The demise of UKXIRA and the regulation of solid-organ xenotransplantation in the UK

Sheila McLean, Laura Williamson

The new regulations on xenotransplantation pay insufficient attention to the broad ethical (and legal) problems raised by this technique and that the abandonment of a national body with overall regulatory authority in this area is a mistake.

Following reports from the Nuffield Council on Bioethics¹ and, most importantly, the Advisory Group on the Ethics of Xenotransplantation² (the Kennedy report), the UK Xenotransplantation Interim Regulatory Authority (UKXIRA) was established in 1997. The existence of a national body to govern xenotransplantation was deemed to be of critical importance by the Kennedy report (and by the government of the time) given the practical and ethical issues associated with xenotransplantation. Indeed, the Kennedy report recommended that ultimately UKXIRA should be placed on a statutory footing.² The remit of UKXIRA was to advise the Secretary of State on particular applications, gather information on issues such as safety, and assess whether the preconditions identified by the Kennedy report had been met.³

In December 2006, UKXIRA was quietly disbanded, and the Department of Health issued a statement of guidance, the terms of which now govern xenotransplantation in the UK. This document superseded procedures that had been in place since 1998, which had placed the overall regulation of applications to conduct xenotransplantation in the hands of UKXIRA and, ultimately, the Secretary of State.⁴ The revised guidance defines xenotransplantation as being: "... any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live tissues or organs retrieved from animals, or, human body fluids, cells, tissue or organs that have undergone ex vivo contact with live non-human animal cells, tissues or organs."⁵ (emphasis added). Given the range and nature of the procedures covered by the guidance, it is surprising, not to say a little worrying, that it is so brief and so short on substance. Nonetheless, the purpose of the new guidance is said to be "to help clarify

requirements and allow research to continue to develop with open discussion and debate".⁵ The revised guidance encourages "further development of xenotransplantation",⁵ in line with international recommendations. According to the new guidance "...it is right to explore the potential of xenotransplantation in a cautious, stepwise fashion... in a controlled research context".⁵ This cautious approach is important because: "The major issue around xenotransplantation is one of public safety, particularly the risk that infectious disease/agents might be transmitted from the animal tissue to the recipient and potentially to the wider population. Much attention is focused on the possibility that [porcine] endogenous retroviruses (which exist harmlessly in animals) may be transferred into humans and become activated – potentially spreading new diseases to the human population".⁵

The revised guidance outlines two primary routes for the consideration of applications to conduct xenotransplantation procedures in the UK: one for clinical trials and the other for experimental procedures. The document describes experimental procedures as being those "where a clinician offers a particular course of treatment tailored to a particular patient's needs, either a brand new treatment or a new use of a drug or product licensed for use in other ways."⁵ The safety and efficacy of xenotransplantation clinical trials is now to be assessed by the Medicines Healthcare Products Regulatory Agency and ethically reviewed by local research ethics committees (LRECs); experimental treatments are assessed by each Trust's clinical governance committee (CGC), and experimental research by an LREC or by the Gene Therapy Advisory Committee (GTAC) in cases where the xenogeneic product is genetically modified. However, the remit of GTAC expressly precludes xenotransplantation of solid organs.⁶

Although it is possible to criticise the way in which UKXIRA operated (and we have done this elsewhere⁷), the new guidance seems to weaken rather than strengthen the controls available to protect the public (and individual patients, their families and healthcare staff) from the risks of infectious disease that may be associated with animal to human organ transplantation. This is particularly the case for experimental treatments and research that does not fall within the remit of GTAC, because such procedures are to be assessed and ethically appraised on a local basis, either by CGCs (whose role in this is somewhat hazy) or by local LRECs, whose workload has increased significantly since the introduction into UK law of the Clinical Trials Regulations and whose expertise in xenotransplantation has yet to be established.

In a rather weak acknowledgement of some of the difficulties associated with the performance of xenotransplantation procedures, the guidance notes that: "Clinicians considering offering experimental treatment outside a research framework are encouraged to take public health issues and long-term health surveillance of patients into account."⁵ (emphasis added).

That the experimenters in xenotransplantation are only encouraged, not required, to consider the very issues that are the source of legitimate ethical (and legal) concern is a far cry from the previous position in the UK that all xenotransplantation procedures should be assessed seriously – so seriously that a national body was seen as necessary to advise the government on whether applications should be accepted and permitted to proceed.

The form of xenotransplantation that is arguably most likely to avoid any form of national oversight under the new guidance is that which has long been seen as carrying the greatest infection risk for humans: solid-organ xenografting.⁸ The history of xenotransplantation testifies that solid-organ xenografts have generally taken place in an experimental context—that is, not as part of clinical trials. This is partly because, internationally, such surgery has been led by clinical urgency.^{9–12} The situation differs from work on cellular xenografting techniques, which has tended to be developed and tested within clinical trials.^{13–14} According to the new guidance, then, experiments in animal to human solid-organ transplantation would only require the authority of each Trust's CGC.

