

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

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Retired (Sort of)

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Seattle, WA

- **2004**

World Health Assembly Resolution WHA57.18 Cell, Tissue and Organ Transplantation

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**;



**Governments
are responsible**

2. URGES Member States:

...

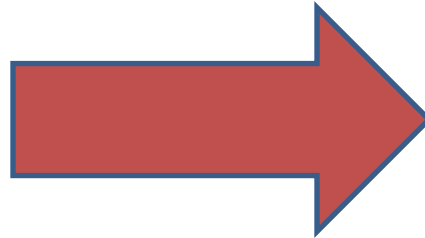
(7) to collaborate in collecting **data including adverse events and reactions**, on the practices, safety, quality, efficacy, epidemiology and ethics of donation and transplantation;

(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**;

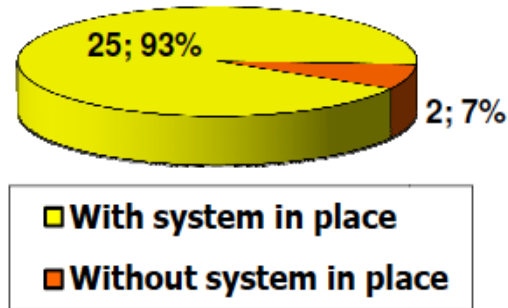


WHO is a Partner as Vigilance and Surveillance must be global



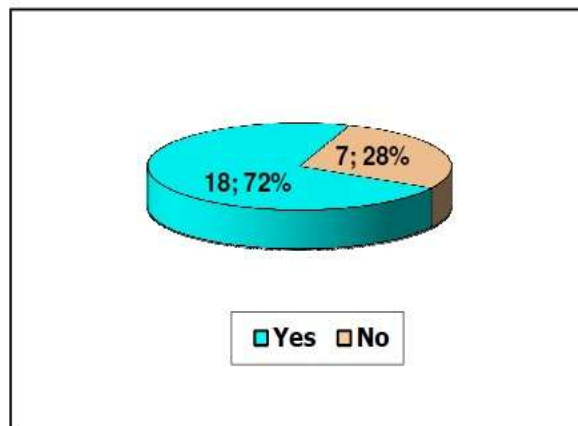
www.sohovs.org

European SOHO V&S Systems

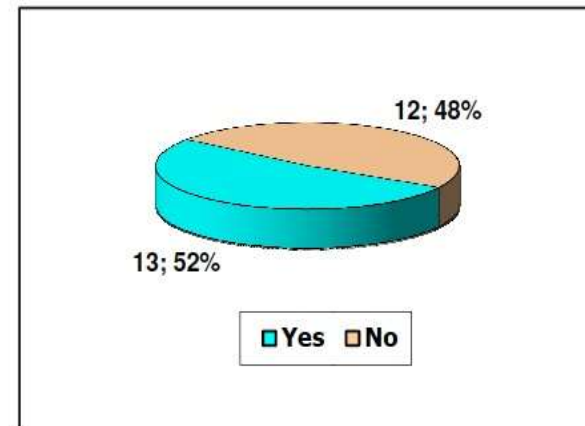


Interaction/Cooperation with other reporting systems

Haemovigilance



Pharmacovigilance



- 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

Project Notify

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Home

Project Definition

The Team

To-Dos

Time Tracker

Project updates

Files

Benchmark Dates

Workgroup Worksheets

Sitemap

13 days since Group 6 - 10 Documents Due Date

Join Our Discussion

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Home The project Who we are V&S Investigation V&S Guidance for Clinical Users V&S in Assisted Reproduction Contacts

Vigilance and Surveillance of Substances

Centro Nazionale

10 global working groups led by international experts

Co-ordinated by D. Michael Strong

A joint initiative co-sponsored by WHO, the SOHO V&S Project (click on link above to take you to the SOHO site) will culminate in a Global Consultation on the Vigilance of Organs, Tissues and Cells (for transplantation and for assisted reproduction) in Bologna, February 7-9 2011. Prior to the conference, a series of four working groups will develop...

attend from around the world and we have a really broad ...

