Centro Nazionale Trapianti

ISTITUTO SUPERIORE DI SANITÀ

NOTIFYLIBRARY

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"Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation" – VISTART

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Deliverable 5.1 - How to select and prepare SARE cases of didactic value for insertion in the Notify Library - a user guide for Competent Authorities

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1. INTRODUCTION

Work Package 5 - Part A of VISTART Joint Action (JA) aims at increasing the involvement of European Union (EU) Member State (MS) Competent Authorities (CAs) in the WHO didactic tool developed and managed by CNT: the Notify Library of adverse occurrences in transfusion, transplantation and assisted reproduction (see link: www.notifylibrary.org). The Notify Library is an open access database of reliably documented didactic cases of adverse occurrences arising from the donation, preparation or clinical application of Substances of Human Origin (SoHOs), from donation to follow-up of donors and recipients. Cases are analysed, linked to their source reference (scientific publications, formal vigilance programmes) and regularly updated by editorial groups of international experts in the fields of transplantation, transfusion and assisted reproduction.

The main objective of the Notify Library is to share published vigilance information for teaching purposes as widely as possible, to build knowledge and create awareness. Sharing the lessons learned from adverse outcomes can allow significant process improvements for the greater protection of donors and patients. These benefits apply where the incident occurred but also anywhere else where an identical or similar incident might occur. The purpose of the Notify Library is not to be a register of registries but to be a comprehensive tool, describing all types of reactions or events that might have didactic value and assist in the estimation of risk.

These Guidelines provide instructions to facilitate EU CAs in the selection and analysis of case types with didactic value from their annual SARE reports to the European Commission for insertion in the Notify Library. The Working Group will support MS CAs to use this didactic tool in order to improve their vigilance investigation activities (policy making, risk assessment, unusual donor suitability questions, training, etc). Editorial Groups (EG) of Experts will be asked to each review their topic-specific records for accuracy and to add missing information and expert comments, where possible. The CA that submitted the record will review and approve any comments or information added by the EG before publication.

1.1 Selection criteria

A case is suitable for inclusion in the Notify Library when it:

- offers a description of an adverse occurrence that **has caused harm** to a donor or a recipient of a substance of human origin (SoHO), or to a fetus or embryo created through gamete or embryo donation, *OR*
- offers a description of an adverse occurrence **has represented a risk of harm**, *AND*
- is **reliably documented** in the scientific, clinical or legal literature or in a formal vigilance programme, *AND*
- has **didactic value** (for example: uncommon/unexpected event, unusual signals or severity, assists in the estimation of risk for donation or clinical application, etc.).

Figure 1 summarises the steps from the case selection to its submission to the Notify Library. Examples of "triggers" that could assist CAs to recognise a relevant case with learning points are listed below (at least one trigger should be present). Subsequently, a specific Notify Library search will be useful to decide if the case is suitable for inclusion in the Library's database. You could search by adverse occurrence type, by keyword or by free text. If you consider that the new case provides didactic value that is different to any existing database record, proceed to propose it.

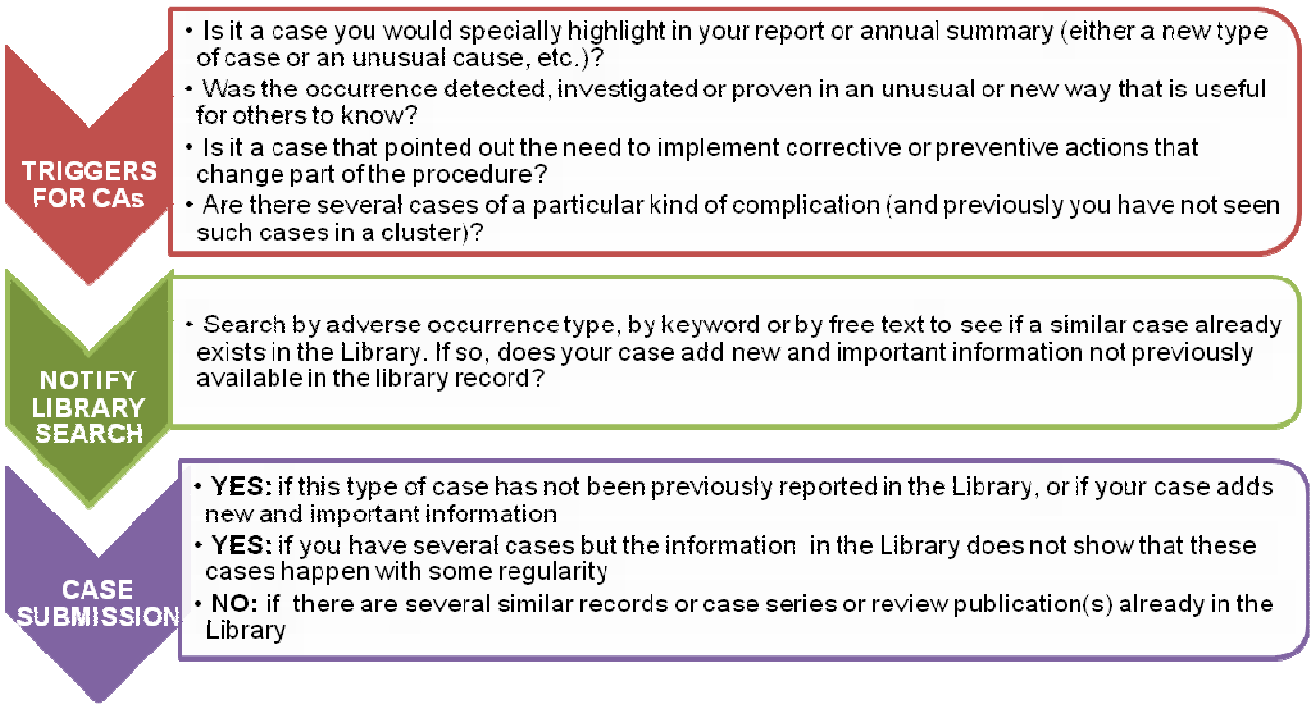


Fig. 1: Steps from the case selection to its submission to the Notify Library

1.2 What constitutes a Notify record?

The description of an adverse occurrence in transfusion, transplantation or assisted reproduction that has been documented in scientific or grey literature or in an official vigilance system and has didactic value constitutes a Notify record. Expert analysis focuses in particular on how the adverse occurrence was recognised and how it is shown to have been associated with the donation, process or clinical application of the SoHO. A unique record ID number will refer to a specific Notify record once linked to its source reference and uploaded in the Notify Library (see Annex 4.6 for case examples). Each record in the Notify Library describes a type of adverse occurrence for one type of substance (Medical Product of Human Origin, MPHO) (Annex 4.6.1). CAs submitting records for inclusion in the Notify Library's database should make two records for the same type of occurrence with the same MPHO if they consider that are substantially different from each other in terms of cause, method of confirmation of imputability or any other factor that is considered to have major didactic value (Annex 4.6.2). Where one record describes many cases, the experts should summarise the findings using ranges, averages, etc. (Annex 4.6.3).

