PROJECT NOTIFY

Sharing vigilance experience and knowledge globally
The NOTIFY Project
WHO’s Initiative for Medical Products of Human Origin
Medical Products of Human Origin (MPHO)

- From human Donor to human Recipient
- The challenge of meeting patient needs with solidarity and reciprocity
  - Equity in donation and in allocation: relying on receiving implies willing to give
  - The Self-Sufficiency paradigm
  - Commitment of Society through authorities
  - Education to donation and prevention
  - Trust through professionalism and transparency
- A common Humanity
- The need for Global governance
- The power of global V&S to improve
  - Regular practice, traceability, risk based quality management,
  - Crisis management
  - The understanding of the importance of MPHO
3 Global Requirements for MPHO

Standards of practice inherent to the Human Origin

Universal use of ISBT 128 for all MPHO

Optimized Vigilance and Surveillance
The NOTIFY project

- Mutualizing the global experience of V&S in MPHO services
  - Risk identification
  - Risk assessment
  - Risk based quality management
  - Risk education
- Associating Competent Authorities and Scientific and Professional Societies
- Promoting V&S as a crucial mechanism of quality and transparency in MPHO services
- Deserving trust
History of the NOTIFY Project

2010

Pre-Bologna – The Notify Google Site

2011

Bologna – The Meeting

2012

Post Bologna
BIG V&S
Bologna Initiative for Global Vigilance and Surveillance

2013

Rome

2014

Brasilia

Medical Products of Human Origin
The Bologna Meeting Participants

• 116 attendees

• Regulators, government agencies, professional societies, international organisations, scientific and clinical experts in organ, tissue and cell transplantation and in assisted reproduction.

• 36 countries (Bulgaria, Italy, USA, Switzerland, Spain, France, Germany, Netherlands, Japan, India, Argentina, Portugal, Ireland, Denmark, Czech Republic, Lithuania, Slovenia, Australia, Brazil, Norway, Slovakia, Luxembourg, Thailand, Canada, Poland, Belgium, Singapore, Austria, Iran, South Africa, Russia, Croatia, Cyprus, Malta, Romania, Nigeria)
NOTIFY

EXPLORING VIGILANCE NOTIFICATION FOR ORGANS, TISSUES AND CELLS

A Global Consultation

Organised by CNT with the co-sponsorship of WHO and the participation of the EU-funded SOHO V&S Project

February 7-9, 2011
The NOTIFY Tools

- NOTIFY Website  [http://www.notifylibrary.org](http://www.notifylibrary.org)
- NOTIFY Library of didactic cases of events and reactions
- NOTIFY Booklet
- NOTIFY Journal
- NOTIFY Network for horizon scanning ECDC+ USCDC+ ...
THE NOTIFY LIBRARY OF ADVERSE EVENT AND REACTION TYPES

Welcome to the Notify Library site where experts from across the globe collaborate to share didactic information on documented adverse outcomes associated with the application of human organs, tissues and cells. We aim to support continued improvements in safety and efficacy in transplantation and in assisted reproduction.

<table>
<thead>
<tr>
<th>Notify Library site officially launched in Brasilia in December 2013</th>
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<tbody>
<tr>
<td>Marie-Paule Kieny</td>
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<tr>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

Do you have Questions? Corrections? Additions? Suggestions?
Please contact us at notifylibrary@who.int
The NOTIFY Library

A database of all **types of severe adverse events and reactions** that have been reported arising from procurement and processing to clinical application of cells, tissues and organs for transplantation as well as of medical products of human origin used in assisted reproduction technologies.

