An integrated project in the European Sixth Framework Programme

XENOME WP5

DRAFT

DEBATE PAPER ON XENOTRANSPLANTATION

1. INTRODUCTION

1.1. Short introduction about the XENOME project

The acronym XENOME stands for a project entitled: "Engineering of the porcine genome for xenotransplantation studies in primates: a step towards clinical application" –Xenome (FP6 LSHB-CT-2007-037377) - and the Project web site is this one: www.xenome.eu

Xenome is an integrated Project in the European Sixth Framework Programme (Life Sciences, Genomics and Biotechnology for Health). Xenome is also a multidisciplinary effort through which the EU will be present in this scientific field for five years.

Recent scientific developments indicate that transplantation of organs, tissues or cells between species may at some stage become a realistic option, ultimately resulting in an increased supply of organs to meet medical demand. However, in order to allow the clinical application of xenotransplantation, several immunological, biosafety, physiological, regulatory, social and ethical issues still need to be adequately addressed.

The ultimate goal of this Project is to generate the necessary data that might allow the transition of xenotransplantation from a pre-clinical phase to its initial clinical phase. The data that will be generated during the five year duration of this Project will encompass not only efficacy and safety aspects of xenotransplantation but also a strong ethical, social, educational and regulatory framework within which xenotransplantation research (and possibly clinical application) should take place.

To these ends, this multidisciplinary effort involves more than twenty academic/private institutions across eleven European countries. The key areas of research include immunology, safety, genetic engineering, physiology, ethics, social and regulatory aspects of xenotransplantation.

It is believed that this carefully designed Integrated Project presents all the potential to translate the proposed research into future gains for human health.

Xenome aims to consult widely with the general public and all stakeholders on the issue of xenotransplantation. Therefore it invites submissions on this paper. Respondents are asked to structure their comments around the questions included in Appendix A.

1.2. The aim of this document

1.2.1. The principal goal

This public debate paper has been prepared in order to prepare draft guidelines for the regulation of xenotransplantation clinical trials in Europe. This document has been written to facilitate public consultation on xenotransplantation research and related practices. In other words, it has been prepared to facilitate community input into the issues that need to be addressed to produce guidelines for human research ethics committees (HREC) and animal ethics committees (AEC) on the assessment of xenotransplantation research proposals.

While acknowledging that the ethical and safety issues associated with xenotransplantation require careful consideration, it has been decided to proceed with research under agreed guidelines. The most prudent thing to do in this regard is to proceed under guidelines that take account of ethical issues, protect the interests of research participants, ensure the animal welfare concerns are met and safeguard public safety. Draft guidelines will be presented for public comment with this document outlining the issues considered by Xenome in developing those draft guidelines.

In this regard, it will be considered as a main term of reference to produce guidelines covering scientific, ethical and technical aspects of xenotransplantation research involving humans, including consideration of: animal issues and accepted practices and undertake wide consideration in the preparation of guidelines.

1.2.2. The specific purposes

As has been mentioned above, it is important by this means to reflect the community input from consultations or submissions. Therefore, this document aims to: inform the community about the present state of xenotransplantation research and clinical application; stimulate debate and public contributions about xenotransplantation research, including the ethical concerns, potential benefits and risks associated with this research; and provide a framework for guidelines on the assessment of xenotransplantation research proposals.

The issues related to humans and animals involved in xenotransplantation research are considered. The focus is on research rather than established clinical practice because the latter is still likely to be a long way in the next or distant future. The document is also focussed on aspects of xenotransplantation research that are directly related to the provision of xenotransplantation as a therapy to replace, for instance, diseased cells, tissues or organs in humans.

In summary, the aim of this document is to facilitate a public discussion on xenotransplantation research, including the ethical and safety issues associated with it. Therefore it is desirable that this document should be widely circulated and discussed. It is important for Xenome to hold an extensive public consultation process including public meetings, media publicity and opportunities for professional and community groups to present submissions to the Xenome.

1.3. The structure of this discussion paper

To introduce the subject of xenotransplantation to the general community, Chapter I explains what xenotransplantation is, what are the main reasons for reviving the research in this field, the main aspects which defines the preclinical studies and the clinical trials, some of the questions involved in the efficacy of these procedures, the main promise and the main obstacles of xenotransplantation and, finally, the importance of ethical criteria to assess the issues involved in this field. In Chapter II are included some of the main ethical issues of xenotransplantation. In Appendix A are described some key issues to be discussed; that is, to help determine where community support and concern lie in relation to the complex and important areas which form the basis of this document, respondents to those questions are invited to write submissions to each of those issues which are summarized in that Appendix A.

The discussion paper is intended to inform the community about the issues relating to xenotransplantation, including, for instance, the following groups:

- Health professionals (particularly those involved in transplantation);
- Transplantation researchers (experimental, preclinical and clinical);

- members of human and animal ethics committees;
- biotechnology companies/sponsors of transplantation research;
- Health agencies
- State and Territory health departments; and
- Consumer organizations, animal welfare groups and the general public.

Readers are asked to review the information contained in the discussion paper, with particular emphasis on the questions summarized in Appendix A. Readers are then asked to prepare a submission to the Xenome project members that presents their response to the issues raised.

The Xenome project members are seeking comment so as to prepare the corresponding draft guidelines and the proposed regulatory controls in this field. However, responses to all questions and issues raised in the discussion paper and others suggested by the readers are welcome and will inform the Xenome in the preparation of its final recommendations in this regard.

Guidance for preparing submissions is included as an attachment at the end of this document.

2. CHAPTER I: DEFINITIONS, PROMISES AND PROBLEMS

2.1. What is xenotransplantation?

By definition, xenotransplantation is the transplantation of body tissue between "foreign" or different species. Much of the biomedical research that takes place in this area is conducted by transplanting tissue and organs between different non-human animal species. But the primary objective of such research is to transplant animal organs and tissue into humans for therapeutic benefit. The Council of Europe highlights that it is also widely agreed that xenotransplantation does not include the use of non-living parts such as heart valves or vaccines that are made from animal sources[1]. This agreement over the general features of xenotransplantation is disrupted somewhat by debates over precisely which biomedical techniques should be included within this broad definition for reasons of public policy.

Xenotransplantation has been also defined as a term used for the transplantation of cells, tissues or organs from one species to another (such as from pigs to humans), as distinct from allotransplantation, in which cells, tissues or organs are transplanted between members of the same species. Although allotransplantation can be very successful way of treating a variety of human illness, very few human donor organs are available for transplantation compared to the demand. Many patients who would benefit from a transplant wait in vain for donor organs to become available. Transplant specialists have therefore focussed their attention on animals as a possible source of organs and tissues for human transplantation. Xenotransplantation was initially thought to be very unlikely to succeed, but recent advances in molecular biology and immunology have made it appear more feasible. Many transplant research groups are now trying to understand and overcome the physiological and immunological problems involved.

Organ and tissue transplants can be distinguished according to the source of the transplanted material as follows:

[1] Council of Europe (2003), Report on the State of the Art in the Field of Xenotransplantation, Council of Europe: Strasbourg, p. 16.

- **Autotransplantation** –transplantation (relocation) from and to the same individual[2].
- **Allotransplantation** –transplantation between individuals of the same species (normally between human beings matched by tissue typing); and
- **Xenotransplantation** –transplantation between individuals of different species (eg from a pig to a human being)

Xenotransplantation is **defined** -according to *Recommendation Rec* (2003)10 *of the Committee of Ministers to Member States on xenotransplantation of 19 June 2003*-, as any procedure that involves the transplantation or infusion into a human recipient of:

- Live animals cells, tissues, or
- Human body fluids, cells, tissues or organs that have had *ex vivo* contact with live animal cells, tissues or organs (article 3).

Broadly understood, the term 'human xenotransplantation' refers to any procedure that involves the transplantation, implantation or infusion into a human recipient of cells, tissues or organs from a nonhuman animal source[3]. The forms of transplant are subdivided as follows:

• *In vivo transplantation*:

– Organ transplants (eg heart, kidney, liver);

– Tissue transplants (eg skin);

– Cellular transplants

- Without a semipermeable capsule (eg fetal pig neural cells transplanted into the human brain for treatment of Parkinson's disease); and
- enclosed in a semi-permeable capsule (eg encapsulated islets of Langerhans cells transplanted into the peritoneal cavity to treat diabetes)[4].

• *Ex vivo procedures*:

- perfusion of human body fluid through animal tissues or cells, which may or may not be separated by a semipermeable membrane (eg perfusion of human blood through a dialysis-like system containing animal liver cells, or perfusion of human blood through a whole pig liver); and

– growth of human cells on a feeder layer of animal cells for transplanting back to the same individual (eg growth of human skin or human stem cells on a mouse cell feeder layer).

This terminology will be used throughout the discussion paper because different considerations apply to the different types of procedures[5].

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[2] For instance, it is possible the relocation of skin from the thigh to the arm so as to repair burn damage.

[3] In addition, the United States Food and Drug Administration (US FDA 2001) has distinguished two forms of xenotransplantation: • any procedure that involves the transplantation, implantation or infusion into a human recipient of live cells, tissues or organs from a nonhuman animal source (called an '**in vivo transplant**'); and • any procedure that involves the transplantation, implantation or infusion into a human recipient of human body fluids, cells, tissues or organs that have had contact outside the body with live nonhuman animal cells, tissues or organs (called an '**ex vivo procedure'**).

[4] A semi-permeable capsule allows active molecules to pass through to the host while isolating the transplanted cells from the host blood circulation, thus reducing the risk of rejection and infection.

[5] The term *xenotransplantation* has been also defined in this manner: It refers to the transplantation, implantation, or infusion into a human recipient of live cells, tissues, or organs derived from non-human animals. The procedure includes the use of human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live, non-human animal cells, tissues, or organs. The source animals or their cells may or may not be genetically modified. The different types of xenotransplantation procedures being performed or considered include the following: **Solid-organ xenotransplantation** is a procedure in which a source animal organ such as a heart, lung, kidney, or liver is transplanted into a human. In such cases, the vascular supplies of the source animal and the recipient are connected; **Cellular and tissue**

In summary, based on the definition used by the United States Food ND Drug Administration (US, FDA 2001, 2003), two forms of procedures can be distinguished:

- "*in vivo transplants*" involving transplantation, implantation or infusion into a human recipient of live cells, tissues or organs from a nonhuman animal source; and
- "ex vivo procedures" involving the transplantation, implantation or infusion into a human recipient of human body fluids, cells, tissues or organs that have had contact outside the body with live nonhuman animal cells, tissues or organs.

It has been also developed new terminology by the Xenotransplantation Working Party established by the National Health and Medical Research Council (NHMRC), which distinguish three different types of animal-to-human transplantation procedures:

- **Animal external therapies (AETs**), a range of procedures involving contact between human and animal cells/tissues outside of the body of the patient, such as: a) cells or fluids from the patient are perfused through animal cells and returned to the patient; or b) human cells or tissues pieces are cultured with animal cells in the laboratory in order to obtain a larger supply of human cells or tissue for transplantation. Examples: passage of blood from a patient with liver failure through an external device (Hepatassist machine) containing pig liver cells (similar to a kidney dialysis machine); Growth of human skin grafts for wound healing (eg for burns) on a feeder layer of animal cells.

This procedure covers a wide a wide range of procedures and hence there are also a range of reasons behind their development apart from a shortage of human organ donors. For example, growth of human skin on an external feeder layer of animal cells has been seen as a method to quickly provide a source of skin (eg for a burns victim) and the use of an animal cell feeder layer in this case is due to the ready availability of existing animal cell culture lines. Furthermore, the animal cell lines that can be used as feeder layers have been grown in laboratories for many years, have well-understood growth characteristics and properties, and their continued use does not require the death of any further animals.

External liver perfusion techniques have been developed to assist people with liver failure, either until a suitable human liver donor is found, or until the liver failure is resolved spontaneously. An unlimited supply of human liver donations would reduce the number of people requiring a bridging procedure, while a readily available source of human cells (eg from fragments of liver obtained during liver surgery or by growth of human liver cell lines) may meet the need for short-term perfusion. However, these options are currently either unreliable, not feasible, or at the experimental stage so that researchers have turned to animal liver cells as the only readily available source of viable functioning liver cells for such use.

As with ACTs, alternative approaches to the use of animal products in external therapies, may be developed in future thus reducing the rationale for continued work with

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xenotransplantation is the grafting of tissues and cells from a source animal without surgical connection of any animal blood vessels to the recipient's vessels. These xenotransplantation products may be implanted directly into a recipient's organ; **Extracorporeal (natural and artificial organ) perfusion** occurs when human blood is circulated outside of the human body through an animal organ, such as a liver or kidney, or through a bioartificial organ produced by culturing animal cells on an artificial matrix; **Exposure to living animal-derived material** occurs when any of a variety of human cell types are grown ex vivo with non-human animal cells. If these human cells are subsequently transplanted or infused into a human patient, the procedure is considered a form of xenotransplantation. U.S. Department of Health and Human services. Secretary's Advisory Committee on xenotransplantation. *Draft Report on the state of the science in xenotransplantation.* September 2004.

animal products. Ongoing monitoring of such developments will therefore be needed to ensure that procedures with the most potential benefit and fewest ethical and safety concerns are developed.

- **Animal cell therapies (ACTs)**, procedures in which animal cells are transplanted or implanted into a human patient to compensate for deficient functioning of the patient's own cells. Transplanted cells can either be enclosed in a semipermeable capsule (encapsuled) or have no such capsule. Example: animal pancreatic cells to produce insulin for people with diabetes; Animal brain cells to produce dopamine for people with Parkinson's disease.

The development of ACTs has been in response to increasing knowledge about, and technical ability to manipulate, individual cell types. This has opened possibilities for biological therapies for diseases and conditions involving lack or imbalance of biological molecules. Researchers have come to hope that transplantation of suitably stimulated cells that are able to produce the required molecules and correct the deficiency may become a method to treat a range of conditions, providing longer-term and safer 'cures' than lifelong drug therapies.

Undoubtedly, if there was an unlimited supply of suitable donated human tissues that could be used to obtain the cells required for cellular therapies, there may have been less reason to consider animal cells as the source of such therapies. However, a supply of different human cell types based on cadaveric donation would never provide a sustainable option for either research or, in the future, for therapeutic use. Hence, researchers have turned to animals as a more readily available and sustainable source of cellular materials for the development of these therapies.

It has been also pointed out that, in recent years, stem cell research has provided the promise of an alternative source of human cellular materials that may ultimately replace the need to use animal cells. However, despite the enthusiasm about stem cell research, the growth of different cell types from either adult stem cells or embryonic stem cells is, at present, no more than an experimental possibility. It will require many years of careful and particular research to further develop the necessary methods for specific cell growth and biological stimulation. It is not yet known whether the technology will ever prove as successful as is hoped.

On the other hand, animal cells of the required types can be readily obtained, and preclinical (animal-to-animal) research has indicated that, with some further refinements, cellular therapies may prove efficacious for some otherwise incurable diseases, such as,

Parkinson's disease. However, if alternative approaches to cell therapy, such as human stem cells, prove more effective in future, the rationale for continued work with animal cells may decrease. Therefore, there needs to be ongoing monitoring of developments across the spectrum of biotechnology and biological therapy so that the procedures with the most potential benefit and fewest ethical and safety concerns are developed

- **Animal organ transplants (AOTs)**, procedures in which whole organs or tissues from an animal are transplanted or implanted into a human patient to replace a diseased or damaged organ or tissue. Example: heart, kidney, liver, skin, adrenal glands, etc.

The current interest in research on AOTs is in direct response to a worldwide shortage of human organ donors and the increasing number of people waiting for organ transplants.

2.2. Why reflect on xenotransplantation?

Recent scientific advances in genetic technology, immunology and other molecular and cellular techniques have made xenotransplantation much more feasible. In addition, an increasing range of conditions is now being considered for possible treatment using organs, tissues and cells, employing *ex vivo* as well as *in vivo* methods. Therefore, xenotransplantation research is attracting increasing attention and funding throughout the developed world. It is therefore vital to consider the ethical, social and scientific implications of these new technologies before the demand for clinical trials becomes widespread. In this way, decision makers will have access to suitable guidelines and society will be prepared for further developments as they occur.

Because of the shortage of human organs and tissues for transplantation and the lack of another suitable alternative (at least in the short term)[6], the use of animal organs and issues as transplantation products for humans has emerged as a potentially viable option.

As we continue to better understand and manage the body's immune response to transplanted tissues, many scientists believe that successful xenotransplantation may be possible and that further research on this technology could lead to an increased supply of organs for transplantation.

However, it is necessary for stakeholders and the community to become aware and to discuss about the issues involved and for government to develop a regulatory process.

Before proceeding to study the main issues involved in xenotransplantation research, it is important to describe briefly the ***parallel or alternative strategies to xenotransplantation***. As been said, in addition to xenotransplantation, a number of other approaches are under development for the treatment of conditions involving cellular, tissue, and organ destruction:

[6] With regard to the alternative sources of organs and tissues, various options have been suggested to overcome the shortage of human organs, tissues and cells available for transplantation. The options are, for instance, the following ones: It has been argued that public policy should be changed to one in which consent to being an organ donor is presumed unless the deceased person has earlier made clear that he or she does not want to donate. This system is used in some countries (such as Spain and Norway) and the number or organs available for transplantation has increased significantly in those countries. On the other hand, policies and procedures in hospitals could be changed to overcome the obstacles preventing recovery of organs and tissues from a person whose death has been determined by the brain function criterion and who registered consent before death. Another way of solving the organ shortage problem is for living donors, for example relatives, to donate an organ or part of an organ. For instance, the donation of kidneys in this manner has become accepted practice. To date, there have been more than 1000 living donor transplants worldwide. Another proposal is to use mechanical or artificial organs. However, the production of safe and effective mechanical alternatives that can be used over a long term is probably some decades away. Currently, some mechanical devices are used as a short-term "bridging" procedure for people waiting for an organ to become available. Another way of solving this problem is related to the culture of human stem cells. This option has raised hopes for future treatments to repair human organs and to treat a range of diseases. Stem cells can, under certain conditions, be induced to mature into specialised cell types (eg heart, muscle, liver), which, it is hoped, will provide a source of human transplantation products (for both autotransplantation and allotransplantation). Although the field of "tissue engineering" using stem cells is developing rapidly, there are still many hurdles that must be overcome before it will be possible to grow complex organs "in a test tube". In addition, the extraction of stem cells from human embryos is ethically controversial. On the other hand, stem cell technology cannot be regarded as an "alternative" to xenotransplantation because current stem cell lines are grown on animal feeder layers and therefore come within the definition of xenotransplantation as ex vivo procedures.