2. WORKFLOW AND EDITORIAL PROCESS

The Notify team will carry out a check of every record for consistency (terminology, spelling, etc.) and will assign it to an EG (there are currently 5: infection transmissions, malignancy transmissions, living donor reactions, process, clinical complications including transfusion reactions not covered by the other groups). All records will be reviewed and approved by the specific EG. A final revision and approval by the CA is requested before publication. Up to that point, all work on pending cases is invisible to the public.

Figure 2 summarises the workflow from the record submission to its publication in the Notify Library. The following sections provide users with more detailed instructions for the operational steps to follow.

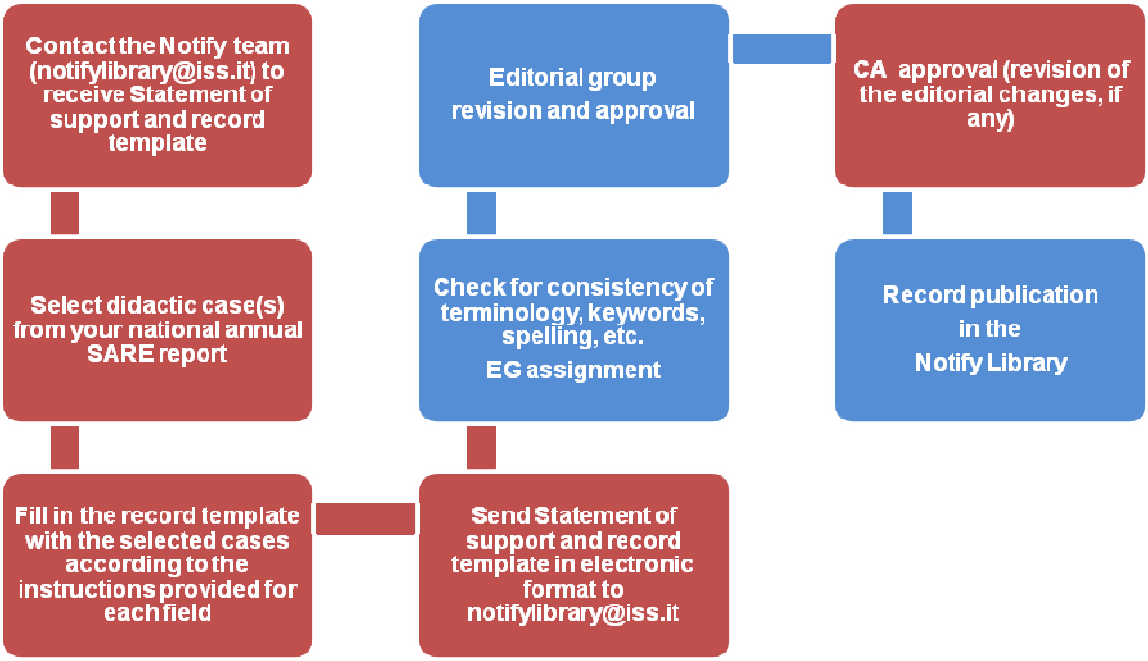


Fig. 2: Workflow and editorial process (actions highlighted in red, CAs; in blue, Notify team and Editorial groups)

2.1 Statement of support, data protection and confidentiality

By signing the Notify Library Statement of Support (Annex 4.1) regarding the provision of selected data from your national vigilance system you will officially contribute to the content of the Notify Library. There are two ways of referencing the submitted cases: for CAs who want their report to stay confidential it will be referenced as: "European Union Annual Vigilance Report, year ..."; alternatively, the specific official Health Authority vigilance programme will be specified. The statement of support should be filled just once. Only the deviation from the default referencing option should be highlighted in the reference field of the record template (see also section n. 3.10).

The completed form should be returned by email to notifylibrary@iss.it. CNT and the Notify team will take the responsibility to anonymise, when asked, all stakeholders (CA, hospitals, tissue establishments, blood banks, etc.), and will consider the information provided as confidential data accessible only to Notify experts for editorial work before publication in the Notify Library.

3. PROPOSING A CASE FOR SUBMISSION IN THE NOTIFY LIBRARY: RECORD TEMPLATE

For consistency reasons, and to allow the transfer of information to the editorial tool of the Notify Library website avoiding transcription errors, it is necessary to standardise the way in which the data is presented.

Please refer to the Notify record template (Annex 4.2). The form should be completed in the following fields (*required fields, minimum data set for proposal submission):

3.1 ADVERSE OCCURRENCE DESCRIPTION*

Please enter here a title that describes the type of adverse occurrence you wish to enter, standardising terminology to what you consider most appropriate, using reference dictionaries, such as MESH, wherever possible.

3.2 ADVERSE OCCURRENCE TYPE

please refer to the Adverse Occurrence taxonomy (Annex 4.3) and select the appropriate term for this type of occurrence. If you consider that new categories should be added to the taxonomy for more effective searching, please propose the new category in the NOTES field.

3.3 MPHO TYPE*

Please refer to the MPHO taxonomy (Annex 4.4) and select the appropriate term for this type of substance. If you consider that a new substance type is needed in the taxonomy, please propose the new category in the NOTES field. Where there is a characteristic of the MPHO that is considered important in the occurrence but is not described in the taxonomy (e.g. method of preservation, microbial inactivation or sterilization, etc.) it is very important to include that information in the keywords (see section n. 3.9 below).

3.4 TIME TO DETECTION*

Please enter the time, in minutes, days, months or years from the adverse occurrence to its detection. In case of more than one occurrence is described, please summarise the findings using ranges, averages, etc.

3.5 ALERTING SIGNALS, SYMPTOMS, EVIDENCE OF OCCURRENCE*

Please enter the signs and symptoms that have been described for that occurrence and substance type.