Posted Jan 21, 2011 9:01 AM by deirdre.fehily@iss.it

https://sites.google.com/site/whoprojectnotify/home/CNT.png?attredirects=

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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, 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

Substance	Leaders
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

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	A	B	C	D	E
1	Known Reaction	Typical alerting signal (i.e. first symptoms/triggers/laboratory findings etc.)	Demonstration of Imputability (how was it confirmed that the donation/transplant/application caused the reaction?)	Related to Group 6-10	References
9	Delayed engraftment	delayed hematological graft recovery	EUSTITE criteria	9	EUSTITE V&S, 2010
10					
11	Infection/Sepsis (product-related)				
12	Bacterial infection/sepsis	fever; sustained hypotension; nausea; vomiting; shock; positive surveillance blood culture	Positive product sterility testing with the same pathogen	6	EUSTITE V&S, 2010
13	Viral infection (donor-transmitted)	fever, interstitial pneumonia, flu-like symptoms; positive serology or NAT	Positive donor testing (same virus)	6	Sun et al, 2009
14	Viral infection (HBV) lab contamination	Symptoms consistent with acute HBV infection; HBV in multiple recipients of product from same facility	DNA sequence analysis of contaminant matched DNA of 4 bone marrow recipients from the contaminated storage tank	6,8	Hawkins, et al, 1996 (see Tedder et al 1995 for clinical information)
15	Fungal infection (product-related)	fever, flu-like symptoms, fungal septicemia; blood culture positive for fungal elements	Positive product fungal testing (same specie)	6	Mele, et al, 2005;
16	CMV (new)	diarrhea, interstitial pneumonia/pneumonitis, fever; positive CMV PCR in prior CMV-negative recipient	highly suspected with CMV-negative recipient transplanted with CMV-positive donor, in absence of CMV-positive blood transfusion or other exposures		Mori T, Kato J, Cytomegalovirus infection/disease after
17	Toxoplasma sepsis, CD34 selected cells, autologous	Sepsis at day +69, death	EUSTITE criteria		
18	Syphilis	Syphilis seroconversion; day +63	BMTx from recipient's sibling who was serologically positive for syphilis recipient had TPHA that went down with treatment		

