Annual report : 1998-1999 / United Kingdom Xenotransplantation Interim Regulatory Authority.

UNITED KINGDOM XENOTRANSPLANTATION INTERIM REGULATORY AUTHORITY

SECOND ANNUAL REPORT SEPTEMBER 1998 – AUGUST 1999

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Chairman's Foreword

Over the last year the UKXIRA has made progress in a number of important areas. Draft reports have been produced on infection surveillance and on biosecurity considerations. The Authority has also contributed to the development of the Home Office Inspectorate's draft Code of Practice for the housing and care of xenotransplant source animals. Each of these documents has been issued for widespread public consultation, underlining our continuing commitment to open working. The written comments received, together with discussion at the forthcoming Open Meeting, will no doubt help to consolidate our thoughts on these important areas prior to formal publication.

The UKXIRA also received its first applications to undertake clinical trials in xenotransplantation. Ultimately, neither of the applications progressed to the stage at which the Authority would have been required to make a recommendation to UK Health Ministers. This is, perhaps, a slightly surprising position in the light of earlier predictions about the pace of development but it undoubtedly reflects the fact that xenotransplantation is an immensely complex issue – both in terms of the science involved and in the ethical considerations surrounding it. If the move to clinical trials has not occurred at the rate predicted when the UKXIRA was first established in 1997, this has at least provided a useful opportunity to consider and develop appropriate regulatory requirements.

It has also allowed time to take account of emerging research evidence. New data has become available during the course of the reporting year and, indeed, since the body of this report was written. All new evidence is of assistance to the UKXIRA in its task of regulating xenotransplantation, and the Authority is very much aware of the need to continually update itself on developments. The views, advice and expertise provided to the Authority have been greatly appreciated. We hope that such co-operation between all those interested in xenotransplantation will continue - and continue to develop – in the next year and beyond.

The nature of biotechnology is such that it affects everyone. This report describes several initiatives, either under way or in various stages of preparation, to further public understanding of the issues around xenotransplantation. The UKXIRA intends to be fully involved in these initiatives.

Finally, this reporting year has seen the introduction of devolution in the United Kingdom. Broadly, responsibility for many aspects of government, including the NHS, public health and social services has been devolved to the new administrations in Scotland and Wales and, in due course, Northern Ireland. Xenotransplantation, however, is designated as a *"reserved matter"* (that is, non-devolved) and remains the responsibility of the UK Parliament[1]. The UKXIRA will, therefore, continue to act as a UK-wide body and remains the focal point for all xenotransplantation activity throughout the UK.

Lord Habgood of Calverton

[1] *The Northern Ireland Assembly will also be able to legislate on xenotransplantation and other reserved matters with approval of the Secretary of State and subject to Westminster veto*

SECTION ONE Overview

The UKXIRA's task

1.1. The Box below, replicated from last year's report, sets out the three main areas of the Authority's work:

> The UKXIRA's terms of reference set out its role, but it is possible to see the Authority's work as falling into three main strands of activity:
>
> - a **focal point** on xenotransplantation activity in the UK;
> - a means of **regulating xenotransplantation** – and in particular to provide a process through which applications to undertake xenotransplantation in humans can be considered;
> - to consider the **underlying evidence** about xenotransplantation developments and to consider whether clinical trials – or particular types of developments – can be justified.
>
> The Authority's role as a **focal point** on xenotransplantation issues is important given the number of interests which xenotransplantation brings together – animal and human, industry, public health, and the other regulatory systems which exist for medicines and medical devices. The Authority exists to advise all government departments and has developed close working relationships with regulatory agencies with an interest in xenotransplantation and a range of other organisations that have an interest and expertise to offer.
>
> This has been important in developing a **regulatory system** for considering xenotransplantation procedures. In July 1998, the Authority published guidance on how to make applications to conduct clinical trials. This outlines both the information any applicants will need to submit and the scrutiny each application will undergo.
>
> Clearly, to advise properly on the regulation of xenotransplantation and to submit advice on particular applications, we need to be sure that we are acting on the best possible and most up-to-date knowledge. In considering the **underlying evidence**, porcine endogenous retroviruses have been the infectious agents provoking the most concern ...

1.2. Over the last year, the UKXIRA has sought to consolidate its position on these key areas of its work.

1.3. As the focal point for xenotransplantation activity in the UK, the UKXIRA has maintained a close interest in various developments taking place both in this country and abroad. The attention attracted by biotechnology generally has been reflected in the Government's review of the area. The newly created Human Genetics Commission will have close links with UKXIRA and we look forward to a productive relationship between the two bodies.

1.4. These are issues in which the public rightly wishes to be kept informed of developments. The UKXIRA remains committed to working in as open a way as possible. The first Open Meeting, held on 7 December 1998, provided a useful opportunity for the many diverse parties interested in xenotransplantation to air their views and was, generally, well received. We hope that this year's Meeting, to be held on 6 December, will be similarly beneficial. The Annual Report, the UKXIRA website, and the publication of two documents – on *Infection Surveillance*

and on *Biosecurity* – in draft format for widespread consultation are further indications of the Authority's commitment to open working.

1.5. On regulatory matters, the Authority received many useful comments in response to the publication of *Guidance on making proposals to conduct xenotransplantation on human subjects*. These were discussed in detail at the Open Meeting and several changes agreed. Since then, the opportunity has arisen to undertake a practical assessment of the application process following receipt of the first applications to the UKXIRA. In the light of this experience, we will be considering further refinements which, it is hoped, will result in a clearer yet comprehensive consideration process.

1.6. Two new initiatives undertaken by the UKXIRA were in the development of guidance on *Infection Surveillance* and *on Biosecurity*. These are important areas in considering safety, particularly so whilst the infection risks attached to xenotransplantation are still being evaluated.

1.7. Clearly, in considering xenotransplantation issues, the UKXIRA needs to work from a position of the best available evidence and knowledge. During the year, a considerable amount of new evidence has emerged. Views expressed and information supplied by individuals and organisations from all viewpoints have helped to keep the Authority abreast of developments. Equally, the publication of the *Report of the Workshop on porcine endogenous retroviruses* has helped to inform the xenotransplantation community worldwide on the current state of play and where further work is needed. The systematic literature review, now under way, will we hope prove to be an equally useful resource.

1.8. As was highlighted in last year's report, xenotransplantation is developing on an international scale. The UKXIRA continues to further links with scientific and medical organisations, government and regulatory bodies with an interest in xenotransplantation worldwide. We are pleased to have been able to assist the efforts of the Organisation for Economic Co-operation and Development (OECD) to promote international co-operation on xenotransplantation by leading the development of guidelines for infection surveillance. The Electronic Discussion Group instigated jointly by the World Health Organisation (WHO) and the OECD has generated considerable interest and has done much to open up debate. Archived material can be accessed on www.oecd.org/dsti/sti/s_t/biotech/xenosite/country.htm.

