Qu'est que la biovigilance?

TRIP
Hemo-en biovigilantie

What is biovigilance?

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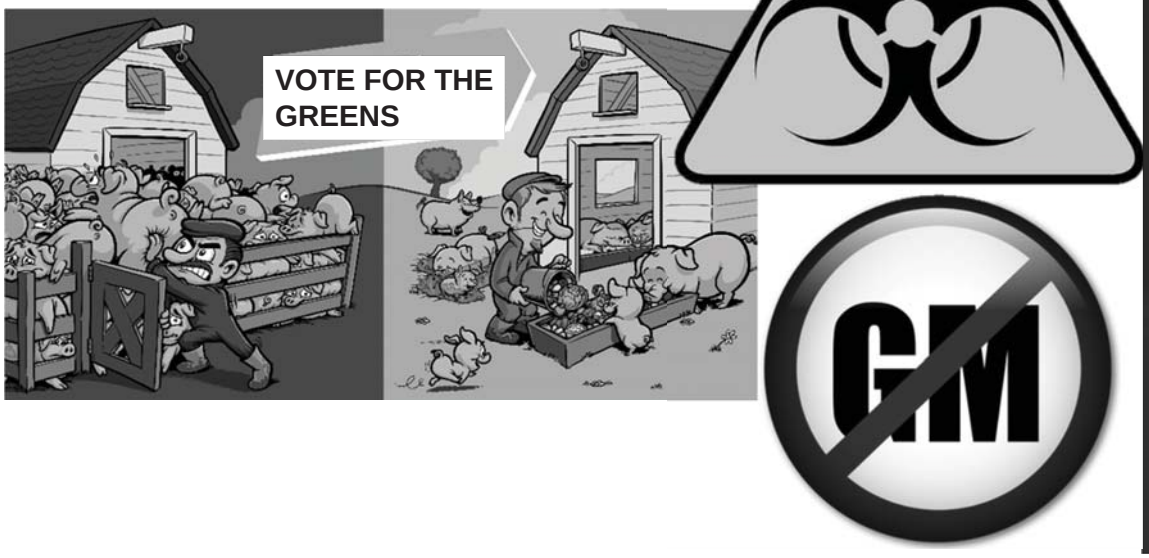
TRIP
Hemo-en biovigilantie

- What biovigilance isn't
- Biovigilance reporting in The Netherlands
- EU biovigilance
- 2007-2015 NL results
- Lessons

Biovigilance isn't

- Politics or activism



Biovigilance also isn't

- Receiving reports (for the sake of it)

- Reiterating (known) side effects
- Pharmacovigilance

->depending on needs of professional groups

(e.g. monitoring ovarian hyperstimulation?)

What is biovigilance?

"**Biovigilance** is a set of surveillance procedures covering the entire chain from the donation of **blood, tissues, cells and organs** to the follow-up of recipients, intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of medical products of human origin, and to prevent their occurrence or recurrence"

(adapted from RRP de Vries et al, Hemovigilance: an Essential Tool for improving transfusion practice)

Quality of a biovigilance reporting system

- Safe, accepted by professionals
- Standardised definitions and methods
- Events externally reviewed by experts; statement of 'nil to report'
- Denominators
- % coverage
- Active vs passive
- Rapid alert system?
- Recommendations, dissemination

Need for a national bioviligance system

European Directive 2004/23: national system for biovigilance declared mandatory.

- TRIP "Transfusion and Transplantation Reactions In Patients" foundation created by representatives of hospitals and clinical users of blood
  - hemovigilance data collected since 2003
  - Network of hemovigilance professionals in hospitals

- Tissue + cells vigilance pilot in 2006, system "live" from 2007
- Term "biovigilance" introduced in 2011

National reporting

Objectives

- Legally compliant
- EU: comparable safety of products)
- Safety of living donors, respect for deceased donors
- Safety of application, transparency

TRIP recommendations
Professional guidelines
Training
Organisational policy
↓
Practice

SAE/SAR (2004/23/EC)

- ‘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;
- ‘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;

