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## **XENOME WP6**

**DRAFT**

**PUBLIC GUIDE FOR THE COMMUNITY**

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**APPENDIX A: About this community guide and the need of obtaining your participation by making a written submission**

## 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<sup>1</sup>. 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:

- **Autotransplantation** –transplantation (relocation) from and to the same individual<sup>2</sup>.
- **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,

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<sup>1</sup> Council of Europe (2003), Report on the State of the Art in the Field of Xenotransplantation, Council of Europe: Strasbourg, p. 16.

<sup>2</sup> For instance, it is possible the relocation of skin from the thigh to the arm so as to repair burn damage.

tissues or organs from a nonhuman animal source<sup>3</sup>. 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)<sup>4</sup>.

- *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<sup>5</sup>.

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

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<sup>3</sup> 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**’).

<sup>4</sup> 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.

<sup>5</sup> 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 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.

- “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.

- **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 (encapsulated) 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.

- **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.

In summary, Xenotransplantation has been defined in line with international terminology to include a range of procedures that involve the use of living animal products in human therapies.

## 2. What is the rationale of carrying each type of animal-to-human transplantation procedure?

- 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.

- 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.

- With regard to **AETs**, 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 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.

In summary, although the rationale for animal-to-human transplantation is usually stated as being a shortage of human organs, which is certainly the case of whole organ donations, the reasons for pursuing **ACTs** and **AETs** are more complex — relating to a combination of new technological possibilities opening up and difficulties in accessing and working with human products in the context of these therapies. These conditions may change rapidly over the next few years as progress is made in other areas of biotechnology and biological therapy. Careful monitoring of these developments will be required for some years to

ensure that, at any time, only research proposals that offer the best chance of benefit to the recipients and to the community as a whole are supported.

### 3. What is xenotransplantation research?

Researchers are working out the science of xenotransplantation step by step. They start with laboratory studies on cells and tissues to work out the underlying science. Then they conduct studies on small animals (such as mice, rats or rabbits) to test possible procedures. The same approach is used in other medical research, such as cancer research or the development of new drugs. If these early studies are successful, further thorough research is needed to develop procedures that can be used to treat humans. This research, which is the focus of this guide, includes:

- **Animal-to-animal studies:** in which the source and recipient animals are as similar as possible to the proposed human treatment, - (for example, from pig to baboon)-. These *preclinical studies* are needed to make sure a procedure can be conducted safely and effectively on animals before it is tried on humans.

- **Animal-to-human trials:** in which animal cells, tissues or organs are used for human treatments in closely monitored **clinical trials**. These trials, which are most likely to involve pig-to- human transplants, would be attempted only if animal-to-animal studies show a high likelihood of benefit to humans.

Clinical trials can be either **therapeutic** (in which participating patients are expected to benefit from their involvement in the study) or **nontherapeutic** (in which the study is designed to obtain further knowledge but may not be of direct benefit to the participant).

Because of the potential risks involved, only research with some prospect of therapeutic benefit is considered to be acceptable for clinical trials of animal-to-human transplantation. As with other medical technologies, the process of testing new therapeutic procedures through clinical trials can take many years and involve several phases.

### 4. What are the main challenges for considering animal-to-human transplantation?

As has been seen, human-to-human transplantation has become a successful way of treating various human diseases and conditions (such as heart disease or kidney failure). However, human organ and tissue transplantation usually depends on donations from people who have died, most often as the result of brain damage (such as a tumor or stroke) or accidents. Over the past twenty years, transplants have become more frequent and successful. The number and scope of transplant procedures has also increased to include a broader range of organ, tissue and cellular transplants (such as transplants of insulin-producing pancreatic islet cells for treatment of diabetes). However, the number of donors has not risen to the same extent. This is not a minor shortfall that can be easily overcome by greater effort or funding; it is extreme and it is increasing. Many people die while on a waiting list for a suitable transplant.

The costs to society of these shortages can be measured in the deaths and illness of patients; in emotional, social and economic costs to their families; and in direct and indirect economic costs to the wider community. Therefore, medical researchers face two challenges:

- The first is to keep people alive while they wait for a suitable organ or tissue donation.

- The second is to find suitable alternatives to human donations for repairing or replacing damaged or diseased organs and tissues. Animal external therapies, such as liver perfusion, may help to overcome the first challenge, while transplants of animal organs, tissues or cells may offer a solution to the second — but only if several major obstacles, including rapid immune rejection and structural or functional incompatibility of the animal transplant, can be overcome.

With the rapid development of genetic technology over the past decade, some scientists believe that it might be possible to overcome these problems by genetically modifying the source animals to make their organs and tissues more compatible with humans.

Hence, the shortage of human organs, combined with developments in **genetic technology** has stimulated increased interest in animal-to-human transplantation. However, the use of **animal transplantation products** as human therapies raises ethical, social and scientific issues. These need to be considered before animal-to-human clinical trials, are allowed to go ahead.

## 5. Is animal-to-human transplantation ethical?

As has been seen, clinical efforts to transplant animal organs into humans have been driven by a desire to treat critically ill patients for whom no other treatment options have been available. Dedicated researchers and programs have sought to develop animal to human transplantation into a technique able to overcome the shortfall of organs. In addition, different forms of cellular transplantation are being developed as therapeutic options for a variety of degenerative diseases. Thus, like allografting, the primary aim of xenotransplantation is to improve the quality and length of human life. To be adopted as treatment options, xenogeneic therapies must be ethically acceptable as well as scientifically and medically viable. Previous chapters have shown that the development of xenotransplantation raises a host of ethical concerns. This section is focused on a number of these ethical issues; namely the concerns which surround the use and treatment of animals and the potential impact of xenotransplantation on individuals and wider society.

- With regard to **the use of animals**, it has been suggested that the use of animals in xenotransplantation (for research and clinical purposes) is ethically problematic. In this respect, difficulties have been identified with the main approaches that have been used to support the use of animals in biomedical procedures like animal to human transplantation cost-benefit analysis and the assessment of animal capacities. In respect of cost-benefit assessment it has been noted by some authors that lack of information on the nature of animal experience, the incommensurability of human and animal experience and concerns over what constitutes a cost to animals are all areas which problematize this method of assessment.