1.9. The UKXIRA Members and Secretariat met with a wide variety of interested groups and individuals in the course of the year. These have included regulators from other UK bodies and from overseas, the industry involved in developing xenotransplantation, medical and scientific experts, animal welfare advocates, and media representatives. These meetings have been immensely useful. The Chairman and Members wish to record their thanks to all those who have given their time and expertise to assisting the Authority.

SECTION TWO Developments in the UK and elsewhere

Introduction

2.1. The exploration of xenotransplantation is just one of many developments taking place within the field of biotechnology. Inevitably, these developments have aroused considerable public interest and raised concerns that work in this area needs to be carefully regulated. In the UK, a review of the regulatory framework for biotechnology has been held. Reviews of xenotransplantation have been commenced in several countries and also within pan-European organisations. The UKXIRA has been pleased to contribute advice to each of these reviews.

UK Government review of biotechnology

2.2. Advances in biotechnology and genetic modification have the ability to impact on many aspects of everyday life, from health and the healthcare we receive, to agriculture and the food we eat and the environment in which we live. This being the case, there is understandable public concern that advances in these sciences should be properly monitored and controlled. For this reason the Government last year undertook a wide-ranging review of the framework for overseeing developments in biotechnology and genetic modification. Comments were invited from the UKXIRA and a comprehensive response was submitted to the review.

2.3. The main concerns to emerge from the review were that regulatory and advisory arrangements:

- were of necessity complex but difficult for the public to understand;
- needed to reflect broader ethical and environmental questions and the views of potential stakeholders;
- needed to be forward-looking to encompass a rapidly advancing technology.

2.4. In response to these findings, the Government decided to implement a strategic advisory structure. This included the establishment of two new bodies to oversee developments in biotechnology of which one, the Human Genetics Commission, will oversee subject matters with a direct bearing on xenotransplantation.

Establishment of The Human Genetics Commission

2.5. The Human Genetics Commission (HGC) will offer advice to government on issues relating to the impact of human genetics and biotechnologies both on healthcare and on the everyday lives of the population.

2.6. It is anticipated that the HGC will meet for the first time early in 2000. Work is currently taking place to determine its terms of reference and to clarify lines of communication between the Commission and other related regulatory bodies, including the UKXIRA. The establishment of the Commission is welcome, not least for the role it will perform in furthering public understanding of these complex issues.

Report of international conference: Xenotransplantation, a solution for the future?
Held in Madrid, 9–10 February 1999, by the Organizacion National del Transplante

Kate Darwin from the UKXIRA Secretariat attended this conference and was invited to give an overview of the current regulatory situation in the UK. A presentation of the position in Spain was also provided where there are currently no laws specifically relating to xenotransplantation. Spain has almost twice the transplantation rate of kidneys as the UK; long-term survival rates are 30+ years for kidneys and 20+ years for other organs. Xenotransplantation would need to offer comparable success rates to be considered a viable alternative in Spain.

Presentations were made on hyperacute, vascular and cellular rejection that impressed upon delegates the large amount of work still to be done. Although genetic modification had overcome the hyperacute response to some extent, other forms of rejection had still to be controlled. Further sessions considered the functional validity of xenotransplanted organs if and when rejection problems were solved, followed by an overview of the risks of transmitting infections.

The conference continued with bioethical considerations of patients' involvement in experimental rather than therapeutic treatments. Whether or not there was a moratorium, public education would need to continue: the point at which the technical problems were solved and trials went ahead, would be too late to begin the process. Wide consultation and discussion were needed to avoid the extremes of naive optimism and doomsday alarmism.

The conference closed with a presentation of the recently published report of the Spanish Xenotransplantation Commission which makes specific recommendations about the conditions that must be fulfilled before xenografts might be allowed (for example, the length of survival of graft in non human primate models). There was also some speculation on the impact a successful xenotransplantation programme might have on the current, highly successful rate of donations to the transplantation programme in Spain.

Questions were raised about whether cloning and tissue engineering might offer better alternatives than xenografts, but the conference ended with the recognition that research on xenotransplantation would need to continue while these other possibilities were being explored.

The Council of Europe

2.7. The Council of Europe was founded in 1949 for the purpose of achieving *"a greater unity between its members for the purpose of safeguarding and realising the ideals and principles which are their common heritage and facilitating their economic and social progress"*. It seeks to achieve these aims *"by discussion of questions of common concern and by agreements and common action ..."*[2].

2.8. The Council comprises 41 member states giving it the widest representation across Europe. The two organs of the Council are the Committee of Ministers comprising the Foreign Ministers of the 41 member states, and the Parliamentary Assembly consisting of 291 representatives appointed by national parliaments. Advice to the Council is offered by a number of expert groups, including committees on bioethics and on health matters.

The call for a moratorium

2.9. In January 1999, the Parliamentary Council of the Council of Europe adopted a recommendation which, amongst other things, called for a moratorium on all clinical trials in xenotransplantation involving humans.

2.10. The Committee of Ministers of the Council of Europe, in considering this recommendation, chose not to take a definitive position. Instead, it decided to establish a Working Party on Xenotransplantation tasked – under the joint responsibility of the Steering Committee on Bioethics and the European Health Committee – with drawing up draft guidelines on xenotransplantation within three years.

2.11. Two UKXIRA Members, Dr David Cook and Dr Maggy Jennings, have been appointed to the Working Party which comprises twelve members, specialising in ethics, law, medical research, clinical practice, epidemiology, immunology and animal welfare. The first meeting of the Working Party took place in April.

2.12. The Working Party will give particular consideration to information for the public and establishing a debate on the future prospects of xenotransplantation.

European Union interest

2.13. It is understood that the European Commission intends to establish an expert committee to offer advice on xenotransplantation. While further details are not known at this stage, the UKXIRA welcomes any moves to assist public understanding of the issues involved and to foster international co-operation.

[2] *Article 1 of the Statute, Council of Europe.*

Meeting with Silke Schicktanz, Technology Assessment Office, Germany – 10 November 1998

The UKXIRA Secretariat met with Silke Schicktanz, a research student at the University of Tubingen which, in conjunction with the Fraunhofer Institute, had been commissioned to carry out a review of xeno-transplantation on behalf of the Office of Technology Assessment at the German Parliament (TAB). Professor Sewell also met Ms Schicktanz on 11 November.

Ms Schicktanz's group was conducting a review primarily on the medical and scientific aspects of xenotransplantation. Simultaneous reports were being conducted on ethical and legal aspects. Research was known to be proceeding in Berlin (extra-corporeal liver devices) and in Hanover (pre-clinical research into lungs and kidneys).