Over 1,700 references in total – Endnote Library

Recipient Adverse Reactions ▼

Adverse Events

Donor--Marrow

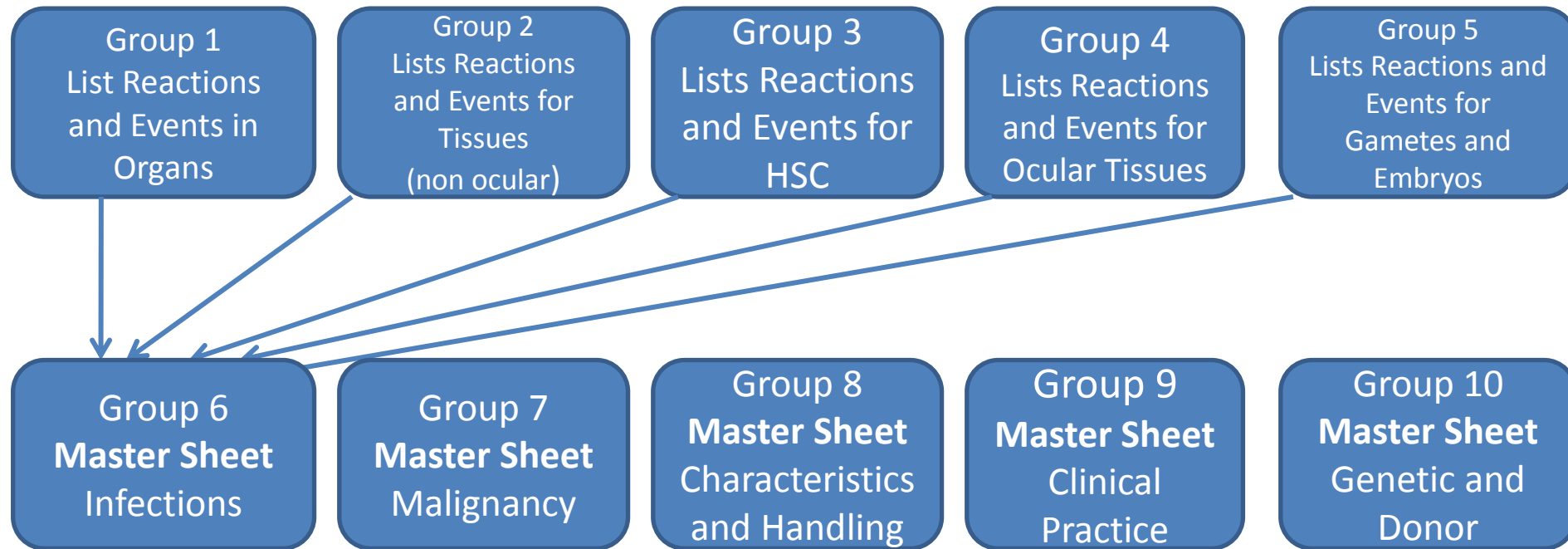
Donor--Apheresis

References

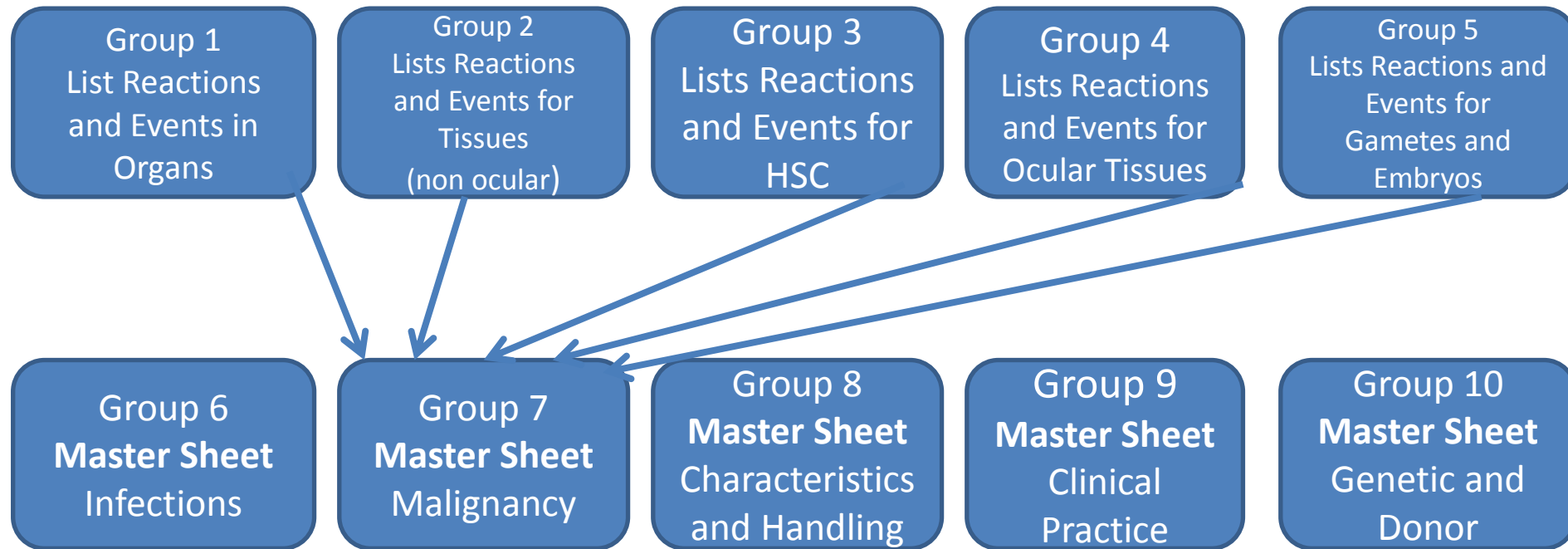
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Known Reaction

