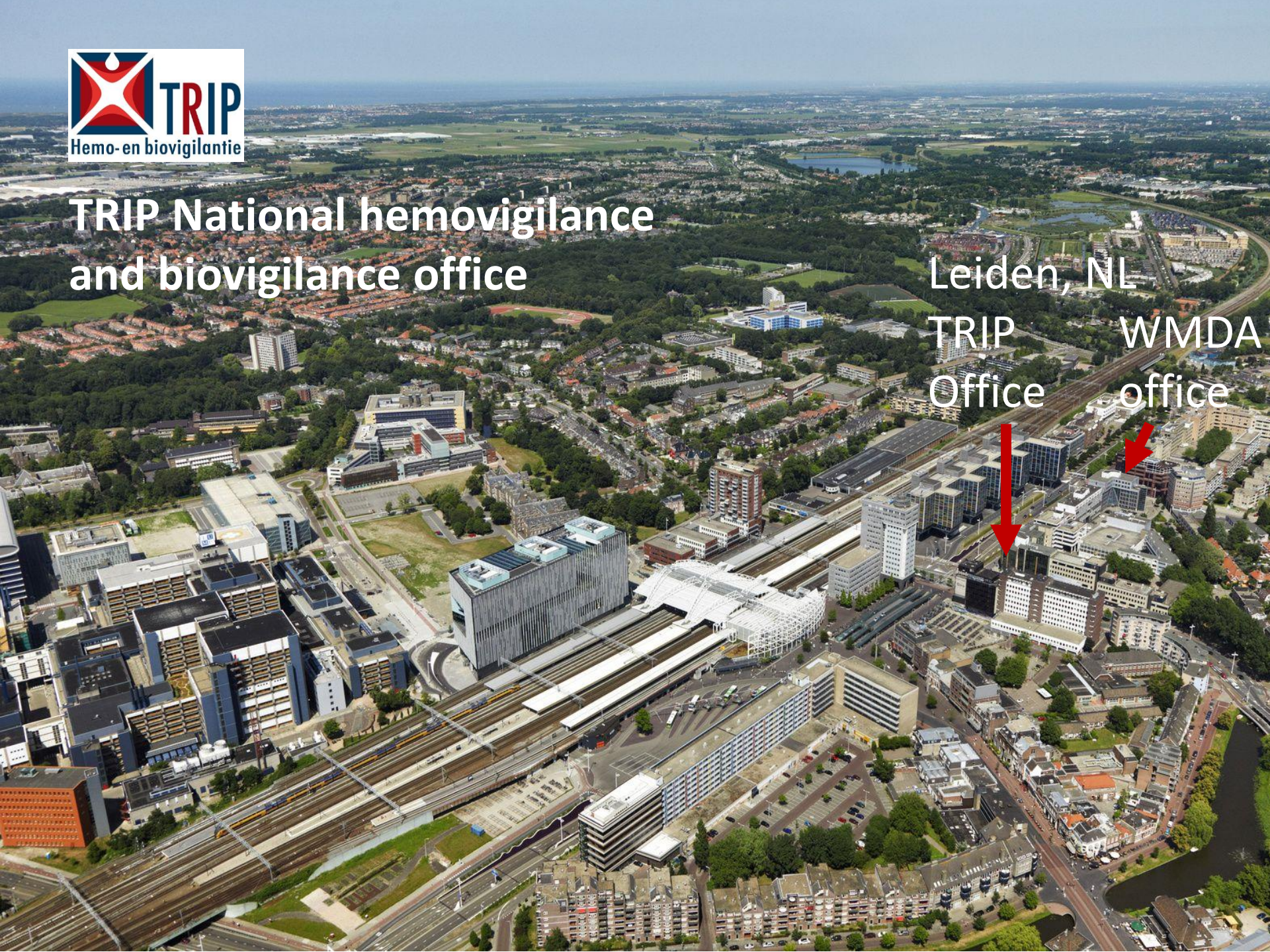
Reporting Adverse Events and Reactions

MDPB education sessions

Mechelen, November 28th 2019

Johanna Wiersum-Osselton, TRIP national medical coordinator

on behalf of Thilo Mengling, chair of the WMDA S(P)EAR Committee

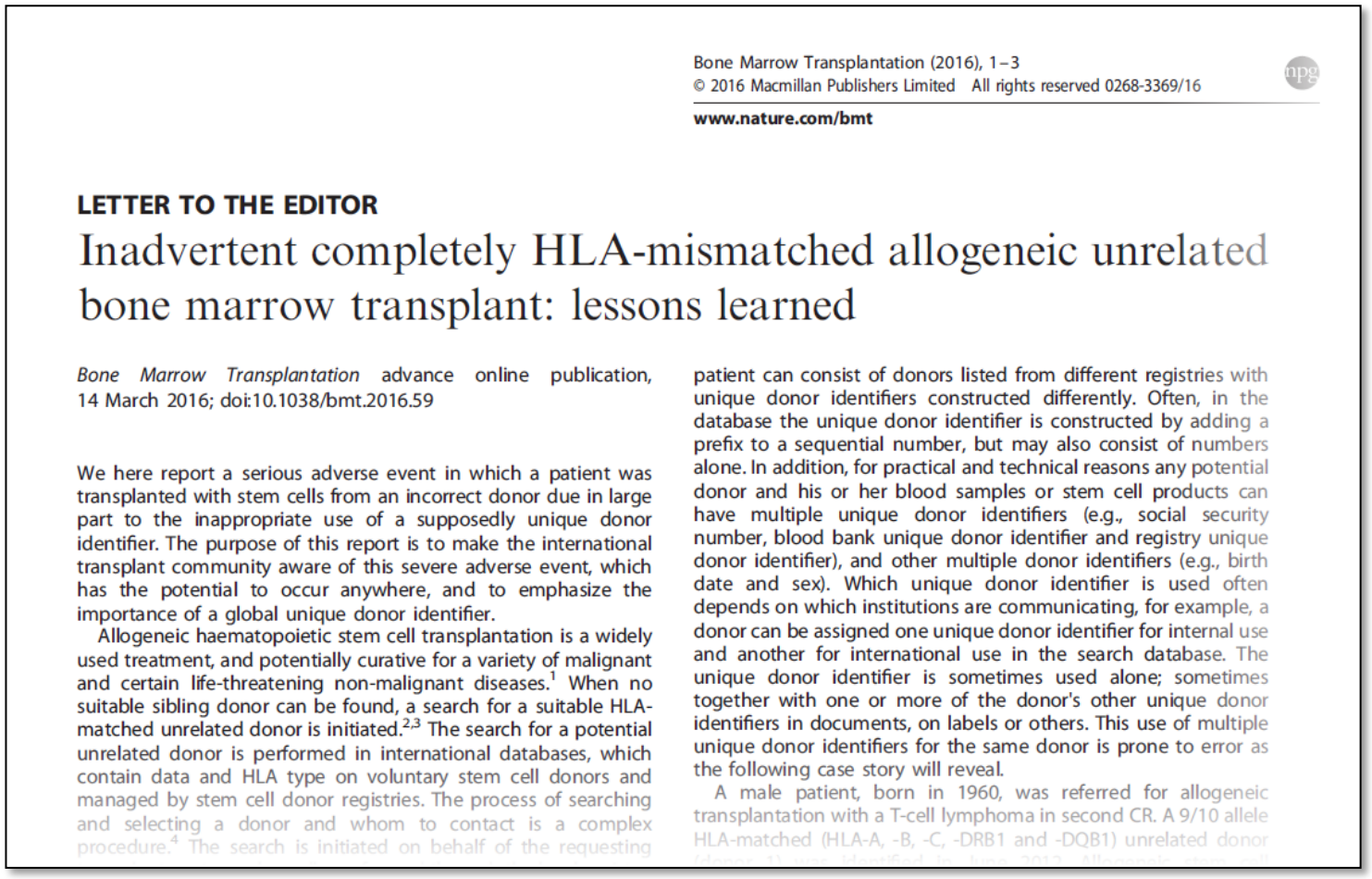

TRIP
Hemo- en biovigilantie
TRIP National hemovigilance and biovigilance office
Leiden, NL
TRIP Office
WMDA office

