A Training Model for Competent Authorities In the Investigation and Management of Vigilance and Surveillance of Human Tissues and Cells

January 2013

Vigilance and Surveillance of Substances of Human Origin (SOHO V&S)

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Deliverable 9

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CHAPTER 1: INTRODUCTION AND BACKGROUND

Background

Directive 2004/23/EC, and its associated Commission Directives 2006/17/EC and 2006/86/EC, require EU Member States (MS) to nominate Competent Authorities with responsibilities for the implementation of a series of regulatory activities in the field of human tissues and cells for transplantation and for assisted reproduction. A key function that must be put in place in each MS is a system for vigilance and surveillance (V&S) of these activities, with reporting and investigation of serious adverse events and reactions. Surveys conducted by the Public Health Directorate of the European Commission and presented to the Competent Authorities meetings indicate that many MS are establishing new Competent Authorities and most are developing new systems for V&S in this field. This was confirmed during the EUSTITE (European Union Standards and Training in the Inspection of Tissue Establishments) project (Fehily et al. 2007[1], 2008[2]). A review of tissue and cell V&S systems, conducted as part of the EUSTITE project in 2007, indicated that only two MS had well developed systems, namely France and UK; all the others were adapting related vigilance systems or developing new systems and procedures.

Vigilance in this field is complicated by the broad scope of application, the degree of importation from third countries and distribution between EU MS and the mixture of public and private sector service providers.

Building on the Work of EUSTITE

EUSTITE was a three-year EU-funded project that was completed at the end of 2009. The project promoted standardisation of inspection and vigilance across the EU through the development of common inspection guidelines, vigilance tools[3] and training for Competent Authority officials in these activities. The vigilance tools included:

- Criteria for reporting Serious Adverse Events (SAEs)
- A Severity grading system for Serious Adverse Reactions (SARs) with guidance on which level to report
- An Imputability grading system for SARs
- An Impact grading system (risk matrix including wider system implications) for SAEs and SARs.

The tools were tested during a one year pilot study involving 20 MS[3]. Over 300 reactions and events were reported to the pilot and evaluated using the tools. The tools were amended following the pilot and are currently in use in many MS. In its final recommendations, the project identified V&S as a field that needed considerably more work at an EU level. A number of areas were identified and formed the basis of a new project proposal, 'Vigilance and Surveillance of Substances of Human Origin (SOHO V&S)' which was granted EU funding and was launched in March 2010.

SOHO V&S Project Objectives

The project took forward the work of EUSTITE and addressed a number of areas that were identified as requiring wide consultation and discussion. This included working to develop a shared view of how serious adverse events and reactions associated with tissue and cell donation or human application are reported, evaluated and investigated. It aimed to address harmonisation of terminology and documentation and a consensus on how information should be exchanged between EU MS, the European Commission and third countries.

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[1] Fehily D, Delvecchio C, Di Ciaccio P. et al. 2007 *The EUSTITE project: working towards harmonised implementation of European regulation of tissues and cells.* Organs, Tissues & Cells, Volume 10(1): 31-36.

[2] Fehily D, Kurz J, Hornez T. et al. 2008 *The development of EUSTITE guidelines for the inspection of tissue and cell procurement and tissue establishments in the European Union.* Organs, Tissues & Cells, Volume 3: 167-174.

[3] Fehily D. Sullivan S. Noel L. et al. 2012 *Improving Vigilance and Surveillance for Tissues and Cells in the European Union: EUSTITE, SOHO V&S and Project NOTIFY.* Organs, Tissues and Cells vol. 15, no. 2:85-95.

The Team

SOHO V&S was co-ordinated by the Italian National Transplant Centre (CNT). It had a Steering Committee and a large number of collaborating partner organisations, including all of the major European professional societies in the field.

Steering Committee

National Transplant Centre, Italy (Project Co-ordinator)
Donor Action Foundation, Belgium
Irish Medicines Board, Ireland
National Transplant Organisation, Spain
Biomedicine Agency, France
French Agency for the Safety of Health Products, France
National Centre for Tissue and Cell Banking, Poland
Human Fertilisation and Embryology Authority, UK
Human Tissue Authority, UK
World Health Organisation, Switzerland.

The involvement of the World Health Organisation, and many collaborating partners from outside the EU, ensured that the guidance produced in this project reflected international needs and realities, in the context of global movement of human tissues and cells for human application.

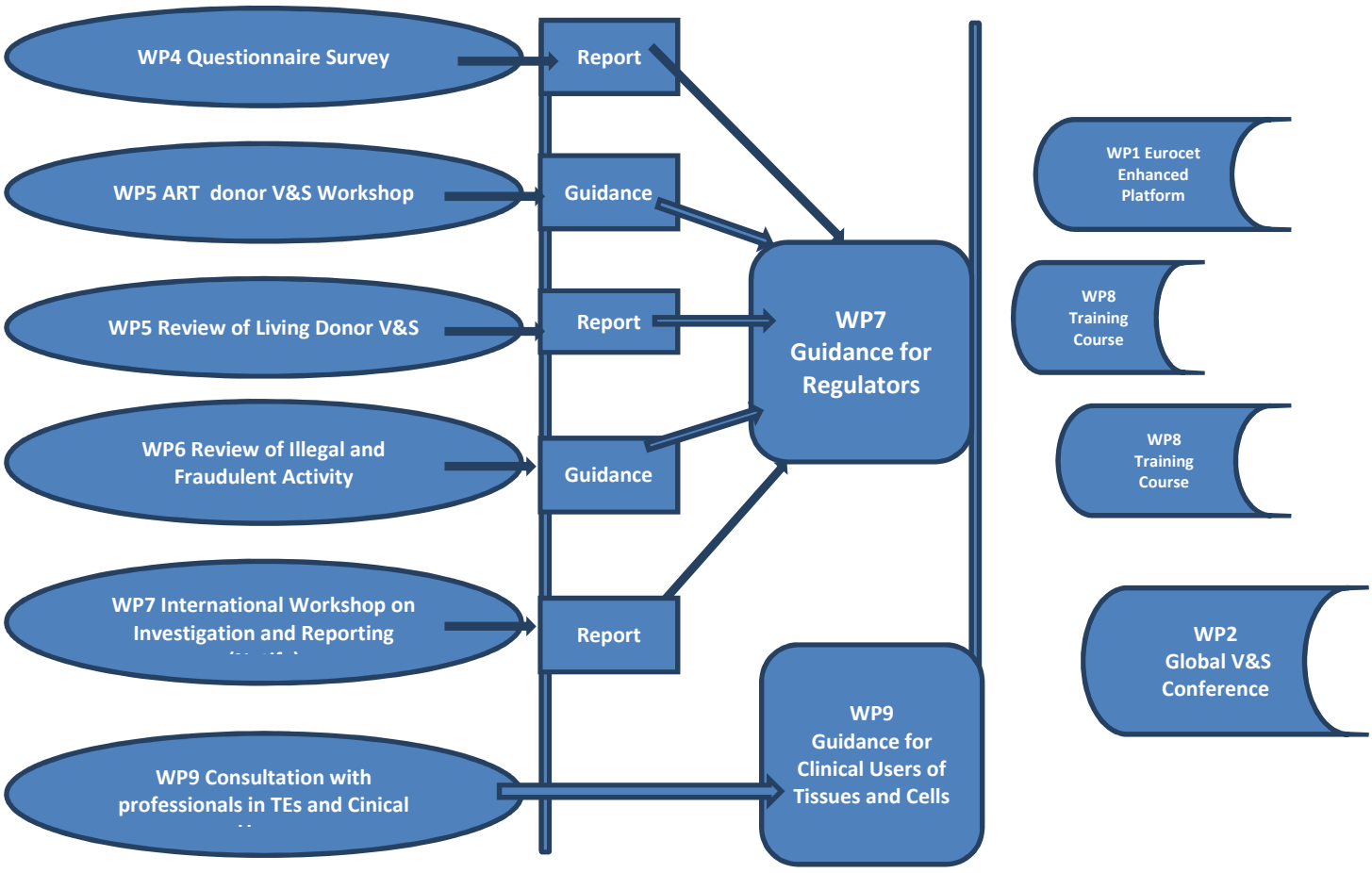


Figure 1.1 SOHO V&S Project outline (WP = work-package)

Work Package 8: Aims and Objectives

This document (Deliverable 9) is the key output of work package 8 (WP8) of the project. The objective of the work package was to develop and provide training in the investigation and management of vigilance and surveillance associated with human tissues and cells to representatives from EEA countries. The training was to be provided in the form of two training courses each comprising a 4-week e-learning module followed by a 2-day interactive residential module.

The aim of the e-learning module was to provide participants with background information and theory which would be applied during the residential course. The e-learning module was to include:

- Papers describing the rationale and practical application of different methods of investigation and problem solving;
- Published examples of different incidents and how they were investigated;
- Data relating to SAR/E in the EU and in particular sectors: ART, haematopoietic stem cell transplantation, tissues for transplantation etc.
- A forum for the discussion of real cases;
- All reports and guidance produced by the project particularly that produced in WP7.

The aim of the residential module was to apply the guidance and theory provided during the e-learning module to a series of case studies in working groups. Throughout the residential modules:

- Experience was presented from the tissues and cells and related fields;
- Techniques for root cause analysis and other methods of problem solving were applied in practice;
- Approaches to dealing with illegal and fraudulent activity were compared and evaluated.

This work package was led by the Irish Medicines Board and supported by all SOHO V&S Project Partners. The e-learning module platform was provided by the University of Applied Sciences in Vienna through the efforts of the Austrian Ministry of Health, a collaborating partner in the project. The same platform had been used during the EUSTITE project for the training of inspectors. The residential courses were held in Ireland and Italy during 2012. Each course was thoroughly evaluated by the participants and both were attended by one or two representatives of the Evaluation WP, the Donor Action Foundation. After the first residential course, the tutors and evaluators remained for a third day to review the evaluations and to make changes to the course design.

This document (Deliverable 9) outlines the structure of the training courses (both e-learning and residential modules) developed and provided during the SOHO V&S Project. Key documents provided during the modules are listed and case studies utilized during the courses are provided. It is anticipated that this document may be used by Competent Authorities to facilitate delivering similar training to staff within their own agencies.

Work Package 8: 2012 Training Courses

In January 2012, a planning meeting was held in Dublin between the Irish Medicines Board and the Project Co-ordinator to discuss and agree a draft agenda for the E-Learning Module and the Residential Course. Tutors were allocated and invited, according to the project plan, from the SOHO V&S project associated partners. The Irish Medicines Board co-ordinated the invitations to all Member States and the registrations from interested parties. The courses were co-ordinated as follows:

Course 1: Ireland		**Course 2: Italy**	
E-Learning Start Date:	8th May 2012	E-Learning Start Date:	10th September 2012
Residential Course Start Date:	18th – 20th June 2012	Residential Course Start Date:	22nd – 24th October 2012
Venue:	Brooklodge Hotel, Macreddin, Co. Wicklow. Ireland	Venue:	Barceló Aran Blu Hotel, Ostia, Rome, Italy.

