XENOTRANSPLANTATION

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SUMMARY

There is a desperate need for organs to be transplanted. In an effort to curb the ever-increasing demand, scientists are thinking of xenotransplantation, using animal organs to help suffering human beings. Xenotransplantation raises many legal and ethical questions that will need to be answered before such transplantations might be acceptable or even considered. There is currently no legislation or regulation addressing xenotransplantation directly in South Africa. Should such research be allowed, scientists will have to get ethical clearance from both animal ethics committees as well as ethics committees allowing research where human participants are involved.

1 INTRODUCTION

In 1954 a kidney transplant between identical twins was the beginning of a whole new dimension in medicine and organ transplantations. Thousands of people with organ failure could suddenly be helped by receiving a donor's kidneys, liver or heart. Unfortunately, the constant demand for transplantable organs[1] poses a dilemma. To address the ever-increasing shortage of human transplantable organs scientists are experimenting with using the organs of animals.[2] The procedure to transplant tissue or an organ from an animal into a human being is called xenotransplantation, taken from the Greek word *xeno*, meaning stranger.[3] The "ideal" donor animal should be of compatible anatomy and physiology as humans, no cross-species infection should exist, the animal should not be expensive to feed and to breed and

[1] Levy "Animal Organs for Human Transplantation: How Close are We?" 2000 13(1) *Proc (Bayl Univ Med Cen)* 3. See also Michler in his Commentary "Xenotransplantation: Risks, Clinical Potential, and Future Prospects" 1996 2(1) *Emerging Infectious Diseases* 64. For organ shortage statistics in South Africa see Muller "Organ Donation and Transplantation in South Africa − An Update" 2013 (31) *Continuing Medical Education Journal* 221.

[2] Agnew "Xenotransplants: Using Animal Organs to Save Human Lives" 2012 http://science.education.nih.gov/newsnapshots/toc_xeno/xenoritn/xenoritn.html (accessed 2015-01-02) 1. See also Sykes, d'Apice and Sandrin "Position Paper of the Ethics Committee of the International Xenotransplantation Association" 2003 (10) *Xenotransplantation* 195.

[3] Agnew 2012 http://science.education.nih.gov/newsnapshots/toc_xeno/xenoritn/xenoritn.html (accessed 2015-01-02) 2. See fn 2 in Bach, Ivinson and Weeramantry "Ethical and Legal Issues in Technology: Xenotransplantation" 2001 (27) *American Journal of Law and Medicine* 284. The USA defines "xenotransplantation as "any procedure that involves the transplantation, implantation or infusion into a human recipient of either (a) live cells, tissues, or organs from nonhuman animal source or (b) human body fluids, cells, tissues or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues, or organs."

such an animal should also present no immunological barriers to transplantation into humans. However, an animal species meeting all these demands does not exist.[4]

The advantages of xenotransplantation are similar to the use of a living kidney donor in that the transplant can be scheduled and is thus not dependent on a time limitation as is the case with cadaver organs. The recipient can be pre-treated with immunosuppressant medicine and genetic engineering can be utilised to minimise rejection and optimise the functionality of the organ. Recipient selection can also be broadened as pre-transplant testing can be done more thoroughly. Xenogenetic transplants might also not be susceptible to the human autoimmune diseases or viral infections that caused organ failure in the first place.[5]

Various attempts have been made to transplant animal organs into humans in the past but with limited success. In 1964 a woman suffering from renal failure received a chimpanzee kidney.[6] She died 9 months later; the survival of 9 months gave scientists evidence of the feasibility of xenotransplantation as this is the longest survival recorded.[7] In 1977 Dr Christiaan Barnard transplanted the heart of a 30-kg baboon into a 25-year old woman. The heart stopped beating after 5 and a half hours. The death was attributed to the difference in size between the heart of the donor and that of the recipient but hyper-acute rejection was also present. Dr Barnard's second attempt was the transplantation of the heart of a chimpanzee in a 60-year old man, but in spite of strong immunosuppression medication, rejection caused his death in only four days.[8]

The best known example of a "successful" xenotransplantation is that of the American "Baby Fae". She was born prematurely in 1984. She had hypo-plastic left-heart syndrome and received an ABO-mismatched[9] baboon heart. Except for the ABO incompatibility, the conditions for success were present: the heart of the donor and that of the recipient were of comparable sizes and the immunosuppressant cyclosporine was available.[10] Unfortunately, Baby Fae died 20 days after surgery and most of the hopes put on xenotransplantation died with her.[11] In 1997 an Indian surgeon performed a cardiac xenograft, but the patient died a week after the

4 Levy 2000 13(1) *Proc (Bayl Univ Med Cen)* 2.

5 Sykes *et al* 2003 (10) *Xenotransplantation* 195.

6 Hardy, Chavez, Kurrus, Neely, Eraslan, Turner, Fabian and Lacecki "Heart Transplantation in Man: Developmental Studies and Report of a Case" 1964 (188) *JAMA* 114−122.

