REPORT

WHO CONSULTATION ON VIGILANCE AND SURVEILLANCE FOR MEDICAL PRODUCTS OF HUMAN ORIGIN NOTIFY PROJECT – FIRST TECHNICAL MEETING

23-25 February 2015
Barcelona, Spain
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REPORT

23-25 FEBRUARY 2015
FOREWARD

This publication reports on the deliberations and outcomes of the First Technical Meeting of the WHO consultation on vigilance and surveillance for medical products of human origin, NOTIFY project that took place from 23rd to 25th of February in Barcelona, Spain. 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 Organitzcaó Catalana de Trasplantaments (OCATT) and the Organización Nacional de Trasplantes (ONT) for hosting the meeting in Barcelona.

This technical meeting 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, who judiciously chaired the meeting, as well as to the rapporteurs, Ines Ushiro-Lumb and Barbee Whitaker, for their thorough work, with the support of the OCATT team.

José Ramón Núñez Peña
HIS/SDS
WHO Headquarters
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1. INTRODUCTION

1.1 Welcome
The first Notify Technical meeting was opened by Jose Ramon Nunez (WHO), Alessandro Nanni Costa (CNT), Jaume Tort (OCATT) and Beatriz Dominguez (ONT).

Dr Alessandro Nanni Costa welcomed the participants to the First Technical Meeting of the Notify project thanking the collaborating partner Organitzcaó Catalana de Trasplantaments (OCATT) and the Organización Nacional de Trasplantes (ONT) for hosting the meeting in Barcelona.

This technical meeting enabled participants to advise the World Health Organization’s work for the Vigilance and Surveillance of Medical Product of Human Origin seeking excellence in V&S through global tools necessary to draw the trust of the public and encourage their donation.

The technical meeting considered the progress of the NOTIFY Library thanks to the tremendous work of its editorial groups and the operational team and officially opens the addition of a blood editorial group to the NOTIFY Library was officially announced.

1.2 Introduction of participants
For the full list of participants, please see appendix 2

1.3 Election of chairs and rapporteurs
Alessandro Nanni Costa was elected chair of the meeting; Ines Ushiro-Lumb and Barbee Whitaker were elected as rapporteuses.

2. THE NOTIFY LIBRARY: CURRENT STATUS

2.1 The Notify Project: A Global Responsibility
(Luc Noel)

Luc Noel spoke about the fundamental concept of a global service for donation and management of medical products of human origin (MPHO) intended for human clinical application. The need for universal governance mechanisms, in order to promote quality, safety, efficacy and ethics, was explained.

“Blood and other medical products of human origin”
Summary points of WHO Report EB136/32 for the 136th session of the Executive Board, 5 December 2014:

Medical products of human origin (MPHO) are derived wholly or in part from the human body and intended for clinical application. They include blood and blood products, organs, bone marrow, cord blood, corneas and tissues.

Over the years, their type and use have broadened, and many are widely used.

The main issue is the existence of a human being at the origin of these products, giving rise to high levels of complexity and responsibility for health systems and health-care providers.

Essential principles that ought to be observed include:

- Meeting patients’ needs: Equitable adequate access, quality, safety and efficacy
- Doing no harm to the recipient, donor and the society as a whole
- Maintaining Safety
- Observing individual and community ethical values

The Executive Board, having considered the report by the Secretariat on blood and other medical products of human origin, -

1) recalled the guiding principles of the safety, quality and availability of blood and blood products supported by the Health Assembly, through resolutions WHA28.72, WHA58.13 and WHA63.12, as well as the WHO Guiding
Principles on Human Cell, Tissue and Organ Transplantation endorsed in resolution WHA63.22

2) noted that several medical products of human origin, which are intended for human clinical application, have significant commonalities in terms of sharing some characteristics inherent in their human origin

3) recognized that protection of the donor is a prerequisite in order to meet the needs of patients for access to safe medical products of human origin, which is of high importance in the context of access to health and universal health coverage

4) acknowledged that medical products of human origin may raise safety issues for donors and recipients

5) recognized that global consensus on the donation and management of medical products of human origin intended for human clinical application, based on good governance mechanisms, is needed in order to protect the fundamental human rights of donors

6) further recognized that appropriate standards to guarantee quality and safety of medical products of human origin and to ensure traceability, vigilance, surveillance and equitable access to these products are essential for the well-being of recipients

7) requested that the Director-General convene consultations with Member States and international partners, to support the development of global consensus on guiding ethical principles for the donation and management of the mentioned medical products of human origin; good governance mechanisms; and common tools to ensure quality, safety and traceability, as well as equitable access and availability, as applicable, to result in a document to be submitted to the Seventieth World Health Assembly for its consideration

The concepts above were illustrated in the following picture:
Global self-sufficiency is a responsibility that needs to be supported by all Member States.

The issue of self-sufficiency in MPHO was also mentioned.

Regardless of the MPHO, the following elements of the self-sufficiency paradigm apply:

- Government support & oversight
- Equity in donation and allocation of MPHOs
- Donation education & health promotion to prevent needs
- Societal trust, achieved through transparency and professionalism
GLOBAL OBSERVATORIES

- Transparency on donation, access to and need for and use of the various MPHO
- In collaborations with scientific and professional societies regional and national authorities through Collaborating Centres
- ONT GODT and WHO’s GDBS
- Glossary revised to provide common terminology for essential terms
- Agreement on criteria of quality
- Analysis through global collaborations

CONSISTENT CODING SYSTEMS – INTERNATIONAL STANDARD BLOOD AND TRANSPLANT 128

- Global terminology and nomenclature
  - Translations
- Unique identifiers
  - Centres
  - Donations
  - (Donor(s))
  - (Recipient(s))
- Coding
- Formatting standards
- Delivery means
- Inter-operability across Medical Products of Human Origin
- Transparency
SHARING LESSONS OF ADVERSE OCCURRENCE GLOBALLY
- THE NOTIFY PROJECT

