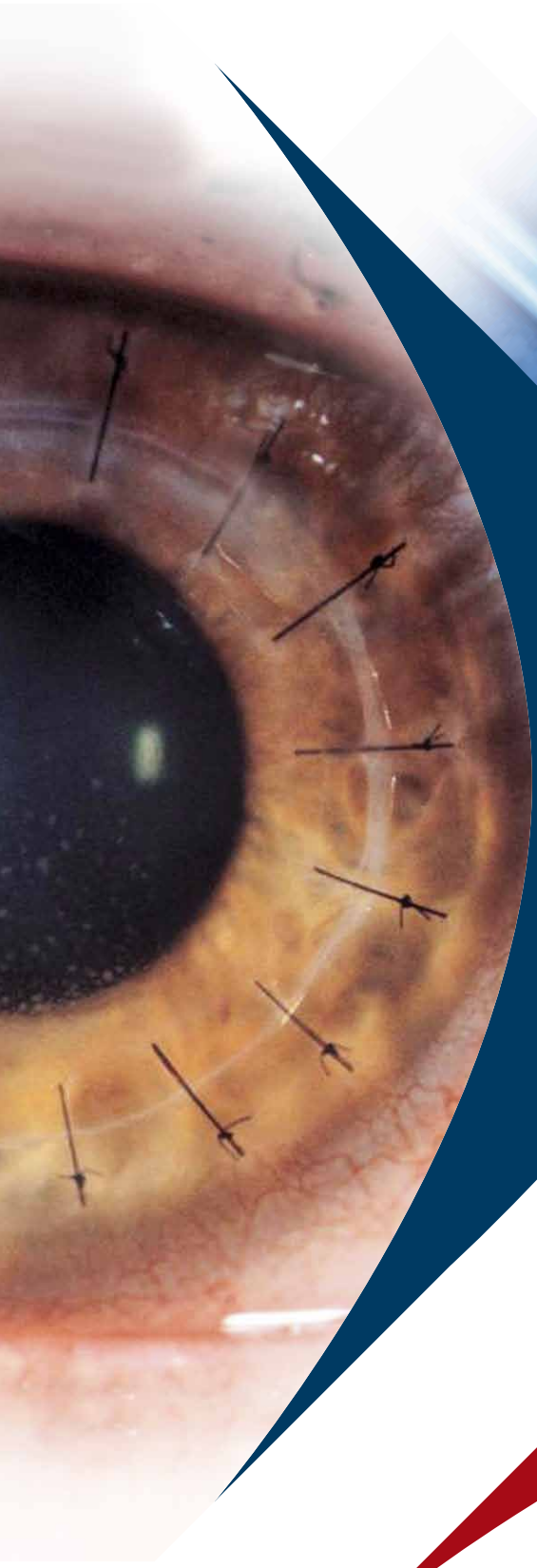
TRIP report 2012

Biovigilance



TRIP
Hemo- en biovigilantie

TRIP report 2012

Biovigilance

Extended version

The TRIP report 2012 regarding biovigilance in The Netherland is published under responsibility of the TRIP (Transfusion & Transplantation Reactions in Patients) Foundation

TRIP
Hemo- en biovigilantie

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Part 1

Biovigilance reporting

1.1 Foreword

Dear reader,

It is my great pleasure to present you the sixth annual TRIP report describing the latest state of affairs with regard to tissue and cell vigilance in The Netherlands.

Compared to the 2011 tissue vigilance report there are some notable changes. First of all there is the new name of Biovigilance. In 2012 the TRIP Foundation statutes changed; TRIP now stands for Transfusion and Transplantation Reactions in Patients and the office is called the TRIP National hemovigilance and biovigilance office. Secondly TRIP has endeavoured to improve clarity and readability of the annual report by including more tables and figures than in previous years. Finally a new format was chosen. The first part provides general information on TRIP and biovigilance reporting. The second part presents the developments in 2012 and trends in recent years per tissue and cell type. The third and last part provides a reflection and includes conclusions and recommendations for the promotion of quality and safety of tissue and cell transplants.

Generally it can be concluded that in 2012 there were approximately the same number of reports as in the two previous years. However, there was a rise in the number of serious adverse reactions and events. Fewer non-serious reports were submitted. The 2012 biovigilance report also draws attention to the reporting of serious adverse reactions and events which should be submitted to the Healthcare Inspectorate as well as to TRIP.

TRIP hopes that this report will once again contribute to quality and safety of application of substances of human origin. I conclude by commending its findings to your attention. I look forward to meeting many of you professionally, either at the 2013 TRIP Biovigilance symposium or at other future events.

Dr. Martin R. Schipperus, hematologist
President, TRIP Foundation

1.2 Introduction and TRIP working methods

The TRIP (Transfusion Reactions in Patients) Foundation was established in 2001 for the purpose of hemovigilance. In 2006 at the request of the Ministry of Health a pilot project for biovigilance data registration was set up. Since 2012 biovigilance has been a formal task for the TRIP foundation. This necessitated modification of the statutes and the name of the TRIP foundation was adapted in Transfusion and Transplantation Reactions in Patients. The TRIP Office is now called TRIP National hemovigilance and biovigilance office.

The European law on safety and quality of human tissues and cells requires member states to have a system for the reporting of adverse reactions and events with regard to the application of these substances of human origin (EU Directive 2004/23/EG). This is called biovigilance and refers to the systematic monitoring of (serious) adverse reactions and events throughout the transplantation chain of substances of human origin from donor to recipient with the aim of a safer and more effective use of tissues, cells and organs.

In 2007, at the request of the Ministry of Health TRIP developed a reporting system for adverse reactions and events related to the application of substances of human origin as mandated according to European and Dutch law. The online reporting system was adjusted in 2011 to allow reporters to simultaneously submit serious adverse reactions and events to the Healthcare Inspectorate. The Healthcare Inspectorate is the competent authority on behalf of the Ministry of Health. The mandatory reporting applies to tissue establishments

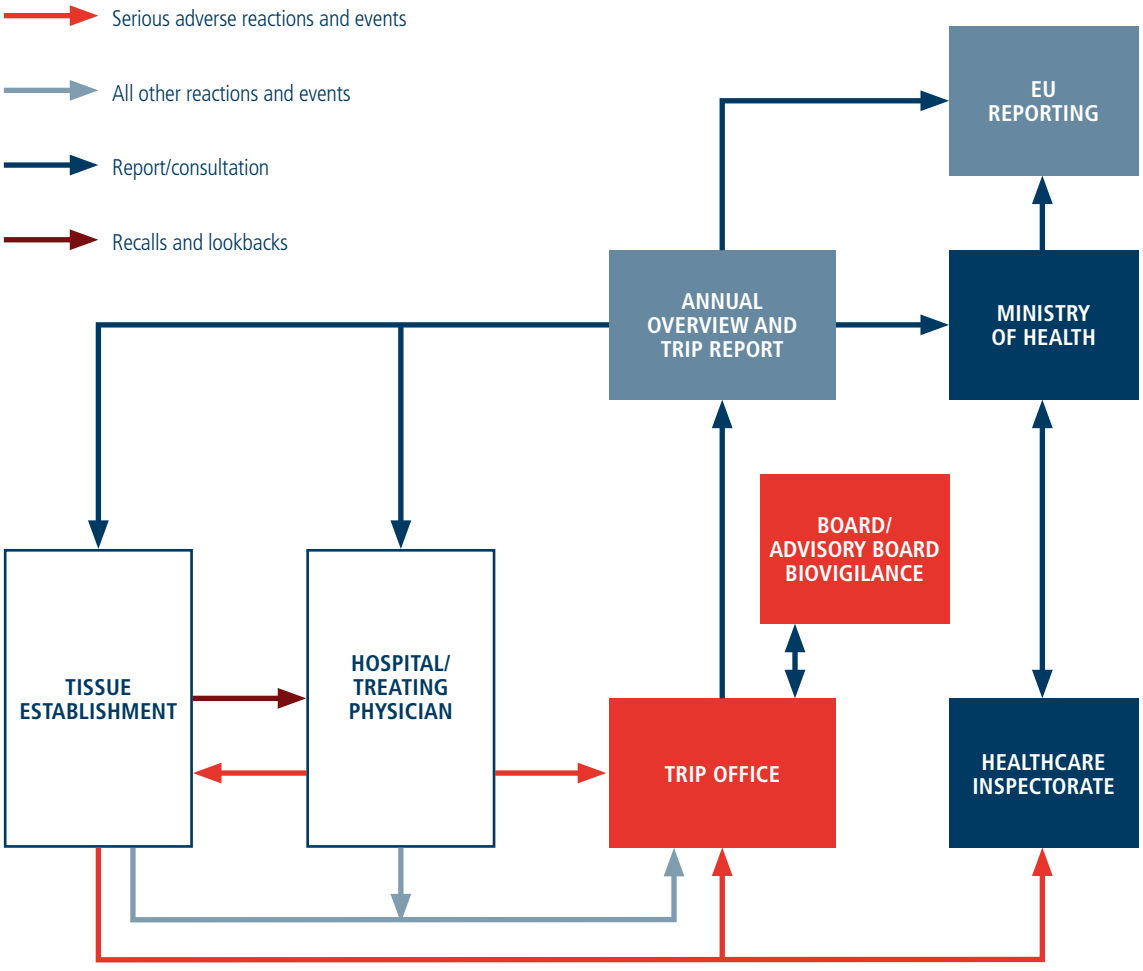


Figure 1. Flowchart of reporting

according to the Law on safety and quality of substances of human origin and the Decree on substances of human origin (2006). In 2012 the Decree was updated according to EU Directive 2010/53/EG. Figure 1 presents a flowchart of serious and non-serious reporting in The Netherlands. Chapter 1.4 of this report describes the assessment of the severity of an adverse reaction or event and whether it should be reported to the Health Care Inspectorate.

The scope of the Law on safety and quality of substances of human origin covers all substances of human origin (from deceased and living donors) with the exception of autologous material that is obtained and transplanted in the same procedure. If autologous tissues are preserved or processed (this includes preparation or processing in another location, distant from the patient) the Law on safety and quality does apply to autologous tissues as well. The Law on safety and quality always applies to allogeneic application (derived from a human donor).

TRIP is an independent foundation that cooperates closely with the users of human substances and tissue establishments. The TRIP reporting system has collected tissue and cell data since 2006 from hospitals, private clinics and licensed tissue establishments and serves to support the monitoring and improving of the quality and safety of substances of human origin. All submitted reports are registered, analysed and reviewed by experts. The results and conclusions are reported annually.

TRIP also conducts an annual inventory of numbers of processed, distributed and applied substances of human origin in all Dutch hospitals, clinics and tissue establishments, in accordance with European regulations. The information is aggregated as a denominator for the TRIP data on adverse reactions and events and is submitted to the European Commission. On behalf of the Healthcare Inspectorate TRIP drafts the annual mandatory overview of serious adverse events and reactions to be forwarded to the European Commission.

1.3 Participation in 2012

Participation of all stakeholders in the TRIP reporting system is essential for the quality of the biovigilance. Participation is determined on the one hand by submission of reports to TRIP and - if relevant - to the tissue establishment in question and/or the Healthcare Inspectorate. On the other hand annual numbers of processed, distributed and transplanted units of human tissues and cells need to be provided along with the numbers of recipients. The quality and completeness of reports as well as of the submitted figures are also important.

In looking at participation rates TRIP distinguishes two categories of institutions: the suppliers (tissue establishments and organ banks) and the users (hospitals and clinics). A tissue establishment is a tissue bank, hospital department or other institution that performs activities like processing, storage or distribution on human tissues and cells[1]. A hospital can be a user of human tissues and cells and can also harbour one or more tissue establishments.

A tissue establishment cannot procure tissues and cells after donation without an additional licence. Procurement after harvesting of human tissues and cells is reserved for tissue establishments which are licensed as an organ bank[2]. Organ banks are licensed to subsequently process, store and distribute human tissue and cells and must be not-for-profit organisations. All organ banks are also tissue establishments; however, not all tissue establishments are organ banks. The scope of activity determines the required licence type, as organ bank or tissue establishment.

1.3.1 Tissue establishments

In 2012 all responsible persons of licensed tissue establishments and organ banks were contacted by letter: this involved both independently operating organ banks and tissue banks as well as tissue establishments that are part of a hospital or clinic. Previously hospitals and clinics (sometimes holding several licences) were contacted through the board of directors or the tissue vigilance officer. Due to this new procedure in 2012 the number of contacted tissue establishments is much larger (n=118) compared to 2011 (n=20). Table 1 presents an overview of the numbers of tissue establishments and organ banks in The Netherlands. A number of hospitals house several tissue establishments and/or organ banks.

Table 1. Number of tissue establishments and organ banks in 2012

	Tissue establishments	Organ banks	Total
Independent institution	10	9	**19**
Located in hospital/clinic	60	39	**99**
Total	**70**	**48**	**118**

[1] *Law on safety and quality of substances of human origin, article 1.1.k*

[2] *Law on safety and quality of substances of human origin, article 1.1.l*

Figure 2 shows the number of licences issued by Farmatec for each type of human tissues and cells. Farmatec is an executive body that grants licences and permits with regard to pharmaceuticals, medical devices, blood components and substances of human origin on behalf of the Ministry of Health.

