TRIP REPORT 2016

Biovigilance

Extended version

TRIP
Hemo-en biovigilantie

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Biovigilance

Extended version

The TRIP report 2016 regarding biovigilance in
The Netherlands is published under responsibility of the TRIP
(Transfusion & Transplantation Reactions In Patients) Foundation

TRIP
Hemo- en biovigilantie

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Introduction

It is over ten years since TRIP started collecting data on adverse reactions and events related to the application of human tissues and cells. The 2016 TRIP Biovigilance report describes the tenth annual collation of reports of adverse reactions and events alongside the data on units of tissues and cells and participation by tissue establishments and healthcare institutions involved in the chain of tissue and cell transplantation.

In 2016 a new version of the TRIP online reporting system was installed. The updated reporting system is more user-friendly for both reporters and TRIP and was designed based on ten years of biovigilance experience, current developments and the needs of reporters. The new reporting system allows reporters to upload of a document giving extra details concerning an adverse reaction or event and TRIP can add details regarding a case's inclusion in the annual reporting to the European Commission or NOTIFY library.

In 2016 there were 77 reports, out of which 29 reports were classified as serious. There was a lower number of reports compared to previous years (2015: 120 reports including late reports). In particular, there were fewer reports of donation complications related to stem cell collection and fewer adverse events and reactions concerning ocular tissue in 2016. There were five late 2015 reports that were submitted after the closing date for the 2015 report. The 2016 reports are discussed and analysed in this annual report. Participation of tissue establishments and healthcare institutions is stable and almost complete. For the third year running there is an increase in participation of oral implantology practices.

There were six reports of congenital malformations, five of which involved the application of donor semen, that were (possibly) related to genetic abnormalities. Since 2012 there have not been so many reports in this category in one reporting year. For the second year reports of donation complications related to oocyte retrieval were submitted. Another three reports concerned equipment failure (cryo-preservation straws for embryos).

2016 was TRIP's tenth year of reporting on biovigilance and various chapters give attention to this milestone. The relevant paragraphs on various tissues and cell types present ten-year overviews of reports and of distribution or applied numbers of units. Chapter 3 is dedicated to ten years of biovigilance and the progress that has been achieved at national and international level. In anticipation of the revision of Directive 2004/23/EC the accomplishments within the European Union are highlighted and future goals are commented on.

TRIP foundation would like to thank all involved professionals for their indispensable commitment during ten years of biovigilance reporting and hopes this report will play a part in further increasing quality and safety of the chain of human tissues and cells.

Findings and recommendations

2016 findings

1 In 2016 there were fewer reports compared to previous years. This is mainly due to a smaller number of reports concerning ocular tissue and fewer donation complications associated with hematopoietic stem cell apheresis.

2 Participation of both tissue establishments and healthcare institutions remains high. Among the oral implantology practices that are known to TRIP participation is increasing.

3 In 2016 there were five serious reports that concerned a (possible) genetic abnormality in the fetus or neonate after the application of donor semen in assisted reproductive treatment. Since 2012 there have not been as many reports in this category in one reporting year.

4 There were two submitted reports that related to the application of embryos after preimplantation genetic diagnosis. Both cases concerned (possible) transmission of a genetic abnormality. Hitherto only one report to TRIP(in 2014) concerned preimplantation genetic diagnosis.

5 Three reports related to a technical error of cryopreservation straws for embryos. One of these cases could have been avoided if the tissue establishment had removed the complete batch of straws after recall by the supplier.

6 Modification by the manufacturer of the connector for anticoagulant dosing in a stem cell collection kit led to a report of clotting of a stem cell product.

7 In a number of adverse events (cord blood, bone, cornea) the clinical outcome or consequences for the recipient are reported incompletely or not at all to the tissue establishment. This hampers the reporting of unintended adverse reactions and events by the tissue establishment in the context of the Dutch Law on safety and quality of substances of human origin.

8 From 2012 a total of four reports have been submitted that concerned the rupture of a tendon during preparation for transplantation in the operating theatre. Transplanting institutions may not always report these events to the tissue establishment as usually another stored tendon is immediately available and there are no adverse consequences for the recipient.

9 Twelve corneas were lost due to bacterial contamination of home produced transportation medium. The medium production process was modified in consequence.

10 One report concerned the Law on organ donation where an ambiguity was noted whether a long time partner who did not reside at the same address as the donor was entitled to give consent for tissue donation.

2016 recommendations

1 Congenital abnormalities in a fetus or newborn that could (possibly) be genetically transmitted by donor gametes used in assisted reproductive techniques constitute a serious adverse event according to the EU criteria and should also be reported to the Healthcare Inspectorate.

2 Recalls by suppliers of materials or equipment used in processing or storage of substances of human origin should be acted on immediately: all involved materials should carefully be retrieved and discarded or returned to the supplier.

3 After modification of materials or auxiliary substances used in the chain of substances of human origin a check should be done before release to verify whether procedures need to be adapted.

4 In case of an adverse reaction or event transplanting institutions should always state the clinical outcome and consequences for the recipient. The biovigilance officer could support this process.

5 Rupture of allogeneic tendons during the preparation for transplantation or during application should always be reported to the tissue establishment, even if there is no adverse consequence for the recipient, in order to gain insight into the incidence of this type of event.

6 When tissue establishments produce auxiliary materials like additive solutions they should follow relevant laws and regulations and must have a functioning quality system including documented and validated procedures.

Actions and developments following recommendations in the 2015 TRIP report

In the TRIP 2015 Biovigilance report four recommendations were made. Recommendations followed by relevant developments are mentioned here.

1 In accordance with EU recommendations tissue establishments are requested to report to TRIP serious adverse reactions following pharmaceutical stimulation of stem cells or egg cells for donation. TRIP will include this information in its annual review of relevant data with Lareb, the Dutch pharmacovigilance agency.

Development: For the second consecutive year reports of donation complications concerning oocyte retrieval were submitted, both in oocyte donors and patients undergoing IVF treatment, including reports of ovarian hyperstimulation syndrome (OHSS). There was one report concerning a pulmonary embolism in a patient who received granulocyte colony stimulating factor (G-CSF) before autologous stem cell collection.

2 As there has been an increase in reports concerning loss of oocytes or embryos that remained stuck in pipettes, a risk analysis of these adverse events including type and make of pipettes used may identify possible causes.

Development: In 2016 there were no reports concerning oocytes or embryos that remained stuck in pipettes. As far as TRIP is aware a risk analysis has not been performed and based on the 2016 reports it would no longer be necessary.

CHAPTER 1

Reports to TRIP

1.1 Reports in 2016

In reporting year 2016 there were 77 reports of adverse reactions and events related to human tissues and cells. There were 63 adverse events (82%) and 14 adverse reactions (18%), out of which six concerned donation complications. The closing date for inclusion in the 2016 Biovigilance report and overview for the EU overview was 1 March 2017. Out of the total, 29 reports (38%) were judged to be serious (Annex 3). These serious reports were included in the annual overview for the European Commission (Annex 4). There was a decrease in the number of reports compared to 2015. Looking at a period of several years the decrease concerned adverse events and reactions related to corneal tissue and donation complications in stem cell apheresis. Figure 1 shows the number of registered reports, subdivided in serious and non-serious reports and in Figure 2 they are broken down according to tissue and cell type. In Table 1 gives an overview of the numbers of serious and non-serious 2016 reports per tissue or cell type. The percentage of reports relating to reproductive tissues and cells is 66% (51 out of 77) out of the total number of registered reports. The absolute number is lower than in 2015, but falls within the range of previous years.

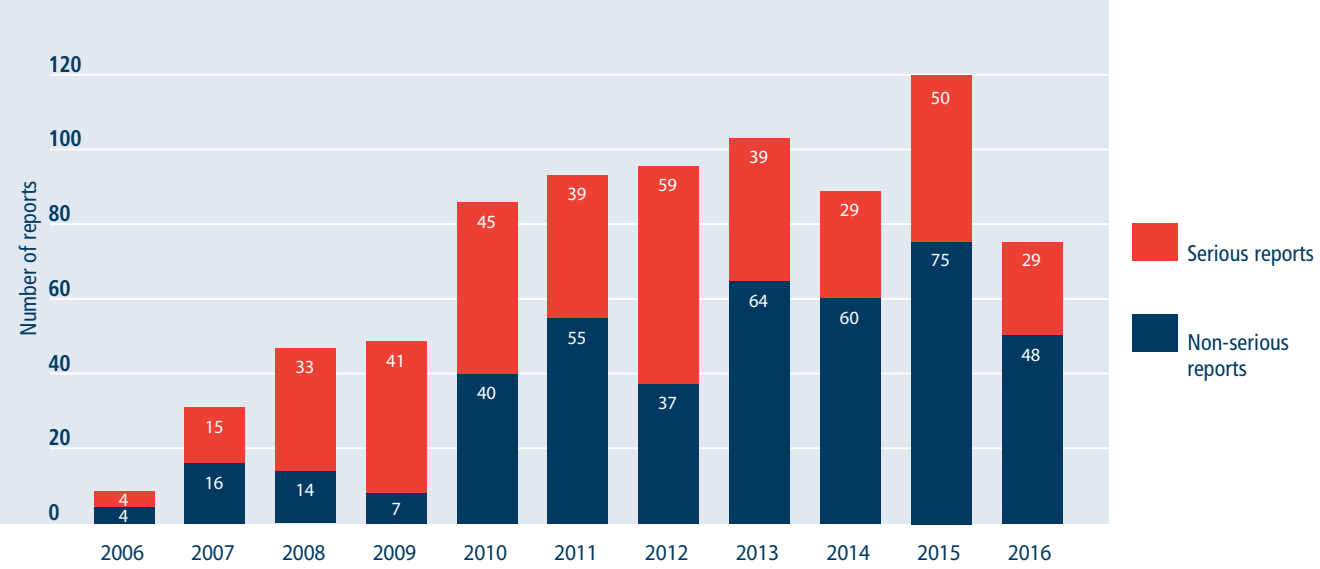

Figure 1. Reports to TRIP, 2006-2016

Table 1. Reports per type tissue or cell type in 2016

	Total	Non-serious	Serious
Gametes, embryos and gonadal tissue	51	25	26
Hematopoietic stem cells and therapeutic cells	15	13	2
Bone and other musculoskeletal tissue	7	7	0
Skin	0	0	0
Ocular tissue	3	2	1
Cardiovascular tissue	0	0	0
Other tissues and cells	1	1	0
Total	**77**	**48**	**29**