7 Deschamps, Roux, Sai and Gouin "History of xenotransplantation" 2005 (12) *Xenotransplantation* 97. See also Michler 1996 2(1) *Emerging Infectious Diseases* 64.

8 Deschamps *et al* 2005 (12) *Xenotransplantation* 98. Cognisance should be taken that these operations were performed before the existence of the Constitution of the Republic of South Africa, 1996 and the coming into operation of the National Health Act 61 of 2003.

9 ABO are the blood types A, B, AB and O. See also Michler 1996 2(1) *Emerging Infectious Diseases* 64.

10 Deschamps *et al* 2005 (12) *Xenotransplantation* 99. See also Michler 1996 2(1) *Emerging Infectious Diseases* 64.

11 Deschamps *et al* 2005 (12) *Xenotransplantation* 99 and 104.

transplant. The laboratory where he did his (illegal) research was burned down and he was sent to prison.[12]

Despite primates (chimpanzees, gorillas and baboons) being immunologically very similar to humans because of the risk of infectious disease transmission they are no longer used for clinical xenotransplantation.[13] A chimpanzee's genome is more than 98 per cent identical with the human genome, but chimpanzees are endangered species, they are costly to raise and they grow slowly to adulthood.[14] Scientists thus moved their attention to pigs as pigs are in size, anatomy and physiology similar to humans. They are prolific and it is possible to produce pathogen-free pigs which make them suitable organ donors even though they are genetically more distant to man than primates.[15] Pigs also have large litters (up to 10 littermates), a short gestation time (4 months) and they also have a history in providing medicinal (skin, insulin, cardiac prostheses and clotting factors) for humans. Pigs have thus become the most likely candidate for considering them as organ donors.[16]

Consequently pig-heart valves and tissue for ligament reconstruction have been used in patients for decades.[17] The pig cells are removed from the tissue and after the transplantation the tissue is repopulated with human recipient cells.[18] To transplant genetically unmodified pig organs like a heart, a liver or the kidneys are currently not possible because of hyper-acute rejection.[19] Hyper-acute rejection means that the human's antibodies pre-primed to attack tissues from another species, will reject the animal organ within hours or even minutes.[20] The human body attacks animal organs more vigorously than it does foreign human organs. These attacks can be suppressed by the immunosuppressant cyclosporine[21] but in xenotransplantation heavier doses are required which may cripple the patient's immune defences against infectious organisms.[22] The main concern of

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12 The case is unreported but see www.bbc.co.uk/1/hi/world/south_asia/122680.stm (accessed 2015-06-06).

13 Deschamps *et al* 2005 (12) *Xenotransplantation* 103. See Levy 2000 13(1) *Proc (Bayl Univ Med Cen)* 3 "An almost insurmountable obstacle for advocates of nonhuman primates as xenograft donors has been the recently concluded studies that showed HIV to be such a zoonosis. The Ebola virus may ultimately be found to fall into this category as well."

14 Agnew 2012 http://science.education.nih.gov/newsnapshots/toc_xeno/xenoritn/xenoritn.html (accessed 2015-01-02) 3.

15 Deschamps *et al* 2005 (12) *Xenotransplantation* 103.

16 Levy 2000 13(1) *Proc (Bayl Univ Med Cen)* 2. See also Melo, Brandao, Rego and Nunes "Ethical and Legal Issues in Xenotransplantation" 2001 (15) *Bioethics* 431.

17 Yong "Replacement Parts" 2012 *The Scientist Magazine* 1 August http://www.the-scientist.com/?articles.view/articleNo32409/title/Replacement-Parts/ (accessed 2015-01-02) 2.

18 Ekser, Ezzelarab, Hara, Van der Windt, Wijkstrom, Bottino, Trucco and Cooper "Clinical Xenotransplantation: The Next Medical Revolution" 2012 (379) *The Lancet* 672.

19 *Ibid*.

20 *Ibid*.

21 Cyclosporine is an immunosuppressant drug widely used in organ transplantation to prevent rejection. It was discovered in 1972 in Switzerland.

22 Ekser *et al* 2012 (379) *The Lancet* 672.

xenotransplantation is thus xenozoonoses, an infectious disease transmitted from an animal to a human after transplantation.[23]

Although the aim of xenotransplantation is therapeutic and to help those patients in desperate need of an organ transplant, until such time that rejection is overcome and there is proof that the animal organ will not give rise to unknown viruses, xenotransplantation is just a possible hope for the future.