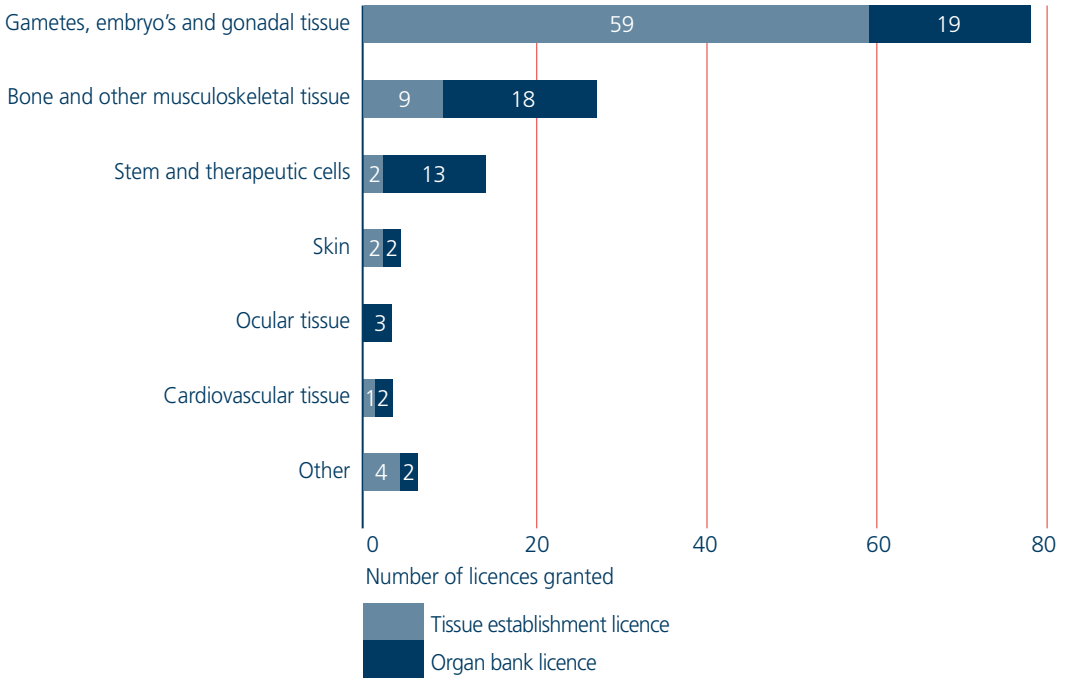


Figure 2. Number of licences granted to tissue establishments and organ bank per tissue type

Figure 3 shows the percentage of tissue establishments that provided data on processing and distribution and whether they submitted biovigilance reports. Two tissue establishments did not send any information. Both hold a licence for semen processing. Three tissue establishments indicated that they did not perform any activities in 2012 that were within the scope of the Law on safety and quality of substances of human origin. Participation of tissue establishments in 2012 amounted to 98% (116 out of 118). In 2011 this percentage was 100%.

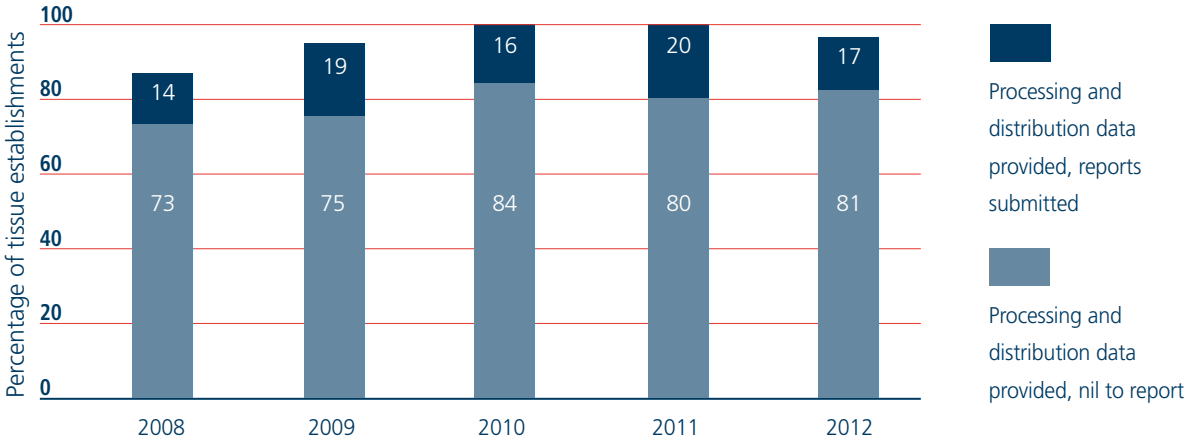


Figure 3. Participation by tissue establishments (2008-2011: n=20, 2012: n=118)

1.3.2 Hospitals and clinics

In all, TRIP contacted 97 hospitals and eight clinics for information on numbers of applied tissues and cells, the number of recipients and reports of reactions and/or events in 2012. After 2011 two private clinics and two fertility clinics were added (total n=101 in 2011). The participation by hospitals and clinics lay at 97% in 2012 (102/105). This constitutes an increase of 12% compared to 2011. Participation from 2008 onwards is presented in Figure 4.

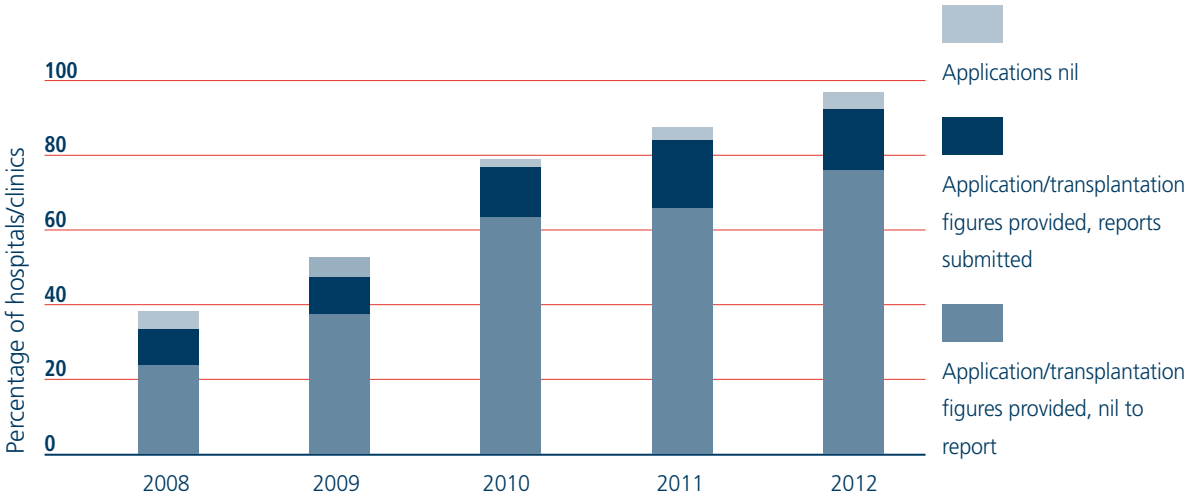


Figure 4. Percentage of Dutch hospitals/clinics that provided information on application of tissues and cells and/or vigilance reports (n= 101-105)

Figure 5 shows the degree of completeness of the information provided by hospitals and clinics. Information was deemed complete if, after inventory, numbers were provided on all types of tissues and cells applied in that particular institution. Information was deemed incomplete when numbers on some types of tissues and cells and/or the number of recipients were lacking. No applications signifies that the institution stated it did not use any tissue or cells.

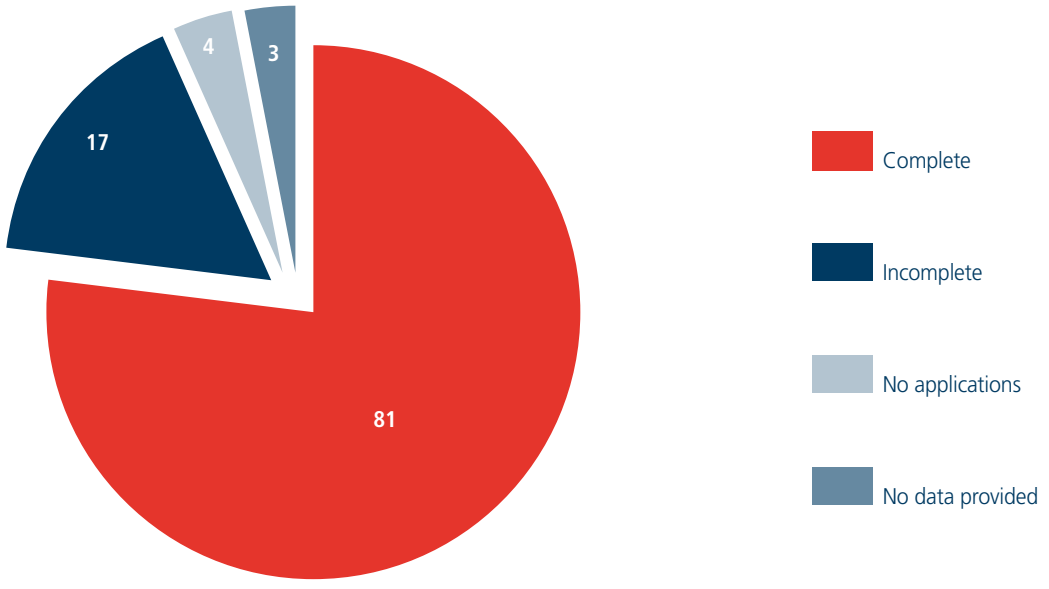


Figure 5. Degree of completeness of information on application of tissues and cells provided by hospitals and clinics (n=105)

1.4 Reports in 2012

1.4.1 Reports analysed in 2012

In all TRIP received 90 reports concerning 2012. The closing date for inclusion in the annual biovigilance report 2012 and EU overview was April 1 2013. Out of the total number of reports, 53 (59%) were assessed as serious based on the criteria of the *"Common approach for reportable serious adverse events and reactions as laid down in the tissues and cells Directive 2004/23/EC"* and were included in the annual overview for the European Commission.

In 2011 TRIP registered 84 reports before the closing date for the annual report. Including 12 late report the total number comes to 96 reports. Figure 6 shows the number of reports submitted from 2006 onwards broken down in serious and non-serious reports.

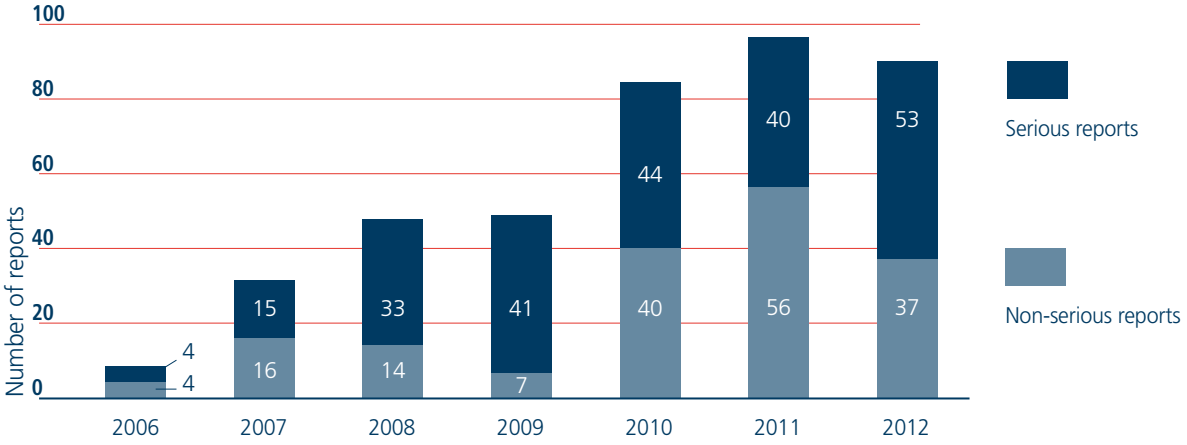


Figure 6. Number of reports, 2006 - 2012

Table 2 presents an overview of reports per human tissue or cell type in 2012.

Table 2. Reports per human tissue or cell type in 2012

	Total	Non-serious	Serious
Gametes, embryos and gonadal tissue	50	20	30
Hematopoietic stem cells	19	7	12
Ocular tissue	12	6	6
Bone and other musculoskeletal tissue	8	4	4
Skin	0	0	0
Cardiovascular tissue	0	0	0
Other cells	1	0	1
Total	**90**	**37**	**53**

1.4.2 Late reports from 2011

After the closing date for the TRIP report 2011 another 12 reports were registered including two serious reports. This brought the total number of reports regarding 2011 to 96. Ten late reports concerned gametes and embryos, one report concerned tendinous tissue and one report related to ocular tissue. These late reports have been included in all relevant tables and figures in this report.

1.4.3 Reporting to the Healthcare Inspectorate

Reporting of serious adverse reactions and events relating to substances of human origin is laid down in article 8.1 of the Dutch Decree on Substances of Human Origin 2006. This article states that the tissue establishment is responsible for reporting, investigation, registration and forwarding of information on serious adverse reactions and events that could be related to quality and safety of substances of human origin or that are found after application and could be linked to the applied human tissues or cells. In The Netherlands the Healthcare Inspectorate is the designated competent authority to be notified of serious adverse reactions and events relating to human tissues and cells; the TRIP digital reporting system facilitates the forwarding of serious adverse reactions and events to the Healthcare Inspectorate so that reporters need to submit information only once.

Hospitals and clinics are responsible for reporting (possible) product related serious adverse reactions and events to the tissue establishment that supplied the human tissues or cells and may also report to TRIP. If a calamity has been caused by human tissue or cells the hospital must also report this to the Healthcare Inspectorate.

Calamity

A calamity is defined by the Dutch quality law for healthcare institutions as follows:

A calamity is 'an unintended or unexpected adverse event related to the quality of healthcare and leading to death or serious adverse consequences for the patient or client of an institution'.

Serious adverse reaction

A serious adverse reaction is an unintended response, including a communicable disease, in the donor or in the recipient associated with procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity. (EU Directive 2004/23/EC Article 3)

This definition corresponds to adverse reactions with severity grade 2 or higher. Table 3 shows the definitions of severity grades of adverse reactions.

Table 3. Severity grade of adverse reactions

Grade 0	No morbidity
Grade 1	Minor morbidity, not life-threatening
Grade 2	Moderate to serious morbidity, may or may not be life-threatening; or leading to hospitalisation or prolongation of illness; or associated with chronic disability or incapacity
Grade 3	Serious morbidity, directly life-threatening
Grade 4	Mortality following a transplantation reaction **NOTE** Grade 4 does not apply if the patient recovers after a transplantation reaction to a stable clinical condition and subsequently dies of causes unrelated to the tissue or cell transplantation

Donor complications can be graded for severity in the same manner. Serious donor complications are not yet subject to mandatory reporting. TRIP does collect donor complications for the overview of serious adverse reactions and events that is annually sent to the European Commission.

