Second Global Consultative Meeting for the BIG V&S Project

(Bologna Initiative for Global Vigilance and Surveillance)

14-16 November 2012, Rome

Final Draft Report

Introductory Note from the Secretariat

This consultation was made possible thanks to the generous support of the Centro Nazionale Trapianti, CNT, the Italian National Transplantation Centre. The CNT has been the partner of WHO in the Bologna Initiative for Global Vigilance and Surveillance (BIG V&S) since its inception. It recently became a WHO Collaborating Centre on Vigilance and Surveillance (V&S) for Human Cells, Tissues and Organs. The collaboration between the CNT and WHO has led to the development of the NOTIFY website and the NOTIFY Library.

This publication reports on the deliberations and outcomes of the Second Global Consultative Meeting of the BIG V&S Project, held in Rome from 14 to 16 November 2012. It followed the first of such meetings held in Geneva in July 2011.

These global consultations enable participants to advise on WHO's work for V&S of cells, tissues and organs (CTO) for transplantation according to the requirements of World Health Assembly Resolution WHA63.22 on Human Organ and Tissue Transplantation adopted in May 2010. In particular the consultations consider the progress of the tools for global V&S in particular the NOTIFY website and the NOTIFY Library.

The consultation was prepared with the invaluable help of the CNT team, in particular Deirdre Fehily, Daniela Minutoli, Stratos Chatzixiros and of course its Director, Alessandro Nanni Costa, and with the effective contribution of Mike Strong.

This report represents the views of the participants, 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 the Chairmen of the meeting, Jagdish Prasad and Jeremy Chapman, and to the Rapporteurs, Hiwot Araya, Laura Saint-Martin and Haibo Wang.

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

Luc Noël, Coordinator Clinical Procedures
HIS/HPW

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1. Executive Summary

This report summarizes the discussion and outcomes of the Second Global Consultative Meeting of the Bologna Initiative for Global Vigilance and Surveillance (BIG V&S) Project held in Rome, Italy from 14 to 16 November, 2012. BIG V&S is a project coordinated by the World Health Organization and funded by the Italian National Transplant Centre (CNT), a WHO Collaborating Centre for Vigilance and Surveillance of Organs, Tissues and Cells. The First BIG V&S Consultative Meeting was held in Geneva from 5 to 6 July 2011.

This was a follow-up meeting to continue development of Project NOTIFY, a project that aims to develop mechanisms to improve clinician recognition of, and global communication about, serious adverse events and reactions (SAE/Rs) related to clinical use of cells, tissues, and organs including the use of gametes in assisted reproduction technologies (ART). The purpose of this second consultative meeting was to review progress on activities begun through the Bologna Initiative and develop a path forward for continued development of the framework for global information sharing.

This meeting in Rome focused on refinement of the NOTIFY Library website (www.notifylibrary.org) and the database of case summaries with supporting references hosted on the website. The NOTIFY Library had been launched for public access on November 7, 2012.

The participants discussed potential audiences for and uses of the NOTIFY Library, and the importance of maintaining a well-defined scope and clear objectives. The participants agreed on the importance of providing some context for the information on SAE/Rs, such as the volume of procedures performed annually, so the public has balanced information about risks and benefits of donating and receiving substances of human origin. The participants also discussed the need for standardized terminology for the content of the Library and developed definitions for terms used in the NOTIFY Library.

Working groups refined the cases in the database and developed criteria for determining whether to include or exclude specific cases from the Library (such as whether to exclude cases if they pre-dated important changes in clinical practice or test technologies, they reported lack of transmission to the recipient even though the donor was infected with an agent or had a particular malignancy or they were documented only in popular press). Participants considered several mechanisms to raise awareness

of the existence of the NOTIFY Library and database, such as through notification of professional medical groups and organizations that maintain registries.

The NOTIFY Library and database will undergo further refinement. Additional cases reviewed during the working group break out sessions will be added to the Library. Discussion about further refinements or specific cases will be conducted through online closed forums.

2. Welcome and Opening of the Meeting

The first morning was held at the Italian Ministry of Health and the remainder of the meeting was held at the Spallanzani Hospital, Rome. Dr Alessandro Nanni-Costa welcomed participants from 20 countries and representing all WHO regions. The full participant list is given at Appendix 1. The draft programme of work was adopted by the meeting participants (see Appendix 2). Participants unanimously agreed that the meeting be chaired jointly by Drs Jeremy Chapman and Jagdish Prasad. Drs Haibo Wang, Laura St Martin and Hiwot Araya agreed to act as rapporteurs for the meeting and to write the final meeting report.

3. Introduction

The BIG V&S project, objectives of the second consultation by Luc Noel

Luc Noel emphasized that, as per WHO Guiding Principle 10, the safety, efficacy and quality of human cells, tissues and organs for transplantation requires quality systems including traceability and vigilance in which adverse events and reactions are reported nationally and internationally. World Health Assembly Resolution WHA63.22 requests the Director General:

- To continue collecting and analyzing global data on donation and transplantation of human cells, tissues and organs; and
- 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.

WHA Resolution WHA63.22 was the driving force that led to the Bologna Initiative for Global V&S project supported by CNT. The Global Consultation on exploring vigilance notification for organs, tissues and cells was held 7-9 February 2011 in Bologna, Italy. Participants at that meeting identified global governance issues such as the need for ongoing global collaboration and annual consultative meetings, and identified the need for harmonized standard terminology, guidance for the

development of global vigilance and surveillance, and a comprehensive database of didactic cases (the NOTIFY Project). The NOTIFY Project focused on three tools to promote global vigilance and surveillance:

- The NOTIFY Website
- The NOTIFY Library (the library of evaluated cases with references)
- The NOTIFY Booklet

The First Global Consultative Meeting was held 5-6 July 2011 in Geneva to further development of global vigilance and surveillance tools.