This article does not address the scientific issues and barriers in xenotransplantation in depth;[24] it is focused on the legal and ethical controversies in using animal tissue or organs for transplantations into humans. Legally, informed consent is a problem in xenotransplantation as not even scientists are sure about the possible risks posed by these transplantations. Possible violations of the right to privacy may also occur. Although xenotransplantation also extends to the milieu of animal rights only a few comments will be made in this regard as it is a philosophical debate that warrants more research. Xenotransplantation is not performed in South Africa,[25] but should scientists want to do such research, they will have to get approval from research ethics committees approving research on humans as well as get permission from ethics committees in animal research. This is explored in order to see whether xenotransplantation research could possibly be done legally authorised in South Africa.

2 LEGAL AND ETHICAL CONSIDERATIONS

2 1 Informed consent

2 1 1 Individual and close contacts

Experimentation on humans requires voluntary informed consent from the participant.[26] If xenotransplantation is a clinical trial the extent of information disclosed to the recipient of a xenograft should conform to standards even higher than those applied in a therapeutic interaction.[27] In order to give

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[23] Daar "Ethics of Xenotransplantation; Animal Issues, Consent, and Likely Transformation of Transplant Ethics" 1997 (21) *World J Surg* 975.

[24] For a discussion of the scientific barriers to xenotransplantation see McLean and Williamson *Xenotransplantation* (2005) 62−70.

[25] In an article in *Die Burger* of 13 January 1993, it is stated that the transplantation of pig organs might be a reality within 2 years in South Africa. Since then there is no proof of a xenotransplantation although the same article refers to scientists of the University of Cape Town who have already been busy for some years trying to cross the acute rejection of animal organs. See Medical Reporter "Varke se Organe Binne Twee Jaar op Mense Oorgeplant" 13 January 1993 *Die Burger* http://m24arg02.naspers.com/argief/berigte/dieburger/1993/01/13/9/6.html (accessed 2015-01-02).

[26] Melo *et al* 2001 (15) *Bioethics* 429, "Respect for a patient's autonomy is an indisputable principle of medical ethics". See also Bauchamp and Childress *Principles of Biomedical Ethics* 6ed (2009) Chapter 4. For the position in South Africa see the Regulations to the National Health Act 61 of 2003 "Regulations relating to research with human participants" s 5 of *GG* R719 2014-09-19.

[27] McLean and Williamson *Xenotransplantation* 198. This requirement exists because of the atrocities that happened in the Second World War after which the Nuremberg Code was

informed consent disclosures made to the participant must be detailed and comprehensive, made in the language of choice of the participant and in a manner that facilitates understanding.[28] This implies indicating all the possible risks associated with the intervention in the greatest detail possible to the person involved.[29] The potential risk of infection, the outcomes of previous procedures, the form of monitoring that might be required following the procedure, the fact that this might be life-long, and the implication for the person's close contacts need to be explained.[30] The nature of the procedure, including the source of the tissue, the breeding, genetic modification and raising of the animal should also be included in the explanation.[31]

The biggest problem with xenotransplantation is that not all risks associated with an organ transplant using an animal organ can be highlighted to the recipient, as the medical profession or scientists are unable to state with precision the extent of all the risks.[32] New infections unknown to scientists could be introduced into the human participant and could eventually spread to a whole community.[33] Viruses that do not cause diseases in their original hosts may modify themselves once transmitted to humans and become severely pathogenic. If this should occur and the human recipient spreads the infection to other human contacts, society could be placed at risk of an epidemic from an unidentified pathogen, particularly if the clinical manifestations of the infection have a long latent period as is the case for HIV-1.[34] This danger should be highlighted to the receiver of an animal organ before informed consent can be given. Cognisance should also be taken of the fact that the researcher may have to breach a legal duty of confidentiality if this should happen.

It should also be explained to the animal-organ receiver that in most types of research with humans, risks apply to the subject only, but the benefit is for society at large. In other words, the recipient of a xenotransplantation might face some biological risks but the benefit is for society in that animal organs can help solve the ever increasing demand for transplantable organs. But in xenotransplantation the risk may be to society as well as the subject because the organ receiver might spread a disease to his or her close contacts. This is a unique characteristic of xenotransplantation and com-

drawn up. Article 1 addresses the informed consent, see the content of Article 1 in McClean and Williamson 200.

[28] HPCSA "Guidelines for good practice in the health-care professions: general ethical guidelines for biotechnology research" Booklet 7 12-15. See also Recommendation (2003) 10 of the Council of Europe's Committee of Ministers Article 13.1.