In the case of adverse occurrences that involve 'Risk of Harm' rather than actual harm, you should describe how the occurrence was detected. Spell out any abbreviations, putting the abbreviation in brackets. Standardise terminology to what you consider most appropriate, using reference dictionaries, such as MESH, wherever possible.

3.6 ESTIMATED FREQUENCY*

Please add this information where quantitative data is available and relevant (for example, inserting a number of occurrences per number of interventions). You can also refer to Eurocet and Council of Europe data (for example, SAR rate for particular tissues/ cells per number of transplants of this type of tissue/cell) .

Alternatively, since there is a large variation in epidemiology, in levels of system development and in information available across countries, descriptive information without quantitative data may also have didactic value so please give some idea of frequency from your own experience and knowledge even if imprecise, or use a general term such as 'very rare', 'common', etc.

3.7 DEMONSTRATION OF IMPUTABILITY OR ROOT CAUSE*

Please enter free text to describe the methods used to confirm imputability for this type of occurrence. It will be searchable using keywords. Spell out any abbreviations, putting the abbreviation in brackets. Standardise terminology to what you consider most appropriate, using reference dictionaries, such as MESH, wherever possible. In the case of adverse occurrences that involve 'Risk of Harm' rather than actual harm, you should describe what is considered to be the root cause of the adverse occurrence.

3.8 IMPUTABILITY GRADE*

Select a score for imputability from the "Imputability grade" tab of the record template (provided for consultation also in Annex 4.5). Please note that an imputability score is not applicable for occurrences involving Risk of Harm but no actual harm.

3.9 KEYWORDS

Please type one or more keywords for this type of adverse occurrence associated with this type of substance. Include the substance type, the occurrence description, keywords from the 'alerting signals' or 'demonstration of imputability' fields and any other keyword that you think will be useful for free searching. Standardise terminology to what you consider most appropriate, using

reference dictionaries, such as MESH, wherever possible. Please note that the taxonomy does not describe MPHO in great detail; for example, it does not allow the description of how the MPHO is processed or stored, whether it is virally inactivated or if the record refers to autologous, allogeneic, allogeneic-related donation etc. circumstances. Where characteristics such as these are relevant to the occurrence, and you consider that users might search by these attributes, please ensure that they are entered as keywords. The keywords will be linked to this specific adverse occurrence once the record is published by the Notify team.

3.10 REFERENCES

Refer to your published annual vigilance report or, if your SARE report is not published please give the name of the vigilance programme. Alternatively, for CAs who want their report to stay confidential it will be referenced as: "European Union Annual Vigilance Report, year ..." (see also section n. 2.1 and Annex 4.1).

3.11 EXPERT COMMENTS FOR PUBLICATION

Use this space for didactic comments that will appear on the website when the case is uploaded. All editors are strongly encouraged to use this field for comments on a specific adverse occurrence or substance type in terms of latency, alerting signals, demonstration of imputability, etc., or for any other information that comes from their knowledge and experience. This field will be an additional value of the Notify Library since it represents an invaluable didactic information source. Even if you do not add comments in this section, an editor from an EG may add one which you will subsequently be able to check before publication.

3.12 NOTES

You can use this field as a message board for EG members and/or interaction with the Notify team (text NOT for publication).

The completed form should be returned by email to notifylibrary@iss.it

Please record and share all your comments and practical suggestions from your own experience for improvement to this guide!

4. ANNEXES

4.1 Notify Library - Statement of support

NOTIFY LIBRARY - Statement of Support

Annex A

Name of Organisation:_____

Status of Organisation (circle one):

- Governmental national
- Governmental International
- National Professional Society
- International Professional Society
- Other Non-governmental Organisation

Mission/Key Objectives of the Organisation

_____
_____
_____
_____
_____

On behalf of the Organization named above, I declare our support for the Notify Project in its objective to collect and share didactic information on adverse outcomes in transplantation, transfusion and assisted reproduction with the aim of improving safety and quality in these fields.

As we share this objective, we will:

1. provide expertise, as and when available, to help in the identification, review and editing of documented serious adverse reactions and events for inclusion in the Notify Library website (www.notifylibrary.org) hosted by the Italian National Transplant Organization (WHO Collaborating Centre for Vigilance of Cells, Tissues and Organs);
2. disseminate the Notify Library tool among stakeholders (e.g. by putting a link on our website);
3. give permission for the inclusion of our name and logo on the Notify Library homepage to indicate our support for the initiative. YES ☐ NO ☐

It is noted that this statement does not extend to the provision of vigilance data or cases from our national vigilance system to the Notify Library.
Regarding the provision of such data:

☐ **We give our permission for the publication of the provided didactic cases available on our National Vigilance Report in the Notify Library;**
☐ **We wish that our National Vigilance Report stays confidential and that all the provided cases are referenced with a generic term, such as "CA EURO/AMRO/SEARO .. etc for the year..." in order to define the WHO Region's origin and guarantee confidentiality[1].**