The combined reports to the TAB were expected to result in recommendations for future regulation of xenotrans-plantation. Parliamentary consideration was anticipated towards the latter half of 1999.

Report of meeting between UKXIRA and representatives of Carlton Television, 30 March 1999

Lord Habgood, Dr Janet Dewdney, Mrs Jean Gaffin and the UKXIRA Secretariat met with Mr Frank Simmonds (Producer/Director, Carlton Documentaries) and Ms Polly Bide (Controller of factual programmes, Carlton).

Carlton Television was exploring the possibility of producing a series of up to four documentaries tracking developments in xenotransplantation. The programmes would cover the full range of issues around the current organ/tissue shortage as well as issues specific to xenotransplantation. Discussions would be held with all relevant players in xenotransplantation – the companies involved in its development, medical and scientific experts, patient groups and opponents of xenotransplantation. Carlton was seeking input from the UKXIRA to gain a sense of the regulatory process.

The UKXIRA's commitment to open working was explained though it was acknowledged that commercial and patient confidentiality imposed constraints. In general, though, the possibility of a documentary series was felt to be a very useful means to further public understanding of issues around trans-plantation and xenotransplantation.

Media interest in xenotransplantation

2.14. Xenotransplantation has received widespread media coverage over the last year. While much of the reporting has been informative and well balanced, factual errors have on occasions resulted in some confusion on particular issues. Over the coming year, in conjunction with the other bodies referred to in this section, the UKXIRA intends to look at ways of ensuring greater public understanding of the issues involved.

Campaigns

2.15. Xenotransplantation provokes strong feelings and diverse opinions. While the current view of the Government is that this technology should continue to be explored in a cautious, step-by-step fashion, it is also recognised that some people for a variety of reasons object to xenotransplantation.

2.16. The UKXIRA has a duty to consider all views expressed and accordingly a standing item is included in all meetings to discuss representations made. Postcard campaigns have been initiated by two groups opposed to xenotransplantation. Prior to the UKXIRA meeting on 10 June, a total of 18,568 postcards had been received by the UKXIRA Secretariat.

2.17. Reservations about the development of xenotransplantation have also been expressed within Parliament. In July 1998, a petition was presented to Parliament by Simon Hughes, MP for Southwark North and Bermondsey, calling for a ban on xenotransplantation. In March 1999, Norman Baker, MP for Lewes, tabled a Private Members' Bill *"to prohibit the transplant of living cells, tissue or organs from animals to humans"*. The Bill did not reach its second reading.

2.18. In November 1998, the UKXIRA received a report issued jointly by the British Union for the Abolition of Vivisection (BUAV) and Compassion in World Farming, titled *Animal organs in humans: uncalculated risks and unanswered questions*. The UKXIRA studied the report in depth and, while much of the information it contained was already known to the UKXIRA, the Authority nevertheless considered it to be a useful contribution to the debate, bringing together some helpful summaries of information. The Authority did, however, take issue with a number of points, and in particular the report's references to "chimerism". That cells from transplanted animal tissue may disperse or that they may also survive in other areas of the recipient's body is not disputed. But the report's suggestion that this process might render the transplant recipient less than fully human was, in the UKXIRA's view, unjustifiable.

2.19. In July 1998, the BUAV submitted a report of an investigation into a breeding establishment for research animals. The report made a number of allegations about the welfare of animals, which, it was claimed, were being reared for xenotransplantation research. Although the welfare of animals used in research is the responsibility of the Home Office, this is an issue that the UKXIRA takes seriously. An investigation into the allegations made was launched by the Home Office. It is understood that the report is due to be submitted to Home Office Ministers shortly and the UKXIRA will consider its findings and any recommendations carefully.

SECTION THREE The regulatory role

Introduction

3.1. One of the UKXIRA's primary tasks is to offer advice to the Government on applications to undertake clinical trials involving xenotransplantation procedures in human subjects. The regulatory process by which applications will be considered was launched last year. Since then, the UKXIRA has considered ways in which this system can be improved – taking account both of views expressed to the Authority and in the light of handling two applications.

3.2. The UKXIRA received its first applications in late 1998. The Authority's position on information handling and brief details of how the two applications received were considered are set out in this section.

The regulatory process: refining the application process

3.3. In introducing *Guidance on making proposals to conduct xenotransplantation on human subjects* the UKXIRA acknowledged that the procedures outlined were new and that there may be ways in which the system could be improved. Comments on the system were invited and the Open Meeting in December 1998 discussed suggested changes.

3.4. One suggestion was that the categories of information required should be clarified. In this respect, the UKXIRA has developed a proforma for use by future applicants detailing the information to be included and where in the application specific data can be found. A copy of the proforma is included at Annex Four of this Report.

3.5. Since the Open Meeting, the Authority has further refined its thoughts on the application process, in particular the requirement that applications involving approval from other regulatory bodies have to be submitted sequentially. For example, as currently set out in the *Guidance*, a xenotransplantation cell therapy constituting a medical product and therefore also requiring submission to the Medicines Control Agency, would only be considered after prior consideration by the UKXIRA.

3.6. The UKXIRA is currently exploring with relevant regulatory bodies mechanisms by which the process of considering applications could in future be expedited by permitting parallel applications. If discussions prove successful, the intention would be to issue revised Guidance possibly in late 2000.

The regulatory process: the appointment of expert external assessors

3.7. The process for considering applications to the UKXIRA provides for assessment by a pool of external assessors. At the Open Meeting in December, criticism was made of the absence of an assessor to consider animal welfare considerations. Although the welfare of animals involved in xenotransplantation is the responsibility of the Home Office – and a Code of Practice setting out requirements in this respect has been issued for consultation – it was acknowledged that there may be circumstances in which an animal welfare assessor would be appropriate.

3.8. The UKXIRA has therefore expanded its pool of external assessors to include animal welfare representation.

The regulatory process: information handling

3.9. The UKXIRA fully acknowledges that the public has a right to be kept informed of progress in its work of regulating xenotransplantation as a possible solution to the shortage of organs and tissue available for transplantation.

3.10. Receipt of the first applications to the UKXIRA attracted considerable interest and a number of calls were received from the media and campaigning groups requesting information about the applicants and the procedures involved. The UKXIRA had considered this issue in depth previously and, whilst mindful of the public's wish to know, had also to take account of applicants' right to commercial confidence. Clearly striking an appropriate balance between these two principles is a difficult task.

3.11. The UKXIRA, with the agreement of the Government, has determined that details of any application that, having received full consideration by the UKXIRA, subsequently receives approval from UK Health Ministers, will be made public. Prior to approval, as is common in many other regulatory processes, details of applications will not be released – though, of course, it remains open to any applicant to release details of an application if it wishes to do so.

