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Vigilance and Surveillance of Tissues and Cells in the European Union
Final Recommendations

Deliverable 11

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Introduction

As part of work-package 4 of the EUSTITE project, a group of experts in the clinical application of tissues and cells and its associated risks, notably of disease transmission, reviewed existing systems for adverse event and reaction notification and management in MS and in related fields globally. The report of this review was made available on the EUSTITE website. It showed that, at that time, in 2007, systems for the vigilance and surveillance (V&S) of tissues and cells used in transplantation and in assisted reproduction were at an early stage in the European Union (EU) and that most Competent Authorities (CA) were in the process of establishing these systems for the first time.

Two major meetings on this topic were organised by the Vigilance and Surveillance Medical Advisory Committee (V&SMAC) of the EUSTITE project in 2007. Annex 1 shows the membership of the V&SMAC and the organisations that participated in the V&SMAC meetings. The first meeting, held in Madrid in March 2007, identified several key areas which required further development. The second meeting took place in Rome in July 2007. At this meeting, systems for classification and reporting of Serious Adverse Reactions (SAR) and Serious Adverse Events (SAE) were discussed with the aim of developing a model for reporting and investigating SARE (SAR and SAE) possibly related to, or influencing, the quality and safety of tissues and cells. This meeting was combined with a WHO meeting bringing together a global representation of experts in the field and representatives of national regulatory authorities in charge of cells and tissues. This facilitated addressing the need for harmonized global understanding of adverse events and reactions and their reporting as well as agreement on aspects specific to the European Union.

The outputs of the Madrid and Rome meetings were considered through further exchanges between the EU participants and small working group sessions hosted by WHO and at a further meeting of the V&SMAC in Bratislava in January 2008. These discussions led to the drafting of the recommendations contained in a guidance and tools document which was submitted to the European Commission as Deliverable 10 of the EUSTITE project. That document provided proposed tools for the definition, classification and evaluation of adverse events and reactions and a model for notification and management of SARE and for communication within and between EU MS. The tools were designed to support compliance with the EU tissues and cells directives although it was recognised that an individual CA is free to require the reporting of events or reactions, within its national system, which fall beyond the scope of the European Directives.

The tools published in Deliverable 10 of the EUSTITE project were applied to all reported SARE by 22 CA in the 20 European Union Member States that participated in the EUSTITE V&S pilot which ran from July 2008 to the end of June 2009. A detailed final report including a series of recommendations from that pilot was produced and is submitted to the European Commission together with this Deliverable. The application of the tools and guidance allowed their evaluation in practice on a large scale. In the course of the pilot, a number of recommendations arose for modifications to the tools and for V&S practice in general in this

field. In parallel, the tools were applied to real and invented cases of SARE during 4 EUSTITE Inspector Training courses, at professional society congress workshops, such as the European Association of Tissue Banks (EATB) and the European Eye Banking Association congress (EEBA) and at EU national training courses for inspectors and professionals. They were also presented at international professional and regulatory conferences and workshops in the US, Asia, Australia and Canada.

During the course of the pilot, and the numerous presentations and discussions on the EUSTITE tools and guidance, comments and recommendations were collected. This document captures approved modifications and recommendations, and presents amended versions of the EUSTITE V&S tools.

