

ESHRE position paper on the EU Tissues and Cells Directive EC/2004/23

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Introduction

The European Union Tissues and Cells Directive (EUTCD) is a legal document originating from the European Union's public health programme. The EUTCD covers donation of all tissues and cells within EU (except blood and blood-products). It aims at preventing threats to human health related to the application of cells and tissues to the human body. Within this background the EUTCD foresees common standards of safety and quality for donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications. The requirements were laid down in a single "mother" Directive 2004/23/EC and two subsequent Technical Directives 2006/17/EC and 2006/86/EC. Assisted Reproduction Technologies (ART) is considered as covered by this directive. This applies to all ART units in all European Union (EU) and European Economic Area (EEA) member states (Iceland, Liechtenstein and Norway).

The directive is basically concerned with increasing quality and safety in application of human tissues and cells to the human body.

In an ART perspective this involves basically minimizing the risk of two severe adverse events, namely transmission of infections and prevention of gamete/zygote/embryo exchange (mix-up). The directive is not concerned with pointing at specific ways of increasing "performance" such as success rates. Instead, the directive aims at increasing quality through mandatory implementation of a quality management system. This involves the presence of adequately trained and certified staff, full documentation and formulation of standard operating procedures, quality control and quality assurance at all units performing assisted reproduction.

Based on this ESHRE considers initiatives aiming at improving performance must be covered outside the framework of the directive. As a consequence ESHRE has initiated a number of initiatives including a revision of the "ESHRE Guidelines for good practice in IVF laboratories" which should be seen as a complement to the requirements issued by the Tissues and Cells Directive.

ESHRE, as the European representative society in the area of reproductive medicine, considers it to be important to work for harmonization of implementation, inspection and certification throughout EU member states. One ESHRE initiative was therefore to install the European Assisted Conception Consortium (EACC). The primary aims of the Consortium were to understand all implications of the EU Tissues and Cells Directives, to identify areas problematic to the ART community, and to provide interpretations to be used locally in all the European countries. ESHRE considers it pivotal to a successful implementation that a good dialog be established between EU, the profession and the national regulative authorities. During this process the EACC has had a key role in bringing together ART professionals and competent authorities of the EU member states. In EACC each EU member state is represented by one clinician, one embryologist and one representative of the competent authority. Non - EU member states are allowed to join for information.

Implementation of the directive:

As implementation of EUTCD is coming close by in several EU member states, ESHRE wants to clarify its position on EUTCD. The aim is to assist ART professionals and representatives of competent authorities in their dialogue on the EUTCD. Further, suggestions for minimal requirements in selected areas will be provided.

It is important to realize that the EUTCD will have to be interpreted and implemented through national authorities in each individual country. Depending on the national interpretation of the text, the directive may be implemented differently in the different European member states. This is also reflected in the initial approaches already taken by the profession in the different countries in preparing for the directive. Further, the national implementation is subject to national regulations that may be already in place in each member state.

As a consequence, this ESHRE position paper and interpretation cannot ensure equal regulation in all countries. However, it will be a useful document to be used by the professionals when working together with the authorities towards implementation of the directive in each member state.

ESHRE strongly encourages its members and the national societies to identify the relevant national bodies responsible for translating the EUTCD into national legislation and the bodies involved in the practical implementation of the directive in order to establish a constructive collaboration.

Impact of the directive:

The EUTCD will have a profound impact on all units conducting assisted reproduction. All units will have to be licensed or accredited as decided by the national authorities. Further, all units must implement a quality management system with written standard operating procedures and ensure full documentation of all activities in the clinic/unit - including full traceability for all materials used in each treatment. This documentation must be kept for 30 years.

ESHRE acknowledges that non-partner gamete donation is an area with specific requirements. However, assisted reproduction involving the usage of husband/partner sperm in combination with the woman's own eggs represent more than 95 % of all ART in Europe.

Further, with the implementation of screening of all patients seeking assisted reproduction it is possible to make a clear distinction between infected and non-infected patients. It is clearly stated in the EUTCD that testing positive for HIV or Hepatitis does not automatically exclude patients from treatments. However, ESHRE estimates that an overwhelming majority of all patients will be non-infected. On this background ESHRE recommends that the national authorities clearly define how and where viral positive patients should be treated as this could minimize the organizational and financial negative impact of the EUTCD on many clinics/units.

EUTCD areas that are clearly defined

- The directive applies to fresh and cryopreserved reproductive tissues and cells for application to the human body. This covers gametes, zygotes, embryos and ovarian and testicular tissues.
- The directive is concerned with issues of safety and quality in ART such as prevention of transmission of infectious disease and prevention of misidentification or mix-up of gametes, zygotes or embryos. Each tissue establishment has to put in place and update a quality management system based on the principles of good practice.
- The directive applies to all ART procedures where reproductive cells and tissues are being processed, cultured, banked or stored. This means that intra-uterine insemination falls under the EUTCD. The terminology "direct use" is not applicable on reproductive tissues and cells that will be processed, cultured, banked or stored.
- "Donor" means every human source, whether living or deceased, of human cells and tissues. Partner donation means the donation of reproductive cells between a man and a woman who declare to have an intimate physical relationship. In a couple, man and woman are considered donors to each other.
- Biological testing of the donor is necessary whenever the donated cells will be processed, cultured, banked or stored. Biological testing for HIV 1, 2, for Hepatitis B surface Antigen, Hepatitis B Core antibodies and Hepatitis C antibodies is requested.
- For non-partner donation, additional screening for syphilis and in case of sperm donation for Chlamydia is required.