Participant countries at the course in Ireland

Competent Authority	Number of Participants	Country
Spain. Organización Nacional de Trasplantes	3	Spain
Human Tissue Authority	1	United Kingdom
Autoridade para os Serviços de Sangue e da Transplantação	1	Portugal
Italian National Transplant Centre (CNT)	1	Italy
Danish Health & Medicines Authority	1	Denmark
Agency of Medicines	1	Latvia
Bundesministerium für Gesundheit/Ministry of Health	2	Austria
Irish Medicines Board	1	Ireland
State Agency of Medicines	1	Estonia
HFEA	1	United Kingdom
Agence de la Biomedecine	1	France
Ministry of Health	1	Romania
Donor Action	2	Belgium
Ministry of Health	1	Cyprus
NPHMOS - Office of the Chief Medical Officer	1	Hungary
Dutch Health Care Inspectorate	1	Netherlands
Irish Medicines Board	2	Ireland

Participants countries at the course in Italy

Competent Authority	Number of participants	Country
Ministry of Health and Institute for transplantation and Biomedicine	2	Croatia
AFSSAPS	1	France
Paul-Ehrlich-Institut	1	Germany
Danish Health and Medicines Authority	1	Denmark
Ministry of Health	1	Slovakia
Ministry of Health	1	Cyprus
Agence de la biomedecine	1	France
Banque de Tissus Humains	1	France
CNPMA	1	Portugal
National Transplant Bureau under the Ministry of Health	1	Lithuania
JAZMP	1	Slovenia
Human Fertilisation and Embryology Authority	1	United Kingdom
Autoridade para os Serviços de Sangue e da Transplantação	1	Portugal
The Norwegian Directorate of Health	1	Norway
ONT	1	Spain
Donor Action	1	Belgium
Human Tissue Authority	2	United Kingdom
Krajowe Centrum Bankowania Tkanek i Komórek	1	Poland

List of Tutors

A number of tutors also attended the courses as participants and were involved fully in all discussions and workshops also. Their assistance in preparing case studies and facilitating workshops when required was hugely appreciated.

First Name	Last Name	Competent Authority	Country
Pravat	Bhattacharyya	Human Tissue Authority	United Kingdom
Michael	Cox	Danish Health & Medicines Authority	Denmark
Deirdre	Fehily	National Transplant Centre	Italy
Donna	Harkin	Irish Medicines Board	Ireland
Chris	O'Toole	Human Fertilisation and Embryology Authority	United Kingdom
Ann	Pariente-Khayat	Agence de la Biomedecine	France
Carolina	Stylianou	Ministry of Health	Cyprus
Sinead	Masterson	Irish Medicines Board	Ireland
Patrick	Costello	Irish Medicines Board	Ireland
Victoria	Gauden	Human Tissue Authority	United Kingdom
Fewzi	Teskrat	Agence Nationale de Sécurité des Médicaments et des Produits de Santé	France
Johann	Kurz	Ministry of Health	Austria
Ioana-Raluka	Siska	European Commission	Belgium
Angelo	Ghirardini	National Transplant Centre	Italy

CHAPTER 2: THE E-LEARNING MODULE

Aims and Objectives

The aim of the e-learning module was to provide participants with background information and theory which would be applied during the residential course. The e-learning module was to include:

- Papers describing the rationale and practical application of different methods of investigation and problem solving;
- Published examples of different incidents and how they were investigated;
- Data relating to SAR/E in the EU and in particular sectors: ART, haematopoietic stem celL transplantation, tissues for transplantation etc.
- A forum for the discussion of real cases;
- All reports and guidance produced by the project particularly that produced in WP7.

The programme of the e-learning module is shown at Appendix 1 to this chapter.

Week 1

Vigilance and Surveillance: History, Legislative Requirements and Examples from the Professional Societies:

The aim of this week was to allow participants to get to know each other and to become familiar with the e-learning platform. In addition, an overview of the History of Vigilance and Reporting Systems, their origins in the Aviation Industry and their development from Haemovigilance to Biovigilance was provided. An example of a reporting system from the Professional Societies, in this case the SEAR/SPEAR Reporting System of the World Marrow Donor Association (WMDA) was also provided. The Legislative Requirements (in the form of the Directives) and the SARE Annual Reporting form, with the current version of the Common Approach document, was also reviewed.

Participants were requested to read the articles provided in relation to the history of vigilance and surveillance, to delve into the WMDA Reporting System by reading the documents provided and visiting the WMDA website for further information including standard operating procedures relating to the operation of the system. Participants were also requested to ensure they were familiar with the legislative requirements relating to Vigilance and Surveillance including the SARE Annual Report and Common Approach Document. Finally, participants were required to complete an assignment which analysed the strengths and weaknesses of the Vigilance and Surveillance System in place for Tissues and Cells in respective competent authorities.

Week 2

The EUSTITE Tools, their use and their adaption for ART:

The aim of this week was to allow participants to become more familiar with the EUSTITE Tools (for assessing SARE associated with non-ART Tissues and Cells) and the Tools which have been adapted during the SOHO V&S Project for assessing SARE associated with ART. A number of background documents which led to the development of the EUSTITE Tools, the EUSTITE Tools in their original format and the guidance document (including Tools) which was developed during the SOHO V&S Project for ART were provided for reference.

Participants were requested to read the background documents that were provided in relation to the Vigilance and Surveillance Work undertaken during the EUSTITE Project and also Deliverable 11 (of the EUSTITE Project) which led to the work being undertaken in the SOHO V&S Project. The participants were also required to become familiar with the EUSTITE Tools and their use. A presentation on the tools and their use, including worked examples was provided. Finally participants were required to complete an assignment. A document containing a number of examples of SARs and SAEs was provided. Participants were requested to apply the EUSTITE Tools and attempt the questions that were posed. These cases were then discussed at the Residential Course.

Week 3

The SOHO V&S Project: Background, Aims and Outputs to date:

The aim of this week was to become more familiar with the objectives and outputs of the SOHO V&S Project. Participants were required to review a presentation and brochure that described the SOHO V&S Project.

They were also required to:

- Review the survey results to understand the level of development of tissue and cell vigilance in the EU;
- Review the guidance document on Illegal and Fraudulent Activity and consider how this topic was addressed at their CA;
- Review the draft SOHO V&S guidance on Communication and Investigation;
- Review the draft SOHO V&S guidance for Clinical Users;

Finally, as an assignment, participants were required to complete an on-line quiz based on the outputs of the SOHO V&S Project.

Week 4

The Notify Project and Analysis of a Specific Serious Adverse Reaction or Event for discussion at Residential Course:

The aim of this week was to become more familiar with the objectives and outputs of the Notify Project and to evaluate an SAE or SAR that occurred in the participant's country or that the participant had read about in the literature.

Participants were required to review a presentation that described the Notify Project. They were also requested to review the Notify Bologna meeting report. In addition, each participant was requested to select a serious adverse reaction or a serious adverse event with which they were familiar, either from their own experience or from the literature and to analyse the incident following the template provided. The participants were then requested to upload this document on the e-learning platform and be prepared to present the case during the residential course.

Forums

Participants were able to post questions in a forum dedicated to each week's topics. The e-learning platform continues to be available to all course participants and provides a useful communication tool between CA vigilance officers in the EU for informal discussions.

List of Key Documents provided on the e-learning platform

Background Documents

Fehily D. Sullivan S. Noel L. et al. 2012 *Improving Vigilance and Surveillance for Tissues and Cells in the European Union: EUSTITE, SOHO V&S and Project NOTIFY.* Organs, Tissues and Cells vol. 15, no. 2:85-95.

Michael Cox and Mikkel Walmar. *The Challenges of Implementing European Regulations on Human Tissues and Cells*. Affairs Journal Pharma; July 16, 2007.

Global Glossary on Donation and Transplantation. World Health Organisation, Geneva, November 2009.

Week 1 Documents

The History of Vigilance and Surveillance:

Reynard, W.D., C.E. Billings, E.S. Cheaney, and R. Hardy. 1986. *The Development of the NASA Aviation Safety Reporting System*. NASA Reference Publication 1114.

An Overview of Haemovigilance by P.F.W Strengers of the International Haemovigilance Network (IHN).

R.R.P de Vries, J.C. Faber, P.F.W. Strengers. 2011. *Haemovigilance: An effective tool for improving transfusion practice*. Vox Sanguinis Volume 100, Issue 1, pages 60–67.

Strong D.M, AuBuchon J., Whitaker B, Kuehnert M.J. 1998. *Biovigilance initiatives*. *ISBT Science Series* (2008) **3** , 77–84.

D.M Strong, Debbie Seem, Gloria Taylor, Jory Parker, Darren Stewart, Matthew J. Kuehnert. 2010. *Development of a transplantation transmission sentinel network to improve safety and traceability of organ and tissues*. Cell Tissue Bank 11:335–343.

The Worldwide Expansion of Biovigilance– AABB News, October 2011.

An Example of a Reporting System from the Professional Societies (WMDA):

The following documents available from the WMDA website:

- WMDA Common Terminology for Adverse Events.
- WMDA SEAR / SPEAR Reporting System Description.
- WMDA SEAR / SPEAR Examples.
- WMDA Summary 2003 – 2010.
- WMDA SEAR Annual Report 2011.

The Legislative Requirements:

- European Directive 2004/23/EC
- European Directive 2006/17/EC
- European Directive 2006/86/EC

European Commission SARE Annual Report Form and Common Approach Document

Week 2 Documents

EUSTITE: Rome Report: Vigilance and Surveillance of human tissues and cells.

EUSTITE: Vigilance and Surveillance Pilot Report

EUSTITE: Deliverable 11: Vigilance Recommendations.

EUSTITE: Deliverable: Vigilance Tools and Guidance.

Presentation on the use of the Tools with Worked Examples.

SOHO V&S: Deliverable 5: ART Vigilance

Combined Tools Document (See Appendix 2)

Examples for Evaluation using Tools (See Appendix 3)

Week 3 Documents

SOHO V&S Project Brochure 2010.

SOHO V&S: Deliverable 4: Survey of European Vigilance Systems.

SOHO V&S: Deliverable 5: ART Vigilance.

SOHO V&S: Deliverable 7: Guidance on Illegal and Fraudulent Activity.

SOHO V&S: Deliverable:8: Guidance for Competent Authorities (Draft).

SOHO V&S: Deliverable 10: Guidance for Clinical Users (Draft).

Self-Assessment Quiz (See Appendix 4)

Week 4 Documents

Bologna Report and guidance documents. *NOTIFY. Exploring Vigilance Notification for Organs, Tissues and Cells*. Organs Tissues & Cells, 2011, November, 14, 3: Suppl.

Template for Evaluation of an SAR/SAE (See Appendix 5).

Appendix 1: Agenda for E-Learning Course

SOHO V&S Training Course

E-Learning Module

Week 1

- Getting to know each other
- Learning to use the moodle
- Review of the History of Vigilance – Haemovigilance to Biovigilance
- Vigilance - Legislative Requirements – Definitions, Directives, SARE Annual Report
- Introduction to Vigilance Systems of the Professional Societies
  WMDA – (CEARs/SPEARs)
  American Eye Bank
- Strengths / Weaknesses / Opportunities and Threats (SWOT analysis) of the vigilance and surveillance systems in place in each represented Member State – Template to be provided -Upload slides to Moodle and be prepared to present / discuss the slides during the residential course.

Week 2

- The EUSTITE Project Outputs
  - Tools and Guidance
  - Pilot Report
  - Final Recommendations
- Examples of Use of the EUSTITE Tools
- Adaption of the EUSTITE Tools for ART: SOHO V&S – Deliverable 5 – ART Tools
- Examples of the Use of the ART Tools
- Submission of Examples to Moodle

Week 3

- SOHO V&S – Background and Aims
- SOHO V&S – Project Outputs
  - General Guidance on V&S Investigation (Deliverable 8)
  - Guidance on V&S in ART (Deliverable 5)
  - Guidance on V&S in Living Donors (Deliverable 6)
  - Detection and Management of Illegal and Fraudulent Activity (Deliverable 7)
- Self-Assessment Quiz

Week 4

- The Notify Project
- Each Participant to provide a specific SAR/SAE from their own member states, their own experience or from the literature and in five slides:
    - Provide a Summary
    - Perform an evaluation by applying the EUSTITE / ART Tools and determine:
        - SAE/SAR
        - Severity
        - Imputibility
        - Impact
    - Describe the Key Points of Investigation
    - Describe the associated Communication Issues
    - Highlight the Lessons Learned
- Upload slides to Moodle and be prepared to present the slides during the residential course.

Appendix 2: The Combined Tools

SOHO V&S tool for ART investigation reports

Serious Adverse Event (SAE): In the case of assisted reproduction, any type of gamete or embryo misidentification or mix-up shall be considered to be a serious adverse event. In addition, the definition of SAE should include the total loss of germinal tissues, gametes or embryos for one cycle.