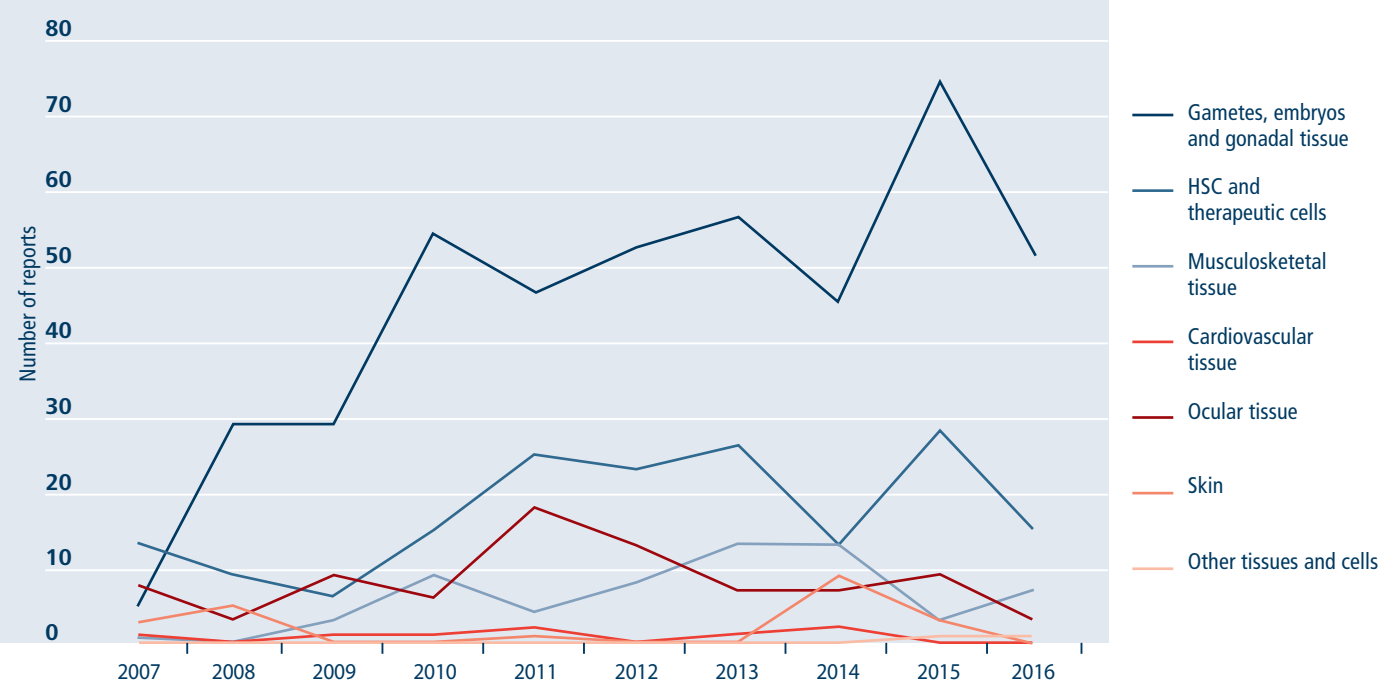

Figure 2. Reports per tissue or cell type, 2007-2016

1.2 Late 2015 reports

After the closing date for inclusion in the 2015 Biovigilance report another five reports were submitted. These concerned four adverse events and one adverse reaction. One adverse event report was assessed as serious: following donor sperm insemination a baby was born with a severe congenital metabolic disease (congenital glycosylating defect type 1, CDG-1c). The adverse reaction concerned ocular tissue and the other adverse events involved cord blood (1), donor semen (1) and tendinous tissue (1). The late reports have been included in the relevant figures and tables in this report. The total number of 2015 reports came to120 out of which 41 were judged to be serious adverse events or reactions.

Figure 3 shows the number of late reports per reporting year over the past ten years. The 2013 recommendation regarding timely reporting was successful, partly because reporters are also sent reminders each year about timely reporting.

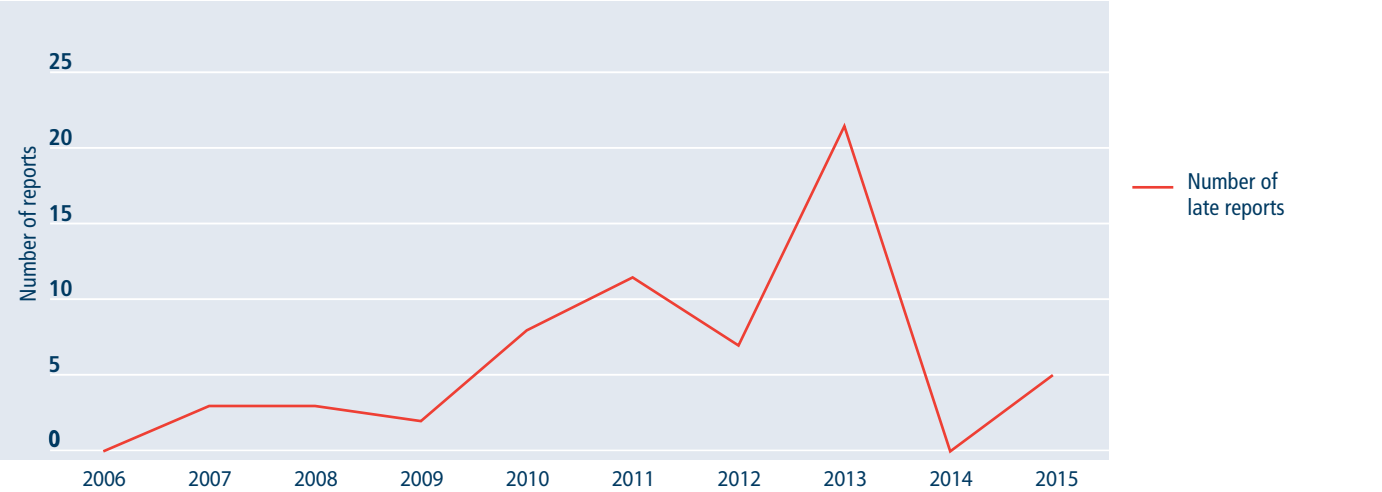

Figure 3. Number of late reports, 2006-2015

CHAPTER 2

Tissues and cells

In this chapter the processing and distribution data are presented alongside application data for each type of human tissue and cells. The 2016 adverse event and reaction reports are briefly described and analysed. Some reports are highlighted as case descriptions.

2.1 Gametes, embryos and gonadal tissue

In 2016 two fertility laboratories that provide IVF and ICSI procedures merged. In The Netherlands 12 fertility laboratories (tissue establishments) now carry out both IVF and ICSI procedures. They may also process gametes from patients treated in other clinics (so-called transport clinics). There are 56 licensed tissue establishments, mostly hospital biomedical laboratories, that process semen (sperm) for IUI. Only semen laboratories which are licensed as organ banks may process and store donor sperm. One clinic is licensed for the processing of semen as well as oocytes but does not actually carry out IVF or ICSI processing (IVF preparatory laboratory).

Processing, distribution and application

Tables 2 and 3 present the numbers of reproductive tissue and cells processed, distributed and applied. Some cryopreserved embryos are found not to be viable after thawing, which explains the difference between the numbers of distributed and applied cryopreserved embryos.

Table 2 a-b-c. Processing and distribution of gametes, embryos and gonadal tissue in 2016

Semen and testicular tissue	No. of tissue establishments	Processed		Distributed					
		From on-site clinic	From transport clinic NL/EU	Unit	NL on-site clinic	NL transport clinic	EU	Non EU	Total
Partner semen, fresh for IUI	69	25254	0	Donation	24923	106	0	0	25029
Partner semen, fresh for IVF	12	12160	0	Donation	0	100	0	0	100
Partner semen, cryo for IUI	18	1953	1 / 0	Straw	2260	658	165	0	3083
Partner semen, cryo for IVF	11	859	185 / 0	Straw	805	479	35	0	1319
Donor semen, fresh for IUI	5	289	0	Donation	94	0	0	0	94
Donor semen, fresh for IVF	4	33	0	Donation	30	0	0	0	30
Donor semen, cryo for IUI	16	5088	9 / 467	Straw	10447	229	45	0	10721
Donor semen, cryo for IVF	10	370	259 / 259	Straw	478	499	12	0	989
Partner semen, MESA/ PESA/ TESE fresh	8	97	0	Aspiration or biopsy	41	0	0	0	41
Partner semen, MESA/ PESA/ TESE cryo	10	711	12 / 7	Straw or biopsy	810	35	83	17	945
Testicular tissue	2	24	0	Graft	0	0	0	0	0

Oocytes and ovarian tissue	No. of tissue establishments	Processed		Distributed					
		From on-site clinic	From transport clinic NL	Unit	NL on-site clinic	NL transport clinic	EU	Non EU	Total
Oocytes, fresh	13	101110	10227	Oocyte	102557	3795 *	0	0	106352
Oocytes, cryo	11	3348	65	Oocyte	531	28	32	0	591
Oocytes for donation, fresh	11	1575	21	Oocyte	580	908	0	0	1488
Oocytes for donation, cryo	4	317	10	Oocyte	143	0 *	0	0	143
Ovarian tissue	3	617	115	Graft	0	0	0	0	0

** Oocytes distributed from IVF preparatory laboratory to IVF tissue establishment member state*

Embryos	No. of tissue establishments	Processed		Distributed					
		From on-site clinic	From transport clinic NL / EU	Unit	NL on-site clinic	NL transport clinic	EU	Non EU	Total
Embryos, fresh	13	31526	0	Embryo	14531	0	0	0	14531
Embryos, cryo	13	26812	109 / 618	Embryo	14368	58	39	6	14471
Embryos from donor semen, fresh	10	2830	0	Embryo	782	0	0	0	782
Embryos from donor semen, cryo	12	1013	3 / 0	Embryo	471	13	0	0	484
Embryos from donated oocyte, fresh	12	467	0	Embryo	244	0	0	0	244
Embryos from donated oocyte, cryo	11	253	37 / 71	Embryo	283	0	0	0	283
Embryos from donated semen and donated oocyte, fresh	3	353	0	Embryo	37	0	0	0	37
Embryos from donated semen and donated oocyte, cryo	3	15	2 / 50**	Embryo	49	6	0	0	55

*** Embryos that were cultured in previous years in a fertility laboratory in another EU member state*
Abbreviation: cryo = cryopreserved

In 2016 tissue establishments were requested to provide processing, distribution and transfer data separately for embryos created from donated oocytes and/or semen. The Eurocet database specifically requests separate provision of these figures.

Table 3. Application of semen, embryos and gonadal tissue in 2016

Type	Hospitals/ clinics	Recipients	Applications					
			Unit	On-site clinic	NL	EU	Non EU	Total
Partner semen, fresh	76	9256	Donation	24884	106	0	0	24990
Partner semen, cryo	17	114	Straw	732	6	0	0	738
Donor semen, fresh	5	36	Donation	94	0	0	0	94
Donor semen, cryo	16	2876	Straw	9097	530	3363	0	12990
Embryos, fresh	13	8814	Embryo	12644	0	0	0	12644
Embryos, cryo	13	7175	Embryo	13161	22	3	0	13186
Embryos from donor semen, fresh	10	506	Embryo	782	0	0	0	782
Embryos from donor semen, cryo	11	261	Embryo	403	3	0	0	406
Embryos from donor oocyte, fresh	12	109	Embryo	228	0	0	0	228
Embryos from donor oocyte, cryo	10	126	Embryo	253	0	0	0	253
Embryos for donation, fresh	3	36	Embryo	37	0	0	0	37
Embryos for donation, cryo	3	26	Embryo	49	0	0	0	49
Ovarian tissue	0	0	Graft	0	0	0	0	0
Testicular tissue	0	0	Graft	0	0	0	0	0

There is a 22% decrease in the application of donor semen from Dutch donors (10555 straws from on-site labs and 1157 from other Dutch labs in 2015) and an increase of 58% in donor semen from other EU member states (1965 straws in 2015). The total number of recipients of donor semen rose by 6% (2698 in 2015). Semen imported from EU member states must meet the Dutch legal requirements that only allow semen application from non-anonymous donors.

The TRIP data concerning IUI treatment with partner and donor semen application have been almost complete since 2011. Approximately 10,000 women are treated annually. The number of recipients of donor semen increased from 1400 in 2011 to nearly 3000 in 2016 (Figure 4).

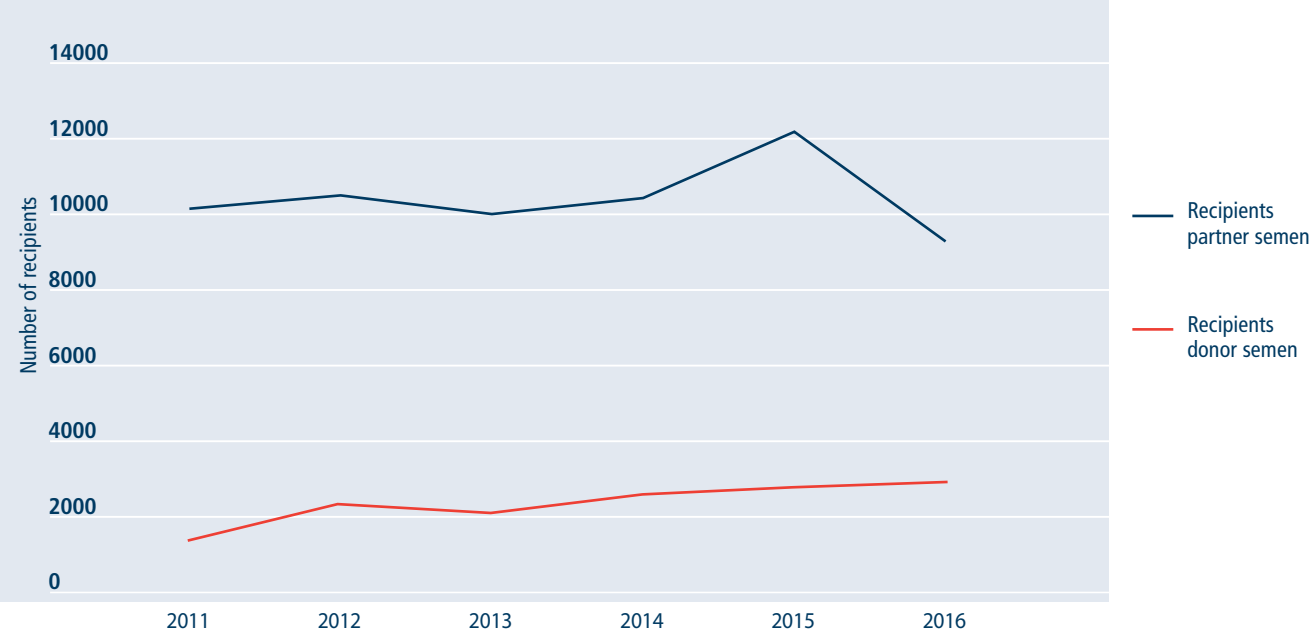

Figure 4. Number of recipients of partner and donor semen, 2011-2016

The number of embryo transfers decreased between 2012 and 2014 from 33.000 to 25.000 (Figure 5). The number of recipients however remained stable. This may be explained by a decrease in the number of two simultaneous embryo transfers in a single fertility cycle and improved pregnancy rates from IVF.

