WHO Initiative on Vigilance for Organs, Tissues and Cells: Project NOTIFY

D. Michael Strong, PhD
Retired (Sort of)
Affiliate Professor, Department of Orthopaedics and Sports Medicine,
University of Washington, School of Medicine
Seattle, WA
URGES Member States:

1) to implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring accountability for human material for transplantation and its traceability;
2010

World Health Assembly Resolution WHA63.22
Human Organ and Tissue Transplantation

2. URGES Member States:
...

(7) to collaborate in collecting data including adverse events and reactions, on the practices, safety, quality, efficacy, epidemiology and ethics of donation and transplantation;

(8) to encourage the implementation of globally consistent coding systems for human cells, tissues and organs as such in order to facilitate national and international traceability of materials of human origin for transplantation;

3. REQUESTS the Director-General:
....

(4) to facilitate Member States’ access to appropriate information on the donation, processing and transplantation of human cells, tissues and organs, including data on severe adverse events and reactions;
WHO is a Partner as Vigilance and Surveillance must be global
European SOHO V&S Systems

Interaction/Cooperation with other reporting systems

Haemovigilance

Pharmacovigilance

Survey of European V&S Systems, 2011
- Recruiting health care professionals and other stakeholders for CTO V&S on the basis of evidence: database of types of SARE
  - Understanding the What, Why, How of V&S
  - Mapping risks according to current global evidence in V&S (NOTIFY Db)
  - Generic information to be adapted by national health authorities
- Progressing towards a common global V&S
- Increasing community involvement and collaboration between stakeholders
- Searching for excellence to match the commitment to donation and transplantation
The Notify Project

- **Scope**: organs, tissues and cells for transplantation and for assisted reproduction.
- **Aim**: to create a compendium of cases of adverse reactions/events for donors and recipients of organs, tissues or cells, noting how they were detected, confirmed and documented and to develop guidance based on the information collected.
PROJECT NOTIFY: The Google Site

10 global working groups led by international experts

Co-ordinated by D. Michael Strong
The NOTIFY Website Participants

• Site shared with 102 people
• From 25 countries
• Governmental organizations – both regulatory and non-regulatory (WHO, European Commission, FDA, CDC, TGA, HTA, FHEA, AFSSAPS, ABM, CNT, ONT, PHAC, DMA, IMB, KFDA, PHA, ANVISA .....)
• Professional Societies (TTS, AABB, AATB, EATB, ESHRE, EEBA, EBAA, EBMT, WMDA, SICOT ...)
• National and international non-governmental organizations (NMDP, UNOS, Eurotransplant, Donor Action)
• European projects: EFRETOS, SOHO V&S
### Working Groups 1-5

<table>
<thead>
<tr>
<th>Substance</th>
<th>Leaders</th>
</tr>
</thead>
</table>
| Organs                | Paolo Grossi (Italy)  
Matthew Kuehnert (CDC, USA)  
Francis Delmonico (The Transplantation Society)  
Sante Venettoni (Italy) |
| Corneas               | Naoshi Shinosaki (Japan)  
Paul Dubord (Canada)  
Marion Macsie (EBAA, USA) |
| Other Tissues         | Ted Eastlund (USA)  
Byoung-Suck Kim (Korea)  
Maurice Hinsenkamp (SICOT, Belgium) |
| HPC                   | Laura St Martin (FDA, USA)  
Dietger Niederwieser (WBMT, Germany)  
Kathy Loper (AABB) |
| Gametes and Embryos   | Luca Gianaroli (ESHRE, Italy)  
Anne Cathrine Bollerup (Denmark)  
Mauro Costa (Italy) |

Groups 1-5 gathered documented cases of adverse reactions and events associated with organ, tissue or cell application in humans (with references), identifying the triggers that alerted clinicians and the procedures followed to clarify imputability.
**An example of a worksheet .... HPC**