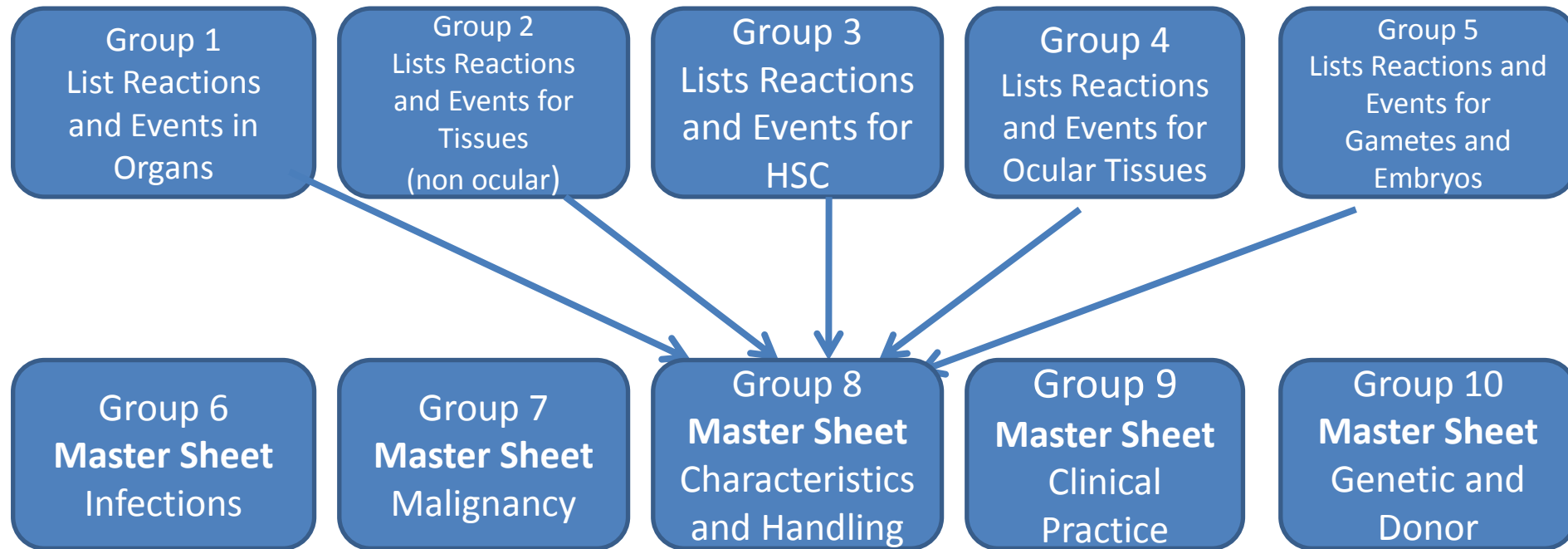
The Development of V&S Didactic Guidance