On the other hand, arguments based on capacities are undermined by the fact that it is difficult to find a criterion which justifies the use of certain animals (such as pigs) and excludes the use of other animals, or for that matter the use of certain humans. In addition, there is disagreement over the level of capacities of different species. Of particular concern is that judgments using such criteria are often assertions of pre-existing social assumptions rather than the product of critical reflection. In this regard, the fact that arguments from capacities are unable to present a clear, morally relevant distinction between animals and humans, or between different animal species, serves further to problematize cost-benefit analysis. This is because cost-benefit assessments are based on the notion that animals are

in some way different from humans. However, if we cannot consistently identify why humans have a higher moral status than non-human animals, then justification for the moral segregation which exists between humans and animals crumbles<sup>6</sup>.

Some authors give voice to the increasing unease that "... today the main concern is the risk of xenozoonoses and the ethics of controlling that risk"<sup>7</sup>. In this regard, it has been argued that an ethical assessment of xenotransplantation which prioritizes public health requires that clinical trials pose a minimal risk to the human community. The primary strategy for reducing the risks which biomedical procedures present to humans is to test such techniques on animals before commencing clinical trials. Thus, a major ramification of the suggestion that research on xenotransplantation should continue until it is safer is that it will increase the burden on animals; a concern that is heightened by the fact that the arguments which are used to justify even the current use of animals do not stand up to scrutiny. This, it has been argued, is because the costs to animals are likely to be substantial; to date these costs are not clearly outweighed by large benefits to humans. In addition it is unclear, as has been seen, that there is ambiguous distinction between the capacities of humans, non-human primate and pigs which justifies the distinct moral value and treatment which is afforded to these species.

Given these concerns, if other less costly ways of addressing the shortage of organs and degenerative brain diseases exist, or could be developed within a time-scale similar to that of animals to human transplantation, society would have a moral obligation to redouble its efforts to develop these alternative strategies. The availability of treatment options which are thought to carry less risk for the human community and impose less of a burden on animals would mean that xenotransplantation would cease to have any claim to be ethically justifiable. In this respect, stem cell therapies and artificial organs may well provide preferable treatment options to xenotransplantation.

It could appear that risk adverse public health ethic might also have a negative attitude towards other avant-garde treatments. Thus, it is important to stress that this cautious approach is specifically concerned with the degree of risk that it is genuinely thought may be associated with transplanting animal tissue into humans. It must be emphasized that it is not medical progress *per se* which a public health ethic seeks to prevent, but the harm which may inadvertently be suffered by the human community as a

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<sup>6</sup> It has been suggested that the proper moral treatment of a being depends on the characteristics it possesses, rather than simply on the species to which it belongs. For instance, in the report of the Nuffield Council on Bioethics -"The ethics of research involving animals" (2005)- five morally relevant features are identified in this regard -(paragraphs from 3.20 to 3.51)-. These features are the following ones: Sentience (the capacity to feel pleasure and pain); Higher cognitive capacities (for example, the ability to use language and learn complicated tasks, such as making and using tools); The capacity of flourish (the ability to satisfy species-specific needs); Sociability (being a member of a community); and Possession of a life (attributing value to life itself). See: <http://www.nuffieldbioethics.org/go/ourwork/animalresearch/introduction>. In general terms, it is supported by many people a "hybrid" approach. This involves a combination of laying down definite limits for what should and should not happen (for example: "animals with higher cognitive capacities, such as chimpanzees, should never be used in research) and weighing up the costs and benefits of a particular action (for example: "research that causes minimum pain to a mouse is acceptable if it helps to ascertain the safety of an important and frequently used chemical"). The costs and benefits have to be weighed for each project and there are specific policies that prevent the use of the Great Apes and the use of animals in the testing of new cosmetics.

<sup>7</sup> See: Daar, A.D., "Ethics of Xenotransplantation: Animal Issues, Consent, and Likely Transformation of Transplant Ethics"; *World Journal of Surgery*, 21, 1997, pp. 975-982, (p. 975).

result of such untried therapies. This means that if safer innovative treatment options were available –all other things being equal- this form of ethical assessment would certainly encourage their development.

A public health ethic has a number of other positive contributions to make to the issues xenogeneic therapies are intended to address. Because public health ethics is driven by the general aim to protect and improve human health, it must conduct a comprehensive assessment of the best way in which to remedy particular concerns. In the context of organ shortage a public health ethic is able to perceive this issue as one which is multi-faceted. Its starting point is the need to minimize the number of organs that are required and find ways to increase the number of human organs which are donated. While such initiatives would certainly not solve the problem of the shortage of organs, they have the ability to save many lives. It is also highlighted that some of the responsibility for alleviating the current shortage of organs must be taken by community-centred initiatives.

According to the aforementioned arguments, it is possible to argue that animal-to-human transplantation raises very serious ethical issues, such as respect for the integrity of humans and whether it is morally wrong to use animals for the benefit of humans in this way (including whether it is acceptable to genetically modify animals).

People have differing views on these issues. This is also influenced by their cultural and religious background, their personal or family members' medical conditions, their understanding of the range of technologies involved, etc.

Most people accept the careful use of animals for the benefit of humans (such as in medical research), provided that the potential benefits of a research project, and the likelihood of the research achieving those benefits, outweigh any likely adverse effects on the animals (which should, in any case, be minimized). In this respect, the ethical debate comes down to disagreement on two questions: What are the limits? And how do we weigh the different morally relevant factors within the permitted limits? To provide answers, it is needed to consider other related questions: What are the goals of research?; What is the probability of success?; Which animals are to be used?; What effect will there be on the animals used in the experiment?; Are there any other alternatives?