Serious adverse event

A serious adverse event is any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to 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 (EU Directive 2004/23/EC Article 3).

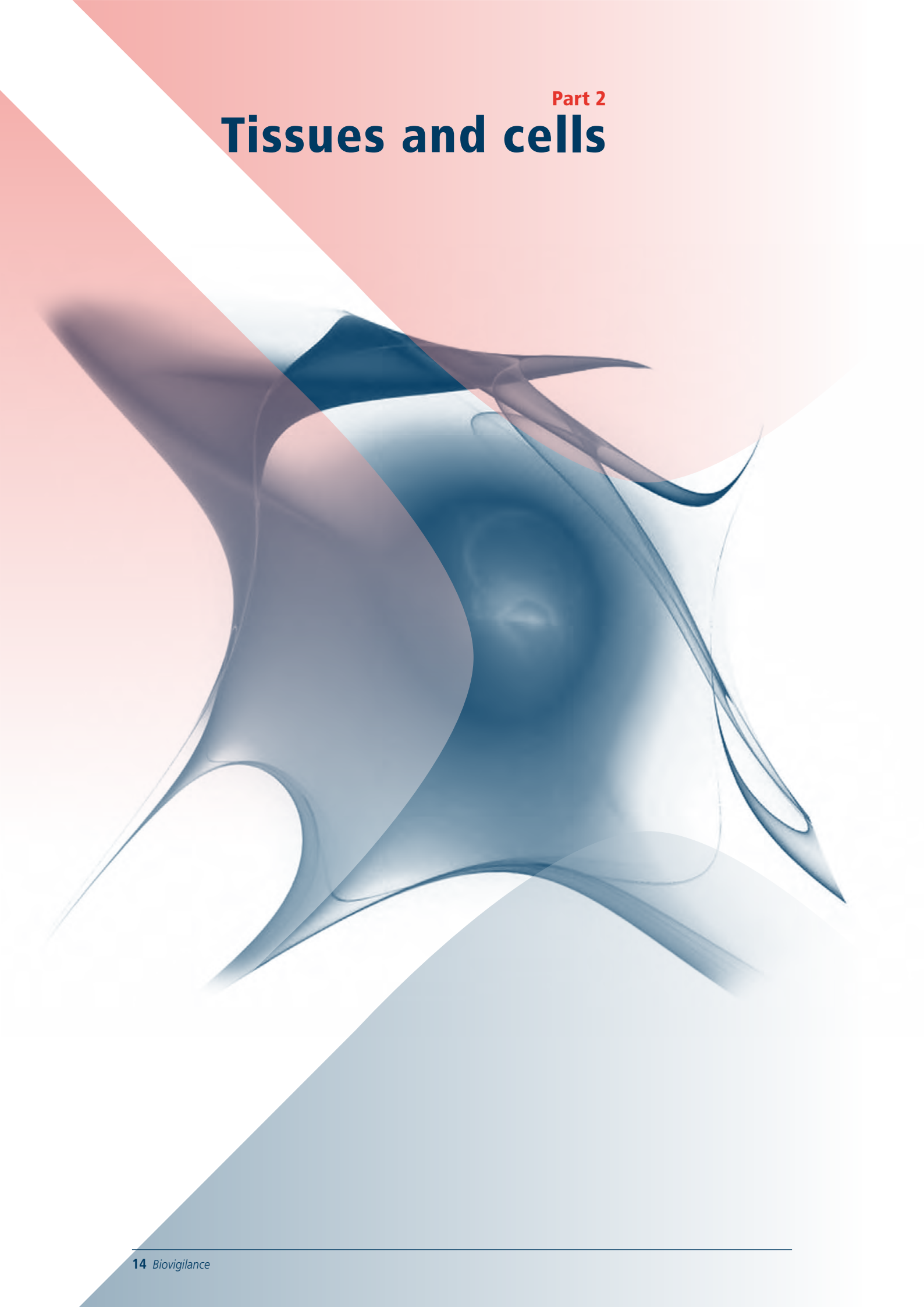
The criteria applied by the European Commission for serious adverse events are presented in Table 4. These criteria were developed by EU projects EUSTITE and SOHO V&S and are published in the *"Common approach for reportable serious adverse events and reactions as laid down in the tissues and cells Directive 2004/23/EC"*.

Table 4. Criteria for serious adverse event

Inappropriate tissues or cells were distributed for clinical use, even if not used
The event could have implications for other patients or donors because of shared practices, services, supplies or donors
The event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells
The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells
The event led to a serious adverse reaction (grade 2,3 or 4)
The event led to misidentification or switch of gametes or embryos
The event led to the loss of a complete fertility cycle in assisted reproductive technologies

Part 2

Tissues and cells



2.1 Gametes, embryos and gonadal tissue

2.1.1 Background

To fulfil the desire for a child sometimes assisted reproductive technologies are needed. Three well-known techniques are: intra-uterine insemination (IUI), in vitro fertilisation (IVF) and intra-cytoplasmic sperm injection (ICSI). The reproductive techniques all increase the chance of the fertilisation of an egg by a sperm cell. They all involve a laboratory phase in which gametes are processed. In IVF and ICSI this is followed by an incubation phase for the development of embryos and subsequent selection of embryos for transfer or cryopreservation.

Donor sperm can be used in cases of male infertility, absence of a male partner or in cases of genetic abnormality. Donor sperm can be applied in IUI and also in IVF and ICSI procedures. Sperm donors are thoroughly screened but it is not possible to exclude all genetic disease.

In The Netherlands the practice of oocyte vitrification and cryopreservation for later use is available on a small scale.

Microsurgical Epididymal Sperm Aspiration (MESA) and Percutaneous Epididymal Sperm Aspiration (PESA) are surgical procedures for the harvesting of mature sperm cells from the epididymis. MESA and PESA are performed in men who produce sperm cells but whose ejaculate contains no viable sperm cells due to sperm duct blockage or after vasectomy that cannot be reversed surgically. TESE (testicular sperm extraction) is an option for men suffering from failure of sperm production. In TESE immature sperm cells are harvested by testicular biopsy.

Gametes, embryos and gonadal tissue can be cryopreserved or vitrified and stored for longer periods of time in liquid nitrogen. These techniques are used in fertility preservation treatment in oncological patients, storage of donor and partner semen, as well as for storing remaining embryos in IVF and ICSI treatment.

In The Netherland 13 laboratories (tissue establishments) perform IVF and ICSI treatment. They may also process gametes from patients in other clinics (called transport clinics). There are 65 licensed tissue establishments that process semen (sperm) for IUI. Only semen laboratories that hold an organ bank licence are authorised to process and store donor sperm. One clinic holds a licence for processing of semen and oocytes but does not actually carry out IVF or ICSI treatments.

2.1.2 Processing, distribution and application

In Table 5 and 6 numbers of processing, distribution and application of reproductive cells are presented.

Table 5. Processing and distribution of gametes, embryos and gonadal tissue

Type	Tissue establishment	Processed	Distributed				Total distributed
			Unit	NL own clinic	NL trans-port clinic	In EU	Outside EU	
Partner semen, fresh	72	41117	Donation	40198	562	116	0	**940876**
Partner semen, cryopreserved	6	2727	Straw	1319	1421	67	1	**2808**
Donor semen cryo-preserved and fresh	14	2726	Straw or donation	13670	18	296	0	**13984**
Semen MESA/ PESA/ TESE	10	677	Aspiration or biopsy	722	29	39	0	**790**
Oocytes, donated	11	2563	Oocyte	0	1886	0	0	**1886**
Oocytes, cryopreserved	13	2786	Oocyte	10	0	0	0	**10**
Oocytes fresh	14	134954	Oocyte	n.a.	n.a.	n.a.	n.a.	**n.a.**
Embryos, fresh	14	37522	Embryo	19631	0	0	0	**19631**
Embryos, cryopreserved	14	24663	Embryo	13758	17	3	0	**13778**

Table 6. Application of gametes, embryos and gonadal tissue

Type	Hospitals/ clinics	Recipients	Transplants				Total applications
			Unit	From NL	From EU	Outside EU	
Partner semen, fresh	79	19966	Donation	39004	0	0	**39004**
Partner semen, cryopreserved	16	628	Straw	1503	0	0	**1503**
Donor semen, cryopreserved and fresh	15	3313	Straw or donation	13338	84	0	**13422**
Semen MESA/ PESA/ TESE	10	524	Aspiration or biopsy	750	0	0	**750**
Embryos, fresh	14	11102	Embryo	19631	0	0	**19631**
Embryos, cryopreserved	14	6001	Embryo	13066	0	0	**13066**

Some cryopreserved embryos are not viable after thawing, hence the difference in number of distributed and applied cryopreserved embryos. The difference in semen distribution and applications arises from the figures for distribution. Some tissue establishments have included semen used in IVF treatment to their distribution numbers. In order to balance numbers the guidance for the 2013 inventory will have clearer instructions for the provision of data.

2.1.3 Reports

TRIP registered 50 reports in 2012 that related to procedures or application of gametes, embryos and/or gonadal tissue in assisted reproductive technologies. This concerns 55% of the total of registered reports. All fertility clinics that carry out IVF and ICSI procedures submitted reports; four tissue establishments that process semen

submitted reports. All reports concern adverse events; no adverse reactions were reported. Figure 7 shows the breakdown in categories of events. As in 2010 and 2011 the majority of reports were registered in the category loss of tissues or cells.

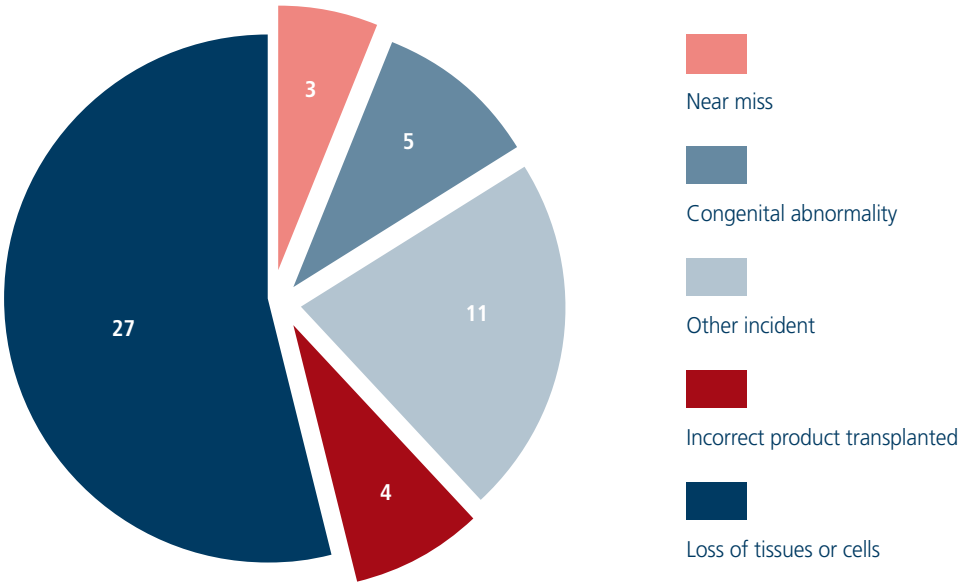


Figure 7. Reports concerning gametes, embryos and gonadal tissue per category of event in 2012

Table 7 gives an overview of numbers and category of event per cell or tissue type. Tables 8-12 offer short descriptions of adverse events reported in 2012.

Table 7. Overview of adverse events reported in 2012

Tissue or cell type	Category of event	Number	Serious*
Semen	Congenital abnormality	5	0
	Loss of tissues or cells	4	1
	Incorrect product transplanted	3	3
	Near miss	2	0
	Other incident	1	0
Oocytes	Loss of tissues or cells	9	6
	Other incident	5	1
Semen and oocytes	Other incident	1	1
Embryos	Loss of tissues or cells	14	12
	Other incident	3	3
	Incorrect product transplanted	1	1
Semen, oocytes and embryos	Near miss	1	1
Ovarian tissue	Other incident	1	1
Total		**50**	**30**

** According to definitions of the Association of Clinical Embryologists*

Table 8. Overview of adverse events concerning semen

Category of event	Number of reports	Type of error	Step in procedure	Number; description
Loss of tissues or cells	4	Administrative error	Storage	• Unique partner semen (cryo) destroyed in error
		Assessment error	Storage	• Partner semen destroyed too soon
		Storage error	Donation	• Semen in non-validated container
		Identification error	Storage	• Cryo semen straw with similar name and date of birth destroyed in error
Incorrect product transplanted	3	Identification error	Insemination Processing	• 2x misidentification at insemination • CMV positive semen selected and inseminated in CMV negative recipient
Near miss	2	Identification error	Donation Processing	• Semen sample not labelled • Mislabelling of straw of directed donor
Congenital abnormality*	5	Other	n.a.	New-born/foetus with: • Anencephaly • Achondroplasia • Congenital heart abnormality • Neurofibromatosis • Trisomy 21
Other incident*	1	Other	n.a	• Hip dysplasia

* *regarding donor semen*

Table 9. Overview of adverse events concerning oocytes

Category event	Number of reports	Type of error	Step in procedure	Number; description
Loss of tissues or cells	9	Identification error	Procurement	• Mislabelled follicular fluid container
		Technical error	Procurement	• Base dropped out of follicular fluid container
		Processing error	Processing	• Oocytes lost in pipette • Oocytes damaged at micro-dissection • 2x oocytes not transferred to culture dish • 3x oocyte culture dish dropped or knocked over
Other incident	5	Storage error	Donation	• 2x oocytes transported in too cold transportation box
		Processing error	Processing	• Part of oocytes not taken out of transportation box • ICSI instead of planned IVF procedure • Oocytes not inseminated; injection performed the next day