• **Prevention** of the acute and chronic conditions that lead to the need for replacement organs, cells, and tissue is the ideal approach, and prevention activities need to be promoted by all available means.
• **Gene therapy**, a relatively new and highly experimental technology for treating human disease, has recently enjoyed some limited clinical success. In organ transplantation, gene therapy approaches could one day be useful in preventing transplant rejection, inducing tolerance, prolonging graft survival, and ameliorating some of the problems associated with systemic immunosuppression.
• **Stem cell therapy** offers the possibility of treatment for a variety of diseases and disorders involving tissue destruction or cellular injury and dysfunction. It offers hope for treating a multitude of clinical diseases and has both advantages and disadvantages when compared with xenotransplantation. Stem cells may have considerable potential for cellular replacement and repair, but their potential for whole-organ replacement is currently unknown.
• **Artificial organs** include left ventricular assist devices, which can improve cardiac function in patients with isolated left-sided heart failure, and an artificial heart (Abiocor) has been developed and evaluated in a small group of patients. Such devices, however, currently face several obstacles, and the potential for the success of these technologies in terms of improving quality of life and longevity are currently unknown[7].

2.3. Some aspects involved in xenotransplantation research

As xenotransplantation is still an unproven technique, the challenge at this stage is for further research to find out if it can work and, if so, whether it is safe for use in humans. There are also broader ethical questions that need to be resolved, including whether one accepts, in principle, the *use of animals* in this way.

Researchers are investigating about the human immunological response to xenotransplants to design methods that might suppress this response sufficiently to allow animal organs or tissues to be accepted by humans and to function normally. This may involve some *genetic manipulation of the source animals* to suppress the immunological factors that would otherwise cause rejection. This is, indeed, one of the most promising strategies in order to address the aforementioned challenges. The research is still at a very early stage of development and a great deal still needs to be done before xenotransplantation can be considered as a routine therapeutic option.

Like all promising advances in medicine, xenotransplantation needs to undergo thorough preclinical studies and clinical trials to determine whether it works and whether it is a safe procedure for use in humans. Throughout this draft discussion paper we refer to **preclinical studies** as '**animal-to-animal studies'** and **clinical trials** as '**animal-to- human trials'**.

2.3.1. Animal-to-animal studies (preclinical studies)

In this document the term '*animal-to-animal study'* is used to describe *preclinical animal research* involving transplantation of cells, tissues or organs from one animal to another in order to determine the efficacy and safety of a proposed procedure in an animal model before proceeding to animal-to-human trials.

At the same time and for new drug research, extensive studies are done to test the pharmacology and toxicology of the substance, including acute, short-term and long-term effects. These studies use mainly small animals (mice, rats, etc.) and some

[7] U.S. Department of Health and Human services. Secretary's Advisory Committee on xenotransplantation. *Draft Report on the state of the science in xenotransplantation*. September 2004, pp. 29-32. In these pages these alternative strategies are described in detail.

larger animals, including nonhuman primates. The studies use strict *protocols* that ensure the most useful results are obtained with due regard to *animal welfare*.

Similarly, for xenotransplantation, a range of research is needed using both small and large animal models. The goal is to obtain good information about what can be expected to happen in a human situation (eg by using nonhuman primates as organ recipients)[8].

2.3.2. Animal-to-human trials (clinical trials)

In this draft discussion paper the term 'animal-to-human trial' is used to describe clinical research involving transplantation of cells, tissues or organs from an animal to a human for the therapeutic benefit of the human to replace diseased tissues (ie therapeutic clinical research). The trials involve cellular transplantation or ex vivo procedures[9].

It is important to distinguish therapeutic and non-therapeutic clinical research, as follows:

• *Therapeutic research* is research conducted with the intent of providing direct benefit to the participants; and

• *Non-therapeutic research* is research conducted in order to obtain knowledge rather than to be of any direct benefit to the participants.

Because of the potential risks involved, only *therapeutic research* is considered to be acceptable for animal-to-human xenotransplantation trials. When the animal-to-animal studies show that a xenotransplantation procedure is successful and safe when used in animal recipients, animal-to-human trials will be designed to test its use in humans.

The process of testing new therapeutic procedures through clinical trials may take many years and involve several phases. For new drugs, the first trials (phase I clinical trials) are to determine safety, pharmacological activity and dosage. For treatments with significant side effects, these trials are necessarily small and exploratory, usually involving only a few participants for whom there are no other therapeutic options and who, after being given all the necessary information, agree to take part in the trial. For other treatments, for which side effects are not an issue, phase 1 trials may be more extensive and include volunteer subjects.

If the phase I trials are successful, the next stage is to set up larger (phase II) trials, involving more subjects, to study efficacy and safety. These are followed by phase III trials, which are much larger still and are usually conducted as randomised placebo controlled trials in several clinical centres to determine clinical health benefit and the incidence of adverse reactions.

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[8] While use of primates as donors for xenotransplantation into humans is regarded as unacceptable, primates may be used as recipients in animal-to animal research.

[9] Researchers are currently investigating whether isolated cells can be transplanted to treat certain metabolic, degenerative and genetic diseases, such as diabetes, Parkinson's disease and Huntington's disease. Cellular transplants do not have all the rejection problems of vascularised organs; for example, "hyperacute" rejection (HAR) can be prevented by avoiding direct contact with the circulation. In rodents, diabetes has been successfully treated by transplanting pancreatic islet cells but this has not yet been successful in primates, large animal models or human clinical trials. A few patients have been treated with pig brain cells to treat Parkinson's disease, with mixed results. With regard to the external (ex vivo) procedures, ex vivo liver perfusion has been developed to 'buy time' while potential transplant patients wait for a suitable donor. Initially, whole animals or whole organs were perfused (e.g. pigs and baboons) but bioreactors containing isolated liver cells are now being developed. Other ex vivo methods, such as human skin culture supported on animal tissue for later grafting for burns, are also being developed.

In the case of xenotransplantation, these conventional phases for clinical trials do not apply in the same way. Phase I trials in this case are likely to involve a very few participants for whom a definite therapeutic benefit should be expected. Such trials are not likely to provide a definitive answer with respect to infectious disease safety. If phase I trials are therapeutically successful, however, phase II trials will involve wider use of the protocol technology and phase III trials may include randomised comparisons with other procedures and a more detailed assessment of infectious disease safety. Clinical trials must follow strict protocols for study design and be approved by the appropriate research ethics committees in the institutions involved.

In summary, one of the ultimate aims of this draft discussion paper is, as has been mentioned, to develop **guidelines** to assist animal and human ethics committees to assess proposals for xenotransplantation research, particularly clinical trials. The focus of the proposed guidelines will be research that is directly related to the provision of xenotransplantation as a human therapy. This includes *animal-to-animal studies* (preclinical studies) in which proposed xenotransplantation procedures are tested on animals; and *animal-to-human trials* (clinical trials) in which animal products are used for xenotransplantation procedures on human beings. A distinction is traditionally made between *therapeutic clinical trials* (conducted with the intent of providing a direct benefit to the trial participants) and *nontherapeutic trials* (conducted in order to obtain knowledge rather than to be of any direct benefit to the participants)[10]. Only therapeutic clinical trials are considered in this draft discussion paper, because nontherapeutic trials of xenotransplantation are neither ethical nor safe.

2.3.3. Assessment of efficacy

As for other clinical trials, researchers and sponsors for animal-to-human xenotransplantation trials will be required to provide data on *efficacy* as part of a comprehensive submission for assessment by the relevant regulatory authority and the human research ethics committee at the institution(s) where the research will be carried out.

In most circumstances the initial evidence for efficacy will be based on relevant animal-to-animal studies, with pigs as the source animals and nonhuman primates as the recipients. Related experimental and animal-to-animal studies, as well as any previous animal-to-human trials, may also provide helpful information. The decision about what defines a *successful animal-to-animal study* will vary according to the *type* of, and *indication* for, *transplantation* (for example, whether it is intended as a *permanent* or '*bridging*' procedure).

However, in general terms, the transplant should have the capacity to provide physiologically relevant and/or life-sustaining support.

In summary, it is an important issue for the assessment of proposals for clinical trials of any new therapeutic procedure, whether it is a new drug, device or other technology, is the potential benefit of the therapy for the patient undergoing the trial (eg the efficacy of the procedure). For therapeutic trials of new drugs, there is generally a large body of preclinical (animal) and pharmacological evidence to support the likely success of the treatment in humans. Trial participants are assured that, provided the trial protocol follows strict guidelines in terms of the entry criteria for participants, the treatment is likely to do more good than harm.

[10] This document focuses mainly on providing a framework for guidelines that will assist ethics committees to assess research proposals, rather than on routine clinical practice. This is because, considering the obstacles that remain to be overcome through animal-to-animal studies and animal-to-humans trials, routine clinical practice is not likely to occur in the foreseeable future.

In order to reflect on all these questions, we must take into account that definitions of success in transplantation research are not fixed milestones that can be simply set. Rather, they depend on the starting point, the history to that point, the alternatives both for the individual patient and for the particular society, and, as has been said, the type of xenotransplant under consideration (eg cells, organs). Most of the information, particularly about vascularised organ xenotransplants, must be derived from animal-to-animal studies, and, as has been also mentioned, there are many difficulties with these.

Unlike animal studies for a new drug, where the information obtained from the animals is usually gained from observation, sampling of body fluids and post-mortem examination of organs and tissues, appropriate animal-to-animal studies of xenotransplantation are very difficult to perform. Baboons — which are the closest model to humans — are *expensive*, very *difficult to work with* and usually require an *anaesthetic* for even simple examinations or blood sampling. They are more prone to infection than humans and their immunosuppression is less well understood. Consequently, estimates of efficacy in baboons may not reflect what is achievable in humans. Therefore, there may be a vague point at which little or no further progress can be made without proceeding to a human clinical trial.

How to identify the necessary data for assessment of efficacy?As with all therapeutic clinical trials, evidence of efficacy will be vital in a decision to proceed. In the case of xenotransplantation, the main evidence will be derived from animal-to-animal studies. The number of such studies will be limited because of:

- *Practical considerations*, the use of nonhuman primates in such studies means that only a few animals will be available for use; and
- Scientific considerations, studies with nonhuman primates, while of considerable value, do not fully determine the equivalent response in humans.
- *Expertise required* the regulatory authority responsible for approving animal-to-human (clinical) trial proposals will need to include members with expertise in the transplantation field, in order to assess all the relevant information available and the potential for success of the procedure in humans.

A template for assessment of xenotransplantation efficacy and for risk analysis should be proposed. This template could include, for instance, consideration of the type of procedure, the source animals and the possible infectious agents involved to ensure that any infectious disease risks are minimised and can be identified and contained should they occur.

2.3. What is the main promise of xenotransplantation?

It is true that a slow development has overcome the most *pessimistic* prognosis of the 1990's. Xenotransplantation is still a well-founded hope to help to relieve one day the organ deman, since the prospects of other techniques in the regenerative medicine (in the short or middle term), namely to grow whole human organs from human stem cells, are less optimistic in this regard and ethically even more controversial[11].

Allotransplantation is a victim of its own success in the sense that this therapy, due to its really positive outcomes, is being increasingly prescribed. This increase has not been followed by a parallel growing of the supply side. As a result, today it is possible to talk about a –worldwide- extreme scarcity of the resource "organ".

[11] Cfr. HWANG W. S., et al., "Evidence of a pluripotent human embryonic stem cell line derived from a cloned blastocyst", Published online *Science*, 12th February 2004.

Thousands of human organs are missing and thousands of people die every year during the waiting time.

The main objective of xenotransplantation is to try covering this gap. If it succeeds in its task, this would bring other positive related consequences. Taking one of the best thinkable scenarios, almost a paradise vision, the use of animal organs for the healing of human illnesses would make it possible to dispose over an unlimited number of organs, which, thanks to genetic engineering, could work (above all immunologically) even better than allo-organs. In any case, and contrary to the allogenic organ donation *mortis causa*, xenotransplantation would allow to plan the operation ahead, to ease pressure on relatives and friends regarding high upsetting situations and decisions –the same applies to the living organ donors- , etc. In addition, organ trade could lose most of its "reason" if the balance between chances and risks becomes more and more unequal for traders –assuming a progressive ideal view of xenotransplantation –so that one day allotransplantation itself (and thus organ trade) would perhaps be redundant and needless.

In summary, despite efforts to increase the number of human organ donors, demand outstrips supply: many people on waiting lists die before an organ becomes available. There is also a shortfall of cell and tissue products and new knowledge is opening up new therapeutic avenues, further increasing demand. To overcome this shortage, changes have been proposed to the consent rules for donation and to procedures for organ collection.

However, the proposed arrangements are either unacceptable and/or do not result in a substantial increase in donations. Living donor programs have boosted the supply of kidneys but extension of these programs to other organs (eg liver), carries risks for the donor, which may not be ethically acceptable. Other alternatives, such as artificial organs and other cell and genetic technologies are also progressing but will not provide clinical solutions in the near future.

In conclusion, the demand for human organs and tissue for transplantation exceeds their availability and the gap between supply and demand is likely to increase. In these circumstances one possibility is that the imbalance could be redressed by using other animals as sources of material for transplantation into human beings.

Xenotransplantation offers promise, not only for organ transplantation, but also for the transplantation of tissue and cells. Xenotransplantation of animal bone, skin, bone marrow, pancreatic islet cells, and fetal neural tissue have all been suggested. Xenotransplantation of tissue is a less drastic procedure than organ xenotransplantation. The immune response is less vigorous for small pieces of tissue which do not have a major blood supply running through them and the surgical procedure is likely to be less risky. The impact on the recipient may also be less severe since it seems that people attach more significance to organ transplantation than to the transplantation of tissue or cells. Moreover, as mentioned above, it is the shortage of human organs that is particularly acute. For this reason, the discussion in this document will largely concern the xenotransplantation of organs. Much of what is said about organs, however, will also apply to xenotransplantation of tissue and cells. Where xenotransplantation of tissue or cells raises particular issues, these have been discussed.

Recent developments suggest that xenotransplantation teams are making progress in controlling the immune response to animal transplants in order to prevent rejection. Even if this becomes possible, there is also the question of whether animal organs and tissue will be able to perform all the necessary functions in a human body.

Nevertheless, it is looking increasingly probable that many of the biological obstacles to xenotransplantation will eventually be overcome.

Proponents of xenotransplantation argue that there would be significant benefits if it were to become a successful and widely available treatment. Most importantly, enough animals could be reared to provide sufficient organs and tissue to overcome the present shortage of human organs and tissue for transplantation. This would eliminate the decline in health, the considerable anxieties, and the loss of life associated with the current long waits for human organs and tissue. Instead, xenografts could be offered as and when they were needed. Xenografts could also be offered to a wider group of patients who might benefit from transplantation but who are currently not eligible for a human organ or tissue transplant. Successful xenotransplantation of genetically modified organs and tissue would also eliminate the need for the careful matching of the organ or tissue with the recipient, required in transplants between human beings in order to reduce rejection by the immune system. This would be of particular benefit to people for whom it is currently more difficult to find compatible organs and tissue: for example, people from ethnic minorities for whom there is a shortage of donors with the same or similar tissue type.

Xenotransplantation would also avoid the need to consult the relatives of dead people about organ donation at times of great stress and emotional turmoil. If there are alternative sources of organs, it will not be necessary for relatives to make such difficult decisions. The need to perform transplant operations at very short notice, as occurs when human organs become available, would also be avoided: patients and health care workers could prepare themselves for the operation in advance. Transplantation would become an easier service to coordinate and administer, and this might bring savings in cost.

Despite legislation in many countries prohibits buying and selling of human organs, especially kidneys, these kinds of practices continue. If xenotransplantation were successful in reducing the shortage of organs and tissue, such ethically unacceptable commercial dealings might stop. Proponents of xenotransplantation have pointed out that, in addition, it might provide an alternative to the use of human tissue from aborted fetuses, and to methods for obtaining human organs such as elective ventilation or live donation, all of which have their difficulties. However, xenotransplantation raises important and wide-ranging ethical concerns which need to be addressed before a judgment can be made about its acceptability. The range of these concerns will be studied in this document.

2.4. What are the main obstacles to the clinical success of xenotransplantation?

The major obstacles to successful xenotransplantation include anatomy and physiology (size, function, biochemistry, etc) and immunology (rejection)[12]. Of these, the main obstacle to any organ or tissue transplantation, particularly any that depend on the establishment of a blood supply, is *rejection*. For *allotransplants*, this has been largely overcome by tissue matching of donors and recipients and immunosuppression of the recipient.

For *xenotransplantation*, the former strategy is not possible and the latter is not adequate to suppress the immune reactions that occur. These include a fast and powerful

[12] Certainly, obstacles remain in at least two major areas: **anatomy** and **physiology** (compatibility in terms of size, function, growth, ageing, biochemistry and so on) and **immunology** (rejection reactions). This section summarises the technical issues relating to these challenges and describes progress in overcoming them for the various types of xenotransplantation procedures.

"hyperacute" rejection (HAR), which occurs within minutes or hours of a vascular organ transplant, and further reactions that occur within a few days, causing blood clotting and death of the transplanted organ.

As has been mentioned, one of the most important limitations with regard to xenotransplantation is referred to the recipient's immune reaction against foreign organ, which by animal experiments has very seldom reached some months survival[13].

2.4.1. Immnology

It has recently been suggested that the immunological obstacles to the successful clinical conduct of xenotransplantation are amongst the "most difficult of hurdles" to overcome. These immunological difficulties exist because the human immune system rejects what it identifies as alien tissue. Such rejection takes place in number of stages; namely, hyperacute rejection –which occurs in seconds or minutes-, acute vascular rejection (AVR) –which takes place within days- and cellular rejection –which occurs weeks after a graft-.

Hyperactive rejection was long regarded as the "first hurdle" that needed to be overcome to make xenotransplantation clinically available. A number of developments in the field mean that it is now regarded as preventable. However, while various researchers agree on the importance of transgenic pigs in overcoming hyperacute rejection, others have pointed out that acute vascular rejection is the greatest hurdle to the transplantation of animal organs into humans and that the solution to this problem will be advanced but today is not solved.

Some studies have reported that "AVR remains a significant obstacle to the use of porcine xenografts in human recipients". However, considerable effort is now being focused on trying to understand the immune mechanisms that lead to AVR, so that ways to overcome it can be developed. In fact, some research in animal models has been successful in delaying or preventing AVR. Although knowledge about the nature of AVR is clearly increasing, all the primary methods being used to address it have their limitations. In addition, it has been studied that even when AVR is prevented, xenografts are susceptible to cellular rejection.