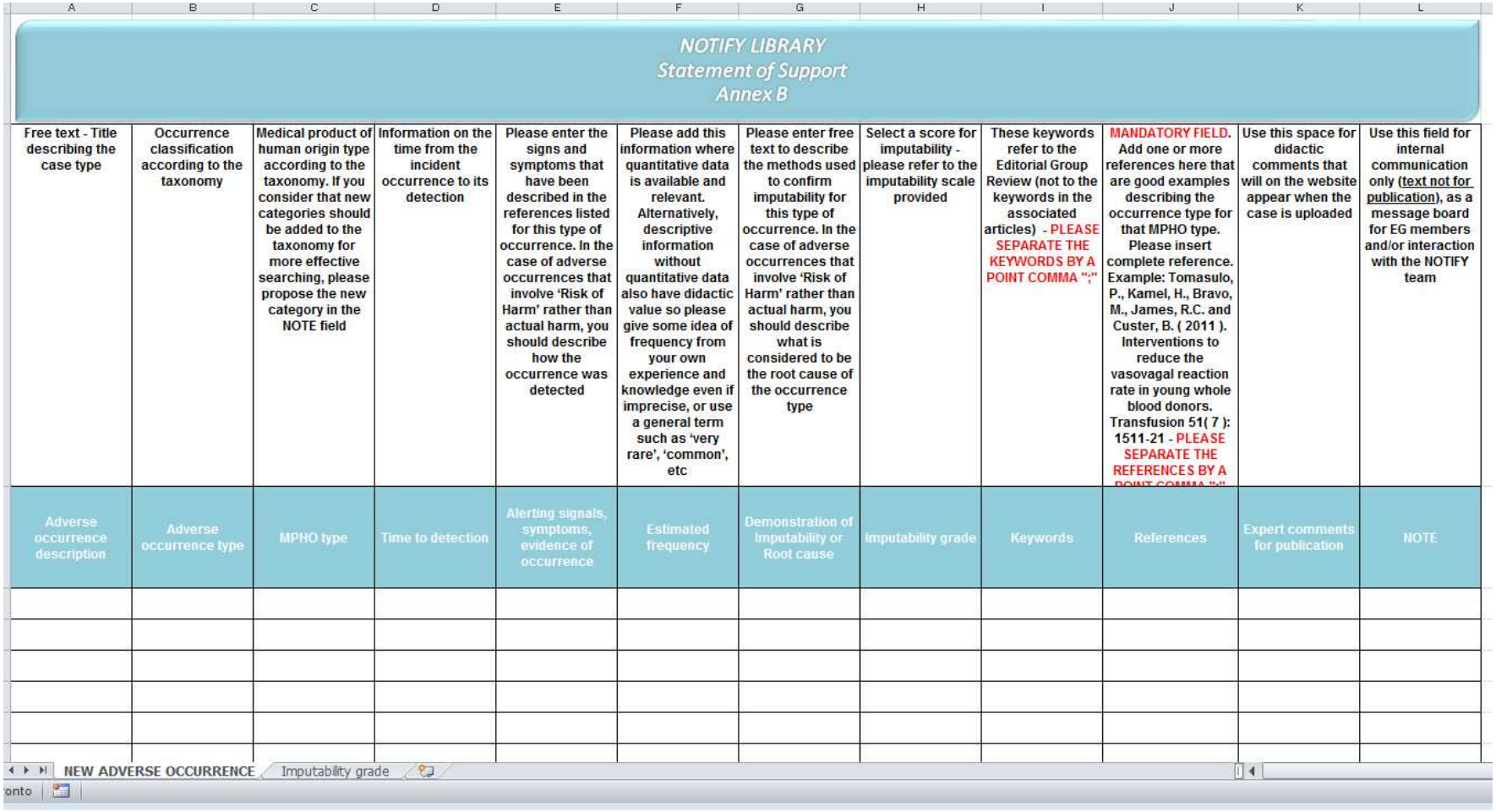
CONTACT PERSON WHO WILL FILL IN Annex A and B

Name:
Surname:
Role in the organization:
Signature:
Date:

PLEASE RETURN THE COMPLETED FORM BY EMAIL TO NOTIFYLIBRARY@ISS.IT

[1] For European Competent Authorities who want their report to stay confidential it will be referenced as: "European Union Annual Vigilance Report, year ..."

4.2 Notify Library - Record template



NOTIFY LIBRARY
Statement of Support
Annex B

Free text - Title describing the case type	Occurrence classification according to the taxonomy	Medical product of human origin type according to the taxonomy. If you consider that new categories should be added to the taxonomy for more effective searching, please propose the new category in the NOTE field	Information on the time from the incident occurrence to its detection	Please enter the signs and symptoms that have been described in the references listed for this type of occurrence. In the case of adverse occurrences that involve 'Risk of Harm' rather than actual harm, you should describe how the occurrence was detected	Please add this information where quantitative data is available and relevant. Alternatively, descriptive information without quantitative data also have didactic value so please give some idea of frequency from your own experience and knowledge even if imprecise, or use a general term such as 'very rare', 'common', etc	Please enter free text to describe the methods used to confirm imputability for this type of occurrence. In the case of adverse occurrences that involve 'Risk of Harm' rather than actual harm, you should describe what is considered to be the root cause of the occurrence type	Select a score for imputability - please refer to the imputability scale provided	These keywords refer to the Editorial Group Review (not to the keywords in the associated articles) - PLEASE SEPARATE THE KEYWORDS BY A POINT COMMA ";"	MANDATORY FIELD. Add one or more references here that are good examples describing the occurrence type for that MPHO type. Please insert complete reference. Example: Tomasulo, P., Kamel, H., Bravo, M., James, R.C. and Custer, B. (2011). Interventions to reduce the vasovagal reaction rate in young whole blood donors. Transfusion 51(7): 1511-21 - PLEASE SEPARATE THE REFERENCES BY A	Use this space for didactic comments that will on the website appear when the case is uploaded	Use this field for internal communication only (text not for publication), as a message board for EG members and/or interaction with the NOTIFY team
Adverse occurrence description	**Adverse occurrence type**	**MPHO type**	**Time to detection**	**Alerting signals, symptoms, evidence of occurrence**	**Estimated frequency**	**Demonstration of Imputability or Root cause**	**Imputability grade**	**Keywords**	**References**	**Expert comments for publication**	**NOTE**

NEW ADVERSE OCCURRENCE | Imputability grade

4.3 Notify Library - Adverse occurrence taxonomy

ADVERSE OCCURRENCE TAXONOMY			
LEVEL 1	**LEVEL 2**	**LEVEL 3**	**LEVEL 4**
Harm to a recipient	**Infection**	Viral	**HIV**
			HBV
			HCV
			HTLV
			West Nile Virus
			Influenza virus
			CMV
			LCMV
			EBV
			HEV
			Arenavirus
			Dengue
			HSV
			Rabies
			Parvovirus B19
		Bacterial	Acinetobacter
			Alcaligenes
			Bacillus
			Bacteroides
			Bartonella
			Brucella
			Citrobacter
			Chlamydia
			Clostridium
			Escherichia
			Elizabethkingia
			Enterobacter
			Enterococcus
			Hafnia
			Klebsiella
			Morganella
			Mycobacterium
			Mycoplasma
			Oerskovia
			Orientia
			Propionibacterium
			Proteus
			Pseudomonas
			Serratia
			Staphylococcus
			Stenotrophomonas
			Streptococcus