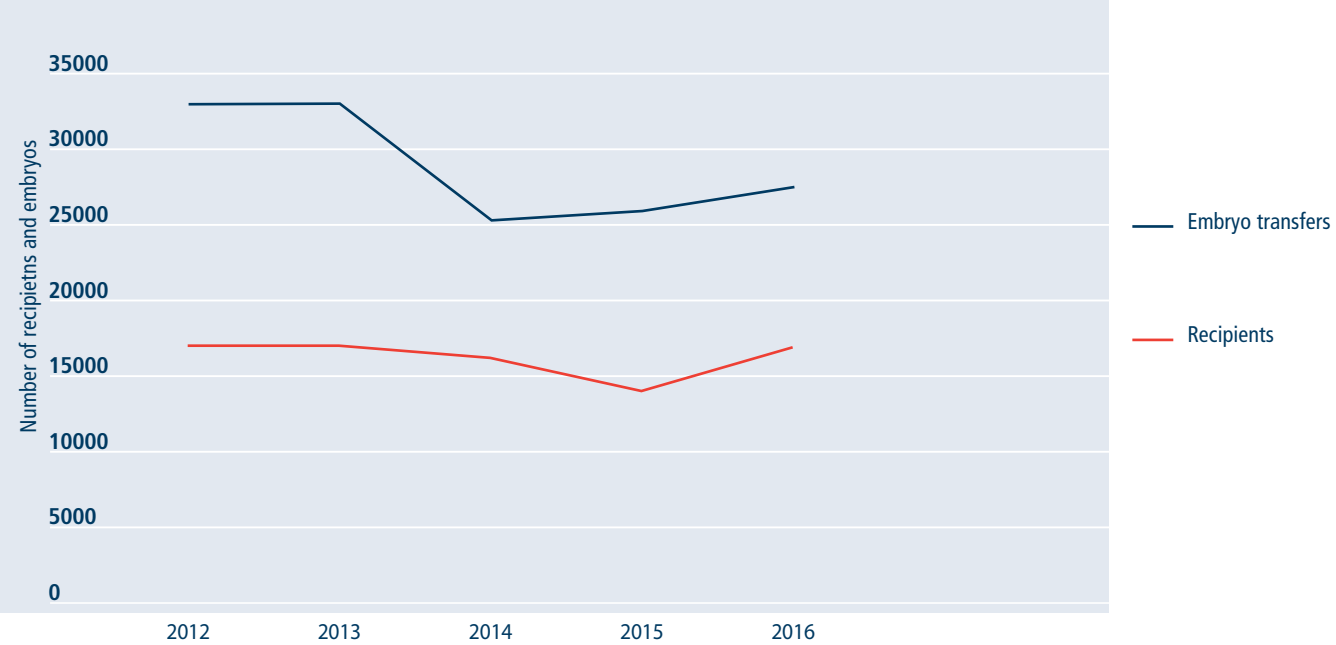

Figure 5. Number of embryo transfers and recipients, 2012-2016

Note: from 2012 onwards IVF laboratories provided complete data

Reports

In 2016 TRIP received 51 reports relating to procedures or application of gametes, embryos and/or gonadal tissue in assisted reproduction. There were 45 adverse events, out of which 20 were assessed as serious, and six adverse reactions. Among the six reactions there were five reports of serious donation complications and one report of a serious reaction in a recipient of donor semen. After a higher number of reports in 2015 the number in 2016 was comparable to 2014 and previous years. Table 4 gives an overview of the number of registered reports in 2016 subdivided per type of fertility laboratory.
Three IVF laboratories and 49 semen laboratories stated there were no reportable adverse events or reactions in 2016.

Table 4. Overview of 2016 reports per type of fertility laboratory

Fertility laboratory	No. in NL	Reports by	No. of 2016 reports	No. of late 2015 reports
IVF laboratory and IVF preparatory laboratory	13	10 (77%)	41	1
Semen laboratory	56	7 (13%)	10	1
Total	**69**	**17 (25%)**	**51**	**2**

Adverse reaction

In 2016 there was one adverse reaction in a recipient. In this case the recipient was admitted to hospital for suspected salpingitis after application of donor semen. There were five donation complications associated with oocyte retrieval in IVF, all being serious. One of these donation complications was ovarian hyperstimulation syndrome (OHSS) after drug-induced stimulation of oocytes for Ovum Pick-up

(OPU). The remaining four adverse reactions were complications related to OPU that came under the EU criterion: "Reactions which result in harm to the donor". In accordance with the EU Common approach serious donation complications are reported to the European Commission (Annex 3). Four of the five donation complications necessitated hospital admission but the patient recovered completely. The fifth case concerned ovarian rupture. The ovary had to be surgically removed, i.e. there was permanent harm. Imputability was definite for all donation complication reports. Table 5 presents an overview of donation complication reports related to oocyte retrieval. Three donation complications concerned voluntary oocyte donors. This is the second year that this type of report has been submitted.

Table 5. Overview of donation complications related to oocyte retrieval

Donation complication	2015		2016	
	Autologous oocyte donation	Allogeneic oocyte donation	Autologous oocyte donation	Allogeneic oocyte dona
OHSS*	7	0	1	0
Bladder lesion	1	0	1	1
PID**	0	2	0	1
Ovarian rupture	0	0	0	1
Hemorrhage	1	0	0	0

* *Ovarian hyperstimulation syndrome*

***Pelvic inflammatory disease*

Over 10 years of biovigilance data collection a total of 21 adverse reactions concerning assisted reproductive techniques have been reported to TRIP. An overview is presented in Table 6.

Table 6. Reports of adverse reactions associated with assisted reproductive techniques, 2007-2016

Adverse reaction	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Totaal
Other reaction	0	1	0	1	0	0	0	0	0	0	2
Post-transplantation bacterial infection	0	0	0	0	1	0	0	1	0	1	3
Donation complication*	0	0	0	0	0	0	0	0	11	5	16
Total	**0**	**1**	**0**	**1**	**1**	**0**	**0**	**1**	**11**	**6**	**21**

** Donation complications have been reported since 2015*

Adverse events

In 2016 there were 45 adverse events involving gametes, embryos and gonadal tissue, out of which 20 reports were classified as serious. With regard to assisted reproductive techniques specific criteria have been set for the assessment of severity of adverse reactions and events (see Table 35 and 36 in Annex 3). Adverse and events. Events which are classified as serious and reportable are those leading to the loss of a complete fertility cycle or to transmission of a genetic disorder by donated gametes or embryos. Up to 2012, the Dutch Association of Clinical Embryologists' (KLEM) guideline was followed for assessing the severity of an adverse event. The loss of reproductive tissues or cells used to be classified as serious if there was a considerable reduction of the likelihood of pregnancy in that cycle (loss of > 50% of tissues/cells). This change regarding reproductive tissues and cells resulted in a drop in serious adverse events in 2013 compared to previous years. In Table 7 an extra column shows the reports that are reportable to TRIP according to the current KLEM guideline.

In Figure 6 an overview of adverse events reported in 2007-2016 is shown, subdivided according to KLEM criteria and EU criteria for a serious adverse event. Table 7 presents the adverse events per category and per type of reproductive tissue or cell, type of error and severity. In Figure 7 the reported adverse categories are shown in the period 2010-2016. As in previous years the category loss of tissues or cells represents the largest number of reported adverse events.

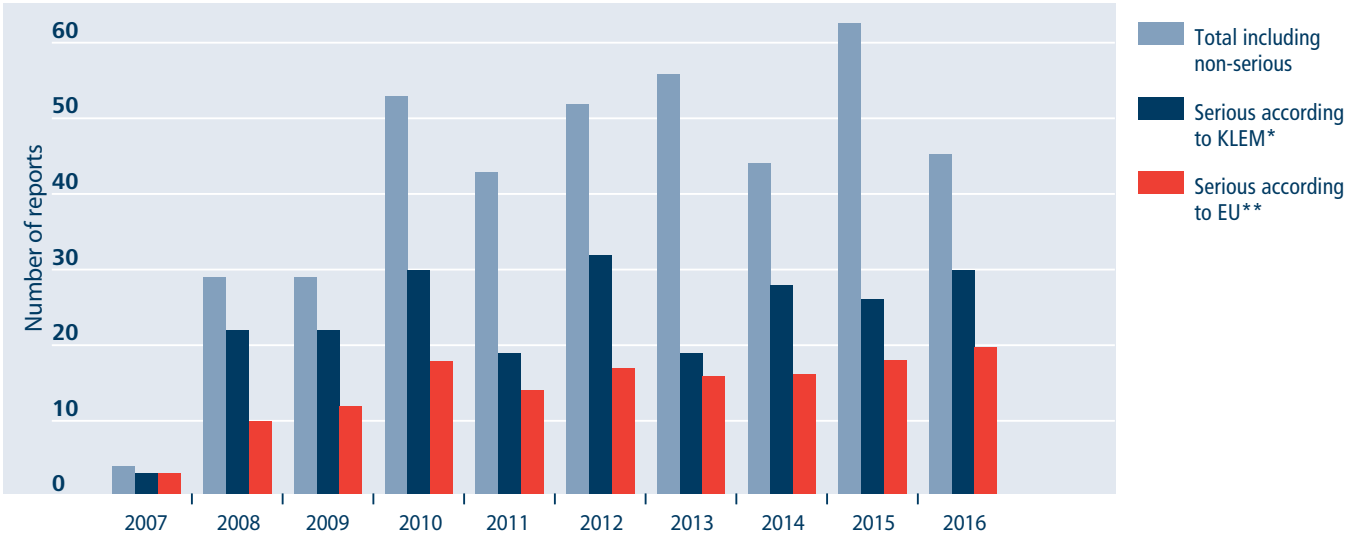

Figure 6. Number of reports of adverse events concerning gametes, embryos and gonadal tissue, 2007-2016

* *Serious according to the Dutch Association of Clinical Embryologists' guideline (KLEM): significantly reduced chance of a pregnancy due to loss of oocytes, embryos or irreplaceable semen*

** *Serious according to EU criteria: loss of a complete fertility cycle*

Table 7. Overview of adverse events concerning gametes, embryos and gonadal tissue in 2016

Type of tissue or cells	Adverse event category	Total	Serious according to KLEM*	Serious according to EU**
Semen	Loss of tissues or cells	2	1	1
	Other incident	4	0	0
	Incorrect product transplanted	1	1	1
	Congenital abnormality	5	5	5
Oocytes	Loss of tissues or cells	8	7	6
	Other incident	1	0	0
Embryos	Loss of tissues or cells	17	12	3
	Incorrect product transplanted	1	1	1
	Other incident	3	0	0
	Bacterial contamination of product	1	1	1
	Congenital abnormality	1	1	1
Ovarian tissue	Loss of tissues or cells	1	1	1
Total		**45**	**30**	**20**

* *Serious according to the Dutch Association of Clinical Embryologists' guideline (KLEM): significantly reduced chance of a pregnancy due to loss of oocytes, embryos or irreplaceable semen*

