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COUNCIL OF EUROPE

COMMITTEE OF MINISTERS

Recommendation Rec(2003)10
of the Committee of Ministers to member states
on xenotransplantation

(Adopted by the Committee of Ministers on 19 June 2003
at the 844th meeting of the Ministers' Deputies)

Preamble

The Committee of Ministers, under the terms of Article 15.*b* of the Statute of the Council of Europe,

Considering that the aim of the Council of Europe is to achieve a greater unity between its members;

Having regard to the European Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine and its Additional Protocol Concerning Transplantation of Organs and Tissues of Human Origin;

Having regard to the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes;

Having regard to the Resolution of the Committee of Ministers (78) 29 on the harmonisation of legislation of member states relating to removal, grafting and transplantation of human substances, the Final Text of the 3rd Conference of European Health Ministers (Paris, 16-17 November 1987) and the Recommendation R (97) 15 of the Committee of Ministers to member states on xenotransplantation;

Bearing in mind Recommendation 1399 (1999) of the Parliamentary Assembly on xenotransplantation;

Bearing in mind recent reports from the OECD, the WHO and other national and international organisations;

Taking into account the shortage of organs and tissues of human origin available for transplantation;

Considering that xenotransplantation might be one of the possible therapeutic responses to this shortage;

Noting that xenotransplantation remains largely an experimental activity and that research is essential for the achievement of progress in this field;

Aware of the risks of rejection and illness xenotransplantation may cause in the recipient patient;

Mindful of the considerable risks which might arise from xenotransplantation in the field of public health and the transmission of diseases;

Considering that it is the responsibility of each member state to adopt adequate measures in order to address them and conscious that in some countries no appropriate regulations exist;

Considering that public health concerns require common provisions applicable in all the member states of the Council of Europe in which xenotransplantation is envisaged;

Considering that worldwide cooperation between states in this field is necessary;

Considering that no clinical xenotransplantation research should take place unless sufficient efficacy and safety is demonstrated through pre-clinical research;

Conscious that the need for such a demonstration will considerably limit the number of xenotransplantations in the coming years, thus allowing for an appropriate risk assessment;

Considering that xenotransplantation of cells and tissues is already being carried out in a number of states and that stringent regulations are thus urgently required;

Mindful of the social, ethical, cultural, legal and psychological problems which might be associated with xenotransplantation;

Mindful of the ethical and welfare issues associated with the use of animals for xenotransplantation and the associated research;

Noting the public concern over the issues related to xenotransplantation and stressing the importance of undertaking a public debate on this subject,

A. Recommends that the governments of member states:

- take the necessary measures to put their legislation and practice in the field of xenotransplantation in conformity with the following principles and guidelines with a view to minimising the risk of transmission of known or unknown diseases and infections to populations;

- co-operate in the setting-up of world-wide surveillance procedures and agreements;

- ensure a wide dissemination of this recommendation, in particular among all persons, organisations and bodies, public or private, responsible for organising and carrying out xenotransplantation;

- take steps to make the provisions of this recommendation subject to public debate.

B. Decides that this recommendation will be re-examined at appropriate intervals and not later than in three years' time.

C. Instructs the Secretary General to bring the contents of this recommendation to the attention of the non-member states and international organisations which have participated in its preparation and to invite them to participate in the setting-up of an international surveillance network.

GUIDELINES

Chapter I - Object, scope and definitions

Article 1 - Object of the recommendation

This recommendation aims

- to protect, in both the short and long term, public health, patients, their close personal contacts and the professional staff involved in xenotransplantation, and

- to provide adequate protection for the animals used in xenotransplantation.

Article 2 – Scope of the recommendation

This recommendation covers all xenotransplantation activities involving human beings as recipients.

Article 3 - Definition

For the purpose of this recommendation, xenotransplantation is defined as any procedure that involves the transplantation or infusion into a human recipient of:

- live animal cells, tissues or organs, or

- human body fluids, cells, tissues or organs that have had *ex vivo* contact with live animal cells, tissues or organs.

Chapter II - General provisions

Article 4 – Xenotransplantation - the setting

No xenotransplantation should be carried out in a member state that does not provide regulation for xenotransplantation activities in conformity with the provisions of this recommendation.