!! Different definition from pharmacovigilance/ clinical trials

2010/45/EC
standards of quality and safety of human organs intended for transplantation
Organ vigilance reporting not yet implemented

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Directorate D – Health Systems and Products
D4 – Substances of Human Origin and Tobacco Control

Brussels, SANCO D4 IS/ac D(2014)

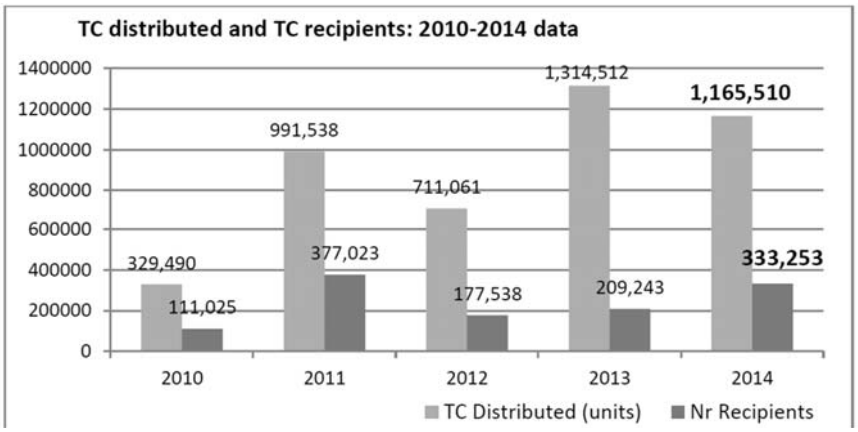
“Common Approach”

- Guidance for counting units (processed, distributed, applied)
  ->However, lack of consensus
- Which SAR should be reported
- Criteria for SAE
- *Donation reactions which did not impact on the quality or safety of the tissues or cells may be reported voluntarily*

EUROPEAN COMMISSION
DIRECTORATE GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety and innovation

Questionnaire to 28 member states +2	Countries provided 2014 data (non-reproductive)	Countries provided 2014 data (reproductive)
TC distributed (units)	24	15
Recipients	15	11
Reports on SAR	12 0.3 per 1000 SAR/TC distr.	10 0.1 per 1000 SAR/TC distr.



EUROPEAN COMMISSION
DIRECTORATE GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety and innovation

Questionnaire to 28 member states +2	Countries provided 2014 data
TC processed (units)	29
Reports on SAE	19

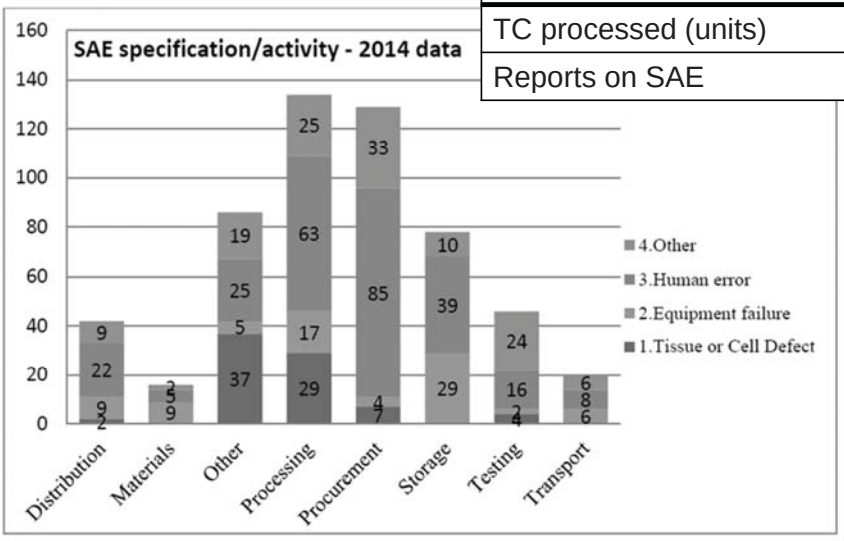


Figure 12. SAE per type and activities - 2014 data.

