STATENS MEDICINSK-ETISKA RÅD
Postadress: Smer, Socialdepartementet, SE-103 33 Stockholm • Besöksadress: Fredsgatan 8
Tel 08-405 10 00 • smer@regeringskansliet.se • www.smer.se

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Opinion on xenotransplantation

Summary

Xenotransplantation refers to the transplantation of living biological material in the form of cells, tissue or whole organs from animals to humans. Experiments with xenotransplantation of organs to one living and a number of brain-dead humans were recently carried out in the USA. An application to conduct a clinical study with more patients is currently being processed (October 2022) by the US Food and Drug Administration (FDA). The future of xenotransplantation is difficult to predict, but it cannot be ruled out that there will be interest in conducting xenotransplantation research and treatments in Sweden.

With this Opinion, the Swedish National Council on Medical Ethics (herein after referred to as SMER, or the Council) aims to highlight the many ethical questions arising from xenotransplantation – in preclinical and clinical research, as well as in a potential future phase of xenotransplantation as treatment. The purpose of this Opinion is to stimulate societal debate and provide a basis for further analysis of regulation and practice in the area.

SMER's assessment is that fundamental questions of animal and human ethics remain concerning xenotransplantation, such as those raised in the report submitted by the Commission of Inquiry on Xenotransplantation in 1999. Even in the research phase, xenotransplantation raises questions concerning animal welfare and instrumentalisation, the boundary between animal and human, the balancing of risks and expected benefits, and informed consent and self-determination. Many potential conflicts of values and interests are raised, such as between animal suffering and the benefits to humans, and between the utility of scientific progress and the protection of individual research subjects and the community at large.

SMER is of the opinion that:

- there is an urgent need to drive progress in the research, but only in ethically acceptable forms;

- there is a balance to be struck between animal suffering and benefits to humans, but that the kind of total instrumentalisation of animal species that occurs in the context of xenotransplantation is ethically problematic, where animals are bred solely to satisfy human needs for organs, tissue and cells;

- questions concerning information, informed consent, risks to individuals and the community at large, and which patients should be asked to participate must be given special attention before early xenotransplantation trials are conducted;

- the prerequisites for proceeding with clinical trials include providing accurate and clear information concerning the expected risks and benefits, as well as the uncertainties involved, that the informed consent of the patient/research subject is sought in a way which allows the person to make an independent decision without being pressurised, and that the clinical trial has been approved by an independent body that has assessed its scientific merits and reviewed its ethics;

- there is a need for renewed social debate on xenotransplantation, illuminating the ethical questions from all sides; and

- an adequate regulatory framework must be in place before any xenotransplantation trials can be carried out in Sweden.

1. Introduction

In January 2022, xenotransplantation became world news when a pig's heart was transplanted into a gravely ill man in the USA, who then survived for two months. Many observers believe that more clinical studies of xenotransplantation of organs will be carried out in the near future. Xenotransplantation refers to the transplantation of living biological material in the form of cells, tissue or whole organs from one species to another, for example from animal to human. Xenotransplantation also includes extracorporeal perfusion, where a patient's blood is circulated outside their body where it comes into contact with live cells from animals, and is then returned to the patient.[1] The transplantation of material from animals that does not contain living cells, such as heart valves, insulin, tendons and blood vessels, does not come under the category of xenotransplantation.

There have been isolated experiments with xenotransplantation of organs since the beginning of the 1900s, although not in Sweden. But no patient has survived xenotransplantation for any significant period of time. In the 1990s, research into various forms of xenotransplantation was being carried out in different parts of the world. In Sweden, clinical trials were being conducted involving xenotransplantation of cells and extracorporeal perfusion. In March 1997, after the research had shown that pathogens could be transmitted to humans during xenotransplantation, the Swedish Government set up a commission of inquiry to assess the ethical, medical, legal and animal welfare aspects of transplanting organs, tissue or cells from animals to humans. The remit of the Commission of Inquiry on Xenotransplantation was to consider and propose the conditions under which clinical trials could be permitted. The Commission's terms of reference referred to the predictions in various contexts that xenotransplantation would become commonplace within the space of 5–10 years.

During the period that the Commission was active however, the Swedish researchers abandoned their clinical trials. In many other parts of the world too, clinical research in this area ceased due to the risk of spreading disease and because the focus shifted to stem cell research instead.

In October 1999, the Commission submitted its report proposing that well-controlled clinical trials should be permitted to a limited extent and where

[1] *Från en art till en annan – transplantation från djur till människa* (SOU 1999:120), 31

the risks were deemed manageable. The Commission further proposed that a separate Act, the Xenotransplantation Review Act, should be introduced to regulate the authorisation application procedure for clinical trials of xenotransplantation, and a committee with broad representation, including a preponderance of lay members appointed by the Riksdag, should examine applications for such trials. A xenotransplantation register and a xenotransplantation biobank should be introduced to facilitate the early detection of incidents which may indicate that a pathogen had been transmitted.

The report by the Commission of Inquiry on Xenotransplantation was referred for consultation and most of the referral bodies endorsed the main features of the proposals and assessments, or did not raise any objections. These proposals were never implemented, however, since it was considered that clinical xenotransplantation would not be relevant in the foreseeable future.

No clinical trials with xenotransplantation have been resumed in Sweden. On the other hand, immunology research is being carried out, the results of which are important for xenotransplantation. However, both preclinical and clinical research into xenotransplantation is being conducted in other parts of the world, such as the USA and China. In order to overcome both the immune response that leads to the rejection of xenotransplants and the risk of pathogen transmission, genetically modified pigs have started being used as source animals.

There are hopes that, with the aid of xenotransplantation, we could remedy the scarcity of donated organs from humans, and cure or alleviate severe illnesses. However, xenotransplantation raises many medical and ethical questions.

2. Objectives and purpose of this Opinion

SMER is responsible in Sweden for analysing medical ethics questions from the perspective of the community as a whole, and assessing the consequences for human dignity and privacy of medical research projects, diagnostics and treatments.

When research into xenotransplantation was being conducted in Sweden in the 1990s, SMER monitored this development. During the period 1997–

2000, the Council held a seminar and a conference on xenotransplantation in cooperation with the Swedish Society of Medicine's delegation for ethical questions and the Swedish Gene Technology Advisory Board, among others. The chair of the Commission of Inquiry on Xenotransplantation was Bertil Persson, who was a member of SMER. Three other members of the Council were also members of the Commission.

The recent breakthroughs in research into the xenotransplantation of organs have brought this issue into focus again. In this Opinion, SMER highlights the many ethical questions arising from xenotransplantation – in preclinical and clinical research as well as in a potential future phase of xenotransplantation as treatment. The Opinion also includes a brief outline of the medical and legal questions related to xenotransplantation. The purpose of this Opinion is to stimulate societal debate and provide a basis for future regulation and practice in the area.

The Opinion has been produced on the basis of a literature review and analysis in the scientific and ethics fields, as well as dialogue with researchers in the area. SMER has also read the 1999 opinion of the Commission of Inquiry on Xenotransplantation and assessed whether its analysis and proposals are still relevant today. Besides discussion at the working group meetings, this issue was discussed and analysed at the Council's meetings in the spring, summer and autumn of 2022. In addition, during the 2022 Almedalen Week, the Council held a debate on the ethics of the issue that was open to the public.

3. Medical questions

3.1 Intended application

The most widely recognised experiments with xenotransplantation concern organ transplantation. One of the hopes surrounding xenotransplantation is that the method could add to the supply of organs needed to meet the demand for transplanted organs. Currently, the shortage of donated organs means that people die while waiting for an organ transplant. In Sweden there were around 800 people waiting for an organ transplant in mid-2022, and in recent years 1–2 people have died each week waiting for a transplant.[2] With xenotransplantation of the heart and lung in particular, potentially more lives

[2] Mer organdonation. *Statistik och rapporter*. https://merorgandonation.se/statistik-och-rapporter, retrieved 2 June 2022

could be saved, and with xenotransplantation of the kidney, symptoms could be alleviated and quality of life could be improved for many people suffering kidney failure. Another idea that has been proposed is that patients could receive animal organs as a temporary solution while waiting for a human organ to become available.