- 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
- NOTIFY Journal

**History of the NOTIFY Project**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>2010</td>
<td>Geneva MPHO Consultation September 15-16 2015</td>
</tr>
<tr>
<td>2011</td>
<td>Pcst Bologna BIG V&amp;S Bologna Initiative for Global Vigilance and Surveillance</td>
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<td>2012</td>
<td>Rome</td>
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<tr>
<td>2013</td>
<td>Brasilia</td>
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<tr>
<td>2014</td>
<td>Medical Products of Human Origin</td>
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<tr>
<td>2015</td>
<td>Pre-Bologna – The Notify Google Site</td>
</tr>
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NOTIFY Library: Main Challenges - Geneva MPHO Consultation September 15-16 2015

- Resources – no robust and long term funding available although CNT is continuing to support the development of the database and website for at least the coming year;

- Making the tool real in everyday life - some participants considered that the application of the tool to normal working practice was not very easy and that the focus should be more on specific practical functions;
– Making the tool accessible and recognized in everyday life – dissemination – some participants considered that many professionals are not aware of the resource and do not regularly consult it.

NOTIFY - Structural Progress

• Collaboration and complementarity
  – WHO
  – Member States
  – IGOs
  – Global NGOs
• Comprehensive representation, including medium and lower income countries
  – Global representation
  • Asia – Latin America – LMICs
  – All type of legitimate stakeholders with MPHO
  – Pharmacovigilance
• Financial stability
  – Investment for global services: towards a core group of promoters

NOTIFY - Progress in Activities

Ensuring the reliability of existing tools

– NOTIFY Library
  • Should represent an exhaustive list of possible occurrences where there is harm to either the donor or the recipient of the MPHO
  – NOTIFY Booklet
  – NOTIFY Website update (+iOS and Android?)

• Increase in Global ownership
  – Asian participation
  – All countries with established V&S program

• Enhance NOTIFY Use and Recognition
  – Monitor increasing audience

NOTIFY - Progress in Activities

– Effectively extend the scope of NOTIFY to more “no harm to donor and recipient” cases and promote risk based quality management
– Adapt to resource limited systems s
• Reviews from the stand point of LMIC (Adapt learning from errors - Illustrate -Prioritize )
  – Develop didactic synthesis, e.g. editorial work products
  – Exist as a source of reference publication
  – NOTIFY Journal
  – Develop services

**NOTIFY Library: Service Provider? - Geneva MPHO Consultation September 15-16 2015**

• Provision of a 24/7 consultancy by the experts that would support those making difficult decisions on organ donor selection
• Proposal of a new area on the website with added value, e.g. access only by registration and payment – institutional, government or individual.
• Potential to develop the tool into an App
• Limitation to assistance to health authorities?

**2.2 Presentation of the New Notify Library Website – The End of Google docs**

(Aurora Navarro and Daniela Minutoli)

Stakeholders and editorial group feedback was used to inform development of the new version on the Notify library website, which was proudly launched at the meeting.

Some of the features covered include:
• Navigation through the new look website
• Visibility of previous work done by the group, with links and documents from previous consultation meetings
• Up to date news in relevant areas
• Tutorial of search tool
• Access through mobile tools
• Notify booklet
• Background documents

Alessandro Nanni Costa also gave his own impression of the site, commented on the ease of use and the improved accessibility from smart phones.

2.3 Updating the notify Library Database: Current tools
Daniela Minutoli and Evangelina Petrisli demonstrated the new version of the database. A user guide with detailed instructions can be found in appendix 2 of this report and will also be available on the Notify webpage (currently under construction).

The editorial group management record tool was the most prominent new feature, with suspension of the Google drive function. Cases awaiting editorial group review were migrated onto the new EGM record. At the time of the meeting in Barcelona, there were 420 pending records, of which 45% were infection cases.
The introduction of this long awaited tool raised great interest and discussion. CNT staff were congratulated and thanked for all efforts to develop the project and deliver the work in time for the technical meeting in Barcelona.

Amongst the various new features, two were particularly useful: audit trail of changes and ability to review current as well as past records, i.e. possibility to add new information to existing records already published in the database.

Suggestions for modification and additions were also invited.

There was a long discussion around the usage of key words, including how the searches might be constructed, power of searches, construction of taxonomy to allow capture of relevant records, etc.

3. THE NOTIFY LIBRARY: EDITORIAL GROUPS WORKSHOPS

The various editorial groups had two sessions to work on outstanding cases, over the course of the afternoon of the first day and the morning of the second day of the meeting.

4. TECHNICAL CONSULTATION GROUP – MAIN ISSUES

The creation of a technical consultation group was first discussed at the Geneva meeting in September 2014 and was approved at the meeting in Barcelona. The composition of the group will be defined once the terms of reference (ToR) have been finalized.

The session started with the demonstration of increased interest in the Notify Library site over time, as captured through the number of site visits:
Visits have been logged from a broad geographical range, with 103 countries captured. Real time figures will be posted on the website.

The value of different metrics was discussed by the whole group and it is hoped that in the near future, we will start capturing qualitative data from visitors to the site and stake holders in general. It was generally thought that we should seek to know what users think about the library, the display and the contents. We are interested to know if we are hitting the target in terms of didactic value, how we promote wide access and how we offer support to those seeking to learn about how to decrease risk of harm.

4.1 Technical Consultation Group – Terms of Reference
DRAFT 2 for approval at the Barcelona Meeting, February 2015

I. Background

Since 2011, experts from across the World Health Organization (WHO) regions have collaborated in ad-hoc working groups to enter vigilance case descriptions in the NOTIFY library database. The aims of the initiative are to share didactic information on reliably documented adverse occurrences to facilitate improvements in safety, quality and efficacy in transfusion, transplantation and assisted reproduction and to provide greater public transparency on the use of all kinds of Medical Products of Human Origin (MPHO). The library aims to be comprehensive, describing all types of adverse occurrence that might have didactic value and/or assist in the estimation of risk for donation or clinical application. There are over 900 records in the NOTIFY library that can be searched in a number of different ways. The experts have added didactic information regarding alerting signals, latency and methods of confirmation of imputability, as well as references to reliable sources.

