World Health Organization

Third WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials

Changsha, China, 12-14 December 2018

The 2018 Changsha Communiqué[1]

Principles

1. Xenotransplantation is any procedure that involves the transplantation, implantation or infusion into a human recipient of either (a) live cells, tissues, or organs from a 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. For the purpose of this guidance, xenotransplantation does not include transplantation, implantation, or other use of acellular animal tissues. 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 otherwise receive a transplant.

2. Animals could potentially provide a plentiful supply of readily available, quality-controlled, live cells, tissues and organs to meet patients' needs for elective transplantation. Genetic modification of the animals may improve the effectiveness and safety 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 without effective regulation by the government of the country, either in the context of a clinical trial or with post-market monitoring after regulatory approval of a safe, effective xenotransplantation product. 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 safety and efficacy should conform to recommendations from the international scientific community, when available, which generally derives from state-of-the-art 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.

6. Proposers of xenotransplantation clinical trials must be able to clearly justify carrying out a particular trial on a specific patient population. Patient selection should be on the basis of informed consent from motivated patients willing to accept the specific conditions that will be required by the trial. Patients and close contacts should be effectively educated about their treatment to encourage compliance, and to minimize risks for themselves and for society.

7. Participation in xenotransplantation clinical trials 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

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

outcomes. Xenotransplant product recipients must be registered in an appropriate database with traceability to the donor animal, while ensuring that patient privacy is protected. Succession should be assured for surveillance, samples and records.

8. Medical teams must have appropriate expertise and understand the risks to the patients, themselves and the community. Because of the risk of infectious disease for the community, there must be a system in place for vigilance and surveillance with contingency plans to identify and respond to any indication of xenotransplantation-related infection in a timely manner.

9. Maintenance of a global system should be prioritized as an international public health imperative and used to exchange information regarding past, current, and planned xenotransplantation activities; detecting and preventing unregulated xenotransplantation; and providing support for member states to coordinate xenotransplantation vigilance, surveillance and response to suspected infections especially across jurisdictional borders.

10. Because of the potential benefits of successful xenotransplantation, consideration should be given to enable future equitable access to effective xenotransplantation therapies and the public sector should be encouraged to support xenotransplantation research and development.

Key Recommendations

To WHO

1. WHO should have a dedicated resource to develop and support a plan for global action for xenotransplantation.

2. WHO should inform Member States of the need to assess xenotransplantation practices in their territories, and encourage Members States to legislate and enforce transparency in xenotransplantation related activities.

3. WHO should encourage and, if requested, support Member States to the extent possible in assessing their capacity to regulate xenotransplantation and in identifying xenotransplantation practices in their territories.

4. WHO should promote public awareness of the potential benefits of successful xenotransplantation and of the enhanced opportunity provided by genetically engineered source animals. WHO should also promote awareness of the dangers of unregulated xenotransplantation, including xenotourism.

5. WHO should facilitate global collaboration for laboratory investigations, in order to have in place a system for the identification of and response to any xenotransplantation infectious disease outbreak in a timely manner.

6. WHO should encourage and, at the occasional request of Member States, foster regular interaction between regulators and xenotransplantation subject matter experts, and support a database of worldwide xenotransplantation practices, as appropriate to the level of xenotransplantation activity.

7. WHO should maintain a register of xenotransplantation trials and a list of experts who can advise Member States on aspects of xenotransplantation and of recommended laboratories able to test for xenotransplantation-related pathogens.

8. WHO should promote equitable access to successful xenotransplantation products.

To Member States

1. Member States should take steps to identify any xenotransplantation practices in their territories and ban those that are unregulated; legislate and enforce transparency in xenotransplantation related activities in their jurisdiction; and promote public awareness of these practices and their possible benefits as well as potential risks.

2. Member States should implement regulations that prohibit statements or advertisements for xenotransplantation trials or products that claim unproven benefits, or that are (or may prove to be) false or misleading with respect to known or unknown risks.

3. Member States should ensure that public health officials are aware of the possible infection risks associated with xenotransplantation, including those associated with patients travelling to receive xenotransplantation products outside their territories; and have plans in place to identify and respond to any such infection.

4. Member States should review their laws to determine whether they have adequate authority to regulate xenotransplantation, ban unregulated xenotransplantation; and provide appropriate sanctions for failure to comply.

5. Member States should assess whether they have the resources and capacity to regulate xenotransplantation effectively. If they do not have such resources and capacity, they should ban xenotransplantation in their territories.

6. If a Member State has the capacity to regulate xenotransplantation and believes xenotransplantation activities should be carried out in its jurisdiction, it should ensure that those activities are conducted consistent with current global standards, and in compliance with ethical and regulatory requirements for conduct of clinical trials in that jurisdiction.

7. Member States should consider assuring access to an independent (third party) reference laboratory with identified expertise in xeno-specific infectious disease assays.

To investigators and proposers of clinical trials using xenotransplantation products

1. Investigators should ensure that source donor animals are bred for the purpose and as safe as possible, using a closed colony of consistently known designated pathogen-free animals housed in a well-controlled environment with high levels of biosecurity. The list of potentially infectious organisms that should be excluded from source animals for a xenotransplant trial should be defined according to best current evidence.

2. The investigators should develop quality control measures and standards for genetically modified pigs to ensure the desired phenotype and function of the xenotransplant.

3. Investigators should be transparent regarding proposed and ongoing xenotransplantation related activities, providing clear justification for the trial, including possible benefits as well as potential risks for trial participants, close contacts, and the public.

4. Investigators should base clinical trial design on reproducible pre- clinical data, usually from non-human primate testing. Pre-clinical studies should rigorously evaluate protocol safety and efficacy, and aim to model the clinical regimen as closely as possible with recognition of limitations imposed by preclinical models, including species differences in specific drug effects and antigenic and/or physiologic disparities.

5. Investigators should select trial participants for whom there is no adequately effective alternative therapy available and who understand the risks and consequences of the procedure, including the need for compliance with life-long follow up and who are motivated to modify their lifestyle accordingly.

6. Investigators should provide appropriately trained and experienced personnel to provide the transplant material and conduct the clinical trial and surveillance.

7. Investigators should have a comprehensive plan for effective communication with public health authorities overseeing the trial.

8. Investigators should promote public awareness of the potential benefits of successful xenotransplantation and of the enhanced opportunity provided by genetically engineered source animals. Investigators should discourage unregulated xenotransplantation, including xenotourism.

9. Investigators should have a comprehensive plan for post-transplant long-term patient follow up and timely identification, reporting, and management of possible xenotransplant-related infection episodes. Xenotransplant recipients should be registered in an appropriate database with traceability to the source animal(s), while ensuring that patient privacy is protected.

10. Investigators should ensure storage of appropriate pre- and post-procedure specimens from animals and patients and maintain both the specimens and records in accordance with national regulatory guidelines and quality management standards. If anything happens to prevent the investigators from continuing the trial, there should be provision for stewardship of all records, data and archived samples.

11. Investigators, Proposers, and/or Sponsors of a clinical trial should assure access to identified expertise in xeno-specific disease assays. Laboratory qualifications should be appropriate to accomplish high quality, reliable, standardized sample processing, storage, and testing, as appropriate to accomplish specific investigative or research goals, respectively.

12. Investigators should ensure that devices and biomaterials comply with current international standards (ISO 10993 - https://www.iso.org/standard/68936.html).