Table 10. Overview of events concerning semen and oocytes

Category event	Number of reports	Type of error	Step in procedure	Number; description
Other incident	1	Processing error	Processing	• IVF instead of planned ICSI procedure

Table 11. Overview of adverse events concerning embryos

Category event	Number of reports	Type of error	Step in procedure	Number; description
Loss of tissues or cells	14	Administrative error	Storage	• Cryopreserved embryos destroyed although couple re-registered for embryo transfer
			Processing	• Remaining embryos after fresh ET not assessed for cryopreservation
		Communication error	Processing	• Gas supply failure in incubator
		Technical error	Processing	• Incorrect gas composition in part of incubator
		Storage error	Storage	• Straw containing embryo not found at registered location in liquid nitrogen container
		Processing error	Embryo transfer	• Embryo lost in catheter for transfer
			Processing	• 3x at cryopreservation, straws placed in liquid nitrogen instead of seeding • Remaining embryo destroyed by mistake • Straw dropped at cryopreservation • Embryo erroneously assessed as unfit for cryopreservation • Embryo left behind in pipette • Pipette containing embryo jolted
Incorrect product transplanted	1	Selection error	Processing	• Transfer of embryo derived from oocyte that contained 3 pronuclei
Other incident	3	Assessment error	Processing	• Embryo of Hepatitis C positive patient stored in regular liquid nitrogen container
		Processing error	Processing	• Incubator alarm incorrectly dealt with; possible quality loss of embryos • In deviation from protocol, 2 embryos transferred instead of 1

Table 12. Overview of adverse events concerning semen, oocytes and embryos

Category event	Number of reports	Type of error	Step in procedure	Number; description
Near miss	1	Processing error	Processing	• ICSI procedure with semen from Hepatitis B positive partner; procedure deferred

Table 13. Overview of events concerning ovarian tissue

Category event	Number of reports	Type of error	Step in procedure	Number; description
Other incident	1	Technical error	Cryo-preservation	• Incorrect device procedure for cryopreservation. Possible quality loss

Figure 8 shows the reports concerning gametes, embryos and gonadal tissue in the last few reporting years. Figure 9 focuses on reports of identification errors and selection errors. The theme of identification and selection errors further analyses these errors in the years 2007-2012 in chapter 3.2.

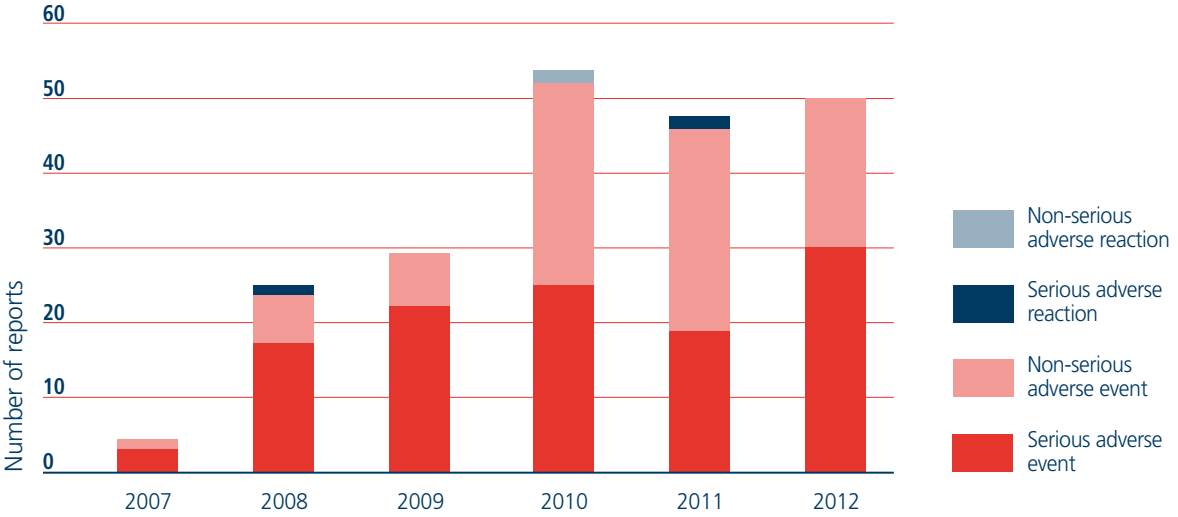


Figure 8. Reports concerning gametes, embryos and gonadal tissue 2007 - 2012

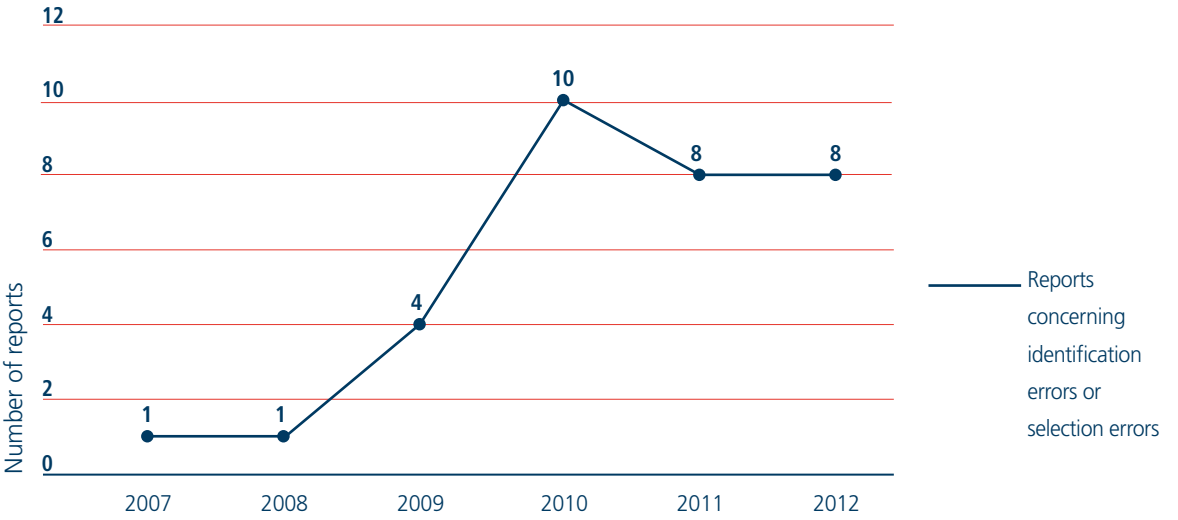


Figure 9. Number of reports of identification and selection errors in assisted reproductive technologies

2.2 Hematopoietic stem cells

2.2.1 Background

Blood stem cells (hematopoietic stem cells HPSC) are located in bone marrow in hollow bones like the sternum, spine and pelvis. Hematopoietic stem cells can be transplanted in patients whose own blood production system needs replacing. The most important hemato-oncology indications are leukaemia, non-Hodgkin lymphoma, Hodgkin's lymphoma and multiple myeloma. Chemotherapy and (often) total body irradiation are applied to eliminate malignant cells but lead to loss of the patients' own blood stem cells; these can be replaced by a hematopoietic stem cell transplant. For non-oncological indications and for older patients the regime nowadays only involves immunosuppression. The immune system of the donor is able to control the malignant cells, the so called Graft versus Leukaemia effect (GVL).

The HPSC may be collected from the patient (autologous) in a phase when the malignancy is in remission or from an allogeneic donor compatible for Human Leukocyte Antigen (HLA) tissue markers (a family member or an unrelated donor) or from HLA compatible cord blood.

Autologous or allogeneic HPSC are harvested by bone marrow aspiration under anaesthesia or collected from the peripheral circulation (peripheral blood stem cells, PBSC) by apheresis after pre-treatment with the growth factor granulocyte colony stimulating factor (G-CSF). In recent years PBSC collected by apheresis has become the procedure of choice for adults as potentially greater numbers of stem cells can be harvested and this procedure does not involve anaesthesia.

Patients who have received a stem cell transplant are sometimes subsequently given lymphocytes from the same donor: Donor Lymphocyte Infusion (DLI). Lymphocytes are white blood cells that are able to amplify the immune reaction against possible remaining malignant cells in the patient (GVL). However, lymphocytes deriving from the donor may also cause the deleterious reversed rejection reaction, Graft versus Host Disease (GVHD), after transplant in the patient. Sometimes lymphocytes are selected and stimulated during laboratory processing in order to obtain a better ratio of GVL/GVHD.

All thirteen stem cell laboratories in The Netherlands collaborate in the Working Group of Stem Cell Laboratories. The stem cell laboratories test, process, preserve and distribute stem cell products from autologous and related donors. Stem cell products from unrelated donors (including cord blood) are distributed by the Europdonor Foundation to all of the eight academic transplant centres for specific recipients, usually via the stem cell laboratory. The stem cell laboratories carry out preservation and/or additional processing (e.g. erythrocyte or T-cell depletion). Unrelated stem cell transplants for Dutch patients usually derive from foreign voluntary donors. Dutch voluntary donors may donate bone marrow, peripheral blood stem cells or cord blood to Dutch or foreign patients. In collaboration with Sanquin, Europdonor Foundation arranges collection of bone marrow and peripheral stem cells in two university hospitals. In The Netherlands there is one (Sanquin) cord blood bank that stores cord blood transplants, available for nonrelated patients.

2.2.2 Processing, distribution and transplantation

Tables 14 and 15 show the figures for processing, distribution and application of hematopoietic stem cells and numbers of institutions performing each activity.

Table 14. Processing and distribution of hematopoietic stem cells in 2012

Type	Institutions	Unit	Processed	Distributed				
				Unit	In NL	In EU	Outside EU	Total distribute
HPSC unrelated*								
Bone marrow	8	Transplant	67	Bag	55	8	4	67
PBSC	8	Transplant	349	Bag	263	5	6	274
Cord blood	7	Transplant	280	Bag	76	4	4	84
HPSC related								
Bone marrow	6	Transplant	21	Bag	21	0	0	21
PBSC	7	Transplant	201	Bag	209	0	0	209
Cord blood	2	Transplant	6	Bag	6	0	0	6
HPSC autologous								
Bone marrow	4	Transplant	50	Bag	121	0	0	121
PBSC	10	Transplant	1612	Bag	3095	0	0	3095
Cord blood**	2	Transplant	18397	Bag	0	0	0	0
Other stem cells								
Mesenchymal stem cells	3	Transplant	245	Bag	258	23	0	281
Lymphocytes (DLI)	7	Transplant	132	Bag	92	2	2	96

* *one institution could only provide the number of transplants instead of bags; this may have led to a lower figure for bags distributed provided than the actual number.*

***preservation and storage is provided by a commercial cord blood bank for parents who choose to pay for preservation of cord blood as a precaution for possible future treatment.*

Table 15. Application of hematopietic stem cells in 2012

Type	Transplant centres	Recipients	Transplants				
			Unit	From NL	From EU	From non-EU	Total number of bags
HPSC unrelated							
Bone marrow	7	18	Bag	1	11	2	14
PBSC	7	256	Bag	8	257	27	292
Cord blood	7	57	Bag	8	27	49	84
HPSC related							
Bone marrow	7	25	Bag	25	0	0	25
PBSC	7	148	Bag	163	0	0	163
Cord blood	0	0	Bag	0	0	0	0
HPSC autologous							
Bone marrow	3	41	Bag	41	0	0	41
PBSC	11	659	Bag	2164	0	0	2164
Cord blood	0	0	Bag	0	0	0	0
Other stem cells							
Mesenchymal stem cells	3	69	Bag	286	0	0	286
Lymphocytes	8	157	Bag	62	22	6	90

The aggregate data on HPSC (Tables 14 and 15) show differences in numbers of processing, distribution and transplantation of hematopoietic stem cells that cannot easily be understood. One factor leading to the discrepancies is the fact that a unit for transplantation (possibly from a foreign country) may be reprocessed by the recipient institution (e.g. T-cell depletion) before transplantation; due to reprocessing the unit is designated and counted as processed and distributed by a Dutch tissue establishment. One institution has provided numbers of transplants instead of bags distributed as the latter figures could only be manually extracted from paper files.

2.2.3 Reports

The reports concerning hematopoietic stem cells regarded 12 adverse events and seven adverse reactions summarised in Table 16 and 17.

Tabel 16. Overzicht voorvallen per soort hematopoëtische stamcellen

Type	Category of event	Aantal
PBSC, autologous	Loss of tissues or cells • 2 out of 5 bags ruptured • 1 out of 2 bags ruptured • Portal of bag leaking	3
	Bacterial contamination of product • 1x Staphylococcus Aureus • 1x Sphingomonas Paucimobilis	2
PBSC, allogeneic related	Other incident, insufficient CD 34+ cells infused due to communication error	1
PBSC, allogeneic unrelated	Loss of tissues or cells: part of harvested stem cells left behind in donation kit	1
	Bacterial contamination of product	1
	Other incident: donor possible XYY karyotype	1
Bone marrow, allogeneic unrelated	Bacterial contamination of product, Staphylococcus Epidermidis	1
Cord blood, allogeneic unrelated	Loss of tissues or cells: bag ruptured during spin cycle	1
	Other incident: leaking bag	1
Total		**12**

Table 17. Overview of adverse rections per tpe of hematopoietic stem cells

Type	Category of adverse reaction	Number
Donor: PBSC, allogeneic related	Donation complication • Donor developed AML 7 years after donation • Donor developed MDS-RAEB* 5 years after donation	2
	• Transient creatinine elevation in donor	1
Recipient: autologous bone marrow	Other reaction, acute renal insufficiency 1day after transplantation	1
Recipient: allogeneic unrelated PBSC	• Post-transplant bacteraemia/sepsis (product culture negative); patient died • Anaphylactic reaction, epileptiform seizure and hypotension (no DMSO in product) • Possible hemolytic reaction with dyspnoea and drop in O_2 saturation (product contained 100 x 10^9 ABO incompatible erythrocytes)	3
Total		**7**

* *Myelodysplastic syndrome with refractory anemia and excess blasts*

Figure 10 shows the numbers of reports concerning hematopoietic stem cells per year in recent years. The number of reported adverse reactions seems fairly stable over the years. The number of adverse events however shows fluctuation. The reduction in non-serious reports is due to a drop in reports of poor/failure of engraftment/ growth.

