Ref. Ares(2017)5267284 - 27/10/2017

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety, innovation

Brussels,
SANTÉ/DF

Ad-Hoc Meeting between Stakeholders and representatives members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718)

22 February 2017, 13:30-17:00
BRUSSELS

This first ad-hoc meeting between selected tissue and cell stakeholders and representatives of the competent authorities for tissues and cells took place on February 22nd 2017. The purpose of the meeting was to provide an opportunity for an informal exchange of views between the stakeholders, representatives of the Member State competent authorities and the Commission services on topics of mutual interest.

PARTICIPATION:

Competent Authorities from all EU-28 Member States were invited, as were competent authorities from Norway, former Yugoslav Republic of Macedonia, Serbia, Montenegro and Turkey. Observers from the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), the Council of Europe and the World Health Organisation were also invited. Sixteen Member States participated, along with the Council of Europe and WHO.

Stakeholders: Representatives of the World Marrow Donors Association (WMDA), the European Society for Blood and Marrow Transplantation (EBMT), the European Society for Human Reproduction and Embryology (ESHRE) and the Common Representation for Substances of Human Origin (CoRe SoHO).

European Commission/DG-SANTE: Mr S. VAN DER SPIEGEL (chair), Ms D. FEHILY, Mr R. MCGEEHAN, Ms I. PUCINSKAITE-KUBIK

1 WELCOME

The chair welcomed participants to this ad-hoc meeting. The agenda was adopted without any changes.

2 INTERACTION WITH STAKEHOLDERS

The Commission services presented the terms of reference for these meetings, reminding the participants in particular that the meeting would only address EU-level topics of relevance for multiple countries. Country-specific topics are to be addressed bilaterally between stakeholders and concerned Member State authorities. It was agreed to draft minutes of this meeting for publication by DG-SANTE.

The Commission services explained that they had issued a call in October 2016 for expressions of interest in participating in ad-hoc meetings with representative members of the competent authorities SoHO expert group. Following review of the applications received, a list of approved stakeholder organisations was published in November 2016[1] and is regularly updated.

The Commission services reminded participants that in future stakeholders will be invited to the meetings depending on the agenda topics of EU-relevance. The meetings will be a focus for gathering views and information in the context of the Evaluation of the EU legislation on blood, tissues and cells that was launched at the beginning of 2017[2].

3 INTRODUCTION OF STAKEHOLDERS PRESENT

The representatives of stakeholder organisations each introduced their organisation and its aims.

WMDA provides access to the global database to search for potentially matched bone marrow or peripheral blood haematopoietic stem cell donors or cord blood products. Their focus is on unrelated volunteer donors and they maintain standards and run accreditation and training programmes. The Bone Marrow Donors Worldwide registry included 94 organisations listing 30,168,410 donors and cord blood products for international search on February 17th, 2016 (www.bmdw.org).

Founded in 1985, ESHRE is a pan European/ OECD professional organisation of 6,000 members that are clinicians, embryologists, psychologists, nurses, midwifes and lab technicians. It also supports a European Patients Association. Its aims are to promote interest in, and understanding of, reproductive science and medicine by teaching and training, development and maintenance of data registries and research and dissemination. It also aims to inform policy makers in Europe.

CoRe SoHO is a consortium of four Scientific Associations (European Association of Tissue Banks, The European Eye Bank Association, The European Society for Blood and Marrow Transplantation and the European Blood Alliance) formed with the goal of providing expert opinion and supporting data to European Union decision-makers and their respective organisations in the field of SoHO. In particular, the consortium aims to actively contribute to legal and regulatory discussions affecting the SoHO field. CoRe SoHO is committed to ensure that activities at EU level are governed by the principles of: not-for-profit/non-financial gain,

[1] http://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/2016_call_ls_en.pdf
[2] https://ec.europa.eu/health/blood_tissues_organs/policy/evaluation_en

voluntary and altruistic donation, sufficiency, cost efficient / patient accessibility to health care.

EBMT is a professional association established more than 40 years ago. EBMT associates transplant centres from across Europe and beyond. The society provides a forum for physicians, pharmacists, nurses, technologists, scientists, with many opportunities for scientific exchanges and collaborations around hematopoietic cell transplant (HCT) and cellular therapies. EBMT offers educational tools for these different categories of professionals. The EBMT major achievements are a registry that contains information on close to 600.00 transplants, and the JACIE accreditation scheme aimed at improving quality and safety of HCT.

4 DONOR SAFETY AND VIGILANCE

This topic was opened by two presentations, one by ESHRE and one by WMDA.

ESHRE highlighted that donor safety is an important issue for female donors where adverse outcomes are reported. The most important are Ovarian Hyper-stimulation Syndrome (OHSS), oocyte retrieval complications (pelvic infection, internal bleeding) and psychological implications. There are also risks associated with surgery when ovarian tissue is collected for fertility preservation. Although the register run by ESHRE shows that these risks are relatively low (Table 1), they are important for donors and patients and ESHRE noted that they are not regulated under the EU Directives.