[29] Bach *et al* 2001 (27) *American Journal of Law and Medicine* 287 and 289−291. See also Daar 1997 (21) *World J Surg* 977.

[30] See McLean and Williamson *Xenotransplantation* 189.

[31] *Ibid*.

[32] Bach *et al* 2001(27) *American Journal of Law and Medicine* 290. See also Shapiro "Future issues in transplantation ethics: ethical and legal controversies in xenotransplantation, stem cell, and cloning research" 2008 (22) *Transplantation Reviews* 211-212.

[33] Sykes *et al* 2003 (10) *Xenotransplantation* 196. See also Bach *et al* 2001 (27) *American Journal of Law and Medicine* 285−286.

[34] Sykes *et al* 2003 (10) *Xenotransplantation* 196. See also Daar 1997 (21) *World J Surg* 977 "HIV … is probably a xenozoonosis". Shapiro 2008 (22) *Transplantation Reviews* 211 "Zoonoses … crossed into the human population … from wild primates in Africa and … the Ebola virus from primate to man".

plicates the giving of informed consent. The question might well be if a participant could ever give informed consent for a xenotransplantation as he or she cannot consent on behalf of everyone who might become infected, or he or she might never understand or appreciate the extent to which consent is given. It might also be impossible to get the informed consent of all the participant's close contacts, and it would be impossible to monitor all of them all of the time.

Patients waiting for an organ might be desperate and would accept any possible solution to stay alive. The voluntariness of giving consent is thus also questionable, especially where it concerns a heart or a liver as the alternative may be death.[35]

A very necessary feature of informed consent is the right of a participant to withdraw from the experiment at any time. In xenotransplantation this would not be possible and would thus be transgressed as the recipient cannot consequently withdraw once he or she has an infection that might endanger public health.[36] The consent given is then not anymore in the interest of the individual, but to the best interest of the society which is a travesty of the concept of consent.[37] Daar feels that in the xenotransplantation arena, consent as it is usually understood in a doctor-patient relationship should have to be disregarded and replaced with a binding contract that leaves many questions unanswered.[38] Moodley speaks of an investigator-participant relationship wherein the benefit to society may be significant enough to consider the research participant as a means to an end.[39] Unfortunately, even this approach will not stand scrutiny in the xenotransplantation debate as it will not only be the participant that could suffer consequences but society as a whole.

2 1 2 Surrogate consent

Some patients needing organ transplants could be in a mental and psychological state in which they are unable to consent for themselves, and another person will be needed to consent on the patient's behalf. The person required to give consent generally focuses on the medical interests of the patient that can be established by a third party possessing all the relevant facts. With xenotransplantation, however, the consent required goes far beyond the medical aspects of the patient's treatment as it also relates to the patient's freedom of movement or privacy in future. Arguably, no one is entitled to make such detrimental decisions on behalf of another.[40] Surrogate consent in xenotransplantation should therefore be outlawed.

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[35] Cooper "Ethical Aspects of Xenotransplantation of Current Importance" 1996 (3) *Xenotransplantation* 265. Cooper paraphrases a patient advocate: "A dying patient is frequently a desperate person, and desperate people do not always make decisions that are in the best interest of society at large or even of patients at large."

[36] Daar 1997 (21) *World J Surg* 977.

[37] *Ibid.*

[38] *Ibid*.

[39] Moodley *Medical Ethics, Law and Human Rights: A South African Perspective* (2011) 317.

[40] Bach *et al* 2001 (27) *American Journal of Law and Medicine* 291.

2 2 A possible violation of privacy and confidentiality

Post-operative monitoring of the recipient of a xenotransplantation is a strict requirement. This might be intrusive and even result in quarantine or other physical restrictions. Privacy and confidentiality would almost certainly have to be signed away – the same might be required of the close contacts of the recipient.[41]

As Bach *et al* say:

> "Xenotransplantation informed consent goes beyond fully explaining the risks and experimental nature of the procedure itself. Due to the unknown risk of cross-species infection, patients must agree to an unprecedented variety of restrictions on the individual freedom. These include restrictions in relation to freedom of association, freedom of movement, freedom of international travel, sexual freedom and privacy. The restrictions will need to be of unlimited duration because of the impossibility of predicting the period in which a possible infection might manifest itself. A patient consenting to such conditions would in effect be giving away important aspects of his or her freedom for life."[42]