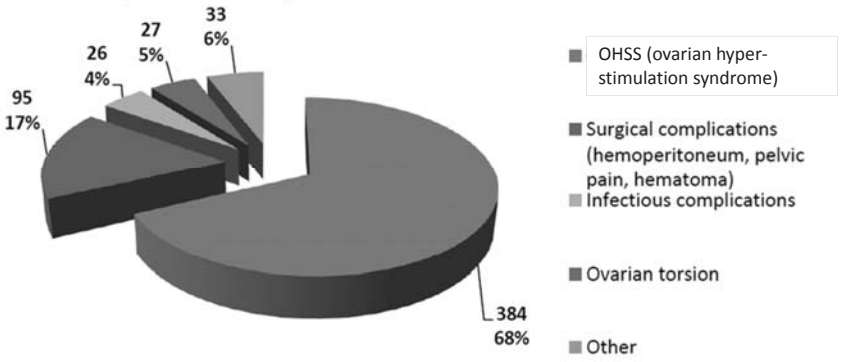
Ref. Ares(2016)5880769 - 12/10/2016

EUROPEAN COMMISSION
DIRECTORATE GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety and innovation

Questionnaire to 28 member states +2	Countries (2014)	Total
Reported on donor SAR (non-reproductive)	12	55 SAR
Reported on donor SAR (reproductive)	15	565 SAR

SAR in oocyte and other reproductive tissue donors: 2014 data

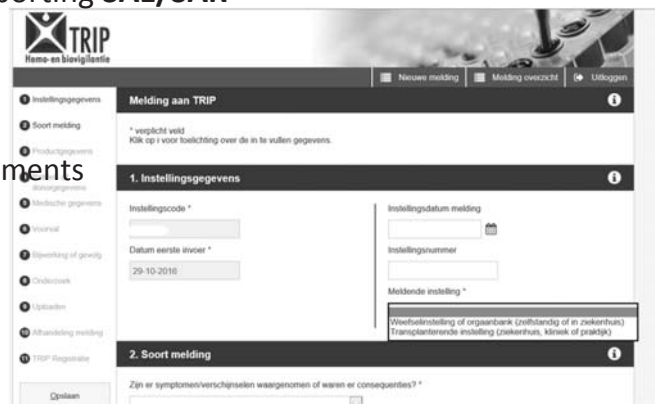


TRIP Hemo-en biovigilantie

NL: Systematic collection of Bioviligance reports from 2007

- Standard data collection form (paper -> web based)
- Definitions
- Identify contact persons (biovigilance officers) in Dutch hospitals, fertility clinics, tisue establishments, implantology clinics
- Site visits to increase TRIP's understanding of processes

- Create awareness for reporting **SAE/SAR**
- Collect data on **numbers of units**
- Advise and support hospitals/ tissue establishments