3.12. The UKXIRA Secretariat will continue to make available information about the number of applications received and number of applications under active consideration at any given time. The Authority will, of course, also take account of requirements for Freedom of Information as the current Bill progresses through Parliament.

The regulatory process: links with the Animal Procedures Committee

3.13. The UKXIRA has liaised with the Home Office and the Animal Procedures Committee (APC) on matters of concern relating to xenotransplantation research. The Authority is also pleased that the Biosecurity Steering Group (see Section Five) was able to offer assistance and advice to the Home Office Working Group charged with producing the draft Code of Practice for the welfare of xenotransplant source animals.

3.14. Animal welfare is a matter that the UKXIRA takes very seriously. Dr Maggy Jennings reports to each Authority meeting on any current issues, on discussions with the industry concerned, and on any matters relating to xenotransplantation of concern to the APC (of which she is also a Member).

Applications

3.15. In September 1998, the UKXIRA received its first application to undertake a clinical trial involving a xenotransplantation procedure. The application was submitted to external Assessors for review in accordance with the procedures laid down in *Guidance on making proposals to conduct xenotransplantation on human subjects.* The view of the Assessors was that insufficient information had been provided in the application to make a reasonable assessment of the proposed clinical trial.

3.16. Accordingly, the UKXIRA Secretariat wrote to the applicant outlining the further information required. The applicant subsequently advised the Secretariat of the intention not to pursue the application for the time being.

3.17. A second application was received in October 1998 and, following review by external Assessors, was submitted to the Authority for formal consideration. After due deliberation, the Authority decided that further clarification should be sought on a number of points. A detailed response was sent to the applicant itemising the information required, and acknowledging that the collation of this information was likely to be a time-consuming task.

3.18. A detailed response was received in April 1999, addressing all the outstanding points. However, in doing so, the applicant also advised the UKXIRA that – as a result of developments in other areas of their research – it was no longer the intention to seek approval for the application submitted. Instead, a new application for a revised study would be submitted in 2000.

3.19. The consideration of this application proved to be a useful exercise for the UKXIRA. In particular, it served to emphasise that, with many varied and complex factors to be taken into account, the assessment of applications may often prove to be a lengthy process. Nevertheless, the UKXIRA considers this to be entirely appropriate and will continue to approach its work with all necessary caution.

3.20. At the time of writing, there are no applications under active consideration by the UKXIRA although, as stated, new applications are anticipated in the coming year.

Report of a meeting between UKXIRA Secretariat and representatives of Genzyme – 3 March 1999

Genzyme's interest in xenotransplantation is in the development of potential therapies for Parkinson's and Huntington's disease. The meeting had been arranged to discuss a number of issues around the regulatory requirements of the UKXIRA for applicants wishing to undertake xenotransplantation procedures in the UK.

Clinical trials involving the implanting of fetal porcine neural cells into the striatum of patients suffering from Parkinson's disease had already commenced in the United States. Genzyme had previously sought the UKXIRA's views on a proposal to conduct some post-transplant monitoring of a number of those patients in the UK. The UKXIRA had discussed this proposal and considered that, while formal regulatory approval for such monitoring was not necessary, further details should be sought from Genzyme. The meeting helped to clarify several points. On the basis of the detailed information and undertakings subsequently provided, the UKXIRA agreed the proposals for monitoring.

SECTION FOUR Infection surveillance

Introduction

4.1. Xenotransplantation is no different from other clinical trials in transplantation in that patients would require long-term follow-up and monitoring. Where it does differ is in the, as yet unquantifiable, concerns about patients' close contacts and possibly the wider population being exposed to infection.

4.2. The UKXIRA is now at the stage where a process for consideration of applications to undertake clinical trials has been established. A high degree of knowledge exists about the various infectious agents transmitted via human organ transplantation. However, the full spectrum of disease agents potentially transmissible via xenotransplantation is still unknown.

4.3. It may be that only xenotransplant recipients will be at risk from xenozoonotic disease. But in view of the *possible* public health risks surrounding xenotransplantation (that is, the chance that disease may be introduced into the general population by the xenotransplantation process), the UKXIRA agreed in June 1998 to establish a steering group to consider screening and surveillance programmes with respect to infections that might stem from xenotransplantation.

Way of working

4.4. The Membership of the Infection Surveillance Steering Group is listed below. Dr Amal Rushdy, from the Communicable Diseases Surveillance Centre of the Public Health Laboratory Service (PHLS), was appointed to draft the report, under the direction of the Steering Group.

4.5. From the outset it was intended the Steering Group's work should be shared with the international community – especially the member states of the Organisation for Economic Co-operation and Development – in the hope that this would stimulate international co-operation in information sharing and data collection. The Steering Group benefited greatly from the support and co-operation of the Communicable Diseases Surveillance Centre of the PHLS, and was informed by discussions with the US Centers for Disease Control and Prevention (CDC), and the US Food and Drug Administration.

Infection surveillance draft report

4.6. The draft report addresses issues surrounding the screening of patients (and possibly contacts) which might be needed before and after any xenotransplantation procedure. It sets out a framework for monitoring the health of xenotransplant recipients and in particular surveilling them for any signs of zoonotic infection that might be the direct result of the xenotransplant.

4.7. The paper considers first the extent of the infection surveillance programme that might be required. It then considers whether compliance with such a programme can be *enforced* by legislation and concludes ***that*** *voluntary consent to compliance* is the only practical option. The nature of fully valid consent in this context is then considered. The paper concludes by looking at how the long-term success of surveillance might be maximised by patient selection and information.

4.8. The Steering Group acknowledged that whatever arrangements are agreed, the programme needs to be reviewed regularly in the light of developing knowledge. It must be capable of adapting to changing circumstances:

either to become less rigorous (if it is judged safe to do so, as would almost certainly have to be the case before xenotransplantation could be used as routine therapy) or to respond rapidly with emergency procedures in the case of a xenozoonotic infection.

Consultation

4.9. In accordance with the UKXIRA's commitment to public consultation, the Steering Group's draft report was issued for formal consultation in August 1999.

4.10. Comments on the document are invited. Closing date for receipt of comments: Friday 15 October 1999.

Steering Group membership

Prof. George Griffin (Chairman), UKXIRA Member
Dr David Cook UKXIRA Member
Ms Sarah Elliston Medical Law Unit, University of Glasgow
Mrs Jean Gaffin UKXIRA Member
Dr Mary O'Mahony Deputy Director, Communicable Diseases Surveillance Centre, PHLS
Dr Phillip Mortimer Communicable Diseases Surveillance Centre, PHLS
Prof. David Oliveira Professor of Renal Medicine, St George's Hospital Medical School
Dr David Paton Central Veterinary Laboratory
Dr Amal Rushdy Communicable Diseases Surveillance Centre, PHLS Consultant to Steering Group
Ms Kate Darwin (Secretary), UKXIRA Secretariat

Steering Group objectives

1. To prepare guidance on infection surveillance issues for those intending to submit a request for permission to carry out xenotransplantation in the UK.