Extensive monitoring of a recipient of a xenotransplantation and his or her close contacts should be paramount as such a person may cross borders and spread unknown diseases world-wide.[43] At present, no country's immigration authorities routinely ask a question whether one has received a xenotransplantation or not. Countries that do xenotransplantation could be flooded by foreigners in need of a transplantation, who then return home, spreading a disease.[44] Apart from the subject giving informed consent it thus seems as if all close contacts of the recipient should also consent to life-long monitoring which effectively denies them the right to withdraw from the study at any time, a fundamental right which is delineated in the Declaration of Helsinki.[45] Notification to close contacts about the potential infectious risks surrounding a xenotransplantation recipient could also violate principles of confidentiality, another fundamental right which human research subjects are entitled to.[46]

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41 Daar 1997 (21) *World J Surg* 977. In South Africa the research participant's privacy is protected by s 14 of the Constitution of the Republic of South Africa, 1996 read with s 14 of the National Health Act 61 of 2003 which states that all "information concerning a user, including information relating to his or her health status, treatment … is confidential".

42 Bach *et al* 2001 (27) *American Journal of Law and Medicine* 293.

43 Specific guidelines for such monitoring have been developed. See, eg, the guidelines of the UK XIRA – Guidance on Making Proposals to Conduct XTs on Human Subjects, 1998; United States Food and Drug Administration – Guidance for Industry: Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of XT Products in Human, Washington DC: US FDA 2001; WHO Xenotransplantation: Guidance on Infectious Disease prevention and Management, Geneva 1998, the Council of Europe' Recommendations no R (97) 15, and no 1399 (99) 1. See Melo *et al* 2001 (15) *Bioethics* 436−442 for a discussion of the international regulatory approach to xenotransplantation.

44 Sykes *et al* 2003 (10) *Xenotransplantation* 198.

45 Sykes *et al* 2003 (10) *Xenotransplantation* 197. See also Bach *et al* 2001 (27) *American Journal of Law and Medicine* 291. See also Dhai and McQuoid-Mason *Bioethics, Human Rights and Health Law: Principles and Practice* (2011) 26−27 "In South Africa, protocols which do not confirm to the *Declaration of Helsinki* usually go unapproved by research ethics committees."

46 Sykes *et al* 2003 (10) *Xenotransplantation* 197.

How will the recipient and his or her close contacts be forced to comply to inform everybody about the risks associated with the xenotransplantation? If an epidemic occurs who would be held responsible? Will it be the research subject, his or her close contacts, the organisation sponsoring the research, the Ethics Committee that allowed the study or the regulatory agency of government which approved the study?[47] All these questions will need human-rights-based answers before xenotransplantation could be either legally or ethically acceptable. It should also be imperative that the public should participate in the decision whether to allow a country or an organisation to proceed with xenotransplantation experiments as they might unknowingly become a victim of such experiments.[48]

2 3 Commerce

Until xenotransplantation becomes common practice it will be expensive as biotechnology companies will keep the price as high as the market accepts. The genetic engineering of animals will be costly. Once there is a market player, an animal organ might become a valuable commodity.[49] There will be no animal-organ donations and the organs will thus be part of commerce in which supply and demand will dictate the price.

Cooper states that the question really hinges on whether the pig organ should be grouped with human-donor organs or with other lifesaving "devices" that have been developed to be sold at a profit. He feels the companies that develop transgenic pigs will expect to make a profit from their investment.[50] Bach and Ivinson hold that xenotransplantation will eventually be another high-cost medical procedure that will widen the gap between the "haves" and the "have nots"; at the same time it might consume precious healthcare resources that could otherwise have been directed to many more people in need of less expensive interventions.[51] This could be a violation of one of the four principles of bio-ethics, namely justice.[52] Nothing about economically disadvantaged persons (who are organ-needing patients) justifies their exclusion from possible solutions albeit xenotransplantation.

2 4 Animal rights

Animal rights activists condemn xenotransplantation as they maintain humans do not have the right to breed and use other animals for their own needs because animals have the same rights as humans. Animals, according to them, have the same awareness as humans to be capable of suffering.[53] In 1780 Jeremy Bentham, a key figure in the development of

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47 Bach *et al* 2001 (27) *American Journal of Law and Medicine* 293.

48 Sykes *et al* 2003 (10) *Xenotransplantation* 197−198.

49 Daar 1997 (21) *World J Surg* 977.

50 Cooper 1996 (3) *Xenotransplantation* 270.

51 Bach and Ivinson "A Shrewd and Ethical Approach to Xenotransplantation" 2002 20(3) *Trends in Biotechnology* 130.

52 The four pillars of bio-ethics: beneficence, non-maleficence, autonomy and justice. See Bauchamp and Childress *Principles of Biomedical Ethics* Chapter 7. See also Dhai and McQuoid-Mason *Bioethics, Human Rights and Health Law* 174−176.