Key Results of the EUSTITE V&S Pilot Programme (July 2009 to June 2010)
Between 12 and 19 reports were received each quarter (average of 16 reports). Eight countries reported no SARs or SAEs during the pilot. A total of 152 SARs and 149 SAEs were reported during the year. These were filtered to meet EU Directive and EUSTITE SARE reporting criteria giving a final number of 71 SARs and 150 SAEs.
Classification of SARs: Hypersensitivity 25% (18), Other 25% (18), Infection from tissue & cells 27% (19), toxicity 1% (1) infection from donor 4% (3) Failure - 16% (11) and Mismatch 2% (1).
Severity - SARs: Serious - 85% (60) Life-threatening - 11% (8) Death - 4% (3).
Imputability: N/A – 1% (1), excluded/unlikely – 14% (10), possible - 30% (21), likely/probably - 41% (29), certain- 14% (10).
Impact Grading SARs : ≥12 - 6% (4), 9 - 7% (5), 8 - 8% (6), 6 - 34% (24), 4 - 34% (24), 3 - 3% (2), 2 - 7% (5), 0 - 1% (1).
Stage at which SAE occurred: Processing 29% (43), Procurement 23% (34), Storage 17% (26), Distribution 19% (28), Testing 7% (10), Transport 2% (4) and Other 3% (5).
Classification of SAEs: Tissue & Cell defect 19% (29), Other 11% (16), Equipment Failure 23% (35), Human Error 47% (70).
Impact Grading SAEs: ≥12=1% (2), 9=3% (4), 8=3% (5), 6=29% (43), 4=23% 35), 3-27% (40), 2 – 11% (17), 0=3% (4).

EUSTITE V&S Pilot Report
A detailed report has been documented of the EUSTITE V&S Pilot programme and is submitted to the European Commission together with this Deliverable.

Conclusions and Recommendations

The pilot demonstrated the feasibility of multi-national co-operation in vigilance and surveillance in the area of tissue and cells for human application. The tools developed during the EUSTITE project were tested in multiple countries on a large number of real SARE and were found to be easily applied by CA vigilance officers, although some reservations were expressed in relation to their direct applicability in the field of Assisted Reproduction. Many CAs will consider extending their application to the tissue establishment level. A willingness to share information regarding SARE was clearly demonstrated and a network of CA officials working in this field was established. The increased value for clinical care for both recipients and donors through learning from consolidated data was demonstrated. The greatest level of reporting was in the fields of haematopoietic stem cells and reproductive cells.

The following specific recommendations are made following the experience of the pilot:

1. The EUSTITE V&S tools should be modified and resubmitted to the EC to take account of a number of enhancements that were proposed during the pilot and the discussion of its results:
   - **a.** *Excluded* from *unlikely* should be separated in the Imputability tool. It is noted that these two categories are together in the haemovigilance tool used in the EU. The use of a standard tool across blood and tissues and cells is much supported but it is proposed that consideration be given to separating these two definitions for imputability assessment for all substances of human origin.
   - **b.** In the criteria for SAE reporting, it should be clarified where mix-ups in ART fit, or a new criterion for this should be added.
   - **c.** In the descriptions of the SAR severity grades, the transmission of genetic illness following ART with donor gametes or embryos should be added.
   - **d.** In the impact assessment tool, the order of numbering should be reversed, the terms should be simplified and the colours changed to the commonly used red, yellow and green.

2. The EUSTITE V&S tools should be adapted more specifically for the field of Assisted Reproduction. A work packaged dedicated to vigilance in this field is included in a follow-up project, SOHO V&S (Vigilance and Surveillance of Substances of Human Origin) which has been funded by the European Commission and which started in March 2010 and runs for 3 years. This project will take this important work forward.

3. The issue of vigilance in donors of tissues and cells needs to be addressed specifically. Consideration should be given to developing a different severity grading scale for donors with the requirement that **any** adverse reaction be reported to a central registry. This is essential to providing the protection and advocacy that donors should be given. The European Directives require reporting of adverse reactions only where they have impacted on safety and quality of the tissues and cells donated. Despite this, the Commission has welcomed the inclusion of donor reactions in the MS annual vigilance reports. A work

package in the SOHO V&S project will address donor vigilance and develop a report and recommendations for the EU.

4. EU-wide guidance and training should be provided for CA vigilance officers and inspectors, as appropriate depending on national management systems, in the investigation of SARE including where there is suspicion of illegal or fraudulent activity. Training courses on SARE investigation are included in the SOHO V&S project to address this requirement.