This meeting, held 14-16 November 2012 in Rome, Italy, was the Second Global Consultative Meeting. The objectives for this meeting were:

- Bring the content of the NOTIFY Library up to date.
- Establish processes for routinely updating the NOTIFY Library, including identifying contributors, creating procedures, standardizing format, and defining terminology.
- Discuss ways to promote global V&S progress, encourage expansion of existing V&S systems, and support the development of new V&S systems.
- Develop a plan of action based on a SWOT analysis of the NOTIFY Library.

4. The BIG V&S Website by Deirdre Fehily

Deirdre Fehily provided an overview of the structure and content of the NOTIFY Library website that was made available for public access on November 7, 2012 (www.notifylibrary.org). She described the Library as a database of all types of severe adverse events and reactions that have been documented, with didactic review and analysis by international experts. She stressed that the database must be:

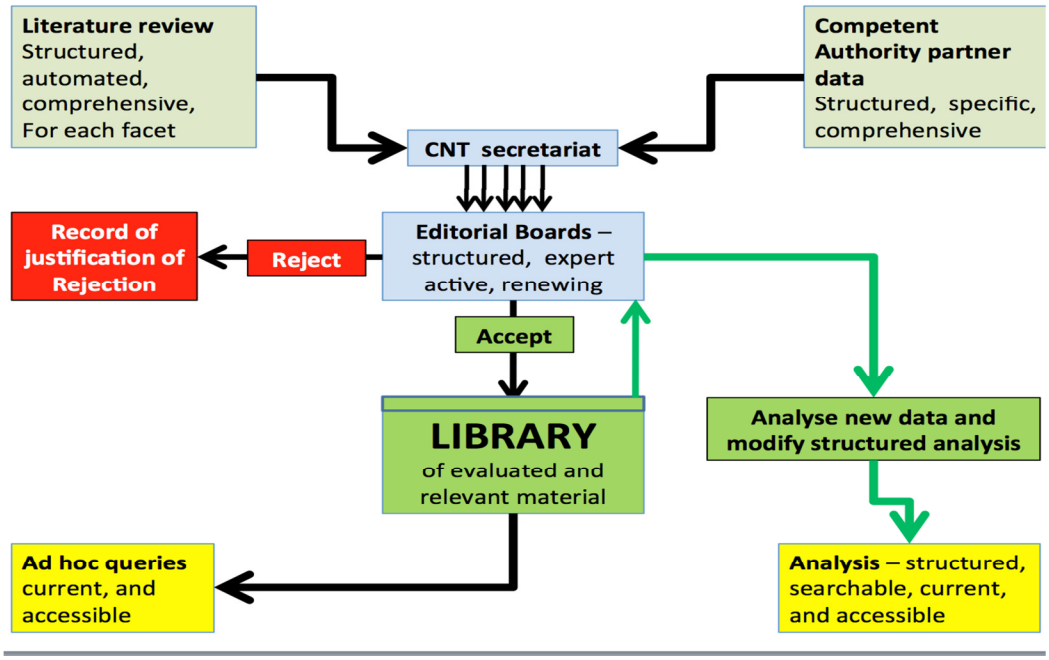
- Accurate
- Consolidated
- Categorized
- Validated: reported cases should have been investigated and there should be reasonable possibility of an association with the organs, tissues or cells donated or applied.

In addition to tools and content tailored to the public and professional audiences, there is a password-protected area that includes forums for collaborators in the NOTIFY Project to communicate about new case reports and other issues relevant to the further development and maintenance of the NOTIFY Library.

5. The NOTIFY Library database structure by Daniela Minutoli

There are two main entities included in the NOTIFY database. These are the analysed records and the bibliography from which the cases are referenced. A record number, an incident description, and the incident type (SAR or SAE) are used to identify cases.

Figure 1: The diagram below illustrates the editorial and selection process for all cases.



The cases are defined and further elaborated upon by the following describing features:

1. **Substance type**: substance classification following a structured taxonomy.
2. **Latency**: the usual time from the incident occurrence to its detection.
3. **Alerting signal**: for SAR, the first clinical symptoms in the recipient or living donor. For SAE, how and when the incident was detected.
4. **Frequency data and estimates**: when available, data or estimate of the frequency of this type of SAR or SAE.
5. **Imputability**: For SAR, a description of the way(s) in which it is normally confirmed that the donation or transplant was the cause of the SAR. For SAE, a description of the root cause of the incident where this is available.
6. **Keywords**: selected words from incident description, imputability, latency, and alerting symptoms texts.

7. **References (publications)**: code for the reference from the master list of NOTIFY references.

References can be journal articles, conference papers, government records, web articles on official government or professional sites and case reports, as well as grey literature such as annual reports from authorities and vigilance programmes. Cases and references can be easily identified in the database. Identification codes can never be modified so they are useful in identifying entities within the database. These codes are used to allow for a quick and easy communication regarding cases. At this time 529 case types and 1750 references have been uploaded. Not all references have been reviewed. In correcting errors or updating already uploaded cases, experts should refer to the relevant code for a particular case and reference. A pdf of any search result can be saved and printed.

Data quality is an important aspect of maintaining the value and usability of the NOTIFY Library. The following parameters/guidelines emerge from errors identified during the first few rounds of upload:

1. Standardize terminology before adding cases
2. Separate keywords using semicolons (;)
3. Spell out all abbreviations
4. Check spelling during data entry
5. Confirm accuracy and consistency of references listed for each case.

Future focus must be placed on consistency of terminology. There needs to be further work on standardization of terminology.

6. Searching the NOTIFY Library and data cleanup by Dr Mike Strong and Stratos Chatzixiros

In order to navigate the database, one may conduct a structured search by substance type and/or incident type by using the drop down menus. It is also possible to search the database rows by keywords or free text and to refine a structured search by adding keywords or free text criteria. Bibliographic searches of the articles can also be performed.

