The NOTIFY project - a general overview

last update September 30, 2020
Resolution 63.22 of the World Health Assembly was adopted in 2010 and gave WHO a mandate to facilitate Member State access to appropriate informations on donation, processing and transplantation of tissues, cells and organs, including data about serious adverse events and reactions.
NOTIFY PROJECT

Sharing vigilance experience and knowledge globally
- the NOTIFY Project (WHO)
# NOTIFY PROJECT: AIMS

<table>
<thead>
<tr>
<th>Aim</th>
<th>Description</th>
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<tr>
<td>1. To provide professionals with relevant information helpful for</td>
<td>determining the suitability of a potential donor.</td>
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<td>2. To draft common guidelines supporting the implementation of</td>
<td>effective vigilance and surveillance</td>
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<tr>
<td>3. To provide practical support to countries that are developing</td>
<td>vigilance systems for Medical Products of Human Origin (MPHO)</td>
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<td>vigilance systems for Medical Products of Human Origin (MPHO)</td>
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*Source: Notify Library*
Joint global initiative (WHO, CNT, SOHO V&S) to raise the profile of V&S of SOHO. Adoption of Resolution 63.22 by the World Health Assembly in 2010 “provide all Member States information about donation, processing, transplantation of tissues, cells and organs, including data about serious adverse events and reactions”.
NOTIFY PROJECT: MAIN COMPONENTS

1. NOTIFY website:  http://www.notifylibrary.org

2. NOTIFY Booklet

3. NOTIFY Library
The website is maintained and updated on this platform and is intended as a communication hub for institutions and organisations worldwide collaborating in the facilitation of access to Vigilance and Surveillance information.

Welcome to the NOTIFY Library site where experts from across the globe collaborate to share didactic information on documented adverse outcomes associated with the clinical use of human organs, blood, tissues and cells. The data presented on the Notify Library site should be seen in the context of impressive success stories in transplantation, transfusion and assisted reproduction across the world.
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Interactive Booklet through an index
NOTIFY LIBRARY

• publically accessible online database of didactic cases of severe adverse reactions and events

• from procurement and processing to clinical application of blood, organs, tissues and cells used in transfusion, transplantation and assisted reproduction

• collected and analyzed by dedicated editorial groups of international experts, regulators and clinicians and linked to their source reference:
  ✓ literature review (published articles in scientific journals and/or books)
  ✓ case reports from regulatory or professional vigilance programs (grey literature)
NOTIFY LIBRARY: ADVERSE OCCURRENCE DEFINITIONS

1. **Severe Adverse Event (SAE)**: any untoward occurrence, associated with the chain, from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalization or morbidity. *In the NOTIFY project these are referred to as cases of ‘Risk of Harm’.*

2. **Severe Adverse Reaction (SAR)**: any unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity. *In the NOTIFY project these are referred to as cases of ‘Harm to Donor’, ‘Harm to Recipient’ or ‘Harm to Fetus/Offspring’.*
Adverse occurrence: Risk of harm

Medical Product of Human Origin type - MPHO: Tissues >> Ocular

[4466] Li, J.Y.
Donors with melanoma history: the risk to ocular tissue recipients

Record ID: 1683

Adverse occurrence description: Subject review: Donors with melanoma history and risk to ocular tissue recipients
Adverse occurrence type: Risk of harm >> Other
MPHO type: Tissues >> Ocular >> Cornea
Time to detection: 2 months

Alerting signals, symptoms, evidence of occurrence: Recipient developed ocular melanoma within two months of surgery.

Estimated frequency: Rare; Review article written in response to single case report of melanoma transmission following keratolimbal allograft. No existing reports in literature documenting melanoma transmission from corneal transplant. Based on the case report a moratorium on use of ocular tissue from donors with melanoma (restricted from all use) and donors with metastatic solid tumors (not to be released for use of vascular components) was issued in February 2016 to be reviewed by the Eye Bank Association of America in October 2016.

Demonstration of Imputability or Root cause: Donor had history of malignant melanoma.