** *Serious according to EU criteria: loss of a complete fertility cycle*

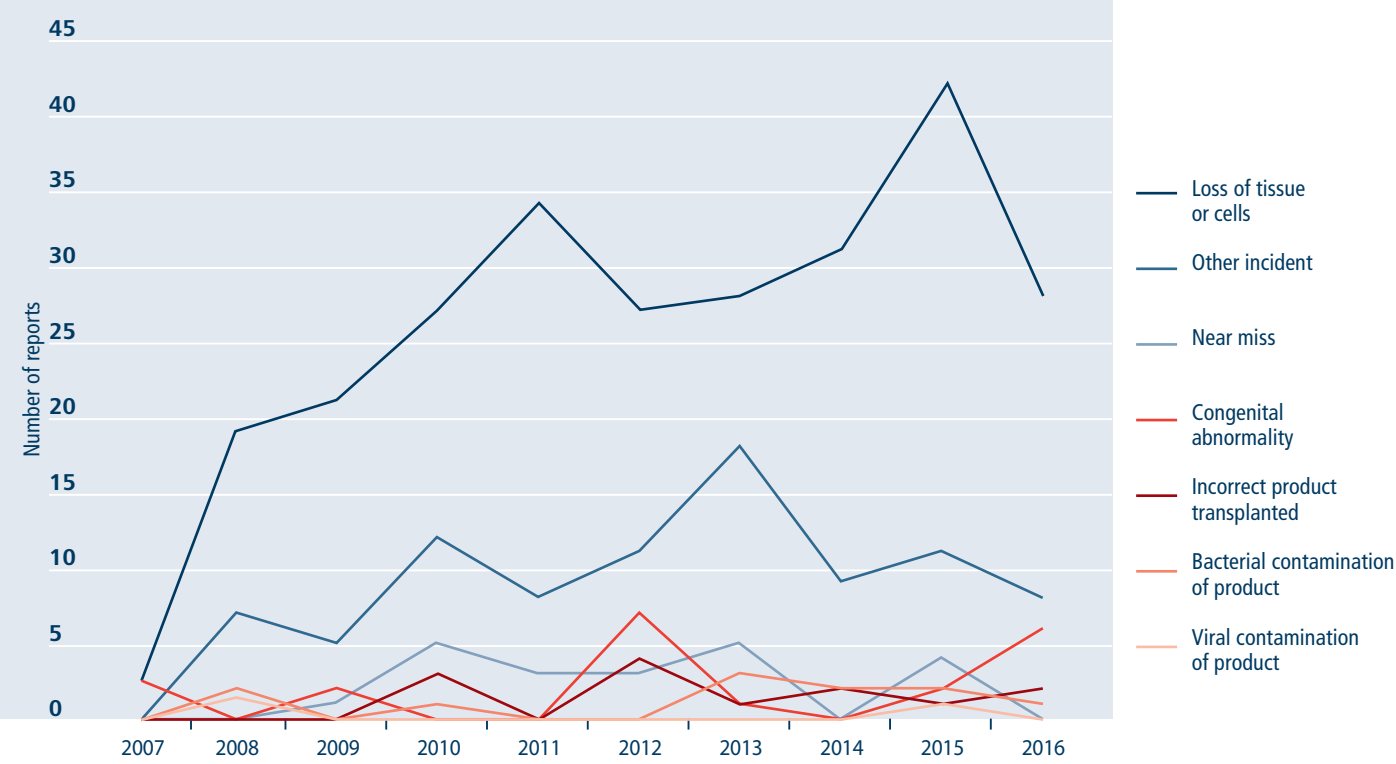

Figure 7. Number of reports per adverse event category concerning gametes, embryos and gonadal tissue, 2007-2016

Loss of tissues or cells

In 2016 there were 28 reports in the category loss of tissues or cells. The percentage of adverse events in this category has varied between 54 and 81% of the reports concerning assisted reproductive techniques in recent years (2016: 62%, Figure 7). Loss of tissues or cells has serious consequences when it leads to loss of a complete fertility cycle or when reproductive tissues for fertility preservation cannot be processed or cryopreserved. Figure 8 presents an overview of the number of reports in the category loss of tissues or cells in the period 2007-2016.

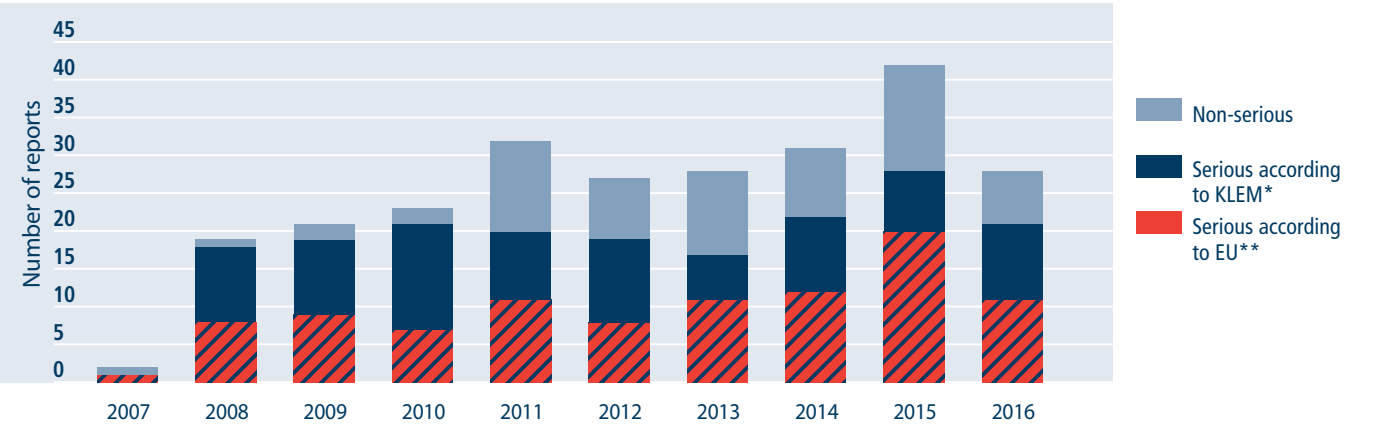

Figure 8. Reports of loss of tissues or cells concerning gametes, embryos or gonadal tissue, 2007-2016

* *Serious according to the Dutch Association of Clinical Embryologists' guideline (KLEM): significantly reduced chance of a pregnancy due to loss of oocytes, embryos or irreplaceable semen*

** *Serious according to EU criteria: loss of a complete fertility cycle*

The largest number of adverse events (16) are processing errors concerning oocytes and embryos. In Figure 9 the 2016 reports of loss of tissues or cells concerning reproductive tissue are presented. They are broken down according to tissue or cell type, step in the procedure and type of error. In Figure 10 processing errors are shown in more detail.

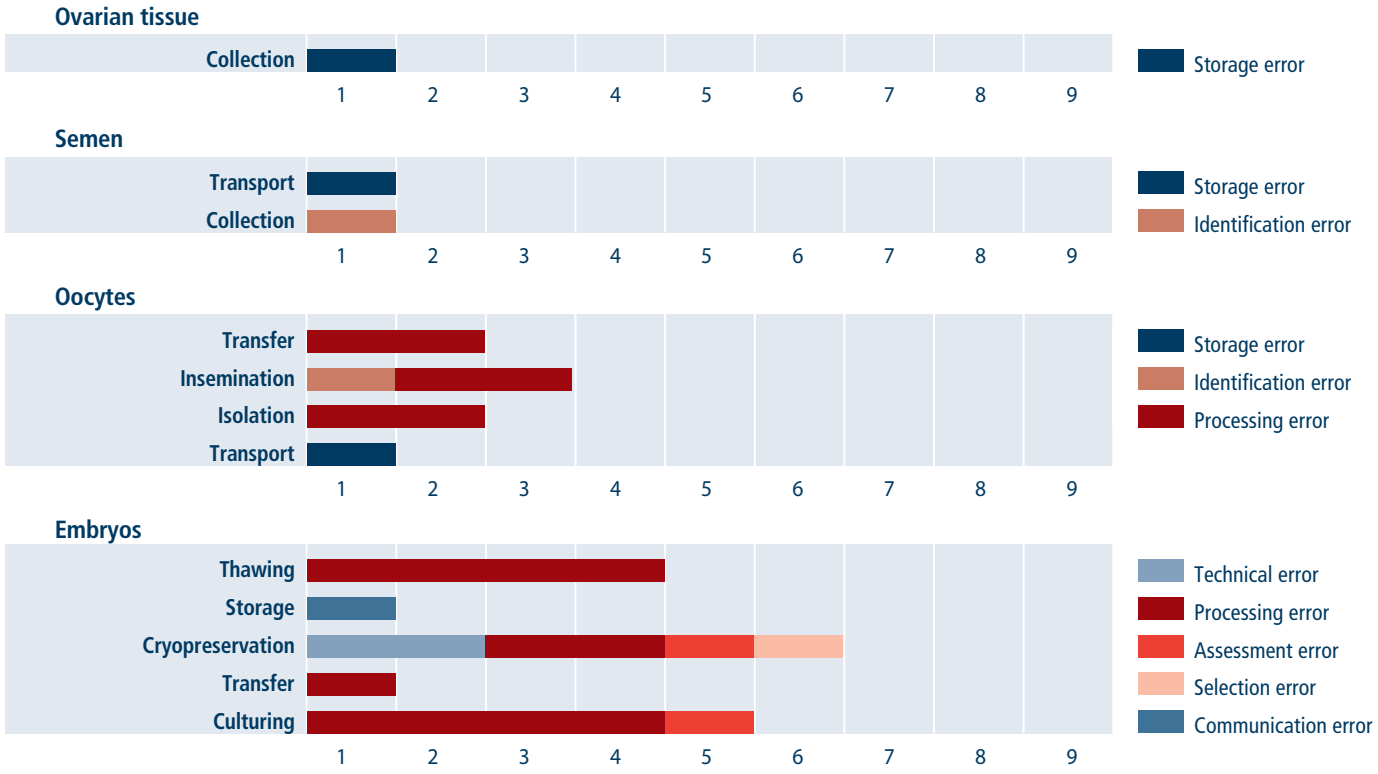

Figure 9. Reports of loss of tissues or cells concerning gametes, embryos and gonadal tissue broken down according to step in procedure and type of error in 2016

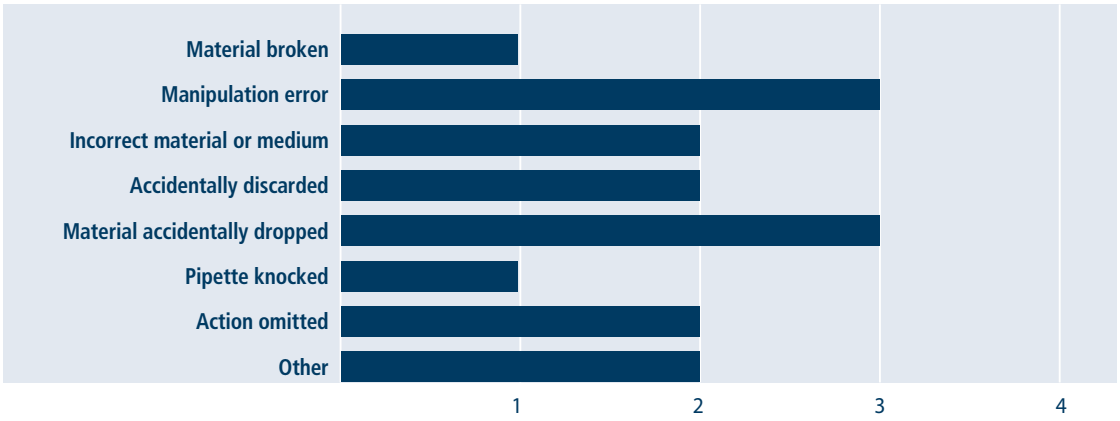

Figure 10. Types of processing errors in category loss of tissues or cells concerning gametes, embryos and gonadal tissue in 2016

Case 1 describes three consecutive adverse events relating to a technical error (fault) in cryopreservation straws. Another noteworthy report involving an identification error at procurement of semen by electrostimulation is described in Case 2. Case 3 involves the loss of ovarian tissue.