Today's topics

- The Wrong Donor Incident
- Role of WMDA S(P)EAR Committee
- Improved S(P)EAR Reporting System 2019
- Annual Report 2018
- Practical Examples
- Take-Home Messages

Dr Thilo Mengling

The Wrong Donor Incident



Bone Marrow Transplantation (2016), 1–3

www.nature.com/bmt

LETTER TO THE EDITOR

Inadvertent completely HLA-mismatched allogeneic unrelated bone marrow transplant: lessons learned

Bone Marrow Transplantation advance online publication, 14 March 2016; doi:10.1038/bmt.2016.59

We here report a serious adverse event in which a patient was transplanted with stem cells from an incorrect donor due in large part to the inappropriate use of a supposedly unique donor identifier. The purpose of this report is to make the international transplant community aware of this severe adverse event, which has the potential to occur anywhere, and to emphasize the importance of a global unique donor identifier.

Allogeneic haematopoietic stem cell transplantation is a widely used treatment, and potentially curative for a variety of malignant and certain life-threatening non-malignant diseases.[1] When no suitable sibling donor can be found, a search for a suitable HLA-matched unrelated donor is initiated.[2,3] The search for a potential unrelated donor is performed in international databases, which contain data and HLA type on voluntary stem cell donors and managed by stem cell donor registries. The process of searching and selecting a donor and whom to contact is a complex procedure.[4] The search is initiated on behalf of the requesting patient can consist of donors listed from different registries with unique donor identifiers constructed differently. Often, in the database the unique donor identifier is constructed by adding a prefix to a sequential number, but may also consist of numbers alone. In addition, for practical and technical reasons any potential donor and his or her blood samples or stem cell products can have multiple unique donor identifiers (e.g., social security number, blood bank unique donor identifier and registry unique donor identifier), and other multiple donor identifiers (e.g., birth date and sex). Which unique donor identifier is used often depends on which institutions are communicating, for example, a donor can be assigned one unique donor identifier for internal use and another for international use in the search database. The unique donor identifier is sometimes used alone; sometimes together with one or more of the donor's other unique donor identifiers in documents, on labels or others. This use of multiple unique donor identifiers for the same donor is prone to error as the following case story will reveal.

A male patient, born in 1960, was referred for allogeneic transplantation with a T-cell lymphoma in second CR. A 9/10 allele HLA-matched (HLA-A, -B, -C, -DRB1 and -DQB1) unrelated donor

Inadvertent completely HLA-mismatched allogeneic unrelated bone marrow transplant: lessons learned
Sorensen BS; BMT 51 https://doi.org/10.1038/bmt.2016.59

Patient M, *1960
T-cell lymphoma in second CR

WU Request sent to DC2, for DID 12345678*

CT

Donor 2 from Donor Center 2
0/10 matched URD, DID **B**12345678*

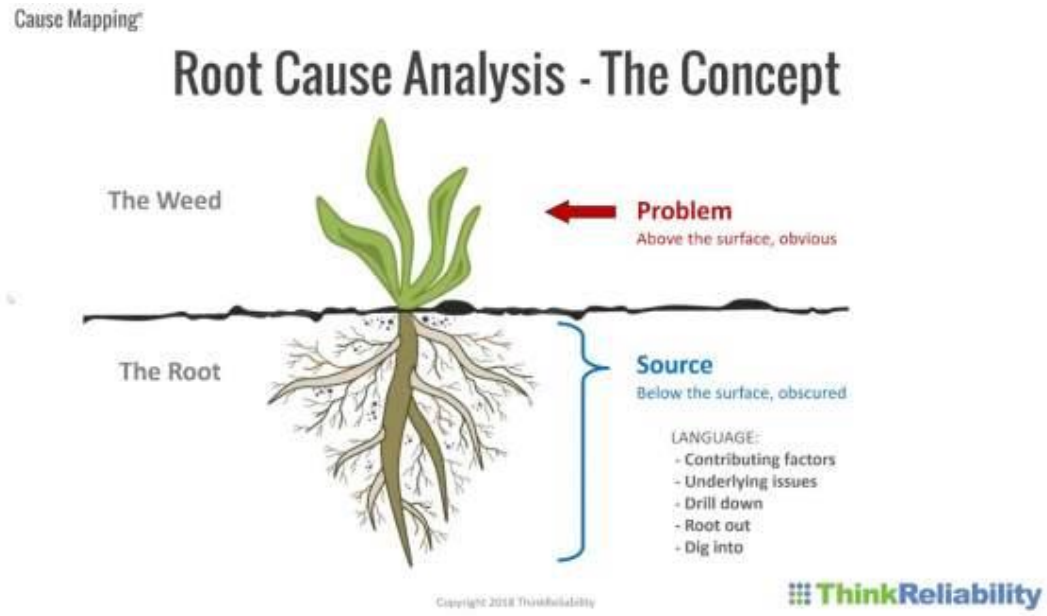
Donor 1 from Donor Center 1
9/10 matched URD, DID **A**12345678*

(* example)

Problem or incident

Root Cause Analysis

Root cause analysis (RCA) is a method of problem solving used for identifying the root causes of faults or problems. A factor is considered a root cause if removal thereof from the problem-fault-sequence prevents the final undesirable event from recurring; whereas a causal factor is one that affects an event's outcome, but is not a root cause.



Root cause analysis

The five why's in wrong donor transplanted

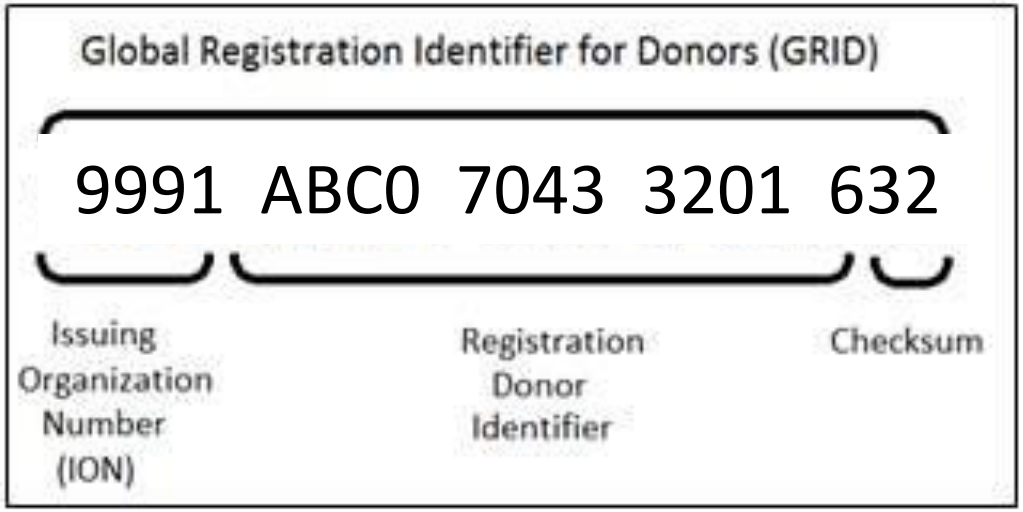
1. Why was the wrong donor transplanted?
   Because the wrong donor was requested.
2. Why was the wrong donor requested?
   Because the wrong ID was sent to the wrong center
3. Why was the wrong ID used?
   Because it was unclear that it was incomplete
   (ICT system truncated the ID)
4. Why was it sent to the wrong center?
   Because the incomplete ID did not indicate which center the donor was from
5. Why was it unclear that it was incomplete?
   Because there was no mandatory format

Global donor identifier (GRID)

With over 30 million donors worldwide, it is important to have a system that uniquely identifies potential donors on a global scale. This helps to:

- reduce the risk of misidentification of donors or their donations due to the lack of global uniqueness of identifiers;
- provide a standard machine-readable format (barcodes) that can be used by computer systems; and
- define a standard presentation for the human-readable identifier.

