World Health Organization

REPORT

WHO GLOBAL CONSULTATION ON VIGILANCE AND SURVEILLANCE FOR MEDICAL PRODUCTS OF HUMAN ORIGIN

NOTIFY

7-9 DECEMBER 2013, BRASILIA

Centro Nazionale Trapianti
Italian National Transplant Centre
WHO Collaborating Centre on Vigilance and Surveillance for Human Cells, Tissues and Organs

Pan American Health Organization
World Health Organization
Regional Office for the Americas

SUS

ANVISA
Agência Nacional de Vigilância Sanitária

Ministério da Saúde

Governo Federal
BRASIL
PAÍS RICO É PAÍS SEM POBREZA

WHO GLOBAL CONSULTATION ON VIGILANCE AND SURVEILLANCE

FOR

MEDICAL PRODUCTS OF HUMAN ORIGIN

REPORT

7-9 DECEMBER 2013, BRASILIA

Table of Contents

FOREWORD

This publication reports on the deliberations and outcomes of the Third WHO Global Consultation on Vigilance and Surveillance for Medical Products of Human Origin that took place from 7-9 December 2013, in Brasilia, Brazil. The meeting was convened by the World Health Organization (WHO) in collaboration with the Italian National Transplantation Centre, "Centro Nazionale Trapianti" (CNT), the WHO Collaborating Centre on Vigilance and Surveillance for Cell, Tissue and Organ Transplantation.

We wish to express our gratitude to the Ministry of Health of Brazil, to the Brazilian Health Surveillance Agency, "Agência Nacional de Vigilância Sanitária" (ANVISA), as well as to the Brazilian office of the Pan American Health Organization, WHO Regional Office for the Americas. The Consultation would not have been possible without their generous financial and technical support.

For the last three years, such global consultations have enabled participants to advise on WHO's work for vigilance and surveillance (V&S) according to the requirements of World Health Assembly Resolution WHA63.22 on Human Organ and Tissue Transplantation, adopted in May 2010. The consultations consider the progress of the tools for global V&S, in particular the NOTIFY website and the NOTIFY Library. This consultation added a new dimension, by recognizing the commonalities across medical products of human origin (MPHO) such as the existence of a donor exposed to donation risks or the risks of transmitting disease, such as infections, to the recipient. Highlighting the exceptional nature of MPHO inherent to their human origin and seeking excellence in safety through global tools for V&S is necessary to justify the trust of the public and therefore encourage donations.

The consultation was prepared with the invaluable help of the CNT team, in particular Deirdre Fehily, with the contribution of Mike Strong.

This report represents the views of the participants and not necessarily those of WHO. All the participants in the consultation should be thanked for their active participation and their will to achieve consensus. The Secretariat owes special thanks to Alessandro Nanni Costa, Geni Neumann de Lima Camara and Phil O'Connell, who judiciously chaired the meeting, as well as to the rapporteur, Ines Ushiro-Lumb, for her thorough work, with the support of the ANVISA team.

The report was submitted to all participants for comment. We are grateful to them for their input. Any errors or omissions are, of course, our responsibility, not theirs.

Luc Noël and José Ramón Núñez Peña
HIS/SDS
WHO Headquarters

SERVICE DELIVERY & SAFETY

Day One - Saturday 7 December 2013

1. INTRODUCTION

1.1. Welcome and introduction of participants

Luc Noël and Geni Neumann opened the meeting by welcoming all participants and thanking all for coming to Brasilia to attend the 3rd Global Consultation on Vigilance and Surveillance for Medical Products of Human Origin (MPHO). The full list of participants is found in Appendix 1 and the Programme of Work in Appendix 2.

Dr Alessandro Nanni Costa continued with the opening of the Consultation meeting by proudly announcing the official launch of the NOTIFY Library, which had already been in use since 2012. The NOTIFY Library is a concept born from discussions held between Deirdre Fehily, Luc Noël and himself in 2011. The project has evolved and achieved important landmarks with the core support of the CNT team, whose dedication, together with the contribution of international experts, has made this project possible. He also joined Luc Noël and Geni Neumann in thanking all participants for their contribution and presence at the event.

Dr Alessandro Nanni Costa and Dr Geni Neumann were elected co-chairs of the Consultation and Ines Ushiro-Lumb was appointed rapporteur. As Dr Nanni Costa could not stay for the whole consultation, Dr Philip O'Connell agreed to take over as co-chair on the second day.

1.2. Global Vigilance and Surveillance (V&S) and the WHO Initiative for Medical Products of Human Origin (MPHO)

(Luc Noël)

Emphasis was given to the overarching common denominator, irrespective of type of substance or event, which is the human origin of the medical products that the global V&S system aims to monitor. Recognition of humanity in MPHO at all times is of paramount importance and must be kept in the minds of all those involved, regardless of the stage in the journey from donation to clinical application.

1.2.1. Practices that should be inherent to the donation and use of MPHO

- ***Responsibility*** for the provision of MPHO is primarily placed with health authorities and through them the individual citizen and resident.
- ***Equity*** in donation and in allocation of MPHO is a principal goal.
- ***Prohibition of financial gain*** from the human body and its parts as such and where profit is allowed, regulation by competent authorities and guarantee of transparency.
- ***Genuine consent*** of donors and recipients and protection of the incompetent.

- ***Use of MPHO justified*** by evidence and absence of a comparable alternative.
- **Duty to constantly optimize** the safety, quality and efficacy of procurement, processing and clinical application of MPHO.
- ***Traceability and accountability*** mandated throughout the process, from donors to recipients, including long-term outcomes and vigilance and surveillance under the oversight of competent authorities.
- ***Transparency*** and openness to scrutiny indispensable, while confidentiality and anonymity are preserved, as appropriate.

1.2.2. The Global Standard for Medical Products of Human Origin - Information Standards for Blood and Transplant 128 (ISBT 128)

The need to harmonize practices as recognized by WHA 57.18, to ensure continuous improvements and to effectively manage the international distribution of MPHO, requires a global governance system. This, in turn, requires a common language supported by standard terminology and consistent coding. Globally agreed product terminology provides a basis for gathering accurate activity data and provides a common platform for vigilance monitoring.

The International Council for Commonality in Blood Bank Automation (ICCBBA), as a non-government organization (NGO) in Working Relations with WHO, which manages a global governance service for the globally meaningful coding and labeling of MPHO, which includes:

- Global Terminology, translated into different languages and codes
- Globally unique donation and product identifiers
- Common information transfer formats.

The objectives of harmonization encompass:

- Comprehensive traceability
- Safety and reliability of data transfer
- Transparency with protection of confidentiality
- National and international circulation of MPHO with safety
- Interoperability of MPHO within and between countries, both in routine and emergency situations
- Cost containment through generalization.

Universal use of ISBT 128 for all MPHO

- The aim is to achieve universal adoption within 10 years, with registration of commitment beginning in 2014-15.

1.2.3. Global vigilance and surveillance

- Mutualizing the global experience of V&S in MPHO services through
  - Risk identification
  - NOTIFY Risk assessment
  - Risk based quality management
  - Risk education
- Promoting V&S as a crucial mechanism of quality and transparency in MPHO services
- Associating professionals, operators and competent authorities
- Demonstrating transparency
- Deserving trust.

1.2.4. NOTIFY tools and global progress

- NOTIFY Website: http://www.notifylibrary.org
- NOTIFY Library of didactic cases of events and reactions
  - Donor selection and management
  - Recipient management
  - Quality system - risk based management
- NOTIFY Booklet is a tool near completion and was presented at the consultation.
- NOTIFY Journal as another proposed tool for the dissemination of knowledge. This new initiative was discussed at a separate session at the meeting.
- The place for ethics in the NOTIFY Library was a specific topic presented and debated at a session on the second day of the event.
- Promoting systems, reporting and sharing:
  - Tool with universal accessibility to share knowledge of events and reactions
  - Dissemination of knowledge and of lessons learnt to gain public confidence.
- Continued focus needs to be maintained in order to keep the NOTIFY up-to-date, improve it and make it simple and universally accessible.

1.3. V&S as a driver for excellence in transplantation - CNT and the European experience

(Alessandro Nanni-Costa)

Reasons for incident reporting can be of immediate or longer-term nature. Prompt action following an incident report is important to facilitate the quarantine and recall of tissues and cells where an unexpected risk to recipients has been identified after release, protection of other potential recipients is clearly the driving rationale.

In the medium to longer-term , the effects of reporting an event or a near miss can reflect on overall improvement in safety and quality.

Although the responsibility for reporting such incidents lies primarily at the local and then national levels, a global approach to sharing the lessons learned is desirable.

To illustrate the principle of learning from vigilance, where sharing bad experiences is key to improving safety and quality, the audience was reminded of the tragic case where three patients received allografts from a common HIV–infected donor. The investigation of this incident led to significant quality improvements in the Italian transplant system. However, the experience was not shared sufficiently at the international level and one year later, Taiwan reported a similar incident.

Examples of similar serious events involving donors and recipients in various parts of the world once again emphasize the importance of sharing information and the need for robust systems to deal with such events. This extends to all substances of human origin and the highly publicized Italian case involving the loss of 94 cryopreserved embryos in 2012 serves as another example where the lessons learned, in this case relating to the management of liquid nitrogen storage, are relevant across MPHO.

According to data presented later in this section, more than 50% of preventable adverse events in transplantation are a result of:

- Inadequate surgical skills
- Absent or inadequate laboratory investigations
- Unreliable donor medical history
- Miss-communication and errors in data entry.

1.3.1. WHO Guiding Principles on Transplantation

Through *World Health Assembly Resolution WHA63.22 (2010)* Member States are urged to collaborate with data collection, *including adverse events and reactions* on the practices, safety, quality, efficacy, epidemiology and ethics of donation and transplantation. Additionally, *the Director-General is requested* 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.*

1.3.2. European Union (EU) Vigilance Legislation

A series of EU directives define responsibilities for the notification and reporting to competent authorities and for incident investigation:

Directive 2004/23/EC sets the standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

Directive 2006/86/EC concerns the implementation of Directive 2004/23/EC, regarding traceability requirements, notification of serious adverse reactions and events and certain

technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

Directive 2010/53/EC is on standards of quality and safety of human organs intended for transplantation.

EU-funded initiatives supporting V&S of organs, tissues and cells. Some examples were given:

- EUSTITE Project (Tissues and Cells)
- SOHO V&S Project (Tissues and Cells)
- Efretos (Organs)
- Serious Adverse Reaction and Event (SARE) EU-wide Annual Reporting Exercises.

1.3.3. Vigilance of Organ Donation and Transplantation in Italy

Notification of Serious Adverse Events and Reactions (SARE) was implemented in 2010, through the Rete Nazionale Trapianti (National Transplant Network) and coordinated by the Centro Nazionale Trapianti (National Transplant Centre).

The diagram below summarizes the framework of the EU legislation transposed into Italian law –

Figure 1: Representation of V&S in Organ Donation and Transplantation in Italy

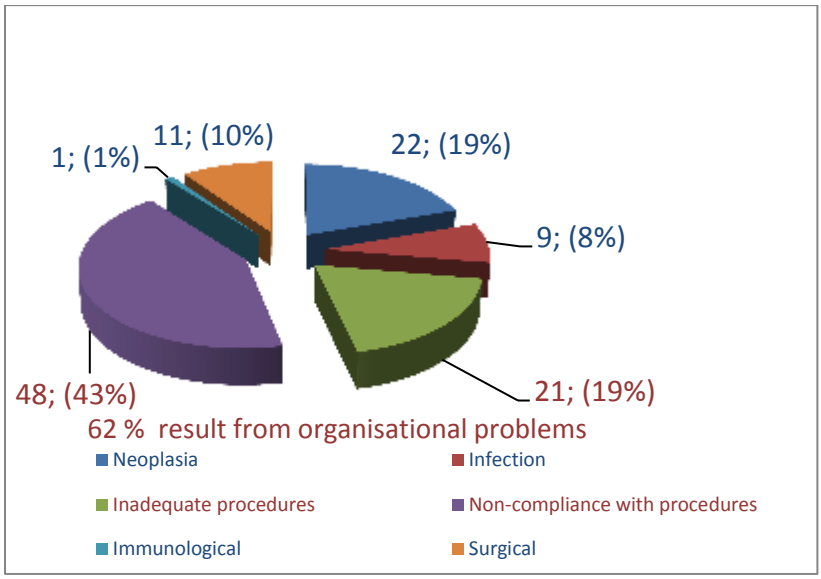
1.3.4 National Registry of Serious Adverse Reactions and Events

Five years of data from the National Registry of Serious Adverse Reactions and Events (February 2008 – June 2013) shows 112 documented cases, distributed as 28.5% near misses, 57.2% adverse events and 14.3% adverse reactions. There has been a steady upwards trend, particularly

in the reporting of adverse events, but this is likely to be due to the introduction of the formal system.

The distribution of SARE according to cause is shown below (figure 2) and highlights the preventable nature of the majority of events.

Figure 2: Italian National Registry of Serious Adverse Reactions and Events (2008-2011)



The classification of incidents takes into account two variables, namely severity and probability of recurrence. The products of these two variables define a score that describes the impact or criticality of the event.

Table 1: Incident scoring matrix

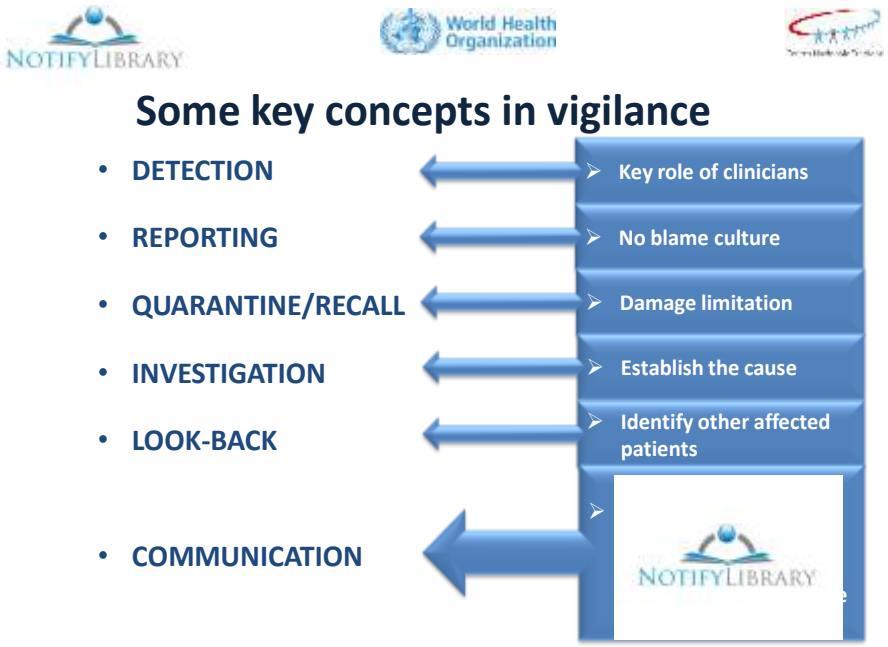
Incident scoring matrix (Consequences x Likelihood)

Impact	Likelihood: Rare 1	Unlikely 2	Possible 3	Likely 4	Almost Certain 5
Insignificant 1	1	2	3	4	5
Minor 2	2	4	6	8	10
Moderate 3	3	6	9	12	15
Major 4	4	8	12	16	20
Critical 5	5	10	15	20	25

1 – 4 (Green) = Acceptable
5 – 8 (Yellow) = Manageable
9 – 14 (Amber) = Significant
15 – 25 (Red) = High

Finally, some key concepts in vigilance deserve mention and are summarized in figure 3. Importantly, they are all underpinned by the fundamental concept of good communication.

Figure 3: Key concepts in vigilance



1.4. The focus of ANVISA on V&S: the example of Medical Products of Human Origin

(Geni Neumann)

Geni Neumann began her presentation by giving a brief geopolitical overview of the largest country in South America, to enable the audience to appreciate the magnitude and complexity of implementation of vigilance and surveillance systems for products of human origin in such settings. Brazil covers an area of 8 515 767 km² and is composed of 27 states, the Federal District and 5565 municipalities. Its population currently exceeds 192 million inhabitants.

It was explained that, in Brazil, health is a right for all and an obligation of the state, inscribed in the Federal Constitution of 1988. This universal right has been implemented through the creation of a Unified Health System (Sistema Unificado de Saúde, SUS). This publicly funded health system is one of the largest in the world. Various systems agencies have a role in vigilance and surveillance.

The Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA) was created by federal law in 1999. It is a regulatory body of the Brazilian government, which coordinates the National Health Surveillance System (Sistema Nacional de Vigilância Sanitária, SNVS) and integrates the Unified Health System (SUS). SNVS has the role of monitoring and controlling procedures, products and substances of interest to human health. It also monitors the quality of food and drinking water.

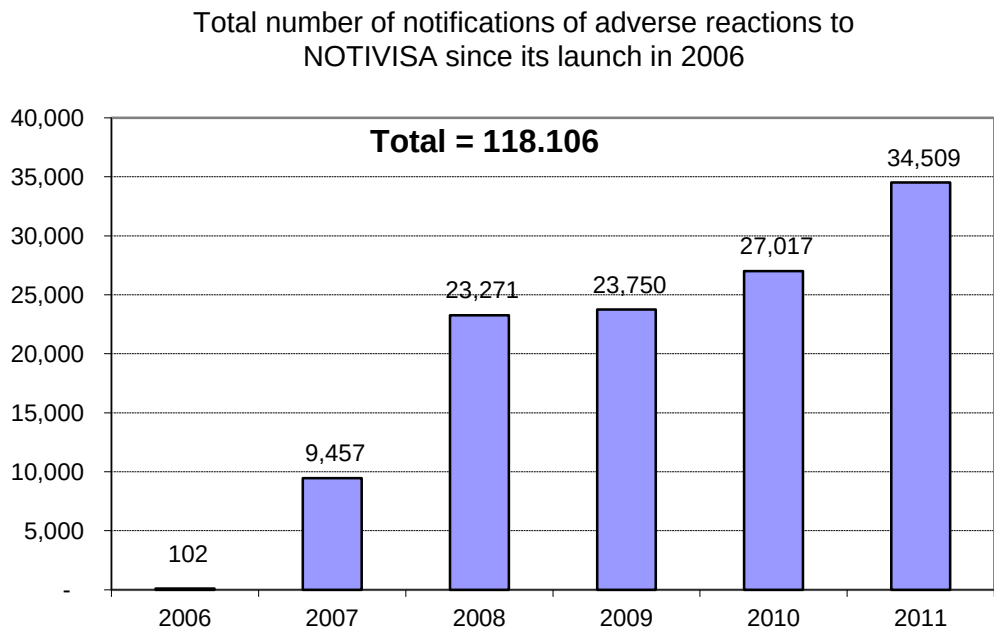
ANVISA is a regulatory authority with administrative independence and financial autonomy, led by a collegiate board of directors and monitored by the Ministry of Health. It is responsible for the regulation of all products and services that are subject to sanitary vigilance and which may affect the health of the population.

A regulatory agenda exists to ensure transparency and efficiency in the regulatory process led by ANVISA. An annual forecast of key activities is published, with dissemination through the official gazette and the ANVISA website.

On the subject of the monitoring and reporting of adverse events and reactions, two initiatives were presented. In 2002, the Sentinel Net Project (Rede Sentinela) was established. Over 100 health facilities entered into a contract with ANVISA, receiving financial incentive to implement risk management systems and reporting adverse reactions.