5. There is a need to progress without delay towards agreeing common definitions for SARE and common tissue and cell nomenclature. Common coding to support traceability, which is essential to effective vigilance, is also a priority and will allow comparison and sharing of information and data in a meaningful way. The *Common Approach* guidance document issued by the European Commission to CAs in 2009, which incorporated a number of EUSTITE V&S tools, made initial progress in proposing product and reaction categories.

6. Although this pilot was limited, in terms of direct involvement, to the CAs for tissues and cells, it is acknowledged that vigilance requires the active participation of all stakeholders to ensure the identification of reactions and events, their correct investigation and reporting with appropriate follow-up information sharing and corrective actions. Systems that are non-punitive, open and transparent and that provide regular feedback to stakeholders will encourage participation and add value to the information reported. The new project, SOHO V&S includes a work package that will develop guidelines for clinical users to promote vigilance at the critical level of the patient.

7. The pilot results showed evidence of significant under-reporting of SARE. This is likely to be largely due to the fact that most systems in the EU are newly established. It will take time for tissue establishments and, particularly for clinicians using tissues and cells, to fully engage in vigilance systems and to report as required. The professional societies will play an essential role in ensuring an adequate engagement of clinicians. The SOHO V&S project will take this issue forward with a work package dedicated to providing guidance to clinicians regarding their responsibilities for traceability and for reporting and investigation of SARE. The guidance produced will provide them with supportive tools. The major professional societies in the field of tissues and cells (ESHRE, EATB, EBMT, EEBA and WMDA) are all cololaborating partners in this new project.

8. Consideration should be given to the use of unique identifiers for individual SARE to avoid double counting.

9. Development of a standardised EU template for the reporting of SARE to the CA, including initial and final conclusions of the investigation, would facilitate comparison of data. As systems become more mature, consideration should be given to developing such a form.

10. The further development of the EUROCET instrument (www.eurocet .org) will facilitate the application of denominators to the EU-wide SARE reports collated by the European Commission[1].

11. The global circulation of tissues and cells and the complex interactions between tissues and cells and other regulated products such as medicines and medical devices means that there is a need for effective communication and discussion between regulators on an international basis. The WHO should play a central role in facilitating this network and in developing global approaches. The WHO Guiding Principles for Transplantation provide a mandate for this work and the WHO has already used the EUSTITE V&S tools to develop a version which was presented to a Global Consultation on the Regulation of Tissues and Cells in February 2010. It was agreed that this document will be the basis for a WHO Aide Memoire on Vigilance and Surveillance in the field. The SOHO V&S project has recruited a number of international organisations (including FDA, CDC and Health Canada) as collaborating partners in recognition of the need for this global approach; the WHO will continue to play a key role in the new project, ensuring that the global nature of tissue and cell circulation is reflected by a global approach to vigilance and surveillance.

Revised Tools

In line with the recommendations listed above, revised versions of the tools are proposed as follows:

Serious Adverse Event Reporting

Deviations from Standard Operating Procedures in TEs, or other adverse events, which have implications for the quality and safety of tissues and cells should result in SAE reporting to the CA when one or more of the following criteria applies:

- inappropriate tissues/cells have been distributed for clinical use, even if not used;
- the event could have implications for other patients or donors because of shared practices, services, supplies or donors;
- the event resulted in a mix-up of gametes or embryos;
- the event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells;
- the event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells.

[1] Eurocet and Council of Europe data were used to estimate rates of serious adverse reactions for some tissues and cells in the EUSTITE Pilot as the data provided to the European Commission in the Member States Annual Vigilance Reports are not yet adequately complete for this purpose. Only those countries that had provided activity data to Eurocet or Council of Europe and had participated in the pilot were included in the analysis.

SAR Severity Grading

It is proposed that all adverse reactions in recipients that are graded as 'serious', Life-threatening or Death should be reported to the CA. It is further recommended that adverse reactions in donors, even if graded as 'non-serious' should be monitored on a national or regional basis.