Imputability grade:

Expert comments for publication: Article was written as a review at the time of active discussion regarding the appropriate response to the cited case report. It is pointed out that donors with solid tumors constitute 30-40% of the ocular donor pool. In the case of melanoma, micrometastases raise concern for the possibility of transmission, but in practice this has not been seen. Possible factors contributing to the absence of known transmissions include the avascular nature of cornea and absence of immunosuppressive drugs. It is also noted that vascularized ocular components (such as keratolimbal allografts) also require immunosuppression and may have tumor transmission risks more similar to solid organ transplants. The article discusses the need to balance restoring sight and patient safety in the difficult setting of limited available evidence.

Keywords: cornea transplantation, cornea, melanoma, subject review, keratolimbal, metastasis, exclusion criteria
NOTIFY LIBRARY:
uploaded records by adverse occurrence type (n=1,733)

- Infection transmission: 604 (35%)
- Clinical complications: 287 (17%)
- Malignancy transmission: 225 (13%)
- Living donor reaction: 247 (14%)
- Genetic (fetus/offspring): 356 (20%)
- Risk of harm: 14 (1%)

2,635 references indexed

(last update September 30, 2020)
NOTIFY LIBRARY:
UPLOADING RECORDS BY MPHO TYPE (n=1,733)

- **Organs**: 725 records (42%)
- **Blood**: 360 records (21%)
- **Cells (HPC)**: 294 records (17%)
- **Tissues (non-ocular)**: 166 records (9%)
- **Reproductive tissues and cells**: 97 records (6%)
- **Other**: 73 records (4%)
- **Ocular tissue**: 18 records (1%)

2,635 REFERENCES INDEXED

*last update September 30, 2020*
Case examples from the Notify Library (1)

OCULAR TISSUE - HARM TO A RECIPIENT

Adverse occurrence
Adverse occurrence description: Subject review: Cornea transplantation from donors with cancer
Adverse occurrence type: Risk of harm => Other
MPHO type: Tissues => Ocular => Cornea
Time to detection: No cancer transmission seen. Recipients were followed for an average of 64.1 months (range 30-86 months).
Alerting signals, symptoms, evidence of occurrence: None in recipients.
Estimated frequency: In this series, 204 of 588 corneal donors (34.7%) had cancer. Of the cancer donors, 86.8% had solid cancer and 13.2% had hematological cancer. No cancer transmission was seen in 325 recipients.

Demonstration of Imputability or Root cause: Histologic study of the enucleated donor eye showed micrometastases in two cases. One donor with breast adenocarcinoma showed a single focus of malignant cells in the posterior pole, in the choroid. One donor with chronic myeloid leukemia showed leukemic infiltrates in the anterior and posterior poles, mainly in sclera and episclera with occasional foci in choroid and iris. None of the recipients developed cancer with 6.5 and 6 year follow up.

Imputability grade:
Expert comments for publication: On the basis of their review, the authors suggest that in cases of donors with cancer: 1. eyes with macroscopic tumor masses should be rejected; 2. cornea and anterior chamber should be examined by slit lamp to discard those with tumor infiltration; 3. histopathological study of the eye should be performed prior to corneal transplantation and cornea should be rejected in cases of tumor cellular infiltration. They also recommend careful recipient follow up during the first two years after transplant.

Keywords:
cornea transplantation  subject review  cancer  malignancy  histologic analysis  exclusion criteria  cornea

Case examples from the Notify Library (2)


Case examples from the Notify Library (3)