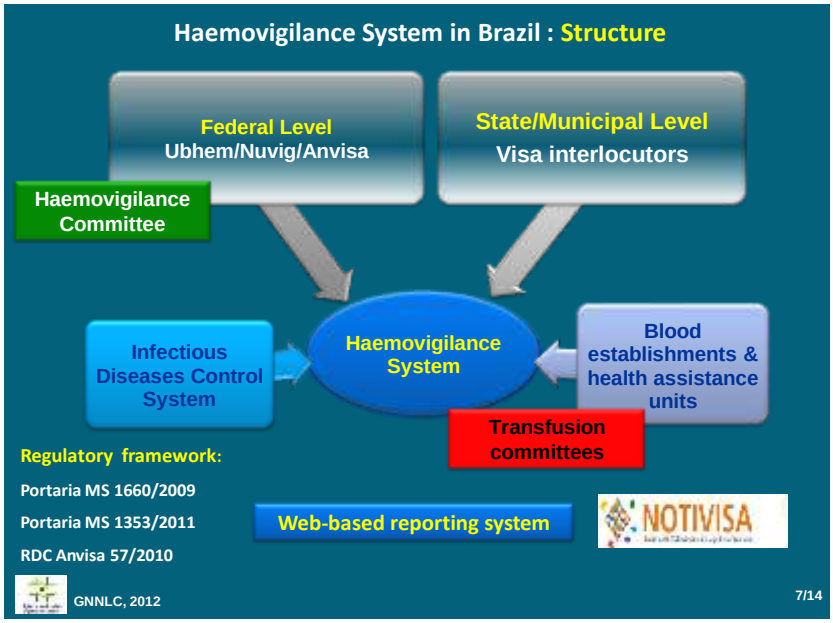
NOTIVISA (Sistema de Notificações para a Vigilância Sanitária) is a Health Surveillance Reporting System that was launched in 2006. It is a web-based tool for the reporting of adverse reactions and non-conformities, accessible by health facilities and health professionals.

Figure 4: Adverse reaction notification to the National Reporting System in Brazil (2006-2011)



The National Haemovigilance System (Sistema Nacional de Hemovigilância, SNH) was created in 2001 and the presenter gave an overview of the different parts that interact with SNH. This is illustrated in figure 5.

Figure 5: Structure of the Brazilian Haemovigilance System



Additionally, in 2009, the Ministry of Health created a Notification and Investigation System, VIGIPOS, under SNVS and part of SUS. This relates to monitoring adverse events and technical complaints in the post-marketing stage, for services and products under public health control, with the perspective of risk management.

The challenges encountered with under-reporting of adverse events and reactions was discussed briefly by showing the stark contrast between the annual tissue banks productivity and the actual number of reported adverse events.

Table 2: Tissue production in Brazil and reporting of adverse events in 2011 and 2012

year	2011		2012	
Tissue	Production	N° of reports	Production	N° of reports
Bone	24,663 units	01	24,028 units	09
Skin	21,195 cm^3	02	57,630 cm^3	00
Cornea	15,983 units	03	16., units	10

This was followed by an explanation of the current Biovigilance situation in the country.

Vigilance and surveillance of MPHO is not fully established yet and it was presented as a "work in progress", despite the achievement of some fundamental milestones. In 2012, a Biovigilance Working group was created as an initiative of ANVISA. During 2013, priorities for the group, a framework and reporting tools were agreed upon. Additionally, a pilot project will be run with a network of establishments. It is hoped that by 2014, reporting incidents on MPHO will be formally regulated in Brazil.

The presentation came to a close with a very warm welcome to Brasilia, a UNESCO Cultural World Heritage site.

1.5. Agenda and objectives of the consultation

(Deirdre Fehily)

1.5.1. Progress since the last consultation

Deirdre Fehily began by reminding the audience of the work accomplished in the 2012 Rome Consultation and presented an activity update of the NOTIFY Library.

During the last Global Consultation, the library was brought up-to-date to 2010 and the work done during those days contributed significantly to the total of 400 new rows added to the library, bringing the total number of records in the database to over 900.

The breakdown of records by incident type (Serious adverse reaction - SAR and serious adverse event - SAE) was given; there are 103 (11.35%) SAE types described in the database and for SAR types, the numbers are: infection 348 (38.3%), malignancy 135 (14.9%), "other" recipient reactions 28 (3.2%), process related 28 (3.1%), genetic 24 (3%) and living donor reactions 242 (26.6%).

As of December 2013, there were 348 records of donor-transmitted infections in the database, distributed by substance type as follows: organs 201 (58%), tissues 72 (21%), ocular tissue 49 (14%), hematopoietic cells [HPC] 20 (6%) and reproductive tissues and cells 6 (2%).

As regard donor-transmitted malignancies, the distribution of the 135 records by MPHO type was: organs 115 (77%), HPC 17 (12.6%), ocular tissue 2 (1.5%), non-ocular tissue 1 (0.7%) and reproductive T&C nil (0%).

The presentation proceeded with a description of the changes and improvements made to the NOTIFY Library web site.

As discussed quite extensively at the Rome Consultation, there is a strong general consensus that the aims and remit of the library ought to be very clearly displayed to avoid misinterpretation, hence risking drawing unbalanced attention to risk without mentioning benefits. This has been addressed by having very clear entry points in the home page, to direct members of the public, health professionals and health authorities to an explanatory page before navigation through the various pages.

Figure 6: Screen shot of the NOTIFY home page, with the entry points for different stakeholders and users

An excerpt from the General Public Introduction page reads:

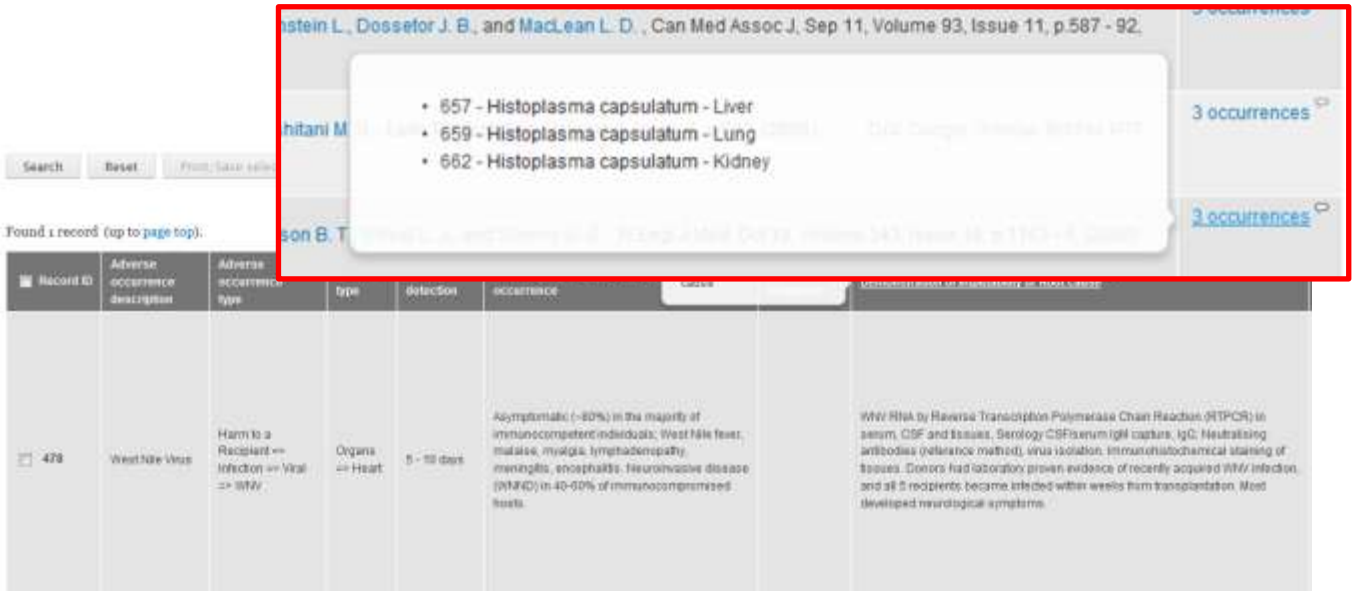
"This site focuses on the rare occasions when unforeseen complications or errors result in negative outcomes. Although such incidents are unusual, they present opportunities for the field to learn and improve, so that these services can be made safer and more effective for future donors and patients. The data presented on the NOTIFY Library site should be seen in the context of impressive success stories in transplantation and assisted reproduction across the world."

Links are clearly displayed so that the general public can easily access general information on donation and transplantation.

The group was also reminded of the importance of using the site and sending comments, corrections and suggestions via the site or by email. This facility is open to everyone who accesses the site.

Some facilities have been added, such as a useful mouse-over tool, which displays an explanation of terms, as illustrated below:

Figure 7: Mouse-over tool introduced to facilitate navigation, with explanation of terms and headings



New search tools have been added as well, such as the possibility of searching by incident number and of running an inverse search. For example, using the Reference Search option, records will be displayed by reference ID, bibliographic reference and number of incidents associated with each reference. By hovering the mouse over the number of incidents, a list with each incident ID will appear. Specific cases can then be accessed as required.

Figure 8: Reverse search tool

New documents have also been added to the Background Documents section, which can be accessed through the tab.

Before moving on to the agenda of the current consultation, Dr Evi Petrisli was announced as a new addition to CNT staff. Evi had already started working in the project by reviewing keywords,

incident titles, merging rows and applying an imputability score to cases. She received a very warm welcome.

1.5.2. Brazil Consultation - Objectives for the NOTIFY Library database

Deirdre Fehily enumerated the list of topics that had been tabled for presentations and discussions over the three days in Brasilia, as well as laying out a work plan for the future development of the database.

- Finalize and edit the remaining cases in shared Google docs where editorial workgroups are preparing them for upload in to the NOTIFY library
- Reach an agreement on the format of (an) electronic form(s) for the submission of future proposed records directly via the website
- Reach consensus on some key principles to guide future work:
  - Imputability definitions and scores
  - Other definitions – MPHO terminology, key words etc.
  - One case per row vs one case type per row
  - Better capture and further classification of SAEs
  - How to make information on non-transmissions accessible
- Add blood and blood products as substance types so as to complete the MPHO 'catalogue'
- Explore language-specific interfaces for the library in order to facilitate a two-way channel of communication for more effective sharing of vigilance information
- Consider ethical breaches as a possible third type of incident
- Discuss the concept of an e-journal on Vigilance and Surveillance of Medical Products of Human Origin
- Collect up-to-date information from participating countries/WHO Regions/Professional entities on the status of Vigilance and surveillance of MPHO
- Review draft vigilance guidance from WHO – the 'vigilance chain'
- Review priorities for the Global Vigilance of MPHO.

2. THE NOTIFY LIBRARY

2.1. Editorial Groups Workshops

The five existing editorial groups and the newly created Transfusion group were tasked to review and resolve remarkable cases, gather achievements updates and orientations for the future. Participants were free to join the editorial groups of their choice rather than staying with the one they were allocated to. The groups were constituted as follows (*denotes the chairperson)

Table 3: Participant list by editorial group, first break-out session

INFECTIONS	MALIGNANCY	PROCESS	GENETIC	LIVING DONOR	BLOOD
Sheick Oumar Coulibaly	Liliana Bisigniano	Richard Lebethe	Edwin Cardenas	Daniel Coradi de Freitas*	Barbee I. Whitaker*
Ted Eastlund	Kathy Loper	Scott Brubaker	Laura Saint-Martin*	Maria-Dolores Perez-Rosales	Arlinke Bokhorst
Matt Kuehnert	Mike Nalesnik	Marian Macsai*	Chris O'Toole	Carlos Soratti	Jorge Condeço
Yoshie Hirose		Adriana Seber	Wimon Suwankesawong	Zulma Valbuena	Ghazi Saleh Saeed
Evi Petrisli	Beatriz Dominguez-Gil*	Zulma Valbuenaj	Deirdre Fehily	Mitra Mahdavi-Mazdeh	Valentina Hafner
Paulo Grossi *	Stratos Chatzixiros	David Axelrod	Ioana Siska	Sergey Khomyakov	Ludo Muylle
Ines Ushiro-Lumb	Alessandro Nanni Costa	Duc Vu	Marìa Cecilia Alen	Marie-Charlotte Bouësseau	Anuj Sharma
Fabiana Souza	Mohamed Salah Ben Ammar	Axel Rahmel	Marina Ferreira	Jose Nunez	Mike Strong
	Philip O' Connell	Esteban Trias-Adroher		Naoshi Shinozaki	Luc Noel
	Lara Alonso da Silva	Marisa Herson		Daniela Minutoli	Geni Neumann
		Mondher Letaief		Diana Hermida Vitar	Paul Ashford
		Ana Carolina Pinto		Marcelo Augusto Medeiros	Andressa Amorim

Day Two, Sunday 8 December 2013

The second day of the consultation kicked off with an introduction by Mike Strong, who reminded all participants of the uniqueness of NOTIFY, which does not only contain published references, as other reliable sources of information are also utilized. Of note, scientific, peer-reviewed journals do not contain extensive publications on adverse events, hence there is an important gap to be filled. The real aims of the editorial working groups were also referred to, highlighting the importance of re-focusing on delivering the assigned tasks. There have been, and continue to be, changes and improvements in the process of making project participation easier and more sustainable. Dedication and interest from members of the working groups were duly acknowledged.

A question was asked regarding the potential danger of health-care professionals and members of the public mistakenly using NOTIFY as a reference for risk assessment, reflecting a genuine concern that still exists. Participants were reminded that there is a clear disclaimer on the web page which addresses this issue.

The morning session proceeded with a presentation from the newly added Blood group, followed by presentations from the existing editorial work groups, reporting the discussions which took place during the first break-out session, the previous day.

2.2. Reports from the Editorial Groups Workshops

2.2.1. New scope with extension to blood

(Barbee Whitaker)

The working group acknowledged the logic and value of incorporating reactions and events associated with blood products in the NOTIFY library. The breadth of experience accumulated through haemovigilance was recognized as an invaluable source of didactic information for the donation and clinical application of other MPHO.

The addition of blood product SARE will require adjustment of the database structure to accommodate the specificities of that field. This work would be feasible to carry out and would represent an enhancement of the existing database. They began with a review of the taxonomy requirements for blood products and blood SARE.

A clear and concise presentation on Blood Taxonomy was elaborated, which proposed products and incident taxonomy, along the following examples:

- Products
    - Level 1: Human Substance
    - Level 2: Blood

- Level 3:
    - Whole Blood
    - Red Blood Cells
    - Platelets
    - Plasma
    - Cryoprecipitate
    - Granulocytes
- Qualifiers
    - Donor to Recipient Relationship Table
        - Autologous
        - Allogeneic
            - Single donor
            - Multiple donors
    - Processing Table
        - Cryopreservation
        - Apheresis
        - Separation: Buffy Coat
        - PRP Derivation
        - Leuko-reduction
        - Irradiation
        - Frozen
        - Pooled
        - Pathogen reduced
        - Additive solutions
        - Anticoagulants

- Incidents
    - Level 1: Adverse Incident
    - Level 2: Adverse Reaction (SAR)
    - Level 3: Recipient Reaction
    - Level 4: Transfusion Reaction
        - Allergic Reaction
        - Acute Hemolytic Reaction: immune
        - Acute Hemolytic Reaction: non-immune
        - Delayed Hemolytic Reaction: immune
        - Delayed Hemolytic Reaction: non-immune
        - Delayed Serologic Reaction
        - TRALI
        - TACO
        - TAD
        - 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)

    - Level 5 Acute and delayed Hemolytic Transfusion reactions
        - ABO

- Other allo-antibodies

- Level 3: Living Donor Reaction
  - Use ISBT Definitions (expected soon)
    - Vasovagal
      - Pre-faint, no LOC (uncomplicated or minor)
      - LOC, any duration (uncomplicated)
      - LOC, any duration (complicated)
      - Injury
    - Local Injury related to needle
      - Nerve Irritation
      - Hematoma/Bruise
      - Arterial Puncture
      - Painful Arm
      - Compartment Syndrome
      - Bleeding
    - Apheresis
      - Citrate
      - Hemolysis
      - Air Embolus
    - Allergic
      - Local
      - Systemic
      - Anaphylaxis
    - Other
- Living Donor Adverse Events (SAEs)
  - Use ISBT definitions

There was some interest regarding blood cell therapies in the control of CMV and EBV, for example, and where these would fit in terms of vigilance. Arlinke Bokhorst clarified that manipulated lymphocytes is regarded as cell therapy hence not under the remit of haemovigilance.

It was also explained that in the European Union, collection of information for haemovigilance applies to high-level categories. EU legislation had to be enacted in each Member State hence high-level has to be used to accommodate as comprehensive a data collection as possible.

Matt Kuehnert asked for views regarding entry of similar or nearly identical cases in NOTIFY and wondered what the criteria should be. In some categories, for example blood, there may be many reports describing very similar events. He also wondered how we should actively seek cases in categories that we do not see many articles published on.

Paul Ashford was of the opinion that there is a difference between knowing an event can occur (commonly) and knowing the reasons why it occurrs, so that lessons can be learnt. It was also said that with variations in type of substances, diagnostic tests and infra-structure in different parts of the globe, the root cause for the incidents may differ even if the incident type is the same. This topic returned for discussion later in the day, under a different working group.

At this point, Luc Noël remarked that NOTIFY is not a substitute for vigilance systems and does not claim to be comprehensive. There are risks in being too prescriptive in a system like this, as the different groups have different issues that need to be addressed separately. It adds a didactic layer and a global dimension in the V&S process and the utility of this tool will improve as work progresses.

2.2.2. Infection Group

(Paolo Grossi)

The task of updating the spreadsheet with cases from 2010 onwards was divided by agent group, i.e. bacteria, viruses, parasites, fungi and prions. Work is in progress and there is a significant amount of work to do post-consultation as the list of agents and substances is substantial.

- Review of the methodology used for parasitic cases.
    - Column headings, terminology and significance.
    - Separate rows for multiple recipients of organs and tissues from the same donor within the same reference.
    - Infection folder with sub-folders created and shared in Google drive, where references should be uploaded for easier review of the cases.
- Suggestion that a Severity column be inserted.
- Removal of cases with "unlikely" imputability.
- Analysis of some cases recently inserted in the Google site and marked for discussion.
- Interesting observations were made about the importance of understanding the life cycle of the infectious agent in order to assess risks and imputability. Two cases involving *S. mansoni* and *P.vivax* were discussed.
- The need to observe consistency with the published definitions of imputability [Garzoni C and Ison MG, Transplantation 2011; 92:1297-1300] was made; for example, the term "proven" to be used instead of "certain".
- Discussion about cases of exposure to risk without transmission, including "intervention without documented transmission" (IWDT) i.e successful intervention resulting in the non-transmission of an agent documented in the donor and cases of "non-transmission" despite the absence of any preventive intervention. Once again, there was a consensus about the validity and importance of collecting these cases in a very clear way, to avoid bias towards cases where transmission occurred. They are of educational and statistical importance but it is still unclear where they could be stored.
    - A suggestion was made to use key words as a way to highlight IWDT and non-transmission cases, but it is recognized that NOTIFY is a database of adverse events and reactions. This matter remains unresolved.
- Consensus agreement that there is an urgent need for search strategies to be devised for consistency, accuracy and sustainable viability of the project.