Efforts to address cellular rejection are even less well developed than those to tackle AVR. In addition, it is also thought likely that xenografts will be chronically rejected. As a response to chronic rejection, some authors have recently suggested that, given that xenotransplantation would supply an unlimited number of organs, chronic rejection could be overcome by replacing the organ.

There are two main approaches for reducing the immune response and preventing organ rejection: First, the antigens on the transplanted organ are matched with the recipient's antigens as closely as possible in order to reduce the immune response. There are many different antigens, and each one varies widely between individuals. This means that it is almost impossible to get a perfect tissue match between individuals (except between identical twins); Second, the patient's immune system can be suppressed with immunosuppressive drugs to help prevent rejection of mismatched transplants. The major drawback of immunosuppression is that it interferes with the operation of the immune system as a whole. This means that the patient has increased susceptibility to infections and to certain types of cancer. Immunosuppressive

[13] TALLACCHINI M., "Commentary: Council of Europe Working Party on Xenotransplantation: stat-of-the-art report on xenotransplantation (2000)", Xenotransplantation 8, 2000, pp. 154-156; Comp. WPXT (Working Party on Xenotransplantation), "Report on the state of the art in the field of xenotransplantation", CDBI/CDSP-XENO (2003) Strasbourg, http//www.coe.innt

drugs work in different ways. Some, such as cyclosporin A, inhibit T-cell activity. Other drugs, for example azathioprine, reduce the numbers of T-cells. Another drug, cyclophosphamide, inhibits the production of antibodies, and prednisone reduces inflammation.

There are also other methods for reducing hyperacute rejection. For instance, a different approach is to try and make the human recipient tolerant of the xenografted organ or tissue so that an immune response is not induced. There is evidence that if an animal receives a bone marrow transplant from an animal of a different, but closely related, species, the recipient can subsequently receive other transplants from the same source animal without mounting a strong immune response. Attempts to transplant pig bone marrow into primates have not yet been successful. In principle, however, it might prove easier to transplant pig bone marrow than pig organs since, like other tissue, it is not susceptible to hyperacute rejection, although graft versus host disease can be a problem. The eventual aim would be to give people bone marrow transplants from a source animal. Once tolerance was induced, other organs could be transplanted.

A number of other methods have been used to try and prevent, or reduce, hyperacute rejection. One approach is to remove the antibodies that recognize pig antigens from the blood of the human recipient. In principle this could be done by passing the person's blood through a filter that contains the pig antigen. The antibodies would stick to the antigen in the filter and thus be removed from the blood. This would allow a xenograft to take place. The human recipient would eventually make more antibodies but it is possible that the pig tissue would not be destroyed at that stage. Another approach is to treat the pig organ with fragments of antibody before transplantation which cover up the antigens and stop the body's antibodies sticking to them. Finally, it is possible to try and treat the recipient with substances that inhibit the complement system.

2.4.2. Physiology

The physiology of the animal organ, given that it seems neither to fit externally into the recipient body at an optimal level (size, aging, etc) nor to assume the original functions of the respective organ properly, is another obstacle in this regard[14]. In other words, given the immunological difficulties that exist with xenotransplantation, there is currently limited information on whether animal organs and tissues will function physiologically in humans. That is, assessments of how successfully xenotransplants will function cannot be made until longer graft survival is achieved to allow more evidence to be gained. Concerns also exist as to whether the organ will produce the appropriate biochemicals that humans require, or respond to the hormones that other human organs produce[15].

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[14] MÁÑEZ MEDILUCE R., "Xenotrasplante: los retos científicos", in ROMEO CASABONA C (ed), "Los xenotrasplantes. Aspectos científicos, éticos y jurídicos", *Biblioteca de Derecho y Ciencias de la Vida*, Comares, Granada, 2002, pp. 19-36.

[15] In summary, transplanting organs, tissues or cells between species presents some physiological and anatomical problems that affect the choice of animal species. An obvious example is the size of the source animal's organs in comparison to those of the recipient. Other problems may include:

• The orientation of the organ in the human recipient compared to the donor (eg vertical orientation of the pig heart in humans versus a horizontal orientation in pigs);

• The growth rate of the transplanted organ in humans (eg if transplanted into a child);

• The life expectancy of the donor animal compared with human life expectancy (eg will the organ survive for the rest of the life of the human or need to be replaced at a later stage?).

In this regard, more research is required in animal models to ensure that xenotransplantation moves to clinical trials only when there is a high probability that they are likely to function in their human recipients, or at least that prolonged and reliable graft survival has been attained in animal models. Some authors consider that in the medium term, it appears that the physiological incompatibilities encountered to date, and those still to be discovered, constitute a significant stumbling block to the progress of xenotransplantation towards clinical trials.

2.4.3. Infectious Disease Risk

It has long been acknowledged that allotransplantation can spread diseases between the donor and recipient of transplanted organs and tissue. As have been noted by some authors: a risk of disease transmission is present in any transplantation system. In allotransplantation, disease transmission is a major cause of illness and death in recipients. This is largely due to the required level of recipient immunosuppression but is also attributable to infected, but usually asymptomatic, human donors.

In addition, it is also acknowledged that animal diseases (zoonoses) can cause disease in humans. Thus, it has been emphasized that: zoonotic viruses have been responsible for at least two major pandemics: the 1918 Spanish influenza pandemic, attributed to infection of humans with a swine influenza virus, and the current HIV/AIDS pandemic, believed to have originated with the infection of humans by a simian immunodeficiency virus endemic to chimpanzees.

Interestingly, it was a zoonosis (HIV infection) that led to calls for "even more careful screening" of transplant donors. This is required not least because the spread of zoonoses via transplantation is likely to be even more efficient than it is by natural means. However, the knowledge that transplantation can transmit disease and that animal diseases can pass to humans did not immediately leas to attention being given to the public health implications of xenotransplantation.

Indeed, there is agreement that the immunological problems associated with the development of xenotransplantation initially attracted more attention than those related to infection. There are a number of reasons for what now may appear from an ethical and regulatory perspective to be a dubious allocation of research attention. But now the xenogenic infection risk -(e.g. the possibility that new pathogens, either through direct transmission or through transformation in the recipient's body-, which springs up or causes new diseases in humans), is regarded as one of the main risks.

As infectious disease began to be discussed in the context of xenotransplantation, different aspects of the issue are highlighted.

There may be other biochemical, pharmacological or endocrinological problems if functional molecules in the xenotransplantation product are mismatched with receptors in the recipient or vice versa. In this regard, technical challenges to xenotransplantation are primarily immunologic and physiologic in nature. Although these changes are common to both human-to-human transplantation (allotransplantation) and xenotransplantation procedures, the various differences and disparities between species tend to exacerbate these issues in xenotransplantation Immunologic problems such as acute cellular refection and chronic rejection are faced in any transplantation procedure. In xenotransplantation, however, a number of factors arising from disparities between species intensify the immunologic processes that mediate rejection. Therefore, obstacles to xenotransplantation include anatomical problems (eg structural issues such as the size and growth rate of the animal organs) and physiological problems (eg biochemical, pharmacological and endocrinological factors that may influence transplanted animal organs, tissues or cells). Such obstacles are likely to be more serious for organs with a complex metabolic function, such as the liver, than for a largely mechanical organ like the heart. Fewer physiological issues are expected in the case of tissue or cellular transplants, because the molecular interactions are less complex and it is hoped that problems can be overcome by genetic modification of the donor animal.

Many articles present parts of the infectious disease issues raised by xenotransplantation. That is, attention is variously given to the risk posed to xenograft recipients, or to transplant recipients and their close contacts. Others note in passing the potential risk to public health. It is underlined the possibility that xenografting will serve as a vector by which new and possibly virulent viruses become established in humans.

Arguably, the topic to have received most attention in the scientific literature that considers the infection risks associated with animal to human transplantation is the potential of Porcine Endogenous Retroviruses (PERVs) to pass to humans. PERVs have been thought to pose a particular risk because they cannot be removed from porcine tissue. Thus, although other viruses can be managed by the introduction of biosecurity procedures, this is not the case with PERVs. In addition, it was unknown how these retroviruses would react when grafted into a human. Such concern was heightened by the fact that PERVs did infect human cells in culture. However, evidence also exists to support the suggestion that PERVs do not transmit to humans or animals. On the other hand, a number of studies have found PERVs to be transmitted in immunodeficient mice. Despite such results a number of researchers in this area now think the risk posed by PERVs are overstated.

However, it should be noted that, although there is no sign that humans have been infected in trials, there are precedents for the adaptation of and spread of animal retroviruses within the human population. This is a possibility that has still not been discounted.

In summary, there are promising approaches to overcoming both the physiological and the immunological barriers to xenotransplantation, but it is important, firstly, to take some scientific and technical issues into account. Most researchers now consider pigs to be the most suitable source animals for transplantation products: the anatomy and physiology of pigs are similar to those of humans, pigs are domesticated and easy to breed, and they are suitable for genetic manipulation[16].

In this regard, it is important to clarify that two main groups of animals have been used as the **source** of xenotransplantation products: nonhuman primates (e.g. baboons, chimpanzees) and pigs. However, the use of nonhuman primates has been discontinued in most countries because of concerns about the potential for spread of infection[17]. Most researchers now consider pigs to be the most suitable source animals for transplantation products.

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[16] At present, pigs are the source animal of choice for whole-organ xenotransplants. It is recommended that nonhuman primates not be used as source animals for xenotransplants because of problems associated with infectious diseases in monkeys and their risk to humans. Porcine infectious diseases are currently being studied and assays are being developed to detect infection in pigs and humans. Many porcine agents are non-infectious for humans, and others can be eliminated through screening and husbandry practices, including closed breeding colonies. Unrecognized infections are likely to circulate in porcine populations and could be a potential risk to humans in xenotransplantation. Efforts should be directed toward preventive measures by 1) developing new assays and methods to detect novel porcine agents and 2) developing methods to reduce infections in swine colonies. [16] ROMEO CASABONA C. M.; MORA URRUELA A.; PEREIRA DE MELO H.; McGLEENAN, Xenotransplantation. Ethical, Legal, Economic, Social, Cultural and Scientific Background, Vol. 4, AVM, 2008; ROMEO CASABONA C. M.; MORA URRUELA A.;"New legal developments in xenotransplangtation: the spanish approach", *Revista de Derecho y Genoma Humano*, No. 29, 2008, pp. 111-129; GUERRA GONZÁLEZ J., "Prevention of the xenogenic Infection Risk and the Spanish and German Constitutions", *Revista de Derecho y Genoma Humano*, No. 20, pp. 123-146.

[17] The limitations of non-human primates as models for studying xenotransplantation in humans include species differences in physiology, immunology, and susceptibility to infections, as well as difficulty in

In this regard, researchers, the biotechnology industry (sponsors) and the wider community generally agree that nonhuman primates are not a suitable source of xenotransplantation products for any of the proposed therapies (organs, tissues or cells; in vivo or ex vivo). Currently, both researchers and ethicists consider pigs to be the most likely and appropriate source of organs and tissues for xenotransplantation. The anatomy and physiology of pigs are very similar to those of humans; as has been said, pigs are domesticated animals that are easy to breed; and, importantly, pigs are suitable for genetic manipulation. However, researchers are considering the use of other species for cellular transplants (including pigs, cattle, fish and mice).

Nonhuman primates are not considered a suitable source for human transplantation for safety reasons, in particular the potential for nonhuman primate retroviruses to cross the species barrier and infect humans[18]. Researchers have therefore focussed their attention on pigs as source animals. A major thrust of current research programs involves the genetic modification of donor pigs with some key human genes so as to reduce the immune response that occurs when pig tissues are transplanted into human recipients. However, as has already been mentioned, a pig retrovirus has recently been identified and there are concerns that it may also be able to cross the species barriers to humans, possibly causing a new zoonotic infection in humans[19]. Therefore, constitutes one of the most important concerns the porcine endogenous retrovirus (PERV). PERV is essentially embedded in all pigs' genomes and could potentially be transmitted to humans with the xenotransplant product.

The most promising approach to overcoming the aforementioned risks is, as has been said, by inserting some key human genes into the donor pigs -that is, by genetic modification of the pig-[20], as well as treating the recipient with immunosuppressive or

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monitoring non-human primates in a clinically relevant manner. Knowledge about optimal drug levels and the ability to monitor drug levels and biochemical and physiologic parameters are far less sophisticated for non-human primates than for humans. Although some of these limitations are insurmountable, others could be minimized by the development of assays and facilities with advanced monitoring capabilities for non-human primates. Core facilities and regional centers could be developed for these purposes. Such developments would require a significant financial investment and access by all investigators to the requisite knowledge, facilities, etc. Unfortunately, even simple primate studies are extremely expensive to conduct, and the funding available for them is limited. Models that are more sophisticated will require resources at a level well beyond those currently available

[18] Although nonhuman primates (apes and monkeys) are the most closely related species to humans, use of their organs, tissues and cells for human transplantation is no longer considered to be an option, for safety reasons. Safety concerns arise because nonhuman primate retroviruses have the potential to cross the species barrier and infect humans as is thought to have occurred with human immunodeficiency virus (HIV).

[19] A *xenozoonosis* would be a disease (nosis) that affects humans which originated in animals (zoo) as a result of a xenotransplantation. The fact that a disease is originated by the xenotransplantation does not probably add anything essential to the usual term "zoonosis" –meaning any human illness coming from animals (eg AIDS, ebola, SARS, and newly the avian influenza). The prefix xeno is however maintained just to stress the origin of the illness as well as to indicate that not every xenozoonosis (due to transformation or recombination of pathogens in the recipient's body) could be easily classified as a zoonosis.

[20] A major thrust in xenotransplantation research is concerned with genetic modification of the source animals. Thus, in many cases, xenotransplantation products will be obtained from genetically modified animals. Certainly, Researchers predict that the best chance of successful xenotransplantation will occur by genetically modifying the source animal as well as treating the recipient with immunosuppressive or other drug therapy. Genetic modification of source animals by inserting some key human genes to help to make xenotransplants behave more like allotransplants is currently the most promising approach to overcoming the biochemical, endocrinological and immunological barriers to xenotransplantation.

other drug therapy. However, there are potential problems associated with these approaches, including the risk of providing an environment in which animal viruses may be able to infect human transplant recipients, initiating a new infectious disease in humans.

One of the ways to overcome the mentioned risks is to isolate the source animals completely from their usual environment (other animals, breeders, air, earth, etc.) so that the possibility for them to be in contact with external potential pathogens is greatly reduced or, if feasible, ruled out. In this context, piglets could be taken directly per caesarean section to avoid any contamination, as it would be the case during natural births, and then live completely isolated. These so called gnotobiotic conditions guarantee a maximum of microbiological security for human beings for a minimum of animal wellbeing[21]. And this was the main ground for their early rejection, either for ethical –pigs are intelligent social animals and would be subdued to enormous suffering under these conditions –or, perhaps rather, for practical and economical reasons: the low survival rate of swine under those (moreover expensive) gnotobiotic conditions[22].

A compromise between epidemic security and animal "wellness" is the breeding of swine for xenotransplantation goals under specific, qualified pathogen free conditions, which with slight different has been proposed in several forums and whose definitive form should be fixed legally at a given moment.

The major advances in gene technology over the past decade have increased *optimism* amongst some researchers. They now believe that it may be possible to overcome the overwhelming innate immune response of human recipients enough to allow an animal transplant to establish. If this occurs, further molecular techniques, plus development of new immunosuppressive drugs, may allow longer-term acceptance and functioning of the transplant. Therefore, a major thrust of current research programs involves the genetic modification of donor animals with some key human genes so as to prevent their tissues from being recognised as 'foreign' by the immune system of the human transplant recipients[23]. This research has been accompanied by a variety of ethical, social and scientific aspects that require cautious consideration.

In conclusion, it can be pointed out that the immunological, physiological and infectious obstacles to xenotransplantation allow us to see that progress has been made

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However, there are potential problems associated with these approaches, including the risk of providing an environment in which animal viruses may adapt to human conditions.

[21] FDA (USA-Food and Drug Administration), "Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans", Final Guidance, U.S. Departament of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, 2004, p. 4.

[22] Nuffield Council on Bioethics, "Animal-to-human Transplants. The Ethics of Xenotransplantation", London, 1996.

[23] The most common method of producing genetically modified (GM) animals is to microinject a purified sample of the donor DNA into the male genetic material (pronucleus) in a fertilised egg before it fuses with the female pronucleus. If successful, the injected DNA integrates into the genome of the embryo that is formed when the male and female pronuclei fuse. Offspring that show the required genetic trait can be further crossbred to produce a purebred GM strain. The human genetic material used to produce GM pigs is identified from a 'library' of sequences produced by systematically fragmenting human DNA molecules and artificially copying (cloning) the fragments required (based on information obtained from genetic mapping techniques, including the Human Genome Project).

It is likely that the optimal pig for xenotransplantation will require multiple genetic manipulations, which could be facilitated by increasing experience with the techniques for porcine genetic modification, developing more efficient techniques for genetic modification, and sharing of proprietary genes or genetically modified pigs to allow their combination in a single animal.

in, for example, overcoming hyperacute rejection. However, it has been also noted that considerable work still needs to be done. It is true that there has been recent progress in overcoming some of the difficulties in preventing xenograft rejection, but many obstacles remain. The most promising approach is the development of transgenic pigs containing human proteins that inhibit the complement reaction to a xenografted organ. Even if hyperacute rejection can be controlled, there will be other immunological barriers to acceptance of the xenograft by the recipient. There may also be biochemical and physiological incompatibilities between pig organs and human beings.

At this stage, xenotransplantation would consequently be an unreasonable burden for the patient. And this would be not the only risk to consider: The introduction of xenotransplantation in the clinical praxis –at first presumably coexisting with allotransplantation but without reaching its positive effects-, could bring negative consequences to the already scarce supply of organ donations and this co-existence would raise a new organ allocation problem (Who gets which organ?); The dignity of creatures and the new instrumentalisation and suffering of the *source animals*[24] would be subdued are important ethical questions concerning xenotransplantation than would require clarification.

In this regard, the often single-minded perspective of medical researchers and clinicians seeking to make animal to human transplantation clinically viable needs to be balanced by the perspectives of other disciplines to determine whether or when the costs of progress area reasonable or too great. Therefore, it is true that recent advances in molecular biology have made successful xenotransplantation more likely and xenotransplantation research is attracting increased attention and funding. It is also true that further diseases are being considered for treatment. In this regard, it is vital to consider the ethical, social and scientific implications of the technology so that guidelines can be adopted to inform decision making in this area.