NL: Systematic collection of Bioviligance reports from 2007

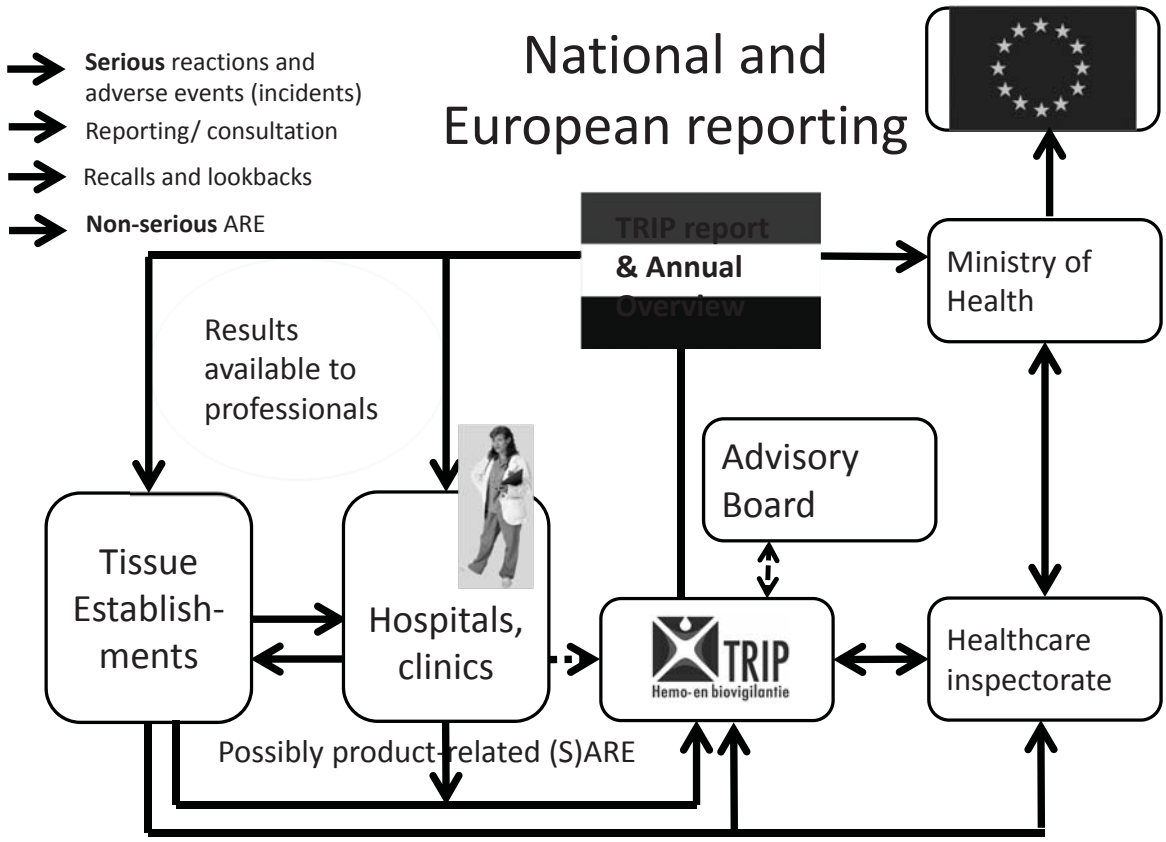
Definitions (www.tripnet.nl)

- Reactions <-> adverse occurrences
- Capture what happened (e.g. loss of material)
- Analysis of type of error/incident
  e.g. technical failure, identification error, bacterial contamination, failures of communication, judgement
  – Step in the chain

- Cases reviewed by advisory committee with experts
- Annual analysis, report with recommendations
- Serious reports (also) forwarded to Competent Authority*
- Certificate of participation

Organisations in NL

- Living donors
  – HPC donor registry (2 departments), bone donation
  – Cord blood bank (anonymous/autologous)
  – Autologous (e.g. chondrocytes, HPC, skull bone)
- Deceased donors
  – National Transplantation Foundation
  – Eurotransplant (organs)
  – Licensed tissue establishments
- ART
  – IVF laboratories
  – Semen laboratories
- Clinical users
  – hospitals, fertility clinics, dental/implantology clinics



Relation to Ministry and Inspectorate

Ministry pays for TRIP biovigilance (below EU tender threshold)