Serious Adverse Reaction (SAR): The definition of SAR should be extended to the offspring in the case of non-partner donation, only for cases of transmission of genetic diseases; *Hospitalisation for observation should be considered as non-serious.

SAEs – Criteria

Criteria for reporting SAEs
Inappropriate gametes, embryos, germinal tissues have been released for clinical use, even if not used
The event could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors
The event resulted in a mix-up of gametes or embryos
The event resulted in a loss of traceability of gametes or embryos
Contamination or cross contamination
Accidental loss of gametes, embryos, germinal tissues (*e.g.* break-down of incubators, accidental discard, manipulation errors) resulting in a total loss of chance of pregnancy for one cycle
The event could have implications for other patients or donors because of shared practices, services, supplies, critical equipment or donors

Severity (SARs)

Non serious	Mild clinical / psychological consequences. No hospitalisation. No anticipated long term consequence/disability.
Serious	- hospitalisation* or prolongation of hospitalisation and/or - persistent or significant disability or incapacity or - intervention to preclude permanent damage or - evidence of a serious transmitted infection or - birth of a child with a serious genetic disease following ART with non-partner gametes or donated embryos.
Life-threatening	- major intervention to prevent death or - evidence of a life-threatening transmissible infection or - birth of a child with a life-threatening genetic disease following ART with non-partner gametes or donated embryos.
Fatal	Death

Imputability (SARs)

NA	Insufficient data for imputability assessment
0. Excluded	Conclusive evidence beyond reasonable doubt for attributing to alternative causes than the ART process
1. Unlikely	Evidence clearly in favour of attributing to other causes than the ART process
2. Possible	Evidence is indeterminate
3. Likely,	Evidence in favour of attributing to the ART process
4. Certain	Conclusive evidence beyond reasonable doubt for attributing to the ART process

Impact (SARs and SAEs)

Step 1 –probability of recurrence

1	**Almost impossible**	Difficult to believe it could happen again
2	**Unlikely**	Not expected to happen but possible
3	**Possible**	May occur occasionally
4	**Likely**	Probable but not persistent
5	**Almost certain**	Likely to occur on many occasion

Step 2 – Consequences

Level	Impact Description	Impact on individual(s) Actual (SAR) Potential (SAE)	Impact on *ART service provision*	Impact on availability of *'reproductive cells'*
0	Insignificant	Insignificant	No affect	Insignificant
1	Minor	Non-serious	Minor damage or some procedures postponed	Partial* loss of gametes/embryos for one couple
2	Significant	Serious	Damage to system – services will be affected for short period Many procedures cancelled or postponed	Partial loss of gametes/ embryos for some couples or total loss for one couple
3	Major	Life threatening	Major damage to system – significant time needed to repair Significant no. of procedures cancelled	Partial loss of gametes/ embryos for all couples or total loss for few couples
4	Severe	Fatal	**System destroyed – need to rebuild All procedures** cancelled	**Total** loss of gametes/ embryos for all** couples

**Partial loss*: loss of embryos, gametes without disappearance of the chance of procreation for one cycle.

***Total loss*: loss of embryos, gametes with disappearance of the chance of procreation for one cycle or final loss for the couple.

Step 3 - Impact

Recurrence probability → / Consequences ↓	Almost impossible 1	Unlikely 2	Possible 3	Likely 4	Almost certain 5
Insignificant 0	0	0	0	0	0
Minor 1	1	2	3	4	5
Significant 2	2	4	6	8	10
Major 3	3	6	9	12	15
Severe 4	4	8	12	16	20

EUSTITE Vigilance tools for non-ART tissues and cells

SAE Reporting Criteria

Deviations from SOPs at any stage from donation to clinical application 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:

1. inappropriate tissues/cells have been distributed for clinical use, even if not used;

2. the event could have implications for other patients or donors because of shared practices, services, supplies or donors;

3. the event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogenic tissues or cells;

4. the event resulted in the los s of a significant quantity of unmatched allogenic tissues or cells.

SAR Severity Grading

Severity	Comments
Nil	No harm, no risk, patient not informed as there was no risk of harm
Non-serious	Mild Clinical/psychological consequences, No hospitalisation, No anticipated long term consequence/disability
Serious	Hospitalisation or prolongation of hospitalisation and/or Persistent or significant disability or incapacity Intervention to preclude permanent damage Evidence of a serious transmitted infection
Life-threatening	Major intervention to prevent death Evidence of a life-threatening transmitted infection
Death	Death

All adverse reactions in recipients that are graded as 'serious', 'life-threatening' or 'death' should be reported to CA

SAR Imputability Grading

Imputability level		Explanation
NA	Not Assessable	Insufficient data for imputability assessment
0	Excluded	Conclusive evidence before 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 a reasonable doubt for attribution to the tissues/cells

Impact (SARs and SAEs)

Step 1: Assessing likelihood of occurrence/recurrence of SARE

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 a SARE should it recur

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

Appendix 3: Examples for Application of EUSTITE / ART Tools

Example 1

In a routine audit of storage tanks the inspection shows that a straw containing two embryos is missing. Further enquiries and checks show that another straw containing three embryos for a patient with a similar name is still in the storage tank although records indicate that the embryos were implanted three months earlier. Supplementary records confirmed that the two different patients – with similar surnames - attended for treatment on the same day.

1- According to the definitions in Directive 2004/23/EC, should this case be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2- If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3- Apply the EUSTITE V&S tools to this case (all three tools if you consider it a SAR, just the Impact Tool if you consider it an SAE). Record the scores allocated.

4- Should this be reported to the Competent Authority?

Example 2

A HPC processing and storage facility reports to you that one of their liquid nitrogen tanks ran out of liquid nitrogen and all the material inside thawed out and was lost. The tank had contained autologous bone marrow collections and directed cord blood collections (collections from siblings of children with conditions that might in the future require transplantation).

1- According to the definitions in Directive 2004/23/EC, should this case be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2- If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3- Apply the EUSTITE V&S tools to this case (all three tools if you consider it a SAR, just the Impact Tool if you consider it an SAE). Record the scores allocated.

4- Should this be reported to the Competent Authority?

Example 3

A former sperm donor has contacted the responsible person at the sperm bank where he donated sperm several years previously and informed them that he has discovered that he has the genetic disorder Malignant Hyperthermia. This is an autosomal dominant condition; hence there is a 1:2 risk of his offspring having the same condition. Malignant hyperthermia is a condition associated with complications after general anaesthesia, with prior knowledge these complications can be avoided altogether and there are no other health risks. An audit of the sperm bank's records show that nine children were born following treatment with sperm from this donor.

1. According to the definitions in Directive 2004/23/EC, should this be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2. If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3. Apply the EUSTITE V&S tools to this case (all three tools if you consider it to be a SAR, just the Impact Tool if you consider it to be an SAE). Record the scores allocated.

4. Should this case be reported to the Competent Authority?

Example 4

A hospital reports to a TE that a frozen tendon recipient has developed hepatitis C infection. They can identify no other possible routes of infection other than the tendon transplant. The TE has noted that 23 irradiated bone grafts, 1 cryopreserved meniscus and 1 other frozen tendon (the tendons were not terminally sterilised) from this donor have been distributed for transplantation. The TE has begun contacting the hospitals where the other tissue grafts from the same donation were used to ask if any of the recipients have been diagnosed with HCV infection. To date, they have learned that the meniscus recipient has tested HCV positive some months earlier but that this had been considered to be associated with previous drug abuse.

1- According to the definitions in Directive 2004/23/EC, should this case be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2- If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3- Apply the EUSTITE V&S tools to this case (all three tools if you consider it a SAR, just the Impact Tool if you consider it an SAE). Record the scores allocated.

4- Should this be reported to the Competent Authority?

Example 5

Following ICSI, 8 normally injected eggs were placed in two culture dishes (4 injected eggs were placed in each dish) and 2 eggs which had been 'injured' during the procedure had been placed in a third dish to be discarded.

During the fertilisation check it was discovered that one dish contained 3 fertilised embryos and one 'failed-to-fertilise' egg and the second dish contained the 2 'injured' eggs. The TE concluded that the discarded dish must have contained the other 4 injected eggs.

The patient had a two embryo transfer but failed to conceive.

1. According to the definitions in Directive 2004/23/EC, should this case be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2. If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3. Apply the EUSTITE V&S tools to this case (all three tools if you consider it a SAR, just the Impact Tool if you consider it an SAE). Record the scores allocated.

4. Should this be reported to the Competent Authority?

Example 6

A HPC centre reports to you that a bone marrow donor suffered a massive stroke during bone marrow harvest and died. The donor was selected from an unrelated donor registry and was donating for a recipient in the USA. Investigation has shown that the donor had suffered 3 transient ischemic attacks in the previous year, a health risk that should have been detected during the donor health screening procedure and that should have excluded him from donating. The donor's family intends to take legal action against the donor registry and the hospital.

1- According to the definitions in Directive 2004/23/EC, should this case be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2- If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3- Apply the EUSTITE V&S tools to this case (all three tools if you consider it a SAR, just the Impact Tool if you consider it an SAE). Record the scores allocated.

4- Should this be reported to the Competent Authority?

Example 7

A patient, undergoing IVF treatment, contacted her clinician at the hospital, 12 hours after having her hCG injection to report that her abdomen was slightly swollen and painful. The clinician told her to drink plenty of fluids and take her normal pain relief tablets. He also advised that she should still attend the hospital for the planned egg collection the following morning. Upon attending the clinic, for her egg collection, the patient said that she was still experiencing pain and she felt slightly nauseous. The clinician told her that she had mild ovarian hyperstimulation syndrome (OHSS) but that she did not need to be hospitalised. The clinician, together with the patient, decided to proceed with the egg collection but as a precaution the clinician decided that the patient should not have any embryos transferred because a pregnancy could lead to her OHSS becoming severe. The patient proceeded to have 16 eggs collected and the resulting 12 fertilised eggs (embryos) were frozen and stored for future treatment. Four days later the patient contacted the clinician to say that she was felling much better and all the symptoms had gone.

1. According to the definitions in Directive 2004/23/EC, should this case be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2. If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3. Apply the EUSTITE V&S tools to this case (all three tools if you consider it a SAR, just the Impact Tool if you consider it an SAE). Record the scores allocated.

4. Should this be reported to the Competent Authority?

Example 8

A cryopreserved blood vessel is sent to a hospital for grafting. When the vessel is thawed in the operating theatre, it fractures into many pieces. The patient was not yet anaesthetised and the operation was postponed. The TE that supplied the graft reports this to the CA, saying that the problem was the fault of the hospital, where the thawing instructions were not followed correctly.

1- According to the definitions in Directive 2004/23/EC, should this case be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2- If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3- Apply the EUSTITE V&S tools to this case (all three tools if you consider it a SAR, just the Impact Tool if you consider it an SAE). Record the scores allocated.

4- Should this be reported to the Competent Authority?

Example 9

A TE in the UK arranged for a patient's sperm samples to be transferred to another TE in Italy for use in the treatment of the patient together with his wife. The 32 straws were placed in two goblets and loaded into a dry shipper. The shipper was then sealed using a cable tie. The dry shipper was transported to Italy using an internationally recognised specialist courier company. Upon arriving at the TE in Italy it became apparent that the dry shipper had been opened and the samples were in the process of thawing. The TE in Italy re-froze the samples but it is unknown whether their quality has been affected.

1. According to the definitions in Directive 2004/23/EC, should this case be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2. If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3. Apply the EUSTITE V&S tools to this case (all three tools if you consider it a SAR, just the Impact Tool if you consider it an SAE). Record the scores allocated.

4. Should this be reported to the Competent Authority, if so to which CA should be case be reported too?

Example 10

A TE runs a living donor femoral head procurement programme in a large number of local hospitals. A package of 3 femoral heads procured during a morning of surgery is accidentally left at room temperature over a weekend in the operating theatre. The driver who should have taken it to the TE had gone home due to illness. The femoral heads were discarded.

1- According to the definitions in Directive 2004/23/EC, should this case be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2- If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3- Apply the EUSTITE V&S tools to this case (all three tools if you consider it a SAR, just the Impact Tool if you consider it an SAE). Record the scores allocated.