1. A reference for professionals focused on **diagnostic and investigation**
2. but also providing evidence for **donor selection**,
3. A source of information for candidate **recipients and living donors**
4. A database for **risk mapping and risk based quality management**
<table>
<thead>
<tr>
<th>Known Reaction</th>
<th>Typical alerting signal (i.e. first symptoms/triggers/laboratory findings etc.)</th>
<th>Demonstration of Imputability (how was it confirmed that the donation/transplant/application caused the reaction?)</th>
<th>Related to Group 6.10</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed engraftment</td>
<td>delayed hematological graft recovery</td>
<td>EUSTITE criteria</td>
<td>9</td>
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</tr>
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<td>Infection/Sepsis (product-related)</td>
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<tr>
<td>Bacterial infection/sepsis</td>
<td>fever; sustained hypotension; nausea; vomiting; shock; positive surveillance blood culture</td>
<td>Positive product sterility testing with the same pathogen</td>
<td>6</td>
<td>EUSTITE V&amp;S. 2010</td>
</tr>
<tr>
<td>Viral infection (donor-transmitted)</td>
<td>fever, interstitial pneumonia, flu-like symptoms; positive serology or NAT</td>
<td>Positive donor testing (same virus)</td>
<td>6</td>
<td>Sun et al, 2009</td>
</tr>
<tr>
<td>Viral infection (HBV) contamination</td>
<td>Symptoms consistent with acute HBV infection; HBV in multiple recipients of product from same facility</td>
<td>DNA sequence analysis of contaminant matched DNA of 4 bone marrow recipients from the contaminated storage tank</td>
<td>6, 8</td>
<td>Hawkes, et al, 1996 (see Tedder et al 1995 for clinical information)</td>
</tr>
<tr>
<td>Fungal infection (product-related)</td>
<td>fever, flu-like symptoms, fungal sepsisemia; blood culture positive for fungal elements</td>
<td>Positive product fungal testing (same specie)</td>
<td>6</td>
<td>Mele, et al, 2006; Mori T, Kato J, Ota T, 2007</td>
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<tr>
<td>CMV (new)</td>
<td>diarrhea, interstitial pneumonia/pneumonitis, fever; positive CMV PCR in prior CMV-negative recipient</td>
<td>highly suspected with CMV-negative recipient transplanted with CMV-positive donor, in absence of CMV-positive blood transfusion or other exposures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxoplasma sepsis, CD34 selected cells, autologous</td>
<td>Sepsis at day +69, death</td>
<td>EUSTITE criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>Syphilis seroconversion; day +63</td>
<td>BMTx from recipient's sibling who was serologically positive for syphilis; recipient had TPHA that went down with treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Over 1,700 references in total – Endnote Library
Group 1
List Reactions and Events in Organs

Group 2
Lists Reactions and Events for Tissues (non ocular)

Group 3
Lists Reactions and Events for HSC

Group 4
Lists Reactions and Events for Ocular Tissues

Group 5
Lists Reactions and Events for Gametes and Embryos

Group 6
Master Sheet Infections

Group 7
Master Sheet Malignancy

Group 8
Master Sheet Characteristics and Handling

Group 9
Master Sheet Clinical Practice

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Master Sheet Genetic and Donor
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</table>

5 Didactic Guidance Documents Published Together with the Bologna Meeting Report
Uploaded records by INCIDENT type
(n. 909)

- Infection SARs: 348, 38%
- Malignancy SARs: 135, 15%
- Genetic SARs: 29, 3%
- Process Related SARs: 28, 3%
- Other Recipient SARs: 24, 3%
- Living Donor SARs: 242, 27%
- SAEs: 103, 11%
Donor transmitted INFECTIONS by SUBSTANCE type (n. 348)

- Organs: 201, 58%
- Tissues (non ocular): 72, 20%
- Ocular Tissue: 49, 14%
- HPC: 20, 6%
- Reproductive T&C: 6, 2%
Donor transmitted MALIGNANCIES by SUBSTANCE type (n. 135)
> over 400 new records were uploaded on April 29th. Database now has > 900 records.

THE NOTIFY LIBRARY OF ADVERSE EVENT AND REACTION TYPES

Welcome to the Notify Library site where experts from across the globe collaborate to share didactic information on documented adverse outcomes associated with the application of human organs, tissues and cells. We aim to support continued improvements in safety and efficacy in transplantation and in assisted reproduction.

