Xenotransplantation guidance

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For Recipient's Use			

Xenotransplantation Guidance

THIS GUIDANCE SUPERSEDES HSC 1998/126

1. Introduction

This xenotransplantation guidance has been designed to explain the DH policy position. It describes the different approval processes that apply in different circumstances, and it points to appropriate sources of expertise and advice for further information and support.

"Xenotransplantation shall mean any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live tissues or organs retrieved from animals, or, human body fluids, cells, tissues or organs that have undergone ex vivo contact with live non-human animal cells, tissues or organs[i]."

Xenotransplantation raises complex ethical issues. It can be viewed as a potential solution to the ongoing shortage of human organs and tissues for transplantation. It also raises concerns – for the safety of the individual and the wider public, for the efficacy of the procedures, and for the welfare of the animals involved.

Currently, there are no xenotransplant trials running in this country. There have been no pig transplants, or any animal organ transplant into humans, in the UK at any time in the past.

The aim of this guidance is to put a framework in place to help clarify requirements and allow research to continue to develop with open discussion and debate.

2. DH Policy position

The Department of Health considers that further development of xenotransplantation should take place in line with international recommendations and guidance. It is recommended that anyone considering xenotransplantation be familiar with these.

Key recommendations include those from the Council of Europe[ii], the European Medicines Agency (EMEA) [iii], the Food and Drug Administration (FDA) [iv], and the World Health Organisation (WHO) [v].

Common themes across all the international recommendations are that:

- Xenotransplantation should only take place when there is an adequate regulatory framework in place;

[i] Part IV of Directive 2003/63/EC (which amends 2001/83/EC)
[ii] http://www.coe.int/T/E/Social_Cohesion/Health/Recommendations/Rec(2003)10.asp
[iii] http://www.emea.europa.eu/pdfs/human/regaffair/119902en.pdf
[iv] http://www4.od.nih.gov/oba/sacx/latestnewssacx.htm
[v] http://www.who.int/transplantation/xeno/en/

- Risks of transmission of known or unknown infections from animal to human should be minimised;
- Traceability and ongoing surveillance of patients is essential;
- Public debate in this area should be encouraged.

The major issue around xenotransplantation is one of public safety, particularly the risk that infectious disease/agents might be transmitted from the animal tissue to the recipient and potentially to the wider population. Much attention is focused on the possibility that [porcine] endogenous retroviruses (which exist harmlessly in animals) may be transferred into humans and become activated - potentially spreading new diseases to the human population. Investigators/researchers will need to bear this in mind as a key factor for consideration by any authorising committee and the regulator. There are also complex ethical issues to be considered.

Given these considerations, it is recommended that all xenotransplant procedures be carried out with a research protocol approved by a research ethics committee. In the following section, we describe these and other approval processes that will apply to xenotransplant procedures under different circumstances.

3. Carrying out a Xenotransplantation Procedure

In this section, we outline the approval processes that will apply to xenotransplant procedures under different circumstances. These processes are also illustrated in the diagram at the end of this document.

The Government believes that it is right to explore the potential of xenotransplantation in a cautious, stepwise fashion. It is extremely important to carry out a xenotransplant procedure in a controlled research context. Clearly, the well-being of the individuals concerned, and the safety of the public in general, must be foremost in the consideration of any proposal to undertake a xenotransplantation procedure. No xenotransplantation procedures involving humans will be allowed to take place unless the approving body is fully satisfied that the evidence put forward is sufficient to justify the particular procedure proposed.

3.1 Clinical Trials

Any proposal for a *clinical trial* of a xenogenic medicinal product[vi] requires approval from MHRA, who will assess safety, quality and efficacy. Such proposals must also go for ethical review. Under the Clinical Trials Regulations[vii], ethical review takes place by a UKECA recognised ethics committee (REC).

If the xenogeneic product is genetically modified, investigators should apply to the Gene Therapy Advisory Committee (GTAC) for ethical approval. For trials of all other

[vi] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Amended by Commission Directive 2003/63/EC.

[vii] (http://www.opsi.gov.uk/si/si2004/20041031.htm)

xenogeneic medicinal products, investigators should book proposals directly with the Central Office of Research Ethics Committees (COREC), who will ensure that the proposal is reviewed appropriately. Any REC considering a proposal for a trail of a xenogeneic product can seek further specialist advice, and to allow for this the Regulations do not apply a time limit for the process.

Directive 2003/63/EC (Annex I, Part IV on advanced therapy medical products) defines xenogeneic medicinal products as follows: "[…] xeno-transplantation shall mean any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live tissues or organs retrieved from animals, or, human body fluids, cells, tissues or organs that have undergone ex vivo contact with live non-human animal cells, tissues or organs. […]"

Please refer to the European Commission document on Clinical Trials to help establish whether the proposal should be treated as a clinical trial[viii].

