Review of reported incidents: UK and EU

Renuka Sornarajah
Outline

- The HTA SAEARs team
- SAR and SAEs reported to the HTA
- Compare HTA data with EU data
Reporting SAEARs to Competent Authorities

- EU requirement - establishments must report SERIOUS adverse events and reactions without delay
- Competent authorities can have additional requirements – timing, reporting of non-serious reactions etc
- HTA – requires reporting of incidents within 24 hours of discovery

Reporting of SAEARs is important for patient safety - enables trends to be monitored to ensure continuous improvement
HTA’s Responsibilities

- Establish a framework for reporting
- Provide licensed establishments with instructions and guidance for reporting SAEARs
- Acknowledge receipt of reports, take immediate action if required
- Retain reports, evaluate SAEAR investigations and follow up corrective and preventative actions implemented
- Provide annual reports to the European Commission
HTA SAEARs team

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HTA – SAEARs Governance

SAEARs team –

• Regulation Managers manage SAEARs
• Provide weekend cover
• Regular meetings to discuss reported SAEARs
• Take action as required - in response to SAEARs, RATC etc
• Monitor the reporting time for incidents
• Provide annual reports to Europe

Regulation Managers review SAEARs reported by an establishment before an inspection

Team members attend training – EUSTITE and SoHO V&S project
SoHO V&S Tool

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SoHO V&S Tool

Human Tissue Authority

Serious Adverse Event (SAE): 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, incapacitating or which might result in, or prolong, hospitalisation or morbidity.

SAE Reporting Criteria

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

Report to HTA

Serious Adverse Reaction (SAR): 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.

Reaction Severity (SAR)

- No harm, no risk, patient not informed as there was no risk of harm
- Mild clinical / psychological consequences
- No hospitalisation
- No anticipated long term consequence / disability
- Hospitalisation or prolonged hospitalisation
- Persistent or significant disability or incapacity
- Intervention to prevent permanent damage
- Evidence of a serious transmitted infection
- Major intervention to prevent death
- Evidence of a life-threatening transmitted infection
- Death

Reaction Imputability (SAR)

- N/A
- Not assessable
- Insufficient data for imputability assessment
- Excluded
- Conclusive evidence beyond reasonable doubt for attributing adverse reaction to alternative causes
- Unlikely
- Evidence clearly in favour of attribution to alternative causes
- Possible
- Evidence in favour of attribution to the tissues/cells
- Likely / probable
- Evidence in favour of attribution to the tissues/cells
- Certain
- Conclusive evidence beyond reasonable doubt for attribution to the tissues/cells

Impact (SARs and SAEs)

Impact (SARs and SAEs)

1. Rare
2. Unlikely
3. Possible
4. Likely
5. Probable

Likelihood of recurrence

0. Insignificant
1. Minor
2. Moderate
3. Major
4. Catastrophic / extreme

Impact of recurrence

0. 0 0 0 0 0
1. 1 2 3 4 3
2. 2 4 6 8 10
3. 3 6 9 12 15
4. 4 8 12 16 20

5. Probable (almost certain)

0.3 Green
Interaction required between establishment and HTA which may request an inspection that focuses on the event or reaction and CAPAs, including evidence of effective recall as necessary. Written communication to professionals in the field might be appropriate.

4-9 Amber
HTA will generally develop or approve the CAPA and possibly set up a task force to address broader implications. Inspection, follow up and written communication and RATC relevant.

10-20 Red
HTA will generally develop or approve the CAPA and possibly set up a task force to address broader implications. Inspection, follow up and written communication and RATC relevant.
Is it a SAE/SAR??
sometimes not easy to decide!

1. Freezer breakdown – depends on quantity and scarcity of tissues/cells affected
2. Graft vs host disease or Graft failure – caused by quality of tissue/cells supplied = yes
3. Citrate or DMSO toxicity – increases hospital stay = yes; goes home on the same day = no
4. Tissues/cells rejected by surgeon but passed release criteria = no
5. The event could have implications for other patients or donors because of shared practices, services, supplies or donors – not easy to decide!
HTA’s experience 2012

13 SARs reported – around 0.03% of total tissues distributed -

- Transmitted viral infection - cord blood recipient experienced graft failure several months after transplant.
- Imported acellular product from skin tissue used at Dental Clinic – recipient developed rash, severe soft tissue inflammation and other allergic symptoms within two days. Product removed, patient recovered within 24 hours.
- Imported bone product - Patient suffered reduced use of legs post surgery. After MRI revealed large mass/fluid, the patient was taken back for further surgery.
- Bone marrow stem cell infusion – recipient became hypertensive, agitated and nauseous and developed acute haemolytic reaction; renal function impaired – probably due to lysed erythrocytes in bone marrow harvest.
Transmitted viral infection

**Incident** - cord blood recipient experienced graft failure five months after transplant. Patient doing well until viral infection – human herpes virus type 6 (HHV-6).