2.5. The importance of ethical criteria to assess the issues involved in xenotransplantation

Xenotransplantation raises, for instance, the question of how far and in what ways it is acceptable for human beings to use other animals as a source of organs and tissue for transplantation. Even if one accepts in principle the use of animals in medicine and in medical research, their use in xenotransplantation may raise particular difficulties.

The use of primates such as baboons would concern many. The use of genetically modified animals, which is likely to be necessary if pigs are to be used for xenotransplantation, also merits special consideration. And if the use of animals to supply organs for xenotransplantation is considered ethically acceptable in principle, can the welfare of the animals be adequately taken into account? These and other issues are discussed in the following sections.

Public health issues arise from the prospect of xenotransplantation. The transplantation of animal organs or tissue raises the possibility, as has been seen, that infectious organisms of animals may be transferred into the human population. Xenotransplantation, like any major innovation, may have wide-ranging and

[24] Other expressions like animal (organ donors) etc. are probably less appropriate to describe animals from which are explanted organs for xenotransplantation purposes. In this case, because animals cannot be legally understood as donors and because it cannot be inferred or presumed that they have any will to donate its organs to humans, what physically (or legally, according to animal protecting laws, to avoid further suffering, in case the organ extraction were not itself lethal will lead to their death.

unpredictable effects. It is necessary, therefore, to identify principles which would provide a basis for dealing with the remote, and unquantifiable, hazards that xenotransplantation could bring.

The treatment of early recipients of xenografts may raise serious ethical issues. So far the survival times for recipients of xenografts have been poor and, in effect, early recipients are being used as experimental subjects for the development of the technology.

It is of high importance to consider whether there is anything inherently unethical or unacceptable about using animal organs, tissues and cells for transplantation to humans. It is thought that the possible ethical objections in this regard can be satisfactory answered. Secondly, it is important that any xenotransplantation research approved in Europe serves the public interest and has broad in this sense public support. Once these considerations have been satisfactorily met, it is necessary to consider a framework of scientific and ethical principles within which specific procedures can be assessed. To this goal, three key areas or issues are identified: practical **animal ethics** (particularly with respect to animal welfare); **efficacy** (effectiveness) and **safety** (for both the transplant recipient and the broader community); and practical **human ethics** (particularly the need to obtain consent from the research participant and to involve close contacts in decision making).

Therefore, xenotransplantation raises a number of ethical issues that will be debated by the community as a whole. These issues are studied in the next sections and include consideration of inherent ethical and social issues relating to whether there is anything wrong *in principle* in obtaining organs and tissues from animals, concerns about respect for human life and concerns about the welfare and right to life of animals. It is unlikely that all members of the community will agree on these issues (as they do not for other issues concerning the use of animals by humans, such as for food or for medical research). We must take into account that ethical deliberation takes place in a social and historical context that is continually changing. There are no timeless solutions, and ethical debate cannot be separated from the domain of social life. In this regard, we recognise that it is not realistic to expect complete consensus across society on the issues addressed in this document. The aim of this debate paper is to seek as much common ethical ground as possible. But it is important to acknowledge differences of opinion. This will help to inform future debate, to try and ensure that, whichever direction society chooses to take, its decision will be based on principles that can be justified as reasonable to most of its members, and to take account of the views of those who dissent from the majority decision.

Another question that it is important to bear in mind is that no single ethical framework can confine all the reasonable perspectives that may be taken on the issues raised by xenotransplantation.

Indeed, the aim of this document is to provide information about xenotransplantation so that a wide and open public debate can be held among all relevant community and stakeholder groups, including the general public.

It has been suggested that if xenotransplantation research might put society at large at risk of an infection, there is an ethical obligation to inform society of that risk and to determine the conditions under which an informed society might be willing to assume that risk[25].

[25] IVINSON, Adrian J.; BACH, Fritz H., "The xenotransplantation question: public consultation is an important part of the answer", *Canadian Medical Association Journal*, vol. 167, 1, 2002, pp. 42-43;

Undoubtedly, a key issue which requires community consideration and debate is the risk of an infectious agent that could cross from an animal to humans, and produce unknown infectious risks for the general community. Cross species transmission of most known viral and bacterial pathogens is preventable by appropriate breeding, housing and testing of source animals. However, there is serious concern that a virus, such as the endogenous retrovirus, present in the pig genome (the pig is –as has been mentioned- currently the preferred source of organs), could "reactivate" in human recipients and, theoretically, later infect close contacts, healthcare workers or the wider community.

This risk of infection brings a new ethical dimension to how consent for xenotransplantation research might be given. It is important to emphasize that not only will any potential recipient need to be fully informed of any risks, but so too will close contacts of the recipient and members of the healthcare team. An additional ethical issue relates to how a prospective recipient might reasonably choose between risking an experimental therapy and waiting for a human organ transplant.

Another issue which requires community debate is the potential use of genetically modified pigs to overcome the intense rejection reaction which, so far, has made xenotransplantation unfeasible. While experimental work to date has involved minimal genetic manipulation, more extensive modification -which could be seen to significantly alter the essential nature of the animal-, may not be acceptable ethically or to our community.

In all human research, a key ethical principle is that the presumed benefits must outweigh the known and theoretical risks. Weighing this balance for any human xenotransplantation research proposal will not be an easy task. It is also of high importance to outline the several conditions which must be met before research can be approved. One such requirement is obtaining convincing data of the efficacy of animal-to-animal experiments (e.g. pig-to-baboon xenotransplantation) before pig-to-human trials can be contemplated.

A further issue relates to which group of individuals should be empowered to weigh up these benefits and risks and give approval for such human research on the community's behalf. Should a National Committee be the responsible of this task? But, if this is the case, that National Committee should be made up of people with relevant scientific, ethical and regulatory expertise, as well as of community members.

Local human research ethics committees would play also a role in monitoring the research, and could reject a proposal, but could not approve a proposal unless it had also received approval from the national committee.

Xenotransplantation research is regarded as one of the more important issues for community consideration, and wishes to actively involve medical practitioners, researchers, lay people, etc in the debate. Medical practitioners and researchers are invited to either develop or communicate their own views, or to assist in stimulating debate in the wider community.

In summary, the main issues involved in xenotransplantation research are the following ones: The efficacy and safety of the procedure and the stage at which it is appropriate to allow clinical research to go ahead; The risks relating to the possibility of a new infectious disease emerging with potentially serious consequences for the wider

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BACH, F. H.; FISHMAN, J. A.; DANIELS, N.; PROIMOS, J., et al., "Uncertainty in xenotransplantation: Individual benefit versus collective risk", *Nature Medicine*, 4, 1998, pp. 141-144.

community; The human ethics of the research protocol relating to information provided to the transplant recipient and their immediate contacts and the consent or agreement to the procedures obtained from these groups, respectively; The animal ethics of the research protocol relating to the acquisition, care and use of animals.

These important areas of concern form the basis of this document. To help determine where community support and concern lie in relation to this complex issue, respondents to the public consultation are invited to respond to each of these issues which are summarized in Appendix A.

It is important to proceed with this public consultation because we should not discard any potentially beneficial technology simply because there are perceived potential risks. There are processes to assess risk activities and develop risk management strategies. These are based on keeping risks below levels that are considered 'acceptable' by a broad consensus of scientific evidence and public opinion. Acceptability is, in turn, related to the benefits of the activity, the distribution of those benefits, and the seriousness of the consequences of the adverse event, should it occur. Acceptable risk is determined by *risk assessment, risk communication, stakeholder consultation, political and deliberative process*, etc.

3. CHAPTER II: ETHICAL ISSUES

3.1. Introduction

To provide a framework for discussing ethical and social aspects of xenotransplantation, it is of high importance to consider ethics not only as a matter of individual preference or cultural convention, but also as a form of human investigation in which it is possible to express reasoned and reasonable principles of conduct. It is true that ethics for individuals can be regarded as a matter of personal ethics. For society it is described as matter of public policy. Questions in relation to the latter have several implications for the kind of society that is desirable to reach. There is no consensus on the satisfactory way of reasoning in ethics. This is a matter of some debate among philosophers. Some authors emphasise attention to the likely consequences of any proposals and some other authors emphasise attention to some basic duties we have towards each other and towards animals. The approach adopted here is that adequate ethical and social consideration of xenotransplantation must include assessment of different issues. To provide a framework for discussing ethical and social aspects of xenotransplantation, it is important to consider, for instance, the following questions: The goals or the appropriateness of the objectives of the research; the way of reaching those goals or the ethical issues that are involved in this field; the possible consequences or the ethical questions raised by proposals to conduct clinical trials; and the wider social significance of xenotransplantations clinical trials.

In other words, it is of high importance to consider the *goals* of animal-to-human clinical trials of xenotransplantation (eg to overcome a shortage of organs for transplantation, to develop new therapies, etc.); the *procedures* which gives rise to some ethical questions (eg whether xenotransplantation violates respect for the dignity of human beings or the welfare of animals, whether consent can be truly informed and truly free and whether close contacts of the research participants should also be asked to consent); the ethical questions about the likely *consequences* of animal-to-human trials of xenotransplantation (eg the risks, consent requirements and animal welfare issues); and the wider *social significance* of xenotransplantation, including questions about justice in the allocation of resources.

This section outlines essential issues related to the use of animal organs or tissues in humans in order to determine if there are any inherent objections to xenotransplantation research that might prevent any further consideration of the issue.

3.2. Ethics of animal research

As described in previous paragraphs, xenotransplantation is currently at the research stage. The research involves the use of animals to provide transplant material and also to act as experimental recipients of transplants. Should xenotransplantation develop into a successful clinical procedure it will involve the breeding and killing of animals on a large scale in order to provide organs and tissue for transplantation. In addition, the use of transgenic pigs for xenotransplantation raises questions about the genetic modification of animals to provide organs and tissue.

This section goes on to consider whether, even if the use of animals for medical purpose in general is held to be ethically acceptable, there are particular concerns about their use for xenografting. In this regard, two questions are discussed:

- The ethical acceptability of the use, respectively, of primates, and of animals other than primates, to supply transplant material;
- The ethical issues raised by the use of genetically modified animals to provide organs for xenotransplantation

3.2.1. The use of animals for medical purposes

The main problem in this regard is that, if animals are to be used for medical purposes in ways that would not be considered ethically acceptable if applied to human beings, then there must be some basis for drawing the distinction between animals and human beings. If there are no convincing reasons to ascribe to animals a lower moral status than that ascribed to human beings, then the use of animals for medical purposes would be hard to justify. In recent years, the argument has been gaining ground that animals should be accorded a higher moral status than has been admitted hitherto. Two distinct philosophical approaches may be used to support this shift in opinion. The first approach starts from the position that the interests of animals, particularly in avoiding suffering, should be taken into account when judging whether it is acceptable to use them for medical purposes that benefit human beings. The second approach argues that animals, like human beings, have rights that must be respected when considering their use for such purposes.

From the first perspective, it is now broadly recognized that many animals, and certainly the mammals that would be used for xenografts, are susceptible to pain and suffering. Some argue that there is no logical reason to distinguish morally the pain and suffering felt by animals from that felt by human beings. Suffering is suffering wherever and to whomever it is caused. It would be wrong to weigh animal suffering less heavily than human suffering, just as it would be wrong to weigh the suffering of one human being less heavily than another. This is a utilitarian argument which holds that ethically acceptable actions are those which increase the benefit, or reduce the harm, to as many individuals as possible. When judging the acceptability of the use of animals for xenotransplantation, or for any other medical purpose, a decision must be made about whether the pain and suffering caused to the animals is justified by the potential benefit to the human being. It is also widely accepted the principle that in some cases, the saving of human life or of significantly enhancing its quality may justify a certain amount of animal suffering, provided this is kept to a minimum.

From the second perspective, if animals share with human beings some or all of those characteristics that, in the case of human beings, would lead us to assert that they have certain rights, then those rights should be ascribed to the animals as well. The ascription of rights, whether to human beings or animals, rests on the principle that the lives of individuals have an inherent value. Such individuals should be treated as ends in themselves rather than merely as means to the happiness or well-being of others.

According to this view, there are fundamental moral constraints on what can be done to those who have rights. Such constraints should not be overridden, no matter how great the benefit accruing to others from so doing. The right to life, for example, dictates that a rights holder, human being or animal, should not be killed, however painlessly, even if countless others could potentially benefit thereby. Similarly, restrictions on the ways in which human beings may be used in medical research should extend to animal rights holders as well. Some argue that any use of animals for medical purposes is a violation of their basic rights, and as such, that it should not be countenanced. The issue of rights, however, remains controversial and is even more so in the case of animal rights. Nonetheless, it is possible to conclude in this regard that animals should be granted protection against certain procedures.

Whether the argument is framed in terms of the interests or the rights of animals, the crucial point is the extent to which animals share the features supposed to be important to human interests and rights. The feature to which most importance has generally been attached is that of self-awareness. This may be described as the consciousness an individual has of his or her own condition and experiences. To be self-aware requires a high degree of intelligence, the capacity to make comparisons and judgments, and a language with which to articulate them. Self-awareness allows individuals to plan, to make choices and to engage in complex social relationships. Most significantly, for the purposes of this discussion, it has been argued that suffering and death are uniquely painful to a self-aware being that not only senses pain but can also perceive the damage being done to his or her self and future.

Individuals that possess these characteristics, founded in self-awareness, may be regarded as persons. Until recently, the moral status of personhood has been supposed to be the unique prerogative of human beings. On these grounds the human being is often regarded as more than a ‘mere animal’, and the human condition as fundamentally superior to that of animals. From this perspective, animals would not merit the same moral consideration as human beings, and animal interests would weigh less heavily than human interests. While great weight would be placed on the reduction of animal suffering as an end in itself, the painless killing of animals for the purposes of saving human life or improving its quality would be considered acceptable.

Current researches into the mental life and intelligence of non-human animals has, however, led to claims that the features qualifying human beings for personhood are also present, to varying degrees, in other species. There is evidence that some animals, notably the higher primates, have much in common with human beings, including self-awareness, complex social relationships and many of the other characteristics that have often been supposed to make human beings unique. If that is son, then these animals should be accorded the same moral status as human beings.

According to this argument, the capacities of human beings and some non-human animals, such as higher primates, may overlap to such an extent that there is no basis for a distinction of treatment. To deny this implication, it is argued, is simply to draw a distinction on the ground that one individual is of the human species and another

is of a non-human species. Such **speciesism**[26], some have claimed, is no more acceptable than racism or sexism. For those who wish to press the charge of speciesism there are two further implications. One is that non-human animals whose capacities match those of human beings should be included within the moral community. A second implication is that it would not be appropriate to include within the moral community human beings whose capacities do not qualify them for personhood. It has been argued, for example, that anencephalic babies, suffering from a fatal neurological condition in which the cerebral hemispheres of the brain are absent, are not persons. Some would regard it as acceptable to use such babies to provide organs for transplantation. It is even argued that to use of animals that qualify as persons for medical purposes, rather than human beings that do not, is morally unacceptable. This second implication leads many to caution against the use of animals as sources of organs for transplantation, since to do so is to embark upon a 'slippery slope'. Once the use of animals is sanctioned, then there can be no principled objections, for example, to the procurement of organs from anencephalic human babies. For many people, the idea that any human being could be used in such a way is deeply abhorrent. Similar sentiments underlie the protection, extended to all human beings, from uncontrolled use in medical research, and the prohibition on using organs from human beings except under conditions of consent. It can be argued that vulnerable individuals, such as anencephalic babies, are more deserving of protection not less so.

In this regard, the notion of speciesism has to be treated with some caution. Our natural emotional response to, and concern for, members of our own species is clearly built deeply into our nature and it is not clear that the option of responding to members of other species, with the same concern in every case, is open to us. We should consider therefore what our treatment of non-human animals should be in its own terms, rather than in terms of consistency with our treatment of human beings.

In summary, the ethical issues raised by the use of animals in medical research are complicated and, in this section, some of the main arguments are briefly reviewed. An ethical discussion about animals as sources of transplantable organs and tissues involves serious questions about, for instance, what violates respect for the dignity of human beings and what violates the welfare of animals[27]. The potential for xenotransplantation to save the lives or improve the health of people currently on

[26] In reply to **speciesism**, one of the arguments relies on the idea that there is a moral equivalence between at least some animals (those who are self-conscious, such as primates) and human beings because they possess the same *cognitive attributes*. Treating animals as resources for humans involves the morally objectionable prejudice of speciesism. A different version of this argument does not assert such moral equivalence, but still claims that higher animals are creatures of moral worth, that they have some moral standing, and that therefore they should not be treated merely as means to human ends. In reply to these arguments, it may be said that though human beings and animals have much in common, including *sensory awareness* and the *capacity to feel pain*, there are *morally significant differences* between human beings and animals, in particular the human capacity for *practical judgment* and *choice*. Any argument that minimises these differences is, for some authors, untrue to both the human and animal ways of life.

[27] **Vatincan's view on xenotransplantation**. Pontifical Academy for life: Prospects for xenotransplantation scientific aspects and ethical considerations. http://www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_20010926_xenotrapianti_en.html; **- Nuffield Council on Bioethics, reports**: The Ethics of Research involving Animals: http://www.nuffieldbioethics.org/go/ourwork/animalresearch/introduction**;** Animal-to-Human Transplants: The ethics of xenotransplantation: http://www.nuffieldbioethics.org/go/ourwork/xenotransplantations/introduction

waiting lists for organ donation or with presently incurable conditions such as Parkinson's disease or diabetes is also an important issue that should be considered in this debate. These arguments deserve careful consideration both by the researchers committed to the potential therapeutic benefits of xenotransplantation and by the community at large.

There are several views on the moral status of animals but it is possible to accept that biomedical research using animal subjects is justified as an undesirable but unavoidable necessity. An agreement in this regard could extend to the following points: In the absence of any scientifically and morally acceptable alternative, some use of animals in biomedical research can be justified as necessary to safeguard and improve the health and alleviate the suffering of human beings and animals; The benefits, in turn, depend on the advancement of fundamental scientific knowledge but even when no therapeutic or other practical benefit can yet be derived from it, any significant advance in scientific knowledge is a good, and may serve as a justification for using animals to that end; However, not every projected improvement to human health or addition to scientific knowledge is sufficiently significant to justify every use of animals. Some uses of animals may have adverse effects too serious to justify them at all, while in other cases the adverse effects may be considered disproportionately serious in relation to the significance of the results gained; In the latter case, both the potential benefits of a particular research project and the likelihood of the project achieving those benefits need to be assessed carefully before they, in turn, are weighed against the likely adverse effects to the animals; the use of animals is permissible providing that use is humane. Therefore, it is of high importance the need to keep to a minimum any suffering or pain experienced by the animals. It is also important to keep the number of animals used to a minimum, and to find alternatives to the use of animals where possible.