Table 1: Methods of conducting a search in the database

Database Search	▪ Type of SAR ▪ Type of SAE ▪ Substance type ▪ Free text (searches texts included in latency, alerting signal, frequency data and estimates, demonstration of imputability) ▪ Keywords (searches keywords identified by the experts from the text in the database record)
Bibliographic search	▪ Authors ▪ Publication year ▪ Keywords (searches the keywords identified by the authors of the publication) ▪ Freeword search (searches words from the title and abstract of the publication)

Mike Strong summarized the first phase of developing NOTIFY as work that involved capturing SAR and SAE cases from the literature by experts in the corresponding fields. The second phase has been organizing these cases and reviewing their content using a standardized format developed to construct the database.

It was noted that the work ahead is to complete reviewing current cases in addition to reviewing the remaining references from the bibliography that are currently not linked to cases in the database. Mike Strong highlighted the need for an ongoing literature review and inclusion of references from the most recent PubMed searches to keep the library up-to-date.

Moving forward the following actions must be undertaken:

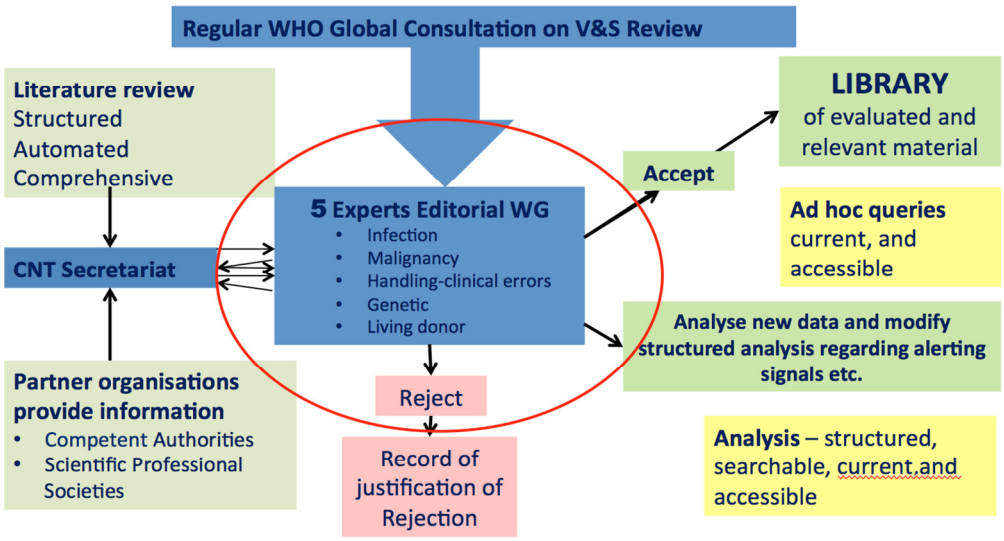
- Review all uploaded cases and identify errors.
- Add from the most recent publications (2010 – 2013).
- Correct errors in the reference authors' list in the database.
- Define terminology extensively. We have already defined SAE and SAR. We need to come to agreement as to what other definitions should be standardised.
- Pay careful attention to "demonstration of imputability." A description using one or two words is not helpful. For SAR, this description should adequately explain the way(s) 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 must be included when available.

- Define requirements with regards to the level of imputability (for example, what should be done with cases with an unlikely imputability?).
- Determine how to deal with newly added "similar cases," as the database expands.

The current system is subjective as far as the information included in the database. It is the responsibility of the editorial groups to make a subjective decision on the basis of their knowledge and experience. One of the Library's unique qualities is the inclusion of grey references. These reports include documents such as annual reports of professional vigilance programmes or of health authorities, such as TRIP (NL), UNOS (USA), the French Medicines Agency Annual Vigilance reports, and the EUSTITE Project. Many incidents, particularly SAEs, are recorded in internal quality systems and not published although a selection were listed in the NOTIFY report and can be referenced there. A possible challenge with the unpublished cases, or those published in unofficial sources, is the risk of obtaining information that has not been validated. We need to develop clear guidelines on how to handle these types of reports.

During the review process, a few cases were taken out due to a lack of evidence that the transmission occurred or was caused by the transplanted allograft. The literature remains in the bibliography as a resource since it can still be useful. For some of these cases, if an agency report and/or published report are identified in future, the case will be added to the Library. It is hoped that partnership with vigilance systems will aid in bringing in validated cases.

Figure 2: The NOTIFY Library operation.



7. Summary of General Discussion

The function/content of NOTIFY Library was further defined and clarified during the discussion. The following principles were agreed:

- ***NOTIFY Library not a registry***

The NOTIFY Library is a historical collection of cases with comprehensive didactic information on cells, tissues and organs (CTO) related SAR/SAE. Information from the database is accurate, categorized, consolidated, and validated by the appropriate regulatory authorities or professional societies. It is agreed that NOTIFY is a library not a registry, not a reporting system. It does not conduct primary investigation. It serves as a tool that links the world of donation and transplantation. It functions as a didactic tool with the collection of global V&S on SAR/SAE and will not replace any existing health authority or professional society reporting systems.

- ***Source and quality of data***

SAR/SAE case reports are extracted from publications in the scientific literature or reports from national health authorities and professional organizations. Collaboration with professional societies is invaluable in maintaining the standard and quality of knowledge presented in the NOTIFY Library. The idea is to gather cases of interest and use the expertise of reviewers by working closely with the national authorities. The NOTIFY Library is different to a PubMed/Google search by virtue of its added value from expert panel review and editorial group comments. Contributions from national health authorities, which have established systems for V&S and Scientific and Professional Societies with reporting systems, are important sources. It was agreed that no formal agreements are necessarily needed with collaborating organizations. NOTIFY will be a forum for these societies who can participate with this unprecedented initiative for global vigilance. It is also suggested that links of national authorities and professional societies should be provided on the Library website to facilitate users to use other resources.

- ***No interventional data collecting for now***

Data on corrective or preventive interventions is relevant and has a potential for great usability. However, there is a danger in extending beyond our capabilities. It is crucial to set some priorities. “Cleaning up” existing references and, in the meantime, “catching up” new data since 2010, are the key priorities at present. It was agreed that expansion possibilities should be determined once current goals specific to the database are met.