The library is maintained by the Italian National Transplant Centre (CNT), as a WHO Collaborating Centre for Vigilance and Surveillance of Organs, Tissues and Cells, on a dedicated website (www.notifylibrary.org). The website and the database are
publicly accessible without the need for usernames or passwords. It is not a vigilance reporting program but a collection and review of information identified primarily by literature review (published articles in scientific journals and/or books) although case reports from regulatory or professional vigilance programs (grey literature) are also considered for inclusion.

The work of the editors is categorized in the following groups:

Infections
Malignancy
Genetic transmissions
Donor reactions
Product properties and clinical complications.

Since early 2014, a further group has been working on transfusion reactions although at least some of this work will be integrated in the existing groups.

II. Status of Editorial Groups

The editorial groups are ad-hoc and have no formal status within the WHO governance structure. Their opinions and conclusions regarding database case records are their own and do not necessarily represent those of their organizations, or of WHO or CNT. Group members are not paid and are not obliged to dedicate any specific amount of time to the project. Their contributions are recognized on the website where their names appear in the area describing the organization of the project.

III. Objectives and Tasks

Cases for inclusion in the database, or additions/modifications to existing cases, can be proposed in a number of ways:

- By the NOTIFY operational team that runs a routine bibliographic search;
- By editorial group members themselves, who become aware of relevant documented cases through their own literature searching or their daily work;
- By any professional or member of the public that sends a message with a related reference to the NOTIFY library website.

The key roles of the editorial groups are to evaluate the proposals, to comment on whether they meet the criteria for inclusion in the database, to propose whether the case provides new information for an existing record or involves a level of new didactic information that justifies the addition of a new record, to note if a new record requires additional categories to be added to the database taxonomy, to add entries for latency, frequency, imputability etc. where necessary and where possible, and to
approve new or modified records, and their associated references, for publication in the database.

IV. Editorial Group Co-chairs

Each editorial group is requested to select a Chairperson and a Deputy Chairperson to oversee the work of the group. As a general rule, their role is:

Co-ordination of the work of the group, keeping them informed on the project’s progress and clarifying any doubts they have regarding individual records;

Communication with the steering group and operational team to ensure smooth progress with the review and approval of new or modified records and the development of the database in general;

Presentation of the work of the group during global consultations and other appropriate events.

The Chairperson and Deputy Chairperson are selected by the group through informal agreement. It is suggested that the roles rotate among the group members with the Deputy Chairperson taking over from the Chairperson after a 2 year period.

V. Editorial Group Members

Members are invited by CNT, on behalf of the project steering group and on the basis of their individual technical expertise. Members may also be co-opted by editorial group chairs. There is no limit to the number of group members although, in the interests of efficiency, the groups should not usually exceed 10 members. Individuals who have not participated in project work for a period of 2 years will be removed from the group’s membership list on the website.

Group members may invite other experts to work with them in informal topic-specific networks and sub-groups that feed information to the full editorial group.

VI. Working Methods

The methods of work can be agreed autonomously by the groups. Normally, however, work will be carried out by email, through the website forums and by telephone/Skype calls. A group call is recommended at least every 3 months. There is no strict time limit for responding to new proposals or approving pending proposals however, it is recommended that all pending proposals are reviewed at least every 3 months (usually during a group call).

As and when required, the steering group will organize meetings of all editorial groups to discuss project development and technical changes to the database. Editorial group members are invited to Global Consultations on the NOTIFY project (usually annual) where they have the opportunity to discuss and disseminate their work with the larger group.
VIII. Publications and Presentations

Editorial group chairs are free to present and publish analyses and summaries of the work of their group. Other editorial group members are also free to write and publish articles on the work of the group, with the agreement of the chairs and their inclusion as co-authors. Editorial groups are requested to inform the steering group of any publications and to provide copies for dissemination on the website.

Editorial group chairs and members are also free to publish articles or make presentations on the NOTIFY library in general although they are requested to do so in collaboration with the steering group and operational team to ensure consistency across the project’s dissemination activities.

5. FEEDBACK SESSION OF THE EDITORIAL WORKGROUPS

The different editorial groups presented their feedback in plenary.

5.1 Infections Editorial Group

(Paolo Grossi, Ines Ushiro-Lumb, Matthew Kuhnert, Ted Eastlund; also present at the workshop Roger Dodd, Iona Siska; not present but contributed to the editorial work: Melissa Greenwald, Oscar Len, Marcelo Radisik)

5.1.1 Current status and achievements so far

• Difficulties in retaining/recruiting stable membership
• Editorial group members availability is an important issue
• Some progress made in the bacteria/viruses/parasites groups but targets not met and work not completed yet
• Addition of blood group added another complex layer of difficulty to deliver the work
• Fungi and prion groups to be defined

5.1.2 Group discussions

Strategic issues -

• Need to define target audience
• Need to define aim of the product
• Creation of a tool that is deemed to be useful by those who will use it
• Strategy for long term work and sustainability
Editorial work issues -

- Keep IWDT cases and non-transmission without intervention in the database due to didactic value
- Purpose of “frequency” field

Suggestions –

- Feedback from users/ field test would be crucial
- Database usage activity is not sufficient, interaction with users would be preferred, with qualitative data collection
- Define section where non-transmission cases will feature

5.1.3 Working towards unresolved cases

- Divided existing work amongst the group members present at the technical meeting:
  - Blood/ virus: RD
  - Blood/bacteria: MK
  - Viruses: PG, IUL
  - Bacteria: TE
  - Prions/Parasites/Fungi: to be allocated, currently being dealt with by IUL