Case 1. Recall of cryopreservation straws

On two occasions an embryo was lost in the IVF laboratory on drawing it up into a cryopreservation straw because the seal malfunctioned so that the embryos with medium were lost in the suctioning syringe. These adverse events were reported to the supplier who carried out a voluntary recall on that batch of cryopreservation straws. A third similar mishap occurred in the same IVF laboratory, again resulting in the loss of an embryo. Analysis revealed that the batch of cryopreservation straws had not been completely removed and a recalled straw had been used in this case. Two reports were registered as technical errors, the third was registered as an assessment error.

Case 2. Loss of semen collected by electrostimulation

Two electrostimulations for two consecutive patients were scheduled on the same day. Electrostimulation is used to effectuate ejaculation in patients for whom natural ejaculation is impossible due to an organic lesion e.g. spinal cord lesion. This procedure is carried out in the operating theatre, usually under general anesthesia. The tubes and request forms for the first patient A were labelled in the theatre in the absence of patient A, thus without proper identification. However, electrostimulation for patient A was cancelled but this was not known in the IVF laboratory. The material labelled for patient A was used for patient B and was processed by the IVF lab. A total of 21 semen straws were cryopreserved under the (incorrect) name of patient A. By coincidence a phone call between urologist and embryologist revealed the error. All semen straws were discarded and patient B will need a second electrostimulation procedure.

Case 3. Loss of ovarian tissue

One ovary was removed for fertility preservation prior to treatment in a patient suffering from breast cancer. The ovary had to be transported from the operating hospital to the IVF laboratory in another hospital. The ovary transport was carried out by the operating hospital using dry ice instead of ice cubes by mistake. The transport instructions of the IVF laboratory had not been followed and the colder transport conditions of dry ice led to irreparable damage and loss of the ovarian tissue

Other incident

The category other incident encompasses mainly adverse events that led to loss of volume or possible loss of quality of reproductive tissues or cells. The percentage of adverse events in this category varies from 8 to 27% from year to year; inn 2016 it amounted to 18%. Figure 11 provides an overview of the reports of other incidents in the period 2007-2016. In 2016 there were eight non-serious other incident reports. Table 8 gives descriptions of these other incident reports.

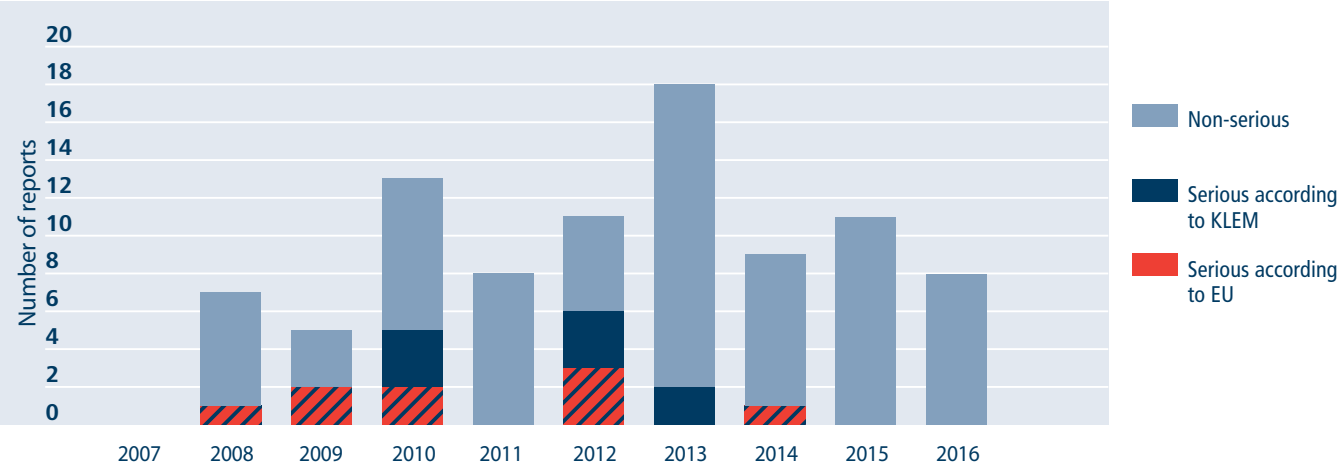

Figure 11. Reports of other incidents concerning gametes, embryos and gonadal tissue, 2007-2016

Table 8. Reports of other incidents concerning gametes, embryos and gonadal tissue in 2016

Type of error	No. of reports	Step in procedure	Type of gamete or embryo	Description
Storage error	1	Donation	Semen	Inappropriate semen container provided to partner
Processing error	3	Cryo-preservation	Embryos	Incorrect cryopreservation run that could be corrected
				Cryopreservation unit incorrectly connected to liquid nitrogen container
		Storage	Embryos	Embryos thawed in error after contract prolongation, could be refrozen
Assessment error	1	Processing	Semen	Semen sample initially processed in non-sterile conditions as for semen analysis instead of sterile processing for fertility treatment
Technical error	1	Storage	Oocytes	Transport box temperature too cold
Administrative error	1	Testing	Semen	Lot numbers of additive solution not registered
Other	1	Storage	Semen	1 donor had one semen straw too many while another donor had one straw missing. Mix up was ruled out

Congenital malformation

In 2016 there were six reports of congenital malformation. A pregnancy involving donated gametes or embryos (i.e. not from the partner) which leads to the birth of a child or termination of pregnancy with a (possible) congenital malformation is considered to be a serious adverse event. This is also the case if a genetic abnormality is found in a donor (non partner) after donation of gametes or embryos. In Table 9 the reports are summarised. All reports of congenital malformation in 2016 were serious (see Annex 3, Table 35).

Table 9. Reports of congenital malformation involving gametes and embryos in 2016

Type of gamete or embryo	Congenital abnormality	Description
Donor semen	Omphalocele, diaphragmatic hernia, hypospadias and dysmorphia	Identical twins born after IUI involving donated semen. One of the twins died after 2.5 months. The other baby also had hypospadias and dysmorphic features. Donor deferred pending further investigation
	Oculocutaneous albinism	Autosomal recessive inherited genetic disorder. Donor not deferred
	Trisomy 21 combined with VSD and ASD	Semen donor with history of small VSD. Donor deferred
	Trisomy 21	At NIPT trisomy 21 was found, ultrasound examination revealed intra-uterine fetal death. Balanced translocation in the donor, maternal age 41 years
	Sickle cell trait	At heel prick testing sickle cell trait was diagnosed. Donor will only remain available for a second or subsequent sibling with informed consent
Embryo	PCH2-mutation with microcephaly and pontocerebellar hypoplasia	Both parents were carriers of this genetic autosomal recessive disorder. In this case after PGD the transferred embryo was found to be heterozygous for this condition. Pregnancy of identical twins ensued who were found to be homozygous for the condition. The failure rate of PGD is 2%. In accordance with the parents' wishes no other prenatal tests had been done

Figure 12 shows an overview of reports of congenital abnormality in the period 2007-2016. The Advisory Committee recommends reporting all congenital abnormalities that could have a possible genetic cause.

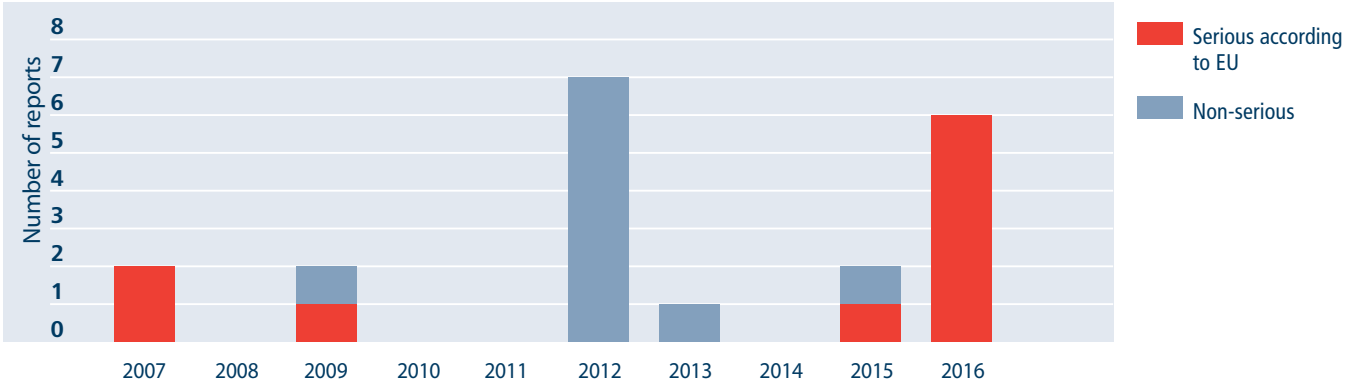

Figure 12. Reports of congenital malformation involving gametes, embryos and gonadal tissue, 2007-2016

Incorrect product transplanted

In 2016 two reports concerned the application of an incorrect product. Reports in this category are always classified as serious. One report regarded five unneeded IUI procedures of semen with serious globozoospermia. This had been detected during semen analysis, but had not been properly communicated to the treating physician. The second report concerned a selection error of embryos during PGD by the clinical embryologist. In error the female embryos were released for transfer instead of the male embryos that were free of the disorder. The patient did not conceive.

In Figure 13 an overview is presented of reports of incorrect product transplanted in the period 2007-2016.

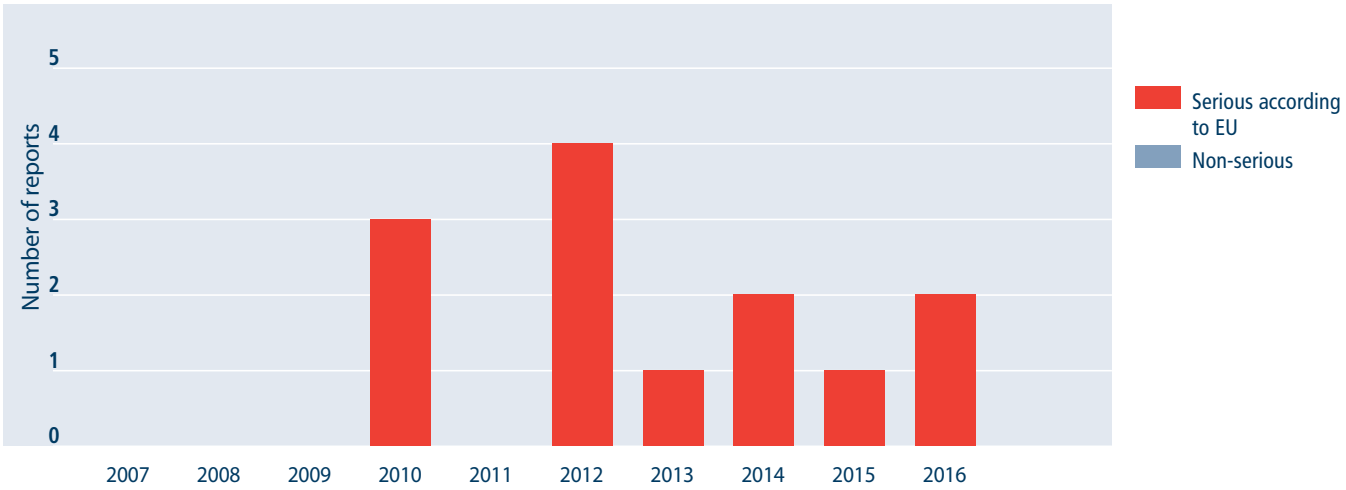

Figure 13. Reports of incorrect product transplanted involving gametes, embryos and gonadal tissue, 2007-2016

Bacterial contamination of product

One report regarded bacterial contamination of embryo cultures by Group B hemolytic streptococci. Semen culture detected Abiotrophia defectiva, medium culture remained negative. The report was classified as serious due to the loss of the complete fertility cycle. An overview of reports of bacterial contamination in 2007-2016 is shown in Figure 14.