- ***No combination of cases***

It was agreed that due to various characteristics of cases, in order to prevent information loss, cases should not to be combined unless they are close to identical.

Suggestions

- ***Partnerships should be established***

It was agreed that partnerships with national authorities/professional associations should be established based on mutual benefits. A global network should be established and local focal points in each area should be identified. Detailed discussion on partnership is outlined in a separate section of the report.

- ***The database should be up-to-date and standardized***

The NOTIFY Library needs to be comprehensive and kept up-to-date. The last updated date should be presented on the website. The editorial group plays a vital role in ensuring information is accurate and current.

There were several suggestions regarding strategies to improve data quality, including that NOTIFY should provide recommendations to current international V&S bodies on the format/information required in the case report, along with standardization of terminology. Issues on partnership, sustainability, risk control, language, dissemination, budget, and standardization were also discussed; detailed information on these topics is provided in separate sections of the report.

- ***Information on website should be user specific***

The NOTIFY Library users should provide different information for different user groups such as transplant coordinators/doctors/organ recipients/organ donors/general public. The Library should provide information tailored to the specific user group. Web design should enable a function with different entry points to be realized. It was agreed that there should be three separate entry points – one for the general public, that emphasizes the benefits of transplantation and assisted reproduction (with links to relevant sites providing data), one for health professionals and one for health authorities.

- ***Risk control***

It was discussed that we must carefully plan different spaces within the Library in which data is presented. At this time the Library is purely knowledge of SAR and SAE cases reported. We need to avoid attributing blame to the source of the reported case. Meanwhile, the potential risks for the users should be highlighted. Information from both publications and experts should be disclaimed on the website and on printouts.

Questions/issues raised with pending consensus

- ***UNOS practice on data collection***

UNOS may be able to provide guidance on future NOTIFY Library data collection based on the level of detail requested from reporting agencies.

In 2005, the national transplant policy enacted a requirement for all transplant centres to report cases of SAE and SAR, which is then submitted to UNOS. UNOS does not provide specific treatment advice. Information regarding the intervention that was used in each case is collected and documented, however, the outcome is not always known to the user. For each case, a one-page summary is prepared and discussed by the committee responsible for summarizing and requesting additional information for completing imputability data.

For the NOTIFY Library, two data collection forms have been designed and will be utilized in collecting new data that is comparable and consistent with current standards of the database.

- ***Presenting exact risks to users***

It was discussed that we must carefully plan different spaces within the Library in which data is presented. The NOTIFY database demonstrates SAE and SAR cases that should be reported. It also provides information with regards to latency and alerting signals relevant to those cases. However, it is not designed to help decision-making in the operating room. At this time it is purely knowledge of SAR and SAE. Participants agreed that knowledge presented in the Library needs to be comprehensive, up-to-date, and curated. The editorial group plays a vital role in ensuring accuracy of information.

- ***Grey literature***

Guidelines on inclusion and validation of the grey literature need to be defined. A possible challenge with the grey literature is the risk of obtaining information that has not been validated.

- ***Rare cases/non transmitted cases***

No consensus has been reached yet on whether rare cases and non-transmitted cases should be included in the database, and where they should be displaced.

- ***"Negative" vs. "positive" information***

The question of how to address "negative" information about SAR/SAE vigilance with the "positive" outcomes of transplantation was raised during the discussion. It still needs to be decided how to provide balanced information on the Library website so the

knowledge of SAR/SAE would not overshadow the potential benefits of CTO transplantation.

8. Editorial Group Work Summaries

General instructions for all editorial groups

All the five editorial groups are working on the task of reviewing group specific Google worksheets to ensure SAR/SAE data transfer quality. Meanwhile, each group also needs to catch up literature searching for new cases since 2010 to keep the database up-to-date. The general instructions are as below:

- **"Cleaning" previous data**

  Preliminary work was done to prepare the SAR/SAE data migration from the Google site to the new NOTIFY Library. Data that was previously inserted in the NOTIFY worksheet on the Google site has been inserted into a standard worksheet following a predefined format to allow automated uploading to the new software.

  To ensure information is accurate and ready for upload, editorial groups needed to "clean" data, meaning each individual group's worksheet on the Google site was reviewed for accuracy, missed information was added, and the references listed were confirmed to be linked to the correct reactions/events. The task was carried out with the use of a set of instructions prepared by CNT, which provided a standardized data format and measures to ensure the accuracy and completeness of the database.

- ***There are two types of existing database cases that needed work***

Cases indicating "not ready for upload" in the worksheet were reviewed and edited. Insufficient information is the main reason for this status. Efforts were made to get required information from the original source or from the corresponding references.

- ***Methodology used for data "cleaning"***
  - One row per substance per incident
    - Where there is variability in case manifestations, it was decided not to compile different cases in the same row in order to avoid loss of information.
  - References
    - The full list of references (for all substance and topic types) is listed in alphabetical order and numbered sequentially.
  - Information was extracted as follows:

- Incident description, substance description, alerting signals, latency, frequency data and estimates demonstration of imputability, keywords, comments including preventative/therapeutic measures, outcome, and type of publication comments from NOTIFY expertise, references.

Catching new data since 2010

- Literature review and data collection need to be up-to-date. New SAR/SAE cases since 2010 need to be collected and put into the new database. In addition, previous missed cases need to be added to the new database as well.

8.1 Malignancy Group

Jeremy Chapman, Stratos Chatzixirios, Kathy Loper, Dietger Niederwieser, Haibo Wang, Beatriz Dominguez-Gil

- References

Publications in English describing original reports of CTO related malignancy transmissions were included. References mainly come from three categories: multicentre follow-up organ transplant registries, individual case reports, and official reports. References exclude: reviews, *de novo* malignancies, recurrent malignancies.

Detailed information on CTO-related malignancy needs to be provided in the references including histology, stage, grade, time period between tumor diagnosis and organ procurement, interventions, follow-up and remission. If transmission has occurred, clinical manifestations, interventions, assessment of imputability and outcome need to be provided.