4- Should this be reported to the Competent Authority?

Example 11

A TE accidentally published all of the donor records for their deceased donors on their website. The information included names, addresses, medical and behavioural history. The information was publicly available for 3 days before it was removed. The Responsible Person has been asked to resign by the hospital's Executive Board.

1- According to the definitions in Directive 2004/23/EC, should this case be defined as a Serious Adverse Event (SAE) or a Suspected Serious Adverse Reaction (SAR) or neither?

2- If you consider it to be a SAE, do you consider that it meets the criteria for reporting to the CA? If yes, which criterion? (if you consider it to be an SAR, go to question 3).

3- Apply the EUSTITE V&S tools to this case (all three tools if you consider it a SAR, just the Impact Tool if you consider it an SAE). Record the scores allocated.

4- Should this be reported to the Competent Authority?

Appendix 4: Self-Assessment Quiz

Question 1:

Directive xxxx implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. Select the missing text.

Choose one answer.

- ☐ Directive 2006/86/EC
- ☐ Directive 2004/23/EC
- ☐ Directive 2006/17/EC
- ☐ None of above

Question 2:

Root cause analysis of an SAE should include which of the following steps (more than one can be selected):

Choose at least one answer.

- ☐ a. Identification of the problem(s) that contributed to the occurrence – this could require a review meeting with relevant personnel involved.
- ☐ b. Identification and agreement on the root causes – the fundamental contributory factors which, if resolved, will eradicate or have the most significant effect on reducing likelihood of recurrence
- ☐ c. Reporting .
- ☐ d. Mapping the Information – possibly in timelines, flowcharts or a chronological narrative of the chain of events allowing the identification of any information gaps and showing contributing factors.
- ☐ e. Gathering Data – to include full details of what happened, as well as relevant policies and procedures.
- ☐ f. Analysis of the contributing factors with prioritization.

Question 3:

According to SOHO V&S Guidance on vigilance communication, in which of the following circumstances should a national rapid alert be issued:

Choose one answer.

- ☐ a. where a risk is identified that requires immediate action but has no implications outside the MS
- ☐ b. where a risk is identified that has implications for only 2 MS

- [ ] c. when the same SAE has been reported 3 times
- [ ] d. where an SAR with high severity has been reported

Question 4:

Which of the following should be reported to the CA as an SAE , according to the EUSTITE criteria (more than one can be selected):

Choose at least one answer.

- [ ] a. Recipient develops HCV after tissue transplant (suspected caused by transplant)
- [ ] b. Bacterial contamination detected in a sample taken at the cornea bank following distribution. Growth detected after transplantation – no symptoms in recipient.
- [ ] c. An unrelated bone marrow donation being transported for immediate use is left at an airport and thaws out.
- [ ] d. Equipment sterilisation failure results in discard of 150 tendons
- [ ] e. A cornea is discarded at the Tissue Establishment due to microbial contamination

Question 5:

According to EUSTITE recommendations, the birth of a child with a genetic disease following non-partner donation of gametes or embryos:

Choose one answer.

- [ ] a. Should be reported as a suspected SAE
- [ ] b. Should be reported as a suspected SAR
- [ ] c. Does not require reporting to the CA
- [ ] d. Should be reported to pharmacovigilance

Question 6:

The Outputs of the SOHOV&S project will be:

Choose one answer.

- [ ] a. recommended by the European Commission for implementation in Member States that are partners in the project
- [ ] b. provided to the European Commission and subsequently presented, if considered appropriate, to the Member States for adoption as non-mandatory good practice guidelines.
- [ ] c. mandated for full implementation in all Member States

- [ ] d. recommended by the European Commission for implementation in all Member States

Question 7:

Member States shall submit to the Commission an annual report on the notification of serious adverse reactions and events received by the competent authority. A Member State has two different competent authorities responsible for SAR/E reporting for tissues and cells, which of the following actions is not appropriate with regard to submitting the report?

Choose one answer.

- [ ] a. One CA should enter their data on the electronic form and save it without submitting; the second CA should then add their data and submit the form.
- [ ] b. One CA should send their information to the other CA which should then submit the form for the Member State
- [ ] c. Submit two separate electronic forms
- [ ] d. The CAs should organise a meeting to complete the form together

Question 8:

According to SOHO V&S Guidance on vigilance investigation, which of the following would be evidence to support or confirm imputability of a viral transmission by tissues or cells (more than one may be selected):

Choose at least one answer.

- [ ] a. the identification of the same agent in the index recipient and in donor material
- [ ] b. the identification of similar symptoms or clinical test results in other recipients of organs, tissues or cells from the same donor.
- [ ] c. positive NAT test for the virus in the recipient
- [ ] d. negative results for environmental microbial monitoring in the processing area on the day when the tissues or cells were processed

Question 9:

A SAR has occurred associated with an Advanced Therapy Medicinal Product containing extensively manipulated tissues and cells. It appears there may have been an untoward occurrence associated with procurement. Would you recommend?

Choose at least one answer.

- [ ] a. None of the above
- [ ] b. Report to pharmacovigilance only
- [ ] c. Report to either CA, having established that they will liaise and share the information

☐ d. Report to both T&C vigilance and pharmacovigilance

Question 10:

According to Deliverable 7 (Report and Guidance on Illegal and Fraudulent Activity) which of the following are key principles which should be considered by Tissues and Cells Competent Authorities in order to assist in the development or strengthening of procedures relating to IFA?

Choose at least one answer.

☐ a. The roles and responsibilities of inspectors and enforcement officers should be clearly set out.

☐ b. Rapid regulatory action must proceed independently of enforcement action where the safety of donors or patients is concerned.

☐ c. CAs should give a second chance to a designated responsible person who may have been previously implicated in a suspected IFA.

☐ d. Advantage should be taken of the experience of inspectors of IFA in other fields (medicines, blood, etc.).

☐ e. Specific training to inspectors and enforcement officers to deal with suspected IFA and if necessary interaction with the media.

Question 11:

Embryos were mistakenly transferred into a Petri dish (unused) labelled for another couple. The error was detected (following distribution) but prior to embryo transfer. Does this require reporting to the CA?

Choose one answer.

○ a. Yes

○ b. No

Question 12:

What does RATC stand for?

Choose one answer.

○ a. Rapid Alert to Competent Authority

○ b. Rapid Alert Tissues Cells

○ c. Really attractive tissues and cells

○ d. Rapid Alert To Commission

Question 13:

According to Deliverable 7 (Report and Guidance on Illegal and Fraudulent Activity) which of the following criticality criteria should be considered by a Tissues and Cells Competent Authority when assessing IFA?

Choose at least one answer.

- [ ] a. Evidence of attempts to conceal information.
- [ ] b. Publication of reports of the IFA in the Media.
- [ ] c. Consequences of the suspected IFA.
- [ ] d. Scale and duration of IFA.
- [ ] e. Evidence of deceit or falsification.

Question 14:

You are based at the national CA responsible for ART and have been made aware of an incident occurring at an ART facility. The incident has resulted in the loss of two embryos and the patient requires a new cycle of IVF. The incident is linked to an incubator failure. What are your reporting recommendations? (more than one answer can be selected)

Choose at least one answer.

- [ ] a. Submit report to the ART CA only
- [ ] b. Submit report to the Medical Device CA only
- [ ] c. Report to either CA, having established that they will liaise and share the information
- [ ] d. Submit reports to both the ART and Medical Devices CAs

Question 15:

In assessing an SAR report which of the following tools would you recommend using:

Choose one answer.

- [ ] a. The Severity Grading Tool
- [ ] b. The Imputability Grading Tool
- [ ] c. The Impact Assessment Tool
- [ ] d. All of the above

Question 16:

The term Direct Use (Art. 1 of the Directive 2006/17/EC) is not applicable to reproductive cells in the following: (more than one answer can be selected)

Choose at least one answer.

- a. Reproductive cells that are being cultured
- b. Reproductive cells that are being processed
- c. Reproductive cells that are donated and used without banking
- d. Reproductive cells that are being banked or stored
- e. All of the above

Question 17:

A bacterial contamination is detected in an allogeneic tissue/cell sample. The donor has been excluded as the source. Which of the following actions do you consider appropriate? (more than one answer can be selected)

Choose at least one answer.

- a. Tissues or cells processed in the same processing area, before and after the implicated tissues or cells should be tested.
- b. The environmental monitoring results on the day of processing should be reviewed
- c. The personnel who processed the tissues or cells should be suspended and tested for the agent
- d. Any reagent or additive batches used in the implicated procurement or preparation process should be tested.

Appendix 5: Assignment: Template for Evaluation of an SARE the participant has managed or read about (for discussion later at the residential course)

Note: This template may used and modified by trainees when evaluating an SARE as part of training.

1. Description of SARE:
   Describe what happened and how the incident was detected?

2. Application of the EUSTITE/SOHO V&S Tools:
   What are the reporting criteria for the SAE?
   Describe and rationalize the Severity and Imputability for SARs.
   Perform and justify the Impact Assessment for SAEs.

3. Key Points of Investigation:
   Who and How?
   Use of Experts / Specialist Laboratories?
   Collaboration with enforcement officers or others?

4. Relevant communication Issues:
   Urgent need for communication?
   Communication to who?
   Need for a rapid alert?
   Media Interest?
   Other Vigilance Systems affected?

5. Key Learning Points from the Case:
   Who and How?
   Use of Experts / Specialist Laboratories?
   Collaboration with enforcement officers or others?

CHAPTER 3: THE RESIDENTIAL COURSE

Aims and Objectives

The aim of the residential module was to apply the guidance and theory provided during the e-learning module to a series of case studies in working groups. Throughout the residential modules:

- Experience was presented from the tissues and cells and related fields;
- Techniques for root cause analysis and other methods of investigation were applied in practice;
- Approaches to dealing with illegal and fraudulent activity were compared and evaluated.

The agenda utilized during the second training course in Rome is provided here as Appendix 1 to this chapter. This agenda may be adapted and modified to suit the needs of individual member states or competent authorities. A brief description of each day is provided below for context.

Day 1

At the beginning of Day 1, a brief presentation on the SOHO V&S Project was provided followed by the introduction of participants and feedback from the e-learning module. Quiz answers were confirmed during this session.

In part 2, a number of participants were selected to present the strengths and weaknesses analysis that they had completed as their assignment during week 1 of the e-learning module. The objectives of the residential course and the anticipated learning outcomes were then discussed in order to see if some of the issues raised in the analysis could be addressed.

In part 3, the application of the V&S Tools was assessed. Feedback was provided in relation to the cases provided as part of Assignment 2 in the e-learning module and three new cases were provided for scoring and discussion (Case Studies 1, 2 &3 in Appendix 2).

Day 2

Part 1 of Day 2 focused on SARE Investigation. Chapter 6 of the SOHO V&S draft Guidance for Competent Authorities (Deliverable 8) was the main reference document used for this section. Four case studies (4,5,6 &7 in Appendix 2) were provided to the participants who divided into groups to discuss. This was followed by a plenary discussion.

Part 2 focused on SARE Communication with Chapter 7 of the draft SOHO V&S Guidance for Competent Authorities (Deliverable 8) being the main reference document. Three case studies (8, 9 & 10 Appendix 2) were provided to participants who were again divided into groups to discuss. This was again followed by a plenary discussion. The use of the European Commission RATC Platform for rapid alerts and the Eurocet Platform for vigilance communication were then presented and discussed.

Part 3 of Day 2 focused on SARE Annual Reporting to the European Commission. This included discussion on the SARE Annual Report Template and Common Approach Document. Individual Member State Reports were presented and approaches to completion of the Annual Report discussed. The methods for Annual Report feedback and dissemination were also discussed.

Part 4 involved the participants dividing into two groups, with one group working on designing a vigilance communication strategy for competent authorities and the other designing a one day seminar that a Competent Authority could run to promote tissue and cell vigilance among stakeholders. The main points from each of these discussion groups were documented and are included in Appendix 3 and Appendix 4, respectively.