2. To publish the guidance and circulate them to all applicants.

3. To assist as appropriate the UKXIRA in ensuring the standards set out in the guidance Steering Group Objectives are met by those seeking authorisation for clinical trials.

4. To review guidance in the light of clinical trials.

Terms of reference

1. With reference to those areas of the UK Xenotransplantation Interim Regulatory Authority's (UKXIRA's) terms of reference that seek to maximise the safety of xenotransplantation procedures and *the acceptability of specific applications:*

   to propose the overall approach and principles, and provide guidance for monitoring and surveillance of potential infections which may be associated with xenotransplantation.

Overview of surveillance (replicated from draft report)

Definition and aim
Surveillance has been defined as the *'on-going systematic collection, analysis, and interpretation of relevant data, closely integrated with the timely dissemination of these data to those responsible for control and prevention'.* The effectiveness and efficiency of public health action is directly related to the quality, and, for many purposes the quantity, of relevant surveillance data.

An essential response to the emergence of any new infection is either an evaluation of existing surveillance data or the creation of a new system to gather data to the appropriate standard.

A key objective of surveillance is to ensure rapid recognition of incidents/outbreaks and other untoward events, to trigger and direct prompt control.

Surveillance usually requires sufficient suitable clinical data as well as data from laboratory specimens. It is important to integrate information from all relevant sources, for example from human and animal sources. There is also a need for a minimum data set for national and international public health purposes.

Thus there will need to be an explicit agreement between the regulatory authorities and those carrying out the clinical trials about access to locally held archives and records.

It is fundamental to any proposed surveillance systems that confidentiality is maintained, and all data handling must comply with data protection legislation.

Overall approach to infection surveillance
The approach adopted should:
- build on current models of public health surveillance for infection
- use existing local, regional and national health and public health structures
- learn from existing successful infectious disease surveillance activities
- set standards for effective infection surveillance

Principles underlying development of infection surveillance

This section describes the underlying principles, which should guide the development of infection surveillance systems for xenotransplantation. These principles are implicit in all the proposals about how surveillance should be developed.

One: Successful outcomes will depend on integrated approaches across all areas of health care delivery, surveillance and policy.

Two: All patients must have access to a uniformly high quality of infection diagnosis.

Three: Clear and accurate information should be readily available to patients about how they can play their role in their treatment, including issues of consent, and how they can help recognise and prevent potential infections. Equally clear information should also be available to the public.

Four: The development of infection surveillance should take account of the views of patients and professionals.

Five: Infection surveillance should be based on the best available evidence and this evidence should be shared with patients and the public.

Six: There should be explicit minimum standards to ensure effective infection surveillance and auditing to those standards.

Outline of infection surveillance post-xenotransplantation international workshop 7 July 1999, Regent's College, London

The workshop was held to launch the draft infection surveillance report prepared by UKXIRA Steering Group. The workshop addressed specifically the questions of what information (including what biological samples) should be collected and recorded, and what the international response to an adverse incident might be. It was intended that the document would promote international discussion about approaches to infection surveillance. Invitations to the workshop were extended to policy makers on xenotransplantation in other OECD countries and their public health colleagues as well as a wide range of people from within the UK.

The first session addressed the public health implications of xenotransplantation: what is known about human exposure to non-human retroviruses, and the current state of knowledge on porcine endogenous retroviruses (PERV). Dr Janet Dewdney, Chair of the UKXIRA Biosecurity Steering Group, provided an overview of the work of the biosecurity group, outlining the proposals that deal with infection risks to xenograft recipients.

Session two covered some possible solutions to the practical problems posed by infection surveillance: the main ethical considerations raised by surveillance, and the conclusions that might be drawn from the experience of counselling and following up families with a member who is HIV+/HCV+; international co-operation on surveillance: a description of international surveillance currently undertaken, using the European Network on Legionnaire's Disease as an example.

The third session considered the framework document. Delegates divided up into groups to consider questions around international co-operation, infection surveillance of patients and close contacts, and infection surveillance data. This was followed by feedback from groups and open discussion.

SECTION FIVE Biosecurity

Introduction

5.1. Minimising the risk of infectious disease transmission will be an essential factor in any clinical trials in xenotransplantation. The facilities where source animals are raised and kept are a key area in this respect. In June 1998, the UKXIRA commissioned an expert steering group to develop guidance on biosecurity for applicants seeking permission to undertake xenotransplantation trials involving humans.

5.2. A working group had also been appointed by the Home Office Animal (Scientific Procedures) Inspectorate to develop a *Code of Practice* covering welfare issues in the housing and care of xenotransplant source animals. The Steering Group fully acknowledged the importance of maintaining high standards of animal welfare and also the desire to ensure the closest possible accord between its guidance and the Code of Practice

Way of working

5.3. The membership of the Biosecurity Steering Group is listed below. An expert consultant, Dr Elspeth Scott, was appointed to draft the guidelines, as directed by the Steering Group. In all, the Group met five times between October 1998 and May 1999. Evidence from a wide variety of sources was considered, including overseas regulatory bodies and international organisations, the industry involved in the development of xenotransplantation, and groups concerned for animal welfare.

5.4. The Steering Group maintained regular contact with the Home Office working group and, on two occasions, met representatives of that group. These meetings proved to be immensely helpful.

5.5. In developing the guidelines the Steering Group took note of, and sought to ensure that its recommendations were fully consistent with, all relevant legislation, codes of practice and guidance already in place.

Biosecurity considerations

5.6. The purpose of the guidance is to set out a framework for the processes and procedures necessary to ensure good practice in relation to the supply, husbandry and care of animals and derived tissues and organs used in xenotransplantation.

5.7. The overall objectives are:

i. to define and minimise the risk of zoonotic disease in those involved in an occupational setting, recipients of a xenotransplant, and the wider population;

ii. to ensure best practice with respect to animal housing, husbandry and care.

5.8. The guidance covers requirements for ensuring that production and source animals are maintained to a high microbiological standard; source animals must be of QPF status (qualified pathogen free). Key features of the proposals are the requirements that the dams of source animals be hysterotomy derived, and that they and their offspring are maintained in full barriered conditions.