Cases with no reference available even after great effort has been made, will be deleted from the database. At the time of the meeting, 99 % of malignancy cases that had been entered in the Google documents had been uploaded to the NOTIFY site.

The general discussion led to recognize that donor-origin malignancies should be included in the database**.** There are two types of donor origin malignancies. 'Donor-transmitted malignancy' is a 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). 'Donor-derived malignancy' is a 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." Thus, a donor-origin leukemia diagnosed in an organ recipient 30 days post-transplant would likely be donor-transmitted malignancy whereas a renal cell carcinoma developing 9 years post-renal transplant is likely a donor-derived malignancy.

Non-transmitted cases: The group discussed the cases of CTO with a confirmed malignancy (identified before or after transplantation), where transplantation took place but transmission to the recipient did not occur. It was recognized that information on non-transmitted cases is important in terms of transmission of malignancy risk estimation and transplantation decision- making etc. But in the current database structure, there is no space reserved for this type of data. The questions remaining are: how to present this data in website? Create a separate space /a secondary tier on the work spread sheet? It was agreed that these cases should be retained for inclusion in a suitable format in a later phase of the project.

- Suggestions
  - It was suggested that Project NOTIFY recommends international agencies to provide structured, consistent, systematic reports with detailed information on SAR/SAE cases. Guidance on information required for case reports could be provided by NOTIFY.
  - It was suggested that Project NOTIFY has a publication series on CTO related malignancy transmission with editorial group comments and disclaimer.
  - It was suggested that Project NOTIFY reaches out and gets more expertise from the transplantation community so that more resources can be accessed in a similar way to that done by Cochrane reviews.

8.2 Process Group

Marian Macsai, Chris O'Toole, Laura St. Martin, Francis Delmonico, Scott Brubaker

- "Grey" literature cases

  It was noticed that many cases collected in this group fit into the "Grey" category. Most of these cases were SAEs and reported by "systems" such as the EUSTITE Pilot, TRIP annual report, and Euro Transplant. As such, most of these cases provide very limited information. A final decision has not yet been made regarding deletion from the NOTIFY Library as contact with these groups is being made to attempt to collect critical information to meet the NOTIFY data standard.
- "Outdated" cases

  The group suggested that very outdated SAE reports (from 1980's) should be deleted as the information they provide is of little value today.
- Validity of cases

  The group questioned the validity of cases that were only reported by media (newspaper). To date, consensus on inclusion/exclusion criteria has not been reached. See section 10 below.

8.3 Living donor reactions

Bronwen Shaw, Daniel Roberto Coradi de Freitas, Carolina Stylianou, Tim Pruett, Tomonori Hasegawa, Naoshi Shinozaki, Ineke Tieken, Hiwot Araya

- The editorial group for living donor SAR and SAE consists of two subgroups. The first subgroup is focused on peripheral stem cell (PSC) and bone marrow cases, while the second subgroup addresses organ cases. Living donor cases with respect to organs such as livers and kidneys are primarily reviewed with Dr Pruett who was not present for the meeting. The plan is for Hiwot Araya to collaborate with Dr Pruett via teleconference in reviewing organ cases.

- Cases with unlikely or low imputability and/or those that do not fit the criteria for the database were identified by the members and will be moved to a separate tab under "tier 2" until a space for such cases is identified on the website.

- Current and ongoing focus for the living donor group is to finalize reviewing cases on the living donor Google spreadsheet. Hiwot Araya will transcribe changes made to the worksheet on the spreadsheets and mark those that are ready for upload.

- Additional goals for this group include adding recent (since 2010) publications to the Google spreadsheet to ensure recent living donor adverse reactions and incidents are included in the database.

8.4 Infections

Michael Ison, Paolo Grossi, Ted Eastlund, Melissa Greenwald, Richard Tedder, Ines Ushiro-Lumb, D Michael Strong

The Infectious Diseases Editorial Group relied heavily on the work that was performed for the Bologna Meeting by five work groups that reviewed the existing literature relative to the various infectious disease categories (Bacteria (including Mycobacteria), Fungi, Parasites, Prions and Viruses). The Editorial Group then reviewed the spreadsheet for each of the severe adverse events and reactions that were collected by the work groups. The primary literature was consulted to attempt to fill in parts of the spreadsheet that were missing during the first round. Obvious gaps in the literature review were noted. Given the large number of events and reports associated with donor-derived infectious disease, major gaps were addressed while minor gaps will be addressed in the next phase of the database update. As much as possible, standard imputability definitions were utilized (Garzoni C, Ison MG. Uniform definitions for donor-derived infectious disease transmissions in solid organ transplantation. ***Transplantation***. 2011; 92: 1297-1300). For many cases, there was inadequate data presented to independently verify the imputability attributed to the severe adverse event or reaction.

As of the beginning of the Rome meeting, far less than half of the cases were reviewed and approved by the editorial group for uploading. Over the course of the meeting, the Editorial Group attendees reviewed and approved about two-thirds of the spreadsheet and completed the work shortly after the meeting so that existing cases could be uploaded before the end of the year.

Several challenges have emerged with the data reviewed to date:

- Handling of Non-Transmitted Infections: There are a number of infections for which an infection can be documented in the donor but, to date, the infection has not been transmitted to a transplant recipient; one such example is *Naegleria fowleri*. There is not a system in place to flag these important infections for which the risk of transmission appears exceptionally low.

- Handling of Complex Infectious Diseases Issues: There are a number of infections, such as hepatitis B virus, in which infection in the donor can be transmitted but the risk of transmission is modified by a number of host and host treatment effects. For example, pre-existing immunity, through prior infection or vaccination, or the use of antiviral/antimicrobial therapy may significantly reduce the risk of disease transmission. This is difficult to address in the current case-based system that is being utilized for Project NOTIFY. Development of Project NOTIFY-specific summaries (i.e., systematic review) for these complex issues could done but will require significant effort on the part of the authors and will need to be revised over time to address changes in epidemiology and treatment/prophylaxis. An alternative approach would be to host or cite guidelines or reviews developed outside Project NOTIFY.