For those who do not accept the use of animals for medical purposes, xenotransplantation will, in principle, be unacceptable. We accept the view that some use of animals for xenotransplantation can be justified in principle. There are specific issues, however, that need further consideration. In what follows the particular ethical implications of the use of primates for xenotransplantation are considered. Attention has focused on the pig as an alternative to the use of primates for xenotransplantation. In this document the ethical issues associated with the use of pigs for xenotransplantation are also studied, including those issues arising from their genetic modification for this purpose.

3.2.1.1. The use of primates for xenotransplantation

Serious ethical concerns are raised by the possible use of primates for xenotransplantation. The sophisticated capacities of primates suggest that any harm suffered by them should be given great weight. There are some regulations which accept the use of very small numbers of primates as recipients of organs for research during the development of xenotransplantation using non-primate animals as sources of organs. In this case, the harm caused by using a small number of primates for research into xenotransplantation, while undesirable, can be justified by the potential benefits if xenotransplantation were to become a successful procedure.

However, special weight must be given to the harm suffered by primates, and additional concerns should be taken into account. The potential risk of extinction, even to species like baboon that are not currently endangered, must be taken seriously. In

addition, xenotransplantation using primates' organs or tissue may pose particular risks of disease transmission.

Given the ethical concerns raised by the use of primates for xenotransplantation, attention has turned to developing the pig as an alternative source of organs and tissue. As studied below, the use of pigs for xenotransplantation raises fewer ethical concerns. To develop the use of primates for xenotransplantation, when there is an ethically acceptable alternative, would not be justifiable. In this regard, if other possibilities for alleviating the organ shortage which do not involve the use of animals exist, -such as increased donation of human organs and the development of artificial organs and tissue, these other possibilities should be actively pursued. Other conditions, such as the possible transmission of disease from higher primates to human beings and the impossibility of maintaining in a high standard the welfare of the animals-, are considered important to regard as ethically unacceptable the use of primates.

It is true that some feel that the use of primates to supply organs for xenotransplantation would never be acceptable. Others feel that according to some circumstances it would be appropriate to reconsider the use of higher primates to supply organs for xenotransplantation. This division of opinion may reflect an ethical dilemma that is currently unresolved for many people.

3.2.1.2. The use of pigs for xenotransplantation

As discussed above, ethical concerns are raised by the use of primates for xenotransplantation. So efforts have been made to develop animals other than primates for use in xenografting. Attention has focuses in particular on the pig for several reasons. Pig organs are comparable in size and, to a lesser degree, physiology to those of human beings, and they reproduce quickly and produce large numbers of offspring. The use of pigs as a domestic animal that is farmed and eaten is long established and many would have fewer concerns about their use for xenotransplantation as compared with the use of primates.

Therefore the main alternative to using primates for xenotransplantation is to use pigs. In consequence, the moral justification for using pigs to provide organs for xenotransplantation must be considered. When considering the use of primates for xenotransplantation, the capacities they share with human beings, notably their self-awareness, led to ethical concerns about their use for xenotransplantation. While unquestionably intelligent and sociable animals, there is less evidence that pigs share capacities with human beings to the extent that primates do. As such, the adverse effects suffered by the pigs used to supply organs for xenotransplantation would not outweigh the potential benefits to human beings. In some European countries, the breeding of pigs for human use is well established. It is difficult to see how, in a society in which the breeding of pigs for food and clothing is accepted, their use for life-saving medical procedures such as xenotransplantation could be unacceptable. In this regard, it has been stated that the use of pigs for the routine supply of organs for xenotransplantation can be regarded as ethically acceptable.

However, the possibility of considering ethically acceptable the use of pigs for xenotransplantation needs to ensure that the conditions in which they are bred and reared are of the highest possible standard from the point of view of welfare, and that any pain and suffering is kept to a minimum.

On the other hand, if pigs are to be used for xenotransplantation, they are likely to have been modified so that they contain genetic material of human origin.

As has been mentioned before, preventing hyperacute rejection will be a crucial first step towards successful xenotransplantation. One promising method for achieving this is to modify the pigs genetically so that they carry human complement regulating proteins (DAF, CD59 or MCP) on the surface of their cells. These are the proteins that prevent complement being activated. The idea is that when an organ from a modified pig is transplanted into a human being, the human complement regulating proteins on the cells of the pig organ will inhibit the activation of complement. The method of modification involves introducing the human gene that produces the complement regulating protein into the pig. The process of introducing a gene into an animal is called transgenesis.

The next section discusses the ethical concerns that may arise from the use of transgenic animals for xenografting.

3.2.1.3. The use of transgenic animals for xenotransplantation

As has been said above, the essence of transgenesis is that a gene from one species is incorporated into another. The transferred gene enables the transgenic animal to produce a particular protein. The transgenic pigs bred for xenotransplantation contain a human gene which produces a complement regulating protein. This reduces the immune response to transplanted organs. It is around the transfer of genetic material that ethical concerns turn. Some see the production of transgenic animals as an unnatural act that attempts to change the nature of animals and violates species boundaries. According to this view, genes have a particular significance because they contain the information that determines the essence of any one species. To move genes around is to destroy the integrity of species as natural kinds, and to create unnatural hybrids. Within the Judaeo-Christian tradition human beings are seen as being created in the image of God which leads, for some, to a specific objection to experimentation using God-like human genes. For others such "'*mutilation' of the human body*" would be sanctioned in the interests of saving life. A number of arguments, however, suggest that the production of transgenic animals need not be viewed as a drastic or unnatural procedure.

In this regard, some consider transgenic techniques as no more than an extension of traditional breeding techniques that artificially produce new animal breeds. There is also evidence that, at a low level, the transfer of genetic material from one species to another occurs naturally. For example, genetic material may be transferred between different types of bacteria. Some would question whether there is any significant qualitative difference between this type of event and the transfer of genetic material from human beings into pigs.

Some people, however, have expressed concern about the implications of genetic modification on animals. It is true that it is necessary to overcome the significant problems of rejection that occur with cross-species transplantation of organs or tissues. Much current research is aimed at genetically modifying animals (eg pigs) with human genes so that their organs and tissues are not rejected by a human body. This may be thought to be contrary to respect for the essential characteristics and dignity of the animal species concerned as it treats animals as (re)designable systems for human use. Some people have also expressed concerns about the implications of genetic modification on animals, because it interferes with the natural processes of reproduction and evolution. A pig that is modified with human genes to minimize rejection by the human immune system may be just like any other pig, but this cannot be assumed.

In reply, it can be said that genetic modification of animals is not a new technique specific for xenotransplantation but has been used as an important tool in scientific research. As a general rule, if the genetic manipulation does not inflict any unnecessary suffering upon the modified animal or interfere with its ability to lead a normal life, such modification has been considered to be acceptable.

In response to the issue of 'naturalness', the consensus reached by several overseas reviews (eg United States, United Kingdom, Canada, the Organization for Economic Cooperation and Development) is that the insertion of human genes (consisting of minute amounts of DNA) into a pig chromosome does not significantly change the essential characteristics or welfare of the pig. However, it is agreed that this position may need ongoing monitoring and review, depending on the extent of the genetic manipulation that is required.

On the other hand, it can be questioned whether genes of human origin represent particular elements of essential humanity. It is only in combination with all the other genes that make up the human genome that a particular gene contributes to the specification of features characteristic of the human species. Considered in isolation, therefore, there is nothing specifically human about a gene that has been obtained from a human source. Similarly, genes obtained from an animal species do not have to be seen as representing a particular element of that animal. If this view is adopted, the transfer of a gene from one species to another is far less significant. In addition, because of the technology involved, the genetic material actually transferred to a transgenic animal is almost certain to be a copy of the gene rather than the original gene that was obtained from the organism.

In addition, many transgenic animals are modified on a very small scale and in a very specific way. Consider the production of transgenic pigs to supply organs for xenotransplantation. At present, it is unlikely that more than one or two genes of human origin will be incorporated into transgenic pigs. It is also important to take into account that the human genes contain information that will make only a very minor and specific alteration to the surface antigens of the pig's cells. The physical appearance and characteristics of the pig will not change in any measurable sense. Will the nature of the pig change in any way that is ethically important? For the reasons set out above, it is not possible to consider that the introduction of very small numbers of human genes into transgenic pigs makes the pigs in any sense human or creates a hybrid species.

With regard to these arguments, two main issues relating to proper respect for human beings are considered: crossing the species barrier, this goes against a deep-stated taboo in human culture[28]; and potential loss of identity of the human recipient, including possible psychological problems and feelings that he or she is somehow less human.

With regard to the first issue, it has been said that xenotransplantation ignores a deep-seated taboo in many human cultures against crossing the species barrier between animals and humans. This taboo was a common theme in ancient mythology, which is full of stories of strange hybrids of human beings and animals and warnings against bestiality. It is also said that in hybridising animals with human beings, xenotransplantation would violate the reverence and respect due to human beings. Such a strongly felt and deep-seated taboo should not be dismissed as a worthless remnant of a primitive belief system.

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In reply, it may be argued that, as long as xenotransplantation does not impair the essential psychological or genetic identity of the human being receiving the transplant (and as long as it can be shown to be safe as well as clinically efficacious), these concerns can be met.

With regard to the second issue, it is said that xenotransplantation may confuse personal identity. Allotransplant recipients sometimes suffer psychological problems, including loss of identity, and fear that they might take on aspects of the donor's personality, sexuality or other life experiences. Such feelings could be worse for xenotransplant recipients, who may feel they are somehow less human than before.

In reply, it may be argued that such 'identity' problems could be managed in the ways in which they are currently managed in allotransplantation programs (e.g. identified as potential psychological consequences of the treatment ad addressed as a part of the process of obtaining genuinely informed and unforced consent with the appropriate medical counselling)

On the other hand, it is said that organ transfer should not be regarded as the trading of consumable goods or even the exchange of community resources. On this view, to be morally acceptable, transplantation between one individual and another should be genuinely an altruistic gift or at least should involve some relationship of solidarity between the individual whose body is the source of the organ and the individual who is the recipient of the organ. This "shared life" model of organ transfer implies that xenotransplantation is unacceptable because it cannot involve either genuine gift-giving or a relationship of compassion and solidarity between the giver and receiver.

In summary, inserting small quantities of genetic material of human origin is not thought to make an animal in any sense human. For many people, genetic modification would be acceptable if it would depend on whether it was intended to preserve or enhance human life. By this criterion the production of transgenic pigs to provide organs for xenotransplantation would be acceptable.

In the light of the arguments aforementioned, it is possible to conclude that the use of transgenic pigs that have been genetically modified to reduce the human immune response to pig organs is ethically acceptable. As with any use of animals for medical purposes, it is important that the welfare of transgenic animals is not unacceptably compromised. This is of particular concern in the context of transgenesis because some of the transgenic animals produced to date have suffered from ill effects. One example is the introduction of growth genes into pigs in order to make them grow faster for food production. The animals suffered from a variety of conditions such as arthritis, ulcers and diabetes. There is no evidence to date that the welfare of transgenic pigs developed for xenotransplantation is adversely affected. It is important, however, to be vigilant in assessing the effects of transgenesis on animal welfare.

3.2.1.4. The care of transgenic pigs

As has been seen, treating animals as a resource for organs and tissue for human beings may be morally unacceptable to some people. However, for the most part, the use of animals by humans is an accepted ethical practice in our society as long as it is done with due regard for the welfare of the animals.

In this regard, proposed protocols will need to be tested in preclinical (animal-to-animal) studies before clinical (animal-to-human) trials of xenotransplantation. Animal-to-animal studies will use nonhuman primates as the xenotransplant recipients, and genetically modified (GM) pigs as source animals. GM pigs will also be the source

animals for most animal-to-human trials, although other species may be involved for some cellular transplant procedures.

Since producing transgenic pigs is a scientific procedure, which may have the effect of causing pain, suffering, distress or lasting harm to animals, it must be monitored and regulated. In this regard, it is necessary the evidence that the transgene or factors associated with transgenesis have no significant effect on the animal's welfare. There are two main ways in which the welfare of transgenic animals may be affected. First, the transgene itself may have a harmful effect on the animal. An example of this would be the harmful effects of genes used to make transgenic animals grow faster. Second, the transgene may cause a harmful mutation when it is inserted into the genetic material of the animal.

There are general criteria for assessing the welfare of these animals, but not specific criteria. Some of the key principles for promoting the wellbeing of these animals, and the animals in general, and the quality of scientific outcomes, make reference to the principles of Replacement, Reduction and Refinement (known as the 3Rs) aim to reduce the impact of scientific activities on animal wellbeing. Underlying these key principles is strong scientific evidence that animals experience pain and distress in a manner similar to humans; decisions regarding an animal's wellbeing must be based on this premise. The 3Rs are defined as follows:

• **Replacement**—if a viable alternative method exists that would partly or wholly replace the use of animals in a project; this require from investigators to use that alternative. Examples of alternative methods include in vitro techniques and computer models.

• **Reduction**—a project must be designed to use no more than the minimum number of animals necessary to ensure scientific and statistical validity. However, the principle of reducing the number of animals used should not be implemented at the expense of greater pain and distress for individual animals.

• **Refinement**—Studies must be designed to avoid or minimize both pain and distress in animals, consistent with the scientific objective. Investigators must also be competent in the procedures they perform. Project design must take into account:

– The choice of animals, their housing, management and care and their acclimatization
– The choice of techniques and procedures
– The appropriate use of sedatives, tranquillizers, analgesics and anaesthetics
– The choice of appropriate measures for assessing pain and distress
– The establishment of early intervention points and humane endpoints
– Adequate monitoring of the animals
– Appropriate use of pilot studies.

Other key principles in addition to the 3Rs include Justification and Responsibility:

• **Justification**—projects require using animals to be performed only after they are justified, weighing the predicted scientific or educational value of the project against the potential effects on the wellbeing of the animals. Thus, the justification must take into account all aspects of the project that may have an adverse impact on the animals.

• **Responsibility**—it states that investigators who use animals for scientific purposes have personal responsibility for all matters relating to the wellbeing of the animals. They have an obligation to treat the animals with respect and to consider their wellbeing as an essential factor when planning or conducting projects. To meet these responsibilities, it is essential that investigators are knowledgeable about all factors associated with the project that may affect the wellbeing of the animals they use,

mechanisms to minimize these effects, the monitoring and assessment of adverse effects on animal wellbeing, and appropriate actions to take if adverse effects are observed.

When considering specifically the welfare of pig used to provide organs or tissue for xenotransplantation, it is necessary to consider the implications of the need to breed animals that, as far as possible, are free from infectious organisms. This is important in order to reduce the risk of infectious diseases of animals passing into the human population. Clearly, it will be important to produce animals that are in good health and, in this respect, they will undoubtedly be taken good care of. But there may be specific procedures that will adversely affect the welfare of the animals. For instance, some procedures for breeding animals free from infectious organisms involve delivery by Caesarean section, after which the animals are reared in 'isolators': incubators that isolate the animal and reduce the chance of infection. This would certainly have adverse effects on animal welfare. An argument against such practice is that monitoring for infectious organisms may be best carried out if animals are kept in small groups. This would allow the rigorous testing of sentinel animals that have been reared with the animals from which organs and tissue will be removed.

Even if isolation is not required, in order to keep animals free from infection, the environment will have to be kept relatively sterile and therefore be easy to clean. So it is likely to consist of monotonous textures and to be free of items which might enrich the life for the animal, but which might also harbour infectious organisms. Human contact, which can be advantageous for animals in captivity, may have to be minimized since human beings harbour some diseases that can be passed on to pigs.

Monitoring the genetic composition of animals and screening them to make sure they are free of infectious organisms will require regular blood sampling and tissue biopsy. Invasive tests may also be required to ensure the organs and tissue to be removed is functioning properly. Even blood sampling can be quite stressful to an animal not used to such procedures. The major stress factors are the need for restraint, which may be physical and/or drug-induced, the process of removal to operating areas and the need for recovery if anesthesia has been used. Some species can be trained for such procedures, but with pigs it is not so easy because of their size and resistance to restraint.

The need to produce animals free from infectious organisms may lead to sensory deprivation and militate against good welfare. Given some forethought, the problems are not insurmountable. Every effort must be made to reduce stress to a minimum. When decisions are made about the acceptability of using animals for xenotransplantation, particular attention is paid to reducing the adverse effects associated with the need to produce animals free from infectious organisms. In this regard, it is also very important the role that animal ethics committees can be developed.

3.2.1.5. The role of animal ethics committees (AEC)

AEC in individual institutions are responsible for considering proposals for research using animals, and giving approval before any research can proceed. Membership of AEC should include at least one individual from the following categories: veterinarian, researcher, layperson and a person with a demonstrated commitment to animal welfare. The person in the last category is required to put aside their personal philosophies, which may oppose the use of animals for research purposes, in order to participate in a system that will assist in improving the welfare of experimental animals.

Much of the decision making by AECs involves weighing up the benefits to animals or humans of a proposed protocol, and the "costs" in terms of the welfare, essential characteristics of the experimental animals involved. Although it may present some particular challenges, the consideration of xenotransplantation protocols is similar to consideration of any other new protocol.

Before the proposed research can be approved, each case requires careful scrutiny through the AEC process to ensure that the animals involved as either donors or recipients of xenotransplants are not subjected to unacceptable conditions.

Concerning the genetic modification of animals, it can be said that, for many years now, AECs have been considering applications based on this issue. This experimental approach is particularly widespread for mice and is increasing for production animals in agriculture. The potential impact of individual changes is considered on a case-by-case basis.

The insertion of one or two human genes into a pig genome to minimise rejection by the human immune system is unlikely to alter the animal in a significant way. However, the nature and extent of genetic modification will need to be assessed on a case-by-case basis to ensure that the animals retain the essential characteristics and dignity of their species.

Overall, AECs will need to be cautious in approving genetic modification of animals for xenotransplantation, to instigate a rigorous monitoring program and to learn from their early experiences of xenotransplantation technology — as they have done with emerging biotechnology in the past.

With regard to other issues in general, it is very important to maintain the highest standard of welfare for those animals used in xenotransplantation research. Institutions involved in research with animals must have facilities that comply, for instance, with appropriately trained staff.

Animals used in preclinical studies have to be held in special colonies at an appropriate level of containment, housed in appropriate family groups that meet all of their special social and behavioural needs.

Pigs to be used as the source animal for animal-to-animal or animal-to-human xenotransplantation research must also be handled, housed and used with appropriate containment facilities, housing and care.