5.1.4 Towards the future (Infection)

- Real time literature search and horizon scanning done centrally by CNT
- Cases filtered; appropriate new reports logged and sent to Ines for distribution to appropriate editor
- Vetting of new submissions and entries is essential, as a set of steps need to be taken, including addition to existing records or entry as a new record, for example
- Where there is a need to discuss- internal group discussion by email/Skype
- Currently, editor will have TAT of 1 month to complete and upload record
- We propose that in future, cases are entered by CNT or other appropriately identified individual so that editors can rapidly validate/amend/reject entry
- Avoid repetition of information entry when several substances are linked to the same donor (prepare one entry and make a note for CNT staff to duplicate the records according to substance type)
5.2 Malignancy Editorial Group

Jeremy Chapman & Rafael Matesanz, Mar Carmona, Beatriz Dominguez-Gil, Carl-Ludwig Fischer-Fröhlich, Kerstin Moench, Michael Nalesnik, Bronwen Shaw

5.2.1 Achievements Update

Objective of the Malignancy editorial group

- To compile information/cases of donor-transmitted (and donor-derived malignancies) related to the clinical use of MPHO.
- To extract and organize the relevant information from selected cases
  - Has this occurred before?
  - What were the alerting signals?
  - What was the latency?
  - How was imputability assessed?
  - Other comments

Progress at the present meeting

- 15 additional cases reviewed and ready for upload
  - 12 of 38 cases previously prepared for review
  - 3 new cases

5.2.2 Working Towards Unresolved Rows Agreeing to Solutions

Working methods of the malignancy group

- Current cases to be divided in aliquots by chairman
  - Primary person designated for paper review, upload to website
    - Pdf of report distributed to all members
  - 3 week limit for review
- Main communication/discussion via e-mail (to all in group)
- Bimonthly conference calls as needed to update group, resolve issues
  - First call scheduled for March
- Primary person responsible for final upload of case to library website
- Email discussions to be compiled and uploaded to forum site to serve as repository of discussions

- New cases received in conjunction with searches by Evi Petrisli/CNT in addition to independent searches
- New cases will be addressed after current cases completed
5.2.3 Towards The Future of Malignancies in the Notify Library

Issues to address on cases included & to include

1. Type of malignancy based on an agreed upon taxonomy. Agreement needed
2. Are we using the grading imputability tool to select cases?
3. Should we maintain donor-derived malignancies in the Library?
4. How should we proceed with the ‘Estimated Frequency’ column?
5. Is the format of one reference per case per substance in a row the correct one?
6. How should we address the risk of harm in the data base (realistically)?

Taxonomy: Starting Point

- Original classification:
  - Appears to have arisen by accrual
    - Common cases included
  - Shortcomings of approach
    - Organization is only partial
      - All cancers occurring in individual organs and specific cancer types are admixed at same level
      - “Malignancy” as main heading, covers many things
    - New cases need to be added “ad hoc”

Current “Malignancy” Classification

- Breast cancer
- CNS neoplasms
- Colo-rectal carcinoma
- Choriocarcinoma
- Liver cancer
- Haematopoietic
- Lung
- Melanoma
- Oesophageal
- Prostate
- Renal cell
- Sarcoma
- Thyroid
- Neuroendocrine
- Angiosarcoma
- Urothelial Tumor
- Oropharyngeal
- Ovarian
- Pancreas
Example: Liver and Intrahepatic Bile Ducts

- Liver and intrahepatic bile duct:
  - Epithelial tumor/Carcinoma NOS (include for cases with no histologic diagnosis)
    - HCC
    - Cholangiocarcinoma

Ovarian

- Surface epithelial tumours NOS
  - Serous ovarian carcinoma
  - Mucinous ovarian carcinoma
  - Endometrioid ovarian carcinoma
  - Brenner tumor/transitional cell carcinoma
  - Include sex cord and germ cell tumors in their own category

Lymphomas and Leukemias

- Myeloid neoplasm NOS
  - Myeloid leukemias NOS
    - Acute myelogenous leukemia
    - Promyelocytic leukemia
    - Chronic myelogenous leukemia
  - Myeloid tumors NOS
    - Myeloid sarcoma

- Lymphoid neoplasm NOS
  - Lymphocytic leukemia NOS
    - Acute lymphoblastic leukemia
    - Chronic lymphocytic leukemia/lymphoma
  - Lymphoma NOS
    - Hodgkin lymphoma NOS
    - Non-Hodgkin lymphoma NOS
      - B Cell lymphoma NOS
        » Burkitt lymphoma
        » Diffuse large B cell lymphoma
        » Follicular B cell lymphoma
        » Marginal zone lymphoma
        » Mantle zone lymphoma
      - T cell lymphoma NOS
      - NK cell lymphoma NOS

- Plasmacytic neoplasm NOS
  - Plasma cell leukemia
    - Multiple myeloma/plasma cell leukemia
  - Plasma cell tumors
    - Extramedullary plasmacytoma

- Histocytic neoplasm NOS
## Bone and Soft Tissue

- **Bone**
  - Osteosarcoma

- **Cartilage**
  - Chondrosarcoma

- **Smooth muscle**
  - Leiomyosarcoma

- **Skeletal muscle**
  - Rhabdomyosarcoma

- **Adipose tissue**
  - Liposarcoma

- **Fibrous/connective tissue**
  - Fibrosarcoma
  - Fibromatosis/desmoid tumor
  - Inflammatory myofibroblastic tumor

- **Fibrohistiocytic tumours NOS**

- **Vascular**
  - Angiosarcoma
  - Kaposi sarcoma
  - Epithelioid hemangioendothelioma

- **Soft tissue other/indeterminate origin**
  - Ewing sarcoma
  - Angiomyolipoma
  - Synovial sarcoma
  - Clear cell sarcoma
  - Desmoplastic small round cell tumor
  - Sarcoma NOS

### Issues to address on cases included & to include

1. Type of malignancy based on an agreed upon taxonomy. Agreement needed
2. Are we using the grading imputability tool to select cases?
3. Should we maintain donor-derived malignancies in the Library?
4. How should we proceed with the ‘Estimated Frequency’ column?
5. Is the format of one reference *per case* *per* substance in a row the correct one?
6. How should we address the risk of harm in the data base (realistically)?
Are we using the grading imputability system?