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Known Reaction</strong></td>
<td><strong>Typical alerting signal (i.e. first symptoms/triggers/laboratory findings etc.)</strong></td>
<td><strong>Demonstration of Imputability (how was it confirmed that the donation/transplant/application caused the reaction?)</strong></td>
<td><strong>Related to Group 6.10</strong></td>
<td><strong>References</strong></td>
</tr>
<tr>
<td>9</td>
<td>Delayed engraftment</td>
<td>delayed hematological graft recovery</td>
<td>EUSTITE criteria</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>Infection/Sepsis (product-related)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<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>
</tr>
<tr>
<td>13</td>
<td>Viral infection (donor-transmitted)</td>
<td>fever, interstitial pneumonia, flu-like symptoms; positive serology and NAT</td>
<td>Positive donor testing (same virus)</td>
<td>6</td>
</tr>
<tr>
<td>14</td>
<td>Viral infection (HBV) lab 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>
</tr>
<tr>
<td>15</td>
<td>Fungal infection (product-related)</td>
<td>fever, flu-like symptoms, fungal septicemia, blood culture positive for fungal elements</td>
<td>Positive product fungal testing (same specie)</td>
<td>6</td>
</tr>
<tr>
<td>16</td>
<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 exsoruses</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Toxoplasma sepsis, CD34 selected cells, autologous</td>
<td>Sepsis at day +69, death</td>
<td>EUSTITE criteria</td>
<td>9</td>
</tr>
<tr>
<td>18</td>
<td>Syphilis</td>
<td>Syphilis seroconversion; day +63</td>
<td>BMf from recipient's sibling who was serologically positive for syphilis</td>
<td>9</td>
</tr>
</tbody>
</table>

**Over 1,700 references in total – Endnote Library**
The Development of V&S Didactic Guidance

- **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

- **Group 10**
  Master Sheet Genetic and Donor
The Development of V&S Didactic Guidance

- 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
- Group 10: Master Sheet Genetic and Donor
The Development of V&S Didactic Guidance

Group 1
List Reactions and Events in Organs

Group 2
List 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

Group 10
Master Sheet Genetic and Donor
The Development of V&S Didactic Guidance

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

Group 10
Master Sheet Genetic and Donor
The Development of V&S Didactic Guidance

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

Group 10
Master Sheet Genetic and Donor
Working Groups 6-10

<table>
<thead>
<tr>
<th>Substance</th>
<th>Leaders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Mike Ison (USA)</td>
</tr>
<tr>
<td></td>
<td>Richard Tedder (UK)</td>
</tr>
<tr>
<td></td>
<td>Francesco Procaccio (Italy)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Rafael Matesanz (Spain)</td>
</tr>
<tr>
<td></td>
<td>Antonietta Derrico Griggioni (Italy)</td>
</tr>
<tr>
<td></td>
<td>Jeremy Chapman (Australia)</td>
</tr>
<tr>
<td>Genetic and Donor</td>
<td>Carolina Stylianou (Cyprus)</td>
</tr>
<tr>
<td></td>
<td>Denis Confer (WBMT, NMDP, USA)</td>
</tr>
<tr>
<td></td>
<td>Emanuele Cozzi (Italy)</td>
</tr>
<tr>
<td>Product Property</td>
<td>Diego Ponzin (Italy)</td>
</tr>
<tr>
<td></td>
<td>Scott Brubaker (AATB, USA)</td>
</tr>
<tr>
<td></td>
<td>Axel Rahmel (Eurotransplant, Efretos Project)</td>
</tr>
<tr>
<td>Clinical Practice</td>
<td>Lorenza Ridolfi (Italy)</td>
</tr>
<tr>
<td></td>
<td>Renee de Vries (IHN)</td>
</tr>
<tr>
<td></td>
<td>Paula Nolan (UK)</td>
</tr>
</tbody>
</table>

Groups 6-10 regrouped the cases collected by groups 1-5 by type of reaction/event and developed guidance for clinicians for early detection and treatment and for establishing cause.
An example of a master worksheet...