Xenotransplantation has a number of potential advantages over the transplantation of organs from human donors. There is no need to wait for a human organ to become available; operations can be planned and scheduled. The quality of the organ is known.[3] Organs could be designed to match the recipient and thus everyone could have access to a new organ if needed. Today, people with unusual tissue types for example, who have developed HLA antibodies, have more difficulty accessing donated human organs than others because the number of donors with the same or similar tissue type is more limited.[4] Patients who are unable to receive a human organ for certain reasons including autoimmune disease, and currently cannot be treated in any other way either, could potentially be treated with xenotransplantation.[5] However, studies also show that there are sections of the population that are not prepared to receive transplanted organs from animals.[6]

Besides xenotransplantation of organs, there are hopes of being able to transplant tissue and cells, such as insulin-producing islets of Langerhans cells and brain cells, from animals. The goal of xenotransplantation of cells is being able to cure or alleviate diseases such as diabetes, Parkinson's disease and Huntington's disease. Significantly more patients would potentially be eligible for xenotransplantation of cells than of whole organs.

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[3] Sykes, M. et al. (2003). Position Paper of the Ethics Committee of the International Xenotransplantation Association. *Xenotransplantation*, 10(3), 194–203. https://www.tts.org/images/stories/ixa/regulatory_documents/10_IXA_Ethics_Committee_Position_Paper_2003.pdf, 195

[4] Nuffield Council on Bioethics. (1996). *Animal-to-Human Transplants The ethics of xenotransplantation*, 7

[5] Growth, C-G. (2002). Xenotransplantation ger framtidshopp. Medicinsk kommentar. *Läkartidningen*, no 4 2002, 252-254. https://lakartidningen.se/wp-content/uploads/OldPdfFiles/2002/24087.pdf

[6] See for example *Från en art till en annan – transplantation från djur till människa* (SOU 1999:120), Chapters 13 and 14.

3.2 Immune response[7]

3.2.1 Organ transplantation

When foreign tissue and organs are transplanted into the human body, its immune system perceives the organ/tissue as an intruder to be fought against. The intensity and nature of the immune response are affected by the degree of difference between donor and recipient. The immune response to xenotransplantation is usually stronger but is also different from the response seen in transplantation between different individuals within the same species (allotransplantation). The immune response to xenotransplantation is more similar to that of allotransplantation if donors and recipients are of closely related species, such as humans and certain types of apes[8] (concordant xenotransplantation).

In discordant (between less closely related species) xenotransplantation of organs, a very rapid and powerful immune response is triggered that usually destroys the transplanted organ within minutes to hours (hyperacute rejection). If hyperacute rejection can be prevented, an acute humoral (or vascular) rejection begins within the first few days. Within days to weeks of the transplantation, cellular rejection of the xenotransplant also occurs. Different parts of the body's immune system are activated in the different phases of rejection. In order to prevent cellular rejection of xenotransplants into humans, strong immunosuppressive drugs must be administered, and these make the patient highly vulnerable to infections.

When immunosuppressive treatment is given to apes who have received pig organs in preclinical trials, blood coagulation problems have occurred, which in some cases have led to the death of the recipient. This is seen as another factor that makes it difficult to get a xenotransplantat to survive for any significant length of time.

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[7] Lu, T. et al. (2020). Xenotransplantation: Current Status in Preclinical Research. *Frontiers in Immunology*, 10, 3060. https://doi.org/10.3389/fimmu.2019.03060

[8] There are many different types of apes. The apes most closely related to man are the hominids – chimpanzees, bonobos, gorillas and orangutans. Then there are Old World monkeys (which include baboons and rhesus macaques) and gibbons. Organs from chimpanzees and baboons were used in early xenotransplantation trials in the USA. In preclinical trials where organs from pigs are transplanted into apes, baboons, rhesus macaques and crab-eating macaque are now used. The use of hominids in animal experiments is generally prohibited in Sweden.

3.2.2 Cell transplantation

In the case of xenotransplantation of cells, the transplanted material does not contain any blood vessels: the cells are injected at a suitable site and ultimately the recipient's vascular system grows into the transplant. Consequently, there are no foreign blood vessels that can be attacked by the rejection response. However, a cellular immune response does occur with the xenotransplantation of cells.

3.3 Transmission of pathogens

Xenotransplantation creates close and prolonged contact between animal cell and human cell and this enables or possibly facilitates the transmission of pathogens such as viruses and bacteria that may be present in the tissue of the source animal. These viruses and bacteria may cause infection. Pathogens can also be transmitted via residual white blood cells in the donated organ in the case of organ xenotransplantation. Immunosuppressive treatment and other measures taken to circumvent immunological barriers, thereby enabling acceptance of the xenotransplant, may further facilitate the transmission of pathogens that under normal circumstances cannot infect humans. Pathogens from animals, especially viruses, could also give rise to new pathogenic organisms if mixed with human pathogens.[9]

A transmitted pathogen could cause disease in the individual who received the transplant. This disease could also be spread to people in the patient's immediate vicinity or, in the worst case, to the general public in the form of a zoonotic pandemic. According to the FDA guidelines for xenotransplantation, it is difficult to predict which pathogens might cause disease in a xenotransplant recipient solely on the basis of an analysis of naturally occurring zoonoses, as there are big differences between normal animal–human contact and the contact that occurs between a recipient and a xenotransplant.[10]

Particular attention has been paid to porcine endogenous retroviruses (PERV). These retroviruses may be latently infectious. In the 1990s, a

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[9] U.S. Department of Health and Human Services, Food and Drug Administration. (2016*). Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans Guidance for Industry (April 2003, Updated December 2016)*. https://www.fda.gov/media/102126/download, s 2

[10] U.S. Department of Health and Human Services, Food and Drug Administration. (2016). *Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans Guidance for Industry (April 2003, Updated December 2016)*. https://www.fda.gov/media/102126/download, s 2

number of studies showed that under certain experimental conditions, PERV can infect human cells. This led to a voluntary halt in further research into xenotransplantation among Swedish researchers, and in many other countries. The EU and other research funding bodies stopped funding such research, and the interests of commercial actors shifted increasingly to stem cell research. However, research into xenotransplantation continued in China, Russia and some Eastern European countries. According to a research overview from 2021, PERV had not been transmitted to the recipient in any of the preclinical or clinical trials of xenotransplantation that had been carried out up until that point in time.[11]

The man who received a pig's heart transplant in January 2022 died after two months. A few months later, data from the experiment was published which showed that the man had been infected with a cytomegalovirus from the pig, but no transmission of the PERV could be demonstrated. The man died because the heart he had received stopped functioning – not because it was rejected. It is not clear at the time of writing whether the viral infection played any role in this course of events.[12]

4. Research and application

4.1 Genetically modified pigs

Currently, pigs are generally seen as the most suitable source animal for xenotransplantation of organs. Pig organs are relatively similar in size to human organs and pigs have a considerably shorter generation time than apes, for example. Due to the risk of transmission of pathogens and for reasons of animal ethics, apes are no longer used as source animals in xenotransplantation.

Since the 1990s, research has been conducted into the production of transgenic pigs with certain human genes with the aim of preventing organ transplant rejection. Different variants of cloned, genetically modified pigs have been produced. In recent years, producing transgenic pigs has been facilitated by the new CRISPR technique, which has made it easier and faster

[11] Denner, J. (2021). Porcine endogenous retroviruses and xenotransplantation. *Viruses*, 13(11), 2156–72.

[12] Griffith, B. P. et al. (2022). Genetically Modified Porcine-to-Human Cardiac Xenotransplantation. *New England Journal of Medicine*, 387(1), 35–44. https://doi.org/10.1056/NEJMoa2201422

to edit individual genes and made it possible to implement several different genetic modifications in the same cell.