AECs must also consider the possible importation or exportation of xenotransplantation products. It should be reviewed that the animals to supply xenotransplantation products are healthy and that they are housed under high standards of animal welfare.

In conclusion, and based on the aforementioned considerations, the investigators and sponsors of a proposed trial will be required to submit information addressing animal welfare issues as part of a comprehensive submission for assessment by the relevant regulatory authority, the AEC and the human research ethics committee at any institution where the research will be carried out.

With regard to the expertise required considering ethical issues relating to animal research protocols, what is necessary to assess the issues raised in this section? The regulatory authority responsible for approving animal-to-human (clinical) trial proposals will need to include members with expertise in the following areas:

• Ethical, regulatory and legal issues relating to the use of animals in research;
• Veterinary considerations and animal husbandry; and
• Animal welfare concerns.

3.2.2. Some principles for the ethical of xenotransplantation research involving animals

According to the aforementioned arguments, it is possible to take these principles into account:

• The research must be justified in terms of establishing information relevant to the understanding of humans or animals, and after weighing the potential effects on the welfare of the animals.

• Researchers must treat animals with respect and consider their welfare as an essential factor when planning and conducting experiments.

• Animals must be used only when it is essential to do so and in the smallest numbers possible. In this regard, it is important to take the principle of three Rs into account.

• Procedures must minimize the impact on the animals.

Protocols for all experiments with animals must be referred to institutional AEC for approval. Much of the decision making of AEC depends on weighing up the benefits (to animals or humans) and the risks (to experimental animals) of a particular protocol. Xenotransplantation presents some particular challenges; each proposal will require AEC study before the proposed research is approved.

In summary, and based on the these considerations, several principles have been identified before xenotransplantation research involving animals is allowed to proceed.

- The research must serve the public interests;
- The research must respect the welfare of animals used;
- The research must be scientifically well-founded;
- The benefits for humans must justify the use of animals;

In addition, the genetic modification of animals for use as the source of xenotransplantation products raises ethical issues. However, AECs already have guidelines for genetic modification and appropriate animal welfare in respect of other research and treat each proposal on a case-by-case basis. As long as the degree or type of modification does not interfere significantly with the overall characteristics of the animal species, it is not considered ethically unacceptable.

3.3. The Costs and Benefits for Individuals and Society

3.3.1. The risk of animal disease spreading from xenograft recipients into the general population

3.3.1.1. Risks, benefits and consequences

Xenotransplantation is unusual among medical procedures because it carries risks for the wider community as well as for the individual patient. The major concern for public health is that viruses from animal xenotransplantation products may infect human transplant recipients. Retroviruses or other unknown, probably latent, viruses are the main concerns. Such viruses may initially show no obvious signs of disease and may spread beyond the recipient into the general population, giving rise to an **epidemic** that only becomes obvious when others have been infected. Therefore, in addition to risks for the *xenotransplant recipient*, there are potential health risks for *close contacts*, *carers* and the *general public*. Such risks must be assessed and weighed against the potential benefits of xenotransplantation, and options considered for their management.

One of the missions of regulators and ethics committees, in consultation with the community, is to determine the “acceptability” of the risks. Acceptability of a risk relates to a number of factors, including:

- The level of risk (how likely is to happen);
- The severity of the adverse effect if it occurs (consequences);

- The benefits that result from the activity associated with the risk.

In the case of xenotransplantation, risks must be assessed at two levels:

1. As for all other medical interventions, the procedures must be sufficiently efficacious and safe to do more good than harm to individual patients. This is related to the central **ethical principal of beneficence**;

2. Xenotransplantation presents a much broader issue of public health/community safety because of the possibility of *human xenozoonosis*, in which a novel infectious agent transfers from the animal donor to the human recipient and then spreads to close contacts, health care workers and the general population. Experiences with other human xenozoonoses such as HIV/AIDS make this prospect the cause of considerable concern.

3.3.1.2. Risk analysis

In recent times, there has been increasing community concern about a range of public health hazards. Consequently, a framework has been developed to *assess* and *communicate* risks and to find *risk management strategies* to minimise risks. In other words, the usual framework for assessment of public health risks is risk analysis, including risk assessment, communication and management.

• Assessment of the potential risk based on all the current scientific evidence available (*risk assessment*). This factor is the scientific evaluation of known or potential adverse health effects that may result from exposure to a hazard[29]. It included hazard identification (What will it do to us?); hazard characterisation (how likely is it and how bad will it be?);

• Communication with the community about the acceptability of the risk identified compared with the benefits derived from the procedure (*risk communication*). Therefore, this is the exchange of information and opinion that must occur among risk assessors, risk managers and all stakeholders (including the general public) in the decision process;

• Management of the risk to maintain the acceptable level (*risk management*). Risk management is the process of weighing policy alternatives to accept, minimise or reduce assessed risks and to select and implement appropriate procedures.

3.3.1.3. General infection risks

Human xenotransplantation procedures are likely to be associated with the same wide range of viral, bacterial and other infections that are associated with allotransplantation and its accompanying immunosuppressive drug therapy.

Public health concerns about the risks of xenotransplantation relate to the possibility that novel infectious agents (most likely latent viruses such as retroviruses) or known animal pathogens may be transmitted from the xenotransplant source to the transplant recipient, causing the emergence of a novel and potentially untreatable human infection.

Such an infection may then be transmitted from an infected xenotransplant recipient to their *close contacts* and subsequently to the *wider community*. The continued emergence of new viral diseases, evidence of the rapid spread of new agents and increased understanding of the pathogenesis of current human pathogens, means that these concerns are justified, although difficult to quantify.

[29] Hazard is a biological, chemical or physical agent that may have an adverse health effect. The risk is the probability of an agent (a hazard) causing an adverse effect and the magnitude of that effect (expressions of risk can be quantitative or qualitative, and should include consideration of uncertainties).

There are many examples of cross-species transmission of infectious agents where the clinical illness and mode of transmission alter in the new host. Xenozoonotic viruses are potentially dangerous, because they may not be diagnosed with current tests and, by definition, their pathogenic behaviour is unknown.

3.3.1.4. Assessing and managing xenotransplantation infection risks

There have been many examples of cross-species transmission of infectious agents. In some cases the disease profile and mode of transmission have altered in the new host (eg HIV/AIDS). Because of the close relationship between human and nonhuman primates, and the existence of known infectious agents, nonhuman primate, as has been said, are no longer considered as the source for animal-to-human transplants. Pigs are considered to be the most suitable source animals for human xenotransplantation products.

A number of zoonotic infections have been transmitted from pigs to humans but it should be possible to control these infections by appropriate group management and laboratory testing. Concern has centred on endogenous retroviruses, which usually remain latent in their host tissues but can sometimes be activated by an external stimulus. Porcine endogenous retrovirus (PERV) has been shown to infect human cells in culture. This has caused concern that there is an unknown risk that this virus may be activated in xenotransplant recipients, causing clinical infection that could spread to others in the community.

Factors that may affect the risk of infection include source animal husbandry and how the xenotransplantation product is produced; the type of xenotransplant, its placement and immunosuppression of the patient; and the infection control procedures used. Further procedures for the management of infection risks include screening and monitoring of recipients and contacts for infectious agents, collection and storage of tissue samples and maintenance of a *national register*.

In order to assess the public health risks associated with PERV, several issues have been considered by several regulatory authorities and in particular by the United States Public Health Service. After an evaluation of the risks and public consultation that organization provided some steps so as to limit the infectious risk to the community. Basically, this was to be achieved by a combination of informed consent, preclinical screening and patient surveillance. It was felt that the implementation of these measures would reduce the risk to the community to a level that was acceptable to health authorities and the community at large. It has been proposed that clinical trials of pig xenotransplantation products could proceed provided there were:

• Sensitive and specific assays for the preclinical detection of infectious PERV in pig xenotransplantation products;

• Appropriate post-xenotransplantation screening for PERV and appropriate clinical follow-up of xenotransplant recipients; and

• The development of informed consent documents that indicated the potential clinical implications of the capacity of PERV to infect human cells in vitro.

It was felt by several of the experts involved with these recommendations that because these exposures occur under controlled circumstances, measures can be implemented to minimise the risk of xenotransplantation-associated infections. It is expected that xenotransplantation patients and their contacts will be monitored more closely than the average allotransplantation patient or the general population. Close monitoring of recipients should enable early identification of adverse outcomes, allowing for intensive efforts both to control infections that may occur and to prevent additional procedures that may result in new infections.

3.3.1.5. Possible strategies to manage the potential risks of infection

Factors that affect the risk of infection include the conditions under which source animals are reared, how the xenotransplantation product is produced, what health care infection control procedures are used during and after the procedure, the type of procedure involved, and the level of immunosuppression of the patient. These issues all need to be taken into account in assessing potential for exposure to infection, and documented procedures that address these issues need to be submitted by any investigator undertaking xenotransplant trials.

New strategies have been proposed that may further limit the infectious risk. These include using xenotransplant products from a herd of pigs that does not express or secrete PERV, elimination of infectious PERV through cloning and gene deletion technology, and vaccination of patients.

A. Source animal husbandry and production of xenotransplantation products

Just as strict safety standards are applied to the preparation of blood and blood products, good manufacturing practice principles will need to be applied to xenotransplant products to minimise infection risks. They should specifically include documented procedures to detect potential infectious agents, the maintenance of pedigreed source animals in specific pathogen free environments, assessment of personnel who manage the animals and prepare the xenotransplant products, assessment of safeguards for the transport of animals and/or xenotransplant products, and continued monitoring for infectious agents.

B. Placement of the xenotransplant and immunosuppression of the patient

The placement of the xenotransplant (e.g. into brain, blood, kidney), or the presence of physical barriers between human and animal cells, may affect the possible emergence of a xenozoonosis and its presentation.

C. Screening and monitoring of infectious agents

Post-xenotransplantation clinical and laboratory surveillance is essential. Transplant recipients should be evaluated for life for transplant-related adverse events. Effective diagnostic facilities must be available for all transplanted patients. Laboratories undertaking recipient xenozoonoses testing should perform at the same level as pathology laboratories approved by the corresponding authorities. This includes documentation of the sensitivity and specificity of the assay in the testing laboratory, testing procedures, the use of appropriate controls, and the recording and storage of samples and test results.

Transplant recipients must be monitored for unexplained illnesses and clustering of illnesses and the results must be reported to the *human research ethics committee* at the institution where the research is carried out and to the national body responsible for overseeing xenotransplantation research. Researchers will need to prepare a protocol for screening and monitoring the transplant recipient (including timing of sample collection) so that any transmission of infection is immediately detected.

In order to maximise the chance of early detection, the most sensitive test available for the infectious agent of concern must be performed. In addition to testing for specific pathogens such as PERV, assays that can detect a broad range of infectious agents will need to be considered.

Relevant animal handlers, health care workers and intimate contacts of the transplant recipient should also be screened, or have blood collected for storage. There must be documented protocols to deal with accidental parenteral exposure by health care workers and intimate contacts of the transplant recipients.

D. Infection control procedures

Due to the infection risks associated with xenotransplantation, guidelines for the assessment and approval of proposed animal-to-human trials must include a requirement for appropriate infection control and public health measures. A xenotransplantation program must include a large number of specialists, from areas such as clinical infectious diseases, clinical virology, medical epidemiology and high-level laboratory support.

Observance to current hospital infection control measures, such as standard and additional precautions, will reduce transmission of possible xenozoonoses.

There should be a procedure for handling a possible transmission of PERV, or other infection, to the transplant recipient, both in and outside the hospital. This should include management of the patient (including isolation), their family and intimate contacts, and health care or laboratory workers. Such precautions will depend on the nature of the transplant and the type of clinical illness, and would be guided by the infection control specialists that advise the investigators. Any suspected xenozoonoses should be reported to the national register and the infectious diseases branch of the local State or Territory department of health. Animal and human health records will need to be stored for the same length of time as tissue samples.

Appropriate designs for infection control support and source animal and recipient testing (including storage) for xenotransplantation programs have been outlined in various published guidelines.

E. Storage of tissue samples

Blood sera, leukocytes, tissue biopsies and transplant samples need to be collected before (baseline) and after xenotransplantation procedures, recorded and appropriately and stored for a prolonged period (a minimum of 50 years has been suggested by the United States Department of Health and Human Services to allow retrospective examination for xenozoonoses. Protocols will also need to include procedures for storage of tissue and other samples in the event of an infection or unexplained illness. Such samples need to be linked to the animal and human health records.

F. National register

All xenotransplant recipients must be recorded on a national xenotransplant register and their information updated regularly, as determined by the national body that will oversee xenotransplant trials.

3.3.1.6. Proposed risk analysis framework

As has been noted, a cost-benefit assessment of the potential impact of xenotransplantation on humans must consider the negative ramifications of the practice on participants in xenotransplantation trial, their immediate contacts, healthcare professionals involved in the treatment and indeed the global human community. However, the unproven nature of xenotransplantation means that if clinical trials proceed, individuals would be opting for treatments of unknown value. In fact it is likely that in any early trials that take place the transplants will fail; if the treatment in question is the transplant of a whole organ then it is also likely that the patient will die. Of course, for those with end stage organ failure this will be their fate in the immediate future in any event. In the case of cellular grafts, it is nonetheless unlikely the patient’s condition will improve in the long term. On the other hand, another possibility which receives much attention is that animal diseases may be transferred to patients, their contacts (including healthcare professionals) and the wider community. Cellular therapies, not only whole organ transplants, may carry a risk. It is of relevance for an

assessment of the harms that the procedures may cause that many zoonoses are particularly burdensome diseases.

Certainly, xenotransplantation of animal organs and tissue carries with it the potential risk that diseases will be transmitted from animals to xenograft recipients and to the wider human population. It is difficult, as has been seen, to assess this risk, since it is impossible to predict whether infectious organisms that are harmless in their animal host will cause disease in human xenograft recipients or whether the disease will spread into the wider human population. There are certain to be infectious organisms of both primates and pigs that are currently unknown, and some of these might cause disease in human beings. There is evidence that infectious organisms of primates, notably viruses, can pass into the human population and cause disease. This is one of the reasons which support the recommendation that non-primate species should be regarded as the source animals of choice for xenotransplantation. The possible risk of disease transmission from pigs, however, also requires careful consideration. As mentioned above, pigs contain endogenous retroviruses and studies are needed to assess whether they can infect human cells. Since they have shorter generation time than primates, breeding pigs free of known viruses should prove more feasible. Pigs, however, will also contain viruses and other infectious organisms that have not yet been identified. Moreover, at least initially, recipients of pig xenografts might require high levels of immunosuppression which would render them very susceptible to infections. However, the hope is that, eventually, relatively low levels of immunosuppression could be used if organs are taken from transgenic pigs that have been genetically modified to reduce the immune response after transplantation.

It is not possible to predict or quantify the risk that xenotransplantation will result in the emergence of new human diseases. But in the worst case, the consequences could be far-reaching and difficult to control. The **principle of precaution** requires that action is taken to avoid risks in advance of certainty about their nature. It suggests that the burden of proof should lie with those developing the technology to demonstrate that it will not cause serious harm. In this regard, the risks associated with possible transmission of infectious diseases as a consequence of xenotransplantation have not been adequately dealt with. It would not be ethical therefore to begin clinical trials of xenotransplantation involving human beings.

With regard to the aforementioned principle of precaution, this offers an alternative method of risk analysis and assessment. This has been developed within the field of environmental policy and applied to the control of pollution and the release of genetically modified organisms. The principle of precaution requires that action should be taken to avoid risks in advance of certainty about their nature. This challenges the view that, until there is evidence that a new technology is harmful, it is acceptable to proceed with its development. It suggests that the burden of proof should lie with those developing the technology to demonstrate that it will not cause serious harm.

An implication of the principle of precaution is that the development of some technologies simply should not be pursued. Since any innovation must by definition carry some unknowable risks, however, it would be unacceptably conservative to restrict innovation merely by appeal to the possibility of risk. For each technology, an attempt must be made to identify and define the risks and to decide on a course of action. It may be that, for some technologies, the principle of precaution would argue that they should not be pursued. For others, it will be possible to identify safeguards that will reduce the risks of the technology.

What are the implications of the principle of precaution when applied to the uncertainties associated with disease transmission via xenotransplantation? The discussion above has set out the potential risk from infectious organisms of animals and highlighted the difficulties in identifying these organisms, determining whether they will cause disease in human beings and predicting whether the diseases will spread to the wider population. In order to address the risks of disease transmission associated with xenotransplantation, it has been also suggested that the following measures should be taken:

- Strict efforts should be made to gather as much information as possible about the risks of disease transmission before further xenotransplantation goes ahead. This would involve reviewing existing research and undertaking new research where necessary on the infectious organisms of primates and pigs and the possibility of transmission of disease to human beings. Therefore, reliable and accurate methods for identifying potentially dangerous infectious organisms in both source animals and human recipients should be in place before clinical xenotransplantation trials are undertaken;
- Xenotransplantation should use only source animals reared in conditions in which all known infectious organisms are monitored and controlled. It is ethically unacceptable to use source organs from animals that are known to be infected with infectious organisms that can be eliminated. Investigators are required to exclude from source animals all the pathogens listed in the specific codes of practices in this regard. Mechanisms should be in place to allow the list of organisms to be updated in the light of experience. These codes of practices should recommend the diagnostic tests to be performed by accredited test centers. In this regard, there should be specific and regulatory mechanism to cover the safety and quality of animal organs and tissue for xenotransplantation.
- There should be thorough monitoring of early recipients, with regular testing for signs and symptoms of disease. In this regard, standards and mechanisms for monitoring xenograft recipients and for the action to be taken in case of disease transmission should be in place before human trials begin. It should be a requirement of clinical trials that the need for monitoring is explained to the patient and that it is made clear that consent to the operation also implies consent to subsequent monitoring. This question will be seeing in the next section in more detail.
- There should be a commitment to suspend, modify or, if necessary, discontinue xenotransplantation procedures at any signs that new infectious diseases are emerging.

Since the possible consequences of developing xenotransplantation are potentially very serious, the principle of precaution should apply. This requires, as has been said, that action is taken to avoid risks in advance of certainty about their nature. To arrive at the necessary consensus about good practice, and the mechanisms to ensure that such good practice is adhered to, a body of expertise, of authority and of independence from the research teams at work on xenotransplantation is required.

Finally, it is necessary to mention, based on the aforementioned considerations, that the researcher and sponsors of a proposed trial in this field will be required to submit data on risk analysis as part of a comprehensive submission for assessment by the relevant regulatory authority and the institution(s) where the research will be carried out. This information will be used to determine if the proposed xenotransplantation procedure presents an acceptable risk to the community.