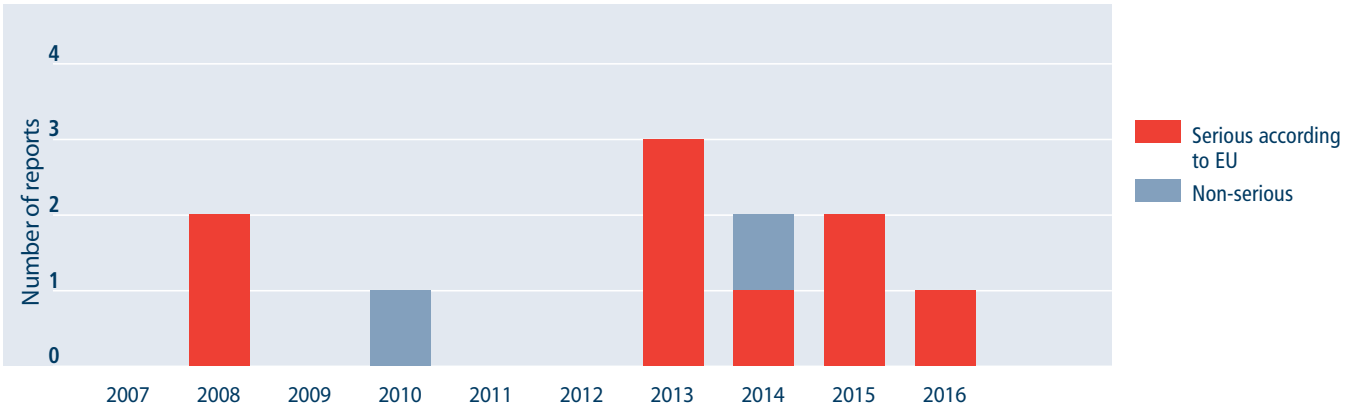

Figure 14. Reports of bacterial contamination involving gametes, embryos and gonadal tissue, 2007-2016

Summary

After an increased number of reports regarding assisted reproductive techniques in 2015 the number of reports is again comparable to previous years. As in previous years the largest number of reports is registered in the category of loss of tissues or cells. The number of serious adverse event reports (20) is slightly higher than in previous years. There were six congenital abnormality reports involving the application of donor gametes. Two reports related to Preimplantation Genetic Diagnosis. Three reports regarded a technical error of cryopreservation straws for embryos. For the second consecutive year reports of donation complications in voluntary egg cell donors were registered.

2.2 Hematopoietic stem cells and therapeutic cells

In The Netherlands thirteen stem cell laboratories are licensed for the collection, processing, preservation, storage and distribution of HSC from autologous and related donors. Stem cell products from unrelated donors (including cord blood) are distributed by Matchis (formerly Europdonor Foundation) to the eight academic transplant centres for specific recipients, usually via the stem cell laboratory. Unrelated stem cell transplants for Dutch patients most commonly come from foreign volunteer donors (88% in 2016 compared to 95% in 2015, see Table 12). In collaboration with Sanquin, Matchis arranges collection of bone marrow and peripheral blood stem cells from Dutch volunteer donors in two university hospitals. A minority of these donations is applied in Dutch patients; the majority of donations is distributed via Matchis to foreign transplantation centres.

In The Netherlands there is one cord blood bank (Sanquin) that processes and stores cord blood transplants, making them available for unrelated patients in The Netherlands and abroad through the Matchis registry. Two private cord blood banks store cord blood for potential future autologous application.

Processing, distribution and application

In Tables 10, 11 and 12 the figures for processing, distribution and transplantation of hematopoietic stem cells (HSC) and therapeutic cells are presented with the number of institutions performing each activity.

Table 10. Processing of hematopoietic stem cells and therapeutic cells in in 2016

Type of cells	No. of tissue establishments	Transplants processed*			
		From NL	From EU	From non-EU	Total
HSC unrelated					
Bone marrow	4	23	16	1	40
PBSC	7	15	236	20	271
Cord blood	7	366	44	22	432
HSC related					
Bone marrow	7	43	0	0	43
PBSC	7	136	0	0	136
Cord blood	1	2	0	0	2
HSC autologous					
Bone marrow	3	22	0	0	22
PBSC	10	2432	0	0	2432
Cord blood	2	779	3645	140	4564
Therapeutic cells					
Mesenchymal stem cells unrelated	2	7	2	0	26
Mesenchymal stem cells autologous	1	7	0	0	7
Lymphocytes (DLI) unrelated	7	37	129	20	186
Lymphocytes (DLI) related	7	82	0	0	82
Dendritic cells unrelated	1	0	2	1	3
Dendritic cells related	1	1	0	0	1
Dendritic cellsautologous	2	48	0	0	48
Natural Killer cells unrelated	1	1	0	0	1
Bone marrow mononuclear cells autologous	1	23	0	0	23
TC-Til cells autologous	1	5	0	0	5
TCR cells	1	4	0	0	4

* *If a transplant unit is reprocessed in the receiving stem cell laboratory it is counted a second time*

Table 11. Distribution of hematopoietic stem cells and therapeutic cells in 2016

Type of cells	No. of tissue establishments	Distributed units			
		In NL	In EU	Outside EU	Total
HSC unrelated					
Bone marrow	4	42	7	5	57
PBSC	7	317	15	8	340
Cord blood	7	103	1	1	105
HSC related					
Bone marrow	5	15	0	0	15
PBSC	7	151	0	0	151
Cord blood	0	0	0	0	0
HSC autologous					
Bone marrow	3	8	0	0	8
PBSC	10	3406	0	0	3406
Cord blood	0	0	0	0	0
Therapeutic cells					
Mesenchymal stem cells unrelated	2	59	22	0	81
Mesenchymal stem cells autologous	1	24	0	0	24
Lymphocytes (DLI) unrelated	7	131	15	3	60
Lymphocytes (DLI) related	7	87	0	0	87
Dendritic cells unrelated	1	6	0	0	6
Dendritic cells related	0	0	0	0	0
Dendritic cells autologous	1	3	0	0	3
Natural Killer cells, unrelated	1	1	0	0	1
Bone marrow mononuclear cells autologous	1	23	0	0	23
TC-Til cells autologous	1	4	0	0	4
TCR cells	1	4	0	0	4

Table 12. Transplantation of hematopoietic stem cells and therapeutic cells in 2016

Type of cells	Transplant centres	Recipients	Transplanted units			
			From NL	From EU	From outside EU	Total
HSC unrelated						
Bone marrow	3	30	1	25	4	30
PBSC	7	308	15	258	37	310
Cord blood	7	69	4	61	31	69
HSC related						
Bone marrow	7	39	38	1	0	39
PBSC	7	123	131	0	0	131
Cord blood	0	0	0	0	0	0
HSC autologous						
Bone marrow	3	4	8	0	0	8
PBSC	12	986	3425	0	0	3425
Cord blood	0	0	0	0	0	0
Therapeutic cells						
Mesenchymal stem cells unrelated	3	34	90	0	0	90
Mesenchymal stem cells autologous	1	6	24	0	0	24
Lymphocytes (DLI) unrelated	6	124	33	87	12	132
Lymphocytes (DLI) related	6	63	64	0	0	61
Dendritic cells unrelated	1	2	6	0	0	6
Dendritic cells related	0	0	0	0	0	0
Dendritic cells autologous	1	3	3	0	0	3
Natural Killer cells unrelated	1	1	1	0	0	1
Bone marrow mononuclear cells autologous	1	22	22	0	0	22
TC-Til cells autologous	1	4	4	0	0	4
TCR cells	1	4	4	0	0	4

There is a 75% decrease in the number of processed allogeneic units cord blood units compared to 2015. This is because in 2016 only cord blood collections with a high cell count were processed. Also the number of processed autologous cord blood collections shows a decrease of 51%. As is shown in Figure 15 a-b-c there is an increase in the number of recipients of autologous stem cell transplants (18% compared to 2015). There is an increase in the number of recipients of related bone marrow transplants. The overall number of bone marrow transplants shows a gradual decline, but related bone marrow recipients more than doubled in 2016 compared to 2015. The increase is probably explained by an increase in haploidentical stem cell donations. Unrelated donor lymphocyte infusions increased by 68% in 2016 compared to 2015.

Figure 15 a-b-c. Number of HSC recipients per type of transplant, 2012-2016

Reports

In 2016 there were 15 reports of adverse events and reactions concerning hematopoietic stem cells and therapeutic cells. Figure 16 gives an overview of reports over the past ten years. In 2016 eight (non-serious) adverse events and seven adverse reactions were registered, out of which two reactions were serious. One serious adverse reaction regarded a pulmonary embolism after autologous stem cell apheresis in a patient with an underlying condition predisposing for thromboembolic complications (imputability possible). The 2016 adverse events and reactions are summarised in Table 13 and 14 subdivided per type of hematopoietic stem cell.

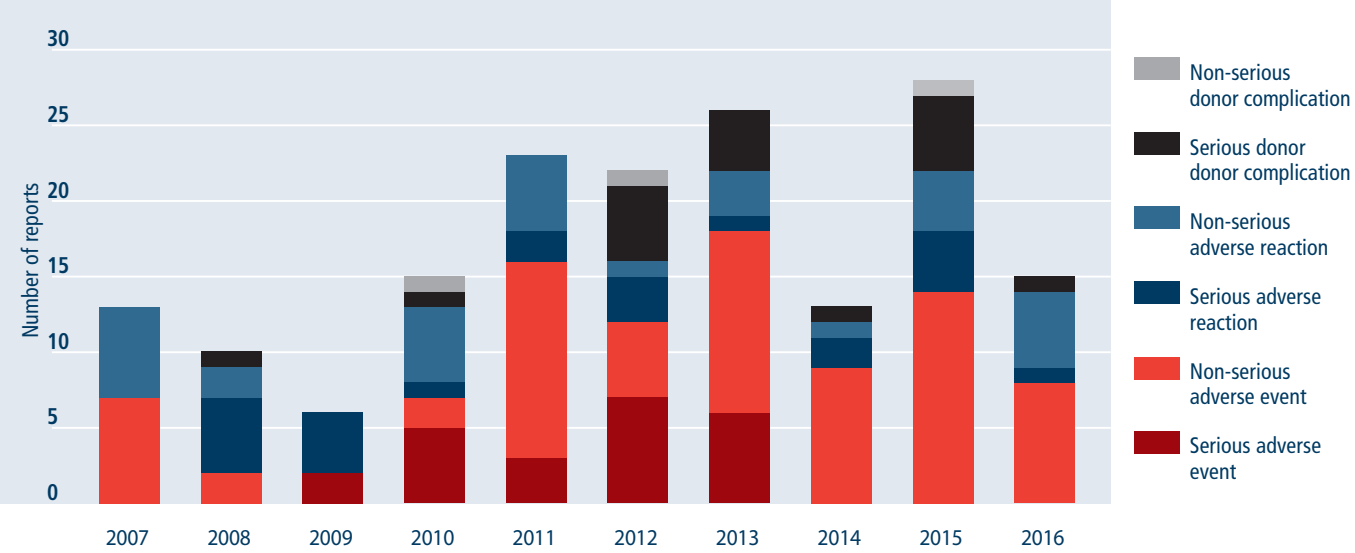

Figure 16. Reports concerning HSC and therapeutic cells, 2007-2016

Table 13. Adverse events per type of HSC or therapeutic cells in 2016

Type of cells	Adverse event (category and description)	Number
PBSC, allogeneic	Other incident • Mix-up of samples for blood grouping of two donors on the HLA typing lab. Correct donor collected and transplanted	1
Bone marrow, allogeneic	Risk of transmission of an other disease/condition • In a donor minor bone marrow dysplasia was found after the transplant had been carried out. Hematology consultation: no intervention needed in the donor, complete engraftment in recipient	1
Cord blood, allogeneic	Loss of tissues or cells • Cord blood unit had thawed on arrival abroad. Cause and actual consequences for recipient unknown • Minor loss of cord blood due to rupture of unit caused by cryopreservation with too much air in unit. No adverse consequences for recipient	2
PBSC, autologous	Loss of tissues or cells • 1 of 6 units of cryopreserved autologous PBSC fell from dry shipper and ruptured. Patient can have 2 instead of the planned 3 transplant procedures • Insufficient anticoagulant used during PBSC collection, patient underwent an extra day of apheresis	2
	Bacterial contamination of product • Staphylococcus hemolyticus and Staphylococcus epidermidis in stem cell product. Due to low cell count (unrelated to contamination) patient had to have another collection procedure	1
	Other incident • Based on cell counts prior to collection two days were needed for stem cell collection with an extra dose of G-CSF. After the start of the 2nd apheresis procedure cell count results from day 1 were determined and showed that sufficient cells had already been harvested. In future cell counts will be done immediately after each collection procedure	1
Total		**8**

In 2016 there were two reports of leaking stem cell units. In contrast to previous years, a clear cause could be determined, i.e. dropping a unit and cryopreservation of a unit with too much air in it (from a foreign tissue establishment). Figure 2017 shows the numbers of reports concerning leaking units or collection sets for stem cells in 2010-2016.