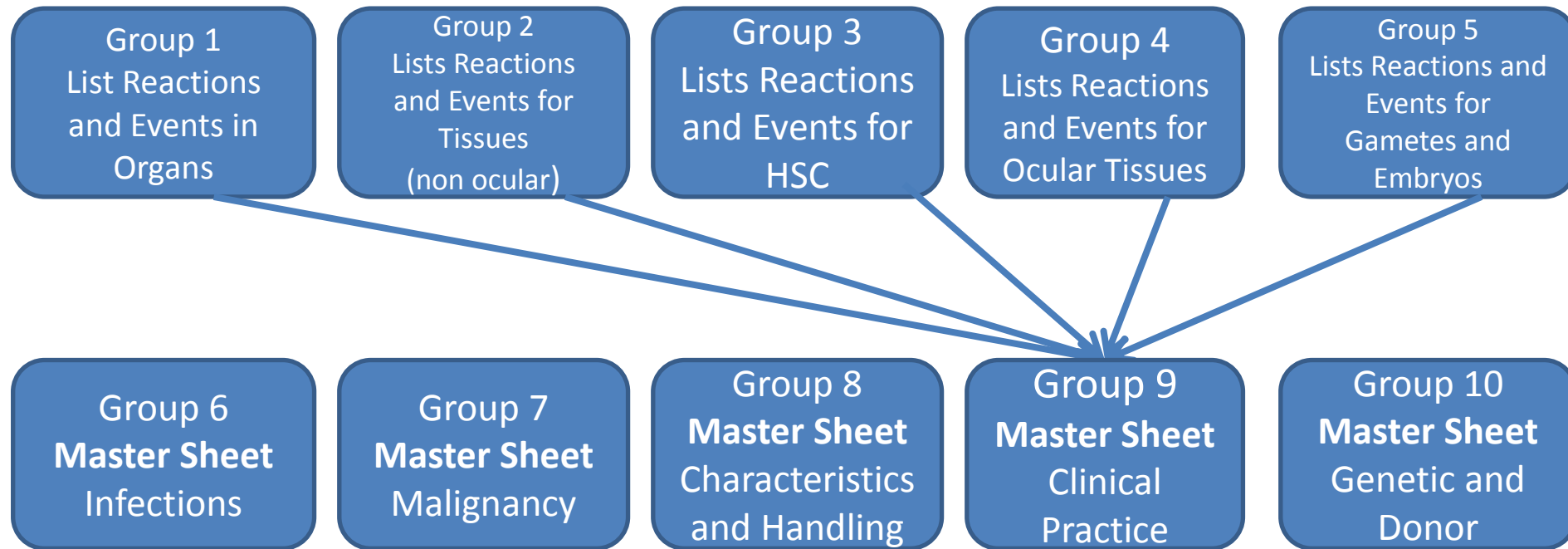
The Development of V&S Didactic Guidance



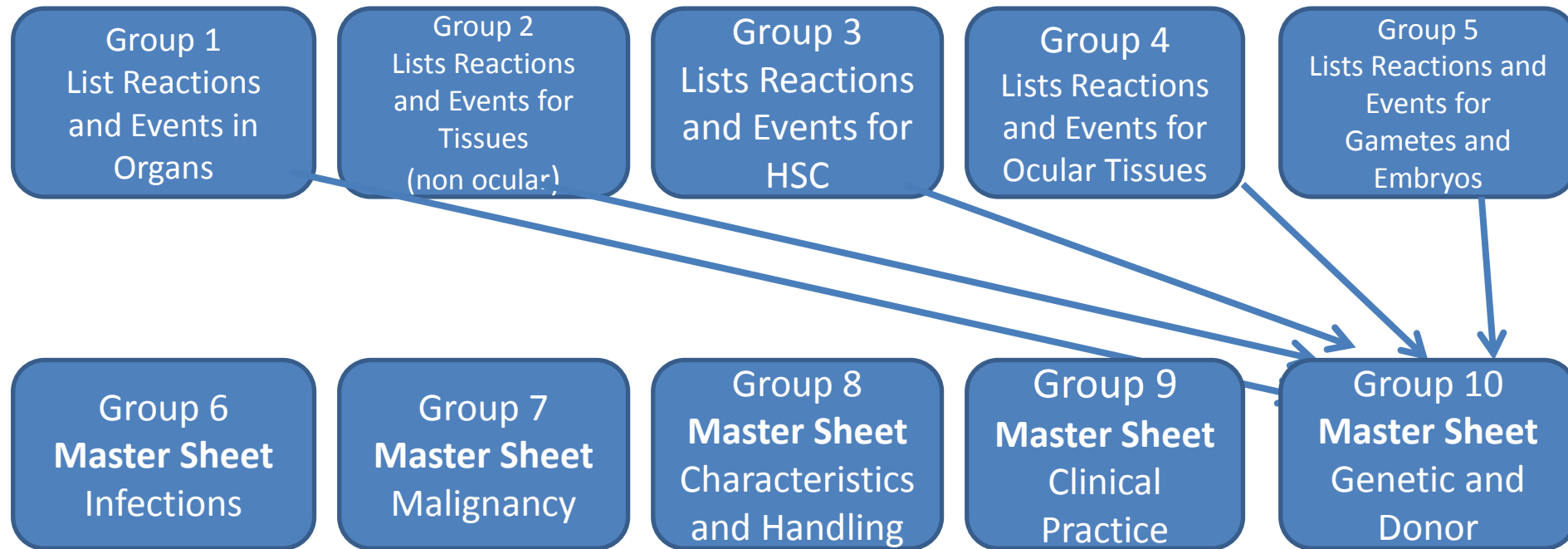
The Development of V&S Didactic Guidance



The Development of V&S Didactic Guidance



The Development of V&S Didactic Guidance



Working Groups 6-10

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

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...