Article 5 – Xenotransplantation authorisation

No xenotransplantation activity should be carried out in a member state unless authorisation is given by a body officially recognised as competent for this purpose, in accordance with the provisions contained in the following two paragraphs:

1. Authorisation for clinical xenotransplantation research should only be given if:

a. pre-clinical research has demonstrated, in accordance with internationally accepted scientific standards, that:

i. in the light of current scientific knowledge it is highly probable that there is no risk, in particular of infection, for public health;

ii. the potential level of efficacy and safety for the patient may justify the intervention having regard to the risks incurred;

b. all substantive and procedural conditions generally applicable to clinical research are fulfilled.

2. Xenotransplantation should not be authorised other than in clinical research unless, on the basis of clinical data:

i. there is adequate evidence, in accordance with internationally accepted scientific standards, that no risks, in particular of infection, to the general population exist, and

ii. the therapeutic benefit of the xenotransplantation has been established.

Article 6 – Xenotransplantation teams and centres

No xenotransplantation should be carried out unless it is undertaken by an accredited team in an authorised centre.

a. The teams carrying out the xenotransplantation should be appropriately qualified and comprise all the necessary scientific and medical expertise.

b. The centres should have received an authorisation by the competent bodies prior to beginning the xenotransplantation.

Chapter III – Protection of Public Health

Article 7 – Public Health protection plan

Member states should have a plan in place to address any events, in particular of infection, possibly related to a xenotransplantation which could compromise public health.

In particular, public authorities should take appropriate measures, in conformity with the principles of necessity and proportionality, to respond to events of transmissible or previously unknown illness related to xenotransplantation. These measures, if exceptional circumstances so require, might include isolation.

Article 8 – Collection and storage of biological samples and information

Information and biological samples concerning the source animals used in xenotransplantation and the recipients should be collected and stored in order to ensure traceability and long-term monitoring.

Article 9 - Follow-up

1. All protocols for clinical research should be accompanied by a plan to ensure the traceability and monitoring of the recipients, their close personal contacts and the professional staff involved in xenotransplantation in order to detect and deal with any adverse events, in particular of infection, possibly related to xenotransplantation.

The plan should include communication without delay to the competent body at national level of any such events.

2. Any xenotransplantation other than in clinical research should be accompanied by a plan to:

- ensure the traceability of the recipient as well as, depending on the circumstances, of other persons mentioned in paragraph 1;

- monitor, wherever necessary, the persons mentioned in paragraph 1.

The plan should include communication without delay to national public health authorities of any events, in particular of infection, possibly related to xenotransplantation and which could be of relevance to public health.

Article 10 – Precautions relating to the transmission of disease

All appropriate measures, in accordance with internationally recognised criteria, should be taken to prevent the risk of transmission of infectious agents from source animals.

Only animals bred specifically for xenotransplantation should be used. An appropriate Quality Assurance system encompassing all the stages from the production of the source animals to the final collection of the xenotransplants should be set up.

Article 11 - Prohibition relating to the use of non-human primates

1. Non-human primates should not be used as source animals for xenotransplantation.

2. Exceptionally, authorisation for the xenotransplantation of cell lines obtained from non-human primates may be given if :

- the conditions under Article 5 are fulfilled, and

- specific protective measures for these animals have been addressed. This implies that Great Apes should not be used as source animals in xenotransplantation.

Chapter IV - Protection of patients and close personal contacts

Article 12 – Conditions for patient participation

No xenotransplantation should be carried out unless the following specific conditions are fulfilled:

i. There is no other appropriate therapeutic method of comparable effectiveness available for the patient.

ii. The data resulting from pre-clinical research suggest or, where appropriate, the data resulting from prior clinical research indicate a clear therapeutic benefit for the xenotransplantation patient. In particular these data should:

- have demonstrated an adequate function of the xenotransplant in relevant models for an appropriate period of time through a clinically applicable methodology,

- provide sufficient reasons to believe that rejection can be overcome and that the xenotransplant can function adequately in humans.

iii. The risks which may be incurred by the patient are not disproportionate to the potential therapeutic benefit of the procedure.

In particular, the evaluation through pre-clinical research of the risks for adverse events and transmission of infectious agents to the recipient, as based on international standards for laboratory results and diagnostic assays, should have demonstrated sufficient safety.

Article 13 – Information to be given to patients

1. Patients participating in a xenotransplantation should be adequately informed in a comprehensible manner of the nature, objectives, possible benefits, potential risks and consequences of the procedure, as well as of any constraints that may be linked to it.