To this end, the WMDA has developed a unique global donor identifier to ensure secure, reliable and unambiguous assignment of donors: the Global Registration Identifier for Donors (GRID).



Terminology

DIRECTIVE 2004/23/EC

'**serious adverse reaction**' means an **unintended response**, including a communicable disease, **in the donor or in the recipient** associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity;

WMDA terminology: Harm to a Donor / Recipient

'**serious adverse event**' means **any untoward occurrence** associated with the procurement, testing, processing, storage and distribution of tissues and cells **that might lead** to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity;

WMDA terminology: Risk of Harm

All EU documents at https://ec.europa.eu/health/blood_tissues_organs/tissues_en
Aligned with the definitions of the WHO project 'Notify'.

Terminology

‘**resilience**’ is the ability (of a person or system) to cope with errors or crises and maintain functionality. To improve resilience, possible risks and challenges need to be identified and appropriate measurement implemented.

- ⇨ The GRID checksum prevents consequences of a simple typing error
- ⇨ GRID cannot prevent requesting the wrong donor from a registry, as long as the DID is technically correct
- ⇨ Taking that into account, automated HLA checks between recipient and requested donor were established

Role of WMDA S(P)EAR Committee

Concerns against Reporting

1. Fear of reputational damage to
   - Own institution
   - Stem cell donation in general

2. Malpractice liability; audits

3. Resources
   - Capacities for thorough investigations
   - Bureaucratic workload

Reporting Serious Adverse Events and Reactions to the WMDA

Purpose and scope

To collect and analyse information on recipient and donor Serious Adverse Events (SAE) and Severe Adverse Reactions (SAR) which affect donors and/or products from all WMDA regular member organisations.

To have in place a rapid alert system for disseminating information on SAE/R to all WMDA regular members and of the international community in contact with allogeneic donors and patients.

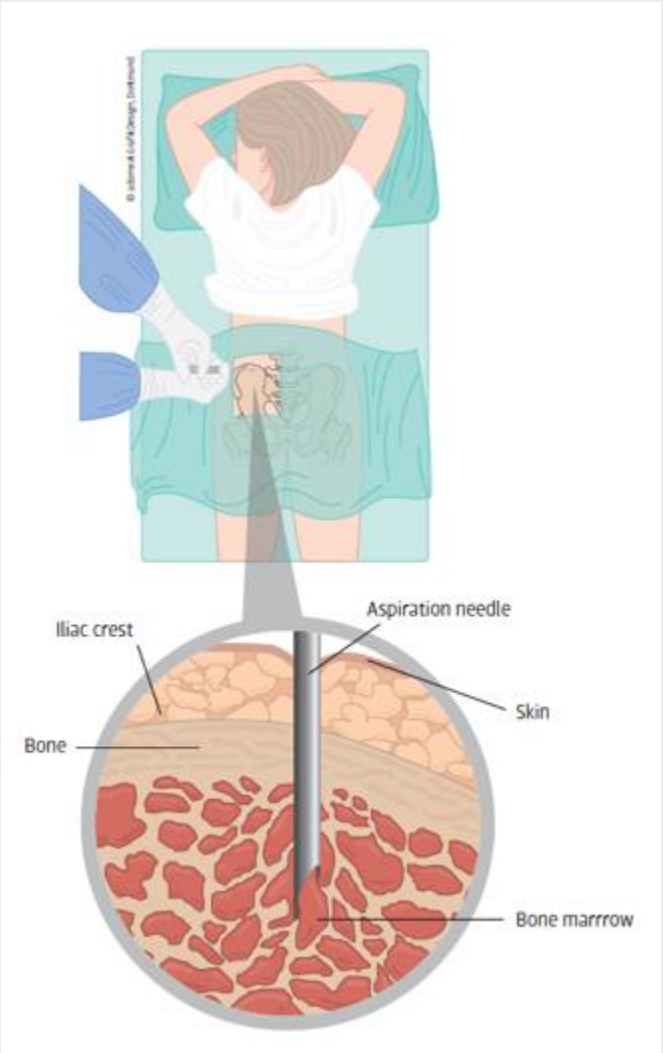
20170517-SEAR-S(P)EAR SOP

Why Serious Adverse Events and Reactions Reporting on a global scale?

- As 50% of the HPC donations cross international border; donor and patient safety requires a global strategy;
- Global data collection enhances the likelihood of recognition of relatively rare adverse events;
- In continuity of analysis a global institutional memory can be developed.

Needle breakage during Bone Marrow Donation

- Breaking of the bone marrow extraction needle during collection
- It was successfully removed during the same intervention causing no acute or chronic secondary damage
- Three incidents took place from 10.000 bone marrow extractions



Collect and analyse

Collect as many cases as possible to

- Investigate improbable, rare and/or long term consequences of donation or transplantation

Analysis of cases by **expert committee**

- Rapid alert?
- Is all relevant information provided?
- Imputability (Relatedness to donation, transplantation)
- Similar cases, higher than expected incidence?
- Educational value?
- Implications for standards, suitability criteria, etc.?
- Involving other WMDA working groups (standards, quality, cord blood)?

S(P)EAR Committee (2019)

- Thilo Mengling – DKMS Germany, ***Chair***
- Ann Woolfrey – Fred Hutchinson Cancer Research Center
- Chloe Anthias – Anthony Nolan *(**WG Medical**)*
- Danielli Cristina Muniz de Oliveira – REDOME
- Elizabeth O'Flaherty – Australian Bone Marrow Donor Registry *(**Transport**)*
- Heidi Elmoazzen – Canadian Blood Services OneMatch *(**WG Cord Blood**)*
- Jeff Szer – Australian Bone Marrow Donor Registry
- John Miller – NMDP
- Mirjam Fechter – Matchis, ***WMDA medical consultant***
- Rachel Pawson – NHS
- Tigran Torosian – DKMS Poland

- Brian Lindberg – NMDP *(**Legal expert,** non-voting member)*
- Lydia Foeken – WMDA *(non-voting member)*
- Monique Jöris – WMDA (***WMDA office)***
- Esther Pustjens – WMDA (***WMDA office)***

Objectives for S(P)EAR Reporting

1. Collect and analyze adverse events and reactions in ‘reasonably possible’ connection to stem cell donation **to improve donor and recipient safety**

2. Participation in S(P)EAR reporting **in no way replaces** or removes the need for organisations to comply with the **legal reporting requirements** of their national/competent authorities or other regulatory or pharmaceutical bodies, but: Existence of a worldwide database is an **important framework** for evaluation of locally reported rare incidents

3. Register severe events as long as connection to stem cell donation cannot be ruled out **to fulfill organizational or professional requirements**
    - WBMT
    - NOTIFY / WHO: relevant SEAR are forwarded by WMDA
    - EU cell & tissue directives: stakeholder in re-evaluation
    - Insurances
    - WMDA (re-)accreditation

WMDA Standards 2017

9.04
SAR (either short- or long-term) affecting donors undergoing collection of HSC and/or cellular product must be submitted to a WMDA international centralised database of such events (S(P)EAR).