Day 3

Part 1 of Day 3 focused on the presentation of selected difficult cases which were submitted by participants during week 4 of the e-learning module. This included a discussion on how the cases may have been handled differently based on lessons learned during course. The course finished with an evaluation exercise, presentation of certificates of attendance and a discussion on the summary of course outcomes / learnings and priorities going forward.

Appendix 1: Agenda for Residential Course

SOHO V&S Training Course

Day1

Part 1

Summary of SOHO V&S Project

Introduction of participants and tutors

E-Learning Feedback - General discussion (including quiz answers)

Part 2

Strengths and Weaknesses of Vigilance and Surveillance at my Competent Authority

- Presentation of Strengths and Weaknesses Analysis – selected participants to present their work.
- Summary of Strengths and Weaknesses Analysis
- Objectives of Residential Course & Learning Outcomes
  (How can we address some of the issues raised in the Strengths and Weaknesses analysis?)

Part 3

Review of E-learning Assignment 2 – Applying the V&S tools - results and discussion
(To include discussion and scoring of 3 new cases)

Day 2

Part 1

SARE Investigation

Introduction and Presentation of Case Studies:

- Infectious Disease Transmission
- SAE – ART
- Processing – HPC
- ART Genetic

Divide into Groups and Discuss Case Studies

Plenary Discussion

Part 2

SARE Communication (to include Illegal and Fraudulent Activity (IFA))

Introduction and Presentation of Case Studies:

- Communication within a MS

- European – RATC
- IFA

Divide into Groups and Discuss Case Studies

Plenary Discussion

Presentation of the new **EC RATC** procedure and electronic platform
Presentation of the **Eurocet** platform and its role in Vigilance communication

Part 3

SARE Annual Reporting to the European Commission

- Common Approach Document
- Presentation of individual MS reports submitted in 2011 and in 2012
- Annual report feedback and dissemination – how should MS achieve this?
- General Discussion of key issues identified

Part 4

Promoting Vigilance at MS level

Participants will work in 2 groups

Group1: Design a vigilance communication strategy for a CA

Group 2: Design a one day seminar that a CA could run to promote tissue and cell vigilance among stakeholders

Feedback and Discussion

The outputs of this session will be provided to all participants after the course for adaptation and use in their own MS.

Day 3

Part 1

Presentation of Selected Difficult Cases from e-learning Week 4

Followed by open plenary discussion – including discussion of how the presented cases might be handled differently based on the lessons learned during the course.

Part 2

Close of Course:
Summary of Course Outcomes / Learnings
Priorities going forward and closing remarks

Course Evaluation
Presentations of Certificates

Appendix 2: Case Studies Used during Residential Course

Note: The notes used by the facilitators during these courses have been provided for reference. However, participants were allowed to discuss the case before any of these points were raised.

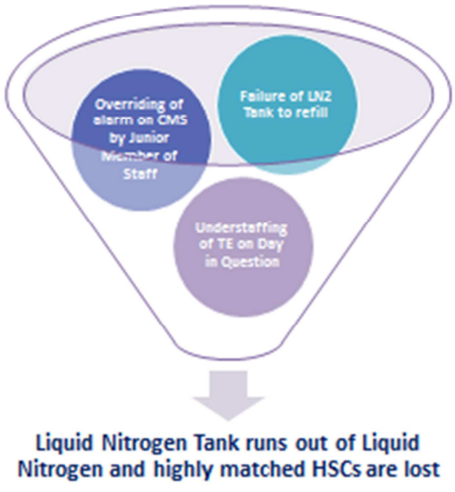
Case Study 1: Subject Area: Haemopoietic Stem Cells

Case background:

A HPC processing and storage facility reports to you that one of their liquid nitrogen tanks ran out of liquid nitrogen and all the material inside thawed out and was lost. The tank had contained autologous bone marrow and directed cord blood collections (collections from siblings of children with conditions that might in the future require transplantation).

Investigation revealed that the liquid nitrogen tank, which was connected by an automatic link to an external fill vessel, failed to fill to the required level on a number of occasions over a period of a few days. Although the tank was connected to a 24 hour alarm system which continuously monitored the temperature in the tank, the alarms were overridden by a junior member of staff in this particular case. The liquid nitrogen tank was not physically checked on the days prior to the discovery of the issue.

On the days in question staffing levels in the laboratory where stretched. The Tissue Establishment staff were assisting with a number of transplants, were performing HPC Processing and a member of staff was on sick-leave. The TE indicated that this may have led to distractions on the days in question.



SOHO V&S Vigilance Training Course Case 1

Key question(s):

Does this require reporting to the CA and if so is it an SAE or SAR?

Who else should be notified?

If you think this is an SAE, check if the reporting criteria apply and apply the impact matrix.

If you think this is an SAR, apply the severity, imputability and impact matrix.

What factors were involved in causing the event and how can they be addressed?

What corrective and preventative actions would you expect the TE to implement in this case?

According to the EU Annual Reporting SARE criteria, what specification would you apply to this case report:

If an SAE, was it due to a deviation in = **Procurement / Testing / Transport / Processing / Storage / Distribution / Materials / Others**

Which specification of SAE would you apply? = **T&C Defect / Equipment / Human Error / Other**

If an SAR, describe the type of serious adverse reaction.

Notes for Facilitators

Storage Tanks should be linked to a continuous monitoring and alarm system which monitors bothe temperature and the level of liquid nitorgen required to maintain the vapour phase of liquid nitrogen for storage of HSCs.

The data from the continuous monitoring system should be reviewed and signed off by a senior member of staff in oder to identify trends or issues and alarm events.

Equipment such as the tanks should be checked routinely and serviced on a regular basis – where there is an automatic re-fill process – this should be regularly checked.

It should not be possible for junior members of staff to override an alarm on a continuous monitoring system. There should be appropriate controls around this.

Provisions for back up and scheduling of transplants / procedures should be available where there are staff shortages.

Eustite Tools

Impact assessment. Imputability (N/A for this SAE)

Likelihood of recurrence: 3 (this could be reduced depending on CAPA)

Consequences: 3 (major 'life-threatening')

Impact: 9

SAE reporting criteria 4 - The event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells.

In this case, the SAE should lead to a root cause analysis with corrective measures and changes to practice and SOPs as appropriate.

Notification:

Others to be notified; The clinical consultants should be informed of the loss of the T&C as this has implications for the treatment plan and to facilitate liaison with the patients concerned. Consider liaison with Medical Device Section regarding the failure of equipment if appropriate.

Specification of the SAE

Due to a deviation in = **Storage**

Specification **=** this could cause some discussion as several influencing factors, depending on the findings of the root cause analysis

Equipment – The liquid nitrogen connection link did not function. Discussion should include the adequacy of the systems in place for the routine maintenance requirements etc. Check if other reports have highlighted issues of a similar nature with this particular equipment. Consider liaison with Medical Device section if appropriate. RATC would only be considered if multiple reports highlight an issue with this particular piece of equipment.

Human Error; Alarm was overridden and Tank was not checked.

Other; System error, as should address poor staffing levels and excessive workload on the days in question.

T&C defect- N/A

While this event could fall witin several specifications categories for the purpose of collating the data for annual report the dominant specification selected is ;

Deviation –Storage / Specification- Equipment

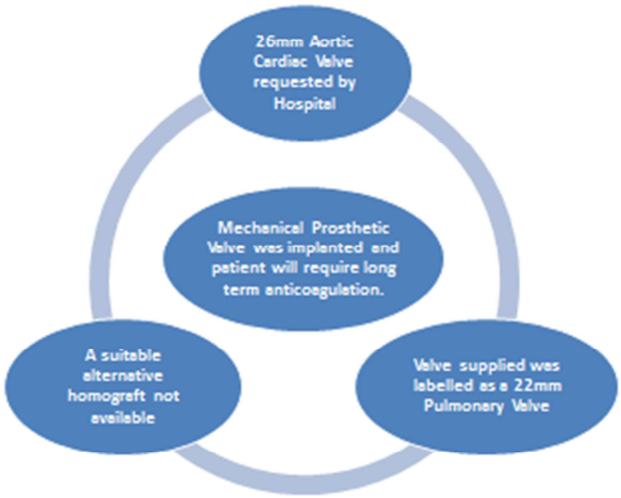
Case Study 2: Subject Area: Heart Valves

Case background:

A cardiac valve is sent from a TE to a hospital. A 26mm Aortic Valve was requested. The patient was anaesthetised in the operating theatre. Upon opening the packaging, it was noted that the valve supplied which was labelled as a 26mm Aortic Valve was in fact a 22mm Pulmonary Valve. A suitable alternative homograft (human aortic) valve was not available and as a result a mechanical prosthetic valve was implanted. The patient will require long-term anticoagulation therapy as a result of using a mechanical heart valve.

From information received it would appear that the aortic valve and pulmonary valve were mixed up at procurement.

The intended recipient is a woman of childbearing age. A mechanical valve is not the ideal choice as clinical management during pregnancy will be further complicated because of the need for anti-coagulation medication.



SOHO V&S Vigilance Training Course Case 2

Key question(s):

Does this require reporting to the CA and if so is it an SAE or SAR?

If an alternative homograft was available on time to continue the operation, would this case require reporting to the CA and if so would it be considered an SAE or SAR?

Apply the EUSTITE V&S tools to this case as described and give the scores and the reporting criteria.

Could there be implications for any other T&C / TE / Hospital?

What factors could have contributed to the incident and how should they be addressed?

In the Annual SARE Report to the EC which category would this fit in?

Notes for Facilitators

SAR reporting criteria - Other Reaction

Eustite tools - (h) Aborted procedure involving unnecessary exposure to risk

e.g. wrong tissue supplied discovered after patient is anaesthetised and

the surgical procedure has begun (undue risk)

Eustite Tools

Impact assessment. Imputability (3) Definite certain

Liklihood of recurrence; (2) Unlikely but possible

Consequence / Severity grading : (2) Serious

Impact: 4

If an alternative homograft was available on time to continue surgery this would be considered an SAE

- Inappropriate T&C have been distributed for clinical use, even if not used.

Follow-up required with regard to the partner valve (aortic valve) which presumably remains in storage mislabelled as a pulmonary valve.

F*or the purpose of collating the data for annual report;*

SAR ; Other serious reaction

Case Study 3: Subject Area: Assisted Reproduction Technology

Case Background:

Two couples received fertility treatment at a London hospital on the same day.

COUPLE A: 16 eggs were obtained at egg recovery for this couple. 10 of these were injected in a single sitting and placed in a labelled dish in a personalised compartment within the incubator.

(The remaining 6 eggs were to be injected in a 2nd sitting.)

COUPLE B:6 eggs were obtained at egg recovery for this couple. These were injected and placed in a labelled dish in a personalised compartment within the incubator.

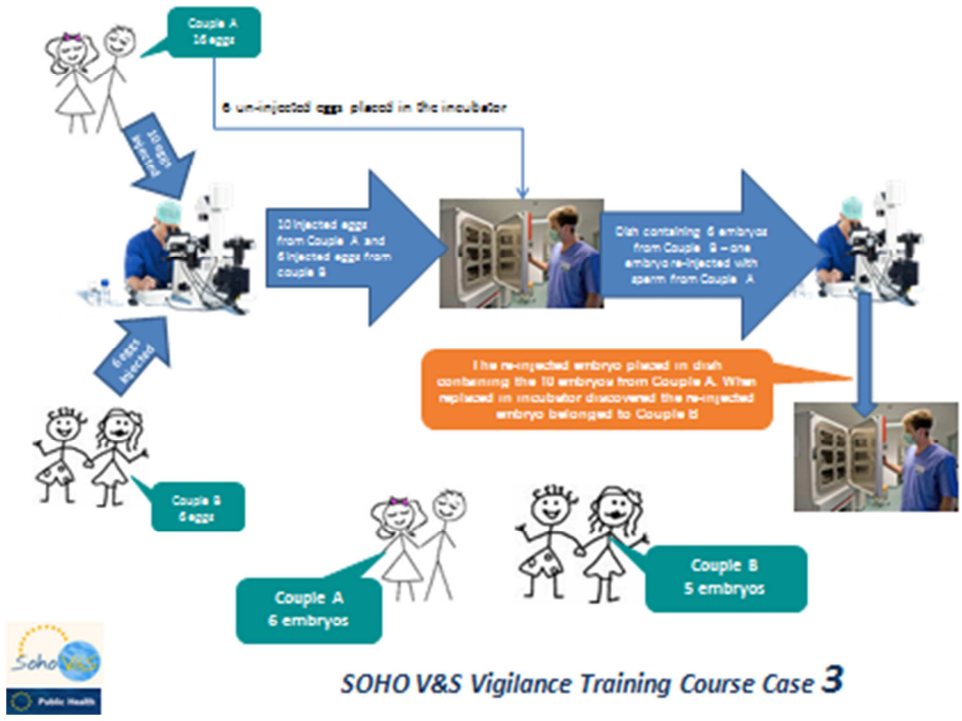
Later in the afternoon one of these six injected eggs, already injected appropriately with the sperm of Couple B, was removed from its dish in error and injected for a 2nd time with the sperm of another couple (Couple A).