2.2.3. Malignancy Group

(Beatriz Dominguez)

The group reviewed terms and definitions related to the transmission of malignancies from donor or cells, tissues and organs (CTO) to recipients.

Malignancy transmission and CTO

1. **A malignancy transmission risk might be identified before the transfer of CTO** and accepted by both the recipient and the physician, when balanced with the risk of not proceeding with such transfer (routine in HSC and organ transplantation).

2. **A malignancy transmission risk might be identified in the donor or CTO after the transfer of CTO has occurred.** **SAE**

3. **A malignancy might be inadvertently transmitted** from the donor or the CTO and be discovered when the clinical manifestations of such transmission become apparent in the recipient(s).

NO TRANSMISSION

TRANSMISSION

SAR

Donor-transmitted *versus* donor-derived malignancies

DONOR- TRANSMITTED MALIGNANCY

malignancy that was definitely, probably or possibly present in the donor and may or may not have been recognized at the time of procurement of the organ (or tissue).

E.g leukemia diagnosed in an organ recipient 30 days post-transplant would likely be donor-transmitted malignancy

DONOR- DERIVED MALIGNANCY

malignancy developing from donor cells but after implantation of the tissue/organ and unlikely to have been present at the time of procurement.

E.g a renal cell carcinoma developing 9 years post-renal transplant is likely a donor-derived malignancy

This was followed by an explanation of the objectives of the Malignancy Editorial group:

- To compile information/cases of donor-transmitted and donor-derived malignancies related to the clinical use of CTO.
- To extract and organize the following relevant information from selected cases to be presented through the NOTIFY library:
    - Has this occurred before?
    - What were the alerting signals?
    - What was the latency?
    - How was imputability assessed?

As of December 2013, more than 140 records on donor-transmitted and donor-derived malignancies had been uploaded to the NOTIFY Library.

As for ongoing and future work, there was acknowledgement of the unique nature of the NOTIFY library and its potential.

The group also put forward some general and some specific points for consideration, with a few listed below:

- The purpose of the library needs to be made clearer to the user.
- User consultation through surveys to specific networks, we need to assess usefulness of the library.
- Taxonomy needs subcategories in malignancies – e.g. subgroups per histologic type
- Suggested modifications to the layout
    - Field to add - outcome of index recipient and other recipients at risk
    - Field to add - comments from the editorial group
    - Remove field -frequency estimates; replace by dedicated space for references (national registries) relevant for risk estimation in a specific format
- Imputability grading
    - Need for a harmonised tool
    - Assessment of imputability to be done by at least two members of the editorial group.
    -

The same topic of **cases of exposure to risk without transmission** was also brought up by the malignancy group. These cases do not feature in the database but there is an identified need to present these cases:

- Information is relevant for estimates of risks of malignancy transmission
- Collaboration with national registries or dedicated registries
- Identify dedicated space to present results of main registries showing exposure to risk with/without malignancy transmission.

Another point for discussion which still needs resolution relates to donor-derived malignancies. These are cases where a malignancy which was not present or was not detected at the time of procurement later develops from donor cells in the recipient of cells, tissues or organs. These are currently listed in the NOTIFY Library but it is thought that a column containing editorial comments regarding expert views on the origin of the malignancy would be helpful. A need for further work was identified because a valid cut-off point to distinguish between donor-transmitted and donor-derived malignancy is difficult to define. The limitation lies in part in the terminology used which was developed some 10 years ago, without access to the scientific and diagnostic tools that we now have. Many publications do not provide sufficient information for a classification to be made with certainty. On the point of terminology, Luc Noël suggested that the word "transmission" could be avoided to circumvent semantic concerns and misinterpretation.

As for the working procedures, the group identified some areas for improvement and suggested secretariat support and chairperson-led assignment of tasks and quarterly conference calls to ensure continuity of work. Again, a suggestion for the creation of a standard literature search tool was also put forward by this editorial group.

2.2.4. Process Group

(Marian Macsai)

Marian Macsai began by giving an update on the number of process cases available in the library, which amounts to 34 [14 from the Bologna NOTIFY report and 20 from the WMDA/WBMT vigilance programme "Serious (Products) Events and Adverse Reaction (S(P)EAR]). The editorial work was done by distributing the PDFs of the articles and reviewing the cases as a group. There was recommendation for some cases to be moved to other, more suitable groups, as they were not deemed to be process events.

A discussion on the matter of source and validity of information for cases to be entered in NOTIFY took place. The process group expressed the opinion that information obtained unofficially could function as a trigger for further investigation, but not as a reliable source. This was exemplified through the case of a live donor kidney which was inadvertently discarded by theatre staff in Ohio, USA. This case was widely publicized in the lay press in 2012 and it still features in local headlines. Mike Strong pointed out that significant adverse events do not necessarily get captured in the scientific literature and that one of the reasons for this may be the need to protect the source of information or the sensitivities around the information, for example. Kathy Loper expressed a view that protected information is very difficult to include in a V&S database, due to the intrinsic difficulties in data verification which brings the risk of reputation and integrity damage to NOTIFY.

Mike Strong also reminded participants that the proposed relationship between NOTIFY and Regulatory Authorities had been discussed previously and is being pursued so as to get cases and reports fed into the library from these official bodies.

Still on the subject of provenance of information, certain areas of the world have publications in their native language hence there is a question as to how this project could reach those sources. Could or should they volunteer directly fed information? This is a difficult question and may be addressed at least in part in one of the sections planned for the third day of the consultation.

This relevant debate extended to the wider issue of the limitations faced by the NOTIFY Library. As it is widely accepted that not all cases of SAREs are made known or are reported, incidence, prevalence and frequency are variables that cannot be calculated. This, in turn, raises the question of which cases should be listed in the database. Opportunity to learn (didactic value) should be a criterion for inclusion. It was also asked whether there is any value in including information on corrective actions so that a contribution towards process improvement could be made. It was felt that clearer guidance would be welcome.

Another question that was raised related to events of the same nature and what the criteria should be to decide on entry in to the database. Although there may be problems with citing similar cases, there was overall consensus that recurrence means lessons are not being learnt hence collecting them and demonstrating they are still happening is of value. More importantly, it is necessary to show how to avoid and manage such adverse events.

2.2.5. Donor Group

(Daniel Roberto Coradi de Freitas)

Most of the members in this group were new to the NOTIFY project and rather than reviewing cases, the breakout discussion concentrated on two topics, namely taxonomy and imputability.

Table 4: Level 4 taxonomy for adverse reactions with living donors

Level 4 taxonomy

SAR	N=242
Peri and post operative complications	67
Toxicity	56
Pain/morbidity	28
Infection	24
Drug related	19
Thromboembolic	4
Metabolic	4
Cardiac	2
Malignancy	1
Other	37

As illustrated in the above table, the majority are peri-operative events. As there are many different types of reactions, there is a need for searches to be run in all different areas. Therefore,

there was a suggestion to create a level 5 in order to avoid overlap and simplify the search stage. The example given was peri- and post-operative complications, with level 5 as pain, morbidity, metabolic, cardiac, thromboembolic.

Level 4 taxonomy needs definitions to avoid misclassification. For example, morbidity is not sufficiently defined as it can be due to a variety of reasons, such as cardiac, infection, etc... It was also mentioned whether the International Classification of Diseases (ICD) could be incorporated for categorization at level 5 or 6.

Imputability: Criteria for the attribution of an imputability score will be defined so that all reactions in the library will be classified according to those criteria.

Participants confirmed that definition of a SAR for living donors should include all types of unexpected adverse outcome regardless of the cause, including donor mismanagement. As there are too many reactions that span across the ones dealt with by the Blood group, there was a suggestion to consider distributing experts from the latter to the Living donor group.

A debate on the subject of untoward donor/recipient outcomes ensued, and whether the most appropriate terminology should be expected/not expected or intended/unintended. Based on the premise that there is never an intention to harm, the terminology used may not be the point in question, but rather, the nature of the cases that should be added to the NOTIFY database. Axel Rahmel gave an example involving living donors who require a transplant as a consequence of donation and the ethical question of right of priority to receive a transplant in these circumstances. With reporting, many more such cases have been coming to light than Eurotransplant had previously been aware of.

2.2.5. Genetic Group

(Laura Saint Martin)

The group reported that the literature review of new Assisted Reproductive Technologies (ART) cases was completed and that the cases were up-to-date. There were no recent cases of genetic transmission through egg donation.

The group was specifically asked to produce definitions for assessing imputability in donor-derived transmission events. The group developed the criteria for ART described in the following table.

Table 5: Assessment of imputability for donor-derived genetic transmission events in ART

Imputability GRADE	Definition
NOT ASSESSABLE	Insufficient data for imputability assessment
0. EXCLUDED	Confirmed genetic disease in foetus/offspring/recipient **and** • Clear evidence of an alternative cause **or** • The genetic mutation was different from that carried by the donor
1. POSSIBLE	Confirmed genetic disease in foetus / offspring / recipient **and** • Genetic disease has only be confirmed in one foetus/offspring/recipient in cases where there was multiple use of the donor's tissue/ cells/ organs **or** • There is unclear evidence that the transmission of the genetic disease could have been attributed to the process or use of the donated tissue / cells / organs; In the case of pre-implantation genetic diagnosis, the transmission of the genetic disorder is within the excepted misdiagnosis rate for the methodology used to detect the genetic disease
2. PROBABLE	Confirmed genetic disease in foetus / offspring / recipient **and** • The genetic mutation is confirmed as being the same in the foetus/ offspring/ recipient and the donor **or** • Confirmed disorder in other foetuses/ offspring / recipients (if multiple use of the same donor's tissue / cells / organs) In the case of pre-implantation genetic diagnosis, the transmission of the genetic disorder is not within the excepted misdiagnosis rate for the methodology used to detect the genetic disease.
3. DEFINITE CERTAIN	Confirmed genetic disorder in foetus/ offspring / recipient and • Confirmed disorder in other foetuses/ offspring / recipients (if multiple use of the same donor's tissue / cells / organs); • The genetic mutation is confirmed as being the same in the foetus/ offspring/ recipient and the donor; • The genetic disease could only be attributed to the use of the donor's tissue/ cells / organs In the case of pre-implantation genetic diagnosis, there is evidence that the transmission was due to the process

A few Hematopoietic Progenitor Cell (HPC) cases were identified, where the evidence for transmission was very weak, for example cases # 519 - alopecia areata, #525 - vitiligo and #526 - asthma. There might have been a genetic/familial predisposition, but no genetic test was carried out and the origin may have been multifactorial.

In situations like these, a decision as to whether or not to include in NOTIFY could be aided by a comment in the column for imputability which would score the degree of evidence for donor association.

2.3. General discussion and final remarks

Having heard the update presentations from all working groups, Mike Strong urged all experts to use NOTIFY, navigate through the pages, run searches and test the system for corrections and improvements. This is an important activity in its own right and the CNT staff would be grateful to receive suggestions.

Philip O'Connell suggested each working group could run a GAP analysis and identify areas for improvement and corrections.

Axel Rahmel reiterated one of the most important functions of NOTIFY, which is the "take home message" and "lessons learnt" role. This function could be highlighted by expanding comments or by adding a specific column.

Matthew Kuehnert restated the import requirement to put information into a meaningful context. It would be helpful to give some idea of frequency even if imprecise, and it was thought that spending some time devising a way to achieve that would be worthwhile.

It was also pointed out that rarer cases could be described in much more detail to help users, as these cases may not be published in peer-reviewed journals.

Barbee Whitaker advised on the diligence required when editing cases, as contextualisation is very important. She referred particularly to significant technological differences worldwide. It was remarked that epidemiological differences are equally relevant when it comes to considering things in the appropriate context.

Luc Noël expressed some apprehension over the repeated concerns regarding lack of quantitative data. He duly reminded participants of the large variation in epidemiology, in resources and levels of system development and in information available across countries. Where quantitative data is available and relevant it should be provided in the frequency column, but if not, descriptive information without quantitative data has some didactic value, nonetheless.

2.4. Specificities and priorities by type of MPHO

The second breakout session of the consultation was planned differently to previous years, this time having groups by type of MPHO so that matters of common interest and overlapping issues could be discussed, with contributions across different editorial groups. No ART group was convened as the number of experts from that field was not considered adequate. The groups were asked to consider the following as an indicative agenda:

- Is the taxonomy adequate for your MPHO?
- Are there missing MPHO types?

- Have experts from your MPHO type contributed adequately to the work of the Infections, Genetic, Malignancy, Process and Donor Reaction editorial groups?
- Please conduct some searches to see if important cases you are aware of are in the database.
- Recommendations for improvement.

2.4.1. Organs Group

(Philip O'Connell)

Solid organ transplantation is a complex process that involves multiple steps that are performed by several different agencies. Surgical donor and recipient teams are often from different institutions and are separate to organ procurement organizations that are responsible for coordinating donor consent, tissue typing, transport and organ allocation. Hence there are several critical points where breaks in the process can occur. Adverse events can occur due to incorrect transcription of data or due to a lack of transfer of essential information between organ procurement organizations and the responsible medical teams.

The process of organ transplantation can be divided into the following critical steps:

- Donor assessment and consent
- Testing – infection, blood group and HLA
- Procurement
- Preservation and transport
- Allocation
- Transplant.

Some of these steps occur in parallel. The major adverse outcomes fall into the following categories:

- Infectious disease risk
- Transfer of malignancy
- Mistakes in allocation
- Events associated with preservation and transport.

In assessing whether the adverse event is expected or unexpected, it is important to consider context. Recently, there have been major changes in assessing disease risk. There are ongoing trials looking at the use of solid organs from HIV-positive donors into HIV-infected recipients. In many jurisdictions, for example, livers and kidneys from hepatitis C positive donors are allocated to hepatitis C positive recipients rather than being discarded. Hence, it is important to capture unexpected or new adverse events in situations like these; importantly, the context of transmission needs to be displayed in the NOTIFY Library summary. When considering infectious disease reactions the following contextual information needs to be considered:

- Mandated test not done

- What methodology was used – NAT vs serological test
- Test done but false negative (inside incubation window)
- Test done but false positive wrongly discarded (this should be captured by NOTIFY in the SAE category)
- Positive donor organ allocated to known positive recipient (problem if patient not truly positive e.g. HCV positive organ to antibody positive but virus negative recipient)
- New or known infective agent not tested for e.g. West Nile virus
- High infective risk donor not identified or identified and decision to transplant based on wrong risk assessment.

Similarly with malignancy risk, there are challenges to obtaining appropriate information in the context of deceased donation. Essential history of past malignancy may not be available to the medical staff or Organ Procurement Organisation (OPO), especially if a prior malignancy occurred outside the region of donation. Obtaining accurate information in such a time critical process can be challenging. When assessing malignancy, the following issues need to be considered:

- History of malignancy not sought, not recorded or not obtainable
- Known malignancy but risk of transmission considered low, e.g. cerebral malignancy
- Unknown malignancy despite adhering to donor assessment protocol.

Again, as with assessing infective adverse reactions, understanding the context of malignancy transmission is essential in evaluating the impact on transplant processes and procedures.

Potential process issues with organ allocation include:

- Incorrect testing of blood group or HLA
- Incorrect interpretation of cross match or not using most recent sera
- Incorrect allocation due either to incorrect testing or process error despite appropriate blood group and HLA testing including misidentification.

Possible process issues associated with preservation, allocation and transport include:

- Unexpected prolonged warm ischemia time – or not adhering to protocol for DCD donors
- Inappropriate or poor perfusion of donor organs
- Unexpected delays in transport or time to transplantation.

In conclusion, the Organ group made the following recommendations regarding the NOTIFY Library:

1. What is the aim of the NOTIFY Library?: The members of this group noted that there was a tension between the stated objectives of NOTIFY and clinicians who wished to use it as a clinical tool to guide them regarding risk assessment for organ donors. NOTIFY is not equipped to be the sole source of data for this type of assessment and it was

recommended that the NOTIFY website should have links to regional and national guidelines as well as context relevant registries that could provide important information on prevalence and frequency which is not obtainable through NOTIFY.

2. Taxonomy: the group recommended that composite tissue allografts be added to the organ Taxonomy.
3. The comments section which is present in the Google submission form be included in the NOTIFY Library.
4. Clarification of the Frequency Column: this is not being used. Either a short assessment of frequency should be included by the expert committee or alternately this column should be removed.
5. Information regarding Latency: the definition needs to be clarified. The committee proposed that latency be defined as the time from transplant to diagnosis in the index case.
6. Adverse reactions as for disease transmission are well captured, but not adverse events consisting of an exposure to a risk of disease transmission, but without transmission. It should be clarified under which category these events should be included.

2.4.2. Cells group

(Chair Adriana Seber)

The group was of the opinion that taxonomy should be revised, choosing as to whether or not to follow the recently changed ISBT128. Substances that should be included:

- Mesenchymal stem cells
- Adipocytes
- Genetically modified cells
- Cord blood - Autologous
- Donor leukocyte infusions
- Cytotoxic T lymphocytes

The group has few individuals with expertise in haematopoietic stem cell (HSC) transplantation and so far there has not been cross fertilisation and contribution to the work of the other editorial groups.

Trial searches were run during the break out but they were unsuccessful; keywords will have to be revised to ensure correct capture of relevant papers.

Some suggestions for improvement and future work were put forward:

- Have an editorial group to review cases and ensure consistency in all columns
- Establish a maximum length for comments
- Link to full article PDF (this would only be possible for free references)

- Keywords should be able to recover the subject – e.g. malignancy – neoplasm – cancer; review keyword selection
- Make it easy to upload new data
- Keep track of access to NOTIFY; its success will depend on the level of usage
- Encourage participants to make presentations about NOTIFY in conferences
- Communication to national organizations
- Use Notify as a database for research and publications in peer reviewed journals
- Work with professional associations.

2.4.3. Tissues group

(Chair Ted Eastlund)

The Workgroup addressed the following:

1. Suggestions for improvement of the NOTIFY Library
2. Possible new cases that have not been entered into the NOTIFY Library

Possible new cases, specifically addressing

- Disease transmission (infection, malignancy, etc)
- Process failures/incidents/accidents/ errors/ deviations

These new cases may have occurred during preparation and use of the following tissue allografts

- Bone and connective tissue
- Heart valves, vessels
- Skin (split thickness and dermis)
- Ocular, including cornea, sclera, limbal cells
- Dura
- Amnion

3. During discussion the following recent cases and publications were offered for consideration to be entered into the database
    - HCV transmission by a cardiopulmonary patch (check to see if in NOTIFY Library database: Centers for Disease Control and Prevention (CDC). Transmission of hepatitis C virus through transplanted organs and tissue-Kentucky and Massachusetts, 2011. MMWR Morb Mortal Wkly Rep. 2011 Dec 23;60(50):1697-700)
        - Clostridial transmission by cornea allograft (check EBAA adverse outcome report at NOTIFY Library office)
        - Process failure: use of a diagnostic rather than approved, validated, donor infectious disease screening test kit and recall of tissues (to be handled by Process editorial group)

- CJD transmission through dura, the end of an era; need to update the entry in the database (add 2013 P Brown article citation to existing row of dura-transmitted CJD)
- Use of corneas with defects that predict graft failure, defects that correspond to Fuchs' dystrophy, a study of endothelial quality (Br J Ophthalmol 2001;85:272-76)
- Deviations when obtaining the donor's medical/behavioral history have led to a number of tissue recalls after a recording of the interview was reviewed and deficiencies in process were discovered.