The database is continually updated and to date 100% of the cases collected (until 2010) by the BIG VxS were examined and uploaded. The next phase of the Notify Project will be to collect new cases (from 2010 to present) and increase the database volume. The search engine is accessible without username and password.
Search Library

Incident search

Adverse incident

- SAR
- All

Substance type

- All substance types

Keywords

(searches keywords identified by the Notify editors)

Free text

(searches the text in the database cases and includes alerting signals, implausibility, and keywords)

Notify library incident ID

(searches by Notify library incident ID, for multiple records separated by commas)

Limit results

10 per page

Notify Library Search

- Incident search
- Reference search
- Bibliographic list

Definitions

SAR - Serious Adverse Reaction
SAE - Serious Adverse Event
<table>
<thead>
<tr>
<th>Incident ID</th>
<th>Incident description</th>
<th>Substance type</th>
<th>Latency (SAR) When detected (SAE)</th>
<th>Alerting signal (SAR) How detected (SAE)</th>
<th>Frequency data and estimates</th>
<th>Demonstration of imputability (SAF) Root cause (SAF)</th>
<th>Keywords</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Human Immunodeficiency Virus (HIV)</td>
<td>SAR -&gt; Recipient -&gt; Infection -&gt; Virus -&gt; HIV</td>
<td>Tissues (non-Glutar) -&gt; Alogenio -&gt; Musculoskeletal -&gt; Iona</td>
<td>Fever, sweats, enlarged nodes, diarrhea, NV. Frozen femoral head used in scoliosis surgery</td>
<td>3 weeks</td>
<td>Proven. Live donor (injecting drug user, large nodes predonation) and recipient developed AIDS after 40 months</td>
<td>HIV (human immunodeficiency virus)</td>
<td>1 reference</td>
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<tr>
<td>203</td>
<td>Human Immunodeficiency Virus (HIV)</td>
<td>SAR -&gt; Recipient -&gt; Infection -&gt; Virus -&gt; HIV</td>
<td>Organs -&gt; Liver</td>
<td>8 days</td>
<td>Lymphocytopenia/Aplastic anemia/Positive test</td>
<td>HIV p24 Ag/Ab</td>
<td>HIV (human immunodeficiency virus)</td>
<td>1 reference</td>
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<tr>
<td>567</td>
<td>Human Immunodeficiency Virus (HIV)</td>
<td>SAR -&gt; Recipient -&gt; Infection -&gt; Virus -&gt; HIV</td>
<td>Organs -&gt; Liver</td>
<td>10 - 148 days</td>
<td>Positive test</td>
<td>HIV p24 Ag/Ab</td>
<td>HIV (human immunodeficiency virus)</td>
<td>2 references</td>
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<tr>
<td>Reference ID</td>
<td>Reference</td>
<td>Incidents</td>
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<tr>
<td>1119</td>
<td>A new miniavascula in a patient with ischaemic bowel-related disease.</td>
<td>2 incidents</td>
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<tr>
<td>741</td>
<td>Successful transplantation of a liver graft with a calcified hydatid cyst after back-table resection.</td>
<td>1 incident</td>
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<tr>
<td>105</td>
<td>Organ selection in intensive care: transplantation of a liver allograft, including calcified cyst of Echinococcus granulosus.</td>
<td>1 incident</td>
<td></td>
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<tr>
<td>577</td>
<td>Rapidly progressive hepatic alveolar echinococcosis in an ABO-incompatible renal transplant recipient.</td>
<td>1 incident</td>
<td></td>
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<tr>
<td>800</td>
<td>Donor Infection and Transmission to the Recipient of a Solid Allograft.</td>
<td>7 incidents</td>
<td></td>
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<tr>
<td>577</td>
<td>Hepatic and intestinal schistosomiasis after orthotopic liver transplant.</td>
<td>1 incident</td>
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<tr>
<td>1320</td>
<td>Donor-to-host transmission of bacterial and fungal infections in lung transplantation.</td>
<td>7 incidents</td>
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<td>1723</td>
<td>Fatal pneumonia caused by Pasteur-Valentine-Leuconea-positive multidrug-resistant Staphylococcus aureus (PVL-MRSA) transmitted from a healthy donor in living-donor liver transplantation.</td>
<td>2 incidents</td>
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<tr>
<td>1320</td>
<td>Strongyloides stercoralis hyperinfection transmitted by liver allograft in a transplant recipient.</td>
<td>2 incidents</td>
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<tr>
<td>335</td>
<td>Pneumocystis jirovecii: first case of transmission of Pneumocystis jirovecii from a white matter donor to four recipients.</td>
<td>6 incidents</td>
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<td>Reference ID</td>
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</tbody>
</table>
History of the NOTIFY Project
Brasilia Participants (Blood)