<table>
<thead>
<tr>
<th>Known Reaction</th>
<th>Allograft</th>
<th>Time of diagnosis after transplant (months)</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>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Promyelocytic Leukemia</strong></td>
<td>Liver</td>
<td>24</td>
<td>24 months after Tx, unspecific symptoms, achy, thrombocytopenia and disseminated intravascular coagulation. Leukemic cells in blood smear. Bone marrow aspiration and biopsy confirmed diagnosis. Tumor related death.</td>
<td>DNA studies (unique sex chromosome- male to female donation- and HLA markers), t-translocation only present in male cells.</td>
<td>Bodo I. NEJM 1999; 341: 807.</td>
</tr>
<tr>
<td><strong>Adenocarcinoma</strong></td>
<td>Liver</td>
<td>6</td>
<td>Abnormal T-tube cholangiogram performed in anticipation of T-tube removal 6 months after Tx, revealed multiple irregularities of intrahepatic ducts. Needle liver biopsy: small focus of moderately well-differentiated adenocarcinoma. No extrhepatic metastases found. 54 weeks after first Tx, second Tx performed. Explanted liver with multiple malignant nodules. Recipient with no evidence of malignancy 25 months after second Tx.</td>
<td>Fluorescence in situ hybridization for the Y chromosome indicated male origin of malignancy (recipient was a female). Donor-related disease confirmed by comparative DNA analysis of genomic sequences from the donor liver, associated tumor, and recipient peripheral blood.</td>
<td>Kauffmann HM Transplantation 1997; 74:358-362. Donovan JA Transplantation 1997; 63: 80.</td>
</tr>
<tr>
<td><strong>Adenocarcinoma</strong></td>
<td>Liver</td>
<td>12</td>
<td>Liver ultrasound of the anastomoses shows a 1.5 cm mass at 1 year follow-up visit. Biopsy shows a moderately differentiated adenocarcinoma.</td>
<td>Tumor, donor and recipient DNA isolated from the paraffin embedded liver biopsy, pretransplant liver donor biopsy and explanted liver tissue, respectively. Microsatellite analysis performed by polymerase chain reaction using 5 markers. DSS336A.</td>
<td>Kakar, et al, 2002;</td>
</tr>
<tr>
<td>Infection</td>
<td>Allograft</td>
<td>Initial symptom, sign, or test</td>
<td>Time between transplant and onset or discovery</td>
<td>Likelihood cause is allograft</td>
<td>Country and Reference</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>HIV</td>
<td>Frozen femoral head (live donor), Nov, 1984</td>
<td>Fever, sweats, enlarged nodes, diarrhea, HIV,</td>
<td>3 weeks, (HIV viral syndrome), 40 mo later developed AIDS,</td>
<td>Proven. Donor (injecting drug user, large nodes predonation) and recipient developed AIDS, Proven: active infection in common donor &amp; many recipients</td>
<td>USA, MMWR</td>
</tr>
<tr>
<td>HIV</td>
<td>Frozen femoral head 1985</td>
<td>Positive test.</td>
<td>1.5 yr: asymptomatic sought testing, was POS. AIDS at 4 yr, died at 5 yr</td>
<td>Proven: active infection in common donor &amp; many recipients</td>
<td>USA, Simonds</td>
</tr>
<tr>
<td>HIV</td>
<td>Frozen patellar ligament, 1986</td>
<td>Fever, rash, pharyngitis, lymphopenia, pos test</td>
<td>3 weeks, (HIV viral syndrome)</td>
<td>Proven : active infection in common donor &amp; many recipients</td>
<td>USA, Simonds</td>
</tr>
<tr>
<td>HIV</td>
<td>Frozen femoral head, 1985</td>
<td>Pt sought Asymptomatic,testing</td>
<td>Approx 1.5 year</td>
<td>proven: active infection in common donor &amp; other recipients</td>
<td>USA, Simonds</td>
</tr>
<tr>
<td>Bacteria, Clostridium tertelli</td>
<td>Refrigerated Osteochondral Distal Femur Condyle 2001</td>
<td>Surgical knee site pain, hypotension day 3, death day 4</td>
<td>5 mo</td>
<td>Possible: (donor not tested)</td>
<td>Taiwan</td>
</tr>
<tr>
<td>HIV</td>
<td>Frozen femoral head, 1996</td>
<td>Routine , testing</td>
<td>3 days</td>
<td>Proven, same m/o on recovered tissue, on contralateral allograft and patient</td>
<td>Walton, 2002</td>
</tr>
<tr>
<td>HCV</td>
<td>Frozen femoral head</td>
<td></td>
<td>Found HCV pos during traceback investigation</td>
<td>Proven</td>
<td>Norway, Eggen NEJM 1992</td>
</tr>
<tr>
<td>HCV</td>
<td>Refrigerated vessels</td>
<td></td>
<td>Found HCV pos during traceback investigation</td>
<td>Proven</td>
<td>CDC 2011</td>
</tr>
<tr>
<td>CJD</td>
<td>Refrigerated cornea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CJD</td>
<td>FD dura</td>
<td>Gait ataxia, dysarthria, dizziness</td>
<td>43 months</td>
<td></td>
<td>Spain, MMWR 1993:</td>
</tr>
<tr>
<td>CJD</td>
<td>Processed dura</td>
<td>CJD Sx</td>
<td>Mean 11.8 yr, (range 1.2 to 24.6 yr) (Japan)</td>
<td>Proven japanese cluster of transmissions</td>
<td>Japan, Canada</td>
</tr>
<tr>
<td>CJD</td>
<td>Dura</td>
<td>Insomnia, anxiety, gait disturbance, ataxia, dysarthria</td>
<td>19 years</td>
<td>Proven</td>
<td></td>
</tr>
<tr>
<td>CJD</td>
<td></td>
<td>Ataxia, blurred vision, dysarthria, dysmetra, progressive dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BOLOGNA NOTIFY MEETING
February 7th to 9th, 2011
PROGRESS OF THE BOLOGNA OUTCOMES
The 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)
• Detailed report by lead rapporteur, Frances Delaney, and support Rapporteurs.
The NOTIFY Project