Guidance

The registry's procedures must include a process for reporting serious adverse events and reactions affecting donors to the WMDA Serious Adverse Events Registry in accordance with the requirements outlined in the WMDA SOP on the WMDA Share website.

Provide with application

Evidence that it takes part to the S(P)EAR programme by providing a completed, anonymised form.

This aspect will be looked at during the on-site audit

Feedback to Community

1) Disseminate Rapid Alerts
2) Share adverse events and reactions
   - Educational SPEARs as rubric in *Stem Cell Matters* (WMDA newsletter)
   - Annual reports
   - WMDA meetings
   - Publications
3) Adjust standards and procedures
4) Response to individual questions
   - How often...?
   - Have you ever seen...?
   - Do I need to report...?
5) New: Direct feedback to reporter about the report (imputability, category)

Rapid alerts

- August 2011

  Fatal outcome unrelated donor after **CVC**

  ➡ Standards about use of CVC to registries

- May 2013 “Clinical alert”

  Fatal outcome after two **large volume RBC-replete CBUs** given by the thaw and infuse method in the context of patients with prior cardiac risk factors

  ➡ EBMT, APBMT, ASBMT and EMBMT

- November 2013

  Use of **incomplete donor ID** by TC led to transplant of 0/10 matched donor stem cells

  ➡ GRID

Improved S(P)EAR Reporting System 2019

matching donors • serving patients

New Adverse Events Reporting System

Status

- Robust test phase successfully completed 2018/ Q1 2019 ✓
- Presentation and workshop during WMDA Spring Meeting 2019 ✓
- Pilot phase until 30/06/2019 ✓
- Go-live and first 50 reports without *critical* flaws Q3 2019 ✓
- S(P)EAR Committee Meeting Prague 25/26th Sept 2019 to refine final requirements and changes ✓
- ToDo: statistical tools, minor bug-fixing

New Adverse Events Reporting System

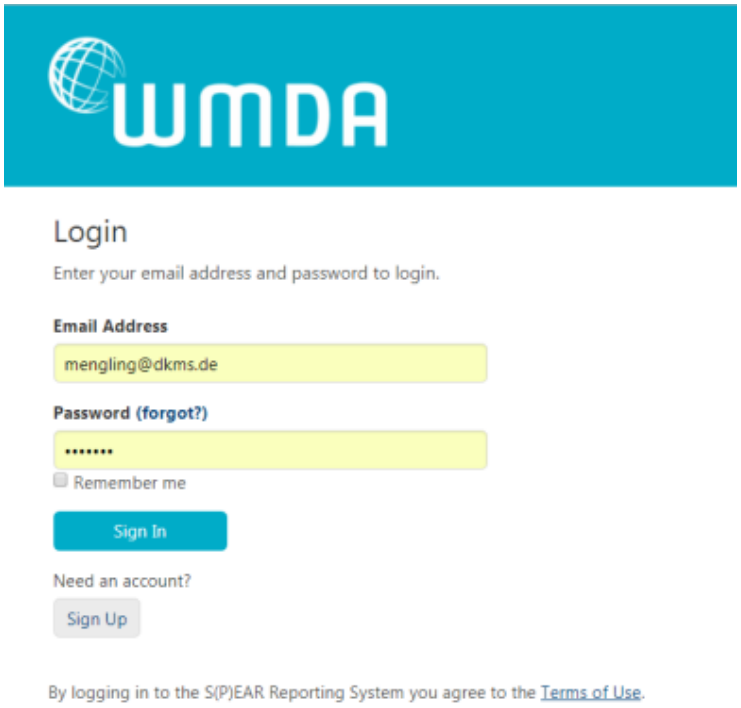
Key features

- Personal log–in
- Dashboard with **all** reports from own organisation (all users)
- Reports are submitted along the reporting line *within* the system
- Focus on events / reactions in **close connection** to stem cell collection
- *Substantially* less burdensome reporting for late events
- Analysis and statistics will be available within the system, not only for WMDA but also for users (to be developed)