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	A	B	C	D	E	F
1	Known Reaction	Allograft	Time of diagnosis after transplant (months)	Typical alerting signal (i.e. first symptoms/, triggers/laboratory findings etc.)	Demonstration of Imputability (how was it confirmed that the donation/transplant/, application caused the reaction?)	References
2	Acute Promyelocytic Leukemia	Liver	24	24 months after Tx, unspecific symptoms, ecchymosis, thrombocytopenia and disseminated intravascular coagulation. Leukemic cells in blood smear. Bone marrow aspiration and biopsy confirmed diagnosis. Tumor related death.	DNA studies (unique sex chromosome- male to female donation- and HLA markers). t- translocation only present in male cells.	Bodo I. NEJM 1999; 341: 807.
3	Adenocarcinoma	Liver	6	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 extrahepatic 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.	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.	Kauffman HM. Transplantation 2002; 74:358-362; Donovan JA Transplantation 1997; 63: 80.
4	Adenocarcinoma	Liver	12	Liver ultrasound of the anastomoses shows a 1.5 cm mass at 1 year follow-up visit. Biopsy shows a moderately differentiated adenocarcinoma.	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: D5S346	Kakar, et al, 2002;

Tissues HPC **Organs** ▼ Cornea Gametes and Embryos References + [Menu icon] Known Reaction

