

April 10, 2005

Mary Groesch, Ph.D.
Executive Director
Secretary's Advisory Committee on Xenotransplantation
Office of Biotechnology Activities
Rockledge I, Room 750
Bethesda, MD 20892

Re: Secretary's Advisory Committee on Xenotransplantation draft reports

Dear Dr. Groesch:

The American Academy of Orthopaedic Surgeons (AAOS/Academy), representing over 19,000 Board certified orthopaedic surgeons, welcomes the opportunity to comment on the draft reports prepared by the Secretary's Advisory Committee on Xenotransplantation (SACX). These reports are meant to advise the Department of Health and Human Services on both the current state of scientific knowledge concerning xenotransplantation and the issues surrounding informed consent in clinical trials involving xenotransplantation. Notice for comment on these reports was initially published in the Federal Register on Wednesday, March 9, 2005.

The Academy holds patient safety as its highest priority, and supports policy that both protects and improves the public's health. The AAOS shares the concerns of the Secretary's Advisory Committee on Xenotransplantation in ensuring that xenotransplantation products are safe for human use. Though much of the research currently being performed is done by private industry, we nonetheless encourage those in the xenotransplantation research community to share findings in this burgeoning field, facilitating development of the global body of xenotransplantation-related knowledge.

Orthopaedic surgeons are frequent users of animal-based transplantable tissue such as pig submucosa and bovine collagen scaffolds. The Academy encourages the SACX to include a section in the revised draft report on processed source animal tissue used in procedures such as cartilage transplantation and musculoskeletal soft tissue reinforcement. We encourage the SACX to specifically consider this type of cellular/tissue xenotransplantation product in future policy discussions.

The Academy monitors developments in xenotransplantation as they relate to orthopaedic and musculoskeletal care, and remains committed to educating our membership on the development and use of xenotransplantation products. Since 2003, the AAOS has offered educational exhibits and information to our Fellows at our annual meeting on the potential risks and benefits associated with the use of xenotransplantation products.

Report on the State of the Science in Xenotransplantation

Xenotransplantation raises significant medical concerns for the patient, primarily the potential for transmission of an infectious agent from the source animal. Though the possibility of infection remains a grave concern even in human-to-human allotransplant, the epidemiologic consequences of transmitting a potentially contagious zoonotic pathogen must be acknowledged as a serious public health threat. The AAOS agrees with the SACX that transmission of an infectious agent from a source animal could result in the undetected spread and establishment of novel infections in humans. However, proper handling and selection techniques along with sensitive microbial detection assays can be implemented to reduce the risks of exogenous infection transmission from the animal. In addition, selection of both the species and individual source animal are identifiable points at which rigorous quality control measures can also reduce the potential risk of transmission.

The AAOS is very concerned with the possibility of viral transmission of disease, especially with clinically latent viruses that appear to be asymptomatic and non-pathogenic in the source animal. These may go unrecognized by presently available detection methods. The current gaps in knowledge concerning latent and active zoonotic agents are of great concern. Specifically, the xenotransplantation community must study the etiology and pathogenicity of latent viruses as well as develop appropriate models for predicting the immune responses of humans to viral introduction to the body.

The AAOS believes that extensive research on the species-specific characteristics of xenogeneic agents is required. Directed clinical research into the transmission and life cycle mechanisms of these microbes in both source animals and humans will ultimately result in the development of safer, more compatible products. Careful study should be devoted to developing detection methods for both bacterial and viral agents, especially those that are latent or asymptomatic. Again, the AAOS calls on the SACX and the xenotransplantation community to develop an appropriate forum to exchange and share this vital information.

The Academy supports the role of the Department of Health and Human Services in maintaining oversight and developing regulatory and policy guidelines for the xenotransplantation community. Specifically, the AAOS praises the creation of the national database of xenotransplantation clinical trials and the national archive for biological specimens. The AAOS agrees with the SACX in the humane and judicious use of animals in clinical study. Since the orthopaedic community is a significant user of xenotransplantation products, the AAOS continues to urge the Secretary's Advisory Committee on Xenotransplantation to expand its membership to facilitate orthopaedic representation.

Report on Informed Consent in Clinical Research Involving Xenotransplantation

The ethical principles for acquiring the informed consent of subjects participating in clinical trials are well established. The AAOS applauds those individuals who selflessly participate in the advancement of medical science, and recognizes the crucial role they play in the development of life-enhancing and life-saving treatments. We believe that the concepts of patient autonomy and protection from harm are best preserved through a comprehensive informed consent process.