- Genetic screening for recessive diseases known to be prevalent in a non-partner donors' ethnic background is requested.
- Cells and tissues have to be traceable from donor to acceptor and vice versa. Traceability is also mandatory to all products and materials coming into contact with tissues and cells. This includes for instance all culture media, all culture media supplements and all disposables,
- A unique European coding system is not applicable to reproductive tissues and cells for partner donation. A unique code guaranteeing traceability remains however required.
- The EU has ordered a workshop at CEN, the European Committee of Standardization, to propose a unique European coding system which will apply in case of non-partner donation.
- In assisted reproduction every misidentification or mix-up of gametes, zygotes or embryos is to be considered a serious adverse event.

Identification of problematic areas for ART with respect to the EUTCD:

ESHRE has identified sensitive and possible problematic areas for ART with respect to the EUTCD and is providing interpretations and possible solutions to be discussed with the local authorities implementing the directive.

Problematic areas

ESHRE considers a number of areas in the directive to be particularly problematic for the ART community. This is a consequence of the wide coverage of the directive in comparison to the very specific nature of ART including numerous repeated procedures on the same patient and the usually long duration of treatments at the clinics/units.

Frequency of screening for HIV and Hepatitis: (Commission Directive 2006/17/EC, Annex III.4.2.)

It is specified in the directive that all donors (patients) shall be tested for HIV and Hepatitis B and C at the "time of donation". It is however not specified if it is required to re-test the patient prior to each treatment or whether a specified interval will be acceptable. This will have a profound impact on the financial consequences of the directive.

For example, the EUTCD has been fully implemented in Denmark. The position of the Danish authorities is that screening for HIV and Hepatitis must be done "prior" egg-recovery and the test is valid for 24 months if the patients are tested negative. For egg donors the Danish authorities have specified that the test must be done no more than 30 days prior to donation. Based on the fact that assisted reproduction often is comprised of a "series of treatments" and that treatment is initiated based on a known status of infection of the couples ESHRE suggests a system where the patients in case of partner donation must be tested no more than 30 days prior to starting the initial treatment and if the test is negative the result should be valid for at least 24 months. If the test is definitely positive the couples are considered positive in all future treatments. All additional testing should only be done as a requirement for treating viral positive couples with ART.

Personnel: (Commission Directive 2006/86/EC Annex I. B .Personnel)

It is stated in the directive that a) staff should be available in sufficient numbers, b) a training program should be available and c) that work descriptions must be clearly documented.

While recognizing these needs ESHRE wishes to specify that the number and the complexity of the treatments can vary profoundly between clinics/units. On this background ESHRE considers it impossible to define a general statement covering all type of clinics/units; staff requirements should be specified at each individual clinic/unit and the number and type of treatments offered. As a consequence of the EUTCD a new ESHRE initiative is the establishment of a certification system for clinical and senior clinical embryologists. The system aims at certifying both practical and theoretical competence of the laboratory staff.

Termination of activities: (Commission Directive 2004/23/EC, Article 21.5)

"Member states shall ensure that tissue establishments have agreements and procedures in place to ensure that, in the event of termination of activities for whatever reason, stored tissues and cells shall be transferred, according to the consent pertaining to them, to other tissue establishment or establishments accredited, designated, authorized or licensed..."

This paragraph specifies what is to be done if a clinic/unit closes. ESHRE considers this the responsibility of the local authorities.

The background for this position is based on the fact that it is the responsibility of the authority to issue or withdraw a clinic/unit's license. Consequently, it must also be the responsibility of the authorities to ensure the transferral of stored gametes, zygotes, embryos and ovarian and testicular tissues to a licensed clinic/unit.

Further, in the EUTCD it is required that clinics/units prior to obtaining a license from the authorities must have an acceptance from another clinic/unit accepting to take over their stored biomaterials in case of closure or termination of activities.

ESHRE considers it inappropriate if existing clinics/units can prevent or block the establishment of new clinics/units by refusing an agreement to accept their stored biomaterials in case of closure or termination of activities.

Air quality: (Commission Directive 2006/86/EC, Annex I.D. Facilities/Premises)

It is stated that the air quality should be a GMP defined Grade A on a background air quality of Grade D unless a less stringent air quality may be justified according to one or more of the provisions set out under section 4. After having performed Assisted Reproduction in Europe for more than 20 years there is no documented evidence of a single case of transmission of infective diseases (hepatitis/HIV etc) that can be attributed to air quality in the laboratory. Further, with the introduction of screening of the patients prior to start of treatment as specified in the EUTCD, we will know the viral status of the patients we treat, enabling us to handle infectious patients in a separate environment from non-infectious patients.

On this background ESHRE considers assisted reproduction to be covered by section 4 and - with reference to historical documentation - that it has been both demonstrated and documented that the chosen environment achieves the quality and safety required for the intended purpose.

Coverage

ESHRE interprets the directive to cover ART "from needle to catheter". This means that procedures outside of this are not covered by the directive. Consequently, it is our opinion that well known side effects to the treatment such as OHSS are considered outside of the scope of the directive. However, although the EUTCD is mainly concerned with the laboratory it also covers clinical procedures involving procurement of reproductive cells such as oocyte aspiration.

Intra uterine insemination:

IUI is included in the directive as it involves processing of gametes and this may have a profound impact on insemination performed outside of regular fertility clinics/units.

Cost

There is no doubt that the implementation of the directive will be extremely expensive for the involved clinics/units and that increased financial support will be mandatory both in the public system and private clinics. Without such a financial support, an increase in cost to patients is to be expected, particularly at private clinics/units.

Link to the directives: http://europa.eu.int/comm/health/ph_threats/human_substance/tissues_en.htm

Link to EACC: <http://www.eshre.com/emc.asp?pagelid=678>