**OCULAR TISSUE – RISK OF HARM**

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<tr>
<td><strong>Adverse occurrence</strong></td>
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<tr>
<td><strong>Adverse occurrence description:</strong></td>
<td>40 sclera destroyed because of blue spots</td>
</tr>
<tr>
<td><strong>Adverse occurrence type:</strong></td>
<td>Risk of harm =&gt; Loss =&gt; Large quantity of unmatched MPH0</td>
</tr>
<tr>
<td><strong>MPHO type:</strong></td>
<td>Tissues =&gt; Ocular =&gt; Sclera</td>
</tr>
<tr>
<td><strong>Time to detection:</strong></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Alerting signals, symptoms, evidence of occurrence:</strong></td>
<td>Detected by treating physician before transplant</td>
</tr>
<tr>
<td><strong>Estimated frequency:</strong></td>
<td>This problem happened before in 2008 at the same tissue establishment.</td>
</tr>
<tr>
<td><strong>Demonstration of Imputability or Root cause:</strong></td>
<td>Investigation by tissue establishment: used materials, electron microscope scan, experiments with used material. Cause most likely originating from disposables. 40 sclera in stock also had blue spots and were destroyed.</td>
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<tr>
<td><strong>Record ID</strong></td>
<td>720</td>
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<tr>
<td><strong>Adverse occurrence</strong></td>
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<tr>
<td><strong>Adverse occurrence description:</strong></td>
<td>Cornea with contact lens supplied for transplant</td>
</tr>
<tr>
<td><strong>Adverse occurrence type:</strong></td>
<td>Risk of harm =&gt; Unsuitable MPHO released for clinical use - no harm</td>
</tr>
<tr>
<td><strong>MPHO type:</strong></td>
<td>Tissues =&gt; Ocular =&gt; Cornea</td>
</tr>
<tr>
<td><strong>Time to detection:</strong></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Alerting signals, symptoms, evidence of occurrence:</strong></td>
<td>Evidence of a poor in situ inspection before retrieval, or inadequate recovery technique. May be discovered by the surgeon upon receiving the tissue, or at the time of surgery: an irregular or insufficient scleral rim, uveal tissue or lens residues, a contact lens still present</td>
</tr>
<tr>
<td><strong>Estimated frequency:</strong></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Demonstration of Imputability or Root cause:</strong></td>
<td>Self evident</td>
</tr>
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*Ehrenhaus, M.P, et al. Eye banking error: report of a donor cornea with a soft contact lens left in place. Cornea 2006; 25 (3) :359 - 60*
Case examples from the Notify Library (4)

The Notify Library includes some well-documented cases of adverse reactions and adverse events in transplantation of ocular tissue; for example:

- A case of donor-to-recipient transmission of the *Herpes simplex* virus (HSV) by cornea transplantation was confirmed by polymerase chain reaction-based DNA fingerprinting of donor and recipient HSV strains (Record Number 429);
- In Record Number 20, a transplant-acquired diagnosis of rabies is supported by temporal association of the recipient’s illness, lack of other exposure to rabies and the retro-orbital pain of the recipient of the corneal transplant;
- In Record Number 338, a case of transmission of T-cell lymphoma is described, whereby molecular analyses were used to detect the same alleles in HLA-DQα testing of the recipient and donor of the graft;
- Record Number 720 reports a case of donor ocular tissue being examined and then shipped to the eye bank with a contact lens on the cornea, thereby highlighting the importance of *in situ* inspection before recovery;
- Record Number 1663 describes metastases from a cholangiocarcinoma in the vascularised limbal region of a corneoscleral disc. There was no evidence of transmission to the recipient of the avascular corneal graft. The authors recommended that tissue from donors with a history of malignancy should not be used for limbal allografting [14].

Further cases of adverse outcomes associated with ocular tissue can be found in the Notify Library at www.notifylibrary.org. The database is publicly accessible and can be searched by the substance type, adverse occurrence type and record number. A
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MPHO safety recommendations related to SARS-CoV-2

A new section for MPHO safety recommendations related to SARS-CoV-2 released by health authorities or professional societies is now available under Background documents. The links are being constantly updated as new information comes in. Further recommendations on COVID-19 outbreak and Rapid Risk assessment are available at the link: ECDC Rapid Risk Assessment, and additional recommendation on MPHO supply in EU/EEA (latest Update April 2020) CDC Rapid Risk Assessment.
CONCLUSION

Notify is a joint Global initiative that supports the sharing of published vigilance information for teaching purposes and greater public transparency on the use of Medical Products of Human Origin.

The Notify Library is the first database that aims to organize the current knowledge about serious adverse events and reactions of organs, blood, tissues, cells and ART available globally in a single, publically accessible database.
THANK YOU