- Handling of Old Data: In the review of the literature, there were numerous examples in which old data suggests a higher risk of infectious disease transmission than is currently experienced in the current era. One example is hepatitis B virus (HBV); early reports noted frequent transmission of HBV from donor to recipient but current data, in the era of robust donor screening, availability of HBV vaccine and HBV-active antivirals, suggests a much lower risk. Although we discussed removing the old data, it was decided that the data should be left in the NOTIFYNOTIFY Library but we need to develop ways to contextualize the changing risk of transmission.

- National/Regional/Local Biovigilance Data: The group recognized that there is a growing Biovigilance effort globally (i.e., OPTN/UNOS Disease Transmission Advisory Committee in the United States and the Agence de la Biomédicine Biovigilance Program in France). These systems will collect and review infectious disease transmissions. Publically available data from these systems generally lag behind the discovery of the events and contain limited data. As such, relying on the publically available data may delay entry of newly recognized infectious disease transmissions into the Library and the reports may contain too limited data to fully populate the Library. Efforts to establish sharing of these vigilance data should be undertake to address theses key challenges.

8.5 Genetics

Mauro Costa, Dennis Confer, Chris O'Toole

- The principal focus for the Genetic group was to review cases on the Google spreadsheet. It was noticed that a new classification had to be defined for genetic

SAR, as there is a third subject besides the donor and the recipient that is the Fetus and/or offspring. So a "fetus and offspring SAR" was established.

- The References mainly came from three categories: individual case reports, grey literature and media reports. Cases with unlikely or low imputability and/or those that didn't fit the criteria for the database were identified and were taken out.
- It was agreed that cases should not to be combined and review articles were explored to extract single cases (particularly the Pre implantation diagnosis cases).
- The main goal of the group will be to catch up new data since 2010**.** As it was realized that many cases of genetic SAR and SAE could not probably be published, it was agreed that a partnership with registries from scientific societies and national institutions must be established.

9. Updating the NOTIFY Database by Jeremy Chapman (Laura St Martin)

Promoting the Database

Dr Chapman gave suggestions for actively promoting awareness and use of the NOTIFY database. This included ways of making the site come up higher on Google search lists, and exploring the possibility of a NOTIFY Library app for smart phones and tablets in the future. Participants agreed that we should pursue opportunities to place links to the NOTIFY web site on professional society web sites.

The NOTIFY database should be marketed in such a way that users are encouraged to give feedback and contribute to the ongoing improvement of the site. The information on the site should be balanced so as not to overemphasize the risks associated with substances of human origin; it could do harm if clinicians refrain from use of these products out of fear of risks.

In preparing case summaries, the expert reviewers should summarize the facts and be careful about attributing blame. There should be text explaining that the expert reviewers have signed declarations regarding conflicts of interest (lack of bias). We anticipate that the NOTIFY Library web site will be helpful for a variety of users; the home page could include buttons for different audiences (e.g., professionals, public, ART) with disclaimers and explanations suited to those different audiences. Every search result should include a disclaimer that the information may not be solely based on literature, but may include expert opinion.

Updating the Database

The NOTIFY database must be relatively up to date. The top of every web page should give the date the site was last updated. We should explore automated literature searches, perhaps using every six months, to find new published cases. The search

parameters initially could be broad to make sure relevant cases are captured; with experience, the expert editorial working group could refine the search. Data from other sources, such as from Competent Authorities, could be entered on a schedule, such as quarterly. Searches for grey literature (such as meeting abstracts, reports, and presentations) cannot be automated easily and the search would require a lot of work. Perhaps meeting abstracts only should be included if peer-reviewed and published in a journal.

The ongoing maintenance of the NOTIFY Library requires a commitment of resources. As a collaborating centre, CNT considers this project as a priority and will continue to support it for the next few years. Success of this project also requires the commitment of experts to review the literature and provide editorial comments—that is the real value of the NOTIFY Library. We need to engage members of professional societies to lend their expertise to the various activities of the working groups.

Other approaches to gathering data on SAEs and SARs and maintaining the NOTIFY Library may include:

- Obtain data from national surveillance systems/registries—some data or reports are available in the public domain. We could start by compiling a comprehensive list of relevant national surveillance systems and databases such as OPTN/UNOS, SEER.
- Develop partnerships for accessing non-public information (from vigilance systems such as EEBA, FDA) through either:
    - Informal personal connections with individual members of relevant organizations
    - Formal requests for data sharing (e.g., letter of request from WHO, CNT)
- Establish a global network with a designated local contact in each geographic area.
- Establish further collaborating centres.

10. Newspaper and anecdotal cases by Deirdre Fehily

Deirdre Fehily presented several examples of SAEs that were highly publicized in the media. These primarily were events involving reproductive tissues, such as an embryo mix up due to a labelling error. One event involved a cryopreservation facility malfunction that resulted in the loss of dozens of embryos as well as ovum and sperm. Some of the events have resulted in lawsuits, or legal action is pending. Events of this type generally do not result in a report in a scientific journal.

Participants agreed that these types of media reports could be brought to the relevant forum for discussion of the issues. For legal cases, it may be possible to find court records to document the case, but court records may not contain detailed information regarding the root cause of the SAE. In some instances, there might be information posted on the web site of a national authority. Media reports would be handled on a case-by-case basis; the editorial group would determine whether there is sufficient documentation/information to include the case in the NOTIFY Library.

11. Glossary and Definitions by Kathy Loper and Richard Lebethe

This session focused on refining terms as they are used in the NOTIFY Library. The working group considered existing terminology in use by national health authorities and other organizations such as SOHO, EU Directive—Organs / Tissues & Cells, ISBT, US CDC, AABB, and adapted the definition to preserve the basic concept while creating a definition that would allow stakeholders to communicate using the same language.