Figure 17. Reports of leaking or ruptured stem cell units or collection sets for hematopoietic stem cells, 2010-2016

Table 14. Adverse reactions and donation complications per type of hematopoietic or therapeutic stem cell in 2016

Type of cells	Adverse reaction (category and description)	Number
PBSC, allogeneic	Hemolytic reaction	2
	• Transient rigors and supraventricular tachycardia during infusion of ABO major incompatible product	
	• Dyspnea, nausea/vomiting, rigors and transient hypotension during infusion of ABO major incompatible product	
	Post-transplantation febrile reaction	1
	• Fever and rigors, product met all quality criteria	
	Anaphylactic reaction	1
	• Tachypnea, expiratory stridor, drop in blood pressure, 2x brief loss of consciousness, administration completed with very low infusion rate	
PBSC, autologous	Circulatory overload	1
	• Tachycardia, dyspnea, drop in O2 saturation*	
	Donation complication	1
	• Segmental pulmonary embolism during collection procedure in a patient suffering from PCNSL; G-CSF had been administered for stem cell mobilisation*	
	Anaphylactic reaction	1
	• Hypotension with drop in O2 saturation*	
Total		**7**

* *Serious*

In contrast to 2015 there was only one report of a serious donation complication related to an autologous stem cell apheresis procedure. In 2015 six serious donation complications were registered, all of high imputability. In Table 15 an overview is presented of all donation complications reported to TRIP in the period 2007-2016.

The follow-up and complication registration for related donors is not yet well established, in contrast to that for unrelated donors. As part of the protection of donor health these complications are registered at the international level by the World Marrow Donor Association (WMDA). TRIP therefore considers it worthwhile to register and report on these complications as well.

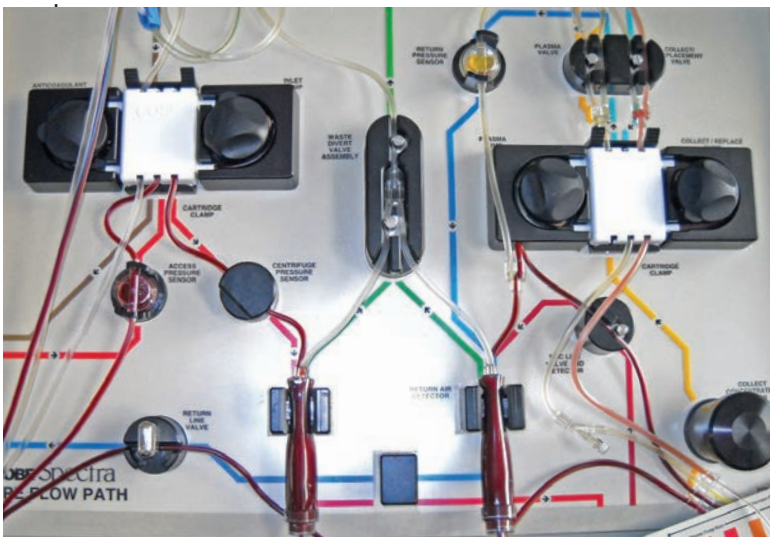

Table 15. Overview of donation complications associated with hematopoietic stem cells or therapeutic cells, 2007-2016

Type of cell	Number	Donation complication	Interval after donation	Imputability
PBSC, unrelated	7	• IgA nephropathy	During G-CSF stimulation	probable
		• Tetany and laryngospasm due to hypocalcaemia	During apheresis procedure	certain
		• Phlebitis	Not stated	probable
		• Stroke	2 months	unlikely
		• Breast cancer	2 years	unlikely
		• Polyarthritis rheumatica	4 years	unlikely
		• Rheumatoid arthritis	6 years	unlikely
PBSC, related	8	• Deep venous thrombosis followed by pulmonary embolism	During apheresis procedure	certain
		• Transient rise of creatinine level	During apheresis procedure	probable
		• Benign paroxysmal positional vertigo	Immediate	
		• Exacerbation of asthma and back pain	7 days	probable
		• Shoulder abscess (S. aureus)	12 days	probable
		• Inflammatory bowel disease	6 months	possible
		• MDS-RAEB	5 years	possible
		• AML	7 years	possible
PBSC, autologous	3	• Thrombocytopenia	During apheresis procedure	possible
		• Pulmonary embolism	During apheresis procedure	certain
		• Splenic rupture	2 days	possible
Therapeutic cells, related	1	• Vitiligo	6 months	certain possible
Bone marrow, unrelated	2	• TIA	8 months	unlikely
		• Breast cancer	2 years	unlikely
Total	**21**			

Summary

As in the last two reporting years there were no serious adverse events concerning hematopoietic stem cells. There were only two serious adverse reaction reports: a serious adverse reaction in a recipient of an autologous peripheral blood stem cell transplant and a serious donation complication following collection of autologous peripheral hematopoietic stem cells. Serious adverse reactions during autologous stem cell collection are not unexpected, not related to safety and quality and may also be related to the patient's underlying disease. Hospitals therefore do not report his type of adverse reaction to the Healthcare Inspectorate.

2.3 Bone and other musculoskeletal tissues

In The Netherlands ten bone banks are located in hospitals and specialised orthopaedic clinics. Two independent bone banks are licensed as organ banks and not allied to a hospital. Another eight tissue establishments import musculoskeletal tissues, mainly from the USA, and are licensed to distribute them in Europe. One tissue establishment cultures chondrocytes for autologous transplantation.

Bone

Processing, distribution and transplantation

In Table 16 the numbers of processed and distributed bone unit are presented. Table 17 gives an overview of the numbers of transplanted bone units with the number of recipients. The data were provided by 20 tissue establishments, one clinic, 40 oral implantology practices and 68 hospitals.

Table 16. Processing and distribution of bone tissue in 2016

Type of tissue	Tissue establishments*	Processed		Distributed				
		From on-site clinic	From NL	Unit	In on-site clinic	In NL	In EU	Outside EU
Bone, whole	3	1	58	Bone	1	90	13	2
Bone filler, mineralised	10	0	1122	Pack	0	5060	5155	2731
Femoral head, living donor	10	521	2564	Bone	434	1838	29	3
Femoral head, post mortem donor	3	0	47	Bone	0	48	172	0
Bone filler, demineralised	6	0	6003	Pack	0	1497	15900	510445
Auditory ossicles	1	0	33	Graft	0	33	0	0
Cranial bone (autologous)	3	35	114	Graft	17	77	0	0

* *Including hospital bone banks (also cranial bone banks) and tissue establishments which only distribute bone tissue*

Table 17. Application of bone tissue in 2016

Type of tissue	Hospitals/ clinics/ practices	Recipients	Transplants					
			Unit	From on-site clinic	From NL	From EU	From non EU	Total
Bone, whole	15	136	Bone	1	133	2	0	136
Bone filler, mineralised	69	2688	Pack	0	2327	484	0	2811
Femoral heads (whole or halved), living donor	38	1143	Bone	451	777	0	0	1228
Femoral heads (whole or halved), post-mortem donor	27	283	Bone	0	326	6	0	332
Bone filler, demineralised	26	432	Pack	60	369	13	0	442
Auditory ossicles	1	24	Graft	0	24	0	0	24
Cranial bone (autologous)	7	47	Graft	22	24	0	0	46

Figure 18 presents figures for distributuion of bone in The Netherlands in the past ten years. A rising trend may be seen in the number of applied units of mineralised bone filler. In contrast the application of femoral heads that need grinding by the transplanting healthcare institution is declining.

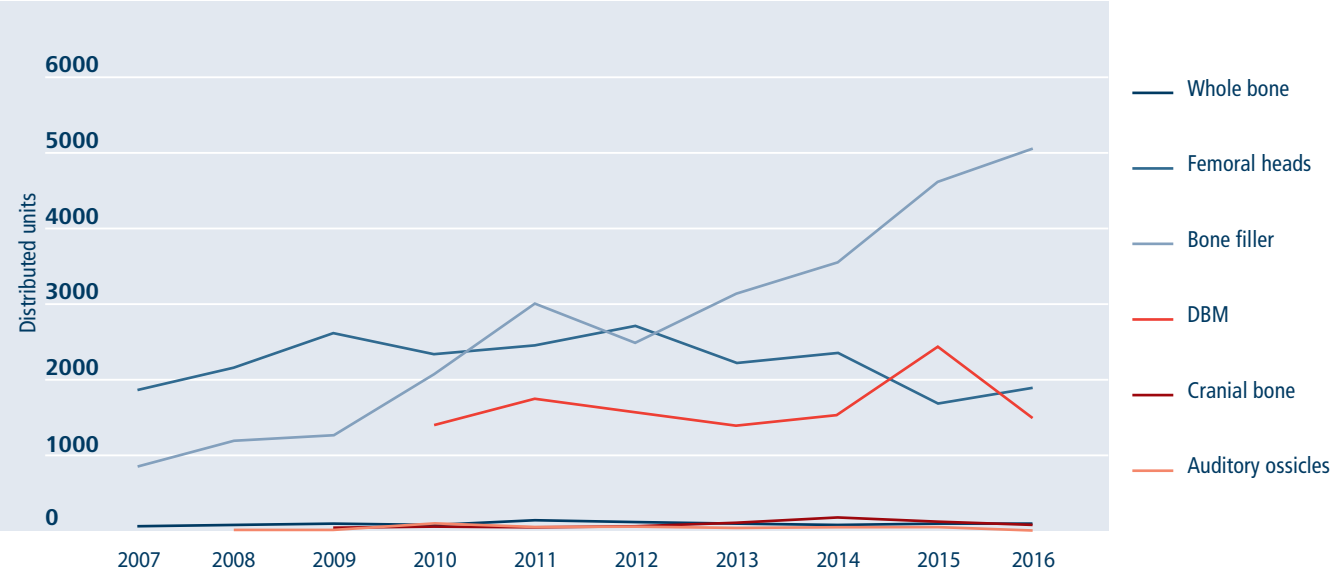

Figure 18. Numbers of distributed bone units, 2007-2016

Abbreviation: DBM=Demineralised Bone Matrix

Reports

In 2016 there were six adverse event reports, all classified as non-serious. A serious complication of bone grafting is the transmission of pathogens as bone infections are difficult to treat. This year, as in 2015, there was no report of a bacterial infection or any other adverse reaction after the transplantation of bone. In Figure 19 the annual numbers of adverse events and reactions concerning bone tissue are shown for 2007-2016. The adverse events in 2016 are summarised in Table 18.