53 Sykes *et al* 2003 (10) *Xenotransplantation* 199.

utilitarian ethics, asked the following concerning animals: "The question is not can they reason? Nor can they talk? But can they suffer?"[54] Singer,[55] who took over the mantle from Bentham in 1975, argues that animals have rights even if they are of a lesser magnitude than those of humans. Ignoring animal rights is a form of "speciesism" which is equivalent to racism.[56]

Caplan argues that there is an inherent problem in the use of animals as they cannot part take in the debate, and humans are therefore restricted to evaluating *Homo sapiens's* own moral sensibilities, principles and values. The question is asked what it is in humans that bestows on them the moral superiority or higher moral value that would justify the killing of an animal to save a human being.[57]

There are laws protecting research on animals,[58] but despite legislation sensible guidelines regulating the use of animals for experimentation should include the 3 Rs of Russel and Burch[59] (reduce, replace and refine) to which Daar adds "reconsider" and "respect".[60] He concludes that it is ultimately the public's acceptance or rejection that will determine the utilisation of animals for transplantations.[61]

Melo *et al* feel to the contrary that animals are not humans and therefore do not have rights, but they stress that research with animals should be conducted with the least possible risk or harm, because xenotransplantation is to the therapeutic benefit of humans it could be a proportionate reason to use animals as long as legal and ethical guidelines are followed.[62]

3 SOUTH AFRICA AND XENOTRANSPLANTATION

In 2004, the 57th World Health Assembly of the World Health Organisation published resolution WHA57.18 urging member states "to allow xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place".[63] No xenotransplantation is taking place in South Africa at the moment; it could therefore be seen as possible research for the future.

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54 Daar 1997 (21) *World J Surg* 975.

55 See Singer *Animal Liberation: The Definitive Classic of the Animal Movement* 40ed (annual) (2015); and Singer *In Defense of Animals* (2013).

56 Singer *Animal Liberation* 4ed (2009). See also Singer *In Defence of Animals: The Second Wave* (2005); Bryant "Similarity or Difference as a Basis for Justice: Must Animals be Like Humans to be Legally Protected from Humans? 2007 (70) *Law and Contemporary Problems* 207; Garvin "Constitutional Limits on the Regulation of Laboratory Animal Research" 1988 (98) *Yale LJ* 369; Pickover *Animal Rights in South Africa* (2005); Hearne "What's Wrong with Animal Rights? September 1991 *Harpers* 59; and Schahmann and Polacheck "The Case Against Rights for Animals" 1995 (22) *Environmental Affairs LR* 747.

57 Caplan "Is Xenotransplantation Morally Wrong? 1992 (24) *Transplantation Proceedings* 722.

58 See the discussion on the position in South Africa below.

59 Russel and Burch *The Principles of Humane Experimental Technique* (1959).

60 Daar 1997 (21) *World J Surg* 976.

61 *Ibid.*

62 Melo *et al* 2001 (15) *Bioethics* 433. See also Cohen "The Case for the Use of Animals in Biomedical Research" 1986 (315) The *New England Journal of Medicine* 865−870. See also Schahmann and Polacheck 1995 (22) *Environmental Affairs LR* 747.

63 Tallacchini "Defining an Appropriate Ethical, Social and Regulatory Framework for Clinical Xenotransplantation" 2008 (13) *Current Opinion in Organ Transplantation* 160.

According to Moodley, research must be conducted so that medical procedures and treatments are advanced and in line with biotechnological developments, but the research must be both scientifically valid and ethically sensitive.[64] Guidelines and legislation related to research ethics are therefore important which involve an analysis of ethical and legal questions to ensure that all participants are protected as well as society as a whole. Xenotransplantation is unique in the sense that it involves both the human participant as well as the animal.

3 1 Animals

The human care and use of non-human animals for scientific purposes in South Africa are governed by the widely accepted ethical framework of the three Rs (mentioned above) – that is, the *Replacement* of animals by non-animal models where possible, the *Reduction* of the number of animals used to the minimum required to yield valid scientific results, and the *Refinement* of scientific procedures and animal-care standards in order to limit the potential for pain, suffering, distress or lasting harm, thus improving animal wellbeing.[65] The South African Medical Research Council first published guidelines on ethical considerations for the use of animals in research in 1979,[66] and in subsequent revisions of this document in 1987,[67] 1993[68] and 2004[69] in order to sensitise biomedical scientists, research institutions and Animal Ethics Committees to the interest and the welfare of research animals.[70]