In 2015, a team at Harvard Medical School created a pig where all 62 known copies of PERV had been knocked out.[13] However, there is no consensus on whether there is a need to guarantee the inactivation of PERV in pigs used for xenotransplantation. Furthermore, it is not known whether these pigs can be reinfected by PERV.[14]

The pig whose heart was transplanted into a human in January 2022 had been bred by a US company. The pig had ten genetic modifications, but none had any impact on PERV. Four genes had been knocked out, three of which produced substances that cause rejection in humans. The fourth gene knocked out prevented the heart from growing too large. In addition, the pig had received six human genes to reduce inflammation and suppress coagulation.[15] German scientists have announced that they are breeding a pig with five genetic modifications which they plan to use in experiments with baboons and subsequently in clinical trials in 2025.[16]

4.2 Treatment for PERV infection

The risk of PERV infection could be reduced by medicines and vaccination, but as yet there are few results from studies investigating this.[17]

4.3 Preclinical research on xenotransplantation of organs

In preclinical trials studying the immune response in xenotransplants of organs, it is currently standard practice to use baboons and macaques as the recipient animals, as they are relatively closely related to humans and have similar immune systems. Such trials have been conducted in the USA.

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[13] McAlpine, K. (15 October 2015). *Transplanting from Pig to Human*. Harvard Medical School News & Research. https://hms.harvard.edu/news/transplanting-pig-human

[14] Lu,T. et al. (2020). Xenotransplantation: Current Status in Preclinical Research. *Frontiers in Immunology*, 10, 3060. https://doi.org/10.3389/fimmu.2019.03060

[15] Alpman, M. (11 January 2022). Första grishjärtat slår i människa. *Forskning&Framsteg*. https://fof.se/artikel/2022/2/forsta-grishjartat-slar-i-manniska/

[16] Alkoussa, R. & Uyanik, A. (3 February 2022). German researchers to breed pigs for human heart transplants this year. *Reuters*. https://www.reuters.com/article/health-transplant-pig-germany-idAFL1N2U71UW

[17] Denner, J. (2021). Porcine endogenous retroviruses and xenotransplantation. *Viruses*, 13(11), 2156–72.

Primates who have received genetically modified pig kidneys have survived for several years.[18] In some cases, baboons who have received heart xenotransplants from genetically modified pigs as life-sustaining treatment[19] have survived for more than six months. Apes that have received pig livers or lungs have not survived for more than one month or two weeks, respectively.[20]

4.4 Clinical trials of xenotransplantation of organs

In autumn 2021, two experiments involving xenotransplants of genetically modified pig kidneys into brain-dead humans were carried out in the USA. The kidneys functioned for the 54 hours that the experiment lasted.[21] In January 2022, as mentioned above, an attempt was made in the USA to transplant a heart from a genetically modified pig into a gravely ill man who died two months later. During summer 2022, pig hearts were transplanted into two brain-dead humans.[22] The FDA is currently processing an application by the University of Alabama to perform xenotransplantation of pig kidneys into 20 patients with end-state kidney disease.[23]

4.5 Xenotransplantation of tissue

Preclinical studies of xenotransplantation of corneas into apes have been carried out in China and South Korea for example[24] but SMER has no knowledge of whether any clinical trials have been started.

In the USA, attempts are being made to treat severely burned people with skin from genetically modified pigs.[25] The skin is intended to act as a

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[18] Sykes M & Sachs, DH. (2022). Progress in xenotransplantation: overcoming immune barriers. *Nature Reviews Nephrology*, Oct 5. doi: 10.1038/s41581-022-00624-6.

[19] A heart can also be transplanted to help the existing heart function better. Such transplantation is not defined as life-sustaining treatment.

[20] Lu,T. et al. (2020). Xenotransplantation: Current Status in Preclinical Research. *Frontiers in Immunology*, 10, 3060. https://doi.org/10.3389/fimmu.2019.03060

[21] Montgomery, R.A. et al. (2022). Results of Two Cases of Pig-to-Human Kidney Xenotransplantation. *The New England Journal of Medicine*, 386(20), 1889-1898. doi: 10.1056/NEJMoa2120238

[22] Neergard, L (12 July 2022). Pig organ transplants inch closer with testing in the dead, *AP News*. Pig organ transplants inch closer with testing in the dead | AP News

[23] U.S. National Library of Medicine. ClinicalTrials.gov. *Porcine Kidney Xenotransplantation in Patients With End-Stage Kidney Disease*. https://clinicaltrials.gov/ct2/show/NCT05340426

[24] Yoon, C.H. et al. (2021). Corneal xenotransplantation: Where are we standing?. *Progress in Retinal and Eye Research*, 80, 100876. doi: 10.1016/j.preteyeres.2020.100876 https://www.sciencedirect.com/science/article/pii/S1350946220300483

[25] U.S. National Library of Medicine. ClinicalTrials.gov. *Evaluation of Safety, Tolerability and Efficacy of Xeno-Skin® for Temporary Closure of Severe Burn Wounds*. https://clinicaltrials.gov/ct2/show/NCT03695939

temporary protective barrier until treatment with autologous skin grafts can take place. The results of the study are not yet published (October 2022).

4.6 Xenotransplantation of cells

For people with Type I diabetes, one way to avoid taking daily insulin injections could be to receive transplants of islets of Langerhans, which are insulin-secreting pancreatic cells. Today, these cells are usually taken from deceased human donors. The first clinical trial of xenotransplantation of islets of Langerhans was conducted at Huddinge Hospital in Sweden, in 1994. At that time, ten patients received islets of Langerhans isolated from porcine foetuses. In four of the patients, it was demonstrated that the transplant was successful, and the cells produced insulin for a maximum of 14 months. However, the insulin production was insufficient to reduce the patients' need for injected insulin.[26] More recent research has focused on producing genetically modified pigs whose islets of Langerhans will not be rejected by the recipient. Clinical trials have taken place in New Zealand and Argentina.[27]

Around the turn of the millennium, several Swedish university hospitals participated in a European research collaboration that aimed to characterise the critical neurobiological and immunological factors affecting the transplantation of nerve tissue from animals.[28] However, no clinical trials were ever carried out. The goal of xenotransplantation of nerve cells is to treat conditions such as Parkinson's disease, Huntington's disease, and epilepsy.

Xenotransplantation of liver cells has been proposed as an alternative to liver transplants for patients with acute and chronic liver failure. Preclinical trials with apes as recipients have been conducted in Brazil.[29]

4.7 Extracorporeal perfusion

An experiment with extracorporeal perfusion was conducted in the 1990s at Sahlgrenska Hospital in Gothenburg, Sweden, where two patients with end-

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[26] *Från en art till en annan – transplantation från djur till människa* (SOU 1999:120), 143–145

[27] Wynyard, S. (2020). Challenges and practical realities of long-term patient follow-up in three xeno-islet clinical trials: the experience in pig islet xenotransplantation trials in New Zealand and Argentina. *Xenotransplantation*, 27(3), e12605. doi: 10.1111/xen.12605

[28] *Från en art till en annan – transplantation från djur till människa* (SOU 1999:120), 147

[29] Bonavita, A.G. Et al. (2010). Hepatocyte xenotransplantation for treating liver disease. *Xenotransplantation*, 17(3), 181–187. https://doi.org/10.1111/j.1399-3089.2010.00588.x

stage renal failure requiring dialysis had their blood circulated through a pig kidney. This experiment aimed to study whether hyperacute rejection could be avoided by significantly reducing the research subjects' natural antibodies to pigs in advance, and studying the immune response and immediate reaction of the research subjects to their blood being circulated through a pig kidney. The trials were halted due to complications arising, but the patients recovered.[30]

5. Proposal of the Commission of Inquiry on Xenotransplantation

In October 1999, the Commission of Inquiry on Xenotransplantation proposed that well-controlled clinical trials should be permitted to a limited extent in Sweden. Based on the current state of knowledge at the time, the Commission did not consider the risks of xenotransplantation to be such that a permanent or temporary prohibition would need to be introduced. In the Commission's view, however, no clinical trials should be carried out before the Government and the Riksdag had considered the Commission's proposal. The Commission proposed that the authorisation application procedure for clinical trials of xenotransplantation should be governed by a specific Act, the Xenotransplantation Review Act, with an associated Ordinance. A committee with broad representation including a preponderance of lay members appointed by the Riksdag would examine the applications for these clinical trials. This committee would then review the clinical trial on the basis of medical, ethical, animal welfare and legal points of departure as part of the authorisation application procedure. The committee would consider in particular: 1) the value of the knowledge, based on science and best practice, that the experiment can be expected to generate; 2) whether and the extent to which the experiment can cure or alleviate the symptoms of the participating patients' disease; 3) the risks of damage to the physical or mental health of patients, research subjects or other persons that the experiment may entail, and the safeguards or other precautions that may be called for therefore; and 4) how the experiment can be anticipated to affect animal welfare and health. The application should also be reviewed in what were then called the research ethics committees (the Ethical Review Act and the regional ethical review boards did not exist yet at that time) and the animal experiment ethics committees.