4. Suggestions and recommendations by the group
    - Increasing representation on the Project NOTIFY effort from more eye bank associations, to get participation from more countries.
    - For a more global coverage, all tissue banking association should be represented ideally through a global entity as for other MPHOs .
    - Give scientific and professional organizations more recognition and visibility through the NOTIFY webpage, to encourage them to submit their ongoing studies and internal registries of SAE and SAR.
    - NOTIFY Library home page could have a tab for "collaborating organizations" containing a list of contributing and collaborating organizations plus links to their own websites.
    - Consider adding a category to the NOTIFY database and worksheets for the topic of transmission of malignant and non-malignant, non-infectious, metabolic, autoimmune and alloimmune donor-derived diseases largely from organ and HSCT transplantation (see Table 6 below).

Table 6: Transmission of autoimmune, alloimmune and metabolic diseases through organ and hematopoietic stem cell transplantation

Hematopoietic stem cell transplant	Organ transplant
Graft versus host disease, acute and chronic	Graft versus host disease, acute
Passenger lymphocyte syndrome (RBC alloantibodies:acute hemolysis)	Passenger lymphocyte syndrome (RBC alloantibodies :acute hemolysis)
Idiopathic autoimmune thrombocytopenia	Idiopathic autoimmune thrombocytopenia
Sarcoidosis	Sarcoidosis
Vitiligo	Vitiligo
Passenger lymphocyte syndrome	Passenger lymphocyte syndrome (platelet alloantibodies, thrombocytopenia)

(neutrophil alloantibodies: acute neutropenia	
Atopy, Atopic dermatitis	Severe peanut allergy
Alopecia areata	Factor VIII deficiency (Hemophilia A)
Autoimmune thyroid disease: autoimmine thyroiditis, thyrotoxicosis	Factor XI deficiency
Coeliac disease	Factor XII deficiency
Type 1 diabetes mellitus	
Gaucher's disease	
G6PDH deficiency	
Thalassemia	
Sickle cell trait	
IgA deficiency	
Myasthenia gravis	
Anti-phospholipid syndrome	
Anti-pancreatic antibodies	
Cyclic neutropenia	

From Eastlund T, Warwick R. Diseases transmitted by transplantation of tissue and cell allografts. Chapter 4. In: Warwick RM, Brubaker SA, editors. Wiley-Blackwell,UK : Tissue and Cell Clinical Use. An Essential Guide.2011, pages 72-113

Table 7: Neoplastic Diseases of Donor Origin Transmitted by Organ, Tissue and Hematopoietic Stem Cell Transplantation

Tissue Allografts	Organ Allografts	Hematopoietic Stem Cell Allografts
Papillary adenocarcinoma (from cornea)	Post-transplant lymphoproliferative disorders	Post-transplant lymphoproliferative disorders
Glioma (from cornea)	Non-Hodgkin lymphoma	Non-Hodgkin lymphoma
	Renal cell carcinoma	Acute myelogenous leukemia

	Choriocarcinoma	Acute lymphocytic leukemia
	Melanoma	Chronic myelogenous leukemia
	Sarcoma	Chronic lymphocytic leukemia
	Astrocytoma	
	Glioblastoma multiforme	
	Medulloblastoma	
	Pancreas adenocarcinoma	
	Colon adenocarcinoma	
	Prostate adenocarcinoma	
	Breast adenocarcinoma	
	Lung adenocarcinoma	
	Lung small cell carcinoma	
	Lung bronchioloalveolar carcinoma	
	Hepatocellular carcinoma	
	Ovarian carcinoma	
	IgA myeloma	
	Multiple myeloma	
	Urothelial carcinoma	
	Undifferentiated small cell neuroendocrine carcinoma	

From Eastlund T, Warwick R. Diseases transmitted by transplantation of tissue and cell allografts. Chapter 4. In: Warwick RM, Brubaker SA, editors. Wiley-Blackwell,UK : Tissue and Cell Clinical Use. An Essential Guide.2012, pages 72-113

2.4.4 Blood Group

The group decided that the next steps would be to share the proposals with the International Haemovigilance Network and the Working Party of ISBT in order to reach agreement on taxonomy and to develop a standard form that could be used for gathering and reviewing proposed records for the library. They considered that the form should be pilot tested with experts. An editorial group would need to be established for transfusion reactions and blood experts would need to be added to existing editorial groups – notably infection and process. The relevant published literature would need to be identified.

3. FUTURE DEVELOPMENTS OF THE NOTIFY LIBRARY

3.1. How to better capture, classify and use didactic adverse events in the NOTIFY Library

(Stratos Chatzixiros)

Stratos Chatzixiros firstly gave an account of the present standing of Serious Adverse Event records in NOTIFY, noting that SAEs are defined as those cases where no recipient or donor has been harmed but where a risk of harm was identified. The category includes near misses, gamete mix-ups, loss of MPHO, etc.

The library currently holds 103 SAE entries which can be distributed by MPHO type as follows:

- tissues (non-ocular) 54.5%
- ocular tissues 20.4%
- HSC 11.7%
- organs 8.7%
- reproductive tissues and cells 4.9%.

According to the current definition for SAE types, the 103 cases can be divided into:

- Unsuitable tissues/cells released for clinical use or applied clinically, 30 (29%)
- Loss of suitable organ(s), 8 (8%)
- Loss of large quantity of unmatched tissues or cells, 5 (5%)
- Loss of highly matched or autologous material, 18 (17%)
- Other, 42 (41%)

For information purposes, some examples of SAEs categorised as “other” were given. Please refer to table 8.

Table 8: Examples of Serious Adverse Events classified as “Other” in the NOTIFY Library

Incident ID	Incident description	Incident type	Substance type
148	Transplant record returned informing tissue not used but no return of tissue. Upon investigation, the tissue had been used but no record on transplant was made	SAE => Other	Tissues (non-Ocular) => Allogeneic => Musculoskeletal => Bone
345	Cord Blood. Seven units of cord blood lost during transit to private cord blood bank because flight diverted and material lost for eight days in system by courier. Cells discarded upon receipt at TE.	SAE => Other	HPC => Cord Blood, Allogeneic
167	Improper rehydration of bone graft resulted in graft fracture at time of implant. Prolonged operating time, surgeon had a back up graft.	SAE => Other	Tissues (non-Ocular) => Allogeneic => Musculoskeletal => Bone

Some 2010 data from the Directorate-General for Health and Consumers (DG SANCO) Annual Reporting of Serious Adverse Events and Reactions for Tissues and Cells were presented, allowing some parallels to be drawn in terms of information analysis and presentation.

Table 9: SANCO 2010 data, breakdown of reported SAEs by type (n=451)

Number of reported cases (% of total)	Type of SAE
74 (16.41%)	Procurement
26(5.76%)	Testing
16 (38,14%)	Transport
172 (38.14%)	Processing
34 (7.54%)	Storage
40 (8.86%)	Distribution
33 (7.32%)	Materials
56 (12.42%)	Other

These 451 reported SAEs cases were attributed to one of the 4 pre-defined specifications:

- Tissues and cells defects: 149 (33.04%)
- Human Error: 168 (37.25%)
- Equipment failure: 81 (17.96%)
- Other: 53 (11.75%)

The group was then presented with a proposed list of categories for Tissue & Cells SAEs, namely:

- Contamination/Sterility
- Packaging
- Preservation
- Handling
- Mislabelling/Mix-ups
- Graft quality
- Transport
- Management

On the basis of the above terminology, this is how the T&C SAE taxonomy would be displayed in comparison to what we currently have in NOTIFY (table 9):

Table10: Proposal of new SAE taxonomy for Tissues & Cells

Incident ID	Incident description	Incident type	Substance type
112	Irradiated tissue discarded due to discoloration and odor	SAE => Loss of highly matched or autologous material	Tissues (non-Ocular) => Allogeneic => Musculoskeletal => Tendon or Ligament
147	Broken bottle of bone graft	SAE => Other	Tissues (non-Ocular) => Autologous => Musculoskeletal => Bone
364	Exceeded cold ischemia time, organ discarded	SAE => Loss of suitable organ(s)	Organs => Kidney
365	Ureteral damage, organ discarded	SAE => Loss of suitable organ(s)	Organs => Kidney
124	Heart valve mislabeled, delay in surgery, unneeded exposure to anesthetic	SAE => Unsuitable tissues-cells released for clinical use and-or applied clinically	Tissues (non-Ocular) => Allogeneic => Cardiovascular => Heart valves

97	Sperm from donor with ulcerative colitis was distributed and used	SAE => Unsuitable tissues-cells released for clinical use and-or applied clinically	Reproductive T&C => Sperm, Non-partner
145	Large osteochondral graft lost by FedEx	SAE => Loss of highly matched or autologous material	Tissues (non-Ocular) => Autologous => Musculoskeletal => Bone
180	Transcription error by collection staff listing an HCV reactive as non-reactive	SAE => Other	HPC => Apheresis, Allogeneic unrelated

REVIEW existing cases according to proposed new SAE Taxonomy

Incident ID	Incident description	Incident type	Substance type
112	Irradiated tissue discarded due to discoloration and odor	Contamination Sterility	Tissues (non-Ocular) => Allogeneic => Musculoskeletal => Tendon or Ligament
147	Broken bottle of bone graft	Packaging	Tissues (non-Ocular) => Autologous => Musculoskeletal => Bone
364	Exeeded cold ischemia time, organ discarded	Preservation	Organs => Kidney
365	Ureteral damage, organ discarded	Handling	Organs => Kidney
124	Heart valve mislabeled, delay in surgery, unneeded exposure to anesthetic	Mislabelling Mix-ups	Tissues (non-Ocular) => Allogeneic => Cardiovascular => Heart valves
97	Sperm from donor with ulcerative colitis was distributed and used.	Graft quality	Reproductive T&C => Sperm, Non-partner
145	Large osteochondral graft lost by FedEx	Transport	Tissues (non-Ocular) => Autologous => Musculoskeletal => Bone
180	Transcription error by collection staff listing an HCV reactive as non reactive	Management	HPC => Apheresis, Allogeneic unrelated

Similarly, the process of organ transplantation can be divided into several phases, namely:

- Consent/Donor screening (Donation)
- Testing/Characterisation
- Procurement
- Preservation
- Allocation
- Transport
- Transplantation/Disposal

The taxonomy for SAE in organ transplantation can therefore be described in the manner shown in table 11.

Table 11: Proposal for SAE taxonomy in organs transplantation

Consent/ Donor screening (Donation)	Consent was not asked	
	Consent was not reported	
	Incomplete donor history	
Testing/ Characterisation	Omission of mandatory test	
	Test not performed correctly	
	Wrong communication of test result	
Procurement	Inadequate perfusion	
	Damage to the parenchyma of the organ	
	Damage to the vessels, ureter etc	
	Contamination of the organ	
Preservation	Wrong/Contaminated preservation fluid	
	Inadequate temperature of preservation fluid	
	Machine perfusion problems	
Allocation	Structural mistake in allocation algorithm	
	Incorect donor testing	
	Incorrect donor typing	
Transport	Logistics problems	Wrong shipping address
		Delay due to missing/wrong information of responsible persons
		Accidents in the transport chain
	Damage to transport box	Contamination
		Warming up
	Missing crossmatch material	
	Mixing up of organs at time of packing/wrong labelling	
Transplantation/ Disposal	Surgical damage in operating theatre	
	Wrong patient	
	Damage/Misplacement	
	Delayed operation	

It is believed that the new proposed taxonomy brings advantages by capturing and classifying events in clearer way; new column(s) could be added to the NOTIFY database to accommodate these proposed changes. The ability to display in which stage of the process the incident has occurred is deemed to be helpful and careful use of correct keywords would aid the users to fine-tune their searches, rendering the tool more useful. At this point, the editorial groups were

reminded of the crucial importance of keyword selection in general, as the efficiency and accuracy of the searches highly depend on this parameter.

There was some concern expressed during the discussion, prompting participants to be mindful about not implementing too rigid classifications that may not meet needs. It was also recognised that categorisation of event by stage of transplantation may not always be easy to establish.

It was clear that a great deal of work is required to review entries already made and define the taxonomy levels for future entries. Stratos closed his presentation by thanking everybody for the contribution made towards the project so far.

3.2. Presentation of an electronic tool for the insertion of new case types, or new information on existing case types

(Daniela Minutoli and Deirdre Fehily)

In this section, Deirdre Fehily introduced awaited proposal for a new electronic tool for submission of new cases or new information on cases already held in the library.

Once the database is up to date, this new tool will replace the current Google document used for the preparation of new cases for upload. The proposal involved separate procedures for health professionals, health authorities and the Public.

3.2.1. Submissions by health professionals

STEP 1- A structured search of the NOTIFY library has to be performed for the incident and substance types before submitting a case, to ensure the case has not already been logged.

STEP 2 - A minimum set of criteria has been set for new case entry, which in shown in step two in the slide below and comprises of:

- Full reference with a PDF copy of the journal article or official document
- Incident type in accordance to the NOTIFY taxonomy
- Substance type in accordance to the NOTIFY taxonomy

If the case has not yet been published or reported through official channels, it can still be submitted and discussed in the BIG V&S Forum.

STEP 3- Once the mandatory elements have been entered, the case is submitted to the CNT team. Additional information should be provided at the time of submission whenever possible. This is particularly important if the source of information is a vigilance system, as reporting systems do not tend to hold detailed information of events and reactions.

The solicited additional information maps to the titles used and displayed in the library:

Incident description

- A proposed title for the incident type

Information on the time from incident occurrence to its detection

- SAR: Latency (quantitative information, i.e. number of hours, days, weeks or years)
- SAE: when event was detected

Alerting signals

- SAR: A description of the alerting signals in the donor or recipient(s)
- SAE: how and when incident was detected

Frequency data and estimates

- Data or estimate of the frequency of this type of SAR or SAE

Demonstration of imputability (SAR) or root cause (SAE)

- For SAR, a description of the way(s) in which it was confirmed that the donation or transplant was the cause of the SAR
- For SAE, a description of the root cause of the incident

Keywords

STEP 4 - CNT TEAM evaluates the "Case" and sends it by e-mail to the appropriate editorial group for consideration

STEP 5 - The editorial group responds within one week to say if the publication should be added to the bibliography

STEP 6 - The editorial group responds within one month to approve or amend the text for the database row

STEP 7 - If the incident type already exists in the library, the health professional needs to consider whether the existing entry is adequate or should be amended in the light of this new publication. In the same was as for a submission of a new case, there are mandatory elements that need to be met for amendment of an existing record.

- Incident ID
- NEW reference: if there is a new reference to add, plus the PDF
- NEW information: if the information under the pre-defined parameters need to be amended (e.g. latency, alerting signs, etc)
  CNT team will review the submission and update the record(s) accordingly

STEP 8 - IF NO INFORMATION HAS BEEN PROVIDED, CNT TEAM sends the submission by e-mail to the appropriate editorial group for consideration.

- The editorial group responds to CNT within one week to say if the publication should be added to the bibliography
- The editorial group responds to CNT within one month to approve or amend the text for the database row

3.2.2. Submission by Health Authorities

The competent health authority will be looking to submit a case from an official report, case review or publication, for instance. This not being the case the authority will be invited to submit the case(s) for publication to the NOTIFY e-journal.

STEP 1 – as per previous description in 3.2.1 above.

STEP2 - When "Mandatory Elements" are submitted the case is sent to CNT TEAM that considers whether it should be a new database record or should be added to an existing row and sends it by e-mail to the appropriate editorial group for consideration along with a PDF of the report. The experts will be asked to complete the missing information where necessary, liaising with the Authority for details that are not available in the report.

The other steps are observed as previously described**.**

3.2.3. Submission by Members of the Public

Members of the public could be able to describe incidents they have knowledge about as long as they are in a position to submit a reference. No specific pathway for such submission was presented as this was put forward as a possibility, subject to discussion.

During the discussion that followed the presentation, a definition of "general public" was requested. There were also concerns expressed regarding case submission by members of the general public. It was thought that highlighting immediately the need for a quotable reference would make it clear that anecdotal cases are not accepted.

3.3. Towards a NOTIFY Journal of V&S for MPHO as a source of reference for the NOTIFY Library

(Mike Strong)

Justification for the creation of an e-journal was considered and some points were put forward:

- Many SARs and SAEs cannot be included in the NOTIFY Library because they have not been published anywhere, not even in competent authorities official reports

- SAEs are often considered not to be of interest to publishers, even though they may have a significant impact on the safety, quality and supply of MPHO
- No journal focuses on vigilance for MPHO – this could have significant didactic value across the scope of these products
- A specialized journal could develop procedures allowing publication of cases while maintaining anonymity.

The proposal was then presented

- An e-journal, in English language published as a WHO publication linked to the WHO Bulletin by the WHO publication team.
- Abiding by WHO standards including Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals
- With a direct link from the NOTIFY Library site and the relevant WHO website pages
- Entitled: NOTIFY - THE JOURNAL FOR VIGILANCE AND SURVEILLANCE OF MEDICAL PRODUCTS OF HUMAN ORIGIN

Types of cases

- **Basic cases events/reactions (minimal information):** A pre-determined structure based on the requirements of a NOTIFY Library Database entry

Can be anonymized authored by a supporting institution

These would be published following rapid review.

- Detailed cases - Reviews - Analysis of series- Editorials – Letters:

A more open structure allowing authors to consider a wide range of vigilance related literature (from the NOTIFY Library or from elsewhere)

These would be reviewed thoroughly as for any scientific journal.

The benefits would be

- Each individual case report would result in the addition of a new row to the NOTIFY Library (or the addition of a reference to an existing row) with an appropriate citable reference
- Review articles could provide opportunities for analysis of trends/observations coming from an overview of cases appearing in the library.

The funding initiative is proposed as follows

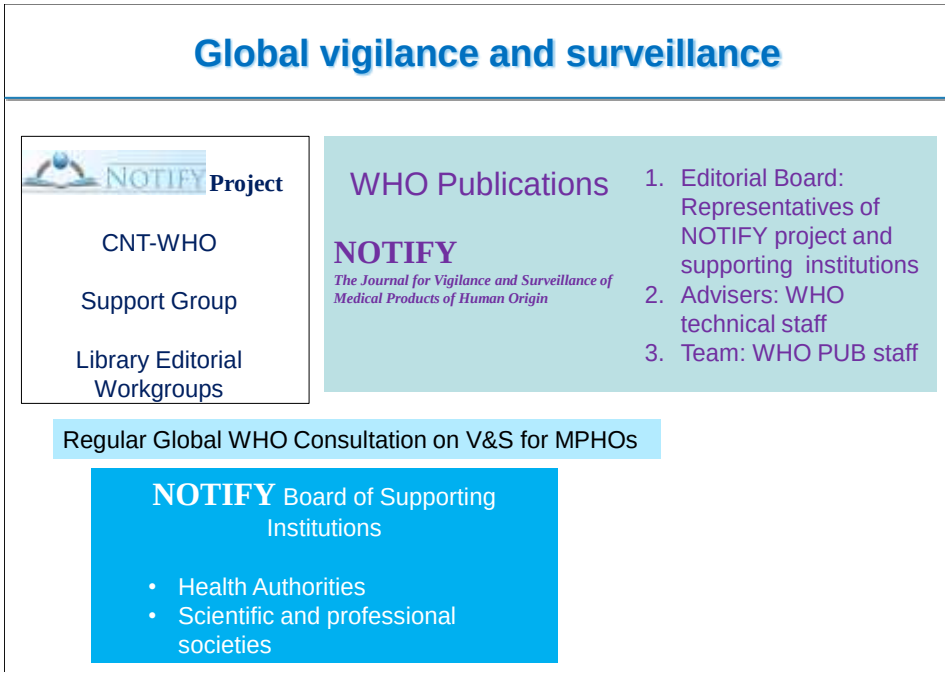
- Case studies would be published without charge (if they meet all the strictly defined criteria) – they would be published without author names
- The publication of Review articles would require payment by the authors – the authors would be named
- For the initial launch of the initiative funding would be required from a series of founding partners

- The e-journal would be freely accessible to all.