SARE reporting by tissue establishments is mandatory

-> HOWEVER tissue establishment decides

-> Can use TRIP reporting system

Organisations voluntarily report non-serious reactions/events

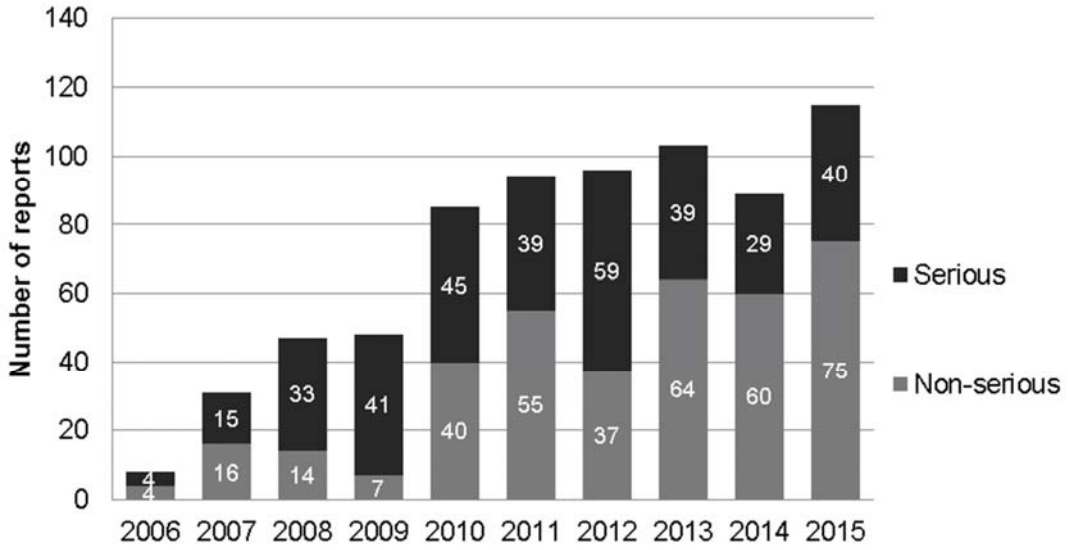
Periodic review of non-serious (anonymised) cases with Inspectorate

Collaboration

- TRIP prepares mandatory annual SARE report for Brussels
- Use of TRIP website and contacts

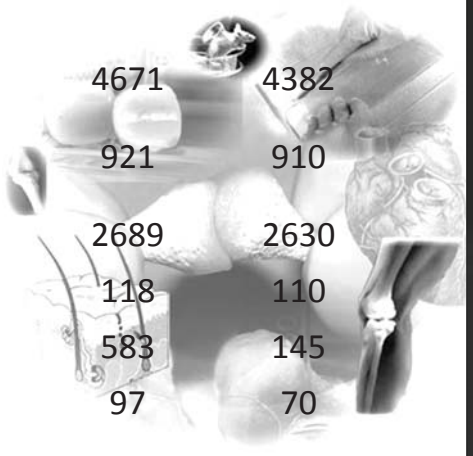
e.g. disseminating information (Zika, introduction of Single European Code)

Biovigilance reports 2006-2015



80,000 products applied annually

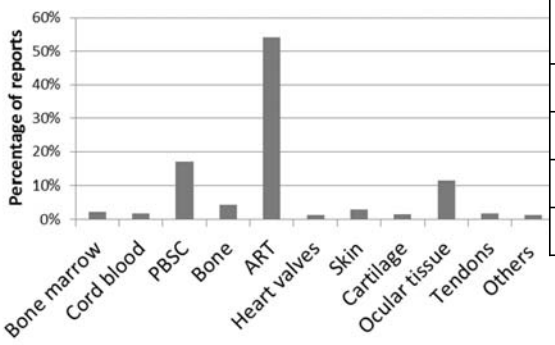
	Processed	Distributed	Applied	Patients
Assisted Reproductive Technologies	241678	195422	63745	29740
Haematopoietic progenitor cells, cellular therapies	15198	3974	3804	1543
Bone	12049	59289	4671	4382
Cartilage, tendons, fascia	880	2361	921	910
Cornea, sclera	3671	3447	2689	2630
Cardiovascular	453	111	118	110
Skin	690	16962	583	145
Others	6044	387	97	70