This egg, after its second injection, was then added to the dish containing the first batch (10 of 16 eggs) of Couple A. These eggs had already been injected appropriately with Couple A's sperm. When this dish was returned to the incubator the error was noted.

It is impossible to be certain which of the 11 eggs in this dish belong to which couple.

The remaining 6 eggs from Couple A were correctly injected with the sperm from Couple A. Four embryos developed and two were used in the provision of treatment services for this couple.

The remaining 6 eggs for Couple B were injected appropriately with the sperm from Couple B. All failed to fertilise so no embryos were available for the treatment of this couple.



Key question(s):

Is this an SAE or SAR?

Is it reportable to the Competent Authority? (If yes, which criterion?)

Apply the SOHO V&S ART Tools to this case.

Notes for Facilitators

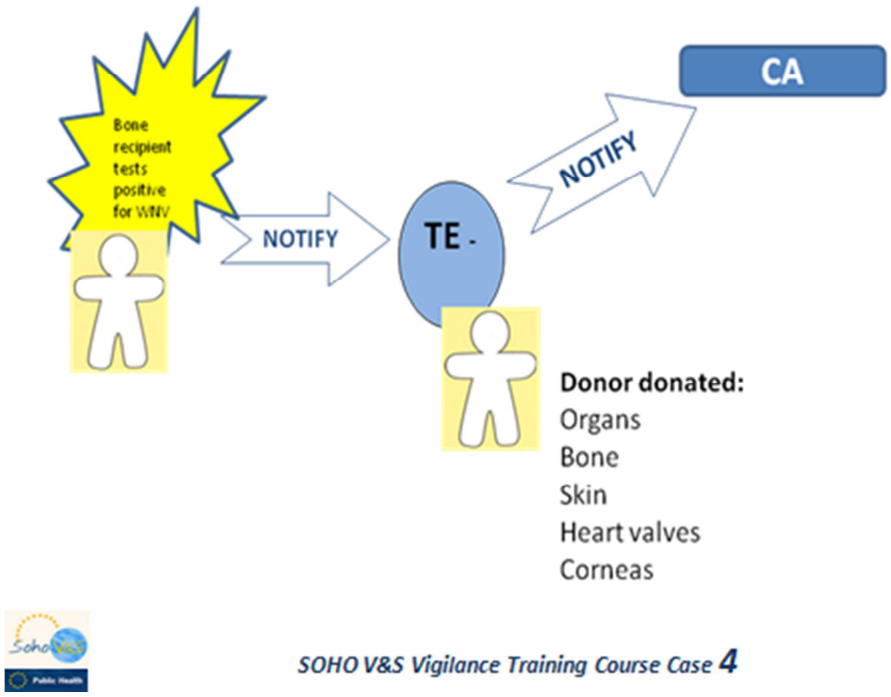
1. This is an SAE.
2. Yes – reportable because of definite mix-up
3. Note the total loss of chance of pregnancy for one couple
4. The issues / areas of practice to be looked at include:
    a. The processes / procedures in place to ensure traceability of gametes and embryos including witnessing of procedures;
    b. Any audits carried out by the TE to ensure all staff were following these processes / procedures;
    c. Training and competence assessment of staff;
5. The Competent Authority should play an active role in the investigation.

Case Study 4: Subject Area: SARE Investigation – Suspected Infectious Transmission

Case background:

A hospital has reported to a TE that one of its bone allograft recipients (large frozen femoral bone graft) developed symptoms suggestive of West Nile Virus infection and tested positive by NAT two weeks after transplant. The hospital is not in an area where WNV is endemic. The TE reported this to you as a suspected SAR with severity 'life-threatening' and imputability 2 (possible). The TE reports that the donor also donated organs, corneas, skin and heart valves.

Two weeks later they send you a final report with the details of their investigation, their conclusions and the actions they have taken.



Key question(s):

List the key steps that you would expect to find in their investigation report.
What role do you think the CA might have had in this investigation?

Notes for Facilitators:

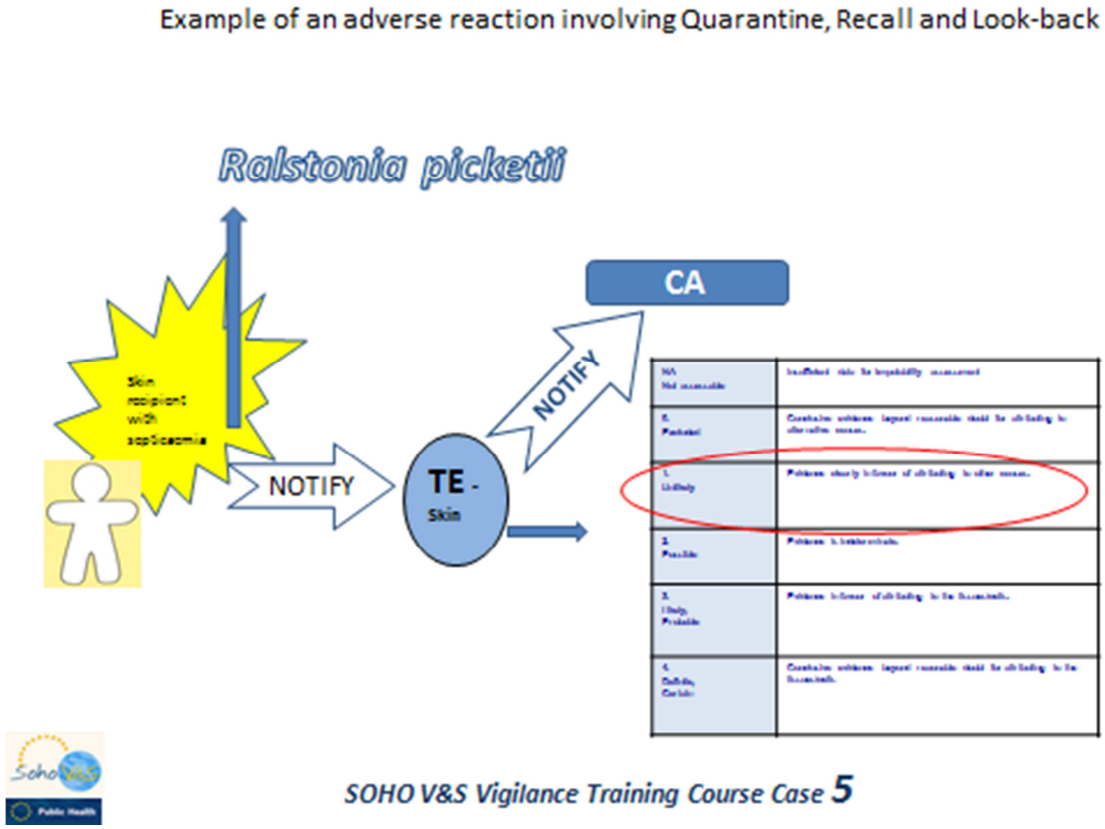
- What laboratory conducted testing for WNV? – was it specialist for this agent? - approved in some way by the CA? Should the CA have helped the TE to identify the most appropriate laboratory?
- Was there a donor archive serum or cell sample available for testing? (not a requirement of the directives but invaluable for these types of investigations) – do MS have national guidelines to address this?
- The other tissue recipients and the organ recipients should be followed up first to see if they have evidence of infection
- Have other cases of transmission of this agent been reported before? If so, are latency and alerting symptoms similar to this case?
- The final report should include a revised assessment of imputability

Case Study 5: Subject Area: SARE Investigation – Bacterial Transmission by Skin?

Case background:

A hospital has reported to a TE that one of its paediatric burns patients has developed severe septicaemia. They have isolated Ralstonia pickettii from the patient's blood. The hospital Burns unit has questioned whether the source may be 500 cm^2 of cryopreserved allogeneic skin that was provided by a skin bank and grafted on the patient. The skin bank has assessed the imputability as 'unlikely' as they consider this is most likely to be a common nosocomial infection very unlikely to have come from the donor.

The tissue bank followed up on the 2 other recipients of skin from the same donor and found no reactions in those patients. They also reviewed the blood culture results of the donor from the hospital records – they were negative. On this basis they closed the SAR.



Key question(s):

Would you agree to close this SAR or is further investigation needed?
If yes – what is your rationale?
If no, what further steps would you expect the TE/hospital to carry out?

Notes for Facilitators:

- To begin with, a literature should be conducted on this bacterium – this will reveal that it is often a contaminant in industrial production of solutions such as sterile water, detergents etc. This is why it is a common nosocomial infection
- The focus here should not be on the donor but on the processing environment and processing solutions/reagents
- The investigation should include follow-up not of other recipients from the same donor but of other skin donations processed before and after this one and of the recipients of those donations.
- This bacterium would not cause serious problems in a healthy patient but can be fatal in an immune-compromised one such as burned patient so finding other recipients who have not been infected is not relevant unless they are immunosuppressed (as burned patients are).
- A tissue bank in the US experienced contamination with this bacterium from a commercially purchased detergent. We will show how it was finally detected and what the outcomes were.

Case Study 6: Subject Area: SARE Investigation – possible misidentification of embryos

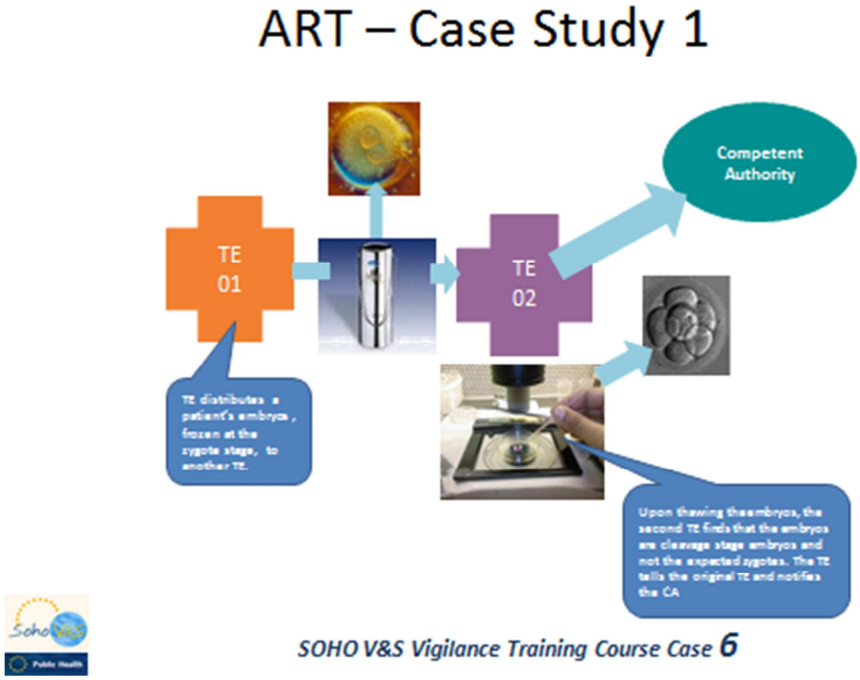
Case Background:

A couple received fertility treatment at a hospital in London. The treatment was successful and the couple had a daughter. During the treatment 6 zygotes (one cell embryos) were frozen in three separate straws and cryopreserved for future use. Two years later the couple relocated to Edinburgh and asked the fertility centre (TE1) to transfer the cryopreserved zygotes to a hospital in Edinburgh (TE2) so they could undergo a further treatment cycle.