Editorial role

- An Editorial Board would be established
- Members would come (primarily) from the Editorial Groups of the NOTIFY Library website
- Editorial oversight would be provided by the WHO Bulletin
- The WHO Bulletin infrastructure would address liability and other legal issues.

The picture of Global V&S of MPHO would therefore look like:



In the discussion that followed various viewpoints were expressed regarding the acceptance of 'anonymous' case reports. It was clarified that this did not imply that the person/organization submitting the case would not be identified. The intention was that the location/individuals involved in the case might not be identified but the case study could be submitted by an identified recognized and authoritative organization.

3.4 Terminology for V & S of MPHO - constraints and necessities

(Geni Neumann and Paul Ashford)

The session started with a brief address about definition of terms used in V&S of MPHO and was followed by a presentation on harmonization of terminology and coding for MPHO.

Geni Neumann made some interesting observations about the sensitivities and different perceptions by health care professionals when it comes to use and contribution to vigilance systems. NOTIFY is a Global V&S tool and, as such, it is important that generic terms used to

refer to or describe it, take into account cultural and semantic differences in a sensitive manner. The following definition was given in order to emphasize the need to accommodate such differences:

Terms = word or compound words that in *specific contexts* describe specific *meanings*

The term "vigilance" may carry a negative perception in some languages, as is the case in Portuguese, where it can have a generic connotation of "policing" rather than "alertness, attention or care". Similarly, the term "imputability" in Portuguese tends to be associated with "legal contravention and breach of law", more than just "causality".

V&S of MPHO can be put in direct context with patient safety , biovigilance, haemovigilance and WHO adverse reaction terminology (WHOART), for example. Other areas such as pharmacovigilance and material vigilance are also indirectly related.

The next topic covered was the one of patient safety and reference was made to the report "*More than Words: Conceptual Framework for the International Classification for Patient Safety*", WHO, January 2009. This technical framework was set out to categorize patient safety information using standardized sets of concepts with agreed definitions and preferred terms to facilitate the description, comparison, measurement, monitoring, and interpretation of information to improve patient care.

Lastly, the definition of some further terms related to patient safety was provided:

- An event is something that happens to or involves a patient and an agent is a substance, object or system that acts to produce change.
- A patient safety incident is an event or circumstance that could have resulted, or did result, in unnecessary harm to a patient.
- Incident: errors, violations, abuses, deliberate or unsafe acts.
- Harmful incident (adverse event)

The terminology used in NOTIFY is not consistent with all of the above. For NOTIFY, for example, an event by definition excludes that harm has occurred to a patient or donor.

3.4.1. Harmonization of terminology

(Paul Ashford)

WHO and ICCBBA have a three year joint programme (2013 to 2016) with the overall objective to ensure improved access, quality and use of medical products and technologies. Moreover, it has been set up to ensure consistency of MPHO terminology used by the NOTIFY Project with core ISBT 128 terminology.

ICCBBA is a member of the Eurocet consortium, which is a “Reference compendia for the application of a single European coding system for human tissues and cells”.

There is a requirement for different levels of classification, which serve distinct needs, as exemplified below:

- High level, Low detail
    - Activity data gathering
    - SARE Categories
- Low level, High detail
    - Inventory management
    - Clinical application

EU generic coding for tissues and cells is a legal requirement, functioning as an umbrella scheme for all 28 member states. The EU generic terminology is set at very high level description, with approximately 90 terms, such as:

- CV, VALVE, AORTIC
- CV, VESSEL, ARTERY
- MS, BONE, FEMORAL
- MS, BONE, SHAPED GRAFT
- OCULAR, CORNEAL
- REPRODUCTIVE, OOCYTE

In contrast to the above, when dealing with clinical aspects, low level, detailed coding is required. The NOTIFY Substance Taxonomy has up to five levels of classification and 42 types of substances, including organs. The current coding table combines two distinct taxonomic concepts, i.e. substance type and donor/recipient relationship, with focus on substance type.

Table 11: NOTIFY taxonomy (substances) with 5 levels of classification

Level 1	Level 2	Level 3	Level 4	Level 5
Human Substance	Ocular Tissue	Cornea		
		Sclera		
	Tissue, non-ocular	Musculoskeletal	Bone	
			Tendon or Ligament	

Harmonization of Taxonomy: How well do the definitions from different systems fit?

- NOTIFY Taxonomy (≈ 42 terms)
- EU Generic Terminology (≈ 90 terms)
- ISBT 128 Classes (≈ 250) – all MPHO
- ISBT 128 Product Description Codes (≈ 9,250)

The current coding situations vary for different substances; for example, mapping is good for ocular tissue, adequate for CT and not so good for tissues (non-ocular). Some examples are given in the tables (12 to 15) below.

Table 12: Taxonomy - Sample mapping for ocular tissue

Level 1	Level 2	Level 3	EU Generic	ISBT 128 Class	ISBT 128 PDC
Human Substance	Ocular Tissue	Cornea	Ocular, Corneal	Cornea	32 PDCs
		Sclera	Ocular, Scleral	Sclera	16 PDCs
		Limbal	Ocular, Limbal		

Table 13: Taxonomy - Sample mapping for CT

Level 1	Level 2	Level 3	EU Generic	ISBT 128 Class	ISBT 128 PDC
Human Substance	HPC	Marrow	Progenitor Cell, Hematopoietic, Bone Marrow	HPC, Marrow	243 PDCs
		Apheresis (PBSC)	Progenitor Cell, Hematopoietic, Peripheral Blood	HPC, Apheresis	101 PDCs
		Cord Blood	Progenitor Cell, Hematopoietic, Cord Blood	HPC, Cord	56 PDCs

Table 14: Taxonomy - Sample mapping for tissue (non-ocular)

Level 1	Level 2	Level 3	Level 4	EU Generic	ISBT 128 Class	ISBT 128 PDC
Human Substance	Tissues non-ocular	M/S	Bone	MS, Bone, Shaped Graft		
				MS, Bone, Calcaneus		
				MS, Bone, Clavicle		
				MS, Bone, Cranial Plate		
				MS, Bone, femoral		
				MS, Bone, Fibular		
				+16 others		

Table 15: Taxonomy - Sample mapping for tissue (non-ocular)

Level 1	Level 2	Level 3	Level 4	EU Generic	ISBT 128 Class	ISBT 128 PDC
Human Substance	Tissues non-ocular	M/S	Bone	MS, Bone, Shaped Graft	Cancellous Bone Cubes	
					Cancellous Bone Dowel	
					Cancellous Femoral Knee Slice	
					Cancellous Bone Peg	
					Strut, Narrow	
					+others	

There are of course areas requiring review and some suggestions were put forward for consideration:

- Add classification for some products, such as
    - Conjunctiva
    - MSC
    - Source Cells
- Separate taxonomic concepts (e.g. donor-recipient relationship from MPHO category)
- Some re-structuring of the taxonomy (e.g. include Dura Mater and Meniscus within M/S)
- Consider more widespread adoption of the EU Generic Codes
- Publish mappings.

The benefits of harmonization of activity and SARE taxonomies are several-fold and include:

- Help with provision of accurate denominator data
- Structured mapping supports the automation of data collection, for example:
    - Every time an ISBT 128 Product Code is scanned the appropriate activity category can be incremented

During the post talk discussion, it was mentioned that many centers in Germany intend to use a different coding system called Eurocode. Amongst 1600 tissue establishments in the EU, 204 facilities in 18 Member States currently use ISBT 128 although this number is increasing steadily

particularly in the field of HPCs. The regulatory situation of each licensed establishment will be publicly accessible once the EC's new TE Compendium database is made public later this year.

Day Three, Monday 9 December 2013

3.5. A place for ethics in the NOTIFY Library?

(Marie-Charlotte Bouesseau)

Marie-Charlotte Bouesseau spoke about ethical principles in transplantation, ethical duties of reporting adverse events, introduced the ethical framework of transplantation and listed a series of ideas and options, should there be a decision to create a place for ethics in NOTIFY.

3.5.1. The ethical duty of reporting *Adverse Events*

Some basic principles of general and medical ethics can be applied to the process of learning from errors.

Primun non nocere

Firstly, the principal precepts *Primun non nocere, beneficence* and its corollary *maleficience* were appropriately evoked.

Data systems shared by all stakeholders are dependent on information collected through reporting of AE; such systems might assist health care providers to improve the quality of care afforded to patients. Learning from information related to AE is pivotal in improving risk:benefit and strengthening good and safe practices.

Transparency and accountability

Health services and professionals must establish reporting systems as good governance mechanisms to maintain public trust and legitimacy

Autonomy

Patients are entitled to have access to transparent information related to health practices, in order to make informed decisions.

WHO has a role and duty in promoting reporting and learning from AE in relation to patient safety.

3.5.2. The ethical framework of transplantation

Some significant milestones were cited:

- WHO: From 1987 (WHA40.13) through to 2010 Guiding Principles (WHA63.22)
- Oviedo Convention (The European Convention on Human Rights and Biomedicine of 1997) and the additional protocol (2001)
- Declaration of Istanbul on Organ Trafficking and Transplant Tourism (2008)
- World Medical Association (WMA) on Human Organ Donation and Transplantation statements (2000 updated in 2006 and 2007).

It is inevitable that in complex matters such as bioethics, conflicts of values and principles will always arise; there are tensions to be resolved and the necessity to balance needs of the individual with quality and safety of treatment and processes.

The ethical basis of the framework can be mapped to the "WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation" and the WMA guideline, with some examples given for illustration:

- Dignity
    - autonomous decisions [*WHO P1, P3]* and privacy
    - protection of vulnerable persons [WHO P4, P5]
- Justice
    - equitable access (UHC) [*WHO P9]*
    - solidarity (altruistic donation) [WHO P6]]
    - Beneficence/non maleficence: Safety [*WHO P 10]*
    - Transparency [*WHO P11]*
- Professional integrity
    - conflicting interests [WHO P2)
    - payment or coercion of donors [WHO P7]
        - WMA (2006): "The obligation (to the patient) is not absolute; for example the physician's responsibility for the well being of a patient who needs transplant does not justify unethical or illegal procurement of organs"
    - WMA (2007): "Financial incentives such as direct payments for donating tissue for transplantation are to be rejected"

Participants from several countries meet to discuss and produce position papers on subjects such as equity and quality of the health services, biobanking, infectious diseases, organ, cell and tissue transplantation and research ethics.

3.5.3. Current ethical challenges

Some of the significant ethical challenges encountered were exemplified, demonstrating the need to identify the level and feasibility of a global consensus and the relevance of specific guidance-

- The diversity of MPHO ((iPS (induced Pluripotent Stemcells), cells, plasma, gametes, organs, etc…)
- The diversity of practices and uses of products of human origin
- Cultural diversity

3.5.4. Implications for NOTIFY

Firstly, some examples of existing cases in NOTIFY where gaps in information can be illustrated, demonstrating the potential benefits of looking at cases from the ethical view point.

NOTIFY Library Reference ID 1496: “Reports received involving unlawful activity including (…) procurement of cornea without adequate consent” - “Potential donors can be properly informed of these risks prior to giving consent.” in Vigilance and Surveillance EUSTITE Pilot Report – 2010

NOTIFY Library Reference ID 370, on the transmission of HCV by tissue transplantation: “Found during look back that some recipients could not be identified due to lack of hospital records. One case as a result of surgeon refusal to inform patient due to failure in obtaining informed consent”.

A series of options and suggestions for future work were presented and open for discussion.

- Provide background information on ethics and law: international and national normative documents (national laws, National Ethics Committees (NECs) publications, etc.)
- Report on legal cases (against existing norms)
- Include ethical aspects in reports (declarant to detect concomitant ethical issues when reporting on AE)
- Develop a section for "ethical incidents" including a large scope MPHO (cases of exploitation, coercion, lack of information, excessive risk taking, breach of confidentiality, discrimination of donors/recipients, etc.)
- Discuss ethical cases (e.g. informed consent process)
- Add training module on ethics of MPHO transplantation
- Avoid duplication with other important tools already available
    - Global Observatory on Donation and Transplantation http://www.transplant-observatory.org
    - WHO http://www.who.int/transplantation/knowledgebase/en
    - Declaration of Istanbul http://www.declarationofistanbul.org
- Focus on added value of Bologna Initiative for Global Vigilance and Surveillance and specificities NOTIFY Library
    - Didactic purpose (learning process)
    - Safety (donors and recipients)
    - Scope (all MPHO)
- Good governance mechanisms
    - Tool aiming to improve transparency and accountability
    - Initiative involving all relevant stakeholders (patients' organizations?)
    - Project based on the principle of equitable access to safe and respectful care
- Decision on relevance and feasibility of a section on ethics and law. If yes, define the best option
- Based on available human, institutional and financial resources, develop a proposal including pilot study to be evaluated during next NOTIFY meeting (2014)
- Explore potential collaborations to strengthen synergies and avoid duplication of work
    - WHO CC for bioethics (e.g. U. Zurich)
    - UN agencies and other intergovernmental organizations (e.g. CoE)
    - NGOs (e.g. WMA)
    - Scientific societies
    - NECs

Following this comprehensive presentation, some interesting discussion followed. One challenging aspect about ethics and law at international level is that legislation varies widely and there is a need to know and understand the legal background in various parts of the globe. In practice, what is illegal in one country may not be in another. Moreover, legislation changes over time and keeping up to date is another challenge.

There was a suggestion to use the NOTIFY Journal as a tool for dissemination of cases involving ethical issues. There was also once again a need to remind that NOTIFY is not a reporting tool and that it holds only a didactic function.

As unethical practice contravenes the WHO principles, it qualifies for entry in the NOTIFY Library. There was a general agreement amongst the participants that a session for bioethics should be added to NOTIFY.

4. Official Launch of the NOTIFY website and library

Geni Neumann emphatically affirmed that Brazil is committed to the mission of making V&S in MPHO a priority. From ANVISA's perspective, hosting the Global consultation in Brasilia was very important, resulting in V&S of MPHO achieving high levels of visibility across the whole of Brazil, through the media.

Dr Marie-Paule Kieny Assistant Director-General, WHO addressed the audience by video link and this is the full transcript of her discourse:

"Ladies and gentlemen, dear colleagues - I have pleasure in representing WHO in the formal launch of the NOTIFY website and library. These were the first outputs of the NOTIFY Project . The NOTIFY Project associated WHO with the Italian National Transplantation Centre. It was born to respond to the need for a global forum for Vigilance and surveillance of adverse outcomes associated with the use of medical products of human origin. MPHO encompass all components of the human body that can be donated to be used clinically from blood, cells and tissues to organs and gametes. It also includes substances such as breast milk. MPHOs have a number of factors in common: donation for most of them, potentially exposes the donor ; and in particular the most vulnerable donors, to exploitation , creating the risk of breach of ethical standards. They also share a risk to the safety of the recipient, in particular leading to potential risk of contamination with infectious agents. V&S are both crucial in ensuring quality and safety of the donor and recipient alike.

The NOTIFY project allows to better identify risks and provide options on to how to handle them. It also aims at increased transparency in the area of MPHO in order to justify the confidence of both the public and professionals. The NOTIFY website is open to everybody. Indeed, we could all one day need to receive a treatment based on a MPHO and we should all be ready to become donors, should the opportunity arise. The NOTIFY website is open to all, but offers different entry points adapted to the lay public, to professionals or to health authorities. The NOTIFY website contains a comprehensive list of background documents and the most innovative part of the NOTIFY tool is the NOTIFY Library. The NOTIFY Library, which is

already in use, is the first of its kind. It constitutes a reference database where everything that went wrong or that could have gone wrong with MPHO is collected and analysed thanks to the input of major scientific and professional societies and from national competent authorities from all over the world. We are now close to 1000 didactic cases of adverse reactions and events in the NOTIFY Library. They are easily accessible, commented and linked with relevant literature references. I would like to take this opportunity to express WHO's gratitude to the Institute Superiori di Sanità for its unfailing support right from the beginning of the NOTIFY project. We would also like to thank ANVISA and the Brazilian government for the generous support to this meeting, and, of course, all health authorities and scientific and professional societies which are contributing to NOTIFY as a global governance tool. Together we aim at optimizing the safety, ethics and efficacy of donation and clinical application of components of the human body for therapeutic purposes.

Next, **Dr Fabrizio Oleari, President of Instituto Superiore di Sanità** conducted the official launch of the NOTIFY website and Library, by delivering a speech via video link. A full transcript of the address is included here:

"As the president of the Instituto Superiori di Sanità, it is an honour to participate in this event in regards to an initiative of high importance in the field of transplantation. The Institute has a long history of co-operation with the World Health Organization in different fields, which resulted in the establishment of four of its departments, having acquired the status of WHO collaborating centres for (1) reference and research on poliomyelitis, for (2) reference and training in tropical diseases control, for (3) research and health promotion in alcohol and alcohol-related health problems, and for (4) environmental health in contaminated sites. Last year we added a fifth department to our task force and we had the pleasure to welcome the National Transplant Centre (CNT) as a WHO collaborating centre for Vigilance and Surveillance for human cells, tissues and organs. Italy has always been present in scientific developments and following a conference in Bologna in 2010, which was attended by over 100 invited experts in the clinical and regulatory fields of organ, tissue and cell donation and transplantation and in assisted reproduction, CNT took the challenge to develop and maintain a comprehensive electronic database, the NOTIFY library of documented cases of adverse events and reactions related to transplantation and assisted reproduction. This task is performed in collaboration with an international team of experts and professionals who provide continuously with new data and analysis. The information is invaluable for professionals, regulators, patients and donors worldwide to help them understand the risks associated with these procedures. The NOTIFY library achieves communication of vigilance and information globally in support of improved safety and quality for donors and recipients. The overall didactic value of the NOTIFY Library has been acknowledged by many international institutions and professional associations. It is increasingly quoted in publications around the globe. Our future goals include reaching a real global representation through multi-language interfaces and developing a tool for e-publications that could become the reference point for all stake holders. The Instituto Superiori de Sanità is proud to be part of such an international initiative and continuously supports The National Centre for Transplantation in accomplishing its mandate as a WHO collaborating centre."