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A Master Worksheet

Group 6 - Infections

Group 6 Master Worksheet

D. Michael Strong

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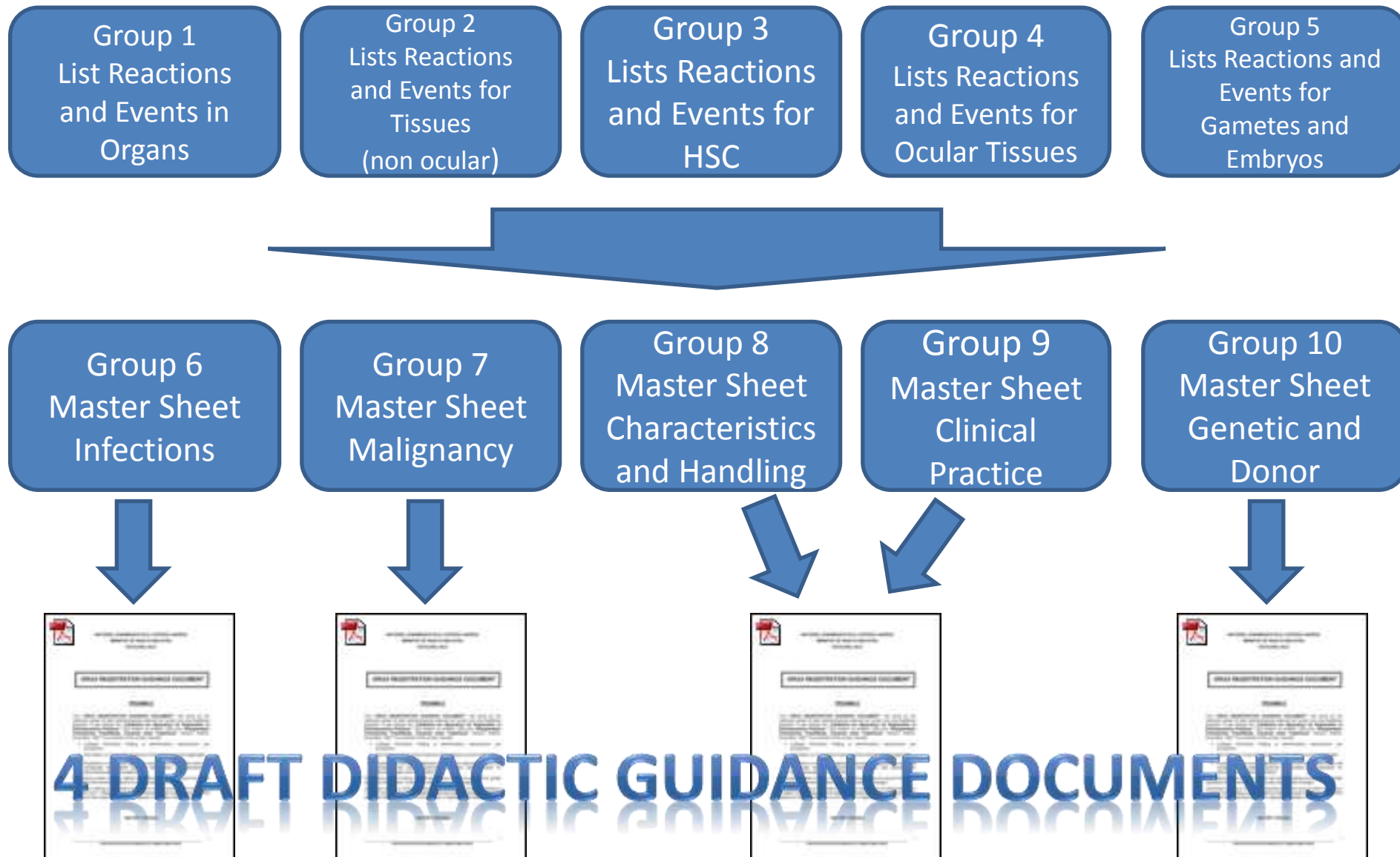
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Infection						Show all formulas
	A	B	C	D	E	F
	Infection	Allograft	Initial symptom, sign, or test	Time between transplant and onset or discovery	Likelihood cause is allograft	Country and Reference
2	HIV	Frozen femoral head (live donor), Nov, 1984	Fever, sweats, enlarged nodes, diarrhea, N/V	3 weeks, (HIV viral syndrome), 40 mo later developed AIDS	Proven. Donor (Injecting drug user, large nodes predonation) and recipient developed AIDS	USA, MMWR
3	HIV	Frozen femoral head 1985	Positive test	1.5 yr. asymptomatic sought testing, was POS. AIDS at 4 yr, died at 5 yr	Proven: active infection in common donor & many recipients	USA, Simonds
4	HIV	Frozen patellar ligament, 1986	Fever, rash, pharyngitis, lymphopenia, pos test	3 weeks, (HIV viral syndrome)	Proven, active infection in common donor & many recipients	USA, Simonds
5	HIV	Frozen femoral head, 1985	Pt sought Asymptomatic, testing	Approx 1.5 year	proven, active infection in common donor & other recipients	USA, Simonds
6	HIV	Frozen femoral head, 1996	Routine, testing	5 mo	Possible: (donor not tested)	Taiwan
7	Bacteria: Clostridium sordellii	Refrigerated Osteochondral Distal Femur Condyle, 2001	Surgical knee site pain, hypotension day 3, death day 4	3 days	Proven, same m/o on recovered tissue, on contralateral allograft and patient	Walton, 2002
18	HCV	Frozen femoral head		Found HCV pos during traceback investigation	proven	Norway, Eggen NEJM 1992
19	HCV	Refrigerated vessels		Found HCV pos during traceback investigation	proven	CDC 2011
20	CJD	Refrigerated cornea				
21	CJD	FD dura	Gait ataxia, dysarthria, dizziness	43 months		Spain, MMWR 1993:
22	CJD	Processed dura	CJD Six	Mean 11.8 yr, (range 1.2 to 24.8 yr) (Japan)		Japan MMWR 57:1152, 2008, USA, Canada
23	CJD	Dura	Insomnia, anxiety, gait disturbance, ataxia, dysarthria	19 years	Proven japanese cluster of transmissions	Japan
24	CJD		Ataxia, blurred vision, dysarthria, dysmetria, progressive dementia,		proven	