5.9. The Steering Group took the view that responsibility for determining the precise list of organisms to be eliminated from source animals should rest with the applicant. The draft guidance does not, therefore, include a list of organisms that must be excluded from all source animals but does outline the *types* of organism that should receive special attention. These include

organisms which are known zoonotic agents, organisms which are known from allotransplantation experience to cause problems in immunosuppressed patients, and those viruses associated with high mutation rates and subject to recombination fall into this category.

5.10. Conditions are defined for the housing and husbandry that should be adopted to ensure confidence risks to human health are eliminated or reduced as far as possible. The need for record keeping, data retrieval and archiving is also stressed.

Consultation

5.11. In accordance with the UKXIRA's commitment to public consultation, the Steering Group's draft Guidance was issued for formal consultation in September. Given the complementary nature of the two documents, the draft Guidance was issued in tandem with the Home Office draft *Code of Practice for the housing and care of pigs intended for use as xenotransplant source animals.*

5.12. Comments on either or both documents are invited. The closing date for receipt of comments is Friday 10 December 1999.

Steering Group membership

Dr Janet Dewdney (Chair of Steering Group),UKXIRA Member
Prof. Peter Biggs Professor of Veterinary Microbiology, The Royal Veterinary College
Prof. George Griffin UKXIRA Member
Dr Maggy Jennings UKXIRA Member
Prof. Ian McConnell Professor of Veterinary Science, Cambridge University
Dr Elspeth Scott Home Office (Scientific Procedures) Inspectorate, Consultant to the Steering Group
Martin Houghton (Secretary), UKXIRA Secretariat

Steering Group objectives

1. To prepare a set of guidance notes on biosecurity issues for those intending to submit a request for permission to carry out xenotransplantation in the UK.

2. To publish the guidance notes and to circulate them to all applicants.

3. To assist, as appropriate, the UKXIRA in ensuring that the standards set out in the guidance notes are met by those seeking authorisation for human trials.

Terms of reference

1. To specify the biosecurity conditions for each stage in the xenotransplantation procedure which minimise the risks to human health from infections and other disorders resulting from the handling of source animals or as a consequence of the transplantation process.

2. To give priority to the consequences of the use of pigs as source animals but to address issues which might arise from the use of other species.

3. To liaise with the Home Office to ensure, as far as possible, that the biosecurity requirements which minimise the risk to humans are compatible with the Home Office Code of Practice relating to the the housing, husbandry, and care of source animals for use in xenotransplantation.

4. To ensure familiarity with all appropriate and relevant legislation, codes of practice and guidance notes relating to xenotransplantation.

SECTION SIX The knowledge base

Introduction

6.1. The advice that the UKXIRA is able to offer government on xenotransplantation, including advice in its regulatory role of considering individual applications, is dependent on keeping abreast of new developments in the field. The UKXIRA has participated in several initiatives to ensure that it has access to the best available evidence. New research is also helping to inform xenotransplant regulators. The results of a collaborative study between Imutran/Novartis and the US Centers for Disease Control and Prevention were published in August 1999.

Report of the Advisory Committee on Dangerous Pathogens

6.2. At a meeting with the Advisory Committee on Dangerous Pathogens (ACDP) in November 1997, the Advisory Committee offered assistance with advice on infectious disease issues. An ACDP sub-group was formed with a remit to *"provide generic advice on the infectious disease risks associated with the different types of xenotransplantation being proposed as therapies, and to provide a report to the UKXIRA"*. The sub-group's report was received in August 1998.

6.3. The sub-group's report concluded that the present state of knowledge was insufficient to be able to differentiate between the infection risks posed by different procedures. While it was not possible to offer advice *generically*, the ACDP would be willing to offer any advice requested on proposed procedures in specific applications. The UKXIRA was grateful for this offer.

Expert briefing on liver transplantation, Monday 1 February 1999

Clinical trials involving liver support devices are known to be taking place in the United States and may be amongst the early applications to be received by the UKXIRA. In recognition of this fact, Dr Mark Hudson, consultant physician in the Gastroenterology and Liver Unit at the Freeman Hospital, Newcastle, was invited to brief the Authority on the problems faced and current treatment regimes for patients suffering from acute liver failure, and to discuss the potential of possible future treatment options – both xenogeneic and non-xenogeneic.

Systematic literature review

6.4. In March 1998, at the request of the UKXIRA, the Department of Health's Research and Development Directorate agreed to commission a systematic literature review of issues around xenotransplantation. Since then, a number of discussions have been held to determine the areas in which the review should concentrate.

6.5. It was decided that reviews should be undertaken in two broad areas. One will consider the latest scientific evidence in the fields of physiology, immunology, and infection risks (including but not exclusively new evidence on PERV). The other will provide updated evidence on ethical and legal considerations, and will encompass animal welfare considerations and also look at new techniques that may be considered as alternatives to xenotransplantation.

6.6. The first part of the review – on infection risks – is due to be commissioned shortly. Proposals for the other parts of the review are under development. It is intended that the

reviews, when completed, will be published and also made available through the UKXIRA website.

Research project on xenotransplantation

In August 1998, an application for funding for a research project relating to xenotransplantation was received by the Department of Health's Public Health Division. The application, from the Centre for Applied Microbiology and Research, sought to investigate the behaviour of porcine endogenous retrovirus (PERV) in animals other than pigs.

The UKXIRA was asked to comment on the proposal and considered that it represented a highly worthwhile project. The application was subsequently peer reviewed and a three-year project grant awarded.

Publication of Retroviruses Workshop Report

6.7. Foremost amongst the potential risks that may influence the move to clinical trials in xenotransplantation are those posed by porcine endogenous retroviruses (PERV). The UKXIRA held a workshop on 6 August 1998, attended by many international experts on the subject, to consider the existing evidence.

6.8. A report of the day's proceedings was published in May 1999. It is hoped that this review of the evidence and the recommendations for areas where further studies would be beneficial will prove useful to all those interested in developing this technology.

Links with regulatory bodies in other countries

6.9. The fact that xenotransplantation is developing on a global scale highlights the importance of international collaboration. The UKXIRA's work in developing infection surveillance proposals with the co-operation of the Organisation for Economic Co-operation and Development provides a useful model in this respect.

6.10. Effective regulation of xenotransplantation requires that, where appropriate, regulatory authorities should be able to exchange information about developments in their respective countries. With this in mind, the UKXIRA has entered into discussions with the US Food and Drug Administration about the exchange of non-public pre-decisional information relating to applications to undertake clinical trials in xenotransplantation. Such an agreement would clearly be of benefit to both bodies in performing their regulatory roles and discussions to this end are continuing.