Alessandro Nanni-Costa, Deirdre Fehily, Mike Strong, Stratos Chatzixiros, Daniela Minutoli

Pre-Bologna
The Notify Google Site
All types of SARE with human CTO

Bologna
The Meeting, Feb. 2011
Review of types of SARE
Towards an ongoing library of didactic cases

BIG V&S
Bologna
Initiative for Global Vigilance and Surveillance
First International Advisory Group on V&S for CTO
Geneva 5-6 July 2011
PROJECT NOTIFY OUTPUTS

• Detailed Meeting Report with 4 didactic documents published in a Special Edition of Organs, Tissues and Cells, November 2011
• An international network of experts sharing expertise on vigilance across organs, tissues, cells, gametes and embryos
• A new public website to host the Notify Library of Adverse Events and Reactions
• A WHO booklet on Vigilance and Surveillance for Clinicians and Regulators
Organs, Tissues and Cells

Nov., 2011

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 VBS Project
February 7-9, 2011

PROJECT NOTIFY OUTPUTS

- An international network of experts sharing expertise on vigilance across organs, tissues, cells, gametes and embryos
- A new public website to host the Notify Library of Adverse Events and Reactions
- A WHO booklet on Vigilance and Surveillance for Clinicians and Regulators
PROJECT NOTIFY OUTPUTS

• Detailed Meeting Report with 4 didactic documents published in a Special Edition of Organs, Tissues and Cells in November 2011

• An international network of experts sharing expertise on vigilance across organs, tissues, cells, gametes and embryos

• A new public website to host the Notify Library of Adverse Events and Reactions

• A WHO booklet on Vigilance and Surveillance for Clinicians and Regulators
The new website will host the new searchable database

<table>
<thead>
<tr>
<th>Substance (e.g. Kidney)</th>
<th>Reaction/Event type (e.g. WNV transmission)</th>
<th>Latency</th>
<th>Usual Alerting Signals</th>
<th>Usual method of confirmation</th>
<th>List of references (scientific literature or vigilance reports) with internet links where possible</th>
</tr>
</thead>
</table>
The NOTIFY Library Operation

Annual WHO Global Consultation on V&S Review

Literature review
- Structured
- Automated
- Comprehensive

CNT Secretariat

Partner organisations provide information
- Competent Authorities
- Scientific Professional Societies

Five Editorial WGs
- Infection
- Malignancy
- Handling-clinical errors
- Genetic
- Living donor

Accept

Ad hoc queries
- current, and accessible

Analyze new data and modify structured analysis regarding alerting signals etc.

Analysis – structured, searchable, current, and accessible

Record of justification of Rejection

Reject
NOTIFY Editorial Groups

- **Infections**
  - Co-chairs: Mike Ison and Paolo Grosso
  - Other members: Ted Eastlund, Melissa Greenwald and Richard Tedder

- **Malignancy**
  - Co-chairs: Jeremy Chapman and Rafael Matesanz
  - Other members: Haibo Wang, Dietger Niederwieser and Kathy Loper

- **Process**
  - Co-chairs: Scott Brubaker and Francis Delmonico
  - Other members: Axel Rahmel, Anne Cathrine Bollerup and Marian Macsai

- **Genetic**
  - Co-chairs: Mauro Costa
  - Other members: Denis Confer, Jun Wu and Chris O’Toole

- **Living Donor**
  - Co-chairs: Bronwyn Shaw and Daniel Roberto Coradi de Freitas
  - Other members: Carolina Stylianou, Tim Pruett and Tomonori Hasegawa
Published Articles
Cases of Adverse Events and Reactions

The Notify Library of Adverse Events and Reactions was developed by the World Health Organization (WHO), the Italian National Transplant Centre (CNT) and the EU-funded SOHO V&S project with the collaboration of experts and regulators across the globe. The scope of the project included organs, tissues and cells for transplantation and for assisted reproduction. Expert groups worked collaboratively to gather and review documented cases of reactions and events across the scope of the substances under consideration, using published articles and vigilance system reports as their sources. Over 1,500 published references have been collected and new cases continue to be added. The cases were used as the basis for developing draft guidance on detection and confirmation of reactions and events. The publication is available on the new website together with a searchable database of the events and reactions by human substance type and by reaction/event type.
PROJECT NOTIFY OUTPUTS

• Detailed Meeting Report with 4 didactic documents published in a Special Edition of Organs, Tissues and Cells, November 2011
• An international network of experts sharing expertise on vigilance across organs, tissues, cells, gametes and embryos
• A new public website to host the Notify Library of Adverse Events and Reactions
• A WHO Handbook on Vigilance and Surveillance, a Guidance for Clinicians and Health Authorities