- Arlinke Bokhorst
- Ludo Muylle
- Jorge Condeco
- Matt Kuehnert
- Luc Noel
- Mike Strong
- Paul Ashford
- Anuj Sharma
- Ghazi Saleh Saeed
- Geni Camara
- Daniel de Freitas
- Deirdre Fehily
- Barbee Whitaker
Next steps Blood as MPHO in Notify Library

- Share with International Haemovigilance Network and the Working Party of ISBT
- Confirm blood taxonomy
  - MPHO Substance
  - Occurrence/Incident/Event Categories
Substance Taxonomy

Human Substance

- Tissues
  - Whole Blood
  - Red Blood Cells
- Blood
  - Platelets
  - Plasma
- Ocular Tissue
  - Plasma Derivatives
- Organs
- ART
  - Cryoprecipitate
- Milk
  - Granulocytes
Blood Taxonomy Attributes

- **Donor to Recipient Relationship Attributes**
  - Autologous
  - Allogeneic: Single Donor
  - Allogeneic: Multiple Donor

- **Processing Attributes**
  - PRP Derivation
  - Cryopreservation
  - Separation: Buffy Coat
  - Apheresis
  - Leukoreduction
  - Irradiation
  - Frozen
  - Pathogen reduced / inactivated
  - Additive solutions
  - Pooled
  - Washing
  - Anticoagulants
  - Thawing
Event Categorization

- Incident or Event
- SAE
- Occurrence
- SAR
- Reaction
- Harm or No Harm
- Recipient or Donor
Recipient (Patient) Harm

Transfusion Reaction

- Allergic Reaction
- Acute Hemolytic Reaction: immune
  - ABO
  - Other alloantibodies
- Acute Hemolytic Reaction: non-immune
- Delayed Hemolytic Reaction: immune
  - ABO
  - Other alloantibodies
- Delayed Hemolytic Reaction: non-immune
- TRALI
- TACO
- TAD

- Delayed Serologic Reaction
- Post Transfusion Purpura (PTP)
- Transfusion Associated Graft versus Host Disease
- Febrile Reaction
- Hypotensive Reaction
- Hypertensive Reaction
- Hemosiderosis
- Transfusion Associated Sepsis
- Under transfusion
- Other (e.g. air embolism, hyperkalemia, other metabolic reactions)
SARE Taxonomy: Donor Harm*

Vasovagal Reactions
- No Loss of Consciousness (LOC)
- LOC
- LOC (complicated)

- Location on site
- Location off site

Allergic
- Local
- Systemic
- Anaphylaxis

Local Injury related to needle
- Nerve Irritation
- Hematoma/Bruise
- Arterial Puncture
- Painful Arm
- Major vessel injury
- Infection
- Bleeding

Apheresis Infusion Reactions
- Citrate
- Hemolysis
- Air Embolus

Other

*Harmonized Definitions
Adverse Occurrences, eg.

- Loss of highly matched or autologous material
- Gamete or embryo mix-up
- Loss of suitable organ
- Loss of large quantity of MPOH (unmatched tissues or cells)
- Unsuitable tissue or cells released for clinical use and/or applied clinically
Adverse Occurrences: Blood

- Wrong blood in tube or Incorrect Blood Component Transfused
- Unsuitable Blood released for clinical use and/or applied clinically
- Loss of highly matched or autologous material
- Loss of large quantity of MPOH (unmatched tissues or cells): equipment failures
- Others...
Next steps Blood as MPHO in Notify Library

- Share with International Haemovigilance Network and the Working Party of ISBT
- Confirm taxonomy
- Develop a reporting form
- Pilot test with experts
- Invite Participation
- Establish editorial groups
  - Published literature
  - Other instructive or exemplary cases
- Incorporate into Notify using agreed upon taxonomy
www.notifylibrary.org

Thank you!

Barbee Whitaker, PhD
Director Center for Patient Safety
AABB