PROF. PETER COWAN (Orcid ID : 0000-0001-9016-4954)

Article type : Review

Version and date: Final, April 22 2020

Manuscript type: Review

Original manuscript received: April 22

Revised manuscript received: April 22

Manuscript accepted: April 22

Abstract number of words: 49

Text number of words: 1859

Number of references: 18

Number of Tables: 0

Number of Figures: 0

Email address authors:

Wayne Hawthorne: Wayne.Hawthorne@Sydney.edu.au

Peter Cowan: Peter.COWAN@svha.org.au

Xenotransplantation in Australia: Development of the Regulatory Process

Wayne J. Hawthorne^{1, 2*}, Peter J. Cowan^{3,4}

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/XEN.12603](https://doi.org/10.1111/XEN.12603)

This article is protected by copyright. All rights reserved

¹Centre for Transplant and Renal Research, The Westmead Institute for Medical Research,
Westmead Hospital, Sydney, NSW, Australia

²Department of Surgery, Western Clinical School, University of Sydney, Sydney, NSW, Australia

³Immunology Research Centre, St Vincent's Hospital Melbourne, Melbourne, Victoria, Australia

⁴Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia

*Address correspondence to:

Prof. Wayne Hawthorne

Department of Surgery

Westmead Hospital

Westmead, NSW, 2145

AUSTRALIA

e-mail: Wayne.Hawthorne@Sydney.edu.au

Running head: Xenotransplantation guidelines in Australia

Abstract

In this commentary, we present a brief history of the development of a national regulatory framework for xenotransplantation clinical research in Australia, including the reasons behind the imposition of a 5-year moratorium in 2005 and its subsequent lifting. We conclude with a summary of current relevant guidelines and standards.

Global Influence on the Regulation of Xenotransplantation in Australia

By the early 2000's the World Health Organization (WHO) had embarked on the development of xenotransplantation policy, adopting a supportive and directed role in consultation with the International Xenotransplantation Association (IXA) ¹. Holding the first of several focussed meetings on the ethical, access and safety issues in tissue and organ transplantation in Madrid in 2003, this was followed by a report which formed the basis of the World Health Assembly Resolution WHA57.18 urging Member States to "Allow xenotransplantation trials once effective national regulatory control and surveillance mechanisms overseen by National Health Authorities were in place." ²

The Australian influence in the field was particularly strong at that time, with Australian groups at the forefront of xenotransplantation research. Indeed, two Australians served consecutively as President of the IXA (Ian McKenzie from 2001-2003 and Tony d'Apice from 2003-2005) along with an Australian scientist (Mauro Sandrin, a member of the original Council of the IXA), provided direction for the development of guidelines and policy, including at the national level. Several additional Australian members of the IXA were instrumental in the establishment of the Xenotransplantation Standing Committee (now the Xenotransplantation Working Group) this group is from the Transplantation Society of Australia and New Zealand (TSANZ), which was tasked to provide advice as required to national bodies such as the Australian National Health & Medical Research Council (NHMRC).

Development of Xenotransplantation Guidelines in Australia

The Role of the Xenotransplantation Working Party (XWP)

The initial work on developing a national regulatory framework for xenotransplantation in Australia pre-dated the WHA57.18 Resolution ³. As in most countries, research in Australia involving humans and animals is regulated at the local level by the relevant institutional committees: the Human Research Ethics Committee (HREC) and the Animal Ethics Committee (AEC). These committees require expert support and guidance, and in 1994 the NHMRC formed the Gene and Related Therapies Research Advisory Panel (GTRAP) to provide specialised advice

on novel cutting edge scientific and medical technologies ⁴. In addition to advising on clinical trials involving gene therapy, the purview of GTRAP was expanded in 1999 to include xenotransplantation, with experts in xenotransplantation and infectious disease added to the panel ⁵.