The London hospital removed the zygotes from storage and placed them in a transport liquid nitrogen dewar and, using a national courier service, sent the zygotes to the fertility centre in Edinburgh. TE1 also sent the laboratory data sheets, detailing information about the 6 zygotes and the methods used to freeze them. TE1 also sent a copy of its standard operating procedure for thawing zygotes.

A senior embryologist, at the Edinburgh fertility centre, received the transport dewar and checked the accompanying documentation. All the information was correct. A second embryologist also checked and confirmed that the information of the straws, containing the zygotes, was correct as was the documentation. The zygotes were placed in storage.

Two months later, the couple attended the Fertility centre for treatment. The day prior to the embryo transfer, an embryologist, witnessed by a second embryologist, removed a straw from the dewar and began the process of thawing the zygotes. However the embryologist noted the embryos were at the six cell stage of development and not at the one cell stage as expected. The embryos were re-frozen and the embryologist alerted the fertility centre in London and also reported the incident to the Competent Authority in the UK.



Key Question (s):

Which tissue establishment is responsible for notifying the Competent Authority?

What areas of practice should be examined as part of the investigation?

What role should the Competent Authority play in the investigation?

If you were the vigilance officer investigating this SAE, what is the first 'why' question you would ask the staff at TE1? (see 5 Whys method of Root Cause Analysis in the SOHO V&S Investigation Guidance)

Notes for Facilitators:

- The first tissue establishment should also report this SAE to the Competent Authority
- The issues / areas of practice to be looked at include:
    - The number of patients who had zygotes or embryos cryopreserved on the same day as the couple mentioned;
    - The processes / procedures in place to ensure traceability of gametes and embryos including witnessing of procedures such has the labelling of straws;
    - Any audits carried out by TE1 to ensure all staff were following these processes / procedures;
    - Training and competence assessment of staff;
    - An audit of all cryopreserved gametes and embryos to determine whether this SAE could have occurred before.
- The Competent Authority should play an active role in the investigation.
- The first 'why' question could be:
    - Why didn't staff follow the TE's SOPs for ensuring traceability?
    - Why didn't a second members of staff check that the couple's zygotes were being placed in a straw correctly labelled with their unique identifying information?
- The final investigation report should include a revised impact score depending on whether this was an isolated incident involving two identifiable sets of patients or whether further patients could be affected.

Case Study 7: Subject Area: ART – Genetic Transmission

Case background:

A Competent Authority in *Country A* received a report from an ART clinic indicating that a child had been born using assisted reproduction with an extremely rare autosomal recessive condition.

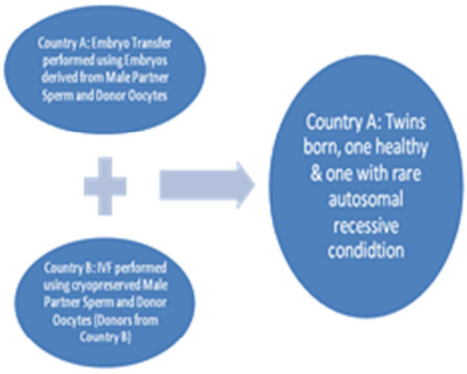
The report indicated that the couple (to whom this child had been born) decided to avail of the donor egg programme operated at the clinic. The female had an embryo transfer in County A using embryos which were derived of her partner's sperm and donor oocytes. The IVF procedure had been performed at an ART Clinic in Country B i.e. a sample of the partners sperm was sent to the clinic in Country B. The embryos were created using donor oocytes retrieved by the clinic in Country B and returned cryopreserved to the clinic in Country A for culture and transfer.

Both clinics are in compliance with the Tissues and Cells Directive and are authorised by the relevant competent authorities in their MS and have a detailed service level agreement in place.

The Mother of the child had contacted the treating ART clinic (country A) to advise that she had delivered twins. One healthy child and one who unfortunately was very ill in an Intensive Care Unit.

The TE notified the CA in (country A) and the clinic where the oocytes had been retrieved (country B). The only TE supplied with oocytes fom the implicated donor was the one who issued the notification in country A.

One other couple in country A had received oocytes from this donor previously and had a healthy baby. The donor was blocked from further donation immediately following the notification and a recall performed of frozen oocytes held at the TE in country A. The Mother was advised and agreed to tell the twins' doctor they were conceived using donor oocytes.



SOHO V&S Vigilance Training Course Case 7

Key question(s):

Does this require reporting to the CA and if so is it an SAE or SAR?
Apply the EUSTITE V&S tools to this case as described and give the scores and the reporting criteria.
What are the key elements that should be included in the investigation?
Could there be implications for others and discuss the communication required.
What factors could have contributed to the incident?

Notes for Facilitators:

Outcome:

Both TEs communicated (countries A and B) and decided on the the use of a Specialist Genetic Centre (in another MS). It was established that both the male partner and the oocyte donor were positive for this rare recessive trait. 1 in 1,000,000 chance of this occurring naturally. Genetic assessment preformed and recommendations communicated (possibility of carrier status for other offspring of this oocyte donor, but unlikely to meet someone in the future with same mutation and have offspring).

EUSTITE Tools:

SAR; *SOHO WP5 - the birth of a child with a genetic disease following non-partner donation of gametes or embryos shoud be reported as an SAR*
Severity : 3 major life-threatening if in ICU?
Imputability : 4 (when diagnosis confirmed)
Probability of recurrence : 2 (in view of rarity of this specific disease) – although higher until the ooctyes that are available from that donor are quarantined?
Impact : 6 (yellow) or higher if the condition is life-threatening

Key points of investigation:

To establish imputability -
Confirmation of diagnosis for affected child and possibility of a genetic link
Confirmation that donor was a carrier for this disease
Review of donor history confirmed the donor was screened appropriately
Donor was blocked from further donation immediately following the notification.
Recall performed (Further use of oocytes based on recommendations of expert advice and Genetic assessment / possibility of carrier status for other offspring of this oocyte donor, but unlikely to meet someone in the future with same mutation and have offspring)
Confirmation that the male partner also positive for this recessive trait
Check other recipients of oocytes from this donor - appropriate follow-up

Communication:

TEs in both countries should communicate and keep CAs inofrmed. CAs of both countries shoul liaise.
Communication required to all centres supplied with oocytes (from the country of donor origin). (RATC not required but could be considered if multiple sites in several countries have been supplied with T&C from the implicated donor)
CAs should check that risk was communicated to all affected ART centres nationally
To all affected couples
To oocyte donor (has own offspring)

Key learning points:

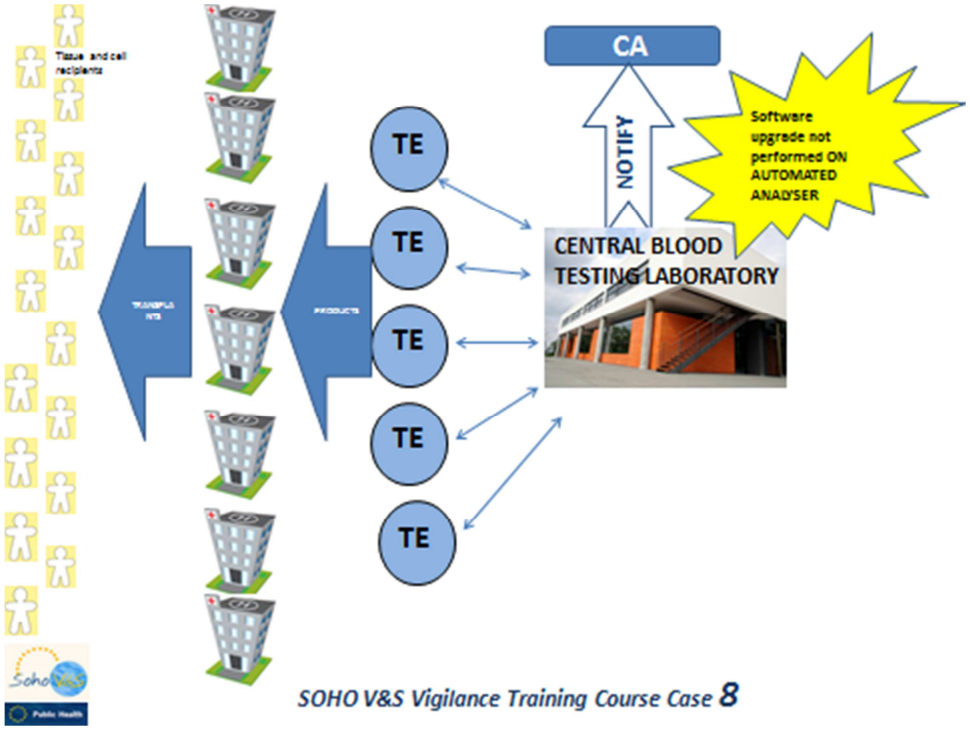
Cross border managment of SARE is complex and requires mutual cooperation
Importance of communication between all relevant parties
Couples should be encouraged to share information with healthcare professionals about the method of conception. Importance of access to clinical genetic expertise.

Case Study 8: Subject Area: SARE Communication – A Donor Testing Case.

Case Background:

Your Competent Authority for Tissues & Cells is contacted by a testing centre that carries out testing of blood samples for infectious markers for 5 authorised tissue establishments in your Member State. It is established that an automated analyzer used to test donor samples for the TEs was inadvertently not included in the latest significant software update by the equipment manufacturer. The testing centre considers the present status to be critical, as the confidence in analyses performed in the past 3 months has not yet been assessed.

An unhappy member of staff in the testing laboratory has given this news to a journalist who has published the story. A number of enquiries from the media and from individual tissue and cell recipients have been received at your centre.



Key question(s):

Define the list of issues to be investigated further.

Consider the communication issues. Who should be informed? Who should manage this?

Notes for Facilitators:

Responses to 1:

- Perform a risk assessment to evaluate potential or theoretical impact – you would need to involve technical experts in testing and from the software company,
- Should this be performed by the testing lab with some CA involvement?
- Prepare a list of clinics/other parties which sent blood samples for testing in past two months,
- Contact equipment manufacturer to review direct impact to test results circulated.
- Should this be before the risk assessment?
- Implement backup systems to be able to continue services to clinics/other parties,

Responses to 2:

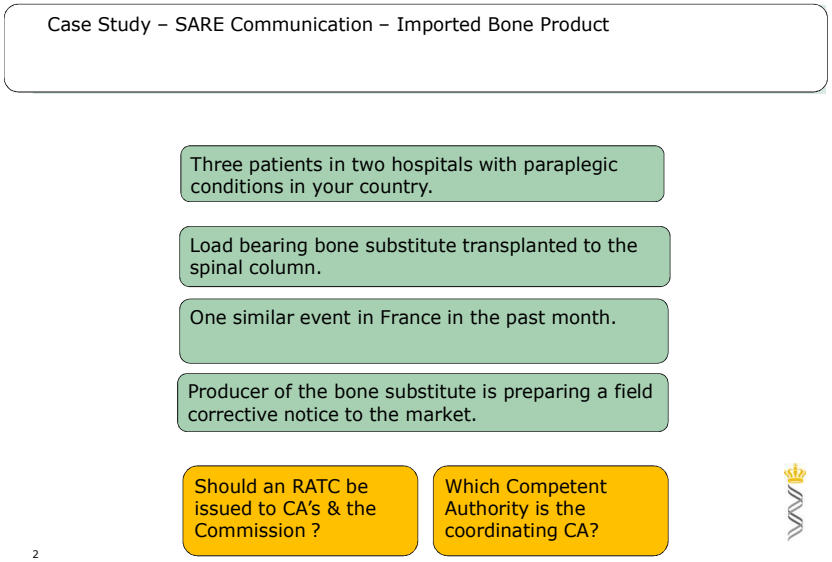
- Prepare information advice for the clinics/other parties who have used the services o the laboratory based on risk assessment.
- Ensure that there is a communications professional who deals with public enquiries providing information that is as accurate as possible.
- The test results performed by the test centre may have been be related to the release of :
  Human tissues/cells for therapeutic use,
  Processed blood and their components for transfusion,
  Medicinal products derived from human origin (insulin).
  In addition the change in software may have had a significant impact on the performance of the test kit, under the jurisdiction of the device sector.
- So a short summary should be sent to medical devices, medicinal and blood colleagues at your national level. To advise of known information and to inform them additional information will follow soon.