<table>
<thead>
<tr>
<th>NOT ASSESSABLE</th>
<th>ADAPTED EUSTITE-SOHO V&amp;S¹</th>
<th>ADAPTED DTAC²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient data for imputability assessment</td>
<td>Insufficient data for imputability assessment</td>
<td></td>
</tr>
</tbody>
</table>

| 0 EXCLUDED/UNLIKELY | Evidence is indeterminate | Suspected transmission event AND at least one of the following conditions is met:  
  • There is clear evidence for an alternative reason for the event  
  • Lack of infection with the same organism in any other recipients, from the same donor, given appropriate testing  
  • Laboratory evidence that the recipient had infection with this organism or malignancy prior to transplantation. |

| 1 POSSIBLE | Evidence in favour of attribution to the OTC | Suspected transmission event AND  
  • Laboratory evidence of the suspected organism or malignancy in a single recipient OR  
  • Data that strongly suggests but does not prove a transmission event |

| 2 LIKELY/PROBABLE | Both of the following two conditions must be met:  
  • Suspected transmission event AND  
  • Laboratory evidence of the suspected organism or malignancy in a recipient  
  AND at least ONE of the following criteria must also be met:  
  • Laboratory evidence of the same organism or malignancy in other recipients;  
  • Laboratory evidence of the same organism or malignancy in the donor;  
  If there is pre-transplant laboratory evidence, it must indicate that the same recipient was negative for this organism prior to transplantation. |

| 3 DEFINITE/CERTAIN | Conclusive evidence beyond reasonable doubt for attribution to the OTC | All of the following conditions must be met:  
  • Suspected transmission event  
  • Laboratory evidence of the suspected organism or malignancy in a recipient  
  • Laboratory evidence of the same organism or malignancy in other recipients (if multiple recipients)  
  • Laboratory evidence of the same organism or malignancy in the donor  
  • If there is pre-transplant laboratory evidence, it must indicate that the same recipient was negative for this organism prior to transplantation |

Algorithmic approach to imputability

Initial Event Donor Disease

Single recipient only

- No pretransplant evidence shows recipient negative for disease: **Important**
- No pretransplant evidence shows recipient positive for disease: **Probable**
- No pretransplant studies possible: **Probable**

Multiple recipients

- Disease present in more than 1 recipient:
  - Pretransplant evidence shows all affected recipients positive for disease: **Important**
  - No pretransplant studies possible: **Probable**

- Disease not present in more than 1 recipient:
  - Pretransplant evidence shows recipient negative for disease: **Important**
  - No pretransplant evidence shows recipient positive for disease: **Important**
  - No pretransplant studies possible: **Probable (unless modified by disease type)**

- Clear evidence for alternative reason for recipient disease: **Important**

- Direct proof of identical donor disease/agent in recipient: **Important**

- Recipient disease at final follow-up: **Important**

  - No intervention given: **Important**
  - Pretransplant intervention given: **Probable**

Single recipient only

- Pretransplant evidence shows recipient negative for disease: **Important**
- Pretransplant evidence shows recipient positive for disease: **Important**
- No pretransplant studies possible: **Probable**

Multiple recipients

- Disease present in more than 1 recipient:
  - Pretransplant evidence shows all affected recipients positive for disease: **Important**
  - No pretransplant studies possible: **Probable**

- Disease not present in more than 1 recipient:
  - Pretransplant evidence shows recipient negative for disease: **Important**
  - Pretransplant evidence shows recipient positive for disease: **Important**
  - No pretransplant studies possible: **Probable (unless modified by disease type)**

- Direct proof of identical donor disease/agent in recipient: **Important**

- Recipient disease at final follow-up:
  - No donor disease present (initially): **Important**
  - Donor disease clearly excluded at final follow-up: **Important**

No donor disease present (initially)

- Pretransplant evidence shows recipient negative for disease: **Possible to Unlikely**
- Pretransplant evidence shows recipient positive for disease: **Probable**
- No pretransplant studies possible: **Probable to Unlikely**

- Disease present in more than 1 recipient:
  - Pretransplant evidence shows all affected recipients positive for disease: **Important**
  - No pretransplant studies possible: **Probable**

- Disease not present in more than 1 recipient:
  - Pretransplant evidence shows recipient negative for disease: **Important**
  - Pretransplant evidence shows recipient positive for disease: **Important**
  - No pretransplant studies possible: **Probable to Unlikely**
Issues to address on cases included & to include

1. Type of malignancy based on an agreed upon taxonomy. Agreement needed
2. Are we using the grading imputability tool to select cases?
3. Should we maintain donor-derived malignancies in the Library?
4. How should we proceed with the ‘Estimated Frequency’ column?
5. Is the format of one reference *per case per substance* in a row the correct one?
6. How should we address the risk of harm in the data base (realistically)?

Conclusions

- Donor-derived malignancies
  - Will remain in for now, additional risk information
  - True cutoff time not established
  - Clearly specify when considered “donor-derived”
- Estimated frequencies
  - Useful information to place case into context
  - Will fill in with brief guidance from Council of Europe, UNOS, etc when available

Issues to address on cases included & to include

1. Type of malignancy based on an agreed upon taxonomy. Agreement needed
2. Are we using the grading imputability tool to select cases?
3. Should we maintain donor-derived malignancies in the Library?
4. How should we proceed with the ‘Estimated Frequency’ column?
5. Is the format of one reference *per case per substance* in a row the correct one?
6. How should we address the risk of harm in the data base (realistically)?