Driven at least in part by emerging concerns of potential infectious risk associated with cross-species transmission of porcine endogenous retrovirus (PERV), the NHMRC established an even more specialised body, the Xenotransplantation Working Party (XWP), which held its first meeting in early 2001 ⁶. The XWP had seven members from the NHMRC Council and its committees including the Australian Health Ethics Committee (AHEC), GTRAP, the Research Committee, the Animal Welfare Committee and the Consumer Health Forum, this working party is separate from the Xenotransplantation Working Group from the active research members of the TSANZ. The separately formulated XWP was tasked to develop guidelines for the assessment of potential animal-to-human transplantation clinical trials and to undertake a public consultation about the issues, perceived or otherwise, in relation to xenotransplantation into humans ⁵.

In July 2002, the XWP published a document entitled “Draft Guidelines and Discussion Paper on Xenotransplantation” on the NHMRC website. The discussion paper included proposals for public consultation regarding the regulation of xenotransplantation research in Australia ⁷. It outlined how any proposed xenotransplantation clinical trial must ‘justify how it serves the common good’; ‘justify any risks’; ‘be scientifically sound’ and ‘therapeutic in design’; ‘protect the safety and rights of close contacts’ of those patients undergoing xenotransplantation defining the term for patients undergoing xenotransplantation as a “participant” of the study; ‘ensure long-term monitoring of participants’; and ‘facilitate adequately informed and voluntary consent’ ⁵.

For the first public consultation, written submissions were invited, and face-to-face meetings were held in the capital cities of several states in Australia. Following review of all responses, the XWP acknowledged that participants did not represent all interested parties, with little if

any input from transplant recipients, potential recipients and patients who could potentially benefit from xenotransplantation⁸. To address this limitation, greater public engagement was sought during subsequent consultations. Additionally, the XWP was expanded to include new members with expertise in clinical trials, animal welfare and infectious diseases⁹. The expanded XWP produced two documents for the second public consultation: 'a laypersons guide' to xenotransplantation that provided more basic overview information, and a Discussion Paper that set out the XWP's responses to the initial consultation and provided focus on the issues at hand⁹. The draft guidelines were revised to incorporate two new topics: animal welfare and patient selection. The animal welfare section included guidance on how preclinical and clinical xenotransplantation studies must meet specific animal welfare standards for protection of the animals as well as the recipients⁹. Additionally, the guidelines required research protocols to clearly specify the process of patient selection for xenotransplantation clinical trials⁹. After release of the draft guidelines in early 2004, the XWP held public meetings in the capital cities of all states. Six months after collation of the data from the public meetings, the XWP submitted their Report and proposed Clinical Guidelines for Animal-to-Human Transplantation Research to the Council of the NHMRC.

The Moratorium on Xenotransplantation Clinical Trials 2005-2009

After reviewing the documents provided by the XWP, the NHMRC Council announced that clinical trials in xenotransplantation should not be considered in Australia for at least five years. The major factor in this decision was that xenotransplantation carried a potential theoretical risk of infection and that current evidence indicated that this risk was not outweighed by the potential for success; 'community concerns of the potential risk of new zoonotic diseases being transmitted to humans' were noted. The final report and draft guidelines were made public in 2005 and the xenotransplantation 'moratorium' was in place from 2005 to 2009⁹.

Despite the moratorium on clinical trials, preclinical research on porcine islet and kidney xenotransplantation continued in Australia, as the NHMRC continued to refine the guidelines¹⁰. The National Statement on Ethical Conduct in Human Research 2007 (updated in 2018),