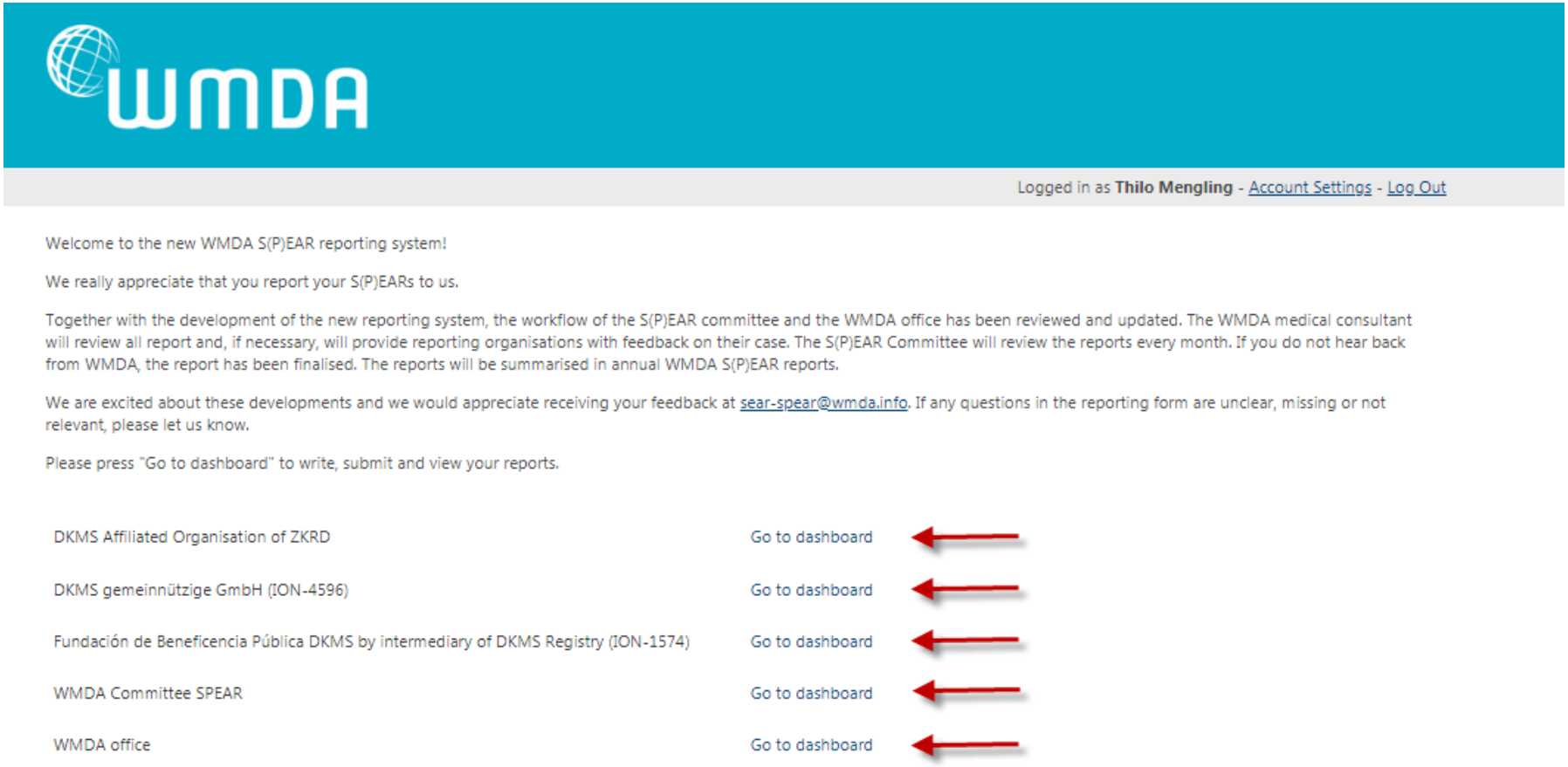
Personal Login

Personal profile may contain **different** roles, e g user from

- donor or collection center (non-member org)
- registry (member org)
- WMDA



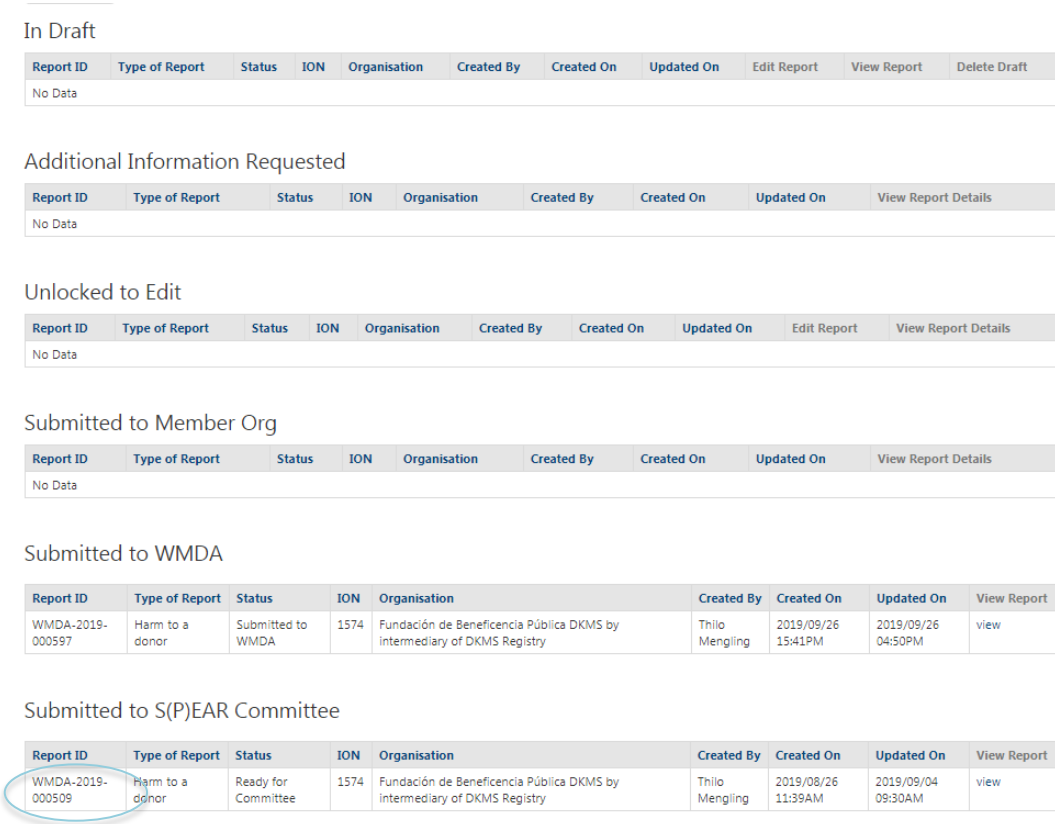
Multiple Roles / Dashboards



Dashboard

- Central location where users can go and view In progress, previously submitted reports and their associated outcome. Therefore its more:
  - Secure as you only see relevant forms pertaining to the user permissions
  - All communication is internally handled so no risk of emails being hacked or erroneously forwarded and no more need to use email correspondence
  - GDPR compliant
  - Doesn't require users to have their own backup of reports submitted

- System **auto generated ID** for traceability of reports in draft or submitted



In Draft

Report ID	Type of Report	Status	ION	Organisation	Created By	Created On	Updated On	Edit Report	View Report	Delete Draft
No Data										

Additional Information Requested

Report ID	Type of Report	Status	ION	Organisation	Created By	Created On	Updated On	View Report Details
No Data								

Unlocked to Edit

Report ID	Type of Report	Status	ION	Organisation	Created By	Created On	Updated On	Edit Report	View Report Details
No Data									

Submitted to Member Org

Report ID	Type of Report	Status	ION	Organisation	Created By	Created On	Updated On	View Report Details
No Data								

Submitted to WMDA

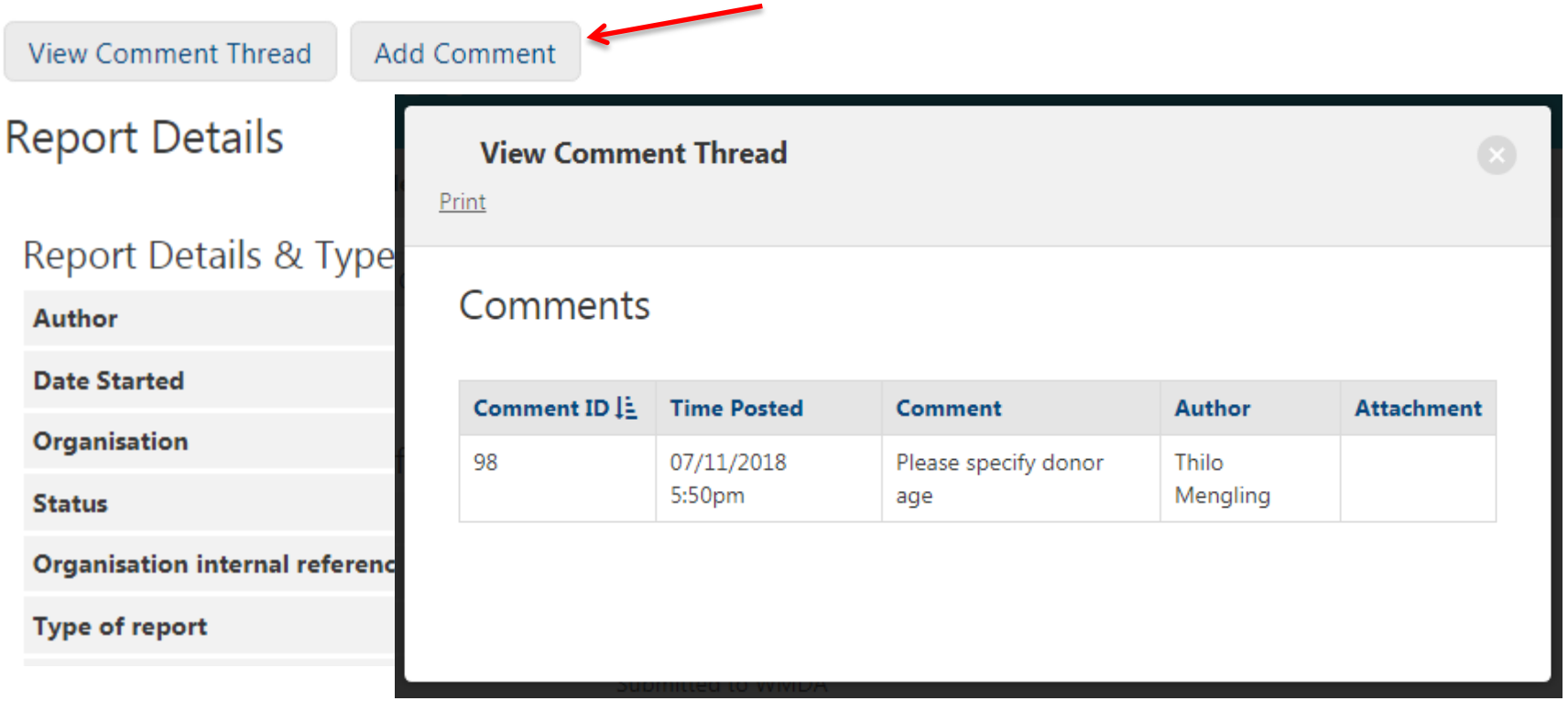
Report ID	Type of Report	Status	ION	Organisation	Created By	Created On	Updated On	View Report
WMDA-2019-000597	Harm to a donor	Submitted to WMDA	1574	Fundación de Beneficencia Pública DKMS by intermediary of DKMS Registry	Thilo Mengling	2019/09/26 15:41PM	2019/09/26 04:50PM	view