Much ethical debate on xenotransplantation has been directed at assessing at what point it would be acceptable to move to clinical trials and which patients

it would be acceptable to include.^{15–17} The development of stringent regulatory frameworks in the UK and elsewhere was designed to ensure that if xenotransplantation procedures took place, they would be both clinically and ethically feasible. When conducted within the context of a clinical trial (which is advised but not insisted on by the revised guidance¹⁸) and if not covered by the Clinical Trials Regulations, scrutiny of xenotransplantation procedures is to be provided by the Trust's CGC. Quite apart from concern about the competence of these committees in this area, local ad hoc decision-making seems to us to be unsuited to practices whose consequences could be national – even international. The failure to retain national regulatory procedures to prevent experimental xenografting makes it possible that any future applications to conduct organ xenografts will be submitted via the experimental procedures route in the new guidance, rather than that for assessing clinical trials. Under the new guidance, this would mean that they would only be assessed locally, because xenogeneic organs fall outside the remit of GTAC.⁶ If not part of a clinical trial, not even LREC scrutiny seems to be required.

The decision to leave the assessment of experimental procedures to local assessment mechanisms might be based on the desire to open the doors to experimental xenotransplantation involving solid organs in the UK. However, we feel that it is more likely that the lack of success to date in developing solid-organ xenografting, along with the fact that UKXIRA did not receive any applications to conduct procedures involving solid organs, has led to the assumption that there is no longer a need to regulate this form of xenotransplantation stringently.

We suggest that this assumption is unsafe for a number of reasons. First, work on solid organs has historically occurred on a cyclical basis: experimental procedures, experiments or treatment failure, further research, new experimental procedures, and so on. Thus, a lack of current efforts to move to clinical application in the UK should not lead to regulatory complacency. Second, this is supported by the fact that research to make solid-organ xenotransplantation clinically viable is continuing in animal models. Thus, in 2005, several studies reported success in overcoming the rejection problems of transplanting porcine hearts and kidneys into baboons.^{19–20} In the same period, a team at the Mayo Clinic achieved the longest survival times to date for a cardiac xenograft in an animal model (96 days), although the graft was heterotopic and was not

life-supporting. However, the researchers claimed that clinical application can be justified on the basis of 90-day graft survival and thus “[d]uplication of these results in the orthotopic life-supporting position could bring cardiac xenotransplantation to the threshold of clinical application”.²¹ More recently, Cozzi *et al* have described xenotransplantation as “moving ahead rapidly”.²²

Those developing xenotransplantation have tended to be overly optimistic about the timescale for successful clinical application. However, while research continues, procedures to regulate *all* forms of xenotransplantation need to be robust to ensure that we do not return to the cyclic performance of experimental xenotransplants, not least because countries with the most liberal xenotransplantation procedures (even if this position has been arrived at inadvertently) may well attract research teams or surgeons who wish to conduct experimental procedures that remain unacceptable in countries with tighter regulation.

The ethical issues raised by regulatory developments in the UK have passed largely without remark. The revised guidance concedes that there are “complex ethical issues” associated with xenotransplantation, but neither offers a full explanation of what these may be, nor any help in debating or resolving them. Yet these issues go to the very heart of the question as to whether or not we should indeed be allowing (perhaps even encouraging) experimental procedures and/or clinical trials of xenotransplantation in the UK. Many of these issues are not specific to the revised guidance and still need to be addressed.

Clinical trials and experimental procedures involving xenotransplantation raise particularly difficult issues in respect of consent. Individuals who are likely to be invited to participate in clinical trials or experimental procedures, particularly in solid-organ transplantation, will surely be fast approaching death. The quality of any purported consent must be carefully scrutinised in these circumstances. However, particularly problematic is the fact that the individual-focused nature of consent as traditionally conceived does not take account of the interests of close contacts and the wider society. The risks of infectious disease potentially associated with xenotransplantation mean that the decision of one patient could compromise the health of third parties: their close contacts, healthcare providers or others. Animal to human transplantation does not represent a simple case of individuals accessing an experimental therapy that may have benefits or risks for them alone. It is necessary, therefore,

to conduct a detailed assessment of how the conflict between individual and social well-being can be addressed most satisfactorily in the context of xenotransplantation. We would argue that this issue requires a national – even international – response rather than local appraisal by RECs.