In developing the definitions, the working group considered the following target users of the site:

- Clinicians
- Regulators
- General Public

The group discussed that the definitions of SAE and SAR must be framed to capture events unique to ART. The website could have short definitions of SAE and SAR, then buttons for “Read More” with longer definitions and examples, including text that addresses ART.

The participants discussed whether we should assess imputability to cases in the NOTIFY database (assigning classifications such as proven or probable), but did not reach a decision. Imputability is applicable to SARs, not SAEs. Instead, we need to prioritize other work we need to do. All agreed that the definitions require continuous expert review and re-adaptation as needed to maintain relevance with future developments in transplantation.

12. Rapid Vigilance Communication

The Rapid Alert System on Tissue & Cells (RATC) of EU was presented by Dr. Paolo Catalani in the meeting. The establishment of RATC provides its member states with

an effective system for urgent exchange of information and measures to ensure the safe use of human tissues and cells.

- User rules:
- Competent Authorities (CA) and Unit D4 (substances of human origin and tobacco control) of DG Health and Consumers - European Commission (EC) are the main stakeholders. The other stakeholders include WHO, other relevant sectors in EC, pharmaceutical sector, epidemiological sector, and other networks (blood, organ).
- CA is responsible for creating, updating, notifying a new alert to other stakeholders, and also for completing the final report and close the alert.
- EC has administration role such as validation of the user access, management of the reference list/library, follow-up of dedicated functional mailbox etc.
- Other stakeholders will be notified of an alert and also can contribute and comment on the system.

The system features:

- An authorized, restricted access online system
- An easy to use and user-friendly computer interface.
- An administration module for a restricted list of users to create, follow-up and consult alerts and final reports on tissues and cells.
- An alert form and notification process
- A set of notifications/reminders (based on deadlines and specific events).
- A search and document functions.
- An annual report on alert statistics.

13. SWOT Analysis

The group conducted an analysis of the NOTIFY Library as it currently stood.

Strengths	• Vigilance and surveillance • Tool for transparency • Unprecedented • Reviewed by experts from diverse countries • Global governance • Living document • Supported by WHO and CNT Collaboration • Strong demonstrated support to date • Standardized approach leading to harmonization • Didactic and educational tool
Weaknesses	• Budget limitations • Human resource limitations • Requires on-going commitment from individuals, scientific institutions,

	and national/governmental agencies. • Not up-to-date yet • Documentation limited to what is published • Information detail can be lost • Format compatible with SAR not SAE • Layperson misinterpretation • Diversity of approach • Yahoo not Google – needs informatics approach o Communication limited
Opportunities	• Learn from SAEs and SARs that have occurred in the past • Useful for countries developing surveillance systems • Promote safe practices globally • Bring international attention to address a shared concern • Global diversity and volumes captured • Captures all type of CTO transplants • Non-HPC cell transplants to be captured as they evolve (e.g. genetic/engineered stem cells, hepatocytes, islets, xenotransplants) captured by both source and by application • Evolve to include clinical trial notifications • Convergence between goals of pharmaco- and biological vigilance • Disseminate grey literature reports
Threats	• Negative interpretation of the data by users, media… • Sustainability • Legal consequences • English and Euro focus limits global applicability and comprehensiveness • Costs

14. Forming partnerships and future direction

Establishing partnerships with other organizations is a necessity in order for NOTIFY to achieve global coverage of V&S information. Partnerships will allow for geographic representation, linguistic and cultural coverage, and regional global responsibility. Dr Luc Noel remarked that expertise and knowledge exchange from one to another is necessary in order to thrive. It was noted that partnership is a two-way street. The terms and conditions must be laid out so that the expectations are made clear for all parties involved.

Participants discussed different levels of partnership. It was agreed that there could be various levels of commitment from partner organizations and individuals. A formal memorandum of partnership would detail these varying levels of responsibilities.

For example:

1. **Working partner** – individuals who can serve as editors, librarians etc. There are professionals in every country, whether there is a vigilance system or not, who can serve as working partners.
2. **Data sharing partner** – collaboration with groups that collect vigilance data such as UNOS, EUSTITE, etc.
3. **Financial partner** – organizations that can provide funding for maintaining and developing the library.
4. **Visibility partner** – organizations that will endorse NOTIFY (low level of partnership).
5. **User partner** – we must work closely with the users as they can provide feedback on how to improve the library.

It was discussed that partnership will provide a reliable conduit for obtaining data currently lacking. For example there is underreporting of ART (assisted reproductive technology) SAR and SAE, which can be addressed by collaborating with national registries or societies who can provide published records. Additionally, SPS of transplant surgeons and eye bank associations may serve as data sharing partners. They can host lectures at their annual meetings on SAE and SAR. They will take a strong interest, as they will benefit from SAE and SAR knowledge provided through the NOTIFY Library.

Participants agreed that partnership is a flexible, mutual, and beneficial relationship, which may vary with regard to the level and type of commitment. Partners can be notified as the Library is updated and new cases are added. It was also suggested that an annual newsletter with a list of partners and events would be beneficial in connecting partners and providing a solid network among individuals and organizations with similar interests in improving quality and outcome of transplantation.

14. Conclusions and closing remarks

Several ideas were raised and put forth during the three-day consultation. Group discussions allowed for an open dialogue between participants regarding the current state of the NOTIFY Library and areas of improvement. Members of the editorial groups worked together in editing and finalizing data review. This real-time collaboration also allowed for the groups to discuss challenges faced while reviewing cases. It provided a setting in which editorial members could work side by side with the operational team in addressing these issues. Participants were able to openly discuss needs that pertain to their region and what they could offer to NOTIFY. For example, representatives from China, Korea, and Latin America raised the issue of the language gap, which must be addressed in expanding the Library's usability. Future

work can be focused in identifying means of making vigilance and surveillance information available in Spanish and Chinese.

Additionally participants acknowledged that the project is currently led and carried out by volunteers. It is essential to be mindful of ways to finance the project. Dr Noel and Dr Chapman summarized the outcomes that will result from this meeting as the following:

- Publish a detailed report of the meeting with the names and contacts of all participants.