However, the potential risks inherent in xenotransplantation studies necessitate additional precautions in the disclosure of clinical trial protocol and risks, including clear and easily understandable information on subject responsibilities. To that end, the AAOS feels it is important to comment upon the following topics outlined in the SACX draft report:

Comprehensible language

As noted in the draft report, a signed patient consent form is not the end goal of the consent process. A subject's thorough understanding of the risks, benefits, protocol, other treatment modalities available, and follow-up is the proper foundation from which voluntary consent is given. The Academy concurs that consent is inadequate when the potential subject does not truly understand the information provided or if coercion or misleading information is used. Principal investigators in clinical trials involving xenotransplantation should emphasize subject education and understanding facilitated in part by consent forms and other informational material for potential subjects that is easily understood in layman's terms. Sophisticated medical terms are not appropriately used in the consent situation.

Similarly, the subject interview should be conducted so that the potential subject (and his or her family members or representatives, if present) has the opportunity to ask questions of the interviewer in a non-judgmental and supportive setting. The PI and his or her research team should at all times remain aware of the sensitive cultural values or language differences of the subject, and take care to answer any pertinent questions such subjects may pose. Finally, the Academy agrees that a patient consent form is not the place to assert lengthy institutional legal protections; legalese and complex legal terms should be avoided.

Education of the IRB

The Academy enthusiastically supports the draft report's concern in educating institutional review boards (IRBs) of the particularities that distinguish xenotransplantation clinical trial protocols from traditional drug- or intervention-type clinical trials. The Academy encourages the SACX to compile the pertinent factors an IRB should consider while evaluating a clinical trial involving xenotransplantation, as noted in this draft report, into a document available for both investigators and IRBs.

The informed consent team

The AAOS does not agree that an informed consent team necessarily requires at least three individuals. The SACX recommends that three individuals with specific areas of expertise are required to obtain informed consent in a xenotransplantation clinical trial: (1) the PI with basic medical and scientific information; (2) a post-transplant care specialist with knowledge of long term complications and effects of xenotransplantation; (3) an individual with knowledge of the social and psychological implications for the subject undergoing xenotransplantation.

The Academy feels that these areas of expertise are not mutually exclusive, and that a properly conducted informed consent process can occur without designating three separate individuals to participate in the process if all areas of expertise are appropriately represented. Oversight of a well-designed clinical trial involves ensuring trial staff are thoroughly trained. In clinical trials involving xenotransplantation, the staff must also be well trained in the unique risks, benefits, and consequences of participation. Individuals obtaining the informed consent of the subject should conduct thoughtful and thorough interviews and should also be prepared to answer all of the subject's questions. Referrals can be made to appropriate trial or institutional staff when the answer to a question posed by a potential subject is unknown, a possibility that may arise regardless of the composition of the consent team.

Participant understanding of compliance with necessary public health precautions

It is critically important for potential subjects of xenotransplantation clinical trials to be informed of the necessity of complying with protocol requirements and of the potential for the application of public health laws. The PI and those charged with obtaining patient consent should carefully explain to the potential subject the reasons for lifelong follow-up of xenotransplant recipients,

even in cases where the implant fails or is removed. It is imperative that the subject agree to disclose to subsequent health care workers their participation in a xenotransplantation clinical trial. Family members and/or intimate partners should also be informed of the potential for disease transmission. It should be clearly explained to potential subjects that public health safety measures such as detention and quarantine may be applied in a situation where the non-compliant subject poses an infection risk to the general public. Furthermore, potential subjects should be made aware that the lifetime, long-term study of the effects of xenotransplantation precludes subjects from actually withdrawing from the clinical trial completely, a concept that is in opposition to the federal rights of subjects enrolled in traditional clinical trials.

True informed consent cannot be obtained unless and until the subject is made aware of the responsibilities to be undertaken and the consequences that may potentially occur in the case of transmission of a novel zoonotic infectious agent to another human from the subject. The Academy supports full disclosure of these concerns to a potential subject as part of obtaining his or her consent.

Continued SACX involvement

The AAOS applauds the Secretary for creating the SACX to study the important and growing field of xenotransplantation. The SACX currently serves to offer oversight and to provide a forum for expert discussion on topics of importance in xenotransplantation. The Academy encourages the SACX to continue leading policy research and development as well as serving as a resource for the scientific and medical communities. The AAOS again requests that the SACX facilitate representation of the orthopaedic community in xenotransplantation policy development efforts.

The AAOS believes that with thorough, rigorous research and proper safety precautions, xenotransplantation will provide patients with greater options for treatment, longevity, and enhanced quality of life. We look forward to working with the Secretary's Council on Xenotransplantation on future efforts to improve the safety and public understanding of xenotransplantation risks and benefits. Thank you for your consideration in this matter.

Sincerely,

A handwritten signature in black ink, reading "Stuart Weinstein". The signature is written in a cursive style with a large, sweeping initial "S".

Stuart L. Weinstein, MD
President
American Academy of Orthopaedic Surgeons