**Initial action** - tests undertaken on recipient and cord blood.

**Investigation and Imputability** – Post-transplant, patient was found to be HHV6 positive. The cord blood was retrospectively tested and found to be HHV6 positive. No indication of medical issues at time of donation. Mother and baby are healthy. Approx 1% of cord blood donations are HHV6 positive.

**Follow up actions** – no changes to procedures as routine testing for HHV6 is not recommended. Continue to monitor these incidents.
Allergic reaction to acellular product

**Incident** – Dental surgeon performed root coverage treatment on healthy patient using acellular dermal allograft tissue. Patient was given antibiotics following treatment, but developed severe inflammation in internal and external tissues, a rash in the region of the neck and other allergic symptoms.

**Initial action** – Graft was removed and the region cleaned. Immediate cessation of symptoms.

**Investigation and Imputability** – This reaction not a batch problem as no other incidents reported. Reaction ceased when graft was removed.

**Follow up actions** – no changes to procedures as possibly one off, due to patient hypersensitivity to dermal allograft product. Product literature states that potential adverse events include allergic reactions.
Reaction to DMSO

**Incident** - Recipient infused with PBSCs. Strong reaction observed within three minutes. Identified as anaphylactic reaction.

**Initial action** - infusion stopped and recipient was immediately treated with adrenaline. PBSCs in the remaining bags were washed to remove DMSO. Recipient tolerated re-infusion until two thirds of the way through and then became unwell. Re-infusion stopped and patient recovered. Engraftment successful at day 18.

**Investigation and Imputability** – Bacteriology, virology tests negative. Review of processing records showed no deviation from SOPs, or product specification. DMSO concentration within specified range. Recipient response consistent with reaction to DMSO.

**Follow up actions** – no changes to procedures as it is a rare event which cannot be predicted, but will continue to monitor these incidents.
HTA – Reports (2012)

SARs = 13

- Bone marrow: 39%
- Cord blood: 23%
- Bone: 8%
- Other - acellular, islets heart valves etc: 15%
- PBSCs: 15%
- Other: 15%
SARs – Tissues and cells involved

**HTA**
- Cardiovascular tissue: 8%
- Skin: 8%
- Musculoskeletal Tissue: 8%
- Ocular Tissue: 24%
- Haematopoietic Stem Cells: 76%
- Other: 0%

**EU**
- Cardiovascular tissue: 2%
- Skin: 0%
- Musculoskeletal Tissue: 11%
- Haematopoietic Stem Cells: 61%
- Ocular Tissue: 24%
- Other: 2%
Serious Adverse Reactions in Donors

HTA –

Two donor reactions –

- Relapse of Post Viral Fatigue Syndrome following bone marrow donation
- Donor suffered symptoms of citrate toxicity during procurement, rapidly progressed to marked tetany (hypocalcaemia). Procedure stopped, required overnight hospital stay and IV fluids.

EU –

24 Donor reactions
## Criteria for SAE Reporting

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HTA’s experience 2012 (1) - SAEs

95 SAEs reported – around 0.13% of tissues processed

- Procurement – leak in apheresis kit, manufacturer informed
- Procurement – untrained staff procured cells/tissues
- Processing – Incorrect programme selected on control rate freezer – cell viability checked
- Processing – following processing, apheresis product contained gram negative coliform bacteria.
- Storage – Bone bank freezer failure due to power failure
- Storage – corneas stored in Optisol - contaminated
HTA’s experience 2012 (2)- SAEs

- Distribution – Courier arrived to collect cells, but only one bag handed over instead of two. Delay to patient treatment.
- Distribution – mix-up between - two sclera. Tissue picked up was for another recipient.

- End user – Bag containing cells dropped when staff removed it from the dewar.