The major concern is with PERVs that have the potential to infect the recipient and the community at large. However, other infectious disease issues also need consideration. At a minimum, animals need to be monitored for their burden of viral and bacterial pathogens.

Another question that should be taken into account is referred to the expert advice required to assess infectious disease safety. In order to assess the issues raised in this section, the regulatory authority responsible for approving animal-to-human (clinical) trial proposals will need to include members with expertise in infectious diseases (animal and human), in order to assess the safety of the proposed procedures, particularly in relation to the risk of transfer of infectious diseases.

A person with experience of public health issues (preferably with experience of risk assessment) would also be required.

3.3.2. Monitoring and surveillance of early patients of xenografts

As mentioned above, there is a need for thorough monitoring and surveillance of early recipients of xenografts. But, what level of monitoring and follow-up would ensure that any signs of infectious disease are picked up early, but at the same time would not constitute too much of an imposition? It is possible to highlight a number of important features of any follow-up. Regular physical examinations with archiving of serum and, where appropriate, tissue samples should continue throughout the lifetime of the recipient. Serum samples taken from health care workers caring for the xenograft recipients should also be archived. The recipient should be required to report any serious unexplained illness. Close contacts, that is, family members, household members, sexual contacts and others with whom bodily fluids may be shared, should also be encouraged to report unexplained illnesses. Recipients should be asked to agree to an autopsy on their death. In addition, xenograft recipients should be asked to take routine precautions to minimize the transmission of any infectious disease. They should not donate blood, tissue or organs. They should be counseled on methods of minimizing the transmission of diseases, for example, by sexual contact.

One of the most difficult questions is what procedures should be followed if it is found that a disease has indeed been transmitted from the animals used to provide organs or tissue to human xenograft recipients? In principle, steps should be taken to prevent transmission of the disease to other people. In practice, this is a very difficult issue. The appropriate response will depend on the mode of transmission and on how infectious the disease is. It would hardly be acceptable to isolate xenograft recipients suffering from an infectious disease, or to ask them to refrain from sexual intercourse or, in the case of a virus transmitted from parent to offspring, from having children. This highlights how difficult it would be to prevent the transmission of an infectious disease originating from xenotransplantation. It is sobering to reflect on the difficulty, despite globally coordinated attempts, of controlling and eliminating infectious diseases such as malaria, hepatitis and AIDS. This demonstrates the importance of taking steps to reduce as far as possible the risk that a new disease will emerge before trials involving human beings take place. For these reasons, standards and mechanisms for monitoring xenograft recipients and for the action to be taken in case of disease transmission should be in place before human trials begin. It should be a requirement of clinical trials that the need of monitoring is explained to the patient and that it is made clear that consent to the operation also implies consent to subsequent monitoring.

In order to facilitate the recording and analysis of information concerning possible disease transmission, it is necessary to record all information concerning

individual xenograft recipients in a xenotransplantation register maintained by an independent body. Suitably anonymised data should be reviewed for evidence of the possible emergence of new diseases. Since, initially, xenograft recipients are likely to be few, and to be spread across several countries, international co-operation should take place to enable effective review of all the available evidence.

The requirement for surveillance and monitoring is endorsed by the major international statements on xenotransplantation[30].

The public health risk associated with xenotransplantation is of such concern that xenotransplantation is usually an issue regulated at an international and national level, rather than one delegated to local or regional forums. In this regard, there are international proposals to minimize the risks associated with xenotransplantation[31]. Despite the importance of such centralized initiatives, their success will ultimately rely on individuals adhering to national and international policy recommendations; a conclusion which is supported by the suggestion of the OECD/WHO that a xenotransplantation surveillance system should operate via a co-operative network at local, "intermediate", country-wide and international levels.

All this suggests that an ethical framework which is based on a commitment to protect the health of the community can, under certain circumstances, allow restrictions to be placed on individual freedoms to safeguard the well-being of the wider community. This point is borne out by the fact that public health law is able to restrict the behaviour of individuals with infectious diseases, or of those with communicable diseases who are thought to pose a risk to the general public.

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[30] Article 13 of the Council of Europe Recommendation (2003) 10 read as follows: "1. Patients participating in a xenotransplantation should be adequately informed in a comprehensible manner of the nature, objectives, possible benefits, potential risks and consequences of the procedure, as well as of any constraints that may be linked to it.

2. In particular patients should also be made aware of the constraints of monitoring and precautionary measures that may become necessary subsequent to xenotransplantation. Such measures will, according to the principles of necessity and proportionality, be adapted to the circumstances and adjusted in accordance with the assessment, based on current scientific and medical knowledge, of the risks generated by each of the procedures involved, and may in particular include:

a. the collection of personal data and inclusion in a register;

b. the provision by the medical team, in accordance with Article 14, of information concerning the risks of infection and the constraints associated thereto;

c. long-term medical monitoring including repeated biological samples being taken and archived;

d. reporting any significant unexplained symptoms or illness that may arise after the xenotransplantation;

e. maintaining contact with the medical team;

f. taking precautions with respect to sexual activity;

g. the need for the patient to agree that information is provided by a medical team to any future close personal contacts, in accordance with Article 14, concerning the risks of infection and the constraints associated thereto;

h. the other constraints which might be applicable if circumstances so require, in particular the possibility of isolation which may become necessary in the event of a contagious or previously unknown illness occurring.

3. Patients should be informed that, in accordance with Article 21, constraints mentioned hereinabove may be imposed if the person concerned refuses to comply with them".

[31] World Health Organization (2001), WHO Guidance on Xenogeneic Infection /Disease Surveillance and Response: A Strategy for International Cooperation and Coordination, WHO: Geneva; WHO (2003), Human Organ and Tissue Transplantation, Report by the Secretariat, 27 November, EB113/14; OECD (1999), Xenotransplantation: International Policy Issues, OECD: Paris; OECD/WHO (2001), OECD/WHO Consultation on Xenotransplantation Surveillance: Summary Report, October, OECD/WHO: Paris; European Commission (2001), Opinion on the State of the Art Concerning Xenotransplantation, European Commission: Brussels.

In this regard, it would be easy to assume that an ethical framework which prioritizes public health would inevitably agree with the strict requirements of xenotransplantation surveillance programmes, but this is not necessarily the case. In fact, there are a number of reasons why the restrictions that may be placed on xenotransplantation recipients and their close contacts are unsatisfactory from the perspective of a public health ethic. Firstly, there is a logical concern as to whether the restrictions on individual liberty would actually prevent the spread of an infectious disease. At a practical level, for instance, it seems most unlikely that it would be possible to prevent individuals who regained their health following a transplant of animal tissue from having children, or to ensure that they informed all of their future sexual partners of their xenotransplantation status. This being so, it is unclear that it would be possible to protect public health by adopting such surveillance requirements; or in the very least, that trying to do so could create a false sense of security and inadvertently jeopardize public health.

Secondly, many proposed xenotransplantation surveillance frameworks aim to side-step concerns that the measures they recommend to protect public health are too restrictive or coercive, by emphasizing the importance of patients consenting to treatment and any monitoring requirements in advance of their surgery. As the Council of Europe emphasizes, the ability of an individual to consent means that it "is ethically permissible for patients to choose to set aside such human rights as the right to begin a family or the freedom to donate blood". But the Council of Europe also states that: "the risks of xenotransplantation are considered potentially so significant that informed consent should usually be obtained from close contacts such as relatives and family. It is hard to see how such people are able to freely give consent…"

Indeed, the value of consent in the context of xenotransplantation is questionable for a number of reasons. For instance, as the following section will see in more detail, it is difficult to regard the consent of critically ill individuals who are desperate for treatment as being freely given, making it difficult to ensure that consent is legitimate. In addition, the legitimacy of consent also risks being undermined by the likelihood that xenotransplantation recipients will not retain the usual right to withdraw from surveillance programmes. Thus, it seems likely that the fact that individuals who participate in xenotransplantation procedures will be required to consent to surveillance procedures will not prevent such requirements from being coercive.

According to the aforementioned arguments, xenotransplantation raises, for example, these questions: at what stage will it be ethical to progress from using animals as xenograft recipients to the first clinical trials involving human recipients xenografts?; how can the welfare of the first patients to undergo xenotransplantation be protected? If it is ethical in principle for them to be offered xenotransplantation as an experimental treatment, what safeguards are needed to ensure that their consent to participation is given freely and with adequate understanding of what will be involved?

3.4. Information sharing and consent

Before any research involving humans is undertaken, the consent of the research participants must be obtained. Ordinarily, for clinical trials, are the individuals who receive the procedure or treatment who are asked to consent to the procedure because they are who will bear the burdens and risks of participation. In the case of xenotransplantation, others will also bear some of the risk, because a virus transmitted to a trial participant may be subsequently transmitted to their immediate contacts (e.g. their health care providers, their family and other intimates).

Therefore, the question arises as to whether these contacts, who may otherwise have no knowledge of the risks to which they are being subjected, should be considered to be '*research participants'* and asked to formally consent to involvement in the study. There are some definitions of research "participants" which include not only those humans who are the principal focus of the research but also those upon whom the research impacts, whether concurrently or retrospectively.

Under this definition, both xenotransplant recipients and their close contacts could be defined as research participants. However, to include close contacts as research participants with formal consent arrangements would require the development of a new set of ethical principles, particularly, in relation to the issues of the right to withdraw and long-term follow-up.

However, it is important that all close contacts of xenotransplant recipients should be given precise, clear and detailed information about the procedure, any risks to themselves and the proposed risk management procedures. The involvement of xenotransplant recipients and close contacts in information sharing and decision making about a proposed trial are discussed further in the next sub-sections.

On a wider level, the risk of infection could potentially affect the whole community (if a new infectious disease emerges), so some form of overall public assent is required before such research is allowed to go ahead at all.

3.4.1. Some criteria to assess when xenotransplantation trials involving human beings is justified

There are significant scientific hurdles to be overcome before xenotransplantation can be clinically successful. Progress has been made in controlling the rejection of xenografts by the immune system, as indicated by the increasing lengths of time that xenografted organs or tissue survive when transplanted into animals used as experimental recipients. The question is: at what point will the results from experiments using animals as recipients justify clinical trials involving human beings?

Xenotransplants should be offered to human patients only when results using animal recipients suggest that these operations will have a reasonable chance of success. There is currently little consensus within the transplantation community as to whether the current data using animal recipients justifies progressing to clinical trials.

The most important problems and the dangerous consequences for the patient and/or for public health will have to be resolved before proceeding to the clinical phase. In relation to this, a series of basic measures will have to be adopted before taking this step. Amongst others the following can be mentioned: In the event that therapy takes place, the preclinical phase will have to provide the necessary data to justify it. The strict regulations regarding the acceptance of this must be observed. The competent authority, the research ethics committees, health professionals and other governmental bodies will have a key role in guaranteeing the appropriateness of the respective methodological, ethical and legal aspects of xenotransplantation and their adequacy for ensuring compliance with the respective preventative measures that must be adopted. The therapy will have to be carried out with approval and supervision at an institutional level to ensure the ethical conduct of the research subject.

3.4.2. Consent considerations

Even when the results from animal experiments suggest that xenotransplantation involving human recipients is justifiable, the early clinical trials will involve unknown and unpredictable risks. The question then becomes how best to protect early patients'

welfare and interests. It is of the highest importance that potential patients give free and properly informed consent to participation in the first xenotransplantation trials. The principal problems that may arise with the early use of xenografts in human beings include: possible suffering for perhaps limited, if any, therapeutic benefit; the raising of unjustified expectations even when every effort is made to explain honestly the low likelihood of success in early cases; poor quality of life that might follow only a semi-successful use of xenografts; the possibilities of disease transfer across species, which would be an unknowable risk for early patients; and the consequences of the need for health monitoring for those who are recipients. It is likely that the first xenografts will be offered only to those with little chance of surviving without it. But these people, who are facing death, require particular protection from over-optimistic or dangerous experiments.

It is a vital principle of contemporary medicine that patients should give properly informed consent to any treatment or therapeutic research, and that human volunteers should give properly informed consent to participation in research. People should be in a position to make a decision on the basis of proper information and without pressure, so that participation can truly be said to be voluntary. Where possible, people should make decisions for themselves.

As with any other procedure, it is of the highest importance that potential patients give free and properly informed consent to participation in the first xenotransplantation trials. Before a trial proceeds, the research participant (eg the xenotransplant recipient) must be asked to give his or her consent to taking part in the trial. The decisions of medical consent should be both free and uncoerced (*voluntary*), and based on a well-founded understanding of what is at stake (*informed*).

• A *voluntary* decision is one made without pressure, coercion, force or persuasion against one's will. A person's decision may not be voluntary if people who are powerful or influential have put too much pressure on them, or if they have not had the opportunity to consider all the relevant aspects of the situation.

Potential xenotransplant recipients may not have any other options for treatment of their condition. This means that there will be a lack of choice, which could be understood as coercion. Investigators need to develop *protocols* that include steps to ensure that this situation is avoided and that consent when obtained is genuinely voluntary.

• An *informed* decision is one based on relevant information about the decision, presented to research participants at their level of comprehension. Any information is relevant if it is important to the particular person making the decision (including purpose, methods, demands, risks, inconveniences, discomforts and possible outcomes of the research).

For xenotransplantation research, it is very important for the person providing information to be honest about the experimental nature of the procedure so that the potential participant does not develop any false preconceptions about the chances of success.

Ensuring that these criteria are met is part of what is involved in respecting the *dignity* of every human being and requires that great care be taken. A person may refuse to participate in a research project and need give no reasons or justification for that decision. Good research ethics traditionally also require that participants should be free at any time to withdraw their consent to further involvement in the research, and that participants understand this before they agree to participate. These conditions form part of the 1996 *World Medical Association Declaration of Helsinki.*

Proposed trial, potential xenotransplant recipients may be seriously, or even terminally, ill and therefore vulnerable to unrealistic expectations of benefits. In these circumstances, some people may be willing to agree to treatment options that are not in their best interests. A question arises about the capacity of such seriously ill people, whose only chance of survival may be to receive experimental therapy, to give genuinely voluntary and informed consent to participation in a clinical trial.

Xenotransplantation is not unique with respect to these issues; similar circumstances can occur for other research on people who are dying (eg cancer research). Terminal care investigators must take particular care not to exaggerate the prospect of benefit from research participation in order to justify a higher risk than that involved in the patient's current treatment. In the case of xenotransplantation, the proposed procedure may carry significant risks for the research participant, which needs to be harmonized by a *real prospect of benefit* compared with *their current treatment.*

Investigators therefore need to ensure that proposed transplant recipients are given significant and compressible information, including the *results of animal-to-animal studies,* and *previous animal-to-human trials if any exist,* so that they have all the available information at hand to make an informed decision based on realistic prospects of a good outcome together with *knowledge of the risks.* Because it may be difficult for the investigator or treating doctor to remain impartial when discussing information about the trial, it may be preferable for an independent counsellor to provide frank information to the research participant.

Even when a careful attempt is made to inform research participants of the point of the clinical trial, sick or vulnerable patients may not understand the complex nature of the trial and the risks involved. Investigators need to develop *protocols* to overcome these difficulties, thus ensuring that potential trial candidates have the necessary information, support and time to make an appropriate decision.

It is true that some researcher, keen to discover whether xenografts are a viable alternative to human transplants, might be inclined to overestimate the chance of success. Even with well-established procedures to protect the human subjects of research, innovators may be more dismissive of the risks, and the pains and stresses, of a particular procedure than may be their patients.

Patients must be made aware, whenever possible, of the extent to which they are 'experimental subjects', involved in unpredictable clinical trials of techniques that are largely in the developmental stages. To ensure that a patient is given a balanced view, an independent and trained person with appropriate counselling skills, not on the research team wishing to carry out the xenografts, should be given the duty of discussing with the patient the proposed treatment, the possible alternatives and the risks. These discussions should be held as early as is reasonably possible. In order to ensure that consent is properly informed and freely given, the consent of patients to participation in xenotransplantation trials should be sought by appropriately trained professionals who are independent of the xenotransplantation team. The information given to prospective recipients should include an estimation of likely success, attendant risks and subsequent quality of life.

It will be extremely important to monitor early xenograft recipients for any evidence that diseases are being transmitted from animals to the early human recipients. This need to monitor closely the outcomes associated with all early patients brings its own ethical problems, most notably that of how far respect for privacy is consistent with the practice of adequate monitoring. Patients consenting to xenotransplantation should be informed that postoperative monitoring for infectious organisms is an integral part of

the procedure, and that their consent to the operation includes consent to this monitoring.

One piece of information of great importance to patients concerns their expected quality of life. The speed of the body's rejection of xenografts to date has, in most cases, been so fast that quality of life considerations have not arisen. If xenotransplantation is successful, however, and the patient survives and the xenograft functions properly, quality of life will become important. Teams conducting experimental trials on patients are under a scientific and ethical obligation to research and report the subsequent quality of life of recipients, covering not only postoperative length of life, but also such matters as pain, mobility, emotional adjustment and social functioning. In this regard, all protocols should include a commitment to a robust description and assessment of the patients' pre-operative and postoperative quality of life. Therefore, the information given to prospective recipients should include an estimation of likely success, attendant risks and subsequent quality of life.

Since xenotransplantation will be an experimental procedure on every occasion on which it is undertaken in the near to medium term, it is essential that those carrying out the procedure report fully on all the important consequences. This will ensure the maximum benefit is obtained from these major and risky procedures. It will improve the information upon which subsequent potential recipients can make a decision. Finally, it will provide more information for public debate on the acceptability of xenotransplantation

With regard to children, it is true that special issues arise in this regard. Xenotransplantation has been proposed as a method of reducing the especially acute shortage of organs for babies and children. Early clinical trials of xenotransplantation will be a form of therapeutic research. Therapeutic research must offer some prospect of genuine benefit for the patient, but it involves greater uncertainties than treatment, and therefore greater caution must be exercised. It has been advised that therapeutic research should not involve children if it could equally well be performed with adults. It would be difficult to justify the involvement of children in major and risky xenotransplantation trials before some of the uncertainties have been eliminated in trials involving adults.

If the first adult trials are successful, and there is greater certainty about the benefits, there would be stronger arguments for offering xenotransplantation to children. The question of consent then becomes important. Children with enough maturity may be considered capable of consenting on their own behalf to participate in therapeutic research. Given the complexity of the ethics and law in this area, a cautious approach would be to obtain the consent of the person with parental responsibility before a minor participates in a major procedure like xenotransplantation. The agreement of any child to participation in therapeutic research such as xenotransplantation should always be obtained.