Conclusions

- One row per case per substance provides good balance of information, allows for specific searches
- Details lost in summary reports
- Issue:
  - No space for clinical course/outcome summary

Issues to address on cases included & to include

1. Type of malignancy based on an agreed upon taxonomy. Agreement needed
2. Are we using the grading imputability tool to select cases?
3. Should we maintain donor-derived malignancies in the Library?
4. How should we proceed with the ‘Estimated Frequency’ column?
5. Is the format of one reference *per case per substance* in a row the correct one?
6. How should we address the risk of harm in the data base (realistically)?
Risk of Harm

- In case of tumor, would include cases where donor had tumor, no transmission seen.
  - Such cases are placed in “risk of harm”, not assessed for imputability by definition
  - General reviews also including non-transmitted donor tumor cases and no details on individual cases of transmission also placed in risk of harm
- Issue:
  - Not seen when searching for tumors, reactions
  - Wish to include these by default in searches for tumors

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 from cells that were 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

Methodology for Worksheet preparation

References:
- **Included**: English written (mostly), follow-up registries, cohorts, single case reports
- **Excluded**: reviews (with exceptions), de novo malignancies, recurrent malignancies
- **Official reports**
- **Row per reference per substance**
- **Information extracted**:
  - Clinical alerting symptoms/signs
  - Latency
  - Assessment of attributability
  - Comments:
    - Preventive/therapeutic measures
    - Outcome
    - Type of publication
- **Uploaded in a Google Docs Site**
- **Uploaded in the Library after editorial review**

Exhaustivity

- Exhaustive Review of the literature for organs- updated
- Non-exhaustive for tissues & cells (HSC included)

References Captured

Multicentric follow-up organ transplant registries:
Australian and New Zealand Organ Donation Registry, Centro Nazionale di Trapianti, Israel Penn Transplant Tumor Registry, Organización Nacional de Trasplantes, United Network for Organ Sharing

Individual Case reports
Official reports

Histology, stage, grade, time period between tumour diagnosis and organ procurement, therapy, follow-up and remission. If transmission has occurred, clinical manifestations, management of the particular case, assessment of attributability and outcome.

Malignancy transmission and MPHO

1. A malignancy transmission risk might be identified before the transfer of MPHO 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 in the donor and/or the MPHO might be identified after the transfer of MPHO has occurred.

3. A malignancy might also be inadvertently transmitted from the donor or the CTO and become apparent when the clinical manifestations of such transmission come out in the recipient(s).
Questions:

1. Revised taxonomy – agreement needed

   • Generic to specific, primary site/tumour type approach adopted
     Based on the WHO classification of tumours (http://www.pubcan.org/)

   • Populated mostly by tumour types transmitted by MPHOs documented in the
     Notify library (with some exceptions)

   • Limits
     o Redundancy
     o Some records (mostly from official transplantation registries) do not
       contain much information on primary site nor on specific tumour type,
       making the use of the term “unknown/unspecified” necessary

2. Should we maintain donor-derived malignancies in the Library?

   • Is it useful to keep them?
   • If we decide not to keep donor-derived malignancies, need to go back into the
     site and delete existing records

3. How should we proceed with the ‘Estimated Frequency’ column? What do we need here?

   • Do we need information on how frequently has the transmission of a given
     malignancy occurred?

   • Do we prefer information on how frequently has the transmission of a given
     malignancy occurred from donors known to have that malignancy?
     o Categories?
     o Free text?

4. Is the format of one reference per case per substance in a row the correct one?

   • Previously decided not to compile the different cases/reports in the same rows,
     due to clinical variability in alerting signals, latency, atributability assessment
     and others.
   • Alternative: one row per incident and substance, summarizing the findings
     of all references related to the case
     o Need to go back to the Library and rearrange all the information included
     so far

5. How should we address the risk of harm in the data base (realistically)?
5.2.4 Towards The Future of the Notify Editorial Group on Malignancies

Terms of Reference I

EDITORIAL GROUPS

Ad-hoc groups with no formal status within WHO. Their opinions and conclusions regarding database case records are their own. Group members not paid and not obliged to dedicate any specific amount of time to the project. Their contribution is recognised on the website where their names appear in the area describing the organisation of the project.

OBJECTIVES & TASKS

Cases for inclusion in the database, or additions/modifications to existing cases, can be proposed in a number of ways:

- By the NOTIFY operational team that runs a routine bibliographic search;
- By editorial group members themselves who become aware of relevant documented cases through their own literature searching or their daily work;
- By any professional or member of the public that sends a message with a related reference to the NOTIFY library website.

Evaluation of proposals:

- Commenting on whether they meet the criteria for inclusion
- Proposing whether the case provides new information for an existing record or involves a level of new didactic information that justifies the addition of a new record;
- Noting if a new record requires additional categories to be added to the database taxonomy;
- Adding entries for latency, frequency, imputability etc. where necessary and where possible;
- Approving new or modified records, and their associated references, for publication in the database.
Terms of Reference II

CO-CHAIRS

- Each editorial group is requested to select a Chairperson and a Deputy Chairperson to oversee the work of the group.
- Co-ordination of the work of the group, keeping them informed on the project's progress and clarifying any doubts they have regarding individual records;
- Communication with the steering group and operational team to ensure smooth progress with the review and approval of new or modified records and the development of the database in general;
- Presentation of the work of the group during global consultations and other appropriate events;
- The Chairperson and Deputy Chairperson are selected by the group through informal agreement. It is suggested that the roles rotate among the group members with the Deputy Chairperson taking over from the Chairperson after a 2 year period.

GROUP MEMBERS

- Members are invited by CNT, on behalf of the project steering group and on the basis of their individual technical expertise. Members may also be co-opted by editorial group chairs. There is no limit to the number of group members although, in the interests of efficiency, the groups should not usually exceed 10 members. Individuals who have not participated in project work for a period of 2 years will be removed from the group's membership list on the website.
- Group members may invite other experts to work with them in informal topic-specific networks and sub-groups that feed information to the full editorial group.

Terms of Reference III

WORKING METHODS

- Agreed autonomously by the groups. Normally, however, work will be carried out by email, through the website forums and by telephone/Skype calls. A group call is recommended at least every 3 months. There is no strict time limit for responding to new proposals or approving pending proposals however, it is recommended that all pending proposals are reviewed at least every 3 months (usually during a group call).

- As and when required, the steering group will organise meetings of all editorial groups to discuss project development and technical changes to the database. Editorial group members are invited to Global Consultations on the NOTIFY
project (usually annual) where they have the opportunity to discuss and disseminate their work with the larger group.

