells) is not discussed within the present framework of neurotransplantation research and therapy.