Sheet1 Pathogen Working Groups Group 5: Gametes Group 4: Ocular Tissue Group 3: HPC Group 2: Tissue Group 1: Organs Fungi Parasites Bacteria Other (Prions, etc) Viruses References

Infection

The Development of V&S Guidance



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



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



Pre-Bologna

The Notify Google Site

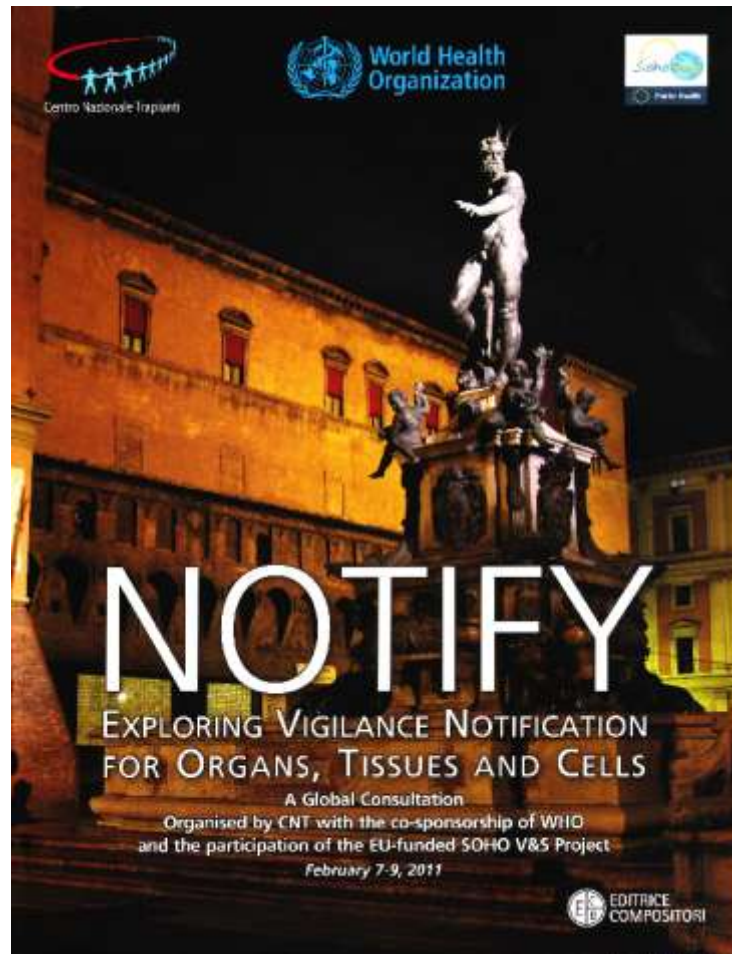
All types of SARE with human
CTO

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



Organs Tissues & Cells. 2011, November, 14, 3: Supp.

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The new website will host the new searchable database

Search Result :

Substance (e.g. Kidney)	Reaction/ Event type (e.g. WNV transmission)	Latency	Usual Alerting Signals	Usual method of confirmation	List of references (scientific literature or vigilance reports) with internet links where possible
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Recommend
Transplants
WHO HCT
WHO Assi

[Database search guide](#)

Disclaimer

The cases, bibliography and associated comments included in this website and database have been provided by experts worldwide and reviewed by voluntary editorial working groups. The data and information is not guaranteed to be complete or to be fully up to date at any particular moment and it reflects the knowledge and views of the experts participating, not those of the World Health Organisation or the Italian National Transplant Centre.

BIG V&S partners



Alerts

Register here to receive email alerts when new information is entered in the database



Contact us

If you have comments, questions or suggestions for the improvement of this site, or new information that should be included in the Notify Library, contact us at notifylibrary@iss.it or click here [CONTACT US!](#)

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

LIBRARY

of evaluated and
relevant material

Ad hoc queries
current, and
accessible

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

Analysis – structured,
searchable, current, and
accessible



Reject

Record of
justification of
Rejection

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

SOHO & EUROCET WEBSITES

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Vigilance and Surveillance ★

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Resources



**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.



Visit the Notify site

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
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- **A WHO Handbook on Vigilance and Surveillance, a Guidance for Clinicians and Health Authorities**