Research study on porcine endogenous retroviruses (PERV)

6.11. To find out more about the possible effects of porcine endogenous retroviruses (PERV), Imutran/Novartis, in collaboration with the US Centers for Disease Control and Prevention, undertook a retrospective study of 160 patients from around the world who had previously been treated with living pig tissue. The study was published in the journal Science[3] on Friday 20 August 1999.

[3] *K. Paradis et al.* "Search for cross species transmission of porcine endogenous retrovirus in patients treated with living pig tissue", *Science 1236, vol 285 (1999).*

6.12. The study, *Search for cross species transmission of porcine endogenous retrovirus in patients treated with living pig tissue*, examined samples from patients who had been treated up to twelve years ago for various conditions. Pig skin grafts had been used for severe burns and pig pancreatic islet cells for the treatment of diabetes. Other patients had previously been treated by perfusing their blood outside the body through pig spleens, kidneys, liver cells or liver. The study's purpose was to determine whether PERV had been transmitted to the patients and, if so, whether there was any evidence of harm.

6.13. No evidence was found of PERV infection in the 160 patients, including 36 patients who had received immunosuppression treatment and who might therefore be considered to be at increased risk of infection. Twenty-three patients were found to have pig cells circulating in their blood (microchimerism) but no active infection was found. Four patients tested positive for the production of antibodies. The researchers concluded that the antibodies were either pre-existing in the patients or were due to cross-reactivity with an unrelated antigen.

6.14. The study provides further useful evidence on the question of infection transmission in xenotransplantation. That no signs of infection were found provides a measure of reassurance though it is recognised that negative responses cannot guarantee safety. At the time of writing, the UKXIRA has yet to consider the study in detail but intends to invite the researchers to a future meeting to discuss their findings.

Virus outbreak in the Far East

6.15. In March 1999, reports began to emerge of a viral epidemic amongst humans in Malaysia. A similar outbreak was reported in Singapore. In excess of 250 cases of febrile encephalitis were reported, including 100 deaths. The apparent source of infection was exposure to pigs.

6.16. The UKXIRA sought further information from the US Centers for Disease Control and Prevention (CDC) who, in collaboration with health officials from Malaysia and Singapore and researchers from Australia, were investigating the outbreak. Laboratory testing suggested infection with Nipah virus and the outbreak appears to have been linked to the touching and handling of pigs. The outbreak was prominent amongst workers in piggeries and abattoirs. Importantly, however, no evidence of any human to human transmission had been observed.

6.17. The circumstances surrounding this outbreak are markedly different from any that might occur as a result of undertaking a xenotransplantation procedure. Nevertheless, any illness involving the transmission of viruses from animals to humans requires careful scrutiny. The type of virus involved and the apparent means of transmission serve to underline the importance of appropriate arrangements for biosecurity in rearing xenotransplant source animals. As discussed in Section Five, the UKXIRA attaches considerable importance to this area and would expect to see comprehensive arrangements in place in considering any application.

ANNEX ONE Terms of reference

To advise the Secretaries of State of the UK Health Departments on the action necessary to regulate xenotransplantation, taking into account the principles outlined in Animal Tissues into Humans, *and worldwide developments in xenotransplantation. In particular to advise:*

a. *on safety, efficacy and considerations of animal welfare and any other pre-conditions for xenotransplantation for human use, and whether these have been met;*

b. *on research required to assess safety and efficacy factors in xenotransplantation procedures;*

c. *on the acceptability of specific applications to proceed with xenotransplantation in humans; and*

d. *to provide a focal point on xenotransplantation issues within government.*

ANNEX TWO Membership

CHAIRMAN

Lord HABGOOD of Calverton

MEMBERS

Dr David COOK
Green College, Oxford

Mr John DARK
Consultant Cardiothoracic Surgeon, Director (Cardio-Pulm. Transplants), Freeman Hospital, Newcastle

Dr Janet M. DEWDNEY
Deputy Chairman and Non-Executive Director of AdProTech plc.

Mrs Jean GAFFIN
Trustee of St Luke's Hospice, Brent and Harrow
Non-executive Director, Harrow and Hillingdon Healthcare NHS Trust

Prof. George GRIFFIN
Professor of Infectious Disease, St George's Hospital

Dr Maggy JENNINGS
Head of Research, Animals Department, RSPCA

Prof. Sheila McLEAN
Professor, Law and Ethics in Medicine, Glasgow University

Prof. Herb SEWELL
Professor of Immunology, Nottingham University

Remuneration

Fees are paid in accordance with the standard rate for attendance at non-departmental public body health committees, set at £131 per meeting for Members (£135 from 1 April 1999) and £161 per meeting for the Chairman (£168 from 1 April 1999).

ANNEX THREE Declaration of interests

Members are asked to make a statement of any direct or indirect pecuniary interest they consider members of the public might reasonably think could influence the judgements they have to make as part of the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) activities.

The declarations form a register of Members' interests, maintained by the UKXIRA Secretariat. Declarations are updated on an annual basis, but Members inform the Secretariat of any changes as they occur.

Lord HABGOOD of Calverton
None

Dr David COOK
None

Mr John DARK
Clinical research supported by Roche
Costs of attending various scientific meetings met in part by Novartis and Roche
Honorarium for editing meeting review on behalf of Roche

Dr Janet M. DEWDNEY
Deputy Chairman and Non-Executive Director of biotechnology company, AdProTech plc, which has research interest in transplantation

Mrs Jean GAFFIN
Non-Executive Director, Harrow and Hillingdon Healthcare NHS Trust
Expenses as member of Appraisals Committee, National Institute for Clinical Excellence

Prof. George GRIFFIN
Consultancy fee from Pharmacia and Upjohn paid to St George's Hospital Medical School
Consultancy fee from Microscience paid to St George's Hospital Medical School

Dr Maggy JENNINGS
Full-time employment with the Royal Society for the Prevention of Cruelty to Animals (RSPCA)

Prof. Sheila McLEAN
None

Prof. Herb SEWELL
None

ANNEX FOUR Proforma for use by applicants to the UKXIRA

PROFORMA FOR COMPLETION BY APPLICANTS SEEKING TO UNDERTAKE XENOTRANSPLANTATION PROCEDURES IN THE U.K.

All applications to the UKXIRA should include detailed information on relevant systems and documentation under the following headings: **"SUMMARY DETAILS", "PRETRIAL DATA", "TRIAL PROTOCOL", "BIOSECURITY"** and **"INFECTION SURVEILLANCE".**

Applicants should indicate the page number(s) of the relevant documentation against each section.

SUMMARY DETAILS

Project title, summary of proposal, applicant's name, sponsor's name, site(s) of clinical trial, proposed number of patients, submission date to UKXIRA, first/second application. A summary flowchart is a useful aid to illustrate the main activities, sites and the responsible parties for sourcing, transplant removal, manufacturing and patient implantation. A statement is required on the National and European regulatory status of the finished product or tissue/organ and the Quality Assurance programme.