Also of relevance in this context is the draft EU Regulation on advanced therapy medicinal products (amending Directive 2001/83/EC and Regulation (EC) No 726/2004)[ix] which is intended to cover the additional regulatory requirements for gene therapy medicinal products, somatic cell (human and animal) therapy medicinal products and tissue engineered medical products and thereby add to existing pharmaceutical legislation. Clinical trialists are encouraged to familiarise themselves with this possible forthcoming legislation so that trials can be designed with specific requirements relevant to future market authorisation in mind.

3.2 Research not subject to Clinical Trials Regulations

Research involving NHS patients that falls outside the Clinical Trials Regulations is also subject to an ethical review by a Research Ethics Committee. As indicated in section 3.1 research involving genetically modified xenogeneic material should be directed to GTAC. All other research involving xenogeneic material in patients should be booked directly with COREC.

3.3 Experimental medicine

Experimental medicine is where a clinician offers a particular course of treatment tailored to a particular patient's needs, either a brand new treatment or a new use of a drug or product licensed for use in other ways. Clinicians are required to seek approval from their Trust's Clinical Governance Committee before proceeding with any new interventional procedures in this way. The Clinical Governance Committee is further required to notify NICE through the interventional procedures programme, in order that safety and efficacy can be assessed once sufficient experience has been built up. These arrangements are set out in a Health Service Circular (HSC2003/011).

As noted above, it is recommended that xenotransplants should take place in a controlled research context. Clinicians considering offering experimental treatment

[viii] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol 10/clinical_trial_qa_april_2006.pdf#search=%22F2%2FBL%20D%20(2006)%20April%22
[ix] http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm

outside a research framework are encouraged to take public health issues and long-term health surveillance of patients into account.

4. Animal welfare

It should be noted that the use of animals in xenotransplantation research or as sources for clinical xenotransplantation requires appropriate authorisation under the terms of the Animal (Scientific Procedures) Act 1986[x]. The Home Office has responsibility for this.

Home Office
Direct Communications Unit
2 Marsham Street
London SW1P 4DF

Telephone: 020 7035 4848
Email: public.enquiries@homeoffice.gsi.gov.uk

5. Other sources of Expertise and Advice

Members of the public, clinicians, researchers and investigators are welcome to call on advice from the following agencies/organisations:

5.1 The Medicines and Healthcare products Regulatory Agency (MHRA)[xi]:

Full information on clinical trials, and advice on classifications of medicinal products, is available from the MHRA website:

http://www.mhra.gov.uk

Clinical Trials Unit, 12-2, MHRA
Market Towers, 1 Nine Elms Lane
London, SW8 5NQ
T +44 20 7084 2327, F +44 20 7084 2433
Email clintrialhelpline@mhra.gsi.gov.uk

5.2 Advisory Committee on Dangerous Pathogens (ACDP) [xii]:

ACDP advises the Health and Safety Commission, the Health and Safety Executive, Health and Agriculture Ministers, on all aspects of hazards and risks to workers and others from exposure to pathogens.

Health Protection Agency
ACDP Secretariat

[x] Guidance on the Operation of the Animals (Scientific Procedures) Act 1986
[xi] www.mhra.gov.uk
[xii] http://www.advisorybodies.doh.gov.uk/acdp/index.htm

61 Colindale Avenue
London
NW9 5DF

T: +44 20 8327 7946; F: +44 20 8327 6008/6009
easo@hpa.org.uk

5.3 Gene Therapy Advisory Committee (GTAC):

GTAC is the UK national research ethics committee (REC) for gene therapy clinical research according to the Medicines for Human Use (Clinical Trials) Regulations 2004[xiii]. It is the only UK ethics committee empowered to approve clinical trials of gene therapy products according to the definition given in Part IV of Directive 2003/63/EC. GTAC is also the relevant REC for approval of clinical trials and research on humans using genetically modified animal cells (but not solid organs).

GTAC Secretariat
Department of Heath
Area 604, Wellington House
135-155 Waterloo Road
London
SE1 8UG

T +44 20 7972 1255, +44 20 7972 4151, +44 20 7972 1346
F: +44 020 7972 1717
email: gtac@dh.gsi.gov.uk
http://www.advisorybodies.doh.gov.uk/genetics/gtac/

5.4 Health Protection Agency (HPA)[xiv]:

The Health Protection Agency (HPA) is an independent body that protects the health and well-being of the population. The Agency plays a critical role in protecting people from infectious diseases and in preventing harm when hazards involving chemicals**,** poisons or radiation occur.
They also prepare for new and emerging threats, such as a bio-terrorist attack or virulent new strain of disease.

Health Protection Agency
Centre for Infections
61 Colindale Avenue
London
NW9 5EQ
T: +44 20 8200 4400 ; F : +44 20 8200 7868

Email: infections@hpa.org.uk

[xiii] http://www.opsi.gov.uk/si/si2004/20041031.htm, see article 14(5)
[xiv] http://www.hpa.org.uk/

5.5 Central Office for Research Ethics Committees (COREC)[xv]:

The Central Office for Research Ethics Committees (COREC) is part of the National Patient Safety Agency and provides help and leadership for RECs and the REC system by co-ordinating the development of operational and infrastructure arrangements in support of their work.