Overall, there does not appear to be any major ethical reason why the medical community should not at least consider animal-to-human transplantation therapies as a possible option for human therapy, as long as the research benefits society as a whole respects the welfare of the animals used and allows for informed personal choice on the part of the recipient. Such research should be scientifically sound and supported by evidence that the likely benefits for humans justify the use of animals and outweigh any risks from the procedures.

## **6. What about the evidence of efficacy of each of the animal-to-human transplantation procedures?**

### **Animal external therapies**

Trials of AETs have been more successful than AOTs or ACTs, with both human skin cells grown on an animal feeder layer and liver perfusion methods suggesting positive outcomes in animal-to-human AET trials.

These procedures do not have the same rejection problems associated with AOTs as the animal tissues or cells are not implanted into the recipient and there is less need for immunosuppression of the recipients.

Overall, the use of external machines containing animal liver cells to treat acute liver failure has been tested in many animal-to-animal studies with some promising results. The Food and Drug Administration in the United States and the relevant authorities in Europe have therefore allowed clinical trials of pig liver dialysis procedures. Although not conclusive, these animal-to-human trials have shown some success with 'buying time' for patients with liver failure who are waiting for a suitable liver transplant from a human donor. Importantly, the use of pig liver cells in this way has not caused any significant adverse effects. Some bigger trials are now planned to obtain better information about the effectiveness of the procedure.

There have also been encouraging results from both animal studies and clinical trials of techniques to grow human skin on feeder layers of animal cells, then using the skin to repair burns.

The current stage of development of AETs can be summarized as follows: Ongoing active trials with some claims of efficacy. Hepatassist currently used as a bridge to transplant for people with liver failure. Skin grafts currently used for severe burns, (but in future could be for all skin grafting).

### **Animal cell therapies**

For ACTs, immune rejection may be a less significant problem than for AOTs and longer-term survival of the transplanted material has been achieved in both animal-to-animal and animal-to-human transplantation procedures.

Cellular transplants have been shown to function therapeutically in some animal-to-animal cell transplantation studies. However, although animal-to-human ACT trials carried out have not shown any major adverse effects of the procedures, the transplanted cells have not provided any therapeutic benefit to the recipient.

Because immune rejection is a less significant issue for ACTs than for AOTs, there is less requirement for immunosuppression and researchers are investigating ways to reduce this requirement further (in the hope that no immunosuppression will be required).

Overall, Animal cell therapies involve transplantation of isolated animal cells or cell clusters. They have the potential to treat diseases, such as type 1 diabetes, Parkinson's disease, and Huntington's disease. They may also be able to repair damaged tissues or organs, thus avoiding the need for more invasive surgery.

Research on animal cell therapies is at an early stage. Some success has been achieved in animal-to-animal studies, with good survival of the transplanted cells and minimal side effects. Based on these results, agencies in the United States and Europe have approved a number of animal-to-human trials of animal cell therapies. Some of these have already been carried out; others are either planned or are in progress.

So far, these clinical trials have included very few patients and the results obtained do not clearly show that animal cell therapies are effective. However, in many cases the cells survived well in the recipient and did not cause unwanted side effects. Further animal-to-animal research is now being carried out to discover how to promote the function of the cells as well as their survival.

The current stage of development of AETs can be summarized as follows: preclinical studies have shown some efficacy. Some clinical trials have been carried out or are in progress and have shown techniques to be safe in the short term but not efficacious. Further trials applications are expected.

## **Animal organ transplants**

For AOTs there are clearly major immunological and physiological barriers to achieving successful outcomes. In animal-to-animal organ transplantation studies to date, transplanted organs always fail within a short timeframe. However, successful genetic modification of pigs over the past couple of years has improved outcomes in pig-to-primate studies and further studies are currently being undertaken in the United States using the most recently created genetically modified pigs<sup>8</sup>.

For a clinical trial of an AOT to be considered, there would need to be data that showed the transplanted organs will function fully outside the laboratory (ie be physiologically competent and compatible with the recipient), which is not currently the case. The aim for current pig-to-primate studies is to answer further biological questions about the compatibility and physiological competence of organ transplants between species rather than to provide direct evidence in support of ethical approval of clinical trials.

In these studies, either the organs fail or there is a secondary complication, such as coagulation. These conditions are identified by routine blood tests and the animals are killed humanely (e.g. death is not used as an endpoint of the studies).

Overall, there are major obstacles to the transplantation of whole organs between species. This was shown by a succession of failed attempts from the 1960s to the early 1990s. For animal organ transplants to be successful, researchers need to prevent the transplant being rejected by the recipient's immune response (because it recognizes the transplant as 'foreign' and attempts to destroy it) and also ensure that the organ functions properly. This presents huge challenges.

In recent years, researchers have been using genetic technology to genetically modify pigs in order to overcome the most severe forms of immune rejection. As a result, the survival times of animal-to-animal organ transplants have increased from minutes or hours to days or weeks or months. Researchers think that these times may continue to improve as the science is better understood, new modifications are made to the donor animals and improved immunosuppressant drugs are developed and tested. However, although animal-to-animal studies are carrying out, there is clearly a long way to go before such transplants can be tested in humans.

The current stage of development of AETs can be summarized as follows: A few animal-to-human organ transplants were attempted overseas from 1960–1993 — all unsuccessful-. In some animal-to-animal studies, organs have survived for about 3 months (maximum 5 months). However, there are still major unsolved immunological and physiological barriers to long-term survival of whole organ xenotransplants. There are therefore no proposals for clinical trials anywhere in the world; and none are likely in next few years (because no benefit has been shown and risks are too high).