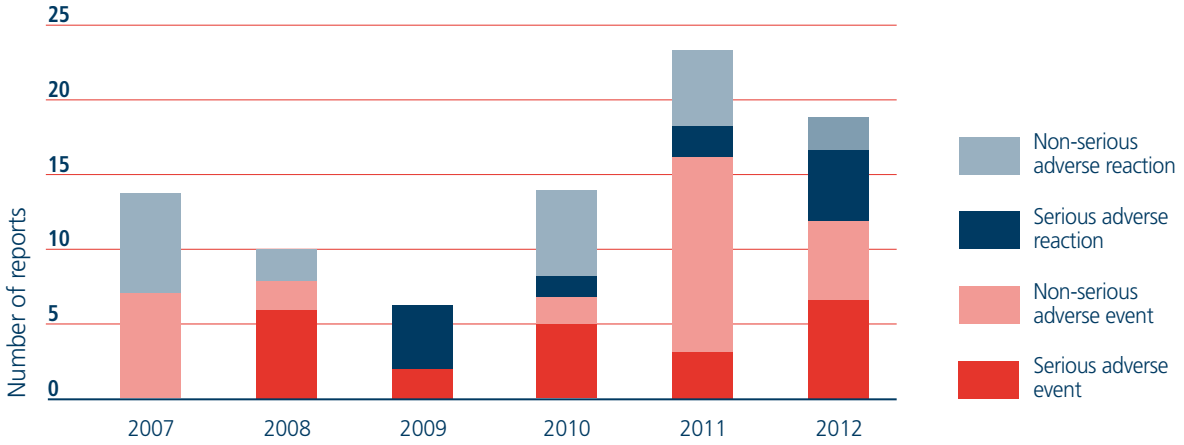


Figure 10. Reports concerning hematopoietic stem cells, 2007-2012

In 2012 five serious adverse events in the category loss of tissues or cells are noteworthy. Four out of these five concern rupture or leakage of bags leading to loss of unique recipient-specific material and these could have potentially serious implications for the recipient. Figure 11 shows an overview of the reports in recent years regarding ruptured or leaking bags for collection or preservation of HPSC. This issue, which was also identified in the 2010 and 2011 data, will be further investigated by the Stem Cell Laboratory Working Group in cooperation with the reporters.

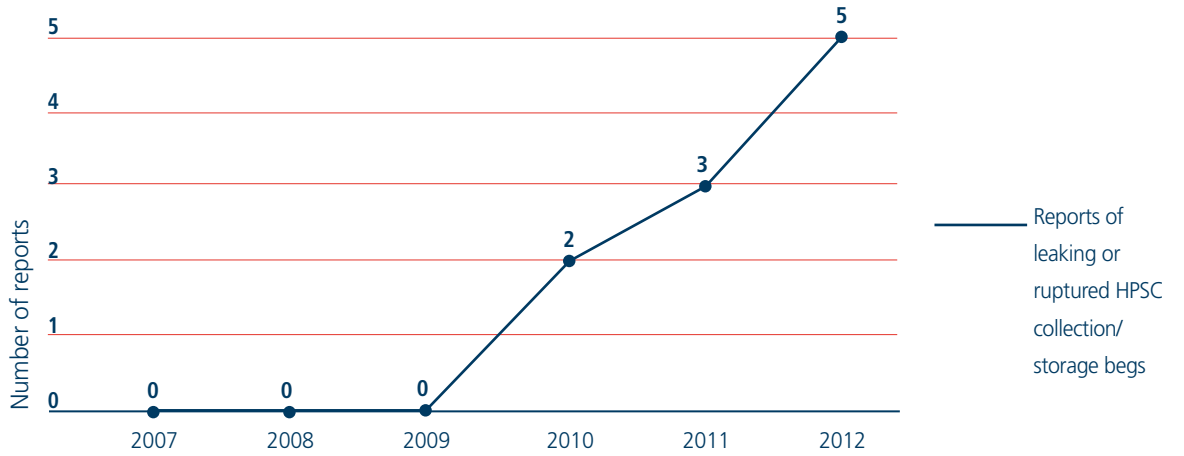


Figure 11. Reports of ruptured or leaking HPSC collection/storage bags, 2007-2012

2.3 Bone and other musculoskeletal tissues

2.3.1 Background

Bone and other musculoskeletal tissues are used for various purposes in the treatment of patients, e.g. reconstruction of the bony skeleton (tumour surgery or severe trauma), in joint injuries, for reconstruction of other parts of the human body, as a filler in reconstruction of bone defects but also as osteo-inductive material to promote healing. Bone is obtained both from post-mortem donors and from living donors, who may donate a femoral head at hip replacement surgery. The femoral head can be processed, for instance into bone chips.

Other musculoskeletal tissues include cartilage, tendons, ligaments, fascia and menisci of post-mortem donors. Tendons and ligaments are applied in reconstructive surgery following severe knee, ankle or shoulder injuries. In exceptional cases ruptured menisci can be replaced by a donor transplant.

Eighteen hospitals and orthopaedic centres in The Netherlands operate a licensed bone bank to provide the required donor bone for their own patients; bone is harvested from voluntary living donors who donate a femoral head in hip replacement surgery. There is also a bone bank that processes post-mortem bone tissue. Several tissue establishments import or process musculoskeletal tissue, including autologous chondrocyte implantation (ACI). This treatment involves in vitro culturing of autologous cartilage cells after a harvesting procedure; the cultured cartilage cells are transplanted in a second procedure. The cartilage cells adhere to the bone surface and start forming new cartilage. The in vitro growing of cartilage is a sophisticated, recently developed technique.

2.3.2 Bone

Processing, distribution and transplantation

In Table 18 the number of processed and distributed units of bone are shown. Table 19 shows the number of transplanted units of bone. The data were provided by 54 hospitals and clinics.

Table 18. Processing and distribution of bone in 2012

Type	Institutions	Processed	Distributed				Total distributed
			Unit	In NL	In EU	Outside EU	
Bone, whole	5	834	Transplant	776	9	0	**785**
Bone filler, mineralised: chips, cubes and wedges	12	3770	Container	2485	4469	1347	**8501**
Bone filler, mineralised: whole and halved femoral heads	14	2528	Transplant	2706	351	0	**3057**
Bone filler, demineralised	6	4835	Container	1566	14836	5298	**21700**
Auditory ossicles	1	52	Transplant	52	0	0	**52**
Cranial bone (autologous)	5	102	Transplant	57	0	0	**57**
Other	1	15	Transplant	15	0	0	**15**

Table 19. Transplantation of bone in 2012

Type	Hospitals/ clinics	Recipients	Transplants				Total transplants
			Unit	From NL	From EU	From non-EU	
Whole bone	8	50	Transplant	52	0	0	**52**
Bone filler, mineralised: chips, cubes and wedges	35	974	Container	1022	0	64	**1086**
Bone filler, mineralised: whole and halve femoral heads	45	1256	Transplant	1317	0	0	**1317**
Bone filler, demineralised	7	125	Container	119	7	2	**128**
Auditory ossicles	4	39	Transplant	39	0	0	**39**
Cranial bone (autologous)	6	116	Transplant	67	0	49	**116**
Other	4	39	Transplant	4	0	40	**44**

There is a large discrepancy in numbers of distributed whole bone transplants and bone filler compared to the transplantation data. Transplantation of bone in hospitals and clinics is insufficiently inventoried. Moreover, private clinics were not included in this inventory. Six tissue establishments import large amounts of bone filler from the USA and other countries and distribute it within The Netherlands and other countries.

Reports

Four reports concerning bone tissue were registered. These concerned one adverse reaction and three adverse events. One of these four reports was assessed as serious. The reports are summarised in Tables 20 and 21.

Table 20. Overview of adverse events concerning bone tissue in 2012

Categorie voorval	Number of reports	Description
Bacterial contamination	2	E. Coli in peroperative culture and post-transplant bacterial infection in recipient
		Staphylococcus Saprophyticus in perioperative culture
Other incident	1	Graft has obnoxious odour (DMSO)

Table 21. Overview of adverse reactions concerning bone in 2012

Category of adverse reaction	Number of reports	Beschrijving
Other reaction	1	New allo-antibody formation (anti-D) in recipient

Figure 12 presents the reports concerning bone tissue in recent years.

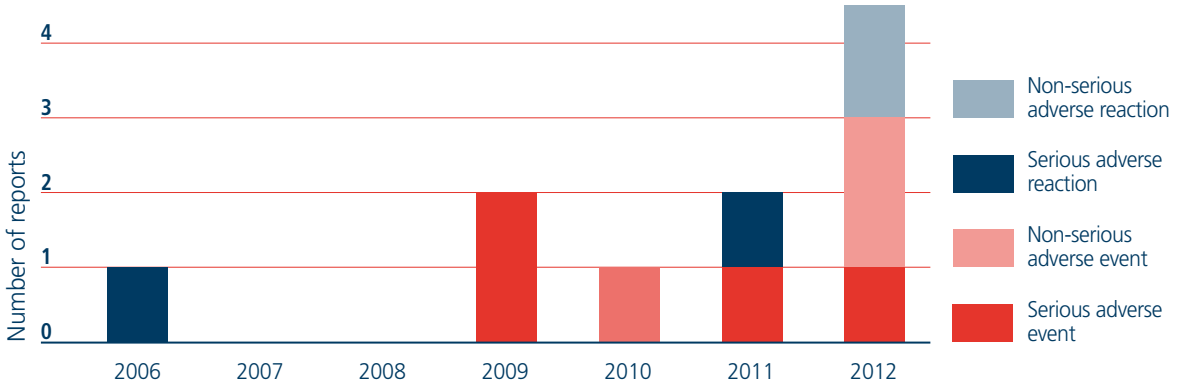


Figure 12. Reports concerning bone tissue, 2006-2012

The largest risk in bone tissue transplantation is transmission of pathogens or malignancies. In previous years TRIP registered five reports that concerned (risk of) bacterial contamination. These reports were registered as adverse events in category bacterial contamination of product or as adverse reaction in post-transplantation bacterial infection.

2.3.3 Cartilage

Processing, distribution and transplantation

In Table 22 numbers of processed and distributed units of cartilage are presented. Table 23 shows the data on transplanted cartilage units.

Table 22. Processing and distribution of cartilage in 2012

Type	Institutions	Processed	Distributed				Total distributed
			Unit	In NL	In EU	Outside EU	
Cartilage	3	153	Transplant	52	0	0	**151**

Table 23. Transplantation of cartilage in 2012

Type	Hospitals	Clinics	Transplants				Total applied
			Unit	From NL	From EU	From non-EU	
Cartilage	5	64	Transplant	14	42	0	**56**

Reports

In 2012 no reports were registered concerning cartilage or chondrocytes. In Figure 14 an overview is presented of reports concerning cartilage in reporting years 2007-2012.

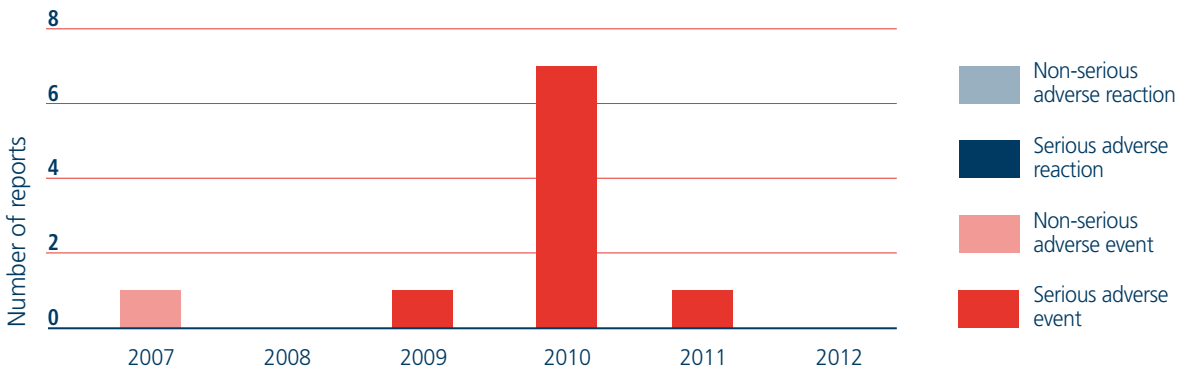


Figure 14. Reports concerning cartilage, 2007-2012

Notably all reports regarded adverse events concerning autologous cultured chondrocytes. In 2010 seven adverse events were reported to TRIP. These reports were submitted by two tissue establishments. In 2010 there were three licensed organ banks and two tissue establishments with a licence for processing of cartilage. In 2011 this decreased to two organ banks and two tissue establishments.

2.3.4 Tendons, ligament, fascia and menisci

Processing, distribution and transplantation

In Table 24 numbers of processed and distributed units of tendons, ligaments, fascia and menisci are presented. Table 25 shows the numbers of transplanted units.

Table 24. Processing and distribution of tendons, ligaments, fascia and menisci in 2012

Type	Institutions	Processed	Distributed				Total distribueerd
			Unit	In NL	In EU	Outside EU	
Tendons	4	581	Transplant	472	112	0	**584**
Ligaments and fascia	2	1827	Transplant	1764	0	0	**1764**
Menisci	0	0	Transplant	0	0	0	**0**
Other	0	0		0	0	0	**0**

Table 25. Transplantation of tendons, ligaments, fascia and menisci in 2012

Type	Hospitals/ clinics	Recipients	Transplants				Totaal transplants
			Unit	From NL	From EU	From non-EU	
Tendons	22	210	Transplant	206	6	2	**214**
Ligaments and fascia	9	288	Transplant	86	202	0	**288**
Menisci	3	45	Transplant	43	0	2	**45**
Other	2	2	Transplant	2	0	0	**2**

Reports

Four reports regarded tendons in 2012. In previous years no reports concerning tendons were registered. Three reports were judged to be serious, two of these regarded the unexpected rupture of a tendon during surgery.