Severity	Comments
Nil	No harm, no risk, patient not informed as there was no risk of harm
Non-serious	Mild clinical/psychological consequences No hospitalization. No anticipated long term consequence/disability
Serious	Hospitalization or prolongation of hospitalization and/or Persistent or significant disability or incapacity Intervention to preclude permanent damage Evidence of a serious transmitted infection Birth of child with a serious genetic illness following ART with donor gametes or embryos
Life-threatening	Major intervention to prevent death Evidence of a life-threatening transmitted infection Birth of child with a life-threatening genetic illness following ART with donor gametes or embryos
Death	Death

SAR Imputability Grading

It is proposed that all adverse reactions are graded in terms of imputability. Grades allocated might change in the course of an investigation and should generally be assigned at the point of initial notification and again at the completion of the reaction investigation.

Imputability level		Explanation
NA	Not Assessable	Insufficient data for imputability assessment
0	Excluded	Conclusive evidence beyond reasonable doubt for attributing adverse reaction to alternative causes
1	Unlikely	Evidence clearly in favour of attribution to alternative causes.
2	Possible	Evidence is indeterminate
3	Likely, Probable	Evidence in favour of attribution to the tissues/cells
4	Definite, Certain	Conclusive evidence beyond reasonable doubt for attribution to the tissues/cells

SAR/SAE Impact Assessment

The Impact Assessment tool assists practitioners and regulators in planning their response to a given adverse reaction or event, taking into account broad consequences, beyond the individual patient affected or potentially affected.

Step 1:
Assessing likelihood of occurrence/recurrence of SAR/E

1	Rare	Difficult to believe it could happen again
2	Unlikely	Not expected to happen again
3	Possible	May occur occasionally
4	Likely	Expected to happen again but not persistent
5	Probable	Expected to happen again on many occasions

Step 2:
Assessing Impact /Consequences of SAR/E should it recur

Impact Level		**On individual(s)**	**On System**	**On Tissue/Cell Supply**
0	Insignificant	Nil	No affect	Insignificant
1	Minor	Non-serious	Minor damage	Some applications postponed
2	Moderate	Serious	Damage for short period	Many cancellations or postponements
3	Major	Life-threatening	Major damage to system - significant delay to repair	Significant cancellations - importation required
4	Catastrophic/extreme	Death	System destroyed - need to rebuild	All allogeneic applications cancelled

Step 3:
Applying the Impact Matrix

Likelihood of recurrence → / Impact of recurrence ↓	1 Rare	2 Unlikely	3 Possible	4 Likely	5 Certain /Almost Certain
0 Insignificant	0	0	0	0	0
1 Minor	1	2	3	4	5
2 Moderate	2	4	6	8	10
3 Major	3	6	9	12	15
4 Catastrophic /Extreme	4	8	12	16	20

Step 4:

The response of a tissue or cell bank or a health authority to a specific SAE/SAR should be proportionate to the potential impact as assessed by the matrix described.

GREEN: The tissue or cell bank to manage the corrective and preventive actions and the health authority to file the report and keep a 'watching brief'.

YELLOW: Requires interaction between the tissue or cell bank and the health authority which may request an inspection that focuses on the SAE/SAR and corrective and preventive actions to be followed up, including evidence of effective recall, where necessary. Written communication to professionals working in the field might be appropriate.

RED: Health authority will generally designate representatives to participate in developing or approving the corrective and preventive action plan, possibly a task force to address broader implications. Inspection, follow up and written communication as previously and possibly notification of health authorities in other countries where relevant.

The effectiveness of the response can be assessed by re-applying the impact matrix following the implementation of the preventive actions. The impact can be reduced by:

- reducing the probability of recurrence through preventive measures
- increasing the detectability of the risk, or
- reducing the severity of the consequences if it should recur.