Similar issues arise for adults who are considered incapable of consenting to participation in therapeutic research because they are mentally incapacitated. The law would appear to be that incapacitated adults may be involved in therapeutic research if this is in their best interests. It would be difficult to justify the involvement of incapacitated adults in the first xenotransplantation trials before some of the major uncertainties have been eliminated in trials involving adults who are capable of weighing the benefits and risks on their own behalf.

One of the starting points of this document was that public policy must reflect the ethical pluralism that characterizes current societies. In this regard, public policy must be able to take account of different attitudes to xenotransplantation. Some people

may wish to refuse xenotransplantation as a form of treatment. If refusing a xenograft reduced a person's priority for a human transplant, consent to xenotransplantation would certainly not be freely given. At any stage in the development of xenotransplantation, patients who, for whatever reasons, refuse xenografts should remain entitled to consideration for human organs on the same basis as before their refusal.

3.4.3. Right to withdraw from trial or follow-up?

Clinical trials in xenotransplantation may increase, as has been said before, the risk of emergence of new infections associated with viruses transmitted from animals to humans Therefore, it has been argued that clinical trial participants should be asked to ***waive*** *their traditional right of withdrawal from the trial* and to *agree in advance to being followed up for the rest of their lives*. It has also been argued that individual research participants and their contacts should be asked to agree in advance to being ***quarantined*** if they develop a zoonotic infection. Two questions arise from these proposals.

• Would it be prudent to assume that sick and vulnerable people will abide by such promises?

• Would it be ethical to require them to make such promises?

In response to the first question, it is common experience among health professionals that research participants do not always abide by agreements made at the outset of a research trial (eg women who are asked to agree not to become pregnant during a trial do become pregnant). This indicates that it would not be prudent to rely on such promises as an infection control measure.

In response to the second question, it is clear that to place such restrictions on research participants or contacts would be oppose to currently accepted ethical practice, as enshrined in the Declaration of Helsinki. Should a new set of ethical principles be developed to justify such measures? Perhaps, it is not necessary because, as discussed above, it would not be prudent to rely on such restrictions as an *infection control measure*.

Taking these considerations into account, investigators should be required to provide *evidence* of the safety of the proposed procedure so that such *restrictive monitoring* or *quarantine* is not necessary. Nevertheless, it is also recognised that information gathered from the first human trials that are conducted will be important in assessing future risk. Therefore, investigators must try to achieve lifelong monitoring of recipients and must have procedures in place that are not onerous for the recipient and that help to ensure compliance with this request. Likewise, having entered the trial, xenotransplant recipients have an ethical and social responsibility to continue to provide information on a long-term basis if at all possible, even if the procedure is not successful in their case.

The risk assessment should take this into account to ensure that it will not produce undue risk for the community.

In conclusion, this section has set out following ethical issues that need to be taken into account in the regulation of xenotransplantation involving human recipients: The timing of the first trials; consent considerations; and what about the possibility of practice or not the right to withdraw from trial or follow-up.

These concerns will best be taken account of if clinical trials of xenotransplantation are restricted initially to a small number of approved centres. The decision to proceed with clinical trials involving human beings will also require an

assessment of whether concerns about infectious organisms have been addressed adequately. This is an important concern both for individual patients, and for the wider population. It would not be ethical to undertake clinical trials of xenotransplantation until a regulatory structure is in place that can take account of all these concerns.

3.4.4. The role of relatives/Contacts

As has been seen, relatives or contacts of the potential xenograft recipient will also be required to be involved in the decision-making process. This raises a number of issues about privacy and confidentiality, but it also adds one further anomaly to the consent issue.

Indeed, because contacts and carers of the trial participant may need to be informed about the trial, the confidentiality normally held between the patient and his or her treating physician may need to be broadened to include the contacts. If not handled carefully, this could lead to discrimination against the trial participant. Trial protocols should minimise this potential problem by providing very clear information about the *benefits* of the trial, the *risks* involved and the *risk management procedures* that are in place to protect the *participant*, *close contacts* and the *wider community*. Participants in early trials may also be subjected to unusual and intense public and media scrutiny and inquiries. These issues should be explained to research participants before the trial. Measures should be in place to protect participants' privacy.

As has been said above, the close contacts of xenotransplantation research participants may be exposed to the risk of contracting a novel infectious disease. They should therefore be identified and counselled about the risks involved. Ideally, close contacts (particularly family members) should be involved from the outset in discussions with the treating doctor and the investigator. The investigator should provide clear information sheets for close contacts and, ensure that they have been sighted.

It has also been suggested that close contacts should be asked to agree to be monitored during the trial. The issue of monitoring and possible quarantine of research participants and contacts has been already mentioned. As has been said, such measures would be difficult to apply and certainly should not be relied on as infection control measures. However, for some trials it may be advisable for the investigators to seek a list of close contacts and obtain blood samples so that people can be contacted and screened if a novel infection develops in a trial participant.

Many factors may affect the ability of close contacts of the research participant to support a decision to proceed. These may include their relationship with the research participant (e.g. carer, family member, and sexual partner), their perceptions of the risk involved, or other life options. Investigators must provide significant information to contacts of xenotransplant recipients.

Family members and sexual partners of the xenotransplant research participant may feel considerable pressure to support the trial. Investigators must develop strategies to ensure that contacts of the research participant have realistic expectations and knowledge about all the issues involved. However, there are some questions with regard to this question.

As we know, it it is a general rule of consent law that the intervention or opinion of a third party is irrelevant to the authority vested in the competent, adult individual to agree to or refuse medical interventions. Indeed, even where the adult is incompetent, there is no common law provision for a third party to agree on their behalf to treatment, although statutory authority now exists following the passing of the adults with

incapacity. Each of these legislative interventions, however, requires that a benefit derives from or best interests are served by the research or treatment, and the question as to whether or not xenotransplantation would satisfy these requirements cannot as yet be answered in the affirmative.

Assuming the recipient of a xenograft to be competent, the involvement of relatives and close contacts takes on a new significance. If close contacts are unable or unwilling to offer a legally valid consent then it seems likely that the individual will not be considered for transplantation, even if they would otherwise qualify clinically. Equally, if relatives/contacts refuse to agree to the intrusions required by the surveillance program, this too would be likely to result in deselection of the individual who would potentially have received a xenotransplant. The question therefore must be asked: if family members or other close contacts are not in agreement with the patient's decision to the transplant, can they prevent it?

Technically, in law, they have no standing to do so, since –as has been seen- their views are generally irrelevant. However, practically, the refusal of the relatives or contacts to participate in the surveillance program would deny the patient the ability to participate. Functionally then, relatives and contacts are being given an authority which they have always lacked in law, thus furthers skewing the legal understanding of consent as authorization.

3.4.5. Assessment of information sharing and consent protocols

3.4.5.1. Data requirements and assessment

Based on the above discussion, the investigators and sponsors of a proposed trial will be required to submit protocols for obtaining informed and voluntary consent of research participants; and informing and consulting with close contacts about infection risk. The information will form part of a comprehensive submission assessment by the relevant regulatory authority and the human research ethics committee at the institution where the research will be carried out.

3.4.6. *Some principles for considering the ethical conduct of xenotransplantation research*

It is necessary to consider some of the practical ethical issues referred to the conduct of xenotransplantation research, in particular, those which make reference, in this section, to human beings (the ethical conduct of animal-to-human trials), as the ethical conduct of animal-to-animal studies and the care and welfare of source animals for clinical trials has been already studied.

Some principles have been established to guide ethical decisions relating to human participation in clinical trials:

- Integrity, respect for persons, beneficence and justice[32];

[32] For the next development of this draft discussion paper it will be necessary to make reference to several social implications, such as the allocation of resources /Funding and the need to consider in more detail the principle of justice. For the moment, these are some considerations. With regard to the allocations of resources, it is true that increasing the supply of organs and tissues for transplantation by the use of xenotransplantation products will inevitably lead to an increase in demand for such products. This has funding implications for the health care system as well as resource allocation implications for the initial research and subsequent health care. Xenotransplantation research may be very costly and there is a possibility that investment in it may divert research funds away from other approaches to organ failure and also from other important health problems. However, the costs involved in transplant procedures themselves, once they are established in clinical practice, vary a great deal depending on the type of transplant. Some transplant procedures, such as heart and liver, are specialized and relatively costly but

- Safety;
- Consent;
- Ethical review and conduct for research.

Under the current arrangements for clinical research, research projects involving humans must be reviewed by the human research ethics committee (HREC) in the institution where the research will take place and the review must follow the guidelines and processes described in the national law.

Much of the decision making of HRECs depends on weighing up the benefits to the research participants (or to the community as a whole) against the risks of a particular protocol. Many novel protocols are reviewed. Xenotransplantation presents some particular challenges: each proposal will require HREC scrutiny before the proposed research is approved.

Researchers are required to suspend or modify their research if the risks to participants are found to be disproportionate to the benefits. The results of the research (however funded) must also be made available to allow public scrutiny and contribute to public knowledge.

In summary, when applied to xenotransplantation, the established ethical principles described above indicate that, given the current state of our knowledge and expertise, very serious ethical, social and scientific consideration is needed before an animal-to-human trial in xenotransplantation can be approved.

In addition, two groups of people can be distinguished whose rights and needs may be affected in xenotransplantation research involving humans:

- Individual xenotransplantation recipients;
- The wider community (particularly careers and close contacts of xenotransplantation recipients), who may be affected by an infection should one arise as a result of using animals organs or tissues.

The national law should define research participants broadly to include those who are the focus of the research and also those upon whom the research has an impact. It is necessary to determine if the close contacts should be also regarded as research participants *per se* or just they need to be given careful consideration in any research protocol for xenotransplantation.

Based on these considerations, several principles for the ethical conduct of xenotransplantation research involving humans have been identified to be met before xenotransplantation research involving humans is allowed to proceed.

- The research must serve the public interest;
- The research must be based on previous preclinical studies;

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others, such as kidney transplants, are less costly than maintaining a patient on hospital-based dialysis (in addition to the non-financial benefits of improvements to health and lifestyle and returning the recipient to a productive lifestyle). At this early stage in the development of xenotransplantation, we cannot predict all the costs that may be involved for ongoing supervision and treatment of xenotransplantation recipients. Ideally, the costs of ongoing treatment and care will eventually be matched by the savings made in restoring recipients to healthy and productive lives, but it is too early to know whether this hope will be realized. In relation to the principle of justice, several social implications need consideration, in particular difficult issues to do with justice in the allocation of health care resources. The technology holds out great promise, but initially it may only be used for a relatively few people at a great cost. These hard questions ought not to be ignored in this context. If xenotransplantation proves to be feasible, the necessary clinical development of the technologies will probably be carried out with the support of biotechnology companies, and xenotransplantation may initially only be available to those who are able to pay a relatively high cost. The health care system may thus be faced with the choice of offering altruistic allotransplantation. These issues are complex and, as has been said, they are beyond the scope of this discussion paper.

- The research must be therapeutic in design;
- The benefits must justify any risks;
- The research should not expose the participant, their close contacts or society to any unreasonable risks;
- The research must respect the dignity of participants;
- Research participants must give adequately informed and voluntary consent.

Two additional factors have been also identified as unique to xenotransplantation research and that need careful consideration.

- Research participants may need to be closely monitored for many years in case of infection. That is, there may need to be more emphasis on keeping participants in a trial than would normally be the case.
- The safety and rights of close contacts of the research participant must be protected. The assent of close contacts may therefore be required so that they can be screened before the trial and further monitored if a research participant develops an infection.

APPENDIX A: Key issues to be discussed

The following questions have been raised in the text of the discussion paper to prompt public and stakeholder over the issues raised. Responses to these and any other issues are invited. In particular, we want to learn if: a) the paper is seen to be thorough and complete; and b) whether any important ethical principles have been omitted

Definitions

- Definitions of xenotransplantation
- Definition of alternative sources of organs and tissues

Have the alternatives to xenotransplantation been adequately identified?

- Definition of animal-to-human xenotransplantation research

Do you agree that animal-to-human xenotransplantation trials should be undertaken only for therapeutic research purposes?

Ethical and social concerns

- Basis for ethical consideration of xenotransplantation

Are there other important ethical issues that need to be considered in this debate about xenotransplantation?

- Inherent ethical issues relating to xenotransplantation

Have any inherent ethical objections to using live animal cells, tissues or organs for xenotransplantation been adequately addressed?

Social significance

Should there be a more extensive discussion with regard to the different issues involved in xenotransplantation, or can these issues be postponed until it becomes clearer that xenotransplantation is likely to become a reality?

Genetic modification of source animals

Do you understand how xenotransplantation work?

Is the central role of genetic modification of source animals in the research clearly described and are the possible problems reasonably stated?

Is it wrong to genetically modify animals to provide suitable xenotransplantation products?

Does the transfer of human genes into another species carry significant ethical implications in terms of both the definition of “humanness” and unknown consequences in future generations if the transferred genes behave in an unexpected way?

Do you think that there will be a psychological impact of mixing animal and human tissues?

The next future of xenotransplantation

- Assessment of efficacy

Will xenotransplantation work?

Is it possible to define a reasonable criterion for success in animal-to-animal studies, on which progression to pause clinical trials (animal-to-human) can be based?

What are the risks?

How would animal-to-human transplantation trials be managed?

How can be defined the xenotransplantation success?

What kind of data requirement should be taken into account for assessment of xenotransplantation efficacy?

- Expertise required assessing efficacy
Are there any other areas of expertise that the regulatory authority responsible for xenotransplantation may need in order to consider the issues addressed in this section?

Safety
- Assessment of infection risks
Are there clear criteria that should be used or developed to allow decisions to be taken about infectious risks involved in human trials of xenotransplantation?
How to assess evidence of benefit with regard to xenotransplantation research?

- Expertise required assessing safety
Are there any other areas of expertise that may be needed by the regulatory authority responsible for xenotransplantation in order to consider the issues addressed in this section?

Human ethics of xenotransplantation trial protocols
-Consent by research participants
Do you agree that only xenotransplant recipients themselves, and not their close contacts, should be regarded as "research participants"?
- The potential spread of the infection is a public health question.
Is it ethically acceptable that only the recipient gives his/her consent to a therapy that could affect their contacts and also to the general society?
Are safeguards in place to ensure that the research participant's consent to the procedure is obtained voluntarily and without coercion?
- Lifelong follow-up and monitoring
Are trials that require lifelong monitoring and follow-up for emerging infectious disease acceptable?
Do you agree that there are should be an ethical and social responsibility on the research participant to remain in the trial for long-term follow-up?
- Informing and consulting close contacts
Does the discussion adequately cover the key issues for informing and consulting with close contacts of xenotransplantation research participants?
Is it acceptable for close contacts of a research participant to be identified and screened before the trial and contacted and tested if a novel infection emerges at later date?
If a patient withdraws from the trial (e.g. he/she does not continue with long-term monitoring), how will this affect the overall risk assessment for the trial?
What kind of measures should include a protocol to ensure that the confidentiality of the research participant is safeguard?
- Expertise required assessing human trial protocols
Are there any other areas of expertise that may be needed by the regulatory authority responsible for xenotransplantation in order to consider the issues addressed in this section?

Animal ethics of xenotransplantation protocols
-Animal welfare
Does this discussion adequately cover the key issue for animal welfare in xenotransplantation research?
Is it ethically acceptable to use live animal cells, tissues and organs as human therapies?

What role does the unavailability of alternatives play in the justification of research involving animals?
Is it wrong to use animals for purposes related to human health?
Is it wrong domesticate and rear animals to obtain xenotransplantation products?
Provided there are substantial benefits associated with animal research, why should the use of animals require special justification?
How can the welfare of animals be protected?
To what extent do you believe animal welfare is a matter of public interest or concern?
From your point of view, what are the major animal welfare problems?
Do formal structures exist in your country to discuss animal welfare issues?
Is it wrong to proceed with xenotransplantation if protocols respect the essential characteristics and welfare of their species?
Do you think that it would be necessary to set up a specific central register of animal-to-animal preclinical xenotransplantation studies so as to give support for the AECs?
Is there legislation in your country to protect public safety in relation to animals?
-Expertise required assessing animal trial protocols
Are there any other areas of expertise that may be needed by the regulatory responsible for xenotransplantation in order to consider the issues addressed this section?
Do you believe that, for instance, the veterinary services of your country have sufficient relevant qualifications, scientific expertise and experience to enable them to make sound professional judgments on animal welfare?
Are postgraduate specialisations in animal welfare available in universities or other awarding bodies in your country?

APPENDIX B: How to Write a Submission

The issues surrounding the present discussion paper are numerous, and the Xenome project members have set up a specific workpackage to investigate and report on those issues. Part of this process includes gathering public views and the Xenome project members would be grateful for any comments that you might like to make.

As background information we have prepared this "discussion paper" but you can find more information in the Xenome web site: www.xenome.eu

In this web site there are a brief description of the project, a dissemination area and a legal and ethical issues area. The dissemination area includes several publications, press releases and events. The legal and ethical issues area provides useful bibliographic references, legal framework and links. Some of the documents deal with the issues which have been commented in this discussion paper. The links area refers to several organizations, institutions, foundations, associations, etc., which are involved in this field. Most of them are focused on the issue related to animal welfare. For instance, some of those associations examine methods of better collaborations between organizations in drawing up welfare rules and codes and to examine ways of improving of animal welfare standards at operational level. In those links one can get information about events which bring together national and international scientific and legal experts (representatives of international organizations, veterinary services and other relevant officials), academic experts, scientists and representatives of civil society involved in the protection of animal welfare. The issue of animal welfare in Europe is an up-to-date topic and worth broad coverage and in-depth study. This is one of the issues of increasing significance for European citizens.

Submissions should be clear and concise, preferably type written and submitted as an original by email to the following email address:

Each submission should include:

- The submitter's name and address;
- Names of any additional contributors to the submission who may wish to be acknowledge;
- Contact telephone numbers in case Xenome project members need to clarify any points, obtain additional information, or advise if the submission appears incomplete (e.g. pages missing); and
- Email address

Submissions to Xenome web site need to include specific information that will help this European project to consider the points presented. Evidence that supports the points being made should include full references and copies of material referred to. If it is not possible to include such references, please include as much detail as possible.

Information in the submission should be in a logical order, preferably following the layout of the **Appendix A.** Quote the page number relevant to the points being made.

There is no set length for a submission and, in fact, the length will vary depending on the complexity of the issue and number of comments a submitter wants to make.

However, submissions should balance the need to provide as much information as possible with a need to be concise. Also it will be helpful if you would identify any special experience that you may have which is relevant for our study.

If you wish to contribute to our work in this project, it will be most useful if you let us have your submissions and comments in writing by XXX.