NHS Research Ethics Committees (RECs) have been established throughout the UK for many years with the purpose of safeguarding the rights, dignity and welfare of people participating in research in the NHS. Potential research participants at NHS organization in the UK will come under the protection of a REC. The REC is entirely independent of the researcher and the organizations funding and hosting the research.

Applications for clinical trials and research in xenotransplantation (other than those involving genetically modified material) must be booked with COREC who will then allocate the application to the relevant REC.

See: http://www.corec.org.uk/applicants/index.htm

5.6 Clinical Governance Committees:

Clinical Governance Committees work to improve and assure the quality of clinical services for patients. They have responsibility for approving any new interventional procedures. The Clinical Governance Committee is further required to notify NICE of any new interventional procedures through the interventional procedures programme, in order that safety and efficacy can be assessed once sufficient experience has been built up. These arrangements are set out in a Health Service Circular (HSC2003/011)[xvi].

5.7 DH Policy:

The Department of Health's Scientific Development and Bioethics Division has policy responsibility for xenotransplantation. For advice or guidance, please contact:

Genetics Science Safety & Regulation
Scientific Development and Bioethics Division
Department of Health
Area 604, Wellington House
133-155 Waterloo Road
London SE1 8UG

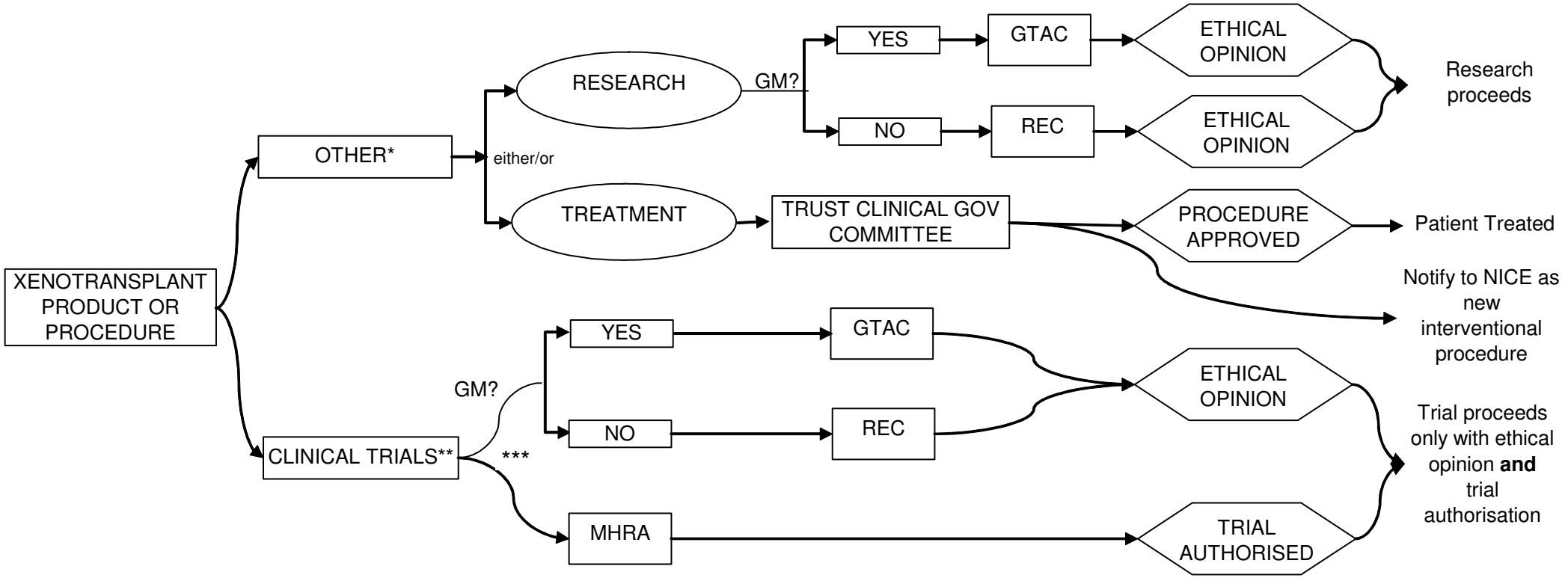
T +44 20 7972 1255, +44 20 7972 4151, +44 20 7972 1346
F: +44 020 7972 1717

email: genetics.policy@dh.gsi.gov.uk

[xv] http://www.corec.org.uk/
[xvi] www.hcsu.org.uk/index.php?option=com_docman&task=doc_download&gid=381 -

Carrying out Xenotransplantation procedures

Please follow the diagram below to establish the direction in proceeding with a Xenotransplantation Procedure



* Includes Experimental Medicine and Research outside Clinical trials regulations
** Should the proposal be treated as a clinical trial? See footnote link (viii)
*** Trial proceeds only with ethical opinion and trial authorisation - both routes to be followed