			Treponema
			Veillonella
		Fungal	Acremonium
			Apophysomyces
			Arthrographis
			Aspergillus
			Candida
			Coccidioides
			Cryptococcus
			Histoplasma
			Paecilomyces
			Rhodotorula
		Prion	CJD
			vCJD
		Parasitic	Acanthamoeba
			Balamuthia
			Clonorchis
			Echinococcus
			Plasmodium
			Schistosoma
			Strongyloides
			Toxoplasma
			Trypanosoma
			Wuchereria
		Type not specified	
	Malignancy	Breast Cancer	
		CNS neoplasms	
		Colo-rectal carcinoma	
		Choriocarcinoma	
		Liver Cancer	
		Haematopoietic	
		Lung	
		Melanoma	
		Oesophageal	
		Oro-pharyngeal	
		Ovarian	
		Pancreatic	
		Prostate	
		Renal cell	
		Sarcoma	
		Thyroid	
		Neuroendocrine	
		Angiosarcoma	
		Urothelial tumor	
	Non-infectious, Non-malignant transmissions	Alloimmune	
		Autoimmune	
		Metabolic	
		Genetic	
		Hypersensitivity/allergy	

	Immunological complications	TRALI	
		Allergic Reaction	
		Acute Hemolytic Reaction	
		Delayed Hemolytic Reaction	
		Delayed Serologic Reaction	
		Graft versus Host Disease	
		Post Transfusion Purpura (PTP)	
		Rejection	
		IgA deficiency	
		Detrimental immunization	ABO immunisation
			Rh immunisation
			HLA immunisation
	Miscellaneous complications	Hypotensive Reaction	
		Hypertensive Reaction	
		Acute Hemolytic Reaction - non-immune	
		Delayed Hemolytic Reaction - non-immune	
		TACO	
		TAD	
		Febrile Reaction	
		Toxicity	Citrate
			Potassium (hyperkalemia)
			DMSO
			Ethlene oxide
		Hemosiderosis	
		Graft failure	
		Delayed engraftment	
		Inappropriate clinical application	Insufficient MPHO use
			Eccessive MPHO use
		Undue exposure to risk/intervention	
		Surgical site complications	
		Catheter related complications	
		Pulmonary complications	
		Cardiovascular complications	
		Neurological complications	
Harm to a donor	**Infection**		
	Malignancy		
	Drug related reactions	Ovarian Hyperstimulation Syndrome	
		GCSF-related	
	Vasovagal Reactions		
	Allergic reaction	Local	
		Systemic	
		Anaphylaxis	
	Toxicity	Citrate	
		ACD	

	Undue exposure to risk/intervention	
	Excessive collection/removal	
	Embolic Complications	Air embolism
		Fat embolism
		Thromboembolism
	Miscellaneous complications	Cardiovascular
		Neurological
		Immunological
		Metabolic
		Insertion of needle
		Surgical site
		Psychological
		Catheterization/Intubation
		Gastrointestinal
		Pulmonary
		Anesthetic agents
	Procurement outside legal framework	
Harm to a fetus or offspring	**Genetic**	
Risk of harm	**Loss**	Loss of highly matched or autologous MPHO
		Loss of suitable organ(s)
		Loss of large quantity of unmatched MPHO
	Mix-up	Gamete mix-up
		Embryo mix-up
		Incorrect MPHO applied - no harm
	Unsuitable MPHO released for clinical use - no harm	
	Wrong blood in tube - product not transfused	

4.4 Notify Library - MPHO taxonomy

MPHO (Medical Products of Human Origin) TAXONOMY			
LEVEL 1	**LEVEL 2**	**LEVEL 3**	**LEVEL 4**
MPHO	**Organs**	Liver	
		Heart	
		Kidney	
		Lung	
		Pancreas	
		Small bowel	
		Combined	Heart lung
			Kidney pancreas
			Multivisceral
		Composite tissue grafts	Hand
			Face
		Type not specified	
	Tissues	Musculoskeletal	Bone
			Cartilage
			Osteochondral
			Tendon and ligament
			Meniscus
		Cardiovascular	Blood vessels
			Conduit
			Heart valves
			Pericardium
		Ocular	Conjunctiva
			Cornea
			Limbal tissue
			Sclera
		Amniotic membrane	
		Other fetal membranes	
		Dura mater	
		Larynx	
		Nerve	
		Parathyroiid glands	
		Placenta	
		Skin	
		Adipose tissue	
		Trachea	
		Umbilical cord tissue	
	Cells	HPC (hematopoietic progenitor cell)	Marrow
			Apheresis
			Cord blood
			Whole blood
		Leukocytes	
		Chondrocytes	
		Hepatocytes	
		Pancreatic Islets	

		Limbal cells
		Fibroblasts
		Adipocytes
		T-lymphocytes
		Keratinoctyes
		Mesenchymal stem cells
		Genetically modified cells
	Blood	Whole blood
		Red blood cells
		Platelets
		Plasma
		Cryoprecipitate
		Granulocytes
	Reproductive	Embryo
		Oocyte
		Ovarian tissue
		Testicular tissue
		Sperm
		Combined
	Other	Milk
		Fecal microbiota
		Topical products of human origin
	MPHO-derived medicinal products	Plasma derivates
		Cell derived medicinal products
		Tissue derived medicinal products
		Tissue and cell derived medicinal products

4.5 Imputability grade

IMPUTABILITY GRADE	ADAPTED FROM EUSTITE-SOHO V&S	CRITERIA FOR INFECTIOUS AND MALIGNANT TRANSMISSIONS ADAPTED FROM DTAC	ADAPTED FROM SOHO V&S IN ASSISTED REPRODUCTIVE TECNOLOGIES
Not Assessable	Insufficient data for imputability assessment	Insufficient data for imputability assessment	Insufficient data for imputability assessment
Excluded	Conclusive evidence beyond reasonable doubt for attributing an adverse reaction to alternative causes.	Suspected transmission and fulfillment of at least one of the following conditions: - Clear evidence of an alternative cause; - The appropriate diagnostic tests performed have failed to document infection by the same pathogen in any recipient from the same donor; Laboratory evidence that the recipient was infected with the same pathogen or had a tumor before the application of organs, tissues or cells.	Conclusive evidence beyond reasonable doubt for attributing to alternative causes than the ART process
Possible	The evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissues/cells, to the donation process, or to alternative causes	Suspected transmission and: - Laboratory evidence of the pathogen or tumor in a single recipient, or Suspected transmission and: - Laboratory evidence of the pathogen or tumor in a single recipient or - Data suggest a transmission but are insufficient to confirm it.	Evidence is indeterminate
Likely/Probable	The evidence is clearly in favor of attributing the adverse reaction to the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)	The following two conditions are met: - Suspected transmission and - Laboratory evidence of the pathogen or the tumor in a recipient. And it meets at least one of the following conditions: - Laboratory evidence of the same pathogen or tumor in other recipients; - Laboratory evidence of the same pathogen or tumor in the donor; If there is pre-transplant laboratory evidence, such evidence must indicate that the same recipient was negative for the pathogen involved before transplantation.	Evidence in favour of attributing to the ART process
Definite/Certain; Proven	The evidence is conclusive beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues/cells (for recipients) or to the donation process (for donors)	All the following conditions are met: - Suspected transmission; - Laboratory evidence of the pathogen or the tumor in a recipient; - Laboratory evidence of the same pathogen or tumor in other recipients (if multiple recipients); - Laboratory evidence of the same pathogen or tumor in the donor; - If there is a pre-transplant laboratory evidence, it should be noted that the same recipient was negative for the pathogen before transplantation	Conclusive evidence beyond reasonable doubt for attributing to the ART process
SOHO V&S Guidance for Competent Authorities: Communication and Investigation of Serious Adverse Events and Reactions associated with Human Tissues and Cells			
http://www.notifylibrary.org/sites/default/files/SOHO%20V%26S%20Communication%20and%20Investigation%20Guidance.pdf			
Uniform Definitions for Donor-Derived Infectious Disease Transmissions in Solid Organ Transplantation Christian Garzoni and Michael G. Ison Transplantation • Volume 92, Number 12, December 27, 2011			
SOHO V&S in Assisted Reproductive Tecnologies in the European Union (WP5 Deliverable 5)			