2. In particular patients should also be made aware of the constraints of monitoring and precautionary measures that may become necessary subsequent to xenotransplantation. Such measures will, according to the principles of necessity and proportionality, be adapted to the circumstances and adjusted in accordance with the assessment, based on current scientific and medical knowledge, of the risks generated by each of the procedures involved, and may in particular include:

a. the collection of personal data and inclusion in a register;

b. the provision by the medical team, in accordance with Article 14, of information concerning the risks of infection and the constraints associated thereto;

c. long-term medical monitoring including repeated biological samples being taken and archived;

d. reporting any significant unexplained symptoms or illness that may arise after the xenotransplantation;

e. maintaining contact with the medical team;

f. taking precautions with respect to sexual activity;

g. the need for the patient to agree that information is provided by a medical team to any future close personal contacts, in accordance with Article 14, concerning the risks of infection and the constraints associated thereto;

h. the other constraints which might be applicable if circumstances so require, in particular the possibility of isolation which may become necessary in the event of a contagious or previously unknown illness occurring.

3. Patients should be informed that, in accordance with Article 21, constraints mentioned hereinabove may be imposed if the person concerned refuses to comply with them.

Article 14 – Information to be given to close personal contacts of the patient

To protect close personal contacts and warn of the possible risks they might pose to the general public, the patient's close personal contacts should, with his or her consent, be informed by the medical team of the patient's envisaged participation in a xenotransplantation, of the risks of infection and of the consequences for them of such participation, and in particular, of the constraints which may be applicable.

The patient should also ensure that such information is provided to any future close personal contacts.

Article 15 – Information to be given to the professional staff involved in xenotransplantation

Professional staff involved in xenotransplantation should be fully aware of the risks of infection as well as the possible consequences and constraints which may derive from their participation in xenotransplantation.

Article 16 – Consent to xenotransplantation

1. No xenotransplantation should be carried out without:

i. the documented, specific, free and informed consent of the patient to the procedure and any necessary specific constraints; and

ii. the provision by the patient to the medical team of the necessary information concerning his or her current close personal contacts and the acceptance by the patient that his or her current and future close personal contacts be given information in accordance with Article 14.

2. Prior to xenotransplantation, the consent to carry out the intervention may be freely withdrawn at any time.

Article 17 - Counselling and support

The patients and their close personal contacts should be given proper information and have access to counselling and support by experts outside the team both before and after the xenotransplantation. This informing and counselling process should include the biomedical, ethical, psychological and social aspects of xenotransplantation.

Article 18 – Right to medical care

A refusal to participate, or a withdrawal of consent prior to the xenotransplantation, should not prejudice the patient's right to receive all other appropriate medical care in due course. The patient's consent to participate in a xenotransplantation should not prejudice his or her right to benefit from an allotransplant that becomes available while awaiting xenotransplantation, if medically indicated.

Article 19 – Patients not able to consent

1. Where xenotransplantation has been authorised for use other than in clinical research according to Article 5 paragraph 2, it may be carried out on a person not able to consent only if the following conditions are fulfilled:

- there is no therapeutic alternative of comparable effectiveness available to the patient,

- taking into account the constraints and conditions to which the person will or may be subjected according to Articles 13 and 14, the intervention is expected to result in a direct and important benefit for the patient, and

- the representative or an authority or a person or body provided for by law, after receiving the information referred to in Article 13, has authorised both the intervention and the provision of the necessary information to the present and future close personal contacts of the patient.

2. Patients unable to consent should not undergo clinical xenotransplantation research as referred to in Article 5, paragraph 1.

Exceptionally, a patient unable to consent may participate in a clinical xenotransplantation research intervention if the following specific conditions are fulfilled:

- there is adequate indication, on the basis of prior clinical research, that the xenotransplantation might be lifesaving,

- there is no alternative means of saving the life of the patient,

- taking into account the constraints and conditions to which the person will or may be subjected according to Articles 13 and 14, the intervention is expected to result in a direct and important benefit for the patient, and

- the representative or an authority or a person or body provided for by law, after receiving the information referred to in Article 13, has authorised both the patient's participation in the clinical xenotransplantation research and the provision of the necessary information to the present and future close personal contacts of the patient.

Article 20 - Confidentiality

All personal data relating to the recipient person and, where such data exist, their close personal contacts should be considered to be confidential.

Without prejudice to the provision of Article 8, such data should be collected, processed and communicated according to the rules relating to professional confidentiality and personal data protection.

Article 21 – Compulsory constraints

If, after the xenotransplantation has been carried out, the recipient or his or her close personal contacts refuse to comply with the constraints associated with xenotransplantation, public authorities should intervene and take appropriate measures, where public health protection so requires, in conformity with principles of necessity and proportionality.