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<sup>8</sup> One of the major advantages of the use of pigs as source animals for xenotransplantation products is their excellent breeding capabilities in captivity. These breeding characteristics facilitate genetic engineering and allow the rapid transmission of introduced genetic modifications into the herd, as well as their combination with other genetic modifications. Several human genes have already been introduced into pigs as transgenes, and advances in nuclear transfer techniques have permitted the recent development of pigs that do not express aGal on cell surfaces. 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

## **7. What about the risk that human transplant recipients may be infected with a virus or novel disease agents from animals and that this infection may spread in the community causing serious epidemic?**

Xenotransplantation may also involve certain risks. This section discusses the risk that using animals to supply organs will result in the transmission of infectious diseases from animals to the human population. Researchers agree that non-human primates would not be suitable source animals for animal-to-human transplantation because of the risk of infectious to the transplant recipient and the wider community. Therefore, xenotransplantation should involve pigs, not primates as source animals. The fact that xenotransplantation of baboon organs and tissue into human beings is proposed and, indeed, already occurring in the US is a further reason for discussing the risks that diseases will pass from primates to xenograft recipients and thereby into the wider population.

Many disease-causing organisms (pathogens) are common to human beings and other animals. For example, the bacterium causing tuberculosis infects both human beings and baboons, and human beings and pigs both carry the virus that causes influenza. Clearly it would be important to make sure that any animal used to supply organs was free from infectious organisms that cause disease in human beings, just as it is important to make sure that human organ donors are free from infections that might be transmitted to a transplant recipient. The use of animals as a source of organs, it is argued, would allow for more thorough screening than is possible with human organ donors, and so the risk of such diseases might be reduced.

In addition to organisms that can infect human beings and other animals, any animal species will be infected with organisms that do not usually infect other species. Xenotransplantation, however, may allow such organisms to infect xenograft recipients who may, consequently, contract previously unknown diseases. There is also a risk that the infectious organisms might cause disease in and destroy the transplanted organ, even if they do not harm the human recipient. Even if not infected with disease-causing organisms when transplanted, the xenografted organ may remain susceptible to infectious organisms of animals. This is most likely to be a problem with lung transplants, where infectious organisms of animals would easily get access to the transplanted animal tissue.

The possibility must also be considered that should an animal organism infect a xenograft recipient the resultant disease might then be passed on to the public at large. In this way, xenografting may pose a risk to public health as well as to individual health. Therefore, it has been emphasized the importance of addressing the risks of disease transmission associated with xenotransplantation. The following paragraphs consider, firstly, the possibility that new diseases will be transmitted from animals to xenograft recipients. It then considers the risks that such diseases might spread from xenograft recipients into the general population.

With regard to the risk that infectious organisms will be transmitted from animals to human beings, researchers agree that there is evidence that human beings are susceptible to some animal diseases. Such diseases are called zoonoses. For example: The human immunodeficiency virus (HIV) virus that causes AIDS is very similar to the simian immunodeficiency viruses (SIV) found in primates. One view attributes the emergence of the HIV virus and the disease AIDS in human beings to the transmission of SIV viruses from primates to human beings. There is evidence that the SIV virus can, indeed, be

transmitted from primates to human beings although, as yet, there is no evidence of disease symptoms in SIV infected human beings.

Xenotransplantation is one way by which disease-causing organisms could be transferred from animals to human beings. Because xenotransplantation involves the direct introduction of animal organs or tissue into the human body, many of the natural barriers to infection are by-passed. Xenograft recipients are also likely to require immunosuppression to prevent transplant rejection. Since immunosuppression lowers the body's resistance to disease, the possibility of infection of a recipient with animal diseases may be increased further.

Most concern about the risks of infection from xenotransplantation focuses on viruses. This is because: viral infections are difficult to treat with drugs; viral infections may have a long latent period during which the person has no symptoms of the disease. If a new disease were to emerge as a consequence of xenotransplantation, it might be several years before the problem was identified. During this time the infection might be spreading throughout the population.

On the other hand, viruses can mutate rapidly and thereby change their characteristics. Mutation might allow animal viruses to infect human beings more readily; to resist attack by the human immune system; or to become drug-resistant.

One type of mutation occurs when viruses from different species recombine with each other and form new and possibly more dangerous viruses. It is thought that influenza epidemics are caused when new types of influenza virus are formed by recombination of two viruses, sometimes from different species. Xenotransplantation would provide increased opportunities for recombination between animal and human viruses.

One group of viruses, known as endogenous retroviruses, is inserted into the genetic material of the host animal and can be passed in this way from parent to offspring. This makes endogenous retroviruses almost impossible to eliminate from any animals that might be used as a source of organs for xenografting. It is possible that, after xenotransplantation, the endogenous retroviruses would move from the transplanted organs and become inserted into the genetic material of the human cells.

As mentioned above, there is considerable evidence that primates do indeed carry viruses that infect and cause disease in human beings. There is also experimental evidence that endogenous retroviruses from baboons can infect human cells. Because the viruses from human beings and other primates are often closely related, the risk of recombination to form new harmful viruses may be high. Another problem is that to breed primates free from known viruses, in so far as this is possible, would require a long-term program because of their relatively slow breeding rates.

In contrast, the more marked biological differences between pigs and human beings, and between their infectious organisms, may make it more difficult for infectious organisms from pigs to cause disease in human beings. Moreover, pigs have been domesticated and used by human beings for centuries, yet there is no evidence for transmission of viral diseases into the human population on the scale seen with viral diseases of other primates. Although the risks are likely to be lower, however, they cannot be ignored. Pig viruses with the potential to infect human beings include those causing porcine influenza, parainfluenza, swine vesicular diseases, encephalomyocarditis and, possibly, pseudorabies. Pigs, like primates, contain endogenous retroviruses and studies are needed to assess whether they can infect human cells. Since they have a 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.

Researchers believe that the risk of infection by known animal diseases would be minimized in the same way as for human infections; that is, by rigorous screening of source animals and appropriate treatment of transplant recipients if an infection occurs.

While known animal infections may not pose a serious problem, animal-to-human transplantation does carry another potential risk that has more serious implications for both the individual patient and the wider community. This is the risk that a previously unknown disease, or a new form of a known disease, might emerge and infect recipients of animal transplants and subsequently spread to **close contacts** and the general public, causing a serious new epidemic.