[30] *Från en art till en annan – transplantation från djur till människa* (SOU 1999:120), 145–146

The Commission proposed that written consent to participation should be obtained only after the research subjects had been able to consider their participation closely and given the opportunity to consult a person who is familiar with the physical and psychological problems that xenotransplantation can entail. The patients or other participants in the experiment would be permitted to withdraw their consent at any time and discontinue their participation in the trial. The Commission also made the assessment that close contacts of the participants/patients should receive information about the risks but not have a right of veto over the research.

The proposed regulatory framework required that the research subjects would be adequately followed up after the operation. According to the proposal, this follow-up could include testing, examination by a physician, or other forms of medical examination. The researchers would report the results of the follow-up at least once per year to the committee.

A xenotransplantation register and biobank should be introduced to facilitate early detection of incidents that could indicate the transmission of a pathogen. It was proposed that the register and biobank should be managed by the then Swedish Institute for Communicable Disease Control (*Smittskyddsinstitutet*).

The Commission were of the view that they could only express an opinion on whether clinical research should be permitted. In the Commission's view, an evaluation and a reconsideration of xenotransplantation by the government would be required before any future transition to xenotransplantation as an established treatment method could be permitted.

6. International guidelines

During the first decade of the 21st century, a number of international organisations published guidelines and recommendations on xenotransplantation. They were unanimous that clinical research on xenotransplantation requires, among other things, adequate preclinical data, authorisation and monitoring by public authorities, as well as global cooperation.

In 2003, the International Xenotransplantation Association (IXA) Ethics Committee recommended that clinical trials with xenotransplantation should only be carried out under the supervision of public authorities. According to

IXA, prior to clinical trials beginning, adequate preclinical data must exist that takes into account the risks to the research subjects and to the community at large. The source animals must come from closed colonies free of known pathogens. The research subjects, and if necessary their close contacts, should be monitored. IXA saw an urgent need for international cooperation and guidelines in this area in light of the possibility of medical tourism for example, where people travel to countries with less stringent regulation to access treatment that involves xenotransplantation.[31]

In 2003, the Council of Europe's Committee of Ministers issued a Recommendation on xenotransplantation. According to this Recommendation, authorisation for clinical trials with xenotransplantation should only be granted if preclinical studies have shown, in accordance with internationally accepted scientific standards, that it is highly likely that there is no risk to public health and that the potential level of therapeutic benefit and safety for the patient is not disproportionate to the risks of the procedure. According to the Recommendation, Member States are required to have a plan in place to address any events, in particular of infection possibly related to a xenotransplantation, which could compromise public health. The pain, suffering and distress of the animals used should be minimised. Member States should take active steps to ensure that the fundamental questions raised by xenotransplantation are the subject of appropriate public discussion.[32]

The World Health Organization (WHO) has held a number of international consultations on xenotransplantation. The Changsha Communiqué was published in 2008 and included recommendations on the regulation of clinical trials of xenotransplantation. For example, the WHO recommends having a system in place for identifying and responding to any infectious disease outbreaks resulting from xenotransplantation. Among other things, the WHO recommends that Member States regulate and maintain a register of xenotransplantation trials, are aware of the infection risks of xenotransplantation, including those associated with patients travelling to receive xenotransplantation products outside their territories, and have plans in place to identify and respond to any such infections in a timely manner.

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[31] Sykes, M. et al. (2003). Position Paper of the Ethics Committee of the International Xenotransplantation Association. *Xenotransplantation*, 10(3), 194–203. https://www.tts.org/images/stories/ixa/regulatory_documents/10_IXA_Ethics_Committee_Position_Paper_2003.pdf

[32] Council of Europe Committee of Ministers (2003). *Recommendation Rec(2003)10 of the Committee of Ministers to member states on xenotransplantation*.

Those conducting trials are recommended to ensure that adequate preclinical data on safety and efficacy exists, usually from non-human primate testing, and that source animals are bred for the purpose and as safely as possible. Trial participants should be selected for whom there is no effective alternative therapy available and who understand the risks and consequences of the procedure, including the need for compliance with life-long follow-up. There must be a comprehensive plan for post-transplant long-term patient follow-up and the management of possible xenotransplant-related infection episodes.[33]

In collaboration with IXA and the University Hospital in Geneva, the WHO has established an international human xenotransplantation database. The database is now being updated in cooperation with a Chinese hospital.[34]

7. Current regulatory framework

The proposal of Sweden's Commission of Inquiry on Xenotransplantation, which included a regulatory framework for clinical trials with xenotransplantation that included a specific Act and a specific committee to approve clinical trials, was not implemented. There is no specific regulatory framework for xenotransplantation in place in Sweden. Research into xenotransplantation is simply subject to the same regulatory framework as other research that involves animals and humans. Since the Commission of Inquiry submitted its proposal, the legislation governing research ethics has changed. For example, there is now an Act concerning the Ethical Review of Research Involving Humans (2003:460), hereinafter the Ethical Review Act. New regulation at the EU level has also come into force. It is not always clear which regulatory framework should apply to xenotransplantation trials.

Advanced Therapy Medicinal Products (ATMP) are regulated at the EU level by Regulation 1394/2007. Under certain circumstances, animal cells and tissue may be regarded as "xenogeneic cell-based medicinal products", and constitute ATMP, depending on whether the cells have been modified and undergone a manufacturing process, for example. ATMP may only be use in humans in the context of a clinical trial or where the product is approved via a central approval procedure at the European Medicines

[33] World Health Organization (WHO). (2018). *The Changsha Communiqué*. https://www.tts.org/images/stories/ixa/regulatory_documents/5_WHO_Global_Consultation_Communique_Changsha_China_-_November_2008.pdf

[34] See https://humanxenotransplant.org/

Agency (EMA). Authorisation to conduct a clinical trial of a medical product is granted by the competent authority(ies) of the Member State(s) in which the trial is to be conducted. In Sweden, the competent authority is the Swedish Medical Products Agency. An application for this authorisation is ethically reviewed by the Swedish Ethical Review Authority and the Authority's assessment is based on the same points of departure that apply to the approval of other research (see below). In the EU, it is also possible to obtain authorisation to use an ATMP which is prepared on a non-routine basis in a hospital to produce a custom-made product for an individual patient (this is termed the 'hospital exemption'). This kind of authorisation is granted in Sweden by the Swedish Medical Products Agency. A number of different conditions must be met, and it is not possible to say in advance whether permission would be given for xenotransplantation. The Swedish Medical Products Agency has assessed that the rules governing ATMP do not apply to research and treatment involving whole organs from animals.[35]

Research involving humans that does not relate to clinical trials or medical devices is governed by the Ethical Review Act and must be approved by the Ethical Review Authority. According to the Ethical Review Act, research can only be approved if it can be conducted in a way that respects human dignity. Human rights and fundamental freedoms should always be respected in an ethical review, while taking into account the interest in potentially developing new knowledge as an outcome of the research. People's welfare must take precedence over the needs of society and science. Furthermore, research may only be approved if the risks it can pose to the health, safety and privacy of the research subjects are outweighed by its scientific value. Research must not be approved if the expected result can be achieved in a different way that poses fewer risks to the health, safety and privacy of the research subjects. Research that involves a physical procedure on a brain-dead person must also be approved by the Ethical Review Authority.

The use of experimental animals is regulated by EU Directive 2010:63 on the protection of animals used for scientific purposes. The Directive aims to harmonise the protection of animals used for scientific purposes within the EU. Fundamental to the EU Directive is the aim to replace, reduce and refine the use of animals in procedures, which is called the 3R principle. According to this aim, as far as possible procedures involving animals should

[35] As reported to the SMER Secretariat in June 2022.

be replaced by methods where animals are not used, and the number of procedures using animals should be reduced and refined in order to improve animal welfare. Apes enjoy special protection and the use of hominids (chimpanzees, bonobos, gorillas and orangutans) is generally prohibited. Provisions on the use of animals in experiments are laid down in Swedish law in the Animal Welfare Act (2018:1192). Under this Act, animal experiments may only be carried out on the condition that the goal of the activity cannot be achieved by any other satisfactory method that does not use animals; that as few animals as possible are used; and that the activity is designed in such a way that the animals are not subjected to greater suffering than is absolutely necessary. A person who intends to use animals in experiments must have obtained ethical approval from a regional animal experiment ethics review committee before their use is started. It is also necessary to obtain a permit from the Swedish Board of Agriculture to breed and to use laboratory animals. In order to breed and keep laboratory animals that are genetically modified, an additional permit from the Board of Agriculture is required.