Table 26. Overview of adverse events concerning tendons in 2012

Category of event	Reports 2012	Description
Other incident	2	Tendon ruptured during surgery, spare tendon available and transplanted
	1	Packaging of tendon had already been opened and accompanying follow-up form had been used for another tendon
Bacterial contamination of product	1	Peroperative culture positive for skin commensals, culture at harvesting positive for coagulase-negative staphylococcus. Cultures during processing negative

In 2012 and in previous years no reports were registered that concerned other musculoskeletal tissues.

2.4 Ocular tissue

2.4.1 Background

The cornea is the clear anterior part of the eyeball, that permits light to enter into the eye. A corneal transplant is indicated when eyesight is decreased due to corneal disease provided that other parts of the eye are functional. Common indications for corneal transplant are opacity, deformation or scarring following infection or injury of the cornea. Often a transplant is the only available option for improving eyesight in these patients. The affected cornea is (partly) replaced by a post-mortem donor cornea. Annually around 850 corneal transplants are carried out in The Netherlands. The shelf life of post-mortem corneas is limited; they only remain in optimal condition for four weeks.

Two types of corneal transplant techniques are available, namely penetrating and lamellar keratoplasty. In penetrating keratoplasty the full thickness of the cornea is replaced by a donor cornea. In lamellar keratoplasty only the affected layer is replaced. Lamellar keratoplasty is subdivided according to the replaced layer.

The sclera is the outermost part of the eyeball and is partly visible as the whites of the eyes. Donor sclera is used in reconstructive surgery of eyes and eyelids. Sclera can be preserved and stored for a year. Each sclera is stored separately in 70% ethanol. Distribution may be in segments of 10x15 mm, in quadrants or complete sclera.

When harvesting cornea and sclera the complete eyeball is explanted in post-mortem donors; processing is done in two organ banks in The Netherlands. Cornea and sclera are both exported and imported. The Dutch Society for Ophthalmology maintains a registry of all corneal transplants in The Netherlands.

2.4.2 Processing, distribution and transplantation

In Table 27 the numbers of processed and distributed units of ocular tissue are shown. In Table 28 numbers of transplantation are presented as provided by the contacted hospitals and clinics.

Table 27. Processing and distribution of ocular tissue in 2012

Type	Institutions	Processed	Distributed				Total distributed
			Unit	In NL	In EU	Outside EU	
Cornea	2	3282	Graft or lamella	1335	283	43	1661
Sclera	2	624	Complete graft or quadrant	934	8	0	942

Table 28. Transplantation of ocular tissue in 2012

Type	Hospital/ clinic	Recipient	Transplants				Total transplants
			Unit	From NL	From EU	From non-EU	
Cornea	9	808	Graft or lamella	807	1	0	808
Sclera	7	696	Complete graft or quadrant	681	0	0	681

There is a discrepancy in numbers of distributed cornea and sclera and the number of transplanted ocular tissues. However, the discrepancy in 2012 is smaller than in previous reporting years. Participation of the ophthalmology clinics and hospitals that perform eye surgery is rising. Collaboration with the Dutch Society for Ophthalmology on registered data on corneal transplants could provide complete and balanced numbers.

2.4.5 Reports

Twelve reports in 2012 concerned ocular tissue. These reports are summarised in Table 29. Six reports were judged to be serious. Three reports can be clustered as they regard loss of three corneas due to debris in the microkeratoma turbine. Another cluster consists of five reports that mention a persistent haze of the corneal graft in the recipient. Two reports were assessed as serious. In 2011 there were five similar reports concerning a persistent haze. Prior to 2011 this problem was not reported. A working party of the Dutch Society for Ophthalmology did extensive investigations but was unable to identify a cause.

Table 29. Report concerning ocular tissue

Category of event	Reports 2012	Description
Other incident	8	Anterior Lamellar Keratoplasty (ALKP): primary graft failure, large macula and flattening of donor cornea leading to unsatisfactory result
		Corneal transport medium culture positive for Candida albicans
		Day 1 after transplant persisting central haze in R+L donor cornea
		Day 1 after transplant persisting central haze, contralateral cornea had been rejected at second evaluation due to 15% cell loss
		Transplanting surgeon finds central haze on cutting posterior lamella, cornea rejected and surgery postponed
		Due to identification error incorrect cornea evaluated and placed in transport medium 2 x infiltrates found on processing in operating theatre, still visible after cutting of posterior lamella; surgery postponed although patient already anaesthetised
Loss of tissues or cells	3	Perforation of corneas due to debris in microkeratoma turbine
Bacterial contamination of product	1	Culture of transport medium positive, other cultures remaining negative

Figure 5 presents registered reports concerning ocular tissue in the past six years.

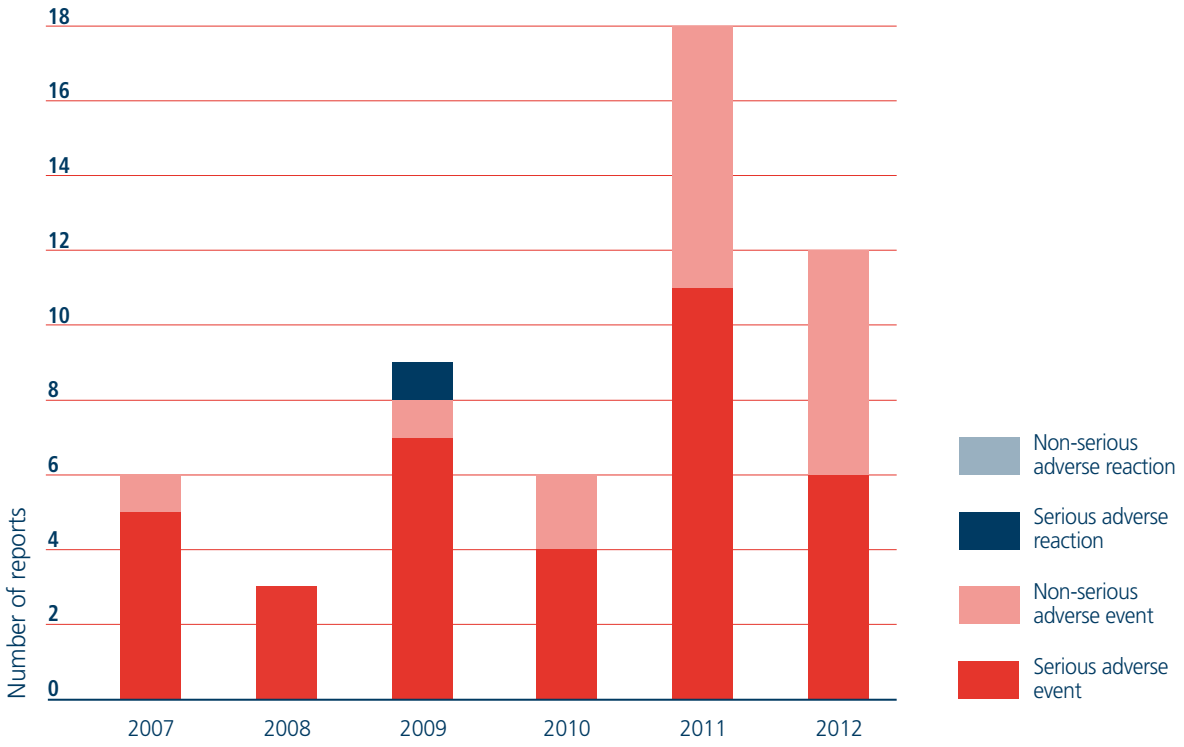


Figure 15. Reports concerning ocular tissue 2007-2012

2.5 Cardiovascular tissue

2.5.1 Background

Heart valves

Surgical heart valve replacement is an effective treatment for patients with damaged heart valves. For replacement of the damaged valve several options are available: a prosthetic (synthetic) valve or a biological valve (of human or animal origin). Human post-mortem donor valves only account for a minority of heart valve replacements as they are used for a few selected indications. Post-mortem human heart valves are particularly used in children and adolescents suffering from congenital heart defects. They are also applied in patients suffering from endocarditis. For the procurement of heart valves the complete human heart is explanted and subsequently the heart valve bank performs dissection and preparation of heart valve grafts. In The Netherlands the valves used for transplantation are the pulmonary and the aortic valve. The worst risks relating to heart valves are transmitted infection or donor conditions that could lead to malfunctioning of the grafted valve.

Blood vessel and patches

For transplant purposes only arterial vessels are used. They are indicated for aortic disease that leads to slackening of the vessel wall and in patients who suffer from an infected synthetic blood vessel prosthesis. Patches are prepared from the pulmonary artery or aortic artery and are used for reconstructions of congenital malformations in paediatric cardiac surgery.

2.5.2 Processing, distribution and application

In Table 30 processing and distribution of cardiovascular tissue and in Table 31 the transplantation of cardiovascular tissue is shown.

Table 30. Processing and distribution of cardiovascular tissue in 2012

Type	Institution	Processed	Distributed				Total distributed
			Unit	In NL	In EU	Outside EU	
Heart valves	1	452	Graft	82	23	1	**106**
Blood vessel	1	27	Graft	0	10	0	**10**
Patches, pericardium or other	1	0	Graft	23	13	0	**36**

Table 31. Transplantation of cardiovascular tissue in 2012

Type	Hospitals/ clinics	Recipients	Transplants				Total transplants
			Unit	From NLEU	From non-EU	From	
Heart valves	1	6	Graft	6	0	0	**6**
Blood vessel	1	9	Graft	0	9	0	**9**
Patches, pericardium or other	1	2	Graft	0	0	2	**2**

Only one hospital provided data on numbers of transplanted heart valves. There are several hospitals in The Netherlands that perform heart valve replacement; presumably the tissue vigilance coordinators contacted by TRIP did not receive data from the cardiac surgeons.

2.5.3 Reports

In 2012 TRIP did not receive any reports about cardiovascular tissues. In previous years a maximum of two reports per reporting year was registered concerning cardiovascular tissue. Figure16 presents an overview of these reports in recent years.

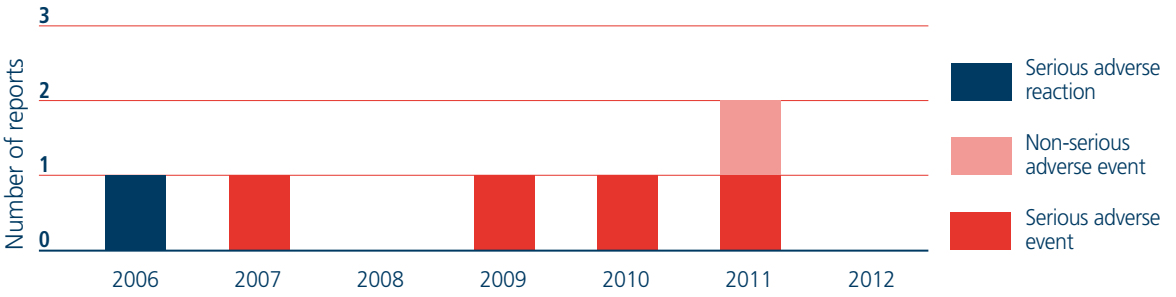


Figure 16. Reports concerning cardiovascular tissue, 2006-2012

All cardiovascular tissue reports in 2006-2012 related to heart valves (both aortic and pulmonary valves). In 2006 and 2007 reports were registered in the categories other reaction and other incident respectively; in the latter case the recipient died of complications unrelated to the transplanted tissues. Reports in 2009 and 2010 regarded bacterial contamination of product. In 2011 two reports of loss of tissues or cells were received, resulting from a communication error in one case and an unspecified other error in the second.

2.6 Skin

2.6.1 Background

Skin tissue is subdivided in three specific types, namely donor skin, cultured skin/skin cells and other. Autologous skin harvested and applied in a single procedure is outside the scope of the Law on safety and quality of substances of human origin. Donor skin is mainly used as a temporary bandage for burn patients. Three specialised burn centres operate in The Netherlands. Second and third degree burns that involve larger areas are temporarily covered by strips of processed post-mortem donor skin. The donor skin is like a bandage on the wound and is effective in preventing infections as well as fluid and protein loss. Donor skin is also applied in the treatment of non-healing wounds like venous ulcers and colostomy ulcers.

The standard treatment of burns by applying (donor) skin often does not lead to acceptable functional and cosmetic outcomes. By growing skin cells (keratinocytes) in vitro to be applied with a meshed split skin graft the burn will heal faster with less scarring. Cultured skin (e.g. Tiscover) is obtained by growing an autologous skin biopsy (from thigh or abdomen) for three weeks to form skin flaps. This skin flap is applied like a plaster on chronic wounds. It is strong, will not be rejected and promotes faster healing and definitive coverage of the wound by stimulating the wound.

In The Netherlands one large organ bank processes and distributes post-mortem donor skin to hospitals and clinics that apply donor skin for wound treatment. Two distributors sell skin products originating from foreign countries. One laboratory cultures keratinocytes.

2.6.2 Processing, distribution and application

Table 32 shows numbers of processed and distributed units of skin. It is noteworthy that around 10.000 units of donor skin are exported from the Netherlands to EU and non-EU countries. Table 33 presents the numbers of applied skin units.

Table 32. Number of processed and distributed skin units

Type	Institutions	Processed	Distributed				Total distributed
			Unit	In NL	In EU	Outside EU	
Donor skin	3	599	Package	1200	8099	1952	**11251**
Cultured skin/cells	1	13	Graft	12	0	0	**12**
Other	1	4	Graft	1	0	0	**1**

Table 33. Number of applied skin units in 2012

Type	Hospitals/ clinics	Recipients	Transplants				Total transplants
			Unit	From NL	From EU	From non-EU	
Donor skin	3	92	Package	167	0	0	**167**
Cultured skin/cells	2	13	Graft	14	0	0	**14**
Other	2	8	Graft	11	0	0	**11**

Distribution amounted to 1200 units of donor skin in The Netherlands, but only 167 units were provided by 3 institutions as applied in patients. Possibly donor skin is also in storage in the burn treatment centres. Not all burn treatment centres supplied application data.