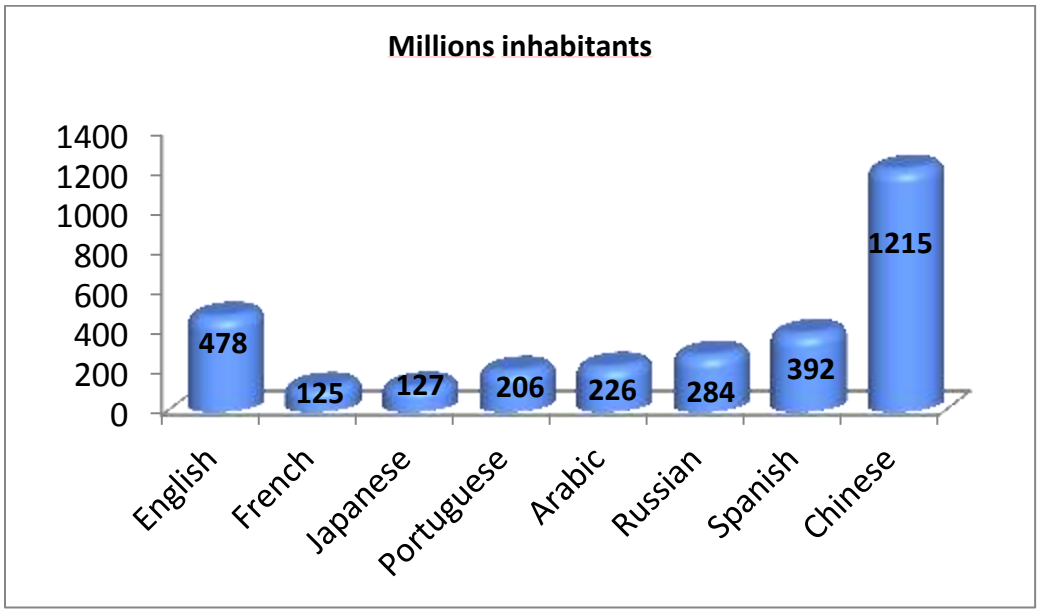
The CNT team informed the participants that these two key addresses would be made available on the NOTIFY website.

4.1. Language specific interfaces for the NOTIFY library and website

(Jose Nuñez)

During the Second Global Consultative Meeting for the BIG V&S Project in Rome, the idea of language-specific web interfaces for NOTIFY was formulated. This would help non-English speakers to benefit from the NOTIFY project and conversely would help the NOTIFY project by allowing the input of cases initially not published in English.

Figure 9: Most spoken languages globally, expressed by millions of native speakers



The plan would be to have twin NOTIFY front pages in WHO's six official languages - Arabic, Chinese, English, French, Russian and Spanish. Portuguese and Japanese will be added to NOTIFY due to the importance and widespread use of those languages too.

The idea is to enable bi-directional use. The proposal is for searches to be done in the individual's own language, **summarized and** translated into English, sent to the editorial group and then uploaded accordingly. Conversely, searches in the **NOTIFY** database could be done, translated and then disseminated locally in the native language **by the local partner organization.**

There is no doubt that the concept is highly desirable so as to facilitate access and dissemination of the didactic messages, as well as facilitating contributions from non-English publication sources. However, the practical questions that ensue are:

Which language(s)/country(ies)?

Who would do it?

Governmental support?

Identification of resources to meet costs**.**

It seemed from **discussion** in the limited time **available for** this topic, that there is need for further assessment and planning to be carried out before a decision can be made. **It is likely that a smaller, dedicated, meeting on this topic will be held.**

5.Promoting reporting systems and disseminating outcomes

This section had oral contributions from several participants, who were asked to give a brief overview of the current situation in relation to V&S for MPHO in their countries, WHO Regions or professional organizations.

5.1. ROUND TABLE: National V & S Systems, lessons learnt, impact on practices and perspectives

5.1.1. Thailand, Food and Drug Administration

(Wimon Suwankesawong)

In Thailand, only Pharmacovigilance has been set up for 30 years. Haemovigilance is just in the process of being set up and has not been implemented yet. The concept of Vigilance & Surveillance for MPHO is quite new in Thailand. However, it is very important and the NOTIFY Library is also very useful. The Thai representatives states that they will endeavor to disseminate this information amongst their health care professionals.

5.1.2. Portugal, Centro de Sangue e da Transplantação do Porto

(Jorje Condeço)

The current situation regarding Vigilance and Surveillance systems for Medical Products of Human Origin in Portugal is as follows:

As part of its responsibilities and with the enforcement of the European Directive, the Portuguese Blood Institute (PBI) implemented the Portuguese Haemovigilance System in 2008. This system

resulted from collaboration between PBI and the competent authority for the Blood Services and Transplantation.

In 2012 there were major changes in the organization of many Portuguese governmental structures. This was the case of PBI, which became the Portuguese Blood and Transplantation Institute (PBTI), where activities related to blood transfusion medicine merged with the areas of transplantation, cells and tissues, making it one of the largest Portuguese institutes. While this happened, the role of the competent authority was also modified. The PBTI is now the competent authority for the area of transfusion and transplantation medicine and the Directorate General of Health (a department of the Ministry of Health) is the competent authority for blood establishments. PBTI is therefore the responsible authority for Haemovigilance and Biovigilance in Portugal.

At this time the Portuguese Haemovigilance system is fully developed and implemented, and collects data on adverse reactions in donors and recipients of blood components, errors and near misses in blood transfusion medicine services and in blood establishments. The system also collects activity data from blood services using them for monitoring the Portuguese transfusion activity and calculation of rates.

As for Biovigilance, this is in a late development phase. Identification of roles and evaluation of the tools designed for the collection of information related to errors, near misses and adverse reactions are currently underway. This is also a responsibility of the PBTI.

With regard to plasma-derived products, in the same way as pharmaceutical drugs, they are subject to supervision and monitoring by the Portuguese National Institute of Pharmacy and Medicine.

5.1.3. Saudi Arabia, Saudi Food & Drug Authority

(Ghazi Saleh Saeed)

A Haemovigilance system has been in place since 2009 but Biovigilance has not been set up in Saudi Arabia yet.

5.1.4 Canada, Health Products and Food Branch, Health Canada

(Duc Vu)

Relevant Legislation:

Food and Drugs Act: sets enforceable safety, quality and efficacy standards governing health products and food through regulations, which are for CTO and blood:

- Safety of Human Cells, Tissues and Organs for Transplantation Regulations (which are based on Canadian Standards Association Standards(CSA)) and Blood Regulations; these Regulations contain safety requirements with respect to processing, storage, record keeping, distribution, importation, error, accident and adverse reaction investigation and reporting

Key Partners:

Health Canada: reports to the Minister of Health, and represents the federal department regulating and ensuring safety of health products, and, in doing so, helps Canadians maintain and improve their health, while respecting individual choices and circumstances. Within Health Canada, the following organizations play an important role with respect to the safety monitoring of CTO and blood and blood products.

- Health Products and Food Branch (HPFB), responsible for regulatory policy development, issuing Guidance Documents, review of applications of clinical trials that involve CTO, participating in the CSA technical committee, verifying compliance with the Regulations, compliance enforcement, inspection of source establishments and acting on reports of errors and accidents, collecting adverse reaction reports, detecting, assessing and managing potential safety concerns (signals), and issuing risk communications
- Public Health Agency of Canada (PHAC): reports to the Minister of Health; the PHAC's Cells Tissues and Organs Surveillance System (CTOSS) and Transfusion Transmitted Injury Surveillance System (TTISS) initiatives collect adverse events related to transplantation and transfusion. Both HPFB and PHAC work in collaboration with provincial authorities in the surveillance of CTO and blood products. Currently, the CTOSS surveillance is carried out through a pilot project implemented in five provinces (New Brunswick, Ontario, Quebec, Nova Scotia and Alberta), and is for tissues only.

5.1.5. India, Ministry of Health and Family Welfare Government of India

(Jagdish Prasad)

Blood vigilance is established in India, ART regulation is in its initial stages and an act related to V&S of stem cells is being put through Parliamentary approval. The Federal Ministry of Health of India is currently focusing on transparency and accountability. A national registration of all organ transplantations is planned to be in place in six months.

5.1.6. Japan, Office for Transplantation Medicine

(Yoshie Hirose)

In Japan there are several systems that collect information about adverse events and reactions following medical interventions with MPHOs. As regards to blood products for instance, there is a separate system focusing on virus infections such as HIV, HBV and HCV.

The National Institute of Infectious Diseases (NIID) submits regular reports on MPHO-related infections to Ministry of Health, Labour and Welfare (MHLW) , based mainly on published journals. From 2007, the Japan Society of Transfusion Medicine and Cell Therapy implemented a pilot reporting system for all kinds of side effects following administration of these MPHOs.

Within the MHLW, various departments are involved in the monitoring of MPHO-related adverse events and reactions. Incident reporting for tissue and organs feeds through basically to the Office of Organs and Tissue Transplantation whereas incident related to cell therapies are are also reported to other Divisions.

Before establishing official co-operation with the NOTIFY project, it is felt that the Ministry of Health needs to consolidate the roles of its internal departments and refine the relationships with academic societies. The Japanese Society for Transplantation has expressed interest in collaborating and participating in the NOTIFY project.

5.1.7. USA, AABB Patient and Donor Safety Center

(Barbee Whitaker)

In the United States, some hospitals voluntarily report adverse reactions and incidents associated with transfusion to the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network Haemovigilance Module. Some of these hospitals choose to also share this data with the AABB Center for Patient Safety, which is a Patient Safety Organization, authorized by the Patient Safety and Quality Improvement Act of 2005. Hospitals are also required to report transfusion related fatalities to the US Food and Drug Administration, which is the regulatory authority for blood. Barbee Whitaker is director of the AABB Center for Patient Safety. They work directly with hospitals to provide feedback on adverse events, benchmarking, education, reports, and quality reviews of the events that are reported.

5.1.10. WHO African Region

(Sheick Oumar Coulibaly)

For the African Region, all countries have regular blood transfusion activities. Cells, tissues and organs donation and transplantation activities currently occur only in a few countries such as South Africa, Ethiopia, Nigeria, Algeria and Kenya, but this might expand quickly. There are issues of human and technical capacity to justify the current status and it is important that very clear regulations are in place to help implementation and guidance of vigilance processes. Whilst transplantation is not a priority in that region yet, protection of donors and safety and quality for recipients is a matter of importance. Therefore the local vision is first to strengthen the regulations of these activities. Of course the NOTIFY project will be an important tool for countries in the African region, helping to keep high standards of quality for the donation processes and related activities, whilst they go through a capacity building process. There are some areas of major concern, including the ethical aspects of organ donation, mostly in countries of low to middle income. Some countries are nearly at the point where they could start thinking about V&S systems, at least in the area of Haemovigilance. Lusophone countries in the African region can benefit from the Brazilian engagement with V&S.

5.1.11. Tunisia, Ministry of Health

(Mohamed Ben Ammar)

The National System for Blood and the National Centre for Tissues and Organs are well established. They are responsible for notification of reported events and reactions. However,

there is no database or system and information supplied is kept for a short period of time, with no feedback mechanism. Interestingly, the same organizations are involved in the production and are responsible for distribution of MPHO to hospitals and their vigilance, raising a relevant issue of potential conflict of interests.

5.1.12. South Africa, Gauteng Health & Social Development

(Richard Lebethe)

A new act has been passed by the National Department of Health namely the "Office of Health Standards and Compliance Act. This states the National Core Standards to be complied with in the National Health Care delivery. Safety and quality is core to the act. Inspectorates as promoters and enforces of compliance.

5.1.13 Colombia, Ministry of Health and Social Protection

(Edwin Antonio Cárdenas Villamil)

Colombia has a regulatory framework for blood and blood components and a separate one for organs, tissues, cells. These frameworks cover processes of , procurement, donation, preservation, storage, transport, and final disposit**ion.**

Competent Health authorities have a role in the monitoring of adverse events reporting within both frameworks. However, they have not yet established national biovigilance or haemovigilance programs integrating all parties involved. . Information systems for registration and analysis of adverse events are yet to be developed.

There are plans to design and develop appropriate biovigilance and haemovigilance programs, based on international guidelines and models from the Colombian Ministry of Health and Social Protection.

5.1.14 Teheran, Iranian Tissue Bank and Research Center

(Mitra Mahdavi-Mazdeh)

Organ transplantation in Iran as any other health programme is under the supervision of the Ministry of Health and Medical Education (MOHME). Each university of medical science has the responsibility to oversee and regulate the management in the medical centers belonging to their province, according to guidelines of MOHME. The registry is kept by the MOHME but there is no system for reporting SEARs. Some professional organizations look at adverse events in a reactive fashion. There is only one National Tissue bank, all others being private, hence no uniform protocol exists. For cells, the system is even more complex.

One of the secretarial offices of the University of Medical Sciences is engaged in coordinating different modalities of renal replacement therapies. One of their tasks is to send a complete list of the data and a detailed report of the expenses related to deceased organ procurement of the transplant centres, covered by the related university of medical science in the province, to MOHME. ten per cent of the kidney transplantation fee is covered by MOHME (90% by health insurance companies). They also provide up-to-date national guidelines to affiliated centres and perform surveillance on distribution of immunosuppressive drugs. However, for tissues, the responsibility lies with the Medical Equipment Department of Ministry of Health.

5.1.15. Russia, Federal Research Center of Transplantology & Artifical Organs

(Sergey Khomyakov)

A Federal Agency is responsible for regulation of blood products. Registries for tissue, cell and organs are held at local level. The plan is to have some level of V&S system through the Russian transplant society at least initially, devolving the task to a National Agency later.

5.2. ROUND TABLE: The roles of Scientific and Professional Associations in V&S as support and complement of National V&S

5.2.1. Transplantation Society

(Philip O'Connell)

The Transplantation Society (TTS) is in official relations with WHO. The Society has 6500 members in over 150 countries. It has numerous collaborative activities, one of which is the participation of TTS in the NOTIFY project. TTS encourages all professionals to contribute to national V&S schemes. In addition it fosters a policy to promoting the establishment of national and regional registries whose aims would include the capture adverse events that would be reportable to NOTIFY.

5.2.2. Organización Nacional de Trasplantes

(Beatriz Domínguez-Gil)

Organización Nacional de Trasplantes (ONT) is an agency, dependent on the Ministry of Health in Spain, in charge of the regulation, oversight and coordination of all activities related to the donation, procurement and transplantation of organs, tissues and cells (excluding gametes). As such, ONT is in charge of the national system for the vigilance of organs tissues and cells.

Working under the framework of Directive 2004/23/EC and Directive 2010/53/EU, national legislation has been issued setting down the basis for the reporting and management of serious adverse events (SAE) and serious adverse reactions (SAR) related to the process of donation, procurement and transplantation of organs, tissues and cells. The vigilance system for tissues and cells is already well consolidated, with national protocols issued and active reporting and management of cases by ONT in cooperation with regional health authorities and centres. An annual report on SAE and SAR is produced and available on the ONT website. The same approach is being developed for vigilance of organs, combined with an active follow-up of recipients transplanted from "non-standard" risk donors.

5.2.3. American Association of Tissue Banks, AATB

(Scott Brubaker)

To address gaps by providing education and uniformity to the processes involved, the association is developing an AATB Guidance Document titled "Identifying, Reporting, and Investigating a Tissue Recipient Adverse Reaction." This will address the following:

1) identify for clinicians clinical "triggers" (recognition criteria) that use clinical and laboratory evidence which could suggest a tissue allograft may have caused in infection;

2) describe expectations for clinicians to report without delay and to cooperate with the investigation, emphasizing the non-punitive aspect for reporting; and

3) provide a thorough, effective process for personnel at tissue banks to follow so there is uniformity and completeness in every investigation of such a report.

AATB works to raise awareness, improve communication, and positively influence the practice of clinicians and tissue banking professionals.

5.2.4. Worldwide Network for Blood & Bone Marrow Transplantation, WBMT

(Adriana Seber)

WBMT , in collaboration with WMDA , runs a well-established reporting system for SAERS in stem cell transplantation.

5.2.5. TRIP Foundation, National haemo- and biovigilance office

(Arlinke Bokhorst)

The Foundation for Transfusion and Transplantation Reactions in Patients is an independent office, with representation from professional bodies, established in 2001. TRIP receives and analyses reports of adverse reactions and adverse events associated with blood transfusion or with the application of human tissues or cells. TRIP also promotes haemovigilance and biovigilance in the widest sense, throughout the chain from donor to recipient, in order to contribute to improved safety of transfusion and transplantation in The Netherlands.

5.3. UPDATE ON THE E.U. VIGILANCE TOOLS

(Ioana Siska)

Currently available Vigilance tools and relevance to Project NOTIFY were presented.

5.3.1. Rapid Alerts Platform

The platform provides EU National Competent Authorities and European Commission with an effective and secure system for the exchange of information and urgent measures related to human tissues or cells transferred across borders for patients undergoing transplantation and medical procedures involving such products.

This tool is used in parallel with existing national vigilance systems which collect and manage alerts on human tissues and cells donated and used within a Member State.

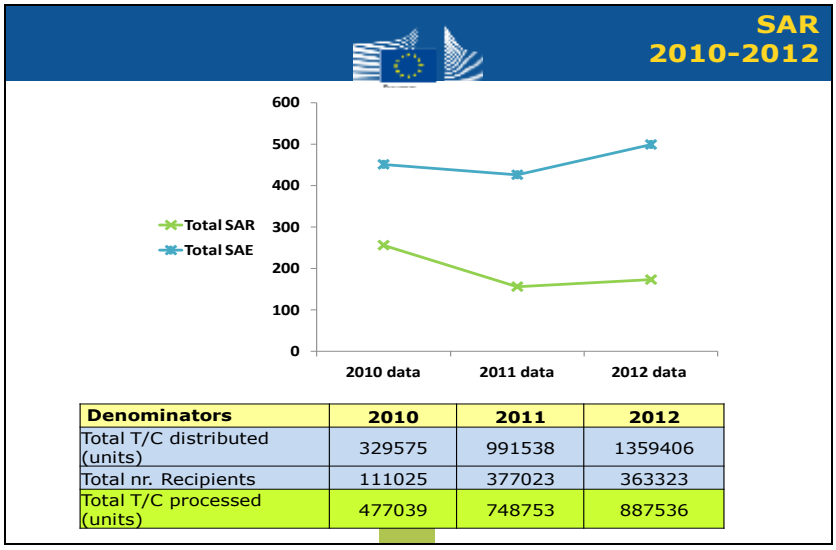
The RATC alert criteria are based on:

- **Coverage**: requires immediate/urgent consideration or follow up measures in 2 or more MS
- **Risk**: a known or potential risk to patients;
- **Severity**: issues (quality and safety defects, illegal and fraudulent activities, notifications from other sectors, outbreaks of communicable diseases) of a serious or potentially serious nature;
- **Public health implications**: may constitute a public health risk to other countries, as defined by the International Health Regulation (2005).

The Rapid Alert System for Substances of Human Origin has existed for Tissues and Cells since February 2012; for the blood & blood components, the system has just been tested with launch planned for February 2014. As for organs, it is still to be agreed.