8. Ethical analysis and discussion

In the following, SMER analyses the ethical questions raised by xenotransplantation. In the late 1990s and early 2000s, a number of ethical analyses of the issue were made by other national bioethics councils, international organisations and Sweden's Commission of Inquiry on Xenotransplantation. In addition, an analysis of ethical questions in the xenotransplantation of the pig heart was recently published by a US bioethics research institute, the Hastings Center. Based on these analyses, SMER has paid particular attention to whether the changes in the current state of knowledge mean that additional ethical questions have been raised compared with the past, and whether new ethical positions should be taken.

8.1 Animal welfare

In xenotransplantation, organs, cells or tissue are taken from animals. This raises questions about animal welfare and rights in relation to the interests of humans. A fundamental ethical issue is whether and under what circumstances humans may use animals as a means of achieving their own ends. There is a large body of literature on the ethics of animal welfare and animal rights and a variety of opinions on how humans should relate to animals. These opinions are often based on a view about what separates humans and animals. This view may be based on religious or philosophical

ideas and/or on knowledge developed about the consciousness and emotions of different animal species.

Xenotransplantation research invokes the animal experimentation paradox. The paradox summarises the dilemma that animal experimentation entails: we use (nonhuman) animals in experiments, because they are sufficiently like us (to achieve relevant results) – and because they are sufficiently different from us (to allow us to justify the suffering we cause them).[36] In Sweden, it is generally accepted that animal testing is needed to develop new drugs and other treatment methods, even if there are divergent views on this. When ethically reviewing animal experiments, a balance is struck between the importance of the experiment and the suffering of the animal. The exact amount of suffering that is acceptable in animal experiments is thus not a given, but in animal testing ethics committees, a balance is struck between the different interests involved. Potential alternatives to animal testing are also taken into account.

If one accepts this principle of striking a balance between human and animal interests, this permits the number of animals used as well as the suffering of each animal to be greater, the greater the expected benefits to humans are. The benefits of functional and risk-free xenotransplantation are, of course, very great, but the probability that such benefits can actually be realised must also weigh in. If the probability of success is small, one should not subject animals to suffering.

In the case of xenotransplantation, the question of which species should be used as donors and recipients in preclinical trials also arises. Ethical and medical as well as practical reasons then come to the fore. In the early trials of xenotransplants of organs into humans, apes were used as the source animals because apes are closely related to humans and therefore the immune response was not anticipated to be as strong as with the transplantation of organs from other animals. Using hominids (chimpanzees, bonobos, gorillas and orangutans) and gibbons as experimental animals is generally prohibited in Sweden. These species are considered to be too similar to humans for it to be ethically acceptable to use them in animal experiments. It is also difficult to breed them in an ethically acceptable way.

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[36] Swedish Research Council. (2017). *Good Research Practice*, 33. https://www.vr.se/download/18.5639980c162791bbfe697882/1555334908942/Good-Research-Practice_VR_2017.pdf

Furthermore, in the context of xenotransplantation, there is a higher risk of transmission of pathogens to humans from apes than from pigs.

Today, genetically modified pigs are the predominant source animals in xenotransplantation research. Pig organs are more like human organs in terms of size, and they grow much faster than ape organs. It is also easier to breed pigs than apes under the strict conditions required to prevent the transmission of harmful organisms to the recipient.

However, baboons and rhesus macaques, which are not hominids, are used as recipient animals in research involving the xenotransplantation of pig organs. The medical reason that the recipient animal should be similar to humans then carries great weight. If animals that are less like humans were to be used, there is a greater risk that the results would be of no use, and it would therefore be unethical to use animals in this research. In other words, xenotransplantation research leads to an increased use of apes in animal experiments.

The Commission of Inquiry on Xenotransplantation accepted that humans keep domestic animals for utilitarian reasons such as research, and decides whether they are born, how long they live, and how they are killed. The starting point for the Committee was that experimental animals should have a 'good animal life', which means compliance with the current animal welfare legislation, that animals should have good health and reasonable opportunities to perform their natural behaviour, and that any genetic modification of the source animal should not in itself cause any additional suffering. The Commission of Inquiry on Xenotransplantation were of the opinion that, for ethical and animal welfare reasons – and taking into account the risk of pathogen transmission – the use of apes as source animals was unacceptable. On the other hand, apes could be used to a limited extent as recipient animals during the preclinical research phase.

The production of the genetically modified and cloned pigs now used for xenotransplantation research purposes raises somewhat new ethical questions. The European Group on Ethics in Science and New Technologies (EGE), which is the EU's ethics advisory group, poses the question of whether research ethics committees for animal experimentation are fully aware of the known and unknown risks and benefits of this new

genome editing technique.[37] The genetically modified pigs used as source animals in xenotransplantation research are unlikely to be able to give vent to their natural behaviour, but must be artificially inseminated, born by Caesarean section, grow up isolated in a sterile environment without contact with other animals, be restrained pharmaceutically, and may be subjected to repeated surgical procedures.[38] The effects of the genome edits on the welfare, consciousness and emotions of the pigs are unknown.

One could also pose the more general question of how far humans can and should go in designing animals and nature to suit their own purposes. In addition to the new questions raised by genome editing, knowledge about animal consciousness and emotions is growing. We know today that pigs are intelligent and social animals. Pigs are capable of playing simple computer games, and they can solve tasks that children cannot do at a certain age. They also have a capacity to plan.[39] This raises questions as to whether pigs are really so different from us that we can justify the suffering we cause them.

If xenotransplantation were to become a common treatment method, it would mean increasing the number of animals used for human purposes. These genetically modified animals would be produced for the sole purpose of providing organs, tissue and cells to humans, which presupposes an entirely instrumental view of these animals. The number of pigs or other animals that would need to be raised for xenotransplantation purposes cannot be predicted based on the current state of knowledge. Furthermore, xenotransplantation could come to be used for far more patients and diseases than those that are the focus of the current research. Questions concerning animal welfare and the extent to which humans may use animals to serve their own interests, as described in this section in relation to animal experimentation, will then come to the fore on a much larger scale.

8.2 The boundary between animal and human

As pointed out above, human use of animals in animal experiments and other contexts is based on the idea that humans differ from animals in some

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[37] European Group on Ethics in Science and New Technologies. (2021). *Ethics of Genome Editing*. Opinion no. 32.

[38] Johnson, L..S.M. (19 January 2022). *Xenotransplantation: Three Areas of Concern*. Hastings Bioethics Forum. https://www.thehastingscenter.org/xenotransplantation-three-areas-of-concern/

[39] See for example. Broom, H. et al. (2009). Pigs learn what a mirror image represents and use it to obtain information. *Animal Behaviour*, 78(5), 1037–1041.

crucial respects. It is often said that animals have a lower moral status than humans. With xenotransplantation, the boundary between animals and humans is softened – as regards the transplantation to humans per se, and where human genes are added to the pigs used source animals for the purpose of facilitating the transplantation. This can raise questions about the ethically decisive boundary between the two categories 'animal' and 'human' that many people take for granted. Many public authorities have come to the conclusion that the very small numbers of human genes in transgenic pigs do not make the pigs in any sense human nor create a hybrid species.[40] However, the question of where the boundary is may become more difficult to determine in a future where more genome edits are implemented or other technologies are developed, such as the cultivation of human organs in animals.