2.6.3 Reports

TRIP did not register any reports concerning skin tissue or cells in 2012. The numbers of reports in previous years are shown in Figure 17. In 2008 five reports were registered that related to the experimental phase of a cultured skin product.

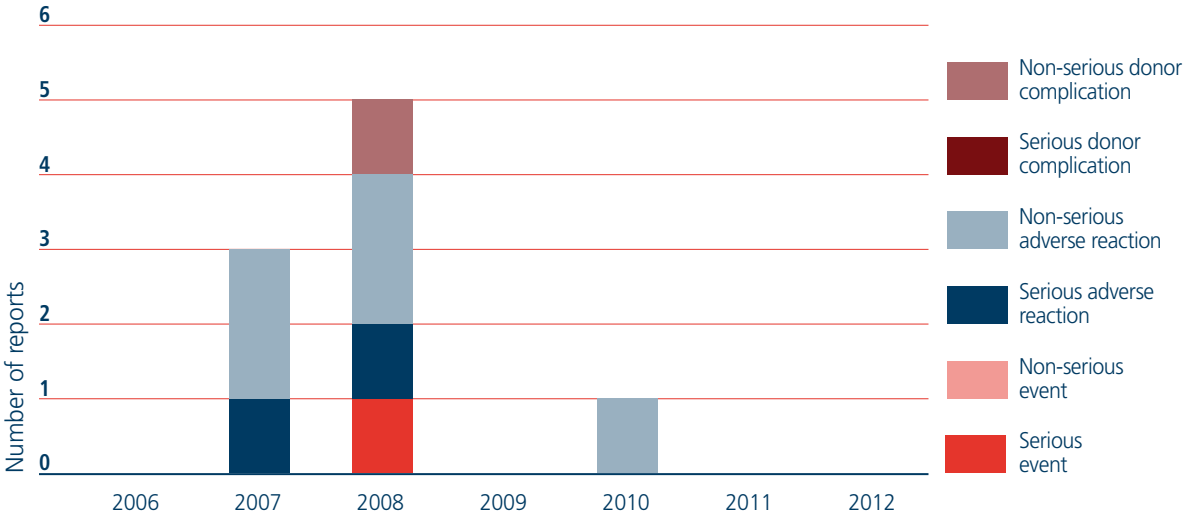


Figure 17. Reports concerning skin tissue or keratinocytes, 2006-2012

2.7 Other tissues and cells

2.7.1 Background

A variety of tissues and cells is ranked in this category, including amniotic membrane, Langerhans' islets, umbilical cord tissue, adipose tissue and (autologous) radio-active labelled erythrocytes and leukocytes.

Amnion is one of the foetal membranes and is used for various applications in ophthalmic surgery as well as for chronic ulcers, skin burns and other skin wounds.

From donor pancreas Langerhans' islets (beta cells) can be prepared. These islets are injected into the liver of a patient suffering from diabetes; the beta cells will synthesise insulin. In The Netherlands this procedure is only indicated for patients with type 1 diabetes who have severe complications.

Umbilical tissue is processed and stored in only one tissue establishment. In 2012 according to provided data no processing or distribution took place. Umbilical tissue contains mesenchymal stem cells that may be used for autologous application.

Adipose tissue is sometimes used in plastic and cosmetic surgery as a source of pluripotent stem cells, up to now only in experimental therapy.

One licensed tissue establishment processes and distributes radio-actively labelled autologous red blood cells and leukocytes for diagnostic purposes. Granulocytes (polymorphonuclear cells) are transplanted as adjuvant treatment in patients suffering from sepsis due to severe bone marrow insufficiency. Donors, usually relatives or acquaintances receive granulocyte colony growth factor (G-CSF) as pre-donation treatment. For unrelated blood/stem cell donors granulocyte donation is not permitted as this therapy is still experimental.

2 7.2 Processing, distribution and application

In Tables 34 and 35 the numbers of processed and distributed units of other tissues and cells and transplanted tissues and cells are shown.

Table 34. Processing and distribution of other tissues and cells in 2012

Type	Institution	Processed	Distributed				Total distributed
			Unit	In NL	In EU	Outside EU	
Amnion	1	1	Package	70	21	0	**91**
Langerhans' islets	1	80	Graft	9	0	0	**9**
Adipose tissue	1	89	Graft	0	74	0	**74**
Red blood cells	1	78	Bag	77	0	0	**77**
Leukocytes	2	157	Bag	130	10	6	**146**

Table 35. Application of other tissues and cells in 2012

Type	Hospitals/ clinics	Recipients	Transplants				Total transplants
			Unit	From NL	From EU	From non-EU	
Amnion	3	31	Package	31	0	0	**31**
Langerhans' islets	1	8	Graft	9	0	0	**9**
Adipose tissue	0	0	Graft	0	0	0	**0**
Red blood cells	0	0	Bag	0	0	0	**0**
Leukocytes	0	0	Bag	0	0	0	**0**

2.7.3 Reports

In 2012 one report of a serious adverse event was received, an other incident involving granulocytes. Due to a communication error the product was collected but not infused. No reports were received concerning amnion, Langerhans' islets, umbilical tissue or adipose tissue, and this event was the first reported to TRIP regarding other tissues and cells since tissue and cell vigilance was launched.

Part 3

Discussion

3.1 Theme: identification and selection errors

An important aspect of the quality and safety of human tissue or cell therapy is the use of the right donor material in the right recipient. Since 2007 TRIP has received 37 reports concerning identification errors or selection errors in the use of human tissues or cells. These reports, 34 identification errors and three selection errors, were analysed in order to evaluate whether double check procedures affected the outcome. Outcomes of identification and selection errors ranged from other incident or near miss to loss of tissues or cells and incorrect product transplanted. Identification and selection errors may result from haste, chaotic situations, often repeated procedures, changes in protocol, invisibility of effects, overestimation or a language barrier.

In clinical practice patients are identified or selected by varying procedures. Patient details or selection criteria are sometimes checked by one member of staff only. The gold standard for identification or selection is a check by two staff members. The patient (or their partner) is commonly asked to countercheck e.g. when delivering a semen sample or when insemination of processed semen is performed. Figure 18 shows the reports concerning an identification error or a selection error according to the check procedure in 2007-2012. In six reports the method of identification was not stated.

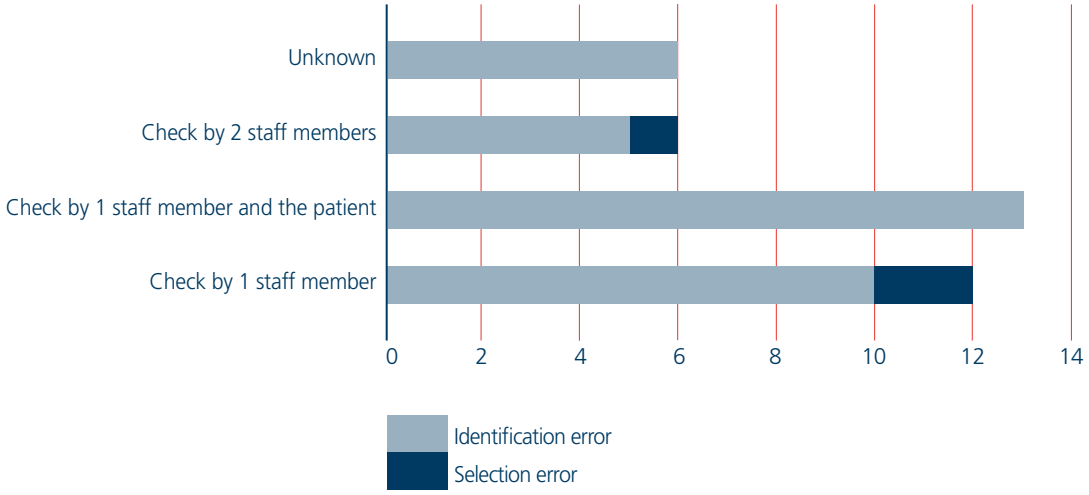


Figure 18. Reports of identification error and selection error according to check procedure, 2007-2012

Identification error

An error is classified as an identification error in the following cases:

- If the identifiers on the accompanying form and/or product are not those of the donor from whom the tissue/cells have been procured or collected.
- If a product has been requested for a different person from the intended recipient.
- If the issued product is not the product which has been requested and selected for the recipient.
- If the product which is in the vicinity of the recipient is not the product which has been issued for that person.
- If the product is applied/transplanted in a person who is not the intended recipient for whom it has been selected and issued.

Selection error

An error is classified as a selection error if the product which is selected for a recipient does not meet all the specifications for an appropriate product for that recipient. All three selection errors in the TRIP annual reports concerned gametes or embryos and they led to the transplantation or application of an incorrect product.

Table 36 summarises the reports concerning identification and selection errors from 2007 to 2012

Table 36. Overview of reports concerning identification selection errors, 2007-2012

Category event	Type of error	Type of tissues or cells	Number of reports
Incorrect product transplanted	Selection error	Embryos	2
		Donor semen	1
	Identification error	Partner semen	2
		Donor semen	1
		Embryo	1
		Donor skin	1
		Chondrocytes	1
Loss of tissues or cells	Identification error	Embryos	6
		Partner semen	4
		Oocytes	3
Near miss	Identification error	Partner semen	6
		Donor semen	1
		Embryos	2
Other incident	Identification error	Embryos	2
		PBSC	1
		Cornea	1
		Pees	1

Figure 19 shows the breakdown of identification and selection errors according to category of event. In cases of incorrect product transplanted the procedural checks failed to prevent the application of an incorrect product.

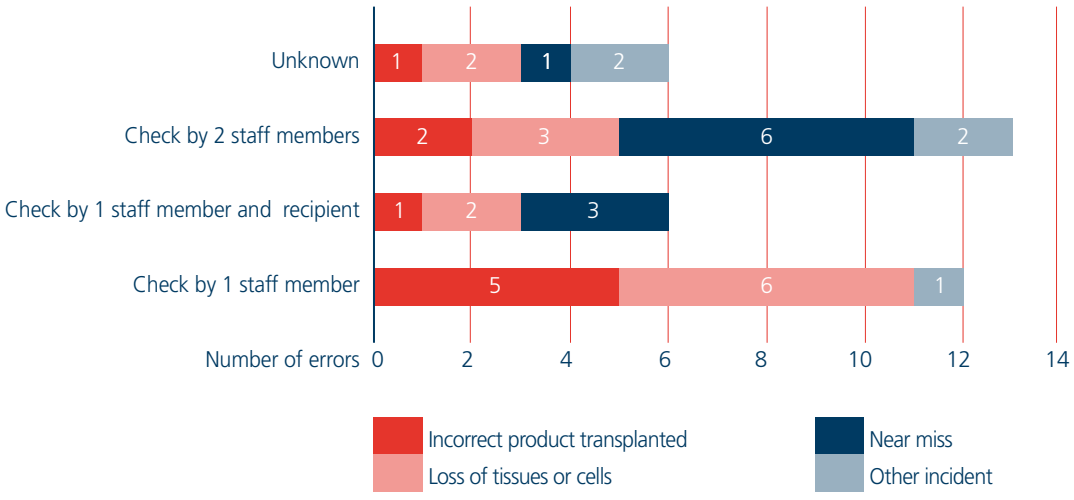


Figure 19. Number of identification and selection errors according to checking procedure and category of event

Summary

The largest number of reports of incorrect product transplanted concerned cases where the identification checks were performed by only one member of staff. This was also the case in two out of the three selection errors. Although the number of reports where two members of staff were involved in the procedural check was larger, the majority of these reports concerned a near miss. The double check by two persons prevented the incorrect tissues or cells from being transplanted or (avoidably) lost. The double check procedure can make a significant contribution in the chain of human tissues and cells in preventing adverse outcomes of identification and selection errors.

Conclusions 11 and 12 and recommendations 10 and 11 in chapter 3.3 are about identification errors and selection errors.

3.2 Summary

TRIP is an independent foundation operating in collaboration with the users and distributors of substances of human origin. The TRIP reporting system, operational from 2006 onwards, collects data from hospitals, clinics and licensed tissue establishments in order to monitor and improve safety and quality of substances of human origin. TRIP annually collects, registers, analyses and reports on adverse reactions and events relating to human tissues and cells in The Netherlands.

Participation by licensed tissue establishments in 2012 was 98% (total n=118). Two licensed tissue establishments did not provide any data on processing and distribution. Hospitals and clinics showed 97% participation (total n=105), however some data were lacking due to incomplete provision by the hospitals and clinics that apply human tissues and cells.

In 2012 TRIP received 90 reports, out of which 53 were assessed as serious according to the criteria for inclusion in the mandatory annual overview for the European Commission. This regarded 48 adverse events, three adverse reactions and two donor complications. The largest number of adverse events concerned processing or application of human reproductive cells. Serious adverse reactions were mainly reported in the application of hematopoietic stem cells; this also applied to serious donor complications. The total number of reports differed minimally from 2011, but in 2012 there was a rise in the number of serious reports (53 in 2012 compared to 40 in 2011). Broken down according to tissue or cell type, 50 reports concerned gametes, embryos or gonadal tissue in assisted reproductive technologies, there were 19 reports concerning hematopoietic stem cells, 12 reports related to ocular tissue, eight reports about bone and other musculoskeletal tissue and one report about other cells.

Out of the total number of reports, the majority related to procedures or application of gametes, embryos and/or gonadal tissues in assisted reproductive technologies. This is due to the large number of procedures performed annually, as well as to the clear guideline for the reporting of adverse reactions and events published by the professional association of clinical embryologists. All reports concerned adverse events. As in reporting years 2010 and 2011 reproductive cells are involved in the majority of reports in category loss of tissues of cells.