In 2008 the South African Bureau of Standards produced a National Standard (SANS) for the care and use of animals for scientific purposes.[71] The majority of South African institutions doing research with or on animals have adopted these standards even though it is not a legal requirement as the responsibility to ensure compliance with SANS rests with the institutional Animal Ethics Committees.[72] SANS must be read in conjunction with the Animals Protection Act 71 of 1962, the Animal Diseases Act 35 of 1984, as well as the Animal Health Act 7 of 2002 or any other relevant legislation as the case may be. All Animal Ethics Committees that evaluate protocols where there could be an impact on human health must be registered with the

64 Moodley *Medical Ethics, Law and Human Rights* 317.
65 Mohr "The Current Status of Laboratory Animal Ethics in South Africa" 2013 (41) *ATLA* 48.
66 South African MRC (1979). Guide to Ethical Considerations in Medical Research. Cape Town, South Africa: South African Medical Council.
67 South African MRC (1987). Guide to Ethical Considerations in Medical Research. Cape Town, South Africa: South African Medical Council.
68 South African MRC (1993). Guide to Ethical Considerations in Medical Research. Cape Town, South Africa: South African Medical Council.
69 South African MRC (2004). Guidelines on Ethics for Medical Research: Use of Animals in Research and Training Cape Town, South Africa: South African Medical Council.
70 Mohr 2013 (41) *ATLA* 48.
71 SABS (2008). South African National Standard: The Care and Use of Animals for Scientific Purposes, 1ed (SANS 10386:2008).
72 Mohr 2013 (41) *ATLA* 48.

National Health Research Ethics Council[73] according to the National Health Act.[74]

No formal reporting requirement or mechanism for compiling national statistics on the use of animals in science exists.[75] Many South African institutions depend significantly on accessing international best-practice recommendations for implementing the three Rs, as the highest ethical standards should be paramount.[76]

3 2 Humans

In South Africa research ethics guidelines when humans are involved are published by the National Department of Health,[77] the Health Professions Council of South Africa (HPCSA)[78] and the Medical Research Council (MRC).[79]

The National Department of Health's Guidelines for good practice in the conduct of clinical trials on human participants in South Africa were issued in September 2000. The preamble states that the aim of the guidelines is to provide "South Africa with clearly articulated standards of good clinical practice in research that are also relevant to local realities and contexts". The Guidelines are applicable to both academic and contract research in South Africa, but unlike the guidelines by the Medical Research Council, they have no statutory basis.

The HPCSA adopted the Ethical Guidelines for Biotechnology Research (Booklet 7) in November 2005. According to the document "in bio-technological research [xenotransplantation] the usual ethical principles applicable to health research involving animals and human participants must be observed and such research must be scientifically sound". An Ethics Committee must review the ethical and scientific rigor of the proposed research. Animals that will be used in xenotransplantation will have to be genetically modified in order not to be rejected by die human body. There is no Research Ethics Committee in the context of genetic modification of organisms, however, the Genetically Modified Organisms Act 15 of 1997 provides for the establishment of an Executive Council to which applications must be submitted.[80] It should be noted that Booklet 7 of the HPCSA addresses biotechnologies, such as gene mapping, DNA sequencing, diagnostics, genetic modification and cloning which indicates that bio-technology is a newly emerging field and researchers in the biotechnology

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[73] S 73 of the National Health Act 61 of 2003. See also Department of Health: Ethics in research – SA www.mrc.ac.za/ethics/DOHEthics.pdf (accessed 2015-01-23).

[74] S 71 of the National Health Act 61 of 2003, read with s 90(1) as well as the Regulations relating to research with human participants R719 *GG* 38000 2014-09-19 September 2014.

[75] Mohr 2013 (41) *ATLA* 50.

[76] *Ibid*. See also Bach *et al* 2001 (27) *American Journal of Law and Medicine* 292.

[77] See Department of Health South Africa 2004 *Ethics in Health Research: Principles, Structures and Processes* as well as *Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.*

[78] Booklet 7 "General Ethical Guidelines for Biotechnology Research".

[79] See Dhai and McQuoid-Mason *Bioethics, Human Rights and Health Law* 168.

[80] Booklet 7 of HPCSA 9.

industry face challenges unlike researchers in other fields. Advances and research in biotechnology are often front-page news and face intense scrutiny by the press, academics, Government and the public.[81] Xeno-transplantation should be addressed in this document as well, either it should be rigorously regulated or forbidden, taking cognisance of what has been discussed earlier in the article.

The MRC Guidelines on ethics for medical research is an important codification of research ethics in South Africa.[82] It is issued in terms of section 17(1) and 17(2) of the Medical Research Council Act.[83] The MRC Guidelines govern all research carried out by or on behalf of the MRC. Van Oosten is of the opinion that the MRC Guidelines are to be followed by other research institutions as well if that particular body does not have its own ethical guidelines.[84] The MRC Guidelines also address the functioning of Research Ethics Committees which, according to Guideline 6.1.9, should "maintain ethical standards of practice in research; protect research participants and investigators from harm or exploitation; preserve the research participant's rights over society's rights; and provide reassurance to society that these roles are carried out."