Depending on the circumstances and in accordance with the procedures provided for by national law, such measures might include registration, compulsory medical follow-up and sampling.

Chapter V - Protection of animals

Article 22 – Compliance with animal protection regulations

All animal use in xenotransplantation should comply with the provisions of the *European Convention for the protection of vertebrate animals used for experimental and other scientific purposes* including the principles of Appendix A and *Council Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of member states regarding the protection of animals used for experimental and other scientific purposes* including Annex II.

These provisions should apply to source animals in addition to their sires and dams in source production units, pre-transplantation holding facilities, tissue harvest areas and during transport.

Article 23 – Husbandry, care, use and requirements of animals

The husbandry and care for all animals used in xenotransplantation should take account of their physiological, social and behavioural needs and should be designed to ensure their well being, particularly where breeding animals are maintained for long periods. The pain, suffering or distress and the number of animals used should be minimised.

Article 24 – Responsibility for husbandry and care of animals

There should be clearly assigned and documented responsibilities for husbandry and care of the animals used in xenotransplantation from birth to death, with a sufficient number of appropriately trained and competent staff available to inspect and care for them.

Article 25 – Surgical derivation and early weaning techniques

Surgical derivation and segregated/medicated early weaning production techniques should only be used where essential to produce animals of appropriate health status for use in xenotransplantation.

Article 26 – Transport of animals

Transport of animals for xenotransplantation should be kept to a minimum. If transportation is necessary, adequate arrangements should be made for the dispatch, receipt, acclimatisation and quarantine of animals in order to minimise the associated stress. The relevant national and international legislation/regulations (including European Union *Directive 95/29/EEC* modifying *Directive 91/628/EEC* on the protection of animals during transport, and the European Convention for the Protection of Animals During International Transport (revised)) should be complied with.

Article 27 – Organ and tissue procurement from animals

Analgesia or anaesthesia should be used for the procurement of organs, tissues and cells for xenotransplantation, where it is necessary to minimise pain, suffering and distress of the animals.

If, as a result of the procurement, the subsequent health and welfare of the animals would be compromised, the animals should be killed by an appropriate method.

Sequential harvest of solid organs from individual animals should not be permitted.

Article 28 – Collection of animal records

Detailed records should be maintained of the derivation, source, use and final disposal of all animals bred for or used in xenotransplantation. Any unusual or unexpected traits or events should be recorded.

Article 29 – Pre-clinical research

The provisions of Articles 22 to 28 should also apply to animals used in pre-clinical research carried out to support clinical xenotransplantation research.

Chapter VI – Provisions relating to the ethical, social and psychological acceptability of xenotransplantation

Article 30 – Public debate

In accordance with the principles stated in Article 28 of the Convention on Human Rights and Biomedicine, member states should take active steps to ensure that the fundamental questions raised by xenotransplantation are the subject of appropriate public discussion particularly in light of relevant medical, psychological, cultural, ethical, legal, social and economic implications.

Chapter VII – Co-operation between parties

Article 31- International co-operation in medical research

Member states should co-operate through international surveillance procedures and agreements. They should also take appropriate steps to facilitate the co-ordination of research in xenotransplantation in order to improve its efficacy and safety, to avoid unnecessary duplication and to minimise animal use and suffering.

Article 32 – International co-operation in public health

Every member state should communicate without delay to national public health authorities of other member states and other concerned states any events, in particular of infection, possibly related to a xenotransplantation which could compromise public health.

Chapter VIII – Compensation for undue damage

Article 33 - Compensation for undue damage

The person who has suffered undue damage resulting from a xenotransplantation is entitled to fair compensation according to the conditions and procedures prescribed by law.

Chapter IX – Reports on the implementation of the recommendation

Article 34 – Implementation of the recommendation

On receipt of a request from the Secretary General of the Council of Europe any member state should furnish an explanation on the manner in which its legislation and practice in the field of xenotransplantation integrate the principles and guidelines of this recommendation, on any xenotransplantation activity and on any adverse event as referred to in Article 9.

Related Documents

Meetings

844 meeting of the Ministers' Deputies / 19 June 2003

Other documents

CM/Del/Dec(2003)844/4.3E / 24 June 2003
CM(2002)132revE / 21 May 2003
CM(2002)132addrevE / 05 June 2003
GR-H(2003)CB8E / 10 June 2003