- Disseminate information about the NOTIFY Project through presentations, articles, and the media.

- Educate the transplant community, health care providers, professional societies, and authorities. Currently there has been a 'soft opening' of the tool. Later, there should be a 'hard opening' of the library once another round of cases has been uploaded.

- Ongoing effort to develop partnerships with authorities, professional societies, and professionals globally.

- Ongoing publication of review papers quoting literature.

- Investigate IT concepts that will simplify data collection and reporting through the NOTIFY Library. For example, an automated way to search and populate data.

- Publish the clinician booklet, which targets healthcare professionals and will be provided to WHO Member States to promote V&S in transplantation. It will be customized to meet national specificities and yet retain and promote a globally harmonized conception of V&S.

Tasks specific to the NOTIFY Library database

- The operational team will work with the editorial groups in uploading the remaining cases currently under review.
- Mike Strong will create a tab in the Google doc spreadsheets where specific directions can be posted. This will aid in facilitating specific tasks for each editorial group. Chairs of each group will also be in charge of posting these tasks on the forum as well as updates post consultation
- WHO will report back regarding utilization of the website.

In closing a successful three-day consultation, Dr Luc Noel and Dr Nanni Costa thanked everyone for their participation, enthusiasm, and hard work in actively supporting the goals of the NOTIFY Project. The meeting was monumental in advancing the progress of the NOTIFY Project as an unprecedented knowledge bank, which promotes vigilance, and surveillance of cells, tissues and organs globally.

Appendix 1: List of Participants

Second Global Consultative Meeting for the BIG V&S Project (Bologna Initiative for Global Vigilance and Surveillance of Human Cells, Tissues and Organs for Clinical Application)

14-16 November 2012, Ministry of Health and Spallanzani Hospital, Rome

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Appendix 2: Programme of Work

World Health Organization

Centro Nazionale Trapianti

Second Global Consultative Meeting for the BIG V&S Project
14 – 16 November 2012
Ministry of Health and Spallanzani Hospital, Rome.

Wednesday 14 November - Ministry of Health

08:30	**Transfer by bus from Hotel Ripa to the Ministry of Health**	
09.00	Registration	
09.30	Welcome from Director, Centro Nazionale Trapianti	Alessandro Nanni Costa
09:45	Welcome from Coordinator, Clinical Procedures, WHO	Luc Noel
10:00	Introduction of participants Election of Chair and Rapporteurs	
10:15	The BIG V&S project, objectives of the second consultation	Luc Noel

The NOTIFY Library: current situation

10:30	The BIG V&S Website	Deirdre Fehily
11:00	*Coffee Break*	
11:30	The Notify Library Database Structure	Daniela Minutoli
11:45	Searching the Notify Library	Mike Strong
12:15	The Notify database 'clean-up' work	Stratos Chatzixiros
12:30	**Transfer by bus from the Ministry of Health to Spallanzani Hospital**	
13:00	*Lunch -* ***Spallanzani Hospital***	

The NOTIFY Library: Review and Resolution of remarkable cases

14:00 General Discussion

14.30 Editorial Group Workshops (no genetic group as the work is almost complete)

Infections Editorial Group Meeting Room Poccia	Malignancy Editorial Group Meeting Room Poccia	Process Editorial Group Lunch Room	Living Donor Reactions Editorial Group Lunch Room	Exploring and Testing the site and the database Press Room
Mike Ison, Paolo Grossi, Ted Eastlund, Ines Ushiro-Lumb, Mike Strong, Matt Kuehnert	Jeremy Chapman, Beatriz Dominguez-Gil, Haibo Wang, Dietger Niederwieser, Kathy Loper; Stratos Chatzixirios	Scott Brubaker, Francis Delmonico, Anne Cathrine Bollerup, Marian Macsai; Chris O'Toole; Laura St Martin, Luc Noel	Carolina Stylianou, Dennis Confer, Mauro Costa, Naoshi Shinozaki, Ineke Tieken, Hiwot Araya	Daniela Minutoli, Deirdre Fehily and all other participants
To work through unresolved rows agreeing to solutions				
Coffee while working				

17:30 Recess

20.30 CNT invites all participants to a dinner at the Ripa hotel
Following dinner, editorial groups will continue their work on the database at the hotel.

Thursday 15 November - Spallanzani Hospital

The NOTIFY Library towards a V&S reference

Welcome from Scientific Director of IRCCS "L.Spallanzani" Giuseppe Ippolito

09:00	Summary by Rapporteurs	
09:30	Feedback from the workshops to the full meeting and open discussion	
11:00	*Coffee Break*	
11:30	Updating the NOTIFY database – introduction	Jeremy Chapman
11:45	Updating the NOTIFY database – new scientific publications	Mike Ison
12:00	Updating the NOTIFY database – newspaper and anecdotal cases	Deirdre Fehily
12:15	Updating the NOTIFY database – new cases documented in vigilance systems (EEBA, EU, EU CAs, FDA, SEAR/SPEAR, KFDA, ANVISA)	Open discussion
13:00	*Lunch*	
14:00	Glossary and Definitions – Consistency with V&S globally	

	and with other health care areas - Introduction	Kathy Loper and Richard Lebethe
14:30	General discussion on achieving consistent terminology	
16:00	*Coffee break*	
16:30	Advocacy and guidance for V&S	Mike Strong
16:45	General discussion	
17:30	Recess	

20.30 CNT invites all participants to a social dinner at a Rome restaurant
Details to be provided during the meeting

Friday 16 November - Spallanzani Hospital

The NOTIFY Library in 2013

09:00	Summary by Rapporteurs	
09:30	Rapid vigilance communication: The EU RATC system	Paolo Catalani
09:50	Partnerships/interfaces between Notify and NHAs, SPS	
11:00	*Coffee Break*	
11.30	Conclusions and the way forward	Luc Noel and Alessandro Nanni Costa
12.45	Meeting close	
13:00	*Lunch*	