Case Study 9: Subject Area: SARE Communication – Imported Bone Product.

Case background:

Two hospitals in your country report three patients with paraplegic conditions have been sent to the critical care unit after the transplantation of a load bearing human bone graft in the spinal column. Your investigation of the product, imported and distributed by a Danish tissue establishment, establishes there has been one other similar case in France two months earlier when a graft supplied from Denmark was used there. The Danish TE has distributed the product to 4 EU countries.

Also it is learnt that the producer of the bone product in the USA is preparing a field corrective notice (i.e. quarantine and return of products) to several European countries, as it is suspected the modified washing phase to remove the chemical treatment may have reduced the mechanical strength of the product substantially.



Key question(s):

Identify the key elements of this case to determine whether a Rapid Alert (RATC) should be issued to all Competent Authorities and the Commission.

If so, consider which Competent Authority may/should act as the coordinating Competent Authority for issuing the RATC to the other CA's via CIRCA. Explain the rationale for this.

What should be the role of the co-ordinating CA in relation to investigation and follow up actions?

How should the actions be co-ordinated if a TE in another MS is also acting as an importer and distributor of this product?

Notes for Facilitators:

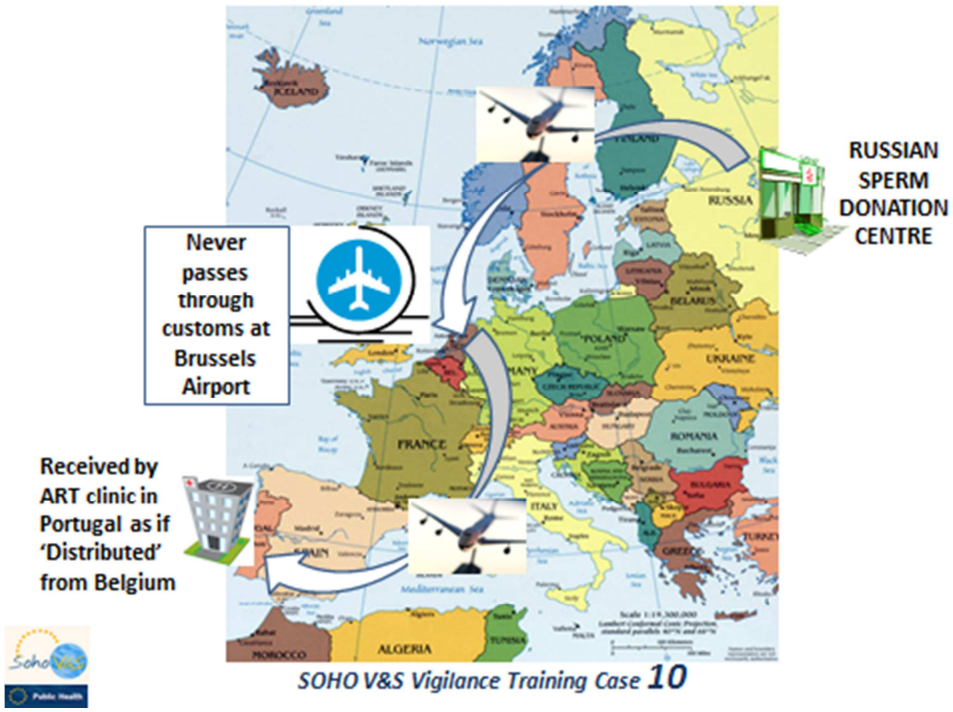
- Several similar events in different hospitals and in at least two Member States - with serious consequences for patients - are the primary indicators for issuing an RATC via CIRCA.
- In addition the American producer has confirmed the same products have been used in several countries, and are subject to a recall.
- The parallel field corrective action being issued by the producer is to be encouraged and the CA is typically involved in the preparation of their communication to hospitals and clinics.
- Corrective actions by a producer are not a replacement to the RATC issued by a coordinating Competent Authority.
- The Competent Authority of the country where the Tissue Establishment resides is expected to be the coordinating Competent Authority for issuing the RATC to others.
- The additional benefit (of the above) is that the follow up actions for identifying probable cause and the remedial measures can be investigated directly by the National Competent Authority (e.g. via an inspection).
- The background information of your own SARE is an important part of the initial RATC notification within Europe. Liaising with the coordinating CA and assisting with the final RATC is fully expected.

Case Study 10: Subject Area: Suspected Illegal and Fraudulent Activity (IFA).

Case background:

You are the ART CA in Portugal. An ART clinic in your MS is receiving sperm from Belgium. They inform you that the sperm originated outside the EU but was imported by Belgium. Your clinic has a written agreement with the TE in Belgium which states that the Belgian TE is checking 'equivalence of quality and safety to EU requirements.

Your clinic reports to you that they have had 3 children born using this sperm who did not seem to match the donor characteristics provided with the sperm. You contact the Belgian CA and discover that the TE is authorised for processing, storage and distribution but not for import of sperm; in fact the sperm is held in the airport and does not pass through customs, therefore there is no need for import authorisation. The sperm is collected in a centre in Russia; a review of the website of the centre reveals heavy advertising for donors with substantial payments offered.



Key question(s):

Who should lead this investigation?

What collaboration is needed with other authorities?

What should be the role of the co-ordinating CA in relation to investigation and follow up actions?

Notes for Facilitators:

- *Some key issues to clarify in Belgium:*
    - *Is the Belgian TE falsely claiming to have authorisation for import? This will need to be investigated by the Belgian CA – how will they check this?*
    - *Was the Belgian TE really confirming appropriate quality and safety of the PO in Russia? – again the Belgian CA will have to check.*

  A lot of work for the Belgian CA even though they have no products in the country and they have not given any authorisation in relation to the case!

- *Some key issues to clarify in Portugal:*
    - *As there was no authorisation in Belgium, the Portuguese TE should have import authorisation. It may be that they have not applied as they didn't realise that they were the importer.*
    - *How many donations have been received in this way and used. Should there be quarantine of un-used donations and a look-back?*
    - *The agreement with the Belgian TE should be reviewed.*

- *In the interests of the patients who have already received treatment with this sperm, there should be an investigation of the Russian centre. With or without the cooperation of the authorities? Should Interpol or others be involved? European Commission? Should it involve some covert actions (e.g. contact by an inspector pretending to be a potential customer TE in an EU MS?)*

- Participants should refer to the IFA guide for ideas on how to proceed.

Appendix 3: Communications Strategy – A Template for Competent Authorities (developed by the participants at the Italy Course)

Objectives:

- To ensure Quality and Safety;
- To provide rapid and effective communication;
- To provide instructions and guidance;
- To reassure the public and recipients;
- To promote and share best practice;
- To promote transparency and confidence;

Stakeholders:

- Tissue Establishments and Procurement Organisations;
- Organisations responsible for Human Applications (Hospitals; Clinics)
- Other Cas (Medicines, Medical Devices, Blood, Organs)
- Recipients;
- Internal Stakeholders;
- Ministries of Health;
- Professional Societies;
- General Public; Media;
- Centres for Disease Control;
- Other Regulators;

Types of Communication:

- Immediate
  - Rapid Alerts
    - National
    - RATC
- Medium Term
  - Feedback and Lessons Learned
  - Annual Report
  - Recommendations and Instructions
  - News Letters / E Magazines
- Long term
  - Website
  - Publications
  - Workshops / Information Days
  - Registries e.g. Notify / Eurocet

Responsibilities:

- Internal Communications Team
- Press Office
- Chairman / Head of Department
- Vigilance Officers
- Inspectors
- SOPs Needed!

Key SOPs:

- National Alerts
- RATC
- External Communication
- Crisis Management
- Promoting vigilance
- Information Dissemination
- FOI
- Dealing with Whistleblowers

Barriers / concerns:

- Time
- Funding
- IT Support / Infrastructure
- Personnel
- Legal Issues
- Periodic Review due to changing environment

Appendix 4: A Seminar to Promote Vigilance and Surveillance among Stakeholders – A Template for Competent Authorities (developed by participants at the Italy Course).

Objectives:

- Importance of Reporting
- Definitions: Reporting What, Why and Where?
- Investigation: Informative Level

Participants:

- End Users - Clinicians
- Tissue Establishments, Vigilance Officers, Responsible Persons etc.
- Number of participants: Depends on MS (number of TE, tissue transplantation activity)

Topics:

- Definitions: EUT/CD, national
- Requirements: legislation, good practice
- Investigation Methods: SOHO V&S
- Reporting System: National, EC
- Use of Data –processing, output, publicity, availability.

Methods:

- Case Studies (from the SOHOV&S course)
- Presentations (as various and dynamic as possible)

Programme Outline:

- Welcome, coffee&cake
- background: legislation, definitions
- data presentation (demonstration of the use and benefit)
- examples: what report/what not to report
- reporting pathway
- investigation at a glance
- Introducing sources: web links, literature, contacts, institutions
- Discussion

Challenges / Barriers:

- Budget
- Availability / Willingness of Stakeholders.

CHAPTER 4: SUMMARY AND CONCLUSIONS

Summary of Learning Outcomes

At the end of each Residential Course, a summary of learning outcomes was provided to the participants. Through the e-learning module residential modules, a broad range of topics were covered. These included:

- The History of Vigilance and Surveillance;
- The EUSTITE and ART Tools;
- The SOHO V&S Project Outputs;
- Project Notify;

Methods for SARE reporting, evaluation, investigation and communication were assessed through the use of case studies and working groups. The EC SARE Annual Reporting System and the new EC Rapid Alert System (RATC) were presented and discussed. Methods of dealing with illegal and fraudulent activity in relation to human tissues and cells were introduced. Many of these topics and themes were raised during the strengths and weaknesses analysis performed by participants during week 1 of the e-learning module and is was hoped that by providing this training, participants now had the means or at least the references to begin to address these issues in their respective competent authorities.

Priorities going forward

At the conclusion of each training course, participants were requested to identify their priorities for implementation or changing in relation to the Vigilance System at their Competent Authority. The following five key areas were identified:

- Development of a National Procedure for Reporting SARE to the Competent Authorities;
- Development of a Competent Authority Procedure for the management of SARE;
- A Rapid Alert SOP for managing both national and EU rapid alerts;
- A Procedure for completing SARE Annual Report to the EC;
- Increased Communication with Clinical Users.

Summary of Feedback from Participants Evaluation

Donor Action was tasked with the evaluation of key deliverables and outputs during the SOHO V&S project. Separate evaluations on the e-learning modules and residential courses were completed by all participants. In summary the feedback provided in relation to both courses was positive with participants considering the courses to be very relevant to their normal work. They scored highly the quality and relevance of the case studies and exercises carried out and greatly appreciated meeting their vigilance officer colleagues from other EU Member States.

Use of this Training Model

It is hoped that this training model and associated documents can be used by Competent Authorities to train vigilance officers within their own agency so that there is a consensus on managing Vigilance and Surveillance in Europe. In addition, it is hoped that the reference documents provided, particularly the case studies, may be used and adapted for use in training and educating stakeholders in the tissues and cells field.

Acknowledgements

The IMB and CNT would like to thank all participants and tutors who attended the courses in 2012. Their feedback and suggestions allowed for moderation of the course content and allowed the course design and content to improve from one course to the next. In addition, we would like to thank the staff and management of both venues who made both courses an enjoyable experience.