Overall, a group of viruses called **endogenous retroviruses** are of particular concern. Instead of actively causing infections like other **retroviruses**, the endogenous viruses remain dormant in their host — embedded in the genetic material — not causing any obvious signs of disease. However, they may be activated occasionally and it is possible that they could then infect other animals, including different species. Little is known about what might make endogenous retroviruses become active but, if an animal transplantation product contains endogenous virus, there is the potential for it to activate at any time in the future and infect the transplant recipient. Such an infection could spread to close contacts of the recipient and, in the worst case, to the general population.

Most pigs have a retrovirus called **porcine endogenous retrovirus** (or ‘PERV’). Recently, researchers have reported that when they mixed pig cells with human cells in the laboratory, some human cells became infected with PERV. This raises the possibility that the recipient of a pig transplant may be infected with PERV or with another, currently unknown, infectious disease agent.

Researchers consider that the risk of a new infectious disease emerging as a result of animal-to-human transplantation is very low. However, such an event cannot be completely ruled out and the consequences were it to happen, could be serious.

Such risks must therefore be assessed and weighed against the potential benefits of animal-to-human transplantation. It is impossible to generalize the level of risk associated with animal-to-human transplantation research (which must be assessed over the long term). The precise risk will vary from one procedure to another, depending on a range of factors. In this respect, further assessment of the risks in individual trials would be a task for a committee with considerable expertise in such matters, but a number of important factors can be identified that are likely to affect the level of infectious disease risk associated with each type of procedure:

- The amount of live animal tissue transplanted;
- The extent of the direct contact between live animal and human products;
- The length of time the contact is maintained;
- How much immunosuppression the transplant recipient receives;
- Whether or not the animal products are genetically modified; and
- The characteristics of the potential pathogen in the source animal.

## 8. How can the welfare of animals be protected?

It is true that animals experience pain and distress in a manner similar to humans; decisions regarding an animal's wellbeing must be based on this premise<sup>9</sup>. For this reason, it is necessary to set up the responsibilities of researchers and institutions for the care and use of animals for scientific purposes, with emphasis, for instance, on the following principles:

- The research must be justified. That is, the benefits to humans of the information likely to be gained must be weighed against the potential effects on the welfare of the animals;
- Researchers must treat animals with respect and consider their welfare as an essential factor in experiments;
- Animals must be used only when it is essential to do so and in the smallest numbers possible;
- Research procedures must minimize the impact on the animals.

With regard to the need of considering the welfare of animals there are general criteria which have been followed by most of the countries in this field. These criteria are referred to the principles of Replacement, Reduction and Refinement (known as the 3Rs). 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, the Code requires 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 acclimatisation
  - 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.

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<sup>9</sup> The concept of wellbeing can be defined as follows:

Animal wellbeing relates to evidence of how an animal is coping with a given situation and a judgment as to how the animal feels in these circumstances. An animal perceives and experiences internal, external and environmental factors, and this affects its wellbeing. Wellbeing is an internal state involving quality of life that is affected by responses to internal and external factors. These factors may be good or bad, positive or negative. Individuals experience wellbeing differently, because of their different needs, goals, motivations and preferences. In addition, wellbeing in one individual can vary from time to time, and changes may or may not be orderly or predictable. As a protective mechanism, departures from optimal wellbeing generally cause normal adaptive coping responses designed to return the animal to its normal state of wellbeing. Ineffective responses may result in distress, disability, disease or death. Assessment of wellbeing involves using a combination of behavioral and physiological measures that indicate: • the animal's health status; evidence of species-specific behaviors; • the status of the key indicators of the physiological and behavioral responses to a stressor.

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

- **Justification**—The Code requires projects 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**—The Code 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.

Scientists using animals in scientific procedures have an ethical and legal obligation to ensure that the principles of Reduction, Refinement and Replacement are used wherever possible. Before developing a new research protocol using animals, the investigator should consider: • whether the use of animals is justified; • if similar projects have been performed elsewhere; • whether the same results could be obtained using tissue culture or computer modeling or other alternatives to animals.

Investigators must weigh up whether the potential benefits of the scientific knowledge gained will outweigh harm to the animal.

Undoubtedly, if a research project does require the use of animals, investigators should follow the principles of Reduction and Refinement, where the minimum number of animals (or amount of animal tissue) is used to obtain the maximum amount of scientific information, and where methods of using animals are selected for their minimum impact. Collaboration between investigators (both intra and inter-institutional) can reduce the number of animals or amount of animal tissue required for a particular research question. Investigators can also collaborate to develop methods of refinement, such as standard operating procedures, to promote animal wellbeing and maintain high ethical research standards.

A summary of the major animal welfare considerations for xenotransplantation research is shown as follows:

- Housing and husbandry (including family grouping, social factors, environmental enrichment and diet) should maximize the health and social wellbeing of the animals.
- Transport arrangements should be sensitive to the needs and welfare of the animals. Transporting animals for use in scientific activities can cause them distress, from excess noise, movement and unfamiliar environment and personnel. The extent of an animal's distress depends on its species, sex, age, health and stage of pregnancy, number travelling together and social relationships. Distress is also affected by the duration and environmental conditions of the transport, and the level and quality of care administered throughout the journey. The conditions and scheduling of transport must be planned to account for extremes of climate, species-specific requirements, and contingencies. To minimize pain and distress during transport, investigators should: • use secure, comfortable and escape-proof containers; • provide appropriate food and water; • ensure all personnel responsible for handling and transportation are skilled and able to recognize signs of distress and pain; and • ensure that appropriate holding accommodation is available on arrival and that there are no unnecessary delays when transferring animals to housing.

- Pre- and post-surgery care, and the use of pain-killers, anesthetics and immunosuppression, should all be carefully monitored by trained personnel and appropriate for the animals and the procedures undertaken.
- The time held in laboratories and the number of experimental and surgical procedures carried out on an individual animal should be minimized.
- The species of animal used should be appropriate to the research and chosen to minimize the impact on animal welfare.

It is also important in this regard to choose the right animal for a proposed research protocol. Biological variability can reduce the power of a research protocol to detect treatment effects, and increase the number of animals needed to maintain an adequate level of precision. On the other hand, biological variability itself may be important to the research. The most suitable animal to achieve the required outcomes must be used, and the reasons for choosing a particular species must be clear in the proposal.