Studies show that people have a range of attitudes to receiving organs, tissue, and cells from animals. There are differences between countries but also within countries. Cultural and religious ideas can play a role. In 1998, the Commission of Inquiry on Xenotransplantation conducted a survey in Sweden according to which 60% of respondents aged 18–75 were in favour of receiving organs from animals for transplantation purposes, provided that the outcomes and risks of infection are the same as for transplantation of donated organs from other humans. Thus, 40% were negatively disposed or uncertain. Patients waiting for kidney transplants were more positively disposed than the general public. However, if the uncertainty surrounding the outcomes and risks of infection was greater than with human organ transplants, only 16% were favourably disposed in both these groups. Both the general public and patients waiting for kidney transplants were more positively disposed to receiving animal cells and tissue than to receiving whole organs.[41] Among those who have received animal cells, there is also a range of attitudes. Some consider that softening the boundary between animals and humans is not problematic, while others feel that it is.[42] However, these types of existential and moral value judgements may, of

[40] Nuffield Council on Bioethics. (1996). *Animal-to-Human Transplants The ethics of xenotransplantation*, 54

[41] *Från en art till en annan – transplantation från djur till människa* (SOU 1999:120), Chapter 14 and Annex 4

[42] Lundin, S. (16 March 2022). Ethnographic Fieldwork Among Pigs and People: What Can We Learn from Previous Xenotransplantations? *Medical Humanities Blog*. https://blogs.bmj.com/medical-humanities/2022/03/16/ethnographic-fieldwork-among-pigs-and-people-what-can-we-learn-from-previous-xenotransplantations/

course, change if xenotransplantation were to be shown to be an effective method of treatment and therefore become common.

An important ethical issue is how to address people's different attitudes to xenotransplantation. If xenotransplantation is permitted, there will probably be people who are not prepared to receive a xenotransplant. Similarly, there will probably be people who are prepared to travel abroad for treatment if xenotransplantation is not performed in Sweden but is in other countries. The question of how to respond to people's different attitudes is further addressed in Section 8.7.

8.3 Risk and benefit

A fundamental ethical problem in research involving humans is the balance between two interests that are both legitimate but at times in conflict with each other. One is the interest in new knowledge that can benefit society as a whole, but also the individual researchers. The second interest is safeguarding the individual, which means that research subjects should be protected against various forms of injury or risk of injury related to the research.

As with the development of other innovative methods in health and medical care, clinical research involving xenotransplantation runs a risk that the experiment will have harmful effects. A feature of xenotransplantation, however, is there are not only risks for the individual research subjects but also for those in their vicinity. If a pathogenic organism is transmitted to the recipient of a xenotransplant, there is a risk of that infection being transmitted to others in their vicinity. In the worst-case scenario, there could be a risk of a new zoonotic pandemic like HIV, SARS or COVID-19 befalling the community.

Before conducting research in people, a balance should be struck between the risks and expected benefits. The research can only be justified if the expected benefits exceed the risks. In treatment situations too, a balance is struck between risk and benefit, but in that case it is a balance between the expected risks and benefits for the individual patient that counts.

The scientific debate on the risk of transmission has focused mainly on porcine endogenous retroviruses (PERV). The risk of transmission of PERV to humans resulted in all experiments with xenotransplantation being

discontinued in the EU in the late 1990s. Since then, new knowledge has emerged. No transmission of PERV to human beings following xenotransplantation has been demonstrated in the clinical trials that have been carried out to date. However, the experiment with the xenotransplantation of a pig heart in January 2022 demonstrated that a virus from the pig was transmitted to the patient despite the fact that the pig was tested several times without finding any trace of this particular virus. Some of the genome edits of source animals aim to reduce the risk of transmitting pathogens. However, there is no consensus in the research community about the need to knock out PERV genes. The ethical and medical literature indicates that there could also be a risk of disease caused by pathogens which are as yet unknown or which mutate when transplanted from pig to human. This risk has been assessed as extremely small but unquantifiable.[43]

There are many uncertainties surrounding the different forms of xenotransplantation in terms of both the risks and the potential benefits. The guidelines on xenotransplantation described above state that the risks should be taken into account and that the risks should be sufficiently small. But what does this mean? Some risks can never be accurately quantified, such as the risk of a new unknown pathogen arising and causing a pandemic. However, such a risk can be judged to be smaller in pace with the number of experiments carried out increasing without any unknown pathogens being detected. The fact that xenotransplantation is a non-reversible procedure makes the risk assessment even more important, since it is not possible to undo the procedure if the outcomes are worse than anticipated. Balanced against this are the expected benefits. There is great value in being able to treat fatal and serious diseases, which today cause great suffering, with various forms of xenotransplantation. But it is also necessary to consider how probable it is that this goal will be achieved. The greater the probability, the greater the expected benefits. Here too, it is a matter of making difficult judgements.

In 1999, the Commission of Inquiry on Xenotransplantation judged that the gaps in knowledge were still too great to enable a reliable assessment of the risk of transmission of pathogens, but came to the conclusion that well-controlled clinical trials should be permitted to a limited extent if a committee had assessed that the risks involved in the experiment were

[43] Nuffield Council on Bioethics. (1996). *Animal-to-Human Transplants The ethics of xenotransplantation*, 73

manageable, in view of the safeguards and other precautionary measures. Most of the referral bodies endorsed the main features in the proposals and assessments or did not raise any objections. Some referral bodies (such as Uppsala University, the Royal Swedish Academy of Agriculture and Forestry, and the Christian Council of Sweden) did convey criticism of the Committee's risk/benefit assessment. One of the main reasons was that the large gaps in knowledge make reliable risk assessment impossible and that the precautionary principle should therefore prevail and take priority. County council representatives for Sweden's Green Party wanted a moratorium.

Although we now know more about PERV for example since the Commission of Inquiry on Xenotransplantation made their analysis, the risk of transmission of pathogenic organisms and disease remains a consistent theme in guidelines on trials of xenotransplantation. The FDA guidelines state that in addition to the human subject protection issues traditionally addressed by those who review clinical trial protocols, the reviewers should also address the potential risks of infection spreading to health care providers, family members, friends, and the community at large, and the adequacy of the proposal to address these risks. The risk/benefit analysis must include risks to public health. Those performing the clinical trials must screen for all possible pathogens and be prepared to develop tests for pathogens not known at the time of the trials.[44]

After weighing up the risks and potential profits, the Commission of Inquiry on Xenotransplantation concluded that clinical trials should be permitted if precautionary measures are taken such as regulation, follow-up and contact tracing in the event of infection. A number of international organisations have arrived at a similar standpoint. However, even with regard to precautionary measures, there is a balance to be struck between different interests. The more stringent the measures are, the greater the inconvenience for the people being followed up and the higher the costs to society.

A key issue in this is who to entrust with the task of balancing the risks and benefits and determining the degree of precautionary measures needed. It is likely that different stakeholders will assess and value risks and benefits differently. The researchers and businesses involved in the development of

[44] U.S. Department of Health and Human Services, Food and Drug Administration. (2016). *Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans Guidance for Industry (April 2003, Updated December 2016)*. https://www.fda.gov/media/102126/download

xenotransplantation may have an interest in their research and its application eventuating, and will thus tend to place less emphasis on the risks and more on the expected benefits. In a situation where no other treatment options are available, even a gravely ill person may be prepared to accept a not insignificant degree of risk and to value highly even small chances of a cure. In Sweden, as described above, all research on human beings must pass ethical review before it can be carried out. The review evaluates and takes a position on the risks and benefits. Research may only be approved if the risks it may pose to the health, safety and privacy of the research subjects are outweighed by its scientific value. In addition, people's welfare takes precedence over the needs of society and science.

8.4 Informed consent

The question of evaluating risks and benefits is related to the question of informed consent from the research subjects. According to the Ethical Review Act, research may only be carried out if the research subject has voluntarily agreed to participate in it after having received information about it. Informed consent from patients is also required in health and medical care. However, in connection with new treatment methods – in research as well as in health and medical care – where there is less certainty, there may be a conflict between respect for the individual's right of self-determination on the one hand, and the great difficulties of giving fully informed consent when knowledge about the effects and potential risks is incomplete. From an ethical standpoint, it is important to analyse the circumstances under which people can be expected to give voluntary informed consent to participate in high-risk research or treatment. Gravely ill people are in a particularly vulnerable position because they are at a disadvantage in terms of knowledge while also being in great need of treatment. In such a situation, it is difficult to make an entirely autonomous decision. Some argue that gravely ill people are in a kind of hostage situation where they cannot fully and properly evaluate risks and benefits. It is therefore important that the patient's risk propensity is not exploited as an opportunity to conduct questionable experiments. Others argue that even people in this situation have sufficient capacity to make decisions on whether to participate in research or receive treatment. A gravely ill patient with a low probability of survival without a new organ may have an intrinsic interest in an operation with a relatively low chance of success and may then consent to a procedure with a high risk of failure. There are also people who are prepared to take risks to advance

medical science so that others will get to receive effective treatment in the future.