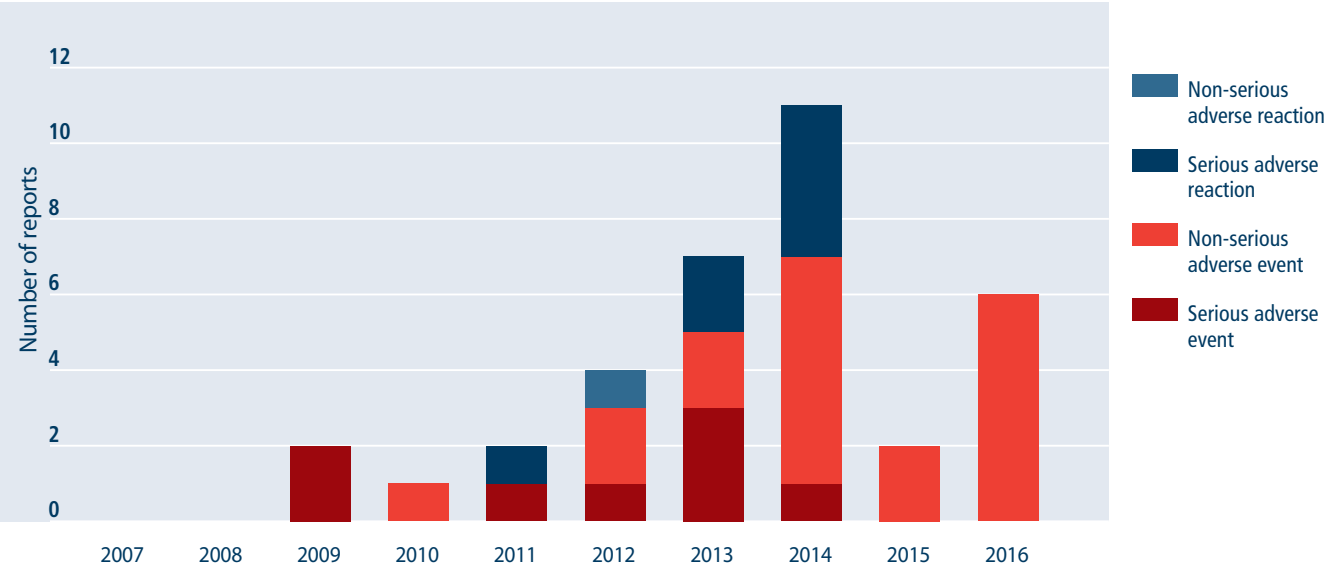

Figure 19. Reports involving bone tissue, 2007-2016

Table 18. Adverse events concerning bone in 2016

Category of event	Description	No. of reports
Bacterial contamination of product	• Cultures prior to transplant of a living donor femoral head revealed Streptococcus sanguinis. Cultures at collection were negative, no adverse sequelae for recipient. Culture results judged to result from as contamination when taking culture sample	1
Loss of tissue or cells	• Packaging of femoral head damaged during storage in hospital	1
Other incident	• Traceability recording insufficient: for 41 bone chip units the information was not recorded in the patient's notes. Recipient may still be traced via the distributing tissue establishment's follow-up form • Following donation of a living donor femoral head the donor was diagnosed with pancreatic cancer. The femoral head had been released, but not yet distributed. Femoral head discarded • Transplanting surgeon reported necrosis in a living donor femoral head. This contraindication for donation was missed by the explanting surgeon • Screening of a post-mortem donor revealed risk behaviour in the past which constituted a contraindication for donation. Previously this donor had donated a (living donor) femoral head that had been applied in a recipient. Analysis concluded that the transmission risk of infection was nil based on negative serology and NAT testing	4

Cartilage and menisci

Processing, distribution and application

In Tables 19 and 20 the numbers of processed/distributed and applied units of cartilage and menisci are presented. The gap between distribution and application data shows that registration in the transplanting institution is still incomplete.

Table 19. Processing and distribution of cartilage and menisci in 2016

Type of tissue	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Cartilage	2	39	Graft	113	0	0	113
Chondrocytes	1	72	Graft	74	22	0	96
Menisci	1	7	Graft	1	0	0	1

Table 20. Application of cartilage and menisci in 2016

Type of tissue	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Cartilage	8	77	Graft	9	68	0	77
Chondrocytes	0	0	Graft	0	0	0	0
Menisci	3	31	Graft	1	30	0	31

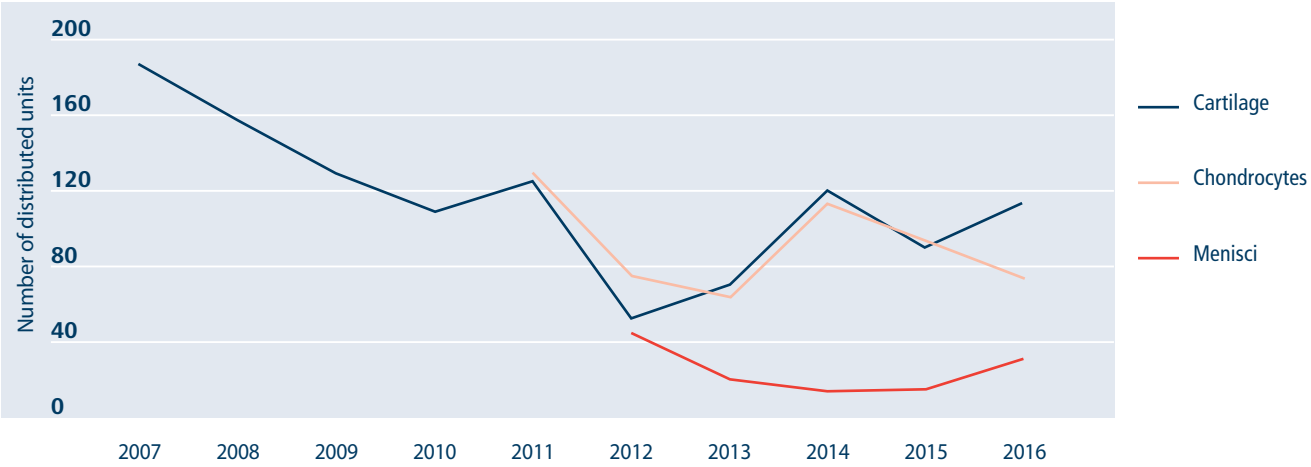

Figure 20. Numbers of distributed cartilage, chondrocytes and menisci, 2007-2016

Figure 20 shows the distribution of cartilage units and menisci in 2007-2016. After an initial decrease the cartilage distribution has slowly risen from 2012 onwards.

Reports

In the reporting year 2016 as in the two previous years there were no reports concerning cartilage. From the start of the TRIP registration there have not been any reports regarding menisci. Figure 21 provides an overview of reports concerning cartilage in the past ten years. All reports related to adverse events concerning the culturing of autologous chondrocytes. In 2010 seven serious adverse events were submitted by two tissue establishments. One of these two establishments has since discontinued the chondrocyte culturing activities.

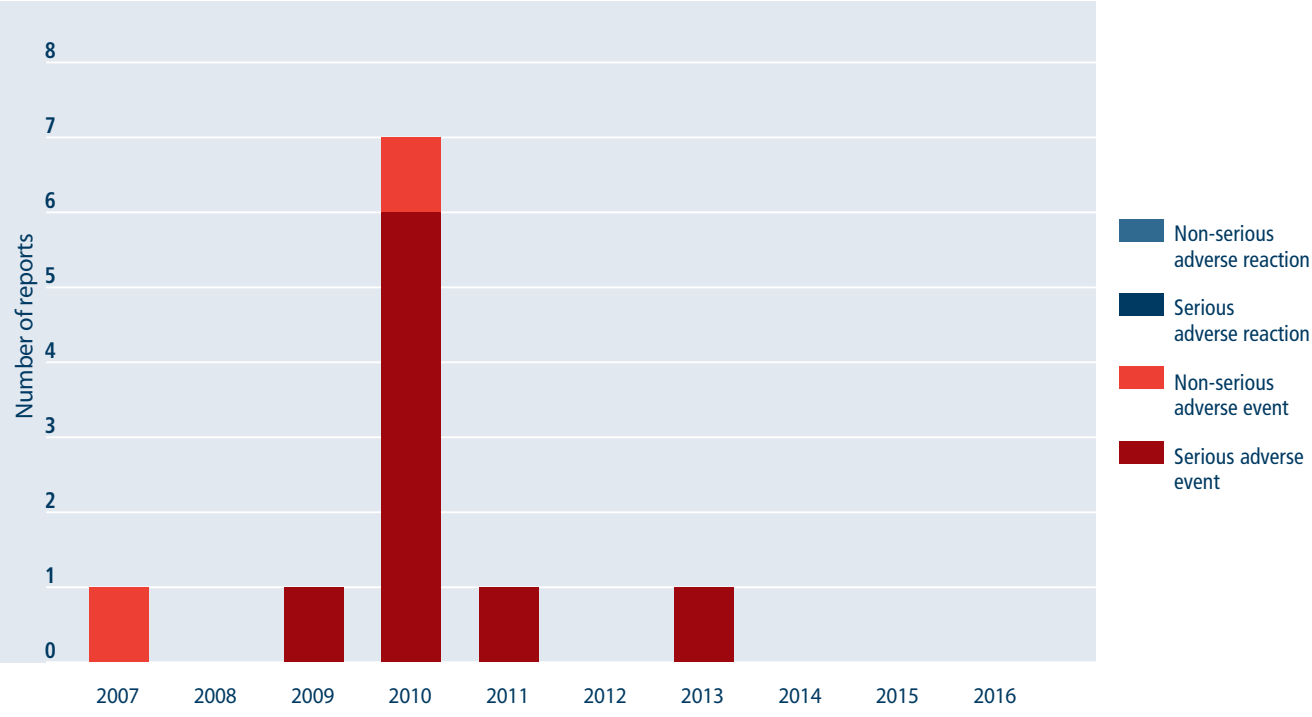

Figure 21. Reports concerning cartilage and chondrocytes, 2007-2016

Tendons, ligaments and fascia

Processing, distribution and application

In Table 21 processing and distribution figures forf tendons, ligaments and fascia are presented. In Table 22 the application data for these tissues may be found. Here also there is a considerable discrepancy

between distribution and application data. This may in part be explained by hospitals keeping tissue in stock. Figure 22 shows numbers of distributed tendons, ligaments and fascia from 2008.

Table 21. Processing and distribution of tendon, ligaments and fascia in 2016

Type of tissue	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Tendons	2	544	Graft	487	50	3	540
Bone-tendon-bone grafts	1	31	Graft	30	17	1	48
Ligaments	0	0	Graft	0	0	0	0
Fascia	3	30	Graft	1361	164	0	1525

Table 22. Application of tendons, ligaments and fascia in 2016

Type of tissue	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Tendons	33	310	Graft	308	4	0	312
Bone-tendon-bone grafts	10	33	Graft	30	3	0	33
Ligaments	2	2	Graft	0	2	0	2
Fascia	18	561	Graft	457	127	0	584

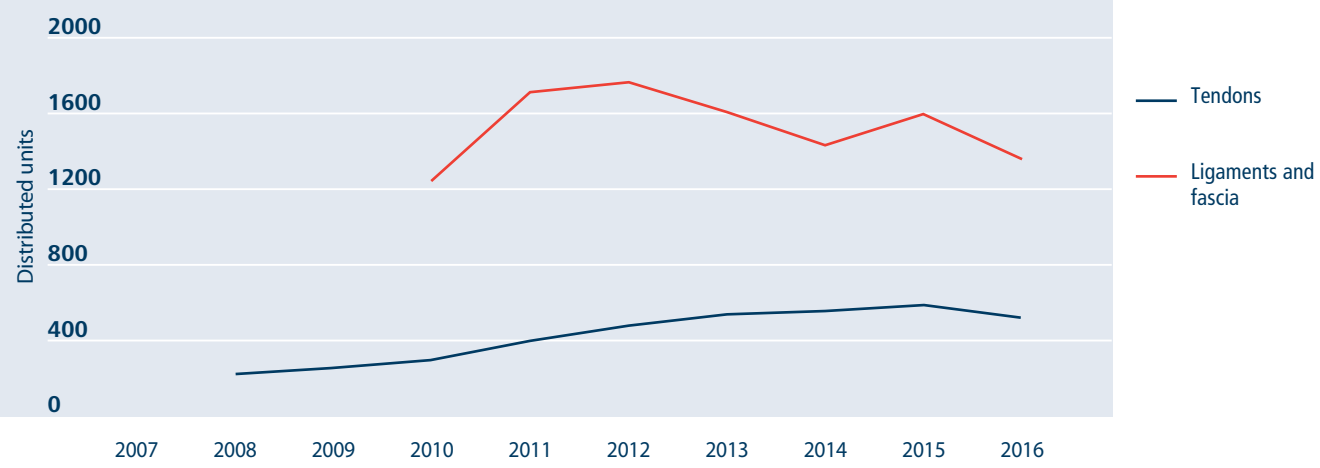

Figure 22. Distributed tendons and ligaments/fascia, 2007-2016

Reports

In 2016 one non-serious report regarding a tendon was registered. In Figure 23 an overview is presented of reports concerning tendinous tissue, ligaments and fascia in the period 2007-2016. The 2016 report concerned the rupture of a tibialis tendon intended for anterior cruciate ligament reconstruction.
The patient did not suffer adverse consequences as reconstruction was done applying another tendon which was in stock in the hospital. Analysis by the tissue establishment did not reveal a cause. In the past years another three reports were about rupturing of a tendon during preparation for surgery or at application. This is a rare occurrence and none of the patients suffered adverse sequelae. In none of these cases was a cause found that could be related to tendon tissue quality or safety issues. It is recommended that transplanting institutions always report the rupture of a tendon to the tissue establishment and TRIP, even if there was no harm for the patient.