Assuming that the new guidance intends to pay serious attention to the surveillance requirements produced in draft by UKXIRA to ensure that any harmful effects are quickly identified and efficiently handled, then not only will any recipient of a xenotransplant require to be followed up for a lifetime, so too will those who are close to them.²³ In this respect, UKXIRA's surveillance document expected xenograft recipients and their close contacts to comply with extensive and invasive requirements. Arguably, a surveillance regime that is less demanding than that proposed by UKXIRA poses its own risks and is unlikely to be able effectively to meet the safety requirements demanded by the potential threat to public health that solid-organ animal to human transplants may pose.

In whatever form they finally emerge, surveillance regimes by their nature require individuals to relinquish a number of freedoms in the interests of possible but unknown benefits and in the face of possible but unknown risks, not only to the individual but to the community as a whole. This is, of course, not uncommon in public-health regulation, but it seems likely that xenograft recipients will need to have more constraints than is usual placed upon them, at least until risk has been satisfactorily measured. For example, at the very least, recipients will likely have certain choices, such as procreation, precluded or restricted. Additionally, although the new guidance recommends public debate on xenotransplantation in line with international recommendations, the fact that the UK government seems to be encouraging xenotransplantation without such a debate is surely cause for concern.

Moreover, there are further ethical and legal considerations to be taken into account. Animal welfare, for example, is given nothing more than a passing nod in the new guidance, which merely notes that “the use of animals in xenotransplantation research or as sources for clinical xenotransplantation requires authorisation under the terms of the Animal (Scientific Procedures) Act 1986.”²³ The wide, often passionate, debate about using animals in this way, which was given some consideration in the reports from the Nuffield Council on Bioethics¹ and the Kennedy report² seems

to be disregarded in this guidance, perhaps on the assumption that those enforcing the 1986 legislation are adequately able to encapsulate it within their deliberations. Yet this was clearly not the view of the Kennedy report or of the government at the time. In any case, as Menache notes, xenotransplantation involves two different layers of experimentation: the first is the creation of the transgenic animal itself and the second the transplantation into human subjects.²⁴ The surveillance regime of the 1986 Act may well be able to cover the former; is it sufficient that a local LREC or CGC considers the latter?

In addition, there are matters concerning public safety that are more than merely practical and relate to our ethical and legal obligations to others, both nationally and globally. International law, for example, requires that "no state is entitled to conduct itself as to create a foreseeable danger to other states...conduct, of course, comprises both acts and omissions".^{25, 26} Thus, were porcine endogenous retroviruses to be spread throughout communities as a result of xenotransplantation, failure to regulate adequately in this area could mean that a third party state "may well be entitled to claim damages against the state which permitted such activity".²⁶ To say nothing, of course, of the effect of the potential health risks on that country's own citizens.

CONCLUSION

In all, we believe that the disbanding of UKXIRA was a mistake. Although considerable reform of that body was needed, particularly to ensure adequate representation of ethics and law in its membership and deliberations, the ability of a national body to scrutinise attempts at xenotransplantation, and to address the full range of ethical and legal questions raised by it in a consistent, transparent and accountable manner has been lost. It is unclear if the plethora of committees now charged with the responsibility of overseeing xenotransplantation have the necessary ethical expertise (or in some cases the remit) to scrutinise such applications in the depth that was available when a national committee existed. When this is coupled with what appears to be the clear desire of the Department of Health that the UK should become a welcoming place for xenotransplantation research, there is reason for real concern. Despite accepting the recommendations

of the Kennedy report, one of which was that a national statutory body should be created to oversee xenotransplantation, the government has reneged on this, leaving control to a variety of bodies, some of whose decisions have been roundly criticised as being of varying quality. In particular, when applications are considered by LRECs, clinicians themselves have complained that what is seen as ethical by one committee will not be seen as ethical by another. The question, therefore, is: can we really afford to have these committees taking decisions that could result in widespread public health problems? The model that these committees are used to (and arguably qualified to address) is essentially one that evaluates a proposal for its scientific content; beyond that, the "ethical" consideration is often limited to the question of consent. As we have argued, the kind of consent needed in xenotransplantation is considerably different from that required in other research or experiments that do not pose public health concerns. Just how these committees are to take account of this (as well as issues about animal welfare, surveillance and international legal requirements) is – to put it mildly – at best unclear. No matter how far off solid-organ xenotransplantation may be, the potential risks posed by continued efforts to make it a reality surely mandate a regime much more stringent than that which is now in place in the UK.

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Authors' affiliations

Sheila McLean, Laura Williamson, Institute of Law and Ethics in Medicine, University of Glasgow, The Stair Building, Glasgow G12 8QQ, UK; s.a.m.mclean@law.gla.ac.uk

Correspondence to: Sheila McLean, Institute of Law and Ethics in Medicine, University of Glasgow, The Stair Building, Glasgow, G12 8QQ, UK; s.a.m.mclean@law.gla.ac.uk

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