For voluntary informed consent to be given, the information given to the participant or patient must be kept neutral and accurate. It has also been recommended that informed consent to participation in xenotransplantation trials should be sought by appropriately trained professionals who are independent of the research team in order to reduce the risk that the research subject will feel pressured.[45]

Xenotransplantation also raises other questions about informed consent. In order to detect potential infections due to xenotransplantation, those who have received a xenotransplant must be monitored for the rest of their lives. Specimens for testing must be taken from them at regular intervals. The question then arises as to whether the researchers must commit themselves to participating in this life-long follow-up. Under the Ethical Review Act, a person has the right to withdraw their consent to participate in research at any time. But what about vital follow-up? In order to avoid the transmission of pathogens, it has been argued that the close family members of the research subjects and health care staff must also participate in similar follow-up. Does this mean that they too must give consent before the research or treatment is started?

8.5 Early human trials

It has been claimed that much of the development in medicine, for example in the field of allotransplantation and other surgery, would not have been possible without the clinical trials that initially meant that some people died. The trials carried out thus far involving xenotransplantation of organs to humans have not been part of actual research studies, but merely isolated trials of an experimental nature. The experiment in the USA with the xenotransplantation of a pig heart in January 2022 was considered successful by the researchers because the person survived for two months. The trial, which had been approved by the FDA, was motivated by expanded access or compassionate use, which means that a patient with a life-threatening condition can be given access to a medical product that has not yet been approved.

[45] Nuffield Council on Bioethics. (1996). *Animal-to-Human Transplants The ethics of xenotransplantation*, 88

Should we accept people participating in experiments that advance the research, but where they risk increased suffering at the end of their lives or a hastened death? People may differ on this point based on how they view the issues of risk, benefit and informed consent discussed above. These issues are brought to a head in the very earliest trials when a new method or technique is being tested on gravely ill people. Prior to the first trials involving people, the uncertainties surrounding risks and benefits are the greatest, and the assessment of them is the most difficult. In the case of xenotransplantation, other medical complications can arise when humans, not apes, will be the recipients of xenotransplants, so sufficient evidence of the effects of the trials on humans cannot be obtained through experimentation with animals alone. It is particularly important that risks and benefits are assessed in the most neutral way possible.

The risk/benefit assessment is not only about estimating the expected survival rate, but also about what quality of life is achievable at the end of life as a high-profile participant in a clinical trial compared to if the person had received palliative care. What is the value of a brief, prolonged survival under difficult circumstances? As described above, individual research subjects or patients are in a particularly vulnerable position because they are at a disadvantage in terms of knowledge while also being in great need of treatment. Therefore, questions concerning the conditions under which voluntary informed consent can be given should be given particular attention in early trials on humans.

Early xenotransplantation trials could be carried out as part of research projects, and as innovative methods in health and medical care that are not developed as part of a research project. In Sweden, the legal scope for using experimental methods outside research projects is judged to be extremely limited, but such methods are used in emergency situations for example, where a patient's life is at stake or where there is a risk of greatly reduced quality of life and there are no established treatment alternatives. SMER's report 2016:1 *Ethical assessments at the border between health and medical care and research* discusses the conditions for the use of innovative treatment methods. In the report, the Council argues that, as a general rule, innovative methods should be used and developed within the context of research studies, in accordance with the regulations that apply to research. However, the Council does not believe that one can ignore the fact that new innovative methods are sometimes used in the treatment of patients outside the context of a

research study. The Council considers that innovative methods should only be used exceptionally outside research studies, in a controlled manner and always in a way that respects fundamental ethical values.

In the USA, experiments involving xenotransplantation of organs in brain-dead people have been carried out, and there is debate on the conditions for and benefits of this method. Using brain-dead persons instead of primates has the advantage of allowing the study of the responses of the human body to the xenotransplantation. However, for ethical reasons, these trials cannot go on for very long. So far, the maximum period has been three days. For example, maintaining circulation artificially long after death can impede the grieving process for the person's relatives. The method also raises questions about respect for the dead, and may raise concerns about whether consent to organ donation or the donation of the whole body for research purposes can entail consent to this type of research as well.

8.6 Follow-up

As described above, precautionary measures need to be taken to minimise any adverse side effects of xenotransplantation in the form of the transmission of pathogens from animals to humans and wider transmission of infections. How powerful these measures need to be is determined by a risk/benefit assessment. The inconvenience to researchers and patients must also be taken into account.

In order to detect potential infections due to xenotransplantation, those who have received a xenotransplant must be monitored for the rest of their lives. Specimens for testing must be taken from them at regular intervals. The person's close family members and health care professionals treating them must also be followed up. Other restrictions may also be applicable to prevent the spread of infections. In the literature, it has been pointed out that recipients of xenotransplants may not be suitable as blood donors and may expose others to the risk of infection during sexual relations. The question of whether it is appropriate for them to have biological children has also been discussed.

This raises questions about the individual's freedom in relation to society's capacity to protect itself from the spread of infections. Should follow-up and restrictions be mandatory or voluntary? What must the person consent to, and what happens if they do not take part in the follow-up? The same

questions arise in a potential treatment phase. Most research subjects and patients would probably not oppose participation in follow-up, but what happens if a person has cognitive impairments due to dementia, for example? Or if a person wants to move abroad? Sweden's legislation on communicable disease control provides for the possibility of coercive measures such as forced medical examinations and isolation of people suffering from a disease that constitutes a danger to the public. It cannot be ruled out that people who have undergone xenotransplantation must be subjected to coercive measures if they do not take part voluntarily in the required follow-up. However, these measures must be proportionate to the risk of transmission of disease. In this analysis, SMER did not investigate whether the legislation on communicable disease control is appropriate for the risks of pathogen transmission in clinical trials and treatment involving xenotransplantation. However, this is an issue that requires further analysis if xenotransplantation becomes a real possibility.

Some ethical analyses of xenotransplantation have pointed out that since strict follow-up is required for both the research subject and their close family members, one might ask whether the family members should also be required to provide their informed consent to the participation of the research subject. The Commission of Inquiry on Xenotransplantation did not propose that the patient's close family members and other close contacts, such as staff, should be subject to any active follow-up and control measures for purely preventive reasons. The Committee's view was that only when the transmission of a pathogen to the recipient of the xenotransplant is suspected should close family members be subject to measures such as examination by a physician and testing.

It should also be pointed out that follow-up is resource-intensive. In the New Zealand and Argentinian studies of xenotransplantation of insulin-producing islet cells, the 38 research subjects and their contacts generated over 30,000 samples over 10 years.[46] The degree of precautionary measures is therefore also a matter of resource priority.

8.7 Treatment

If xenotransplantation were to become an approved treatment method, further ethical questions would be raised. The analysis of these questions is

[46] Entwistle J.W. et al. (2022). Clinical xenotransplantation seems close: Ethical issues persist. *Artificial Organs*, 46(6), 987–994. doi: 10.1111/aor.14255. Epub 2022 Apr 22.

more speculative because there is currently no knowledge of the efficacy and costs of potential treatments.

One of the hopes of xenotransplantation as a treatment method is that everyone can have access to organs customised to the individual. This would mean greater equality in access to effective treatment and health, and increased well-being, provided that the treatments are successful. Another condition is that treatments will not be considered too expensive to be paid for by the society. If treatments have to be financed by the individual, this can instead be anticipated to reduce equality.

It is difficult to predict today whether human organs and animal organs would be equivalent alternatives or whether there would be differences in their efficacy for different groups of patients. At present, it is very expensive to produce organs from genetically modified pigs, but with high rates of production of these organs, the unit cost can be reduced. Xenotransplantation could possibly become a cheaper and better alternative, from the patient's viewpoint, than dialysis for kidney disease, for example. Perhaps organs, tissue and cells from genetically modified animals can be used much more widely than the research is currently exploring.