- End user - Theatre staff did not follow supplier’s guidelines. They did not ensure that Rhesus compatible bone was implanted into females patients of childbearing age.
Error - calculation of citrate (anticoagulant) used for PBSC procurement

Incident - Apheresis Nurse made an error in calculating the donor’s total blood volume. This resulted in overdosage of the anticoagulant (citrate) given to the donor above maximum approved level. Error only noted when procedure was over.

Initial action – No immediate action, as the child remained well throughout the procedure.

Investigation – Human error – calculation was not checked as required by SOP.

Follow up actions – Staff member completed a short re-training session. Change made to procedure - all calculations to be double checked and initialled by checker.
Processing of cord blood

**Incident** – Imported cord blood unit – air present in the bag and discolouration of contents.

**Initial action** – In house testing showed low viability and so product was discarded and not used.

**Investigation** – Photographs taken sent to expert cord blood bankers. They concluded that the cord blood was not correctly cryopreserved. Likely that contents were not sufficiently mixed with DMSO before freezing. Also, air in bag was not fully removed before freezing which would have caused cell death in frozen cord blood in some parts of the bag.

**Follow up actions** – The originating bank was asked to consider these conclusions and perform appropriate corrective and preventive actions.
Processing of acellular product

**Incident** – imported acellular bone product was found to be too friable for use in the planned surgical procedure.

**Initial action** – surgical procedure cancelled

**Investigation** – manufacturer informed. Investigation concluded that the problem is due to the failure of the tissue to withstand the manufacturing process, which can lead to friability in the final product. It is not possible to detect this until the product is eventually removed from the sterile packaging. The manufacturer stated that this is a rare event.

**Follow up actions** – The manufacturer is aware of the issues but no assurance that appropriate corrective and preventive actions will be undertaken.
PBSC bag damaged

**Incident** - Bag dropped in dewar (estimated 2 to 3 inches). Visual inspection showed no damage when bubble wrap removed. When thawing in water bath small leak noted in inner and outer bag.

**Initial action** – inner bag removed, wiped with antiseptic held to prevent further leakage and infused. Patient informed. Discarded cells leaked into outer bag. Intravenous antibiotics given to recipient as precaution.

Patient engrafted promptly

**Investigation** – Human error – bag dropped just 2-3 inches.

**Follow up actions** – staff informed to take extra care when handling bags. Requested and received funding for a dry thawing system for stem cells.
Analysis of PBSC SAEs

No of SAEs

- Procurement
- Testing
- Processing
- Storage
- Packaging
- Distribution

Apheresis
Kits
Equipment malfunction

Control
rate
freezers

Packaging
materials
HTA – SAEs (2012)

SAEs = 95
SAEs – Process involved

**HTA**

- Procurement: 33%
- Processing: 16%
- Storage: 11%
- Transport: 5%
- Distribution: 9%
- Materials: 3%
- Other: 19%
- Testing: 4%

**EU**

- Procurement: 27%
- Processing: 26%
- Storage: 9%
- Distribution: 6%
- Materials: 4%
- Other: 12%
- Transport: 4%
- Testing: 12%
SAEs – cause of event

**HTA**
- Tissue or cell defect: 4%
- Equipment failure: 28%
- Human error: 33%
- Other (materials, IT, Test kits): 35%

**EU**
- Tissue or cell defect: 24%
- Equipment failure: 21%
- Human error: 35%
- Other (materials, IT, Test kits): 20%
Annual Activity

- Establishments send annual activity data to the HTA

We use the data to get an understanding of the ‘flow’ of tissues and cells through the UK from donor to recipient.

The data is collected in terms of procurement, donor testing, processing, storage, distribution, import and export.

The data can also be used as a denominator to understand the distribution of SAEARs in relation to each activity.
UK Annual Activity 2012

SAE s: (43)(6)(4) (10) (7)(1) (10) (1) (1) (1) (1)
HTA – Challenges

- Increase awareness, foster a no-blame culture
- Under reporting, over reporting, double reporting of SAEARs
- Increase our oversight of relationship between suppliers and endusers (clinicians); are all endusers made aware of the reporting requirements?
- Communication - international movement of tissues and cells procurement, tissue processing and clinical users in different countries
- Working with Europe – harmonising the reporting and evaluation of SAEARs
- Is it an SAE/SAR?– sometimes not easy to decide!