Reported by 28 countries	n	%
OHSS	1953	0.4
Bleeding	848	0.2
Infection	101	0.02
Maternal death	3	0.0006
Fetal reductions	485	0.15

Table 1: Risks for Female Donors
(EIM Consortium. Hum Reprod 31:1638-1652, 2016)

It was also noted that in the data shown, non-partner donors are not specifically identified. ART cycles with non-partner donor ooctyes make up 5.2% of all ART cycles.

In relation to the safety of non-partner donors, ESHRE proposed consideration of the following actions:

- to limit the number of oocyte donations per donor (the SEC not adequate to control this);
- to define strict rules on economical compensation (cross-border differences);

- to report complications of oocyte retrieval, including OHSS, in non-partner donations (in the EU SARE system);
- to improve traceability in cross-border ART, eliminating the possibility of direct distribution of gametes to patients.

ESHRE also raised the topic of infectious marker screening in partner donation, arguing that requiring screening in the 3 months before the first ART treatment irrespective of previous screening is not cost-effective given that the validity of the tested is accepted to extend up to 24 months. They noted that seroconversions are extremely rare ("for over 6500 individuals who were tested and re-tested for all three viruses, no seroconversions were reported.". *Hughes et al HR, 2011).* They also note that it is difficult to define HTLV high prevalence areas, particularly in relation to the requirement to establish "where donor's parents originate from these areas". They proposed the adoption of a 'realistic approach' to virus screening of partner donors.

WMDA presented the case for a global strategy for donor and patient safety in their field, noting that 50% of HPC donations cross international borders. They stressed that global data collection enhances the likelihood of recognition of relatively rare adverse occurrences. As an example, a case involving cross-border transplantation was presented where, for the first time, a stem cell donor was shown to have become temporarily positive for HBV DNA following treatment with G-CSF because G-CSF treatment induces proliferation of hepatocytes or hepatic progenitor cells in humans (https://www.ncbi.nlm.nih.gov/pubmed/27240006). Similarly, data showing three incidents if needle breakage during bone marrow extraction were reporting from 10.000 bone marrow extractions, a risk that would not be identifiable in local or regional vigilance programmes.

Also the trend towards more HPC donation by family members, in haplo-identical settings, raise new questions and challenges for donor safety, including the objective evaluation of the motivation and absence of social pressure. Lessons could be explored from similar experiences with the organisation of living organ (kidney) donation.

WMDA highlighted the central role of donor registries for ensuring cross-border vigilance, which can best be organised at global level, noting that only tissue establishments are required to report in the EU SARE system and registries do not have such obligations. It was noted that data protection rules challenge traceability and that late adverse events (malignancies, autoimmune and other) need definitions in order to be appropriately captured. WMDA has set up a robust system for bio-vigilance of unrelated donors including long-term follow-up. Related donors are not yet part of this system but plans are to incorporate them in the future.

EBMT also raised the issue of donor safety, stressing that donors undergo a medical procedure with no benefit to themselves. They consider that incidental findings must trigger proper care and counselling. They noted in particular that among related donors, the average age of siblings is increasing with the average age of recipients and that the practice of collecting donations from children for haplotype-mismatched parent recipients is now seen. There is a need to improve harmonization of procedures for donor selection, donor clearance and donor collection across transplant programs. There is a need to include the need for robust algorithms to establish a hierarchy when several donors are available, which is the rule for haplotype-mismatched HCT.

5 CLINICAL OUTCOME MONITORING AND DEMONSTRATION OF EFFICACY

For this topic, presentations were made by EBMT, CoRe SoHO and ESHRE.

Although the EU Directives do not specify requirements for clinical outcome monitoring, **EBMT** considers that monitoring clinical outcome and efficacy of hematopoietic cell transplant (HCT) and cellular therapies is an individual and collective obligation. Not only do these transplants involve complex therapeutics with significant short-term and long-term toxicity, applied for the treatment of life-threatening diseases, but they are also expensive treatments (an autologous transplant costing around 20 K€ and an allogeneic transplant from approx. 50 to 500 K€). They argued that effective clinical outcome and efficacy monitoring requires appropriately trained healthcare personnel, international standards (FACT-JACIE v6.0 prescribe computation of outcome and benchmarking at the centre/program level) and national and international registries. The EBMT registry currently has data on more than half a million HCT. While registries are considered essential, they also face threats from the need to constantly maintain and update the IT infrastructure.

In principle, EBMT considers that recipients of allogeneic HCT should be followed lifelong, given the importance to assess long-term consequences of these complex treatments on recipients' medical, educational and social conditions. These follow-up activities, however, are placing significant burdens on transplant programmes.

EBMT noted that many significant changes are taking place in the field. “Traditional” HCT is becoming more complex and diversified with different categories of donors, different stem cell sources, sequential administration of a stem cell product, followed by donor lymphocyte infusions (DLI) being some of the significant changes. Some hematopoietic cellular therapies are classified either as “somatic cell therapy medicinal products” or “gene therapy medicinal products” and are close to entering the market (e.g. Zalmoxis® manufactured by Molmed S.p.A, genetically-engineered allogeneic blood donor T-lymphocytes that express a so-called “suicide gene”).