prepared jointly by the NHMRC, the Australian Research Council (ARC) and Universities in Australia, included a chapter devoted specifically to xenotransplantation ¹¹. Chapter 3.4, 'Animal-to-Human Xenotransplantation', provided guidance to HRECs, researchers, and potential participants (i.e., a xenotransplant recipient in a clinical trial) on the regulation of any procedure that involves the transplantation, implantation or infusion of live cells, tissues or organs from another species, or body fluids, cells, tissues or organs that have ex vivo contact with live cells, tissues or organs from another species. Chapter 3.4 focused on ethical considerations particularly relevant to xenotransplantation, including the potential risk of disease transmission from animals to humans and from the participant to close contacts; the need to balance the interests of close contacts with those of the participant; the requirement for long-term or lifelong monitoring; and limitations on the participant's ability to withdraw consent. HRECs were advised to adopt a cautious approach when assessing the ethical acceptability of xenotransplantation research, and to consider the extent to which risks are unknown in the context of public safety and whether the proposed research should proceed in view of these potential unknown risks. All such research required ethical review and approval by an HREC, with consideration of any requirements of the Therapeutic Goods Administration (TGA), the licensing authority in Australia for applications to use a device, agent, drug or cell for clinical work ^{12, 13}.

Lifting of the Moratorium

To decide on the future of the moratorium, the NHMRC held a consultation in 2008 to review the progress in xenotransplantation research in Australia and abroad, inviting experts from within Australia and from New Zealand, Europe and the USA. As part of this consultation, the expert panel reviewed the impact of the moratorium on Australian research. The resulting Discussion Paper, 'Xenotransplantation: A Review of the Parameters, Risks and Benefits', noted that the moratorium had impeded preclinical xenotransplantation research and stifled funding for such research work, and had delayed the development of regulatory guidelines and further support for research infrastructure¹⁴. The Discussion Paper also concluded, based upon new data from several overseas research groups, that the potential risk of xenozoonosis was

relatively low compared to the risk of infection in allotransplantation ¹⁴. Accordingly, the NHMRC allowed the national moratorium to lapse in 2009.

Current Guidelines for Xenotransplantation in Australia

The National Statement on Ethical Conduct in Human Research 2007, updated in 2018 ¹¹, and in particular Chapter 3.4, 'Animal-to-Human Xenotransplantation', is the key current regulatory document for xenotransplantation clinical research in Australia. Chapter 3.4 sets out guidelines for HRECs in the form of 3 'elements'. Element 1 addresses Research Scope, Aims, Themes, Questions and Methods. It poses an extensive list of key questions including: does the HREC have the appropriate expertise to assess the research; what are the potential risks to participants and others; is the research ethically justified in the context of risks that may not be currently known or well understood; how is risk minimised; what monitoring will be required, and for how long; and how will adverse events be managed. Element 2 addresses Recruitment of Participants, and includes questions on assessment of participant suitability, explanation of unknown or poorly understood risks, and management of close contacts. Element 3 addresses Consent, with questions on how consent for long-term monitoring will be managed and what limitations will be placed on withdrawal of consent.

The Australian TGA is responsible for providing standards and guidance for goods that comprise or contain live animal cells, tissues or organs, which since 2017 have been regulated as 'biologicals' in Australia. The relevant standards are Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2013 and Therapeutic Goods Order No. 87 'General requirements for labelling of biologicals' ¹³. TGA guidance on the safe development and use of xenotransplant products, especially in clinical trials, relies on guidance documents published by several bodies including the WHO, the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and the ICA. For cellular products including islets, the TGA has adopted the EMA Guideline on Xenogeneic Cell-Based Medicinal Products, 2010 ¹⁵. For animal-derived tissue that is acellular, it is generally restricted to therapeutic devices or components of

devices which are of animal origin for use in the body or for application to broken skin. These still fall under the jurisdiction of the TGA, but come under the Australian Medical Device Requirements, Version 4, under the Therapeutic Goods Act, 1989 ¹⁶.

Additional legislation relates to the use of animals in xenotransplantation research, which must comply with the requirements of the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes 8th Edition, 2013 ¹⁷. Furthermore, dealings with genetically modified source animals are regulated by the Office of the Gene Technology Regulator (OGTR) under the Gene Technology Act 2000 ¹⁸.

Summary

The regulatory framework for xenotransplantation research in Australia has been developed over more than 20 years, and it continues to be updated and refined in line with progress in field as guided by the NHMRC with critical input from national and international bodies including TGA, WHO, TTS, and IXA, and also from the Australian public including those that may ultimately benefit from xenotransplantation to provide them a cure.

