



Serious Adverse Events and Reactions in Tissues and Cells: THE EUSTITE PROJECT

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EU Directive Definitions

‘Serious Adverse Event’ means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity

‘Serious Adverse Reaction’ means an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity



Vigilance and Surveillance Activity in the First Year of the Project

- **Vigilance and Surveillance systems in the EU and beyond examined in detail – report available on www.eustite.org**
- **2 meetings of EU and Global Experts to explore the best approach to defining, classifying, reporting, managing and reacting to adverse events and reactions**
- **Proposals for EU V&S system advanced**



Key concepts for an EU Proposal

- Criteria for reporting SAEs to CA
- Severity grading system for SARs with guidance on which level to report to CA (based on ISBT system for blood)
- Imputability grading system for SARs
- Impact grading system (risk matrix including wider system implications) for SAEs and SARs
- Guidance on applying these tools
- Guidance on management of SAEs and SARS that have cross-border implications



Reporting of Serious Adverse **EVENTS**

- **Adverse events can be detected at any point from donation to transplantation**
- **Adverse events include what are commonly called ‘near misses’**
- **Competent Authorities will not want to be informed about every deviation from an SOP within a Tissue Establishment**
- **EUSTITE proposes the criteria that should be applied when deciding whether to report an adverse event to the Competent Authority**



Proposed criteria for SAE reporting to Competent Authorities

Deviations should not be reported as SAEs to CAs unless:

- 1. Inappropriate tissues or cells have been released 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) allogeneic tissues or cells**
- 4. The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells**



Some adverse event examples....

Examples

Report to CA?

A dry shipper containing an allogeneic bone marrow donation being transported for immediate transplant is stolen from the courier	YES



Some adverse event examples....

Examples

Report to CA?

A dry shipper containing an allogeneic bone marrow donation being transported for immediate transplant is stolen from the courier	YES
2 corneas discarded in the TE due to technical error during dissection from the globe	NO



Some adverse event examples....

Examples

Report to CA?

A dry shipper containing an allogeneic bone marrow donation being transported for immediate transplant is stolen from the courier	YES
2 corneas discarded in the TE due to technical error during dissection from the globe	NO
Liquid nitrogen container runs out of LN2, 120 heart valves thaw out and are discarded	YES



More event examples.....

Examples

Report to CA?

Bone irradiated twice – grafts released for transplant – all recalled before use	YES



More event examples.....

Examples

Report to CA?

Bone irradiated twice – grafts released for transplant – all recalled before use	YES
A cornea is swabbed in theatre prior to being transplanted – subsequent culture shows growth of bacteria (previous cultures negative)	NO



More event examples.....

Examples

Report to CA?

Bone irradiated twice – grafts released for transplant – all recalled before use	YES
A cornea is swabbed in theatre prior to being transplanted – subsequent culture shows growth of bacteria (previous cultures negative)	NO
All bone and skin tissue from a multi-organ, multi-tissue donor is contaminated with <i>Clostridium difficile</i> (organs transplanted, corneas and heart valves in other banks)	YES



More event examples.....

Examples

Report to CA?

Bone irradiated twice – grafts released for transplant – all recalled before use	YES
A cornea is swabbed in theatre prior to being transplanted – subsequent culture shows growth of bacteria (previous cultures negative)	NO
All bone and skin tissue from a multi-organ, multi-tissue donor is contaminated with <i>Clostridium difficile</i> (organs transplanted, corneas and heart valves in other banks)	YES
A frozen femoral head is held by a courier company for 72 hours in a holding depot rather than being delivered immediately (Courier company used by many TEs in the country)	YES



Adverse **REACTION** reporting by clinicians to TEs

- Primary infections possibly transferred from the donor to recipient (e.g. viral, bacterial, parasitic, fungal, prion)
- Transmitted infection (viral, bacterial, parasitic, fungal, prion) possibly due to contamination or cross-contamination by an infectious agent of the donated tissues, cells or associated materials from procurement to clinical application
- Allergic reactions
- Transmitted malignancy
- Unexpectedly slow or absent engraftment or graft failure (including mechanical)
- Toxic affects from tissues and cells or associated materials
- Unexpected immunological reactions due to tissue/cell mismatch
- Aborted procedure involving unnecessary exposure to risk (e.g. unnecessary anaesthetic and clinical intervention) ??
- Suspected transmission of genetic disease
- Suspected transmission of other diseases



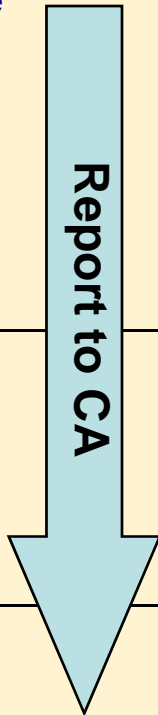
Adverse **REACTION** Evaluation and Reporting to the Competent Authority

Each report of a suspected AR received by a TE should be evaluated using the following tools:

