Overview of Regulatory Guidelines for Xenotransplantation
Osaka, November 2013

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World Health Organization

Human Organ and Tissue Transplantation

From the Eighth Plenary Meeting of the Fifty-Seventh World Health Assembly in Geneva

The Fifty-Seventh World Health Assembly,

Recalling resolutions WHA40.13, WHA42.5 and WHA44.25 on organ procurement and transplantation;
Having considered the report on human organ and tissue transplantation;
Noting the global increase in allogeneic transplantation of cells, tissues and organs;
Concerned by the growing insufficiency of available human material for transplantation to meet patient needs;
Aware of ethical and safety risks arising in the transplantation of allogeneic cells, tissues and organs, and the need for special attention to the risks of organ trafficking;
Recognizing that living xenogeneic cells, tissues or organs, and human bodily fluids, cells, tissues or organs that have had *ex vivo* contact with these living xenogeneic materials, have the potential to be used in human beings when suitable human material is not available;
Mindful of the risk associated with xenogeneic transplantation of the transmission of known or as yet unrecognized xenogeneic infectious agents from animals to human beings and from recipients of xenogeneic transplants to their contacts and the public at large;
Recognizing that transplantation encompasses not only medical but also legal and ethical aspects, and involves economic and psychological issues,

Allogeneic Transplantation

1. URGES Member States:
   (1) to implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring accountability for human material for transplantation and its traceability;
   (2) to cooperate in the formulation of recommendations and guidelines to harmonize global practices in the procurement, processing and transplantation of human cells, tissues and organs, including development of minimum criteria for suitability of donors of tissues and cells;
   (3) to consider setting up ethics commissions to ensure the ethics of cell, tissue and organ transplantation;
   (4) to extend the use of living kidney donations when possible, in addition to donations from deceased donors;
   (5) to take measures to protect the poorest and vulnerable groups from "transplant tourism" and the sale of tissues and organs, including attention to the wider problem of international trafficking in human tissues and organs;
2. REQUESTS the Director-General:
   (1) to continue examining and collecting global data on the practices, safety, quality, efficacy and epidemiology of allogeneic transplantation and on ethical issues, including living donation, in order to update the Guiding Principles on Human Organ Transplantation (*1*);
   (2) to promote international cooperation so as to increase the access of citizens to these therapeutic procedures;
   (3) to provide, in response to requests from Member States, technical support for developing suitable transplantation of cells, tissues or organs, in particular by facilitating international cooperation;
   (4) to provide support for Member States in their endeavours to prevent organ trafficking, including drawing up guidelines to protect the poorest and most vulnerable groups from being victims of organ trafficking;

Xenogeneic Transplantation

1. URGES Member States:
   (1) to allow xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place;
   (2) to cooperate in the formulation of recommendations and guidelines to harmonize global practices, including protective measures in accordance with internationally accepted scientific standards to prevent the risk of potential secondary transmission of any xenogeneic infectious agent that could have infected recipients of xenogeneic transplants or contacts of recipients, especially across national borders;
   (3) to support international collaboration and coordination for the prevention and surveillance of infections resulting from xenogeneic transplantation;
2. REQUESTS the Director-General:
   (1) to facilitate communication and international collaboration among health authorities in Member States on issues relating to xenogeneic transplantation;
   (2) to collect data globally for the evaluation of practices in xenogeneic transplantation;
   (3) to inform proactively Member States of infectious events of xenogeneic origin arising from xenogeneic transplantation;
   (4) to provide, in response to requests from Member States, technical support in strengthening capacity and expertise in the field of xenogeneic transplantation, including policy-making and oversight by national regulatory authorities;
   (5) to report at an appropriate time to the Health Assembly, through the Executive Board, on implementation of this resolution.