Doc Refs

PRETRIAL DATA

Physiological, immunological and pharmacological data on the cell/organ transplant must be available and professionally evaluated before it enters a clinical trial. All existing research data should be collated, reviewed and considered in detail. In particular this should address the current state of knowledge on the potential for infection of porcine endogenous retroviruses (PERV) with a detailed risk analysis for the patient and the community as a whole. The pretrial data should contain comprehensive information that is relevant to the application.

Doc Refs

TRIAL PROTOCOL (1)

General information – project title, clinical investigators, other participants or contributors (animal breeders, surgical team, nurses, statisticians, etc), with details of training, experience and qualifications, the sponsor's name/address, the clinic/department for the trial, objectives and justification for the trial (including an assessment of the likely benefit to the patient and possible benefits to other patients in the future), the knowledge and issues of the technology and a summary of the systematic review of the published literature.

Doc Refs

General design – specification of the trial type, description of the randomisation method, the trial design and specification of other bias-reducing factors. The start and end date for the trial, justification for the timescale, the expected duration of the treatment. Rationale for patient selection (including age, sex, ethnicity, groups, prognostic factors), statement of diagnostic admission criteria, criteria for inclusion, pre-admission exclusions, and post-admission withdrawals of patients from the trial. Product labelling shall include the words "For Clinical Trial Only", the name of the clinician responsible and the trial site.

Doc Refs

Treatment – Descriptive text (with illustrative diagrams) of the product treatment to be used (with justification of the cell quantity in the case of cell transplantation), treatment(s) applied to other group(s) or control period(s), procedure of application, site of application, treatment period for the transplantation and its current comparative treatment, rules for the use of concomitant treatment, measures for safe handling of the transplant, measures to control and promote adherence to prescribed instructions (compliance).

Doc Refs

Legal\Ethics – Legal and ethical considerations of the trial. Comprehensive details and procedures on information to patients (including relatives, contacts, friends), system for obtaining consent and information on compensation.

Doc Refs

Assessment – specification of the parameters to monitor the effects, description of measurement and recording of these effects, times and periods of recording, description and purpose of special analyses or tests to be carried out (e.g. laboratory, clinical, radiological).

Doc Refs

Adverse events – methods and systems of recording adverse events, provisions for dealing with complications, information on where the information code will be kept and its access in cases of emergency, details for reporting adverse events, by whom and to whom, and how fast the reports will be submitted.

Doc Refs

Handling of records – procedures for handling and processing records of effects/adverse events under study, procedures for keeping special patient lists and records for each individual in the trial. Methods to permit easy identification and the retention of report forms.

Doc Refs

Evaluation – a specified account of how the response should be evaluated. Methods of computation and calculation of effects, how to report on subjects withdrawn from the trial, quality control of methods and evaluation procedures. Description of statistical methods, number planned, reason for choice of sample size, including reflections on the power of the trial and clinical justification, the rules for the termination of the trial.

Doc Refs

Finance/Insurance – All financial aspects in conducting and reporting the trial, as well as the long-term surveillance and monitoring, shall be arranged and clearly specified. Patients/volunteers taking part in the trial should be satisfactorily insured against any injury caused by the trial. The liability of all the involved parties (i.e. investigator, sponsor, manufacturer, hospital, clinician) must be clearly defined and understood before the start of the trial.

Doc Refs

BIOSECURITY (2)

Production animal – Species, location, lineage, facilities, welfare, feeding practices, identification of natural pathogens, health monitoring, vaccination programme, rationale and justification for microbiological monitoring programme. Staff training and competence. Maintenance and care of the animals. Husbandry facilities, procedures, specification, transport barriers to isolation facilities.

Doc Refs

Source animal – Location, lineage data, specification requirements of pig from herd to isolation, prerequisite screening requirements, age, functional organ test programme, isolation QPF facilities – structure, welfare, feeding practices, health records, vaccination programme, rationale and justification for microbiological monitoring programme, access, protective clothing, and contact by personnel. Staff training and competence.

Doc Refs

Harvest of material – Site/location of, details of surgical procedure, prerequisite tests and conditions, preservation and/or storage media, protection measures to maintain condition and viability, transport arrangements to site for human implantation or the processing of specialised cells for other manufacturing operations. Procedures for post mortem examination, animal identification, storage of tissues and disposal of the carcass.

Doc Refs

INFECTION SURVEILLANCE (2)

Procedures and practices for the ongoing systematic collection, analysis and interpretation of outcome specific data, and its integration for the timely dissemination to those responsible for control and prevention. Current and projected impact of disease, identifying methods of control, data requirements for control and prevention, data sources and methods of capture. Roles and responsibilities of key personnel. Routine screening and testing programmes for patients, source animals and archived samples. Systems for data analyses and information dissemination, with practices for confidentiality and access. The investigation and response to a reported incident.

Doc Refs

Notes

(1) Information on the trial protocol has been developed from the EEC Note for Guidance for Good Clinical Practice for Trials on Medicinal Products in the European Community, *January 1991, CPMP Working Party.*

(2) Applicants are advised to consult the two reports by the UKXIRA Steering Group

a) Draft Report* of the Infection Surveillance Steering Group of UKXIRA.

b) Guidance Notes* on Biosecurity Considerations in Relation to Xenotransplantation.

(* in consultation)

ANNEX FIVE Meeting dates

Meetings covered by this report:

7 December 1998

1 February 1999

13 April 1999

10 June 1999

Dates for future meetings:

5 October 1999

6 December 1999

Dates for meetings in 2000 will be posted on the UKXIRA Website.

ANNEX SIX Publications and references

Copies of the following can be obtained from:

Department of Health, PO Box 777,
London SE1 6XH
Fax: 01623 724 524
E Mail: doh@prologistics.co.uk

or from the UKXIRA Website:
www.doh.gov.uk/ukxira.htm

Guidance on making proposals to conduct xenotransplantation on human subjects
UKXIRA 1998

Report of the workshop on porcine endogenous retroviruses, 6 August 1998
UKXIRA 1998

First Annual Report, May 1997–August 1998
UKXIRA 1998

Copies of the following can be obtained from:

UKXIRA Secretariat
Department of Health
Room 311
Wellington House
133 – 155 Waterloo Road
London SE1 8UG

or from the UKXIRA Website:
www.doh.gov.uk/ukxira.htm

Draft Report of the Infection Surveillance Steering Group
UKXIRA 1999

Draft Guidance Notes on Biosecurity Considerations in Relation to Xenotransplantation
UKXIRA 1999

ANNEX SEVEN Contact points

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