- ❖ Severity
- ❖ Imputability
- ❖ Impact

Proposed Severity Grading Tool

Grade 1: non serious	Mild clinical consequences which do not necessitate hospitalisation and/or result in long term disability or consequences for the recipient or living donor
Grade 2: severe	Adverse reaction resulted in: <ul style="list-style-type: none"> - hospitalisation or prolongation of hospitalisation and/or - persistent or significant disability or incapacity or - medical or surgical intervention to preclude permanent damage or impairment of a body function or - there is evidence of a serious transmitted infection
Grade 3: life-threatening	The living donor or recipient required major intervention following procurement or tissue or cell application (vasopressors, intubation, transfer to intensive care) to prevent death or there is evidence of a life-threatening transmitted infection.
Grade 4: death	Death



Proposed Imputability Assessment Tool

NA		When there is insufficient data for imputability assessment
0	Excluded: Unlikely:	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes. When the evidence is clearly in favour of attributing the adverse reaction to causes other than the tissues/cells.
1	Possible	When the evidence is indeterminate for attributing the adverse reaction either to the tissues/cells or to alternative causes.
2	Likely, Probable	When the evidence is clearly in favour of attributing the adverse reaction to the tissues/cells
3	Definite, Certain	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the tissues/cells



Proposed Impact Assessment Tool

Step 1: Probability of Recurrence

Step 2: Consequences

Step 3: Risk Matrix

Step 4: Response

The Impact Assessment Tool is essentially a tool for the risk assessment of an event or reaction.



Step 1 – Assess the probability of recurrence of the event or reaction given the controls in place

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

Step 2: Assess consequences (if the event/reaction were to recur)

Level	Impact Description	Impact on individual(s)	Impact on Transplant or Fertility System	Impact on Tissue/cell supply
5	Severe	Death	System destroyed – need to rebuild	All allogeneic applications cancelled
4	Major	Major permanent harm	Major damage to system – significant time needed to repair	Significant no of procedures cancelled - importation required to make-up short-fall
3	Moderate	Semi-permanent harm	Damage to system – services will be affected for short period	Many applications cancelled or postponed
2	Minor	Short-term injury	Minor damage	Some applications postponed
1	Insignificant	No injury or adverse outcome	No affect	Insignificant impact

Step 3: Apply Risk Matrix

Probability of recurrence → Consequences ↓	Almost certain 5	Likely 4	Possible 3	Unlikely 2	Rare 1
Severe 5	25	20	15	10	5
Major 4	20	16	12	8	4
Moderate 3	15	12	9	6	3
Minor 2	10	8	6	4	2
Insignificant 1	5	4	3	2	1



Step 4: Response

The response of a TE or CA to a specific SAR/SAE should be proportionate to the risk indicated by the incident as assessed by the risk matrix



Application of the EUSTITE V&S Tools: Example 1 (invented)

- UK cornea recipient develops symptoms of vCJD 5 years after transplant – reported to TE
- SAE or SAR? **Suspected SAR**
- Need to apply Severity and Imputability tools at TE? **YES**
- Severity Grading: **4 (death) – Report to CA**
- Imputability Grading: **1 (possible)**
- Need to apply the impact tool - **YES**



Application of the EUSTITE V&S Tools: Example 1

Step 1 – Assess the probability of recurrence (UK Context):

4 (likely)

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



Application of the EUSTITE V&S Tools: Example 1

Step 2 – Assess the impact if the event recurs:

5 (severe)

Level	Impact Description	Impact on individual(s)	Impact on Transplant or Fertility System	Impact on Tissue/cell supply
5	Severe	Death	System destroyed – need to rebuild	All allogeneic applications cancelled
4	Major	Major permanent harm	Major damage to system – significant time needed to repair	Significant no of procedures cancelled - importation required to make-up short-fall
3	Moderate	Semi-permanent harm	Damage to system – services will be affected for short period	Many applications cancelled or postponed
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Application of the EUSTITE V&S Tools: Example 1

Step 1 – Assess the probability of recurrence

(UK Context):

4 (likely)

Step 2 – Assess the impact if the event recurs: **5 (severe)**

Step 3 – Risk Matrix

– **20 (red)**

– major active response by CA

Probability of recurrence Consequences	Almost certain 5	Likely 4	Possible 3	Unlikely 2	Rare 1
Severe 5	25	20	15	10	5
Major 4	20	16	12	8	4
Moderate 3	15	12	9	6	3
Minor 2	10	8	6	4	2
Insignificant 1	5	4	3	2	1



Application of the EUSTITE V&S Tools: Example 2 (real)

FDA Orders Biomedical Tissue Services, Ltd., to Cease Manufacturing - Mozilla Firefox

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FDA Orders Biomedical Tissue Services, Ltd., to Cease Manufacturing and to Retain Existing Inventories of Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps)

Under its comprehensive framework for ensuring the safety of human tissue products, the U.S. Food and Drug Administration (FDA) today ordered Biomedical Tissue Services, Ltd. (BTS), of Fort Lee, NJ, a human tissue-recovery firm, and its CEO and Executive Director of Operations, Michael Mastromarino, D.D.S., to immediately cease all manufacturing operations. All tissue products initially recovered from human donors by BTS were recalled. FDA is carefully monitoring these recalls to account for all of the tissue distributed.