PUBLICATIONS & PRESENTATIONS

- Editorial group chairs are free to present and publish analyses and summaries of the work of their group. Other editorial group members are also free to write and publish articles on the work of the group, with the agreement of the chairs and their inclusion as co-authors. Editorial groups are requested to inform the steering group of any publications and to provide copies for dissemination on the website.

- Editorial group chairs and members are also free to publish articles or make presentations on the NOTIFY library in general although they are requested to do so in collaboration with the steering group and operational team to ensure consistency across the project’s dissemination activities.

Working methods of the malignancy group

- Chairs perform a pro-active search every 3 months
  - Literature
  - Biovigilance
- Chairs distribute reports for review among group members
- Chairs compile summaries of reports prepared by group members
- Group review all reports and make concerted decisions (during quarterly conference calls)
- Conference calls performed quarterly on the above and any other
5.3 Product Property/Clinical Complications Editorial Group

(Scott Brubaker and Esteve Trias)

PRODUCT PROPERTY/
CLINICAL
COMPLICATIONS
EDITORIAL GROUP

Suggest to Split the Group
And rename PP back to P

FOR “PEG”

- We need to recruit experts from each MPH0 Type
  - Jennifer DeMatteo
  - Aurora Naranjo
  - Sina Oltibey
  - Paul Ashford
  - Marco Costa
  - Efratios Chatzizisis
  - CD:
    - Barbene Whittaker
    - Jay Bentove
    - Eduard Ruffo

PEG Co-chairs: Esteve Trias, Adolphe, Scott A. Brubaker

PROCESS
Clinical
Complications

Process Editorial Group & Clinical Complications Editorial Group

SUGGESTIONS

- MPH0 Type
  - Multiple same record entries must be made for the same occurrence if multiple MPH0 involved
  - Can multiple selections of MPH0 be made in one record instead?
    - If not, there should be a button to make a new copy of the entire record, then adjust that record to individualize MPH0 type

RESULTS IN A QUESTION

- How many records should be entered when there are multiple occurrences related to one MPH0?
5.4 Living Donor Editorial Group
Bronwen Shaw and Tim Pruett

5.5 Blood Editorial Group
Barbee Whitaker presented the proposed foundations for this newly created group as well as outcomes of the discussions that took place during the workshop. There were many questions and concerns raised, as well as some suggestions. Post meeting, it was decided that the Blood group would work as a Clinical Complications group.

FOUNDATIONAL BLOOD NOTIFY WORK
5.5.1 Blood Transfusion Group Activity/Discussion
Existential questions:

- Purpose
- Audience
- How much work/time it will take to manage this section
- Bring in additional experts
- Address prevention
- Address/propose categorical definitions of frequency, latency, imputability
Next Steps

- Answer existential questions
  - Purpose
  - Audience
  - How much work/time will it take
- Develop materials to present to the recruited SMEs
- Map SHOT report to Notify hierarchy
- Validate Notify hierarchy
- Identify appropriate subject matter expert (SME) groups (immune reactions, donor reactions, etc)
- Sort and filter Notify lists
- Identify SMEs to populate SME groups

Work for Subject Matter Expert Sub-editorial groups

- Provide list of topical papers in Notify and to be reviewed:
  - What belongs?
  - What should be rejected?
  - What can be combined?
  - What is missing?
  - What would be considered new in the field?
- Provide examples of didactic or illustrative presentations or book chapters
- Interpret accepted list to Notify format

5.5.2 Way forward for Blood: New Papers or Findings
Way forward for Blood: New Papers or Findings

Subject Matter
Experts
Editorial
Group
Monitor journals (SME)
PubMed searches (Notify)

New paper/finding/lecture/chapter

Editor

Add new record
Add to existing record

Editor

Contact author request Notify form within 1 week

Add to Notify
Library & Banner

Rules/Format for SME (both old & new)

- Consistent Title with rules
- Confirm appropriate categorization hierarchy
- Latency
- Frequency
- Alerting signs
- Imputability
- Preventive actions
- Comments

Blood Editorial Management

- to be developed
Open discussions happened at every session and there was a final discussion period on the last day. Some issues featured more prominently and are summarized here.

It was commented that some issues are consistently and repeatedly raised, and they should be addressed. One relates to the audience that Notify wishes to target and another relates to finding how to best direct the comments in the library so that they are relevant to users.

It was reminded the group about some important aspects of the library, namely:
1. Aim to offer an easy pathway for relevant information, with easy access to all;
2. Valuable forum that brings all MPHOs together, in a single place;
3. Opportunity for widespread dissemination of didactic information.

It was questioned whether the generation of an annotated bibliography is the way to meet the project’s proposed aims.

It was underlined that a very relevant point on the need to be very mindful of the way information is entered and presented in the library. As it is hoped that this library will become a valuable tool, particularly in less resourceful settings, audiences in those countries may not have access to further bibliography and may need to use Notify as a sole source of information.

It was confirmed the EU interest in the project and added the question of target stakeholders. Is Notify also being addressed to regulators and Health Authorities? Which groups are going to benefit from Notify? The question of prevention is another important one and Iona suggested that we should reflect about how Notify relates to this concept, as questions will be asked about the issue. She also remarked that EU authorities are certain to be interested on users’ feedback hence it is important that we have this information.

There was some discussion about the depth of information entered in Notify. There is an agreement that unqualified information should not be entered; some doubt still exists around the validity in entering information from reports as very often there is insufficient information.

It was asked whether Notify is considering to include information on interventions, to further assist users.

It was asked if guidelines on prevention and management, from different organizations, should be available through the website.

It was underlined that the group should not burden itself with the need to give guidance on management and preventative measures.
The group voiced the importance of seeking answers from other people about Notify, remembering to think not only about our vision but the vision of those who will use the library. There should be a task for Notify, between now and December 2015, to network and circulate a questionnaire to find out if the tool is useful for professional to carry out their duties. Answers should be brought back to the next consultation.