5.3.2. EU SARE Reporting

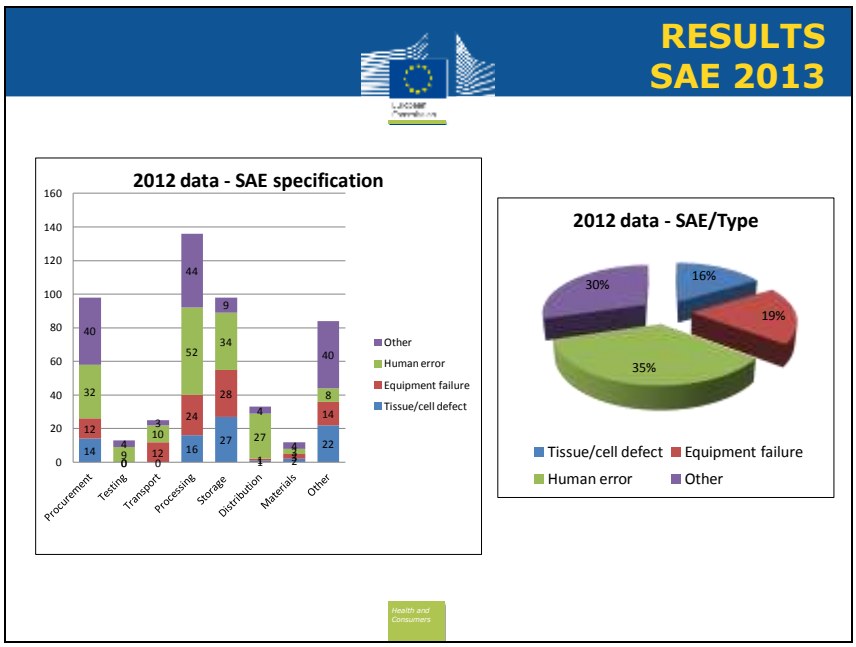
Figure 10: Serious Adverse Reaction and Events reports for tissues and cells in the EU



Denominators	2010	2011	2012
Total T/C distributed (units)	329575	991538	1359406
Total nr. Recipients	111025	377023	363323
Total T/C processed (units)	477039	748753	887536

Legal obligation for reporting lies with the Member state (Directive 2006/86/EC)

Figure 11: Serious Adverse Events



5.3.3. EUROCET 128 - EU tissue establishments compendium

A service contract for the construction of reference compendia for the application of a single European coding system for human tissues and cells was granted to the consortium Eurocet 128 that includes the Italian National Transplant Centre, CNT, ICCBBA and a software company, Artman Technologies**.** Once this system has been implemented, anyone in the EU who is holding a container of human tissues or cells will be able to insert the Single European Code from the label in the publically accessible code translator that will be hosted by the European Commission. This will allow access to the compendium record for the tissue establishment (TE) that is responsible for the safety and quality of that product, providing the authorisation status of that TE and the details of the Competent Authority responsible for its regulation, and the EU generic description of the product itself.

Figure 12: Format of the Single European Code for Tissues and Cells

Donation Identification

ISO Country Identifier	TE Code	Unique Donation Number
2 characters (alphabetic)	6 characters (alpha/numeric)	13 characters (alpha/numeric)

Product Identification

Coding System Identifier	Product Code	Split Number	Expiry Date
1 character (alphabetic)	7 characters (alpha/numeric)	3 characters (alpha/numeric)	8 characters (numeric)

- **Flexible approach**, allowing the use of existing national and international codes
- **Public, free of charge** access to the EU TEs Compendium, EU T&C Product Compendium, code translator application + user manuals
- High-level classification → easier to update
- Mandatory at least in **eye readable format** → implementation also in small TEs

- Lower implementation costs in the short run

5.3.4. Potential Contribution to NOTIFY

- Source of «grey literature » - EU Reports

2010 SARE Report

http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_cells_adverse_events_2011_en.pdf)

2010-2012 RATC Report

http://ec.europa.eu/health/blood_tissues_organs/docs/ratc_report_2008_2012_en.pdf

- EU-funded projects
  - Past: EUSTITE, SOHO V&S
  - 2014-2017: ARTHQS

6. Global tools for the V&S of MPHO

6.1. The links of vigilance for MPHO

The NOTIFY Booklet is a clinician's tool that targets healthcare professionals to justify and encourage participation in V&S and globally harmonized conceptions, in the context of globally shared outcomes. It is to be provided to National Health Authorities (NHA) in WHO Member States to promote V&S in transplantation and it is to be customized to meet national specificities.

The current text has been written by Mike Strong with inputs from Deirdre Fehily, Beatriz Dominguez-Gil, Luc Noël and Matt Kuehnert. It is knowingly a concept with limitations, aspiring for the advocacy of a flyer yet being a didactic booklet with essential V&S information divided in a series of short chapters. The dilemma of not having enough or containing too much is split between the need to cover legal, organisational and technical matters, apart from differing needs based on national settings and clinicians' interests. It was initially conceived for transplantation and ART but will need to be developed to cover all MPHO.

The booklet is a resource to feature on the NOTIFY website, to explain, synthesize and offer guidance on V&S of MPHO. The independent chapters, acting as stacks of cards, can be downloaded or printed individually. Nevertheless, as links of a chain, they are all inter-related and work as a unit.

The links can be enumerated:

1. History of Vigilance and Surveillance
2. Medical products of Human Origin (MPHO) Donation and Ethics.

3. Towards a global governance of MPHO
4. V&S is primarily a responsibility for health authorities
5. Organization for a comprehensive Vigilance & Surveillance System
6. Vigilance & Surveillance first relies on health care staff
7. A comprehensive V&S system includes Quality Management
8. Project NOTIFY
9. Learning from Vigilance – the NOTIFY Database
10. Risks Associated with Living Donation.
11. Risks for Recipients – Investigating Reactions and Events – Malignancy
12. Risks for Recipients – Investigating Reactions and Events – Genetic Transmissions, HSC
13. Characteristics, handling and clinical errors.
14. Traceability the absolute pre-requisite

Each link is introduced by a heading and explanatory text and looks like this

Vigilance & Surveillance first relies on health care staff

Physician and nurses in particular have the responsibility to identify reactions and events and to report them through the appropriate national channel. V&S is a not a punitive system. It aims to improve and maximize safety, and therefore the trust of the public in MPHO donation and transplantation service. Attention to quality management in health care can bring a more rigorous and systematic approach to addressing documented deficiencies and cost savings.

Some gaps may exist and items that are currently missing in the booklet include:

- Chapters
  - Specific to type of MPHO such as organ, cell, tissue , blood, ART and breast milk
  - Using the NOTIFY Website resources
- Introduction of and links to well established national V&S systems
- Introduction of and links to supporting Scientific and Professional Societies
- Links with NOTIFY interfaces in other languages than English.

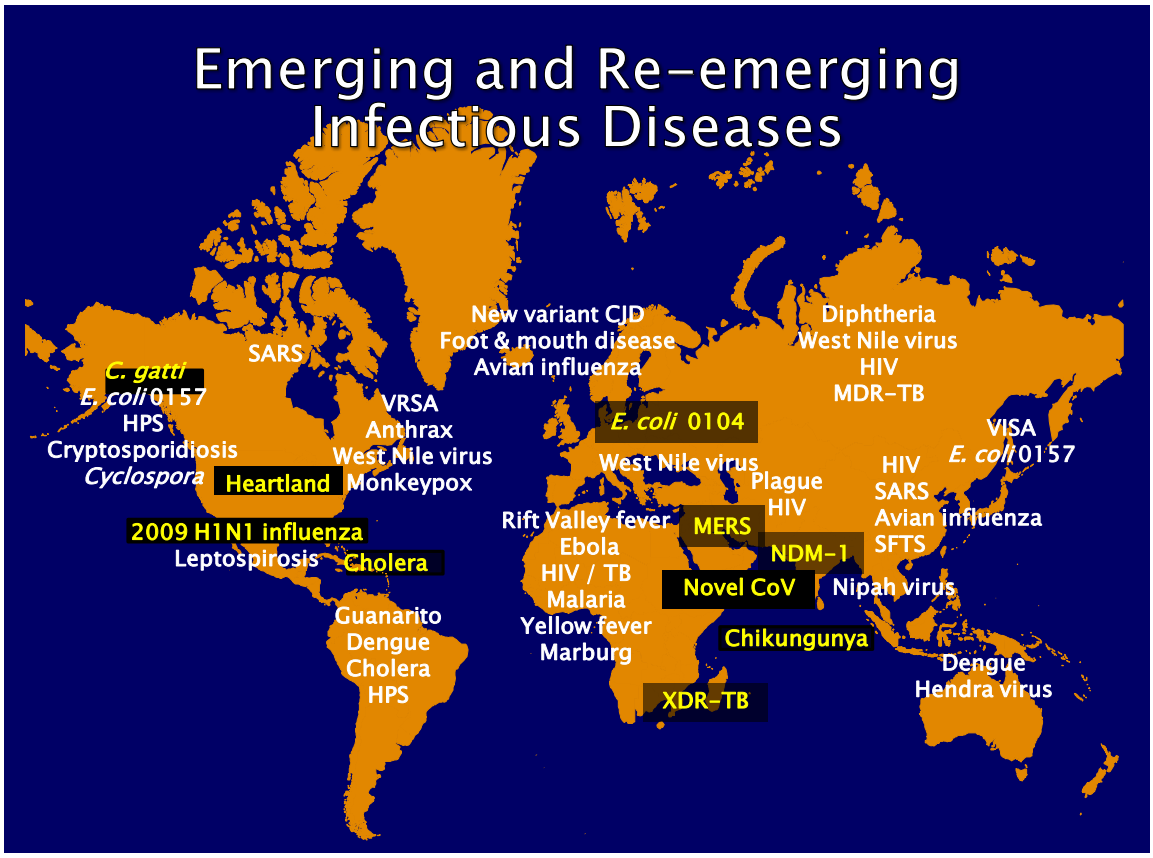
Suggestions from editorial group members will be very welcome once a dedicated restricted forum has been established on the website for this purpose.

6.2. Horizon scanning, a role for a network of CDCs?

(Matt Kuehnert and Dragoslav Domanovic)

This joint section contained material from both CDC and ECDC representatives, but was presented by Matt Kuehnert as Dragoslav Domanovic could not attend the consultation.

The topic of emerging and re-emerging infectious diseases, in the context of relevance to the safety and quality of transplantation was explored. The question of the role of Communicable Diseases Control Agencies in this context was addressed.



6.2.1. Public role of CDCs

US CDC's mission is to **collaborate** to create the expertise, information and tools that people and communities need to **protect their health** – through health promotion, prevention of disease, injury and disability, and preparedness for new health threats.

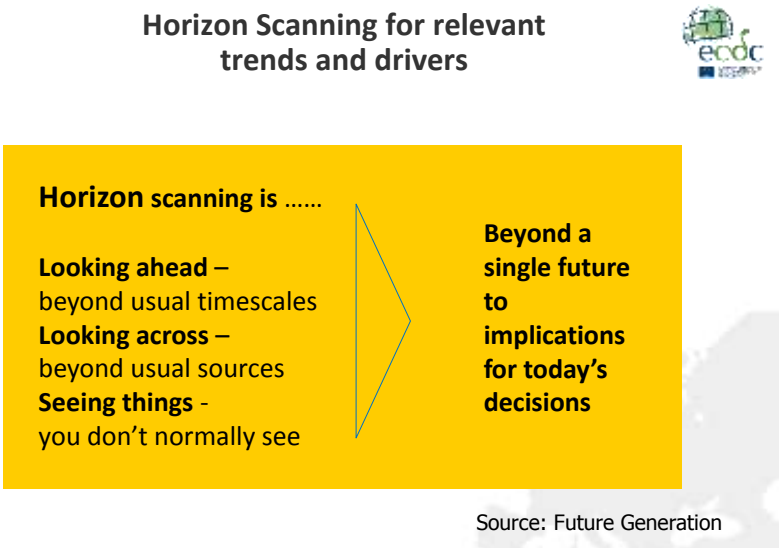
CDC seeks to accomplish its mission by working with partners throughout the nation and the world to

- monitor health
- detect and investigate health problems
- conduct research to enhance prevention
- develop and advocate sound public health policies
- implement prevention strategies
- promote healthy behaviors
- foster safe and healthful environments
- provide leadership and training.

6.2.2. How does "horizon scanning" fit into activities in Vigilance & Surveillance?

Definition of Horizon Scanning: the systematic examination of potential threats, opportunities and likely future developments which are **at the margins** of current thinking and planning. It may explore novel and unexpected issues, as well as persistent problems or trends.

Aim: Horizon scanning by CDCs is intended to improve the efficacy of interventions and evidence base in disease prevention and control.



US CDC role in horizon scanning

- Part of Federal government as a Public Health Service (PHS) agency (e.g., FDA, NIH, HRSA)
- PHS agency with primary responsibility for surveillance and detection of public health risks
    - not a regulator
    - authorized to investigate events on own, only by assisting local and state authorities
    - Creates recommendations in with other PHS agencies (CDC cannot enforce them).

EIDs pose a unique challenge if they cannot be captured as adverse events

- no donor events if asymptomatic
- no recipient outcomes if chronic illness
- need "hypothesis algorithm based on potential risk, e.g.
    - asymptomatic blood borne state
    - transmissibility between humans

6.2.3. How do we scan the horizon and what tools exist for horizon scanning?

Screening criteria for Horizon Scanning prioritization:

- Does it infect humans?
- Is it found in Medical Products of Human Origin (e.g. , blood, organs, tissues, cells)?
- Can it be transmitted person to person?
- Does it cause disease in the recipient?
- Is there a screening test for the pathogen?

Horizon scanning is already an on-going activity delivered through epidemiological intelligence and surveillance.

Issue for discussion and consideration

Horizon scanning for priority setting of which domains?:

- Research
- Regulations & Guidance
- Legislation
- Learning
- As a common interface between CDCs and NOTIFY library.

Suggested Proposals

- First step is to catalogue current horizon scanning
    - How does your public health authority accomplish this activity?
- If a new "horizon scanning" structure is to be built for information exchange on MPHO, what needs to be included?
    - Data points?
    - Definitions?
- What infrastructure is needed?
    - Barriers?
    - Challenges?
    - What's missing to improve awareness for MPHO issues?
    - How are searches that collect data instantly on current threats different from those which collect historical data (e.g., peer review)?

The topic was very pertinent and the points brought up during the presentation, including questions and suggestions merit further in depth discussion.

As far as EID goes, transplant communities may not become aware of relevant events with potential to cause impact on transplantation quality and safety, making this a very relevant issue to consider. Dissemination of relevant alerts, in a proportionate and informative manner is of great value. On that point, the European Centre for Disease Control runs risk assessments and predictions of infection in tissues, for example.

Matt Kuehnert was asked by Mike Strong if there was a place for rapid alerts to be released through the NOTIFY webpage, but there seems to be several factors suggesting that this approach is not viable. Releases can be restricted, at least in the earlier stages, with later releases becoming open for general access. Importantly, verification of information and obtaining of further details may be impossible. The "Program for Monitoring Emerging Diseases" (ProMED) was given as an example, where the quality of releases can vary from very dubious to excellent.

Establishing a dedicated forum for 'CDC-like organisations' on the website is feasible though. It could be used to explore the relevance of changing epidemiological trends to MPHO use. This will be further explored.

6.3. General discussion: priorities for Global Vigilance

All subjects presented and discussed during the three days were of great value and relevance to the Global Vigilance of MPHOs, with some matters featuring on several occasions, perhaps reflecting the pressing nature or level of interest on these particular topics.

6.3.1 Dissemination of information

As for the proposal to create an e-journal, the idea of having another tool for dissemination of information, education and discussion was welcomed. The concept requires refinement and details need to explored, but there was an agreement for it to be moved forwards.

On the issue of dissemination and accessibility of knowledge and information, it was also agreed that associating more non-English speaking regions was a positive move. Portuguese and Japanese are the next languages to be added to the NOTIFY Library interface.

6.3.2. Ethics

The undisputable importance of ethics in the context of V&S of MPHOs saw a worthy addition to the NOTIFY Library. Practical and procedural aspects need further discussions so that the information is captured and conveyed in a useful manner.

6.3.3. Taxonomy

Several extremely didactic and helpful talks on taxonomy classification were presented, allowing useful discussion to take place. A requirement for structured coding and definitions for the sake of clarity, consistency and harmonization is undeniable. A fine balance between the aforementioned needs and too rigid classifications must be struck in order to accommodate global variabilities.

6.3.4. Exposure to risk without transmission

This is a recurrent topic that features in different editorial groups, particularly infection and malignancy. There is still a certain level of inconsistency in the way decisions are made in terms of recording them or not, how and where to keep them. This is clearly a complex issue as it has been discussed on several occasions but remains unresolved. There is a consensus that they need to be made available as their didactic value is great and they allow a more appropriate appreciation of estimates of risk.

6.3.5. Lessons learnt

A fundamental difference exists between knowing an event can occur and knowing the reasons why it occurred, with understanding of the available steps to mitigate effects or avoid recurrence. Lessons can and need to be learnt, regardless of circumstances. This need is to be borne in mind when entering, editing and accepting cases to be entered in the Library, so that the tool serves the didactic role that it proposes to have.

6.3.6. Direct notification of cases and systematic literature searches

The idea of collaboration with national or dedicated registries for reliable sources of information, over and above publications is still alive and needs to be consolidated. The other practical yet fundamental need to automate literature searches for Library updates also needs to be consolidated. The new electronic facility to submit new cases or submit changes to existing cases was welcomed but systematic searches will need to be run periodically.

7. Conclusions and the way forward

This consultation made very significant progress towards achieving a global approach to vigilance and surveillance of medical products of human origin. The NOTIFY library database and website continue to improve thanks to the inputs and suggestions of experts. Discussions at this consultation led to agreement on the creation of mirror-image websites in all WHO languages to enhance global access to the information in the website. The inclusion of adverse occurrences in the field of blood transfusion represents a huge step forward for the project - ensuring that lessons can be shared across the range of MPHO, maximizing the potential for learning and for safety and quality improvements. The inclusion of ethical breaches as a new type of adverse occurrence was welcomed by the experts.

The consultation also moved other NOTIFY project initiatives forward. Notably, guidance on vigilance and surveillance of MPHO will be released for broad consultation following constructive discussion during the consultation; efforts on horizon scanning for new risks will be coordinated with the creation of a global network for information gathering and sharing and plans will move forward for the launching of a new WHO journal to promote the publication of adverse occurrences associated with the donation and use of MPHO.

All those who contributed to the rich and creative discussions during the consultation were thanked.