The National Health Act[85] makes prior approval of health research by a Research Ethics Committee[86] compulsory. All clinical trials must also be registered with the South African National Research Registry which is based at the National Department of Health.[87] Clinical trials are allocated central registration numbers which must be attached to the ethics application on submission.[88] The National Health Act also requires that research should be conducted in accordance with the directive contained in the Constitution.[89] This is remarkable in that the South African Constitution is the only one in the world that entrenches informed consent to participate in medical research.[90] Section 71(1) of the National Health Act determines that:

> "research or experimentation on a living person may only be conducted in the prescribed manner; and with the written consent of the person after he or she has been informed of the object of the research or experimentation and any possible positive or negative consequences to his or her health".

The Constitution states that all persons have the right "not to be subjected to medical or scientific experiments without their informed consent. This

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81 Booklet 7 of HPCSA 7.

82 Van Oosten "The Law and Ethics of Information and Consent in Medical Research 2000 (63) *Journal of Contemporary Roman-Dutch Law* 7.

83 58 of 1991. S 17(1) of the Act determines that the MRC Board must regulate and control research on or experimentation upon humans. S 17(2) empowers the Board to determine ethical directives to be followed in research and experimentation.

84 Van Oosten 2000 (63) *Journal of Contemporary Roman-Dutch Law* 7.

85 61 of 2003 Chapter 9.

86 See Dhai and McQuoid-Mason *Bioethics, Human Rights and Health Law* 170−176, for a discussion on Research Ethics Committees. All Research Ethics Committees must be registered with the National Health research Ethics Council which has the authority to audit Ethics Committees and if necessary discipline their members.

87 S 72 of the National Health Act 61 of 2003.

88 Dhai and McQuoid-Mason *Bioethics, Human Rights and Health Law* 170.

89 S 12(2)(c) of the Constitution of the Republic of South Africa,1996.

90 Dhai and McQuoid-Mason *Bioethics, Human Rights and Health Law* 168.

consent must be in writing.[91] This poses a prenominal problem to xenotransplantation research in South Africa because, as indicated above, informed consent in the ordinary sense of the word is not possible when a xenotransplantation is contemplated.

4 CONCLUSION

Xenotransplantation is a process that involves difficult legal and ethical questions such as safety of the procedure, personal choices, Government intervention, as well as an economic dimension.[92] The obtaining of informed consent seems to be the biggest legal obstacle as indicated above. In South Africa, a developing and multi-cultural country, the issue of informed consent is even more pertinent as many people are unfamiliar with scientific concepts like "biotechnology" or "xenotransplantation".[93] The potential for abuse is thus great and therefore legislative and regulatory specifications should be in place to safeguard against the uncontrolled research concerning the use of animals and human participants. Although it seems to be control over such research by way of ethics committees and that directives xenotransplantation is not specifically addressed in any legal or regulatory document. Mention is made of cloning and genetic engineering but the aspect of xenotransplantation is not directly addressed. This seems to be *lacunae* that should be filled if xenotransplantation is accepted as a possible solution to the organ shortage. The alternative is to prohibit such research altogether and rather focus on other ways of organ procurement to curb the ever increasing demand for transplantable organs.[94]

Fox and McHale ask:

> "Are the boundaries of health, or indeed life itself, destined for inevitable extension or have we reached a point at which it is time to say enough really is enough, and for ethical reasons, including resource allocation, our energies would be better devoted to other health care issues."[95]

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91 S 71 of the National Health Act 61 of 2003.

92 Melo *et al* 2001 (15) *Bioethics* 436.

93 Booklet 7 of HPCSA 22.

94 In this regard see Slabbert "Ethics, Justice and the Sale of Kidneys for Transplantation Purposes" 2010 13(2) *PER* 77−105; Slabbert "This is my Kidney I Should be Able to What I Want With It: Towards a Legal Framework for Organ Transplants in South Africa" 2012 31(4) *Medicine and Law* 617−640; Shafran, Kodish and Tzakis "Organ Shortage: The Greatest Challenge Facing Transplant Medicine" 2014 (38) *World J Surg* 1653−1656; Einollahi "Kidney Transplantation in Iran" 2010 35(1) *Iranian J Med* 1-8; and Matas "The Rationale for Incentives for Living Donors: An International Perspective?" 2015 2 *Curr Transplant Rep* 44−51.

95 Fox and McHale "Xenotransplantation: The Legal and Ethical Ramifications" 1998 6(1) *Medical LR* 61.