In this context, questions are raised about the principles for allocating organs if both allotransplantation and xenotransplantation are being performed. As discussed above, we cannot expect all individuals to be prepared to receive a xenotransplant. Should society provide other, perhaps more expensive, treatments for patients who do not want to undergo xenotransplantation? Should there be different waiting lists for organs from animals and organs from humans? If the transplantation of pig organs becomes a temporary solution while waiting for a human organ to become available, should anyone who has received a pig organ be moved further down the waiting list for a new human organ? And should health care professionals be permitted to refrain from participating in xenotransplantation?

Another issue that has been discussed in the ethics literature is whether xenotransplantation might lead to fewer people being interested in donating their organs, or to human organ donation disappearing entirely. Fears have been expressed that experiments with xenotransplantation may result in fewer people being willing to donate their organs, since they may get the

impression that human organ donation, which has been the norm, is no longer needed.

On a global level, more questions are being raised. Will the treatment method be expensive and therefore benefit only a few individuals? This question is not unique to xenotransplantation: it always arises in connection with biotechnology innovations. Rich countries are responsible for the development costs and are also those that initially have access to the treatments. If the method is then used on a larger scale, costs may be reduced and usage may increase in other parts of the world as well. In that case, the development of xenotransplantation could reduce or stop human organ theft and trafficking in human organs.

9. Considerations and positions

In the USA, there have been recent experiments with the xenotransplantation of organs into living and brain-dead individuals. Many observers believe that regular clinical studies will become a reality in the near future. An application to conduct a large clinical study involving the xenotransplantation of pig kidneys into gravely ill patients has been submitted to the FDA. In Germany, too, there is interest in conducting clinical studies of xenotransplantation with organs. Research into xenotransplantation is also being conducted in other parts of the world. This development raises questions about what development might occur in Sweden and how we should relate to xenotransplantation in different sectors of society.

The future of xenotransplantation will depend on how society approaches the ethical questions raised by xenotransplantation, as well as the outcomes of any clinical trials conducted, whether the transmission of pathogens can be demonstrated, how expensive the method will be, and what other treatment methods are developed. One possible scenario is that there will be interest in conducting clinical studies and raising animals for xenotransplantation in Sweden too, and perhaps also research of this kind in brain-dead people. Another scenario is that research and development in this area will only be conducted in other countries. Yet another scenario is that xenotransplantation research comes to a halt in which case xenotransplantation may never become an established treatment method. Or the method is eventually introduced in some form in Sweden. Another

scenario is that such treatment will only be offered abroad and some Swedes will choose to undergo treatment there.

Since an increased interest in xenotransplantation may arise in Sweden, with this Opinion SMER aimed to focus on the many ethical questions that this area raises. SMER's assessment is that fundamental questions of animal and human ethics remain concerning xenotransplantation, such as those questions treated in the report by the Commission of Inquiry on Xenotransplantation. Some questions are relevant in all activities involving xenotransplantation, while others only become relevant in the research or a potential treatment phase. The Council's considerations and positions in this Opinion mainly concern the general ethical questions raised by xenotransplantation and the ethical questions raised in the research phase. The Council will return to questions about xenotransplantation as a normal treatment in health and medical care in Sweden or abroad should they arise in the future.

A fundamental question raised in animal experimentation and clinical trials as well as treatment involving xenotransplantation is how far humans should be permitted to go when it comes to raising animals and editing their genomes for what are intrinsically human interests. SMER supports the view that there is a balance to be struck between animal suffering and benefits to humans. A certain amount of suffering may be acceptable if the benefits are sufficiently great. However, SMER is currently unable to assess the suffering to which animals are subjected, nor how great the benefits are to humans.

A further aspect of this question of how we treat animals is that xenotransplantation means that genetically modified pigs or other animals are bred solely to meet the needs of humans for organs, tissue and cells. An animal species bred in this way would then become fully instrumentalised and the animals would then not be able to live a life that is natural for the species. Is this acceptable? SMER can agree that even animals in food production, for example, which is a far bigger activity than xenotransplantation, are fully instrumentalised and are raised solely for the purpose of feeding humans. However, according to SMER, the fact that instrumentalisation is already occurring in many instances cannot justify the instrumentalisation of more animals in new areas such as xenotransplantation. SMER considers this type of complete

instrumentalisation of animal species to be ethically problematic, especially when the animals cannot live a life that is natural for the species.

Another fundamental ethical question is how much risk people should be exposed to in order to develop new treatment methods. This question is not unique to xenotransplantation: it also applies to other new innovative methods. A distinguishing feature of xenotransplantation, however, is that not only individual research subjects but also the rest of the community are exposed to risks in the form of the risk of pathogenic organism transmission and the spread of diseases dangerous to society.

Early trials of a new treatment method for humans raise a number of conflicts in values and interests, such as between the interest in promoting the development of medicine on the one hand and giving gravely ill patients a last hope of survival; and on the other hand, the interest in a treatment or trial being as risk-free as possible. Another conflict is between respect for the patient's right of self-determination and how difficult it can be for them to make an informed decision when the risks and benefits are only partly known.

According to SMER's assessment, special attention must be focused on questions surrounding the information provided, informed consent and the risks for individuals and the community at large in early xenotransplantation trials. The question of which patients should be asked to participate must also be considered carefully. For example, should they be the most gravely ill? A condition for proceeding with clinical trials is that the information provided on the expected risks and benefits and the uncertainties is accurate and clear. The patient's or research subject's informed consent must be obtained in a way that allows them to make an independent decision free from any pressure to consent. Questions about who should provide the information, and how and when patients should be asked to participate must be carefully examined. How grave their illness is, and other factors affecting the person's capacity to make fully autonomous decisions, must also be taken into account. Furthermore, the trial must have been approved by an independent body that has assessed its scientific merits and reviewed its ethics.

Innovation and technological development are fundamental to a good health and medical care system. According to SMER, there is an urgent need to

drive progress in this research, but only in ethically acceptable forms. SMER is of the opinion that an adequate regulatory framework must be in place before any xenotransplantation trials can be carried out in Sweden. The Commission of Inquiry on Xenotransplantation proposed specific regulation of clinical trials of xenotransplantation, which most of the referral bodies were in favour of. Since the Committee submitted its proposal, new knowledge has emerged about, for example, immune responses and the transmission of pathogens in connection with xenotransplantation; and new legislation on the ethical review of research has also come into force. SMER has given a general description of Sweden's legislation in this area but has not made a detailed analysis during the preparation of this Opinion of whether Sweden's regulatory framework is adequately designed, and whether decision-making public authorities are sufficiently well prepared to deal with the specific questions arising concerning risks, benefits, informed consent, the right of self-determination, follow-up and safeguards associated with clinical trials of xenotransplantation. This should be investigated.

SMER is also of the view that renewed societal debate on xenotransplantation is needed, where the ethical questions are illuminated from all sides, which can help decision-makers and individuals to be well prepared when they need to consider questions concerning xenotransplantation in various contexts.

SMER hopes that this Opinion can stimulate societal and scientific debate on xenotransplantation and provide a basis for further analyses of its regulation and practice. SMER will continue to monitor developments in this area.

A decision to adopt this Opinion was made at the ordinary meeting held on 28 October 2022.

The decision was made by Sven-Eric Söder (Chair), Åsa Gyberg-Karlsson, Ulrika Jörgensen, Sofia Nilsson, Lina Nordquist and Anton Nordqvist, all members of the Council. Following the meeting, Michael Anefur concurred with the decision. Lilas Ali, Göran Collste, Titti Mattsson, Kerstin Nilsson, Olle Olsson, Bengt Rönngren, Nils-Eric Sahlin, Mikael Sandlund, Marie Sten and Kristina Wikner – all expert members of the Council – also contributed to the preparation of this Opinion.

A working group consisting of Lilas Ali, Göran Collste, Titti Mattsson, Anton Nordqvist and Nils-Eric Sahlin assisted the Secretariat in the preparation of this Opinion. Lotta Eriksson, Secretary General and Head of the Secretariat, participated in its preparation. Carolina Östgren, Inquiry Secretary, was the rapporteur for the Opinion.

For the Council,

Sven-Eric Söder

Chair