CoRe SoHO described current recipient follow up (FU) methods in the field of tissues, involving collaboration with end users and reviewed current methods to collect clinical efficacy data.

They highlighted their view that there is a need to:

- establish mandatory registries & active clinical follow-up by end users of all tissue types
- develop key performance indicators (KPI’s) for clinical FU
- agree timelines for each tissue type (which could be adjusted at Member State level)
- secure adequate funding for set up & maintenance of a data registry
- publish data for transparency
- involve stakeholders in development of the registry & clinical monitoring structures.

Although there are currently no legal requirements for monitoring clinical outcomes and efficacy for tissues, CoRe SoHO considers that monitoring clinical outcomes & efficacy is an essential tool to assure safety & efficacy and to confirm validation of processing methodologies. They differentiated between immediate post-operation follow-up and long-term follow up, noting that tissues are widely distributed to many users so even immediate feedback can be difficult to obtain.

The extent of long term FU ("clinical audit") required was considered to depend upon the type of tissue/cell or processes applied. In general, it should be performed for highly matched life-saving transplants, where "Novel" processes have been applied to the tissues/cells or where a tissue establishment processes new types of tissue for first time. It may also be required following report(s) of adverse reaction following well established tissue/cell transplants or when minor (but critical) changes have been made to the applied processes (e.g. change in one antibiotic).
For clinical outcome monitoring to be effective, there is a need to reach agreement on what is the "desired or intended result" when tissues or cells are applied to patients.

- Is tissue quality defined before distribution (are QA methods validated)?
- Is graft efficacy dependant on presence of living cells?
- Is the graft intended to provide structural / functional integrity?
- Is it uncertain how graft efficacy can be measured?

The answers will be different for each tissue or cell types and it may be challenging agree between tissue establishments, end users & researchers.

CoRe SoHO considers that that clinical outcome monitoring should be regulated. The representative noted that the VISTART Joint Action is formulating regulatory principles for requirements for clinical outcome data as part of preparation process authorisation and that the EuroGTP II project is working on this topic from the perspective of the tissue establishments.

The **ESHRE** representative addressed this topic, describing the challenges that exist to defining efficacy in the ART field. There are many indicators that could be used, including live births per treatment initiated or intermediate indicators (e.g. number of ooctyes retrieved, number of cycles cancelled etc.) but the pregnancy rates per embryo transfer has shown steady improvements in ESHRE registry data (Figure 2).

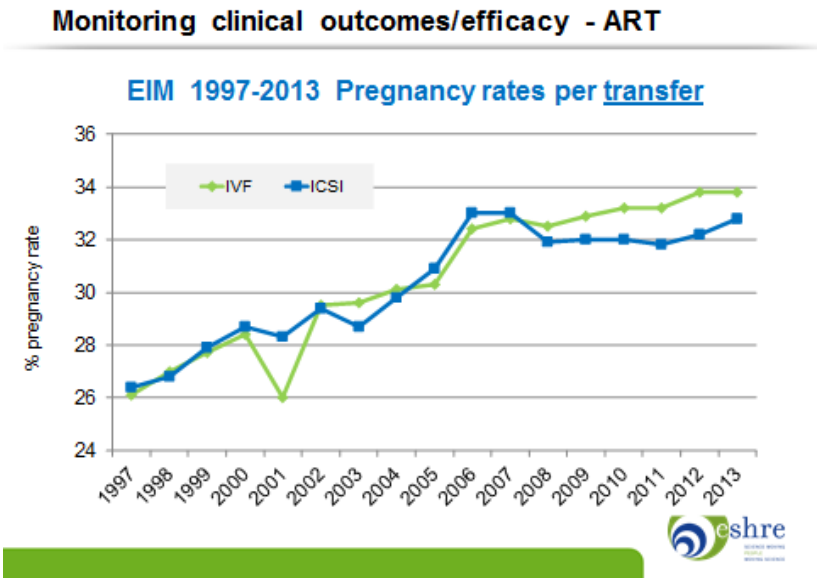

Figure 1: Monitoring clinical outcome/efficacy in ART

While keeping pace with scientific and technological changes is considered by ESHRE to be a legitimate concern, it is considered to be beyond the scope of the Directives. However, ESHRE has published a tool for assessing the degree of novelty of new processes, grading

them as experimental, innovative or established according to defined criteria (*Provoost V et al. Hum Reprod 2014; 29(3):413-417*). They consider registries of follow-up data to be essential and propose that they be made mandatory and including details on babies born. In their view, registries should collect data by cycle. They consider that systematic registries in ART should be implemented/improved.

In general, they propose that any future revision of the EU legislation should take into account the specificities of ART and should clarify scope, should be realistic in terms of technical requirements such as air quality and should reduce the technical requirements for partner donation where the burden to comply is not considered to be justified by the benefits.

6 FINAL REMARKS

All the associations present were thanked for their clear and informative presentations and for the open and constructive discussions. The issues raised will form part of the evidence base for the evaluation of the EU legislation on blood, tissues and cells.