Type of report/ tissue

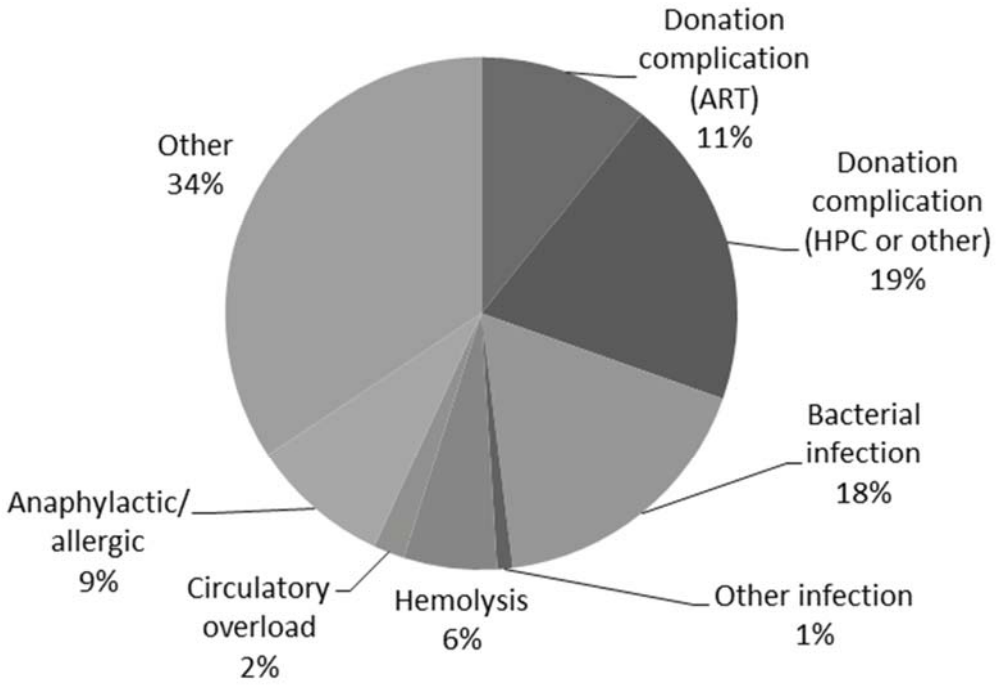
2006-2015: 717 reports submitted

- 85% adverse events (604)
- 15% adverse reactions (113)
- 77% risk for patients
- 14% risk for donors
- 8% related to graft only



Type of SOHO	AR	AE
Bone	11	21
ART	14	375
Heart valves	1	9
Skin	15	6
Cartilage	0	11
Haematopoietic stem cells	73	68
Ocular tissue	4	77
Tendons	1	11
Others	1	9
% Serious	65%	30%