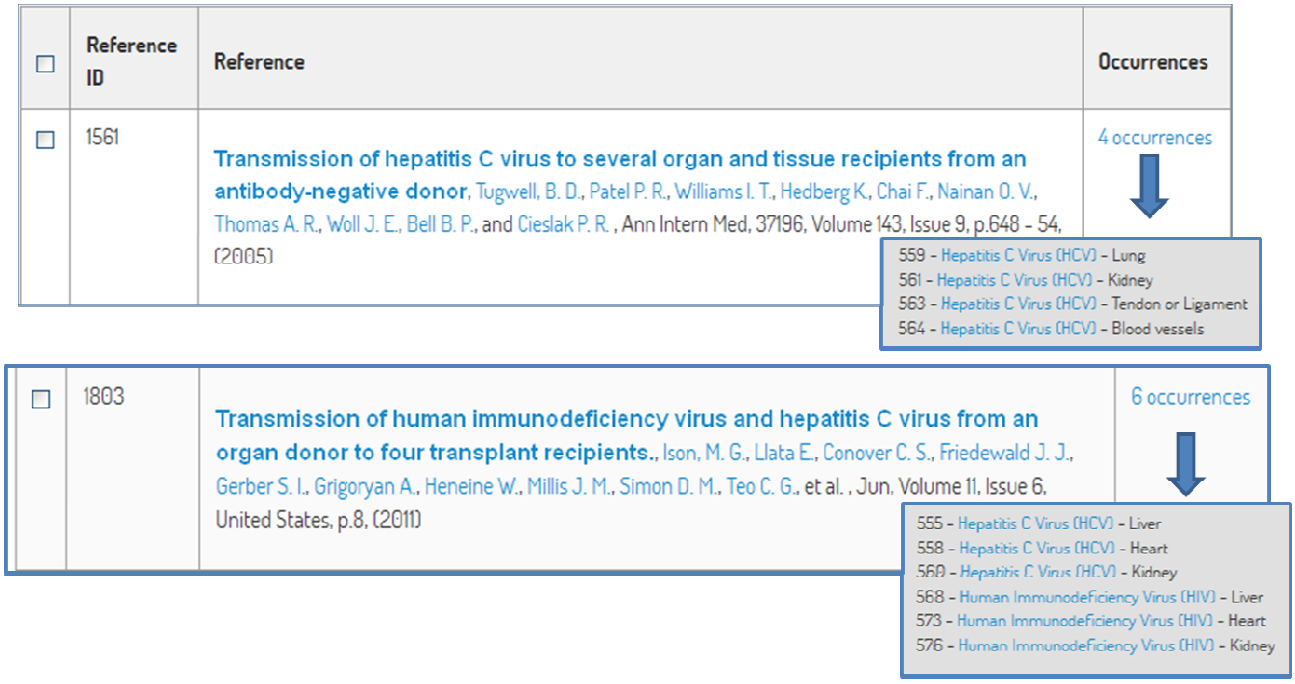
4.6 Case examples

1683	**Adverse occurrence description:** Subject review: Donors with melanoma history and risk to ocular tissue recipients **Adverse occurrence type:** Risk of harm => Other **MPHO type:** Tissues => Ocular => Cornea **Time to detection:** 2 months **Alerting signals, symptoms, evidence of occurrence:** Recipient developed ocular melanoma within two months of surgery. **Estimated frequency:** Rare: Review article written in response to single case report of melanoma transmission following keratolimbal allograft. No existing reports in literature documenting melanoma transmission from corneal transplant. Based on the case report a moratorium on use of ocular tissue from donors with melanoma (restricted from all use) and donors with metastatic solid tumors (not to be released for use of vascular components) was issued in February 2016 to be reviewed by the Eye Bank Association of America in October 2016. **Demonstration of Imputability or Root cause:** Donor had history of malignant melanoma. **Imputability grade:** **Expert comments for publication:** Article was written as a review at the time of active discussion regarding the appropriate response to the cited case report. It is pointed out that donors with solid tumors constitute 38-48% of the ocular donor pool. In the case of melanoma, micrometastases raise concern for the possibility of transmission, but in practice this has not been seen. Possible factors contributing to the absence of known transmissions include the avascular nature of cornea and absence of immunosuppressive drugs. It is also noted that vascularized ocular components (such as keratolimbal allografts) also require immunosuppression and may have tumor transmission risks more similar to solid organ transplants. The article discusses the need to balance restoring sight and patient safety in the difficult setting of limited available evidence. **Keywords:** cornea transplantation · cornea · melanoma · subject review · keratolimbal · metastasis · exclusion criteria	1 reference