From the Eighth Plenary Meeting of the World Health Assembly, 22 May 2004, A57/VR/8. WHA57.18, agenda item 12.14.
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REFERENCE

1. World Health Assembly. Document WHA44/1991/REC/1, Annex 6.

Xenogeneic Transplantation

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Xenotransplantation Advisory Consultation

organized by Dr L. Noel, (WHO), Geneva April 2005

- Launch of an international human xenotransplantation inventory

- Word Health Organization

  International Xenotransplantation Association (IXA)

  Geneva University Hospital

IXA and HUG Hôpitaux Universitaires de Genève in collaboration with World Health Organization

Home

Inventory of Human Xenotransplantation practices

AIMS:

- To collect basic data on all types of human xenotransplantation practices performed since 1995

- To identify countries where such practices exist to provide information for international agencies, national health authorities, health care workers and the public

- To encourage good practices, international guidelines and regulation and foster a better perception of hopes and risks in xenotransplantation

METHODS:

- Scientific publications
- Presentation at International Congresses
- Internet
- Reports by members of the transplantation community

- Electronic questionnaire available on the website

RESULTS:

Since October 2006 Hits = mean = 3000 /month

No	Tissue/Animal/Country	Consult
1	- Kidney cells | Hamster | Switzerland	
2	- Adult cells | Sheep | Germany	
3	- Chromaffin cells | Calf | Switzerland	
4	- Fetal ventral mesencephalic cell | Pig | USA	
5	- stem cells | rabbit, pig, | Nigeria	
6	Embryonic stem cells - | blue shark | Mexico	
7	Embryonic stem cells - | Pig | USA	
8	Embryonic stem cells - | Pig | USA	
9	Embryonic stem cells - - fetal cells, adult cells | rabbits, cattle, sheep | Mexico	
10	Embryonic stem cells - - fetal cells, adult cells | cattle, sheep,rabbits | Germany	
11	Fetal islet like cell clusters - | Pig | Sweden	
12	Hepatocytes - | Pig | USA	
13	Hepatocytes - | Pig | France	
14	Hepatocytes - | Pig | 11 US and 9 European hospitals	
15	Hepatocytes - | Pig | Italy	
16	Hepatocytes - | Pig | Germany	
17	Hepatocytes - | Pig | Italy	
18	Islets of Langerhans - | Rabbit | Russia	
19	Islets of Langerhans - | Pig | New zealand	
20	Islets of Langerhans - | Pig | China	
21	Islets of Langerhans - | Pig | Russia	
22	Islets of Langerhans - - Sertoli cells | Pig | Mexico	

N = 32

Transplantation. 2010 Sep 27;90(6):597-603.

SPECIAL FEATURE

International Human Xenotransplantation Inventory

Antonino Sgroi,[1] Leo H. Bühler,[1] Philippe Morel,[1] Megan Sykes,[2] and Luc Noel[3,4]

Background. Xenotransplantation carries inherent risks of infectious disease transmission to the recipient and even to society at large, and it should only be carried out with strict regulation and oversight. In collaboration with the International Xenotransplantation Association, the University Hospital Geneva, and the World Health Organization, an international inventory has been established (www.humanxenotransplant.org) aiming to collect basic data on all types of currently ongoing or recently performed xenotransplantation procedures in humans.

World Health Organization

1st Global Consultation on Regulatory Requirements for Clinical Trials of Xenotransplantation

Changsha, China, November 2008

In collaboration with the Chinese Ministry of Health, the University of Changsha and the International Xenotransplantation Association (IXA)

Topics

- Xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms are in place
- Human clinical trials, in particular of porcine pancreas islets
- Xenotransplant tourism
- The meeting brought together experts with representatives of health authorities from all regions of WHO.

World Health Organization

First WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials

Changsha, China, 19-21 November 2008

The Changsha Communiqué[1]

Principles

1. Successful xenotransplantation has the potential to treat a wide range of serious diseases such as diabetes, heart and kidney disease. Successful xenotransplantation could provide transplants for people who currently would not get a transplant.

2. Potentially animals could provide a plentiful supply of readily available, high quality cells, tissues and organs for transplantation. Genetic modification of the animals may improve the effectiveness of such xenotransplant material. Animals used in xenotransplantation should be from a closed herd bred for the purpose and housed in a well-controlled, pathogen-free environment with high standards of animal welfare. Source animals should be extensively tested to ensure freedom from known pathogens with appropriate biosecurity and surveillance in place to ensure continued freedom from infectious disease.

3. Xenotransplantation is a complex process which carries risks, including graft rejection, inadequate graft function and transmission of recognized or unrecognized infectious diseases to the recipient. There is the risk of developing serious or novel infections which could infect not just the transplant recipient but also close contacts or the wider human or animal populations.