Appendix 1: List Of Participants

Mrs María Cecilia ALEN
Ministry of Public Health Uruguay
Fernando Otorgues 1158
Montevideo CP 11700
Uruguay
alencecilia@gmail.com
calen@msp.gub.uy

Mr Paul ASHFORD
Executive Director, ICCBBA
48 Cliff Gardens
Minster on Sea
United Kingdom
paul.ashford@iccbba.org

Dr Mohamed Salah BEN AMMAR
MOH Tunisia
23 rue Sidi Hassen
La Marsa 2010
Tunis
Tunisia
msbenammar@gmail.com

Dr Liliana BISIGNIANO
Scientific and Technical Director
Instituto Nacional Central Unico (INCUCAI)
Ministerio de la Salud de la Nación
Ramsay 2250
Caba
Argentina
lbisigniano@incucai.gov.ar

Dr Arlinke BOKHORST
TRIP Foundation
National hemo- and biovigilance office
PO Box 40551
The Hague,
Netherlands
a.bokhorst@sanquin.nl; a.bokhorst@tripnet.nl

Mr Scott A. BRUBAKER
Chief Policy Officer
American Association of Tissue Banks
1320 Old Chain Bridge Road, Suite 450
McLean, VA 22101, USA
brubakers@aatb.org

Dr Edwin CARDENAS
Dirección de Medicamentos y Tecnologías en Salud
Ministry of Health and Social Protection of Colombia
Carrera 13 N° 32-76
Bogotá
Colombia
ecardenas@minsalud.gov.co;
eantoniocardenas@gmail.com

Mr Stratos CHATZIXIROS
Foreign Affairs Division
Italian National Transplant Centre
Italian National Institute of Health
Via Giano della Bella 34
00162 Rome, Italy
cnt.international@iss.it

Dr Jorge CONDECO
Instituto Português do Sangue e da Transplantação IP – Centro de Sangue e de transplantação do Porto
Hemovigilância / Informática
R. de Bolama 133
Porto 4200-139
Portugal
jorge.condeco@ipst.min-saude.pt

Dr Daniel R. CORADI DE FREITAS
ANVISA
Brasilia, Brazil
daniel.freitas@anvisa.gov.br

Dr Dragoslav DOMANOVIC (unable to attend)
Senior Expert Vigilance and Traceability of Cells and Tissues of Human Origin
OCS, Health Impact Section
European Centre for Disease Prevention and Control (ECDC)
Tomkebodavagen 11A
SE-171 83 Stockholm, Sweden
Dragoslav.Domanovic@ecdc.europa.eu

Dr Beatriz DOMINGUEZ-GIL
Organización Nacional de Trasplantes
Sinesio Delgado 6, Pabellón 3
28029 Madrid
Spain
bdominguez@msssi.es

Dr Ted EASTLUND
University of New Mexico
School of Medicine
Division of Transfusion Medicine
Dept of Pathology
139920 East Mail Road
Gordon WI 54838
USA
deastlund@salud.unm.edu

Dr Deirdre FEHILY
Italian National Transplant Centre
Istituto Superiore di Sanità
Via Giano della Bella, 34
00162 Roma, Italy
deirdre.fehily@iss.it

Dr Peter FLANAGAN (unable to attend)
National Medical Director
New Zealand Blood Service, National Office
11, Great South Road, Private Bag 92-071
Epson, Auckland 1142, New Zealand
peter.flanagan@nzblood.co.nz

Dr GAO Guangming
Division Director
Division of Medical Safety and Blood
Bureau of Medical Administration
National Health and Family Planning Commission
1 Xizhimen Wai South Road
Xicheng District
Beijing, People's Republic of China
gaogming@gmail.com

Dr Giuliano GRAZZINI (unable to attend)
Italian National Blood Centre
Via Giano Della Bella N. 27
Rome, Italy
giuliano.grazzini@iss.it

Dr Paolo GROSSI
Professor of Infectious Disease Medical
Clinical Department
University of Insubria
Ospedale di Circolo - Fondazione Macchi,
Viale Borri, 57, 21100 Varese, Italy
paolo.grossi@uninsubria.it

Ms Diana Patricia HERMIDA VITAR
Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos
Ministerio de Salud Publica
Calle 200 no. 1706 entre 17 y 19. Rpto Siboney, Playa, La Habana
Cuba
patricia@cecmed.sld.cu

Dr Marisa HERSON
Senior Lecturer
Department of Surgery
Monash University
c/o Skin Culture Laboratory, Victorian Burns Unit, Commercial Road
Melbourne, VIC 3004 , Australia
herson.marisa@gmail.com

Dr Salwa HINDAWI (unable to attend)
Medical Director of Blood Transfusion Services
King AbdUlaziz University Hospital
P.O. Box 80215
Jeddah 21589
Saudi Arabia
sihindawi@yahoo.com

Dr Maurice HINSENKAMP (unable to attend)
Chef du Service Orthopédie Traumatologie
Hôpital Erasme
808 Route de Lennik
1070 Brussels, Belgium
Maurice.Hinsenkamp@erasme.ulb.ac.be

Dr Yoshie HIROSE
Deputy Director
Office for Transplantation Medicine, Health Service Bureau
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki Chiyoda-Ku
Tokyo, Japan
hirose-yoshie@mhlw.go.jp

Dr Michael G.ISON (unable to attend)
Divisions of Infectious Diseases
and Organ Transplantation
Northwestern University
645 North Michigan Avenue Suite 900
676 N. St. Clair Street
Chicago, Illinois 60611, USA

Dr Sergey KHOMYAKOV
Shumakov Federal Research Center of Transplantology and Artificial Organs
1 Schukinskaya Street
Moscow 123182
Russian Federation
khomjakov-s@rambler.ru

Dr Matthew J. KUEHNERT
Director, Office of Blood, Organ and other Tissue Safety
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
1600 Clifton Road, Mailstop A-07
Atlanta, GA 30333, USA
mgk8@cdc.gov
mkuehnert@cdc.gov

Dr Richard LEBETHE
Medical Advisor: Medico Legal Services
Gauteng Health & Social Development
37 Sauer Str., P/Bag X085
Marshalltown 2107, Johannesburg
South Africa
richard.lebethe@gauteng.gov.za
rlebethe@gmail.com

Ms Kathy LOPER
Director, Cellular Therapies
AABB
8101 Glenbrook Road
Bethesda, Maryland USA
kloper@aabb.org

Dr Marian MACSAI
Chief Ophthalmology
Eye Bank Association of America
2050 Pfingsten Road, Suite 220
Glenview, IL 60025, USA
mmacsai@northshore.org

Dr Mitra MAHDAVI-MAZDEH
Professor of Nephrology
Iranian Tissue Bank and Research Center
ITB Iman Khomeni Hospital Complex
Keshavarz Blv
Tehran, The Islamic Republic of Iran
mmahdavi@tums.ac.ir

Dr Daniela MINUTOLI
IT Manager
Italian National Transplant Centre
Istituto Superiore di Sanità
Via Giano della Bella 34
00162 Roma, Italy
daniela.minutoli@iss.it

Professor Ludo MUYLLE
Federal agency for medicines and health products
Victor Hortaplein 40/40
Brussels, Belgium
ludo.muylle@fagg-afmps.be

Dr Michael NALESNIK
University of Pittsburgh
UPMC-Montefiore, Room E738
3459 5th Ave., Pittsburgh, USA
nalesnikma@upmc.edu

Dr Alessandro NANNI COSTA
Director, Centro Nazionale Trapianti
Istituto Superiore di Sanità
Via Giano della Bella 34
00162 Roma, Italy
3355640988@vodafone.it ; cnt@iss.it

Mrs Geni NEUMANN N. DE LIMA CAMARA
Chefe de Unidade, Unidade de Biovigilancia e Hemovigilancia, Agencia Nacional de Vigilancia Sanitaria - ANVISA
Brasilia, Brazil
geni.camara@anvisa.gov.b

Dr Dietger NIEDERWIESER (unable to attend)
Professor of Medicine
Department of Hematology, Oncology and Hemostasiology
University of Leipzig
Johannissallee 32A
D-04103 Leipzig, Germany
Dietger.Niederwieser@medizin.uni-leipzig.de

Professor Philip O'CONNELL
Westmead Hospital
Renal Medicine
Hawkesbury Road
Westmead
Australia
philip.oconnell@sydney.edu.au;
philip.connell@swahs.health.nsw.gov.au

Dr Adeline Ijeoma OSAKWE
Director Pharmacovigilance and Post Market Safety Surveillance
Plot 2032, Olusegun Obasanjo Way
Wuse Zone 7
Abuja
Nigeria
osakwe.a@nafdac.gov.ng
addyosakwe@yahoo.com

Dr Chris O'TOOLE
Head of Research Regulation
Human Fertilisation & Embryology Authority,
21 Finsbury Tower, 103-105 Bunhill Row,
London, EC1Y 8HF, United Kingdom
chris.o'toole@hfea.gov.uk

Dr Evangelia PETRISLI
Italian National Transplant Centre
Istituto Superiore di Sanità
Via Giano della Bella, 34
00162 Roma, Italy
e.petrisli@yahoo.com

Dr Diana Carolina PLAZAS SIERRA
Instituto Nacional de Salud Colombia
Aveue 26#51-20
Bogotá
Colombia
dplazas@ins.gov.co

Dr Jagdish PRASAD
Director General of Health Services
Ministry of Health and Family Welfare
Government of India
R. No 446-A, Nirman Bhawan
New Delhi, India
dghs@nic.in

Dr Axel RAHMEL
Eurotransplant International Foundation
P.O. Box 2304
2301 CH Leiden
The Netherlands
a.rahmel@eurotransplant.org

Dr Ghazi Saleh SAEED
Director of Pharmacovigilance & Crisis Management
Saudi Food & Drug Authority
3292 Northern Ring road
Al nafal District
Riyadh 13312-6288
Saudi Arabia
gsaeed@sfda.gov.sa

Dr Laura ST MARTIN
Medical Officer
FDA/CBER/OCTGT/Division of Human Tissues
U.S. Food and Drug Administration
1401 Rockville Pike, Room 210S
Rockville, MD 20852, USA
Laura.St.Martin@fda.hhs.gov

Dr Adriana SEBER
Rua Domingos Augusto Setti, 21 ap.22
Sao Paulo, SP 06116-070, Brazil
adriana_seber@hotmail.com

Dr Naoshi SHINOZAKI
Executive Director; Japan Organ Transplant Network
Orix Akasaka Nichome bldg. 2F
2-9-11, Akasaka, Minato-ku,
Tokyo 107-0052
Japan
shinozaki@jotnw.or.jp

Dr Ioana SISKA
European Commission
Rue Froissart 101, 08/82
Brussels, Belgium
Ioana-Raluca.Siska@ec.europa.eu

Dr Carlos Alberto SORATTI
President
Instituto Nacional Central Unico (INCUCAI)
Ramsay 2250
Buenos Aires, Argentina
csoratti@incucai.gov.ar

Dr Douglas Michael STRONG
University of Washington, Seattle
18624 94th Ave West
Edmonds, WA
USA
dmichaelstrong@mac.com

Mrs Wimon SUWANKESAWONG
Food and Drug Administration
Ministry of Public Health, Thailand
88/24 Moo 4 Tiwanon Road,
Taladkhwan, Muang,
Nonthaburi
Thailand
wimon@fda.moph.go.th

Dr Esteve TRIAS
Past President of EATB
Medical Director of Transplant Services Foundation
Hospital Clínic Barcelona
C/Villarroel 170
08036 Barcelona
Spain
etrias@clinic.ub.es

Dr Ines USHIRO-LUMB
Public Health England
61 Colindale Avenue
London NW9 5EQ
NHS Blood and Transplant
Charcot Road
London NW9 5BG
U.K.
Ines.Ushiro-Lumb@phe.gov.uk
Ines.Ushiro-Lumb@nhsbt.nhs.uk

Dr Zulma VALBUENA JIMENEZ
Instituto nacional de Vigilancia de Medicamentos y Alimentos – INVIMA
Carrera 68 D No 17-11
Bogotá
Colombia
zulmavalbuena@gmail.com;
zvalbuenaj@invima.gov.co

Dr Duc VU
Director, Marketed Biologics
Biotechnology and Natural Health Products
Health Products and Food Branch
Health Canada, Health Protection Building
Ottawa, Canada
duc.vu@hc-sc.gc.ca

Dr Silvano WENDEL (unable to attend)
Diretor Médico - Banco de Sangue
Medical Director - Blood Bank
Hospital Sirio Libanês
Rua Adma Jafet 91
São Paulo, Brasil 01308-050
snwendel@terra.com.br

Dr Barbee WHITAKER
Director, Center for Data and Special Programs
Director, AABB's Patient and Donor Safety Center
AABB
8101 Glenbrook Road
Bethesda, MD 20814 USA
bwhitaker@aabb.org

WHO Secretariat

Dr Marie-Charlotte BOUESSEAU
Ethics, Equity, Trade and Human Rights
Health Systems and Innovation
World Health Organization
20 avenue Appia, CH-1211 Geneva 27,
Switzerland
bouesseaum@who.int

Dr Sheick Oumar COULIBALY
AF/HTC Health Technologies
World Health Organization
Regional Office for Africa
Brazzaville, Congo
coulibalysh@who.int

Dr Neelam DHINGRA-KUMAR (unable to attend)
HIS/SDS
Health Systems and Innovation
World Health Organization
Avenue Appia 20, CH-1211 Geneva 27,
Switzerland
dhingran@who.int
Dr Valentina HAFNER (unable to attend)

EU/HCQ Health Care Quality
World Health Organization
Regional Office for Europe
Copenhagen
Denmark
VHA@euro.who.int

Dr Luc NOËL
HIS/SDS
Health Systems and Innovation
World Health Organization
20 avenue Appia
CH-1211 Geneva 27, Switzerland
Noëll@who.int

Dr Mondher LETAIEF
EM/HMS Health Management Support
World Health Organization
Regional Office for the Eastern Mediterranean
Cairo, Egypt
LETAIEFM@who.int

Dr José Ramon NUÑEZ PEÑA
HIS/SDS, Health Systems and Innovation
World Health Organization
20 avenue Appia
CH-1211 Geneva 27, Switzerland
nunezj@who.int

Dr Maria Dolores PEREZ-ROSALES
Blood Transfusion and Organ Transplants
World Health Organization
Regional Office of the Americas
Washington, USA
perezmd@paho.or

Dr Christophe RERAT
Medicines, Vaccines and Health Technologies
Brasilia Country Office
Oficina Sanitaria Panamericana
PO Box Caixa Postal 08
Brasilia 70312-970 , Brazil
reratchr@paho.org

Dr Gunasena Sunil SENANAYAKE
SE/HSM Health Systems Management
World Health Organization
Regional Office for South-East Asia
New Delhi 110002, India
senanayakes@who.int

Dr Anuj SHARMA (unable to attend)
WP/HTL Health Technology
World Health Organization
Regional Office for the Western Pacific
Manila, Philippines
sharmaan@wpro.who.int

Observers

Dr Marcelo ADDAS CARVALHO
Haemovigilance Commission
Brasilia
Brazil
maddas@unicamp.br

Dr Lara ALONSO DA SILVA
ANVISA
Brasilia
Brazil
lara.alonso@anvisa.gov.br

Dr Maria Eugenia CARVALHAES CURY
ANVISA
Brasilia
Brazil
maria.cury@anvisa.gov.br

Mrs Marina FERREIRA GONCALVES
ANVISA
Brasilia
Brazil
marina.goncalves@anvisa.gov.br

Dr Giuseppe C. GATTO
Biovigilance Working Group
Brasilia
Brazil
bepegatto@gmail.com

Dr Suzie Marie GOMES
ANVISA
Brasilia
Brazil
suzie.gomes@anvisa.gov.br

Mrs Andressa HONORATO DE AMORIM
ANVISA
Brasilia
Brazil
Andressa.Amorim@anvisa.gov.br

Dr Auristela MACIEL LINS
ANVISA
Brasilia
Brazil
Auristela.Lins@anvisa.gov.br

Mrs Ana Carolina MACHADO GONCALVES PINTO
Biovigilance Working Group
Brasilia
Brazil
carolmgp@sesa.pr.gov.br

Dr Marcelo Augusto MEDEIROS
ANVISA
Brasilia
Brazil
marcelo.medeiros@anvisa.gov.br

Dr Valéria OLIVEIRA CHIARO
ANVISA
Brasilia
Brazil
valeria.chiaro@anvisa.gov.br

Dr Taciana RIBEIRO SILVA BESSA
Biovigilance Working Group
Brasilia , Brazil
taciana.ribeiro@saude.gov.br

Dr Marilia RODRIGUES MENDES
ANVISA
Brasilia, Brazil
Marilia.Mendes@anvisa.gov.br

Mr Mateus RODRIGUES CERQUEIRA
ANVISA
Brasilia
Brazil
Mateus.Cerqueira@anvisa.gov.br

Dr Fernanda SANTOS BORDALO
Biovigilance Working Group
Brasilia
Brazil
fernanda.bordalo@saude.gov.br

Dr Fabiana Cristina SOUSA
ANVISA
Brasilia, Brazil
fabiana.sousa@anvisa.gov.br

Mr Renato VIERA ALVES
Haemovigilance Commission
Brasilia
Brazil
renato.alves@saude.gov.br

Appendix 2: Programme Of Work

WHO Global Consultation on Vigilance and Surveillance for Medical Products of Human Origin

Programme of Work

7-9 December 2013

ANVISA, Brasilia

Saturday 7 December

13:30 - 14:00	*Coffee - Registration*	
Introduction		
14:00	Welcome and Introduction of participants Election of Chair and Rapporteurs	
14:15	Global V&S and the WHO initiative for Medical Products of Human Origin,	Luc Noël
14:30	Agenda and objectives of the third consultation	Deirdre Fehily
15:30 - 16:00	*Coffee Break*	

The NOTIFY Library: Review and Resolution of remarkable cases
Achievements Updates and orientations for the future

16:00 Editorial Group Workshops

Infections Editorial Group Meeting Room	Malignancy Editorial Group Meeting Room	Process Editorial Group Meeting Room	Living Donor Editorial Group Meeting Room	Genetic Editorial Group Meeting Room	Transfusion Meeting Room
To work through unresolved rows agreeing to solutions					

18:30	*Adjourn*

Sunday 8 December

08:30 -9:00	*Coffee*	
Reports of the Editorial Workgroups		
09:00	Introduction and facilitation	Mike Strong
09:15	Infection - presentation + cases discussion	Mike Ison
09:45	Malignancy - presentation + cases discussion	Beatriz Dominguez
10:15	Process - presentation + cases discussion	Marian Macsai
10:45 - 11:15	*Coffee Break*	
11:15	Living donor - presentation + cases discussion	Daniel Roberto Coradi de Freitas
11:45	Genetic - presentation + cases discussion	Mauro Costa
12:15	New scope with the extension to blood	Giuliano Grazzini
12:35	General discussion	
13:00 - 14:00	*Lunch*	

Specificities and priorities by type of MPHO

14:00 Breakout groups

Organs Meeting Room	**Cells Meeting Room**	**Tissues Meeting Room**	**ART Meeting Room**	**Blood Meeting Room**

15:00	Report in plenary	
15:30	General discussion	
15:45 - 16:00	*Coffee Break*	

Future developments of the Notify Library I

16:00	How to better capture, classify and use didactic adverse events in the Notify Library	Stratos Chatzixiros
16:40	Presentation of an electronic tool for the insertion of new case types, or new information on existing case types (end of Google docs!)	Daniela Minutoli Deirdre Fehily
17:00	Towards using the Notify Library as a medium of publication	Alessandro Nanni-Costa
17:20	Terminology for V&S of MPHO constraints and necessities	Kathy Loper, Richard Lebethe, Paul Ashford
17:50	A place for ethics in the Notify Library?	Marie-Charlotte Bouesseau
18:05	Patients participation in vigilance for Medical Products of Human Origin	Valentina Hafner
18:15	General discussion	
18:30	*Adjourn*	

Monday 9 December

08:30 -9:00	*Coffee*	
09:00 - 09:15	Summary by Rapporteurs	

Official launch of the Notify website and library

09:15	**ANVISA, CNT, ISS, MOH Italy, WHO PAHO, WHO HQ, MOH Brazil** **Video conferencing with Rome and Geneva**

10:00	Language specific interfaces for the Notify Library and website	Luc Noël
10:20	General Discussion	
10:40 - 11:10	*Coffee Break*	

Promoting reporting systems and disseminating outcomes

11:10	Round table: lessons learnt from advanced national systems	Brazil, Canada, France, USA
12:00	Round table: lessons learnt from scientific and professional associations	*WBMT, TTS, ISBT, EBAA*
12:40	Update on the EU vigilance tools	Ioana Siska
13:00	*Lunch*	

Global tools for the V&S of MPHO

14:00	Advocacy : ABC of V&S for MPHO	Mike Strong
14:15	Horizon scanning , a role for a network of CDCs ?	Matt Kuehnert, Drago Domanovic
14:30	General discussion: priorities for Global vigilance	

Conclusions and the way forward

15:30	Conclusions and the way forward	Luc Noël
16:00	*Meeting close*	