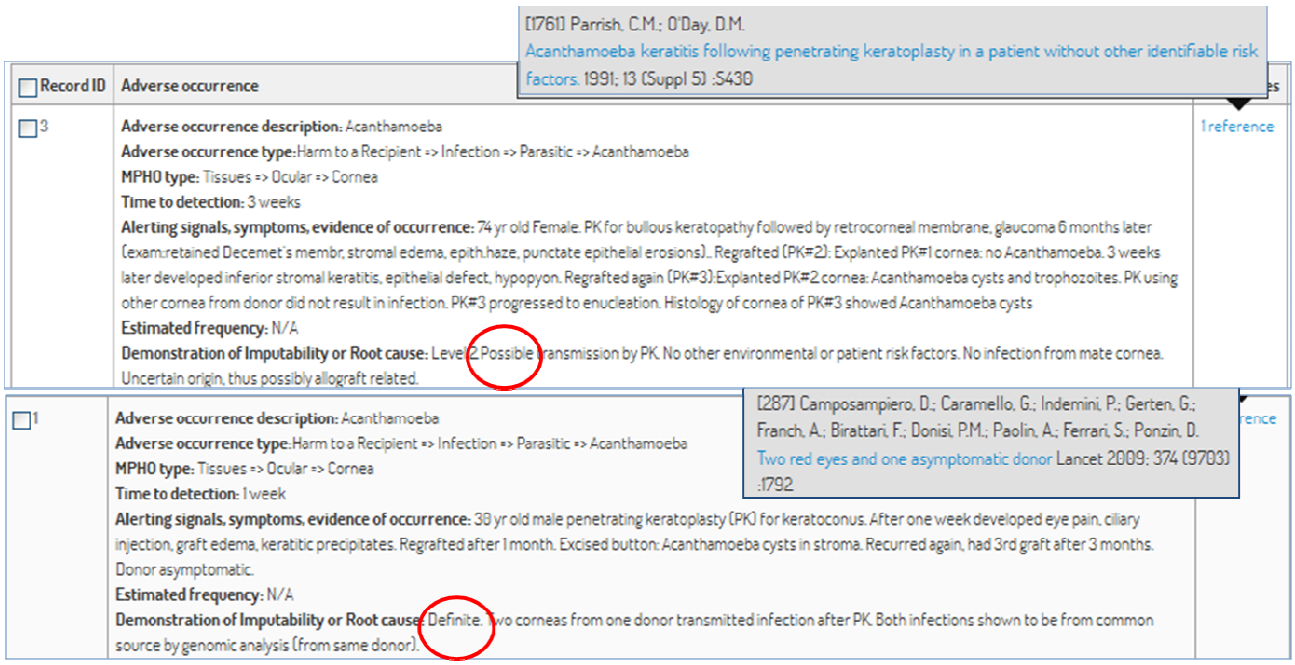
Record ID	Adverse occurrence	References
1705	**Adverse occurrence description:** Babesia duncani **Adverse occurrence type:** Harm to a Recipient => Infection => Parasitic => Babesia **MPHO type:** Blood => Red blood cells **Time to detection:** 139 days **Alerting signals, symptoms, evidence of occurrence:** Immunosuppressed, multi-transfused (over a 10 year time period) recipient with sickle disease, autoinfarcted spleen and several month history of declining health and increasing transfusion requirements, presented with frequent evaluations for weakness, fatigue, shortness of breath and darkening of urine. Laboratory testing showed evidence of hemolysis with elevated bilirubin and reticulocytosis. Eventually he was diagnosed with babesiosis when his blood smears were noted to contact intraerythrocytic parasites and Maltese cross forms in up to 12% of RBCs. Review of previous blood smears showed intraerythrocytic parasites as early as 2 months prior. He was treated with RBC exchange and appropriate antibiotics. CDC investigation showed the source of the infection to be Babesia duncani by DNA sequencing. **Estimated frequency:** Rare: only 3 cases reported in literature (September 2016). **Demonstration of Imputability or Root cause:** Investigation of 38 donors found one donor to be positive with B. duncani IFA, with titers as high as 1:4096. B. duncani was also isolated by inoculating jirds (Mongolian gerbils) with a blood specimen taken more than 18 months after the index donation. Donor was healthy with extensive history of outdoor hiking and mountain biking in Washington, British Columbia, Wyoming, Montana and Idaho. A history of tick bites was confirmed. **Imputability grade:** 3 Definite/Certain/Proven **Expert comments for publication:** This is a rare case of transfusion transmitted Babesia duncani diagnosed 4 months after the implicated transfusion from a donor with known risk factors for tick exposure. Testing of the patient and donor confirmed B. duncani by DNA sequencing (recipient), IFA and inoculation of jirds (donor). **Keywords:** Babesia duncani · RBC (red blood cell) · multiple transfusions · sickle cell disease · hemolysis · IFA (immunofluorescence antibody assay) · DNA sequencing · tick exposure	3 references

1496	**Adverse occurrence description:** Transfer of Selecive IgA Deficiency to a bone marrow recipient **Adverse occurrence type:** Harm to a Recipient => Non-infectious, Non-malignant transmissions => Genetic **MPHO type:** Cells => HPC => Marrow **Time to detection:** 3 months **Alerting signals, symptoms, evidence of occurrence:** Relative lack of specific IgG2 anticarbohydrate antibodies in the donor and the recipient after transplant. IgG2 deficiency is considered as a prognostic marker for permanent lack of IgA. **Estimated frequency:** Rare **Demonstration of Imputability or Root cause:** Bone marrow transplant from HLA matched sibling with selective IgA deficiency, results in IgA deficiency in the recipient. This recipient had normal IgA levels prior to transplant. Both the recipient and donor demonstrated the presence of IgA genes and it was speculated that the IgA deficiency is manifested at stem cell level. **Imputability grade:** 2 Probable **Expert comments for publication:** One of the few published case of transfer of selective IgA deficiency by marrow transplantation.There are other case reports that demonstrate correction of IgA deficiency in a marrow transplant recipient after transplantation from a donor who had no IgA deficiency **Keywords:** IgA deficiency · bone marrow · bone marrow transplantation · stem cell · acquired deficiency	2 references