## 9. What are the animals likely to be used in xenotransplantation?

Researchers, research sponsors and the wider community generally agree that **nonhuman primates** are not a suitable source for any of the proposed animal therapies (external therapies, cell therapies or organ transplants) because of the risk of infections to the recipient and the wider community.

At present, pigs are considered to be the most likely and appropriate nonhuman source of organs and tissues. The anatomy and functioning of pigs is very similar to those of humans. Pigs are domesticated animals that are easy to breed, and, importantly, pigs are suitable for genetic modification.

Animal-to-animal transplantation studies would use a variety of animal species in the early stages of the research (such as mice, rats and rabbits). If these studies show promising results, researchers will need to trial the procedure in an animal study that is as much like the future clinical use of the therapy as possible. This will usually involve the use of nonhuman primates — specifically baboons — as transplant recipients.

With regard to **the use of nonhuman primates**, it has been pointed out that it raises serious ethical issues. The characteristics, for example, of intelligence and complex social interactions, of these closely related higher primates appear to be so like those of human beings that using members of those species as sources for xenotransplantation might well be seen as ethically unacceptable. Many have argued that the same concern should be extended to higher primates as is extended to human beings. The question then is how far this concern should extend. The close evolutionary relationship of higher primates with human beings suggests that they will share the capacity for self-awareness to the highest degree, and there is good scientific evidence that this is the case. Some would argue, however, that any ethical reservations about using higher primates for xenotransplantation should apply much more broadly. Many non-primate species, possibly including pigs, display comparable capacities of intelligence and sociality, albeit in forms that less closely resemble the human and thus appeal less strongly to human moral sensibility. To limit reservations to those species closest to human beings, in this view, is to be swayed by sentimental anthropomorphism.

Contrary to both the above positions, there is a view that, notwithstanding the features that primates (or other species) share with human beings, it would still be wrong not to save a human life even if the price of so doing was the life of a primate. According to

this position, human life has the greater value, and therefore the primate's life can be legitimately sacrificed.

It is difficult to know what sort of argument would resolve this disagreement of value. For the question is whether there is sufficient likeness between human beings and other primates for the same constraints to be imposed upon the use of primates as are imposed upon human beings. This question of likeness is not amenable to empirical resolution, but is one of fundamental moral judgment. The difficulty of resolving the issue is reflected in the diversity of opinions that people hold on the matter. Some consider that there is sufficient difference between the moral value of human life and the value of higher primate life to make the use of the latter acceptable in certain circumstances. Yet many who take this view would nevertheless argue that higher primates should be used only in very restricted and carefully controlled circumstances and only if, for example, the use of pigs for xenotransplantation turned out not to be possible. Others argue that the resemblance between human beings and species like chimpanzees and baboons is too close to justify the use of such primates as a source of material for xenotransplantation. Yet many of these people would accept that no clear boundary separates animals whose use is acceptable from those whose use is not acceptable. This dilemma concerning the moral distinction between human beings and primates is extremely difficult to resolve.

With regard to the welfare of nonhuman primates, it has been pointed out that the similarities in behavior between human beings and other primates may not lead to a consensus about their relative moral status, but they undoubtedly highlight the importance of welfare considerations in the use of primates for xenotransplantation. The routine breeding and maintenance of animals free from infectious organisms might require birth by Caesarean section, rearing in isolation, and repeated monitoring to assess levels of infection. The intelligent and social nature of primates would make such conditions particularly severe for them.

On the other hand, the safety of the use of primate organs and tissue for xenotransplantation must also be considered. A risk associated with the transplantation of animal organs or tissue into human beings is that infectious organisms will also be transmitted into the human population, leading to the emergence of new diseases. Because of the biological similarity between human beings and other primates, the risk that infectious organisms from a primate will be able to infect and cause disease in human beings is greater than the risk of disease transmission from, say, pigs to human beings. There is evidence that infectious organisms do, indeed, pass from primates to human beings and cause disease. This suggests that a cautious attitude should be adopted to xenotransplantation involving primates.

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. Therefore, the main alternative to using primate for xenotransplantation is **to use pigs**. In consequence, the moral justification for using pigs to provide organs for xenotransplantation must be considered. As has been seen, 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.

In this regard, what are the main ethical concerns that may arise from **the use of transgenic animals for xenografting**?

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 as “*‘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<sup>10</sup>; and potential loss of identity of the human recipient, including possible psychological problems and feelings that he or she is somehow less human.

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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.

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 and 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.

What about 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.

In consequence, these issues need to be considered case by case to ensure that the proposed modification does not alter the animal in any other significant way. The aim is to make sure that the animals retain the essential characteristics of their species.

#### **10. When will animal-to-human transplantation trials be justified and managed?**

Many important medical innovations have not been immediately successful. This may well be true for xenotransplantation. This raises many questions: at what stage will it be ethical to progress from using animals as xenograft recipients to the first clinical trials involving human recipients of xenografts?; how can the welfare of the first patients to undergo xenotransplantation be protected?; who will participate in such trials?... 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?... Animal-to-human clinical trial protocols would need to include some special arrangements, beyond those that apply to most other clinical trials

The careful selection of participants would be a very important aspect of any animal-to-human transplantation trials. The wellbeing of the patient would always be the first consideration. Not everyone who may wish to participate in such a trial would be able to do so for many reasons. For example, they would need to be willing to comply with long-term postoperative treatment, which would be vital to reduce infection risks, but might not be acceptable to some people. Thus, participants may need additional psychological assessment to ensure their suitability for the proposed trial.

In the early stages of animal-to-human transplantation research, trial proposals would involve very few patients. It has been agreed that any such trials should be therapeutic trials<sup>11</sup>, so the participants would need to have a realistic chance of benefiting from the procedure and have no other treatment options that offer a greater benefit.