This report also showed that the number of adverse reactions relating to hematopoietic stem cells has been stable over the years. Four out of five adverse events concerning hematopoietic stem cells in 2012 related to ruptured or leaking bags for stem cells. Application of whole bones and bone filler showed a large numerical discrepancy compared to distribution figures. This may in part be due to a group of institutions applying these products and not yet included in the network, i.e. private clinics, as well as to underreporting by the contacted hospitals and clinics. In 2012 no reports involved cartilage or chondrocytes. This reports showed that 6 out of 12 reports involving ocular tissues were serious; three formed a cluster. In 2012 there were no reports relating to skin tissue or cardiovascular tissue. There was one serious report about granulocytes. Table 2 in chapter 1.4 shows the number of reports per tissue type.

The theme chapter 3.1 presents a special analysis of identification errors and selection errors from 2007 to 2012 with the aim of contributing to the prevention of these errors and serious adverse outcomes. Identification and selection still are being performed by one staff member only or by one staff member and the recipient and this may lead to serious adverse events: avoidable loss of tissues or cells or the transplantation/application of an incorrect product. In Chapter 3.3 conclusions and recommendations can be found.

3.3 Conclusions and recommendations

3.3.1 Conclusions

1. Participation of hospitals and clinics rose to 97% in 2012. Quality and completeness of provided data improved compared to previous years but still need to improve.

2. Participation of licensed tissue establishments remained high. Only two out of 118 licensed tissue establishments did not provide data on processing and distribution. The non-participating tissue establishments are both licensed for the processing of semen.

3. The discrepancies between figures for distributed and applied tissues and cells in The Netherlands are decreasing. The discrepancy particularly concerns skin tissue, ocular tissue and bone and other musculoskeletal tissues.

4. The total number of reports in 2012 was stable compared to previous reporting years, however a larger number out of the total were rated as serious.

5. Analysis of an adverse event on several occasions revealed an earlier event which had occurred in the same or a different institution.

6. Both in 2011 and 2012 a number of reports related to ruptured or leaking bags for collection or storage of hematopoietic stem cells. This may point to a structural manufacturing problem regarding one or more manufacturers.

7. Two reports in 2012 and two late reports in 2011 concerned transportation boxes for gametes that failed to maintain a high enough temperature. This may have led to quality loss of gametes and possibly poorer treatment outcome.

8. Three adverse events in 2012 regarded lack of, a non-functioning or non-fail-safe alarm system. This showed that in more than one laboratory processing, culturing and/or storing human tissue or cells the alarm system did not have a fail-safe system for all essential equipment.

9. In 2012 as well as 2011 a cluster of five reports of a persistent corneal haze after corneal transplant were received.

10. Three corneas were lost due to processing in a microkeratoma that contained debris.

11. In 2012 ten reports related to identification or selection errors of different tissue types (corneas, tendons, gametes and embryo's). In three cases this led to application of an incorrect product and in two cases to loss of tissues or cells.

12. Identification based on numerical codes or date of birth can easily lead to identification errors as minor differences may be overlooked.

3.3.2 Recommendations

1. In order to reach full participation TRIP should personally contact non-participating institutions.

2. The gap between distributed and applied tissues and cells requires continued effort. By including private clinics that may use human tissues and cells as well as oral implantologists in the TRIP network part of the discrepancy could be resolved.

3. Tissue establishments should advise hospitals or clinics that were (also) involved in an adverse event to report to TRIP. Full information from the complete chain of human tissues and cells could provide more insight into weak points in both tissue establishments and hospitals/clinics.

4. The issue of leaking units for collection of stem cell transplants needs further investigation and monitoring; the Stem Cell Laboratory Working Group will initiate further investigations.

5. Validated transportation conditions are necessary for assuring the quality of transported tissues or cells. If validation of these processes has not been performed this should be undertaken.

6. Essential equipment like transportation boxes, incubators, cryopreservation devices and storage devices needs an adequate fail-safe alarm system to prevent quality loss or avoidable loss of tissues or cells in case of breakdown.

7. Congenital malformations that occur when using heterologous gametes are reportable adverse events. For confirmation of a genetic abnormality chromosomal and gene investigations of both parents (sperm donor and mother, or egg-cell donor and father) is necessary.

8. To decide if a poor outcome of a corneal graft needs reporting as an adverse event medical professionals should formulate criteria for follow-up time and parameters for determining whether an adverse event is to be classified as serious.

9. In case of difficulties in preparing a cornea with a microkeratoma in a transplanting institution a rejected cornea can be ordered to use as testing material.

10. Double check identification procedures by two members of staff can reduce the number of errors and subsequent adverse outcomes.

11. Extra attention is needed when performing identification based on numerical codes of products or date of birth so that small differences will be noticed.

3.3.3 Actions and developments following recommendations in the TRIP report 2011

1. Hospitals should be aware that provision of data on the number of recipients as well as full traceability of human tissue and cells constitute essential parts of tissue vigilance.

   Development: Participation of hospitals in the inventory of number of recipients but also number of applications improved in 2012 as is demonstrated by decreasing discrepancies in numbers of distribution and application of tissues and cells.

2. For a comprehensive and reliable registration professionals involved in various types of tissues and cells should reach agreement on the most appropriate units for registration purposes.

   Development: The Biovigilance Advisory Committee has been expanded to include experts in the field of skin and ocular tissue. Consultation on units for registration purposes has taken place at EU level but the list needs further adjustment for hematopoietic stem cells and reproductive cells.

3. Further research should be initiated into processing errors occurring in assisted reproductive techniques and possible ways to avoid these errors.

   Development: This subject was discussed at the quality assurance meeting of the Association of Clinical Embryologists.

4. The patient outcomes should be investigated following transplantation of corneas from donors who were later found to have a contraindication for donation according to the definitive autopsy findings. This will give insight into long term consequences (if any) for the recipient.

   Development: This has not yet been discussed with the medical professionals and action remains to be initiated.

5. Follow-up on visual acuity and clinical outcome after corneal transplant, including the need for retransplantation, should be made available in order to complete the tissue vigilance chain from donor to recipient.

   Development: In nine reports related to corneal transplants in 2012; more clinical details were available in 2012 compared to 2011. See conclusion 9 and recommendation 8.

6. Adverse events concerning leakage of units of recipient-specific and potentially irreplaceable hematopoietic stem cells should be reported in order to gain insight into the extent of this problem.

   Development: The Stem Cell Laboratory Working Group, in collaboration with TRIP, has collated all the reports and will initiate further investigations.

7. The boards of hospitals and clinics should ensure annually that all legal obligations regarding human tissues and cells are met as new developments in the field of transplantation of human substances may lead to new areas needing licensing and implementation of tissue vigilance.

   Development: in 2012 only three hospitals did not provide any data for the annual inventory of applied tissues and cells and number of recipients.

8. More professionals involved in transplanting or applying human tissue and cells should be encouraged to also submit non-serious reports in order to contribute to the understanding of adverse reactions and events and possible ways to avoid these.

   Development: In 2012 fewer non-serious reports were submitted. This recommendation is still valid.

9. TRIP should collect further data on numbers of imported tissues and cells in collaboration with stakeholders. The importing and distributing institutions of tissue and cells should be involved in the reporting system and should be made aware of the legal obligations in this regard.

   Development: The 2012 annual inventory requested hospitals to indicate if applied tissues and cells originated from EU countries or outside EU and also to provide the name of their supplier(s).

10. The requirements for vigilance in the form of reporting of adverse events and reactions and the submitting of data on processing, distribution, transplantation and recipients should specifically be pointed out to independent health care institutions and private clinics in order to increase participation of these groups.

    Development: This year five private clinics were added to the database of applying institutions that are contacted annually for the reporting of adverse reactions and events and the provision of numbers of applied tissues and cells and of recipients. In 2013 a large survey of private clinics and oral implantologists will take place followed by an information circular about the regulatory obligations laid down in the Law on safety and quality of substances of human origin.

Annex 1:

Overview of mandatory reports of serious adverse reactions and events (in accordance with EU legislation)

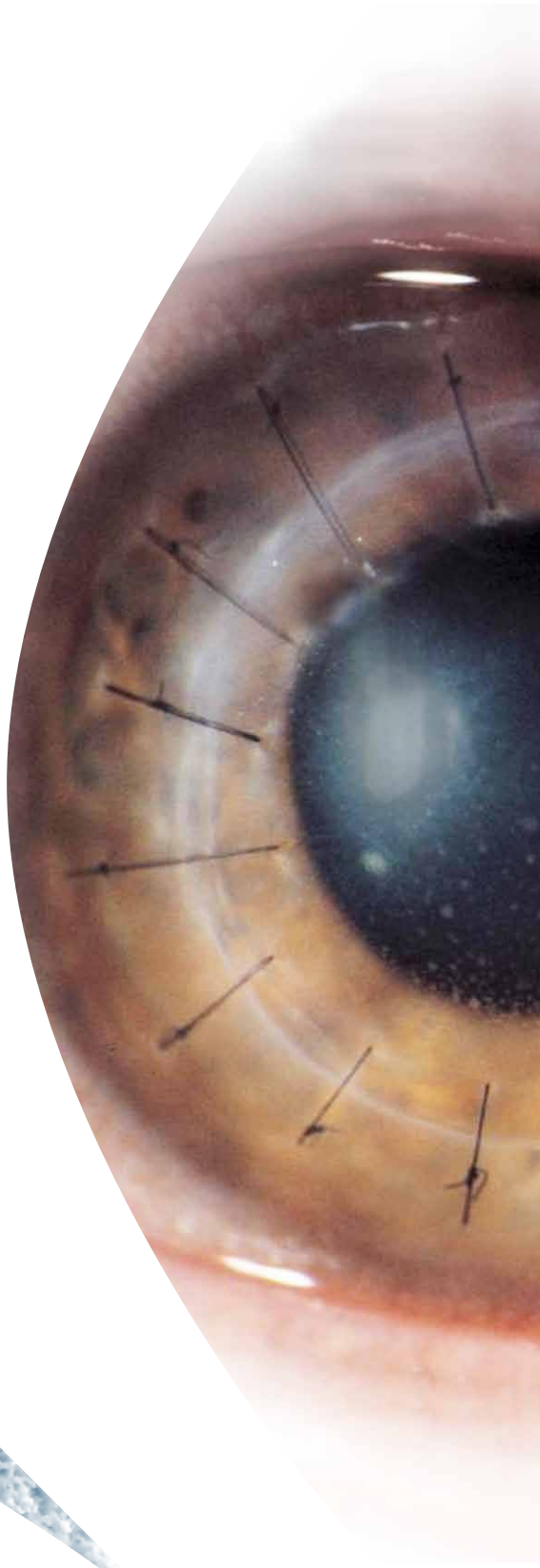
In Table 37 an overview is presented of the number of serious adverse reactions and events that were reported in 2012 that concern human tissues and cells. From the total 53 reports were assessed as serious. There were 48 serious adverse events and three serious adverse reactions. Two serious donor complications were reported.

Table 37. Overview of serious reports in 2012

Type	Serious adverse reaction	Serious adverse event	Serious donor complication	Total serious reports
Semen	0	4	0	4
Oocytes	0	7	0	7
Semen and oocytes	0	1	0	1
Embryo's	0	16	0	16
Semen, oocytes and embryos	0	1	0	1
Ovarian tissue	0	1	0	1
Ocular tissue	0	6	0	6
HPSC	3	7	2	12
Bone tissue	0	1	0	1
Tendon	0	3	0	3
Other: granulocytes	0	1	0	1
Total	**3**	**48**	**2**	**53**

List of terms and abbreviations

ACI	-	Autologous chondrocyte implantation
Apheresis	-	Type of blood donation involving the selective mechanical withdrawal of specific blood components and re-infusion of the remaining components to the donor or patient
Allogeneic	-	Originating from a donor (genetically non-identical)
ALKP	-	Anterior lamellar keratoplasty
AML	-	Acute myeloid leukaemia
Autologous	-	Originating from a person's own body
Clinic	-	Specialised hospital that focuses on selected medical discipline(s)
CMV	-	Cytomegalovirus, type of herpes virus
CNS	-	Coagulase-negative staphylococcus
Cryopreservation	-	Freezing and storage
Distribution	-	Transportation and delivery of human tissues and cells intended for human application
DMSO	-	Dimethylsulphoxide
EU	-	European Union
EUSTITE	-	European Union Standards and Training in the Inspection of Tissue Establishments, EU project
Farmatec	-	Executive body of the Ministry of Health that grants licences and permits with regard to pharmaceutical drugs, medical devices, blood components and substances of human origin
G-CSF	-	Granulocyte colony stimulating factor
GVHD	-	Graft Versus Host Disease
GVL	-	Graft Versus Leukaemia
HLA	-	Human leukocyte antigen
HPSC	-	Hematopoietic stem cells
ICSI	-	Intra cytoplasmic sperm injection (type of IVF treatment)
IUI	-	Intra-uterine insemination
IVF	-	In vitro fertilisation
MESA	-	Microsurgical epididymal sperm aspiration
NL	-	The Netherlands
Oocytes	-	Egg cells
Organ bank	-	A licensed tissue establishment holding an additional licence for procurement of substances of human origin after harvesting
Pathogen	-	Disease agent of biological origin
PBSC	-	Peripheral blood stem cells
PESA	-	Percutaneous epididymal sperm aspiraton
Processing	-	All procedures performed in the preparation, manipulation, preservation and packaging of human tissues and cells
Procurement	-	Process by which tissue or cells are made available
Semen	-	Sperm
SOHO V&S	-	Vigilance and Surveillance of Substances of Human Origin, EU project
TESE	-	Testicular sperm extraction
TRIP	-	Transfusion and Transplantation Reactions In Patients
Vitrification	-	Specialised cryopreservation procedure for oocytes
Tissue establishment	-	A tissue bank, a hospital department or another institution that holds a licence for processing, preserving, storage and or distribution of human tissue or cells



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