It was suggested that such questionnaire ought to have very carefully planned questions, addressing points in a very objective manner.

It was remarked that the tool is beginning to be used for risk assessment in the context of quality and safety. Hence it is very important that we define our role before we ask stakeholders for their opinion. The most important message still is the need to learn from errors.

The group was invited to send proposals for the questionnaire. A focus group could be targeted to generate information on how Notify could be most useful.

It was asked whether we know where the tool is meant to be most useful, particularly outside Europe.

It was suggested to recollect the suggestions from the consultation meeting in Brasilia, as regards to ethics. It seems that there is no need to have a specific, separate section for ethical issues, but relevant information and key words should be collected and inserted when entering and reviewing cases.

It was suggested that to start this work, an index would be needed, to establish what should be categorized as “ethical issues”.

It was suggested that if ethical issues played a part in the event, than the word “ethics” should be entered as a key word, so that the case can be captured. For example, transmission of HBV via SOT because the donor had been illegally procured.

7. TECHNICAL GUIDELINES FOR EDITORIAL GROUPS

During the meeting it was agreed to have a technical guideline for the editorial groups and video tutorial to be published on the Notify Library in the section SEARCH LIBRARY>>EDITORIAL GROUPS

8. CONCLUSIONS AND NEXT STEPS

Based on the activities and discussions that took place during the 1st technical meeting, the Notify team deliberated and released this post-meeting statement-
1. Technical Improvements

Technical/Editorial issues that were identified in Barcelona, regarding:

I. The functionality of the new uploading tool
II. The database in general - standardisation of frequency, imputability etc.
III. The site in general - news updates, background documents etc.

2. Strategy for Work on Adverse Occurrences in Blood

There is a need for a clear strategy for the hemovigilance work - to be agreed with that group. Drafting is underway.

3. Communication/Dissemination

Need for a comprehensive dissemination/communication strategy including the following:

**Roles and Responsibilities of the Operational Team**

a) Provide a 2 page document describing the MISSION and OBJECTIVES of the NOTIFY library that can be used by others to request dissemination support (links on websites etc.).

b) Issue a Newsletter from the website every three months to all those who have participated in the NOTIFY initiative from the beginning. The newsletter will keep them updated of developments and progress.

c) Sliding news on the website homepage will be regularly refreshed to keep the site looking dynamic.

d) Gather testimonials from the new (Planned) feedback questionnaire tool on the site (see below) – making them visible to show the usefulness of the site to others.

e) EU Joint Action - 2015 to 2018 (action funded by the EU and lead by CNT and CNS in Italy). In the action the operational team will work with EU authorities to:

- Provide guidelines for the addition to the NOTIFY library of didactic cases reported to vigilance systems, with appropriate analysis and information (even if not published), and
Support them in using the library to find information of relevance to the investigation and follow up of adverse occurrences reported to them.

This will result in a report that can be provided to authorities in other regions of the World to encourage them to also feed the library with didactic cases from their vigilance programs and to use it to support their monitoring and follow up of adverse occurrences locally.

f) Working with Collaborating partners to develop and document models of dissemination in focused individual regions or countries – initially in Italy (Bologna) and Spain (Catalonia) and through ONT and CNT nationally – measuring the result through Google analytics of site visits in relation to dissemination activities.

g) Using TPM training courses (carried out for organs all around the World and online and for tissues online and in Barcelona each year) to disseminate the tool. I will discuss with Marti Manyalich to verify if it’s happening effectively and provide support to the TPM team to achieve it if not. Brochures will be provided to TPM for inclusion in every participant folder at TPM courses.

**Roles and Responsibilities of WHO**

a) To communicate with all WHO regional offices to:

   i. Facilitate that they have a link to the NOTIFY library website on their website, and

   ii. Encourage them to include a presentation on the topic at any important regional meetings that address safety/quality in MPHO

b) To take the initial necessary steps to identify suitable partners in other parts of the Globe that might host a language-specific mirror version of the website and to support such centres to work towards collaborating centre status as hubs for the global network for MPHO vigilance.

c) To make the initial necessary steps to identify partners that might host a global consultation and to reach preliminary agreements with such Member States.

d) To take forward proposals for the NOTIFY Journal of Adverse Occurrences in MPHO under the auspices of the WHO Bulletin.

**Roles and Responsibilities of Editorial Groups and other Collaborating Experts**
a) To promote the appearance of links to the NOTIFY library on the websites of the scientific and professional societies in which they are active

b) To make presentations at Scientific congresses on the NOTIFY library

c) To describe the tool when carrying out training of professionals

d) To publish articles both on the project in general and on the database content for their particular subject specialist area.

4. Evidence of Usefulness of the NOTIFY library

Need to generate evidence of the usefulness of the site and library by introducing a new questionnaire for visitors to the site, connecting the search they conducted with answers to the questions regarding their professional profile and whether they found the information in the database useful. The results of this questionnaire will allow the following questions to be answered:

a. Who uses the NOTIFY library?

b. What do they look for?

c. Does it help?

The results of this will combined with comprehensive data from Google Analytics to allow useful information to be presented in at the Global Consultation at the end of the year.

5. Terms of Reference – Editorial Working Groups

We need to finalise the ToR of the Editorial groups, including confirming chairs and co-chairs and ways of working for each group. The draft terms of reference has been circulated for comments. The editorial group chairs will be contacted individually to establish their preferred way of working and to ensure that we are giving as much administrative support as possible.

6. Establishment of MPHO-specific Advisory Groups

The project will develop Advisory Groups (equivalent to the organ advisory group that met in Barcelona); one for the field of Tissues and Cells and one for the field
of Blood (possibly a fourth for ART in the future). These groups will have roles in developing guidance, algorithms, consultation and advice to health authorities. Terms of reference for these 3 groups to be developed.

7. **Next Global Consultation:** it will be defined when and where the next Global consultation will take place.

A meeting dedicated to the WHO Regional Office will take place in Bologna, Italy, from 1\textsuperscript{st} to 2\textsuperscript{nd} December 2015.
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