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<sup>11</sup> Procedures, which are experimental but offer the chance of genuine treatment for the patients, are called therapeutic research. The important issue is that medical teams should not compromise the care of the individual patient in the interests of scientific research. Rather they must see themselves as using an experimental procedure for which there is evidence that the benefits will outweigh the adverse outcomes.

There are some general criteria to assess when xenotransplantation trials involving human beings is justified. Firstly, it must be pointed out that, today, there are crucial 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. Given the difficulty of making this decision, and the importance of not putting patients at unnecessary risk, it would seem advisable that xenotransplantation trials involving human beings should not proceed until there has been an opportunity for consensus amongst the transplantation community to develop based on discussion of the evidence as published in peer-reviewed scientific and medical journals.

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.

It will be ethically acceptable to offer xenotransplantation to individual patients only when it has been decided, by the principles and criteria set out above, that the results using animal recipients merit starting human trials. At this stage, the question 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.

In this respect, there are many issues involved in providing all the necessary information so that the participants can take an informed decision about whether to participate in those 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

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Since clinical trials will take place within the context of a doctor-patient relationship, the doctor is legally obliged to act in the best interests of the patient. Thus, there must be grounds for believing that the treatment will be effective and will offer some benefit to the patient. In consequence, xenografts should be offered to human patients only when results using animal recipients suggest that these operations will have a reasonable chance of success.

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.

Another important point that should be taken into account is the need to provide for prospective participants about the infection risks associated with the trial and the need for long-term **monitoring** and **follow-up**. It would be very important for trial participants to understand the importance of continuing with such monitoring — even if the procedure itself is not successful — and to accept that they have a responsibility to comply with such arrangements in return for the opportunity to take part in the trial.

Because of the infection risks, it would also be necessary to discuss the trial with the family and other close contacts and carers of the trial participant and to inform them of any potential infection risks they face as a result of the trial. Close contacts would also need to understand very clearly the implications of the trial and to accept their responsibility to comply with any necessary monitoring arrangements.

After all the information about the trial had been provided and discussed with prospective participants, they would need to sign a form to consent to the transplant procedure itself and to any long-term monitoring arrangements, including storage of tissue samples and inclusion of their own details in a central register for future reference. Close contacts would also need to sign and return information sheets to indicate that they had read and understood the requirements.

The amount of **monitoring and follow-up** needed for participants and close contacts would depend on the procedure used and the potential risks of infection. Trial participants would need to be monitored on a long-term basis to see how they respond to the therapy, so it would not be difficult to include an additional check for emerging infections. However, even if the transplant itself were unsuccessful, it may be necessary for participants and their close contacts to continue to be checked for infectious diseases. This means that, as for all other clinical trials, participants would be able to withdraw their consent for further treatment at any time in the trial but they would not be able to withdraw from the monitoring and follow-up associated with infectious diseases. They would also not be able to donate their organs, tissues or cells at any time during their life or after death.

Tissue samples from all procedures would need to be stored in a central **tissue bank** for future reference. Details of all trial participants and close contacts would also need to be entered in a central register to ensure that they could be **traced and followed-up in future**. This information would also need to be available to other countries so that trial participants and contacts could be traced, even if they were to move or travel abroad.

According to the aforementioned arguments, it has been pointed out that there are a number of reasons which explain why the restrictions that may be placed on xenotransplantation recipients and their close contacts are unsatisfactory from the perspective of a public health ethic. On the one hand, 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. On the other hand, 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...”

In view of the scientific and ethical questions to which xenotransplantation gives rise, it is important to examine other ways of meeting the demand for organs for xenotransplantation. Three approaches will be seen in this document: first, reducing the demand for transplants by promoting health and reducing disease; second, implementing measures to increase the supply of human organs, and third, developing alternative therapies.

## **11. What are the alternatives?**

### Preventive health measures

It has often been suggested that preventive programs and healthy lifestyle education on topics such as exercise and good nutrition could help to reduce the need for transplants. However, many conditions treated by transplantation, such as kidney failure, are not related to lifestyle. They can occur in young, otherwise healthy, people because of an infection or other factor. Similarly, type 1 diabetes and Parkinson’s disease — both active areas of research on animal cell therapies — are not related to lifestyle. For example, type 1 diabetes is usually diagnosed in children and young adults and its cause is unknown; the cause of Parkinson’s disease is also unknown.

There are formidable obstacles in the way of measures to improve health and prevent disease. It is often difficult to establish a precise relationship between a lifestyle or environmental factor and a particular disease. Whilst the relationship between excess alcohol consumption and cirrhosis of the liver is clear, the situation is more complicated for most other conditions for which transplants may be required; for example, a high blood cholesterol concentration is one risk factor in coronary heart disease, but there are many others, not least genetic influences and perhaps also environmental factors encountered in fetal life.

As has been seen, many of the diseases currently treated by transplantation are not amenable to preventive approaches and are unlikely to become so in the near future, if at all. These include all the common causes of kidney failure and the cardiomyopathies which afflict young people. Sufferers from cystic fibrosis, an inherited disease, are unlikely to live beyond the third decade without a lung or heart-lung transplant. Finally, any gains made as a result of preventive measures to reduce disease are likely to be long-term ones. In the meantime, the demand for transplantation remains pressing.

### Increasing the supply of human organs

It has been suggested that animal-to-human transplantation would not be needed if the number of human donors could be increased. Unfortunately, most people do not indicate during their lifetime that they wish to donate their organs and tissues after death and different countries have different legislation to deal with this situation. In some countries, such as Australia and the United States, only people who have indicated their intention to donate before they die are considered to have consented. However, as long as

the person has not registered a specific objection, the law allows close relatives to give consent for the organs to be donated.

Other countries have an ‘opt out’ system of consent, in which it is presumed that people are willing to donate their organs unless they clearly indicate before they die that they do not wish to be donors (presumed consent). The extent to which relatives can influence the donation in this case varies from country to country; for example, in Austria and Belgium, relatives are not consulted, but in Spain they may be.