Submitted to S(P)EAR Committee

Report ID	Type of Report	Status	ION	Organisation	Created By	Created On	Updated On	View Report
WMDA-2019-000509	Harm to a donor	Ready for Committee	1574	Fundación de Beneficencia Pública DKMS by intermediary of DKMS Registry	Thilo Mengling	2019/08/26 11:39AM	2019/09/04 09:30AM	view

Comments

Ability to add internal comments allowing for dialogue between WMDA and submitting registry be stored and audited within the system. This makes it easy to request additional information



Workflow of reports

Benchmarking: How frequent are SAE/SAR?

- Dependent on setting (donor collective, product type, local standards / regulations,...)
- Data for long-term FU (>6 months) not everywhere available
- Underreporting for Harm to Recipient (many TC are not aware of S(P)EAR system, difficult reporting lines for cross-border products)
- Supposed underreporting for Adverse Events / Risk of Harm

Estimated frequency for Harm to a Donor

(from start of procedure until 6 months after)

Expect one SAE / SAR in **0.5 – 1.0% of donations**

Sources: Own data; extrapolation from e.g. **Acute toxicities of unrelated bone marrow versus peripheral blood stem cell donation: results of a prospective trial from the National Marrow Donor Program**

Pulsipher Blood. 2013 Jan 3;121(1):197-206. doi: 10.1182/blood-2012-03-41766

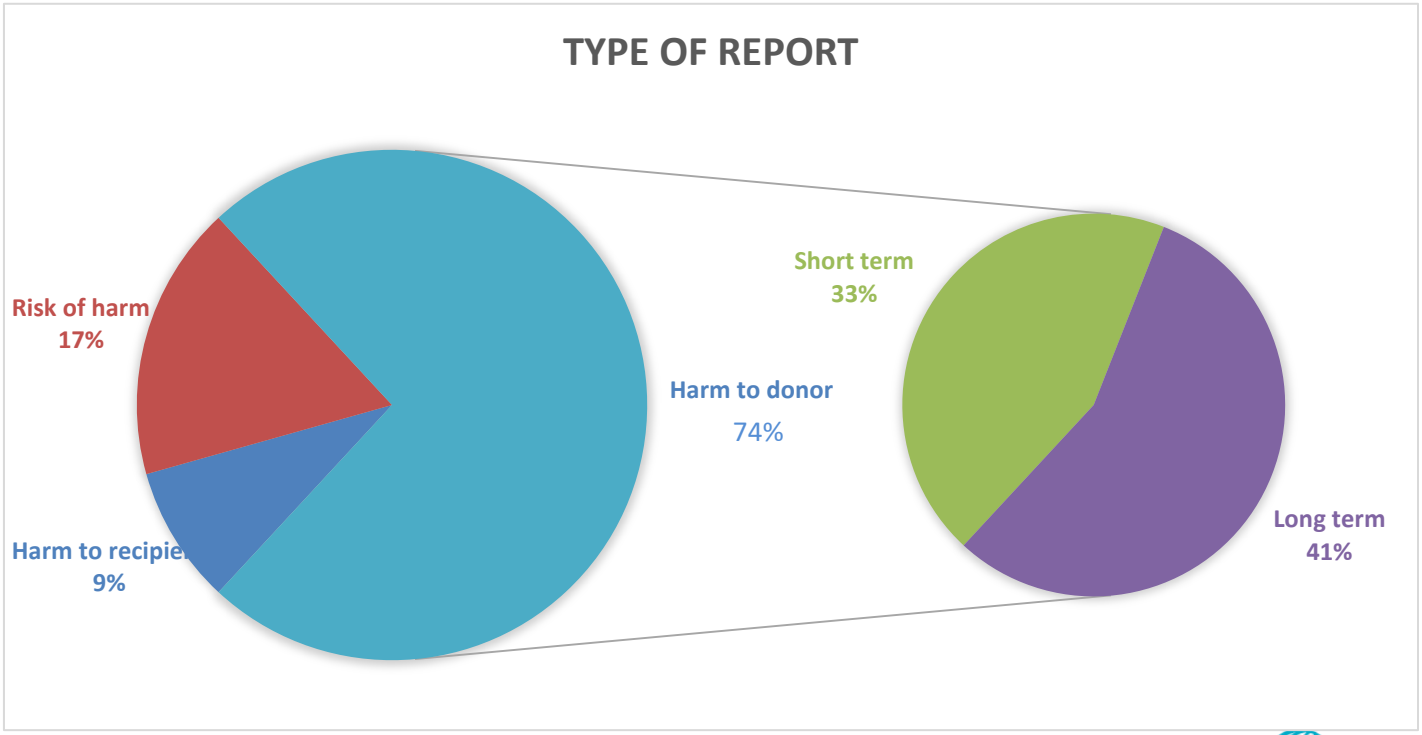
S(P)EAR Annual Report 2018

S(P)EAR Annual Report 2018 on WMDA Share

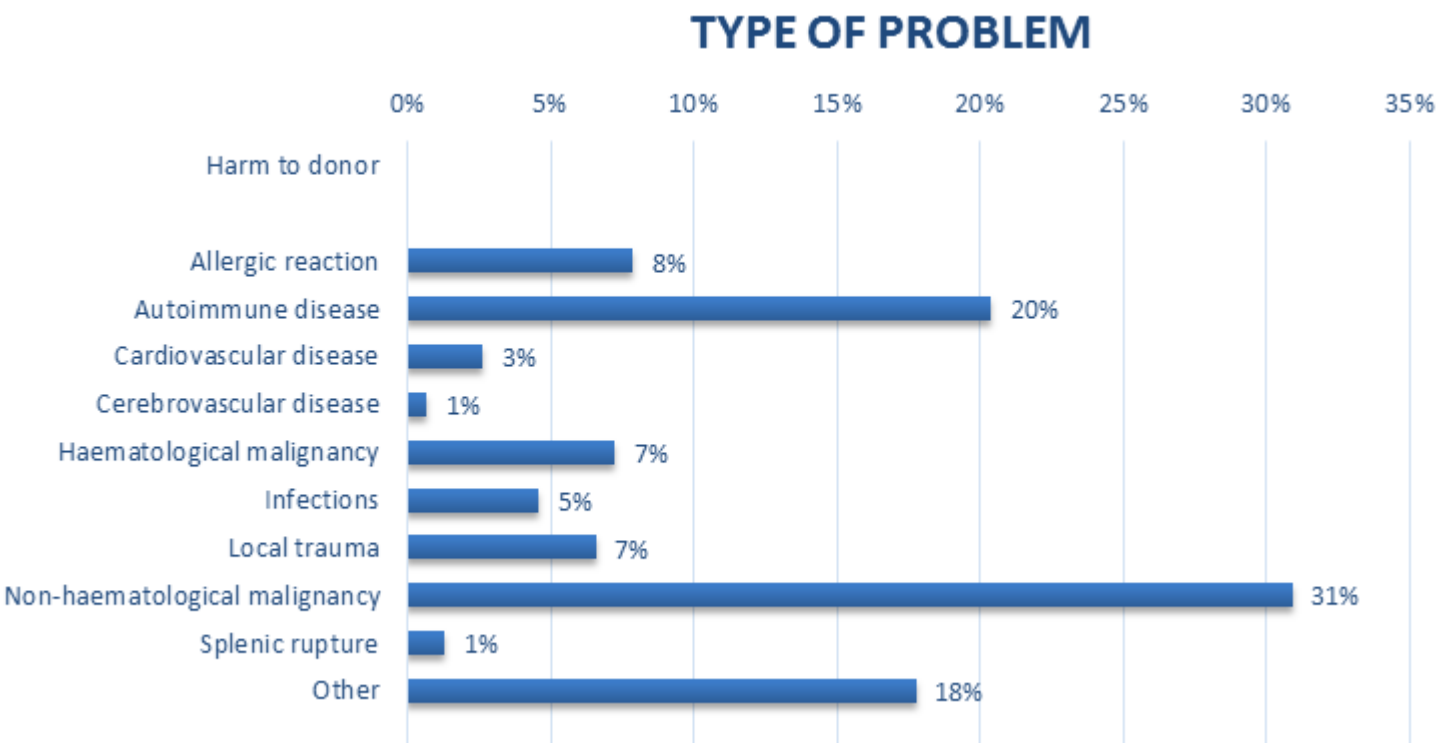
In 2018, WMDA received 206 reports

(complete; no duplicates)

- 152 Harm to a Donor
- 18 Harm to a Recipient
- 36 Risk of Harm



Type of Harm to a Donor



Note that long-term Harm to donor reports represent diagnoses which also arise in non-donors: analysing the reports allows WMDA to confirm there is no increase following the use of mobilising agents

Haematological malignancies