Type of reported adverse reaction



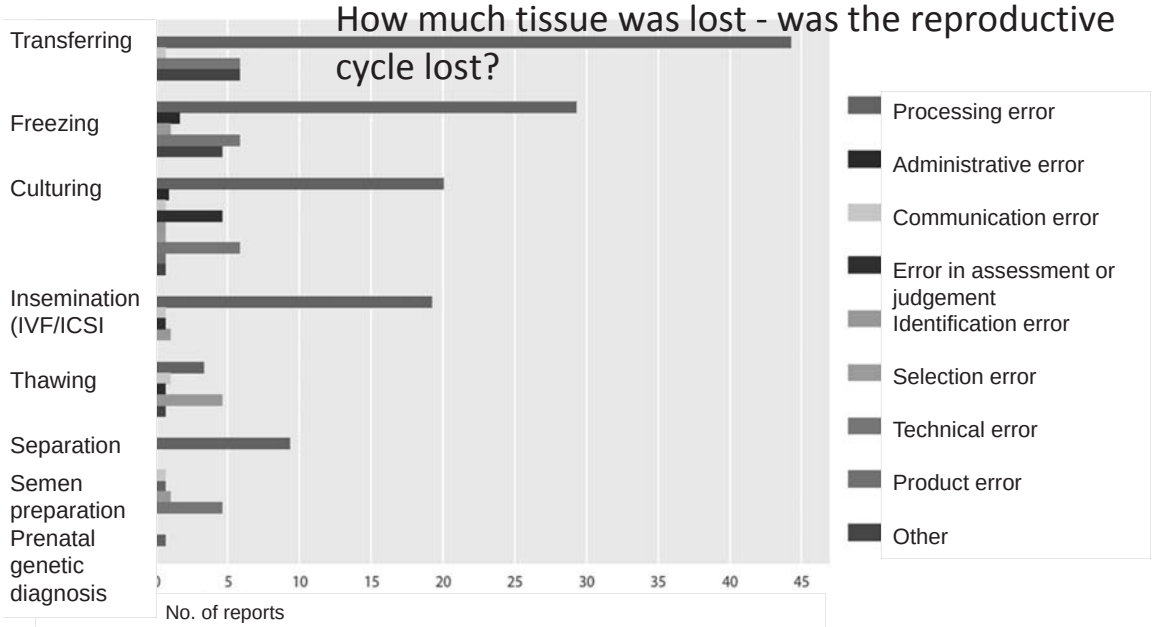
Type of reported adverse event

Type of events	
Wrong product transplanted	16
Substantial loss of cells/tissue	288
Viral contamination	2
Bacteriological contamination	48
Congenital disorder	11
Delayed/failed engraftment	12
Product incident	11
Near miss	25
Other incident	164

- 50% of reports: loss of tissue (82% of these ART related)
- Category “other” :
  - Technical failures
  - Processing issues
  - Product deficiencies
  - Communication
  - Storage conditions

Classification

How did an error/failure or incident occur?
What checks failed?
How was it detected?
How much tissue was lost - was the reproductive cycle lost?



Reports of avoidable loss of gametes and embryos per step in the chain and type of incident, 2007-2015

Annual biovigilance symposium

5-year overview (2014 report)

Table 50. Serious adverse events in relation to numbers of tissues/cells processed, transplanted or per treatment cycle, 2010-2014

Tissue or cell type	Serious adverse event rate estimation	Per 1000
Gametes, embryos or gonadal tissue	1.1	IVF/ICSI cycles with follicle biopsy
	0.02	IUI/KID cycles
Hematopoietic stem cells	3.0	Unrelated stem cell transplants*
	1.0	Related stem cell transplants*
	1.2	Autologous stem cell transplants**
Bone and other musculoskeletal tissues	0.2	Processed femoral heads
	1.4	Processed autologous cranial bone flaps
	11.2	Autologous cartilage biopsies
	2.0	Processed tendons
Ocular tissue	1.7	Processed corneas
Cardiovascular tissues	2.3	Processed heart valves

* *Bone marrow, peripheral blood stem cells and cord blood*

** *Bone marrow, peripheral blood stem cells*

5-year overview (2)

Tabel 51. Serious adverse reactions in relation to distribution data, transplantations or treatment cycles, 2010-2014

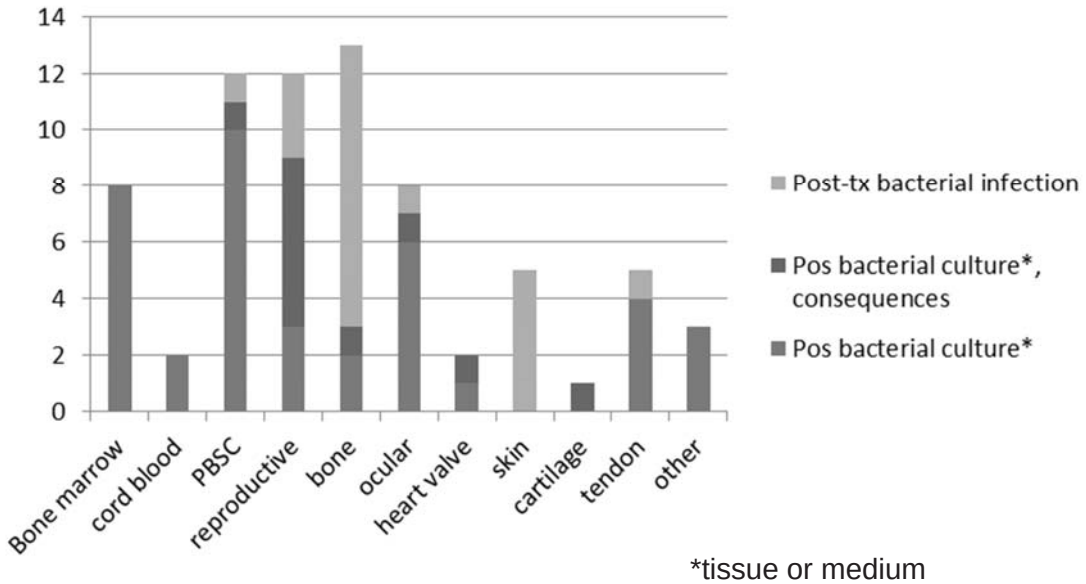
Tissue or cell type	Serious adverse reaction rate estimation	Per 1000
Gametes, embryos or gonadal tissue	0.01	IUI/donor insemination cycles
Hematopoietic stem cells	2.0	Unrelated stem cell transplants*
	1.0	Related stem cell transplants*
	0.4	Autologous stem cell transplants**
Bone and other musculoskeletal tissues	0.2	Distributed femoral heads
	9.6	Distributed autologous cranial bone flaps
	0.5	Distributed tendons