The number of organs and tissues available for transplantation has increased in the countries that have adopted the presumed consent approach, but even this has not been enough to overcome the shortage of organs and tissues.

Payment for organs has also been suggested as a way to increase the availability of human tissues and organs. But this approach is ethically very difficult and has not, so far, been considered acceptable in the majority of the countries. Increased support for emergency care professionals in their work with relatives of accident or sudden death victims could help to increase the number of donations, but would be unlikely to overcome the shortfall.

Living donor programs — in which living donors, often relatives, donate an organ (such as a lung or kidney), part of an organ (such as half the liver), or tissue (such as bone marrow) — are becoming more common. But there are limitations. Although the donation of a single kidney or some bone marrow is now accepted practice, the donation of half an adult liver is ethically controversial because such major surgery carries significant risks to donors. For instance, in Norway, the high kidney transplant rate is due the high number of live donors giving kidneys.

Even if all human cadaveric organs were somehow made available for transplant, the supply would still not meet the potential demand. Continued efforts are needed to increase the number of human donations to transplantation programs. However, it is very unlikely that such efforts will overcome the extreme shortfall of human donors, especially as more new therapies are developed. Therefore, it is necessary to consider how far the use of alternative therapies may provide an alternative to human organ transplantation.

#### Alternative therapies

At the same time as animal-to-human transplantation research is progressing, researchers are exploring other new therapies to overcome the shortage of donated organs and tissues and treat an increasing range of diseases and conditions that have not been treated before.

One such area of work is on **human stem cells**. Stem cells are early, unspecialized cells that can, under certain conditions, be induced to mature into specialized cell types (such as heart, liver, brain and pancreas). It is hoped that these cells will have the potential to repair human organs and to treat a similar range of diseases to those proposed for animal cell therapies. However, human stem cell technology raises a number of ethical issues of its own, and its development will require the use of animals in preclinical studies that are similar to those required for xenotransplantation research (including nonhuman primates). Also, some stem cell techniques cannot be regarded as an ‘alternative’ to xenotransplantation because the stem cell lines are grown on a layer of animal cells, so they come within the definition of animal external therapies.

A second area of research is into the use of **mechanical or artificial organs**, either for short-term ‘bridging’ procedures for people waiting for an organ to become available or

for longer-term replacement or repair. The development of artificial devices may provide solutions to some conditions and diseases that currently require transplants, but not all.

With regard to the **gene therapy**, it has been pointed out that 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.

Like xenotransplantation, research in these areas is in the early stages and it is not clear whether they will be more or less successful than animal therapies across the wide range of diseases and conditions involved. Only further research will determine the best form of therapy for each condition.

## **12. How would resources be allocated?**

At this early stage in the development of animal-to-human transplantation, it is not possible to predict all the costs that may be involved for the treatment and continuing supervision of recipients of animal therapies. Ideally, in the longer term, the costs of ongoing treatment and care would be matched by the savings made in enabling recipients to lead healthy and productive lives.

In the meantime, it is important to ensure that animal-to-human transplantation research does not divert funds away from the other approaches to tissue and organ shortage described above of this document, including research into alternatives such as human stem cell therapies and artificial organs. For publicly funded research, funding bodies would continue to assess these options and ensure that funds are distributed amongst the various alternatives according to their potential for success. For privately funded research, the commercial interests of companies should ensure that the effort and funding focuses on the most promising procedures.

During the research phase, participation in a clinical trial would be free for the patient, as the costs would be borne by the research sponsors — often biotechnology companies. However, if clinical trials were to show that animal transplantation therapies are successful, this would lead to an increase in demand for such therapies, which would have implications for health care funding and resource allocation.

In summary, it is likely that the major cost implications of xenotransplantation would arise from the larger number of transplant that would be possible. Should xenotransplantation develop into a successful procedure, decisions about its provision would have to be made within the context of wider debate about resource allocations within the health system. In this respect, there are good reasons for introducing new and potentially expensive specialist services in a controlled way. Restricting xenotransplantation to designated centers for the foreseeable future would ensure adequate monitoring of its cost and effectiveness.

## **APPENDIX A: ABOUT THIS COMMUNITY GUIDE AND THE NEED OF OBTAINING YOUR PARTICIPATION BY MAKING A WRITTEN SUBMISSION**

This guide has been prepared in order to provide advice on the scientific, ethical and technical issues relating to xenotransplantation research, produce guidelines for assessment of animal-to-human transplantation trials proposals, and consult widely the community about these issues, in particular, about: ethical and social concerns; animal welfare; efficacy and safety; trial protocol (including consent, follow-up, etc); and allocation of resources.

In this respect, a discussion paper will be included in the Xenome web site: [www.xenome.eu](http://www.xenome.eu) in order to provide background material to promote an informed community discussion on this issue. There are also more sections in this web site where it is possible to gather more information about the issues involved in xenotransplantation and links in this regard.

There will be an advertisement on this website, inviting community to comment focused on the key issues that are briefly presented in this guide for the community and to write submission in the mentioned discussion paper, in particular, in the key issues described in its Appendix A. Everyone can make a written submission on the Xenome web site. We want to discover public and professional views by issuing these consultation documents that are uploaded on this web site.

This guide, jointly with the mentioned discussion paper, has been developed to provide background information on what xenotransplantation is, why it is being considered now, and what the main issues are over which the community is being consulted. It is essential to understand that this community guide is not the consultation document. Rather it is designated to complement and introduce the reader to a second document prepared by the partners of the Xenome project, which will include the partners' response to submissions received during the first round of public consultation and invites further input to the matters being inquired into by the partners of the Project. It will also include revised draft guidelines which, if approved, would be used to oversight xenotransplantation research should such research be authorized.

Readers of this community guide who wish to engage in the public debate are encouraged to obtain the discussion paper and, when ready, the response paper, consider the issues and to make a written submission to the Xenome website on the issues raised and, in particular, on the proposed guidelines for the conduct of the research in this field.

The discussion paper and this community guide can be obtained from the address given below: xxx. Both documents are also available on the Xenome web site: xxx