N = 11

Haematological malignancy	Diagnozed	Product
NHL	15 months after	PBSC
Hodgkin's Lymphoma	3 years after	PBSC
Hodgkin's Lymphoma	7 years after	PBSC
Follicular B-Cell-Lymphoma	2 years after	BM
CLL	7 years after	PBSC
B-Cell-Lymphoma (Non-GCB-type)	6 years after	BM
Leukemia („rare form of“)	3 years after	PBSC
B-NHL	5 years after	BM
Waldenström macroglobulinemia	6.5 years after	BM
Nodal T-Cell-Lymphoma	22 years after	BM
MGUS	*13 years after*	*PBSC*

See note on previous slide. These reports represent diagnoses which also arise in non-donors: analysing the reports allows WMDA to confirm there is no increase following the use of mobilising agents

WMDA matching donors • serving patients 25th Anniversary

Non-haematological malignancies

N = 47

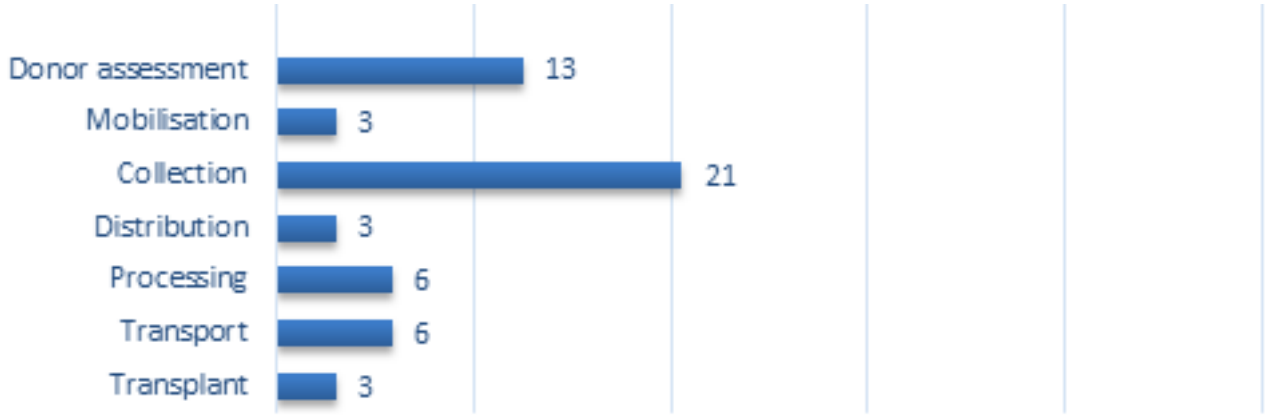
Malignancy	total	after PBSC	after BM
breast	17	14	3
seminoma	6	5	1
digestive tract	6	3	3
kidney	5	3	2
ovary, uterus	4	3	1
melanoma	2	2	
bone	2	1	1
intracranial	2	2	
thyroid	1	1	
lung	1	1	
tongue	1		1

See note on previous slide. These reports represent diagnoses which also arise in non-donors: analysing the reports allows WMDA to confirm there is no increase following the use of mobilising agents

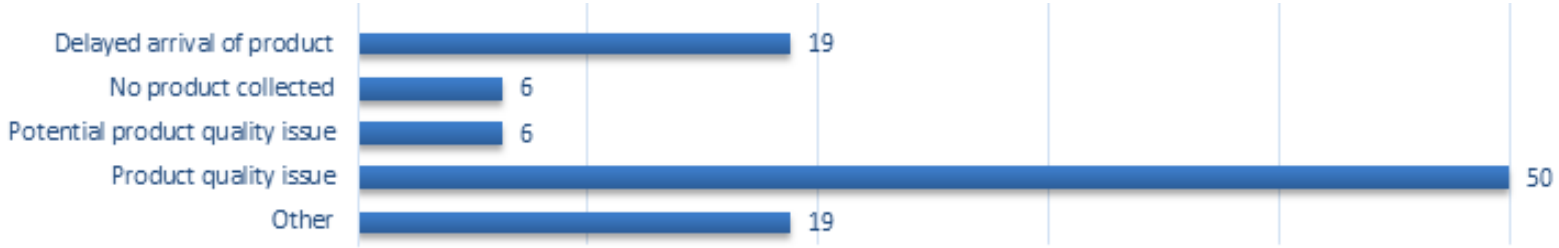
WMDA matching donors • serving patients 25th Anniversary

Risk of Harm

Phase where RoH occured (%)



Type of SAE (%)



Notable reports: Splenic rupture

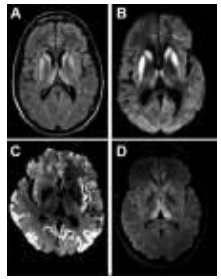
Case 1

- On the 4th day of HPC mobilization with filgrastim, the donor (M, 32 yrs) felt severe abdominal pain, located in the area of upper left abdomen. He was transported to Emergency Unit. Splenic rupture confirmed -> splenectomy
- Examination of spleen revealed 2 small, linear ruptures (1.5 cm and 2 cm). The overall Hb drop was up to 8 g% (the initial level was 13 g%). He did not require blood transfusion and was hemodynamically stable.