* *Bone marrow, peripheral blood stem cells and cord blood*

** *Bone marrow and peripheral blood stem cells*

	SAR/1000
Reproductive EU 2014	0.1
Non-reproductive EU 2014	0.3

Bacterial problems (2008-2015 data)



*tissue or medium

Collaboration with professional groups

- 2011-2013 reports of haze following corneal transplantation
- ART professional guideline for reportable AE
- Reports of leaky/torn HPC bags

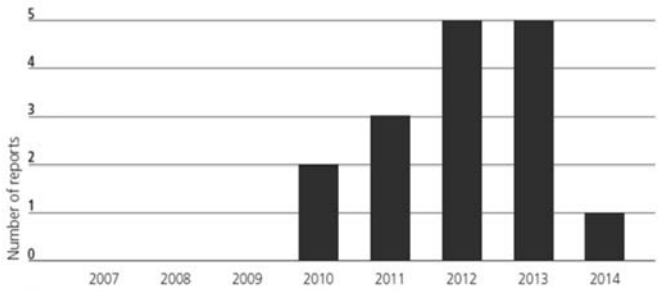


Figure 12. Reports of leaking or ruptured HPSC collection and storage bags, 2007-2014

Lessons and challenges

- Tracing what goes on - denominators
- Cooperation of hospitals and clinics is essential
- Need awareness among clinicians to recognize and report SAR/SAE of tissue/cells
- Central system helps recognize trends/clusters
- Biovigilance also monitors the (living) donor
- Majority of reports are adverse events (incidents). Can lead to cancelled operations or reduced chance of pregnancy
- Not yet joined up with organ vigilance
- Biovigilance data contributes to better information for donor, recipient and professionals on risks involved.

Thank you for your attention

Thanks to all TRIP contact persons and colleagues

For more information and reports (also in English):
http://www.tripnet.nl

j.wiersum@tripnet.nl

Dutch warehouse " de Vigilantie" imported fruits (Alkmaar, 17th C[y])

2006/9 European Union Standards and Training for the Inspection of Tissue Establishments (EUSTITE)

Impact (SARs and SAEs)

Level	Impact Description	Impact on individual(s) Actual (SAR) Potential (SAE)	Impact on Transplant or Fertility System	Impact on Tissue/cell supply
0	Insignificant	Insignificant	No affect	Insignificant
1	Minor	Non-serious	Minor damage	Some applications postponed
2	Significant	Serious	Damage to system – services will be affected for short period	Many applications cancelled or postponed
3	Major	Life threatening	Major damage to system – significant time needed to repair	Significant no. of procedures cancelled - importation required to make-up short-fall
4	Severe	Death	System destroyed – need to rebuild	All allogeneic applications cancelled

Step 2– Consequences of Recurrence

Recurrance probability → / Consequences ↓	Rare 1	Unlikely 2	Possible 3	Likely 4	Almost certain 5
Insignificant 0	0	0	0	0	0
Minor 1	1	2	3	4	5
Significant 2	2	4	6	8	10
Major 3	3	6	9	12	15
Severe 4	4	8	12	16	20

Step 3 - Impact