4. Because of these wider community risks, xenotransplantation clinical trials and procedures need to be effectively regulated. There should be no xenotransplantation in the absence of effective regulation by the government of the country. Regulation should have a legal basis with powers to ban unregulated procedures and enforce compliance with regulatory requirements. The regulatory system should be transparent, must include scientific and ethical assessment and should involve the public.

5. Because of the community risk, in proposed clinical trials of xenotransplantation there should be a high expectation of benefit to balance the risk. The level of this expectation should be in proportion to the level of the risk. The level of safety and efficacy should conform to recommendations from the international scientific community, when available, and requires rigorous pre-clinical studies using the most relevant animal models. Proposers of trials must provide all the information required by the regulatory authority to assess the risks and determine how the risks can be minimised.

[1] Disclaimer: These are the conclusions of the above meeting for which WHO was the Secretariat. These conclusions do not necessarily represent the decisions and policies of WHO.

World Health Organization

10 Principles

Key Recommendations

- To WHO
- To Member States
- To investigators and proposers of clinical trials using xeno-transplantation products

Xenotransplantation 2009; 2:61-3

WHO, Changsha Communiqué

- **Principle 4**
  Because of these wider community risks, xenotransplantation clinical trials and procedures need to be effectively regulated.
  There should be no xenotransplantation in the absence of effective regulation by the government of the country.
  Regulation should have a legal basis with powers to ban unregulated procedures and enforce compliance with regulatory requirements.
  The regulatory system should be transparent, must include scientific and ethical assessment and should involve the public.

WHO, Changsha Communiqué (contd.)

- **Principle 5**

  Because of the community risk, in proposed clinical trials of xenotransplantation there should be a high expectation of benefit to balance the risk.

  The level of this expectation should be in proportion to the level of the risk.

  The level of safety and efficacy should conform to recommendations from the international scientific community, when available, and requires rigorous pre-clinical studies using the most relevant animal models.

  Proposers of trials must provide all the information required by the regulatory authority to assess the risks and determine how the risks can be minimised.

WHO, Changsha Communiqué (contd.)

- **Principle 7**

  Participation in xenotransplantation will usually require the long term storage of animal and patient samples, pre- and post-treatment, as well as records. It will require life-long follow up of recipients and possibly their close contacts.

  There must be rigorous analysis of trial outcomes. Xenotransplant product recipients must be registered in an appropriate database with traceability to the donor animal, while ensuring that patient privacy is protected.

  If anything happens to prevent the proposers from continuing the trial, there must be an adequate provision for all records, data and archived samples such as their transfer to the regulatory authority or other designated organization.

World Health Organization

2nd Global Consultation on Regulatory Requirements for Clinical Trials of Xenotransplantation

Geneva, Switzerland, October 2011

In collaboration with the International Xenotransplantation Association (IXA) and the Transplantation Society (TTS)

The charge to the consultation was

- To review the current status of xenotransplantation science and practice
- To determine whether updates to the Changsha Communiqué's guidance to WHO, Member State health regulatory authorities, and study investigators and/or sponsors of xenotransplantation trials are required
- To discuss and refine draft guidance for infectious disease surveillance, prevention, and response appropriate to support various probable clinical xenotransplantation trial scenarios.

www.who.int

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XENOTRANSPLANTATION

Original Article

Xenotransplantation-associated infectious risk: a WHO consultation

Fishman JA, Scobie L, Takeuchi Y. Xenotransplantation-associated infectious risk: a WHO consultation. Xenotransplantation 2012; 19: 72–81. © 2012 John Wiley & Sons A/S.

Abstract: Xenotransplantation carries the potential risk of the transmission of infection with the cells or tissues of the graft. The degree of risk is unknown in the absence of clinical trials. The clinical application of xenotransplantation has important implications for infectious disease surveillance, both at the national and international levels. Preclinical data indicate that infectious disease events associated with clinical xenotransplantation from swine, should they occur, will be rare; data in human trials are limited but have demonstrated no transmission of porcine microorganisms including porcine endogenous retrovirus. Xenotransplantation will necessitate the development of surveillance programs to detect known infectious agents and, potentially, previously unknown or unexpected pathogens. The development of surveillance and safety programs for clinical trials in xenotransplantation is guided by a "Precautionary Principle," with the deployment of appropriate screening procedures and assays for source animals and xenograft recipients even in the absence of data suggesting infectious risk. All

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