Acknowledgements:

Mr Adwin Thomas (Centre for Transplant and Renal Research, The Westmead Institute for Medical Research, Westmead Hospital, Sydney, NSW, Australia) for review and referencing.

References:

1. Noël L. The proactive role of the WHO. *Xenotransplantation* 2007, 14:348-449.
2. Organization WH. Ethics, access and safety in tissue and organ transplantation : issues of global concern, Madrid, Spain, 6-9 October 2003 : report. 2004. Available at: <https://apps.who.int/iris/handle/10665/42886>.

3. Organisation WH. Human organ and tissue transplantation. *FIFTY-SEVENTH WORLD HEALTH ASSEMBLY* 2004, Pages 56-59. Available at:
https://apps.who.int/gb/ebwha/pdf_files/WHA57/A57_R18-en.pdf.
4. Trent RJ. Oversight and monitoring of clinical research with gene therapy in Australia. *Med J Aust* 2005, 182:441-442.
5. Xenotransplantation Working party. Draft guidelines and discussion paper on xenotransplantation 2002.
6. van der Laan LJ, Lockey C, Griffeth BC, Frasier FS, Wilson CA, Onions DE, Hering BJ, Long Z, Otto E, Torbett BE, et al. Infection by porcine endogenous retrovirus after islet xenotransplantation in SCID mice. *Nature* 2000, 407:90-94.
7. Breen KJ. The xenotransplantation research debate: time to involve the community. *Med J Aust* 2002, 177:175.
8. Party XW. Animal-to-Human transplantation research: a guide for the community. 2003.
9. Xenotransplantation Working party. Animal-to-Human transplantation research: how should Australia proceed. 2003.
10. Hawthorne WJ, Salvaris EJ, Phillips P, Hawkes J, Liuwantara D, Burns H, Barlow H, Stewart AB, Peirce SB, Hu M, et al. Control of IBMIR in neonatal porcine islet xenotransplantation in baboons. *Am J Transplant* 2014, 14:1300-1309.
11. The National Health and Medical Research Council, the Australian Research Council and Universities Australia. *National Statement on Ethical Conduct in Human Research 2007 (Updated 2018)*. Canberra: National Health and Medical Research Council; 2018.
12. Administration TG. Therapeutic Goods Order No. 87 General requirements for the labelling of biologicals. 2011. Available at: <https://www.legislation.gov.au/Details/F2011L01493>.
13. Administration TG. Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2013. 2013. Available at: <https://www.legislation.gov.au/Details/F2017C00967>.

14. National Health and Medical Research Council. Discussion paper Xenotransplantation: a review of the parameters, risks, and benefits. 2009.
15. Cozzi E, Tonjes RR, Gianello P, Buhler LH, Rayat GR, Matsumoto S, Park CG, Kwon I, Wang W, O'Connell P, et al. First update of the International Xenotransplantation Association consensus statement on conditions for undertaking clinical trials of porcine islet products in type 1 diabetes--Chapter 1: update on national regulatory frameworks pertinent to clinical islet xenotransplantation. *Xenotransplantation* 2016, 23:14-24.
16. Administration TG. Australian Medical Device Requirements, Version 4, under the Therapeutic Goods Act, 1989. Available at:
<https://www.tga.gov.au/sites/default/files/dr4-v1-s2.pdf>
17. National Health and Medical Research Council. *Australian code for the care and use of animals for scientific purposes*. Canberra; 2013.
18. Government A. Gene Technology Act 2000. 2000. Available at:
<https://www.legislation.gov.au/Details/C2016C00792>.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Hawthorne, WJ;Cowan, PJ

Title:

Xenotransplantation in Australia: Development of the regulatory process

Date:

2020-06-07

Citation:

Hawthorne, W. J. & Cowan, P. J. (2020). Xenotransplantation in Australia: Development of the regulatory process. XENOTRANSPLANTATION, 27 (3), <https://doi.org/10.1111/xen.12603>.

Persistent Link:

<http://hdl.handle.net/11343/275871>