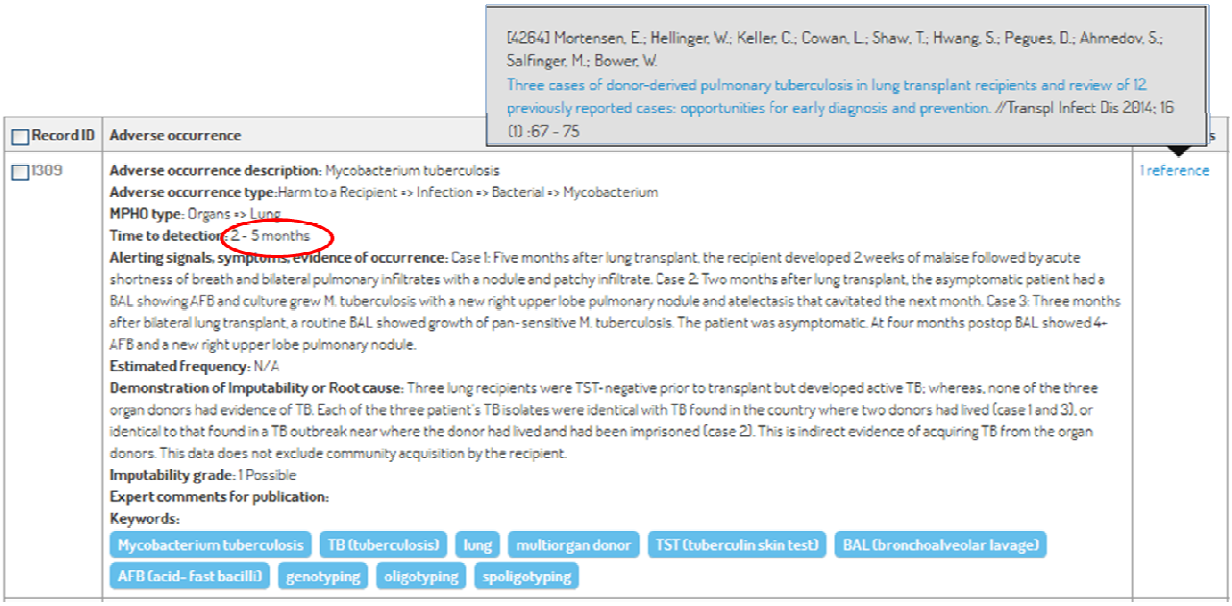
4.6.1 Each record in the Notify Library describes a type of adverse occurrence for one type of substance



4.6.2 CAs submitting records for inclusion in the Notify Library's database should make two records for the same type of occurrence with the same MPHO if they consider that are substantially different from each other in terms of cause, method of confirmation of imputability or any other factor that is considered to have major didactic value.



4.6.3 Where one record describes many cases, the experts should summarise the findings using ranges, averages, etc.



[4264] Mortensen, E.; Hellinger, W.; Keller, C.; Cowan, L.; Shaw, T.; Hwang, S.; Pegues, D.; Ahmedov, S.; Salfinger, M.; Bower, W.
Three cases of donor-derived pulmonary tuberculosis in lung transplant recipients and review of 12 previously reported cases: opportunities for early diagnosis and prevention. //Transpl Infect Dis 2014; 16 (1) :67 - 75

Record ID	Adverse occurrence	
1309	**Adverse occurrence description:** Mycobacterium tuberculosis **Adverse occurrence type:** Harm to a Recipient => Infection => Bacterial => Mycobacterium **MPHO type:** Organs => Lung **Time to detection:** 2 - 5 months **Alerting signals, symptoms, evidence of occurrence:** Case 1: Five months after lung transplant, the recipient developed 2 weeks of malaise followed by acute shortness of breath and bilateral pulmonary infiltrates with a nodule and patchy infiltrate. Case 2: Two months after lung transplant, the asymptomatic patient had a BAL showing AFB and culture grew M. tuberculosis with a new right upper lobe pulmonary nodule and atelectasis that cavitated the next month. Case 3: Three months after bilateral lung transplant, a routine BAL showed growth of pan-sensitive M. tuberculosis. The patient was asymptomatic. At four months postop BAL showed 4+ AFB and a new right upper lobe pulmonary nodule. **Estimated frequency:** N/A **Demonstration of Imputability or Root cause:** Three lung recipients were TST-negative prior to transplant but developed active TB; whereas, none of the three organ donors had evidence of TB. Each of the three patient's TB isolates were identical with TB found in the country where two donors had lived (case 1 and 3), or identical to that found in a TB outbreak near where the donor had lived and had been imprisoned (case 2). This is indirect evidence of acquiring TB from the organ donors. This data does not exclude community acquisition by the recipient. **Imputability grade:** 1 Possible **Expert comments for publication:** **Keywords:** Mycobacterium tuberculosis · TB (tuberculosis) · lung · multiorgan donor · TST (tuberculin skin test) · BAL (bronchoalveolar lavage) · AFB (acid-fast bacilli) · genotyping · oligotyping · spoligotyping	1 reference

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Acute Myeloid Leukemia of Donor Origin After Allogeneic Bone Marrow Transplantation for Precursor T-Cell Acute Lymphoblastic Leukemia: Case Report and Review of the Literature 2006; 81 (3) :7

[666] Hertenstein, B.; Hambach, L.; Bacigalupo, A.; Schmitz, N.; McCann, S.; Slavin, S.; Gratwohl, A.; Ferrant, A.; Elmaagacli, A.; Schwertfeger, R.; Locasciulli, A.; Zander, A.; Bornhauser, M.; Niederwieser, D.; Ruutu, T.
Development of leukemia in donor cells after allogeneic stem cell transplantation--a survey of the European Group for Blood and Marrow Transplantation (EBMT) Haematologica 2005; 90 (7) :969 - 75

Record ID	Adverse occurrence	
681	**Adverse occurrence description:** Acute myeloid leukemia (AML) **Adverse occurrence type:** Harm to a Recipient => Malignancy => Haematopoietic **MPHO type:** Cells => HPC => Marrow **Time to detection:** 17 (4-164) months **Alerting signals, symptoms, evidence of occurrence:** Elevated blood counts; anemia; thrombopenia. 17 (4-164) months from SCT **Estimated frequency:** 7/19489 **Demonstration of Imputability or Root cause:** Case 1: cytogenetics and molecular marker. Case 2: Fluorescence in -situ hybridization (FISH) analysis showed the AML to be of donor origin (i.e., karyotypically female) with an 11q23 (mixed lineage leukemia (MLL) gene) translocation, while the original T-ALL exhibited a male karyotype with abnormalities of chromosomes 6, 8, and a t(10;14)(q24;q11.2). Subsequent molecular short tandem repeat studies confirmed the AML to be of donor origin. **Imputability grade:** **Expert comments for publication:** **Keywords:** cytogenetics · anemia · FISH (fluorescence in situ hybridization) · karyotype · AML (acute myeloid leukemia) · allogeneic · thrombocytopenia	2 references