"FDA's investigation of BTS revealed serious and widespread deficiencies in their manufacturing practices that provide the agency reason to believe that allowing the firm to manufacture would present a danger to public health by increasing the risk of communicable disease transmission," said Margaret O.K. Glavin, FDA's Associate Commissioner for Regulatory Affairs.

"FDA's current regulatory framework for Human Tissue and Cellular and Tissue Based Products (HCT/Ps) provides strong measures that the agency can utilize to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps, and require firms to screen and test donors for relevant communicable disease agents and diseases and to ensure that HCT/Ps are processed in a way that prevents communicable disease contamination and cross-contamination," added Jesse L. Goodman, MD, MPH, director of FDA's Center for Biologics Evaluation and Research.

The FDA order to cease manufacturing and to retain HCT/Ps requires BTS to suspend any and all manufacturing steps, including but not limited to the recovery and shipment of HCT/Ps. FDA's inspection of BTS uncovered serious violations of the regulations governing donor

Done



Application of the EUSTITE V&S Tools: Example 2



FDA's inspection uncovered serious violations of the regulations governing donor screening and record keeping practices, failure to recover HCT/Ps in a manner that does not cause contamination or cross-contamination during recovery, and failure to adequately control environmental conditions.

Despite records maintaining otherwise, the firm had inadequately screened donors for risk factors for, or clinical evidence of, relevant communicable disease agents and diseases.

**Tissues were distributed to many European countries.
Potentially 25,000 grafts distributed in the US.**



Application of the EUSTITE V&S Tools: Example 2

- SAE or SAR? **SAE**
- Reportable to the CA? **YES**
- Need to apply severity or imputability tools
NO
- Need to apply the impact tool - **YES**



Application of the EUSTITE V&S Tools: Example 2

Step 1 – Assess the probability of recurrence (Italian context – 71 implicated tissues imported and transplanted):

2 (unlikely)/3(possible) – only with imported tissues – Directive brings tighter controls

Step 2 – Assess the impact if the event recurs:

2 (minor) – public would not lose trust in the Italian Transplant system

Step 3 - Risk Matrix – **4/6 (green/yellow)** – active limited response by CA



Application of the EUSTITE V&S Tools: Example 3 (invented)

- Fracture in an irradiated massive allograft (femur) 2 months after transplant
- SAE or SAR? **Suspected SAR**
- Need to apply Severity and Imputability tools at TE? **YES**

Severity

Grade 1: non serious	Mild clinical consequences which do not necessitate hospitalisation and/or result in long term disability or consequences for the recipient or living donor
Grade 2: severe	Adverse reaction resulted in: <ul style="list-style-type: none">- hospitalisation or prolongation of hospitalisation and/or- persistent or significant disability or incapacity or- medical or surgical intervention to preclude permanent damage or impairment of a body function or- there is evidence of a serious transmitted infection
Grade 3: life-threatening	The living donor or recipient required major intervention following procurement or tissue or cell application (vasopressors, intubation, transfer to intensive care) to prevent death or there is evidence of a life-threatening transmitted infection.
Grade 4: death	Death

Imputability

NA		When there is insufficient data for imputability assessment
0	Excluded: Unlikely:	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes. When the evidence is clearly in favour of attributing the adverse reaction to causes other than the tissues/cells.
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Application of the EUSTITE V&S Tools: Example 3 (invented)

- Fracture in an irradiated massive allograft (femur) 2 months after transplant
- SAE or SAR? **Suspected SAR**
- Need to apply Severity and Imputability tools at TE? **YES**
- Severity Grading: **2 (severe)**
- Imputability Grading: **2 (likely/probable)**
- Need to apply the impact tool - **YES**



Application of the EUSTITE V&S Tools: Example 3

Step 1 – Assess the probability of recurrence (UK Context):

4 (Likely)

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



Application of the EUSTITE V&S Tools: Example 3

Step 2 – Assess the impact if the event recurs:

2 (minor)

Level	Impact Description	Impact on individual(s)	Impact on Transplant or Fertility System	Impact on Tissue/cell supply
5	Severe	Death	System destroyed – need to rebuild	All allogeneic applications cancelled
4	Major	Major permanent harm	Major damage to system – significant time needed to repair	Significant no of procedures cancelled - importation required to make-up short-fall
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Application of the EUSTITE V&S Tools: Example 3

Step 1 – Assess the probability of recurrence:

4 (likely)

Step 2 – Assess the impact if the event recurs:

2 (minor)

Step 3 - Risk Matrix

8 (yellow)

– active limited response by CA

Probability of recurrence Consequences	Almost certain 5	Likely 4	Possible 3	Unlikely 2	Rare 1
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Minor 2	10	8	6	4	2
Insignificant 1	5	4	3	2	1



EUSTITE Vigilance and Surveillance Pilot

- **The approved EUSTITE ‘tool kit’ and reporting system will be piloted in partner countries and in any other MS that wish to participate for 1 year from July 2008**
- **All SAEs and SARs will be collated and their management and outcome reviewed and reported**
- **The project will make recommendations to SANCO on future management of V&S of tissues and cells in the EU**
- **WHO will publish global recommendations on management of V&S in transplantation**