Case 2

- M, 24 yrs. Ruptured spleen 6 months after PBSC, most likely based on laceration from coloscopy + splenomegaly due to acute mononucleosis; splenectomy; recovered

Notable reports: Creutzfeldt-Jakob disease?



- 18 months after transplantation, patient (M, 66 yrs) was diagnosed with progressive Creutzfeldt-Jakob disease based on *clinical* signs (myoclonus, ataxia and cognitive deterioration)
- Donor center was informed and decided *not* to contact the donor (M, 48 yrs)
- Donor had not reported CJD risk factors (iatrogenic, family, residence) before donation
- Both organizations informed their national competent authority

Notable reports: Creutzfeldt-Jakob disease

- Surprisingly, the patient's condition improved little by little thereafter, and he could be discharged from hospital
- Final diagnosis 'encephalitis', not CJD or other prion disease

- Donor center was informed
- Both organizations informed their national competent authority, again

Don't forget to send updates to WMDA!

Practical Examples

Example 1a:

Uncomplicated and successful GCSF mobilization and PBSC collection; recipient succumbs to an unexpected cardiovascular event after collection was completed, but before transplantation

- Tragic, but not preventable medical complication
- Adequate communication

- No report required  
- Report required 
  a. Report as Harm to Recipient (*product did not arrive in time before death*)
  b. Report as Risk of Harm (*donor risk, potential complication during GCSF and apheresis*)
  c. Report as Harm to Donor (*unnecessary donation*)

Example 1b:

Uncomplicated and successful GCSF mobilization and PBSC collection; recipient had deceased already on d3 of mobilization, but this was not communicated to the donor centre until after collection was completed.

- Tragic, but not preventable medical complication
- **Inadequate communication**

- No report required
- Report required

a. Report as Harm to Recipient *(product did not arrive in time before death)*

b. Report as Risk of Harm *(donor risk, potential complication during GCSF / apheresis)*

c. Report as Harm to Donor *(unnecessary donation / donor burden)*

Example 1c:

Uncomplicated GCSF mobilization until day 4; at this time, donor center is notified about recipient‘s death. Collection cancelled. 3 days later, it turned out recipient is still alive and in need of a transplant; donor is requested again.

- No report required
- Report required

- **Inadequate communication.**
  Evaluate in which institution the initial error occured
  - b. if TC was not involved
  - a. or c. – no clear preference

a. Report as Risk of Harm (*donor risk, potentia complication during GCSF*)

b. Report as Harm to Recipient (*product did not arrive as scheduled*)

c. Report as Harm to Donor (*unnecessary donor burden*)

Example 2:

Uncomplicated and successful GCSF mobilization and PBSC collection (male donor). Recipient (F) has engrafted. During first chimerism analysis, a chromosomal aberration (balanced Robertsonian translocation) is seen in 100% of donor cells.

- Not preventable: chromosomal testing of donors before donation is not appropriate
- No harm to recipient

- No report required (but inform donor centre)
- Report required
  a. Report as Harm to Recipient (*transmitted chromosomal abnormality)*
  b. Report as Harm to Donor (*donor should not have been cleared for PBSC / GCSF*)

Example 3:

Donor refuses to continue after 1st injection GCSF due to "pain", resolved without further treatment.
Alternative donor found and proceeded to collection in timely fashion.

Though not preventable: Report to identify donor profiles with increased risk not to proceed

- No report required (*TX performed*)
- Report required

a. Report as Risk of Harm (*recipient risk, potential delay / no product)*
b. Report as Harm to Recipient (*primary product did not arrive)*
c. Report as Harm to Donor (pain)

Example 4a:

During PBSC apheresis, donor experiences substantial citrate toxicity, but continues. After adequate CD34+ cell dose (4.0 x 10^6 kg/BW) collected, apheresis is stopped although requested cell dose (5.0 x 10^6) was not *fully* met. Donor recovered immediately after Ca^{2+} infusion; recipient has engrafted.

- No harm to recipient or donor, everything went according to protocol (sufficient cell dose)

- No report required (*TX performed and engrafted, no unexpected or unusually severe donor AR*)
- Report required
  a. Report as Risk of Harm (*recipient risk, cell dose lower than requested)*
  b. Report as Harm to Recipient (*cell dose lower than requested)*
  c. Report as Harm to Donor (*citrate toxicity*)

Example 4b:

During BM collection, donor falls into hypotension and anesthesiologist decides to prematurely end collection. At that time, it is unclear if TNC count is adequate, BM volume (900mL) is substantially lower than expected. Donor recovered, one night in-house observation; recipient has

- **(Additional) hospitalisation for *surveillance***
- d. if hospitalisation for *treatment*
- a. or c. also possible

- No report required *(TX perform engrafted*)
- Report required
  a. Report as Risk of Harm (*rec risk, cell dose lower than requested)*
  b. Report as Harm to donor (*u sually severe AR that required substantial interve tion)*
  c. Report as Harm to Recipie t (*cell dose lower than requested)*
  d. Report as Harm to Donor (*anesthesia*)

Example 5:

Uncomplicated and successful BM collection.
Donor develops MDS / and later AML 13 years after donation.
Recipient (child with Fanconi anemia) still alive.

(but inform transplantation centre)

- No report required
- Report required
  a. Report as Risk of Harm to Recipient (*transmission of risk for malignancy*)
  b. Report as Harm to Donor (*hematological malignancy*)
  c. Other ()

Example 6:

Your registry is based in a EU country where a SEC (Standard European Code) is mandatory* for HSC products. You receive a PBSC product for immediate use without SEC, but proper donor- and product-ID, collected in a non-member state.

(*Commission Directive (EU) 2015/565 amended Directive 2006/86/EC)

Not preventable if collection centres cannot issue SEC

- No report required 
- Report required 

a. Report a SPEAR (*incomplete documentation*)

b. Report as Harm to Recipient (*product may not be used for a patient within the EU*)

Take home-Messages

Concerns against Reporting - *resolved*

1. Fear of reputational damage to
   - Own institution ⇨ Appropriate measurements to minimize (future) consequences demonstrate competence and professionalism; WMDA will generally not disclose the identity of the reporter
   - Stem cell donation in general ⇨ Adverse Events & Reactions registry improves donor safety; downplaying risks will cause even more damage

2. Malpractice liability; audits ⇨ AE registry can provide data on incidences and help putting single incidents in the right context

3. Resources
   - Capacities for thorough investigations ⇨ WMDA can support you with expertise and background data
   - Bureaucratic workload ⇨ new reporting system substantially reduces time for documentation

Take home messages

- Reporting and evaluation of SAE/SAR improves safety for stem cell donors and recipients
- A comprehensive AE database is the best argumentation against conjecture and distrust
- Focus on SAE/SAR where a connection to donation is reasonably probable. Don‘t focus on the outcome, but the underlying cause
- **When in doubt, report**

Questions or Comments?

Thank you for your attention!

If you have any questions about the currrent or upcoming system or S(P)EAR in general or are not familiar with the reporting tool, please contact

sear-spear@wmda.info

Thanks to all who have submitted S(P)EAR reports
Thanks to all members of the S(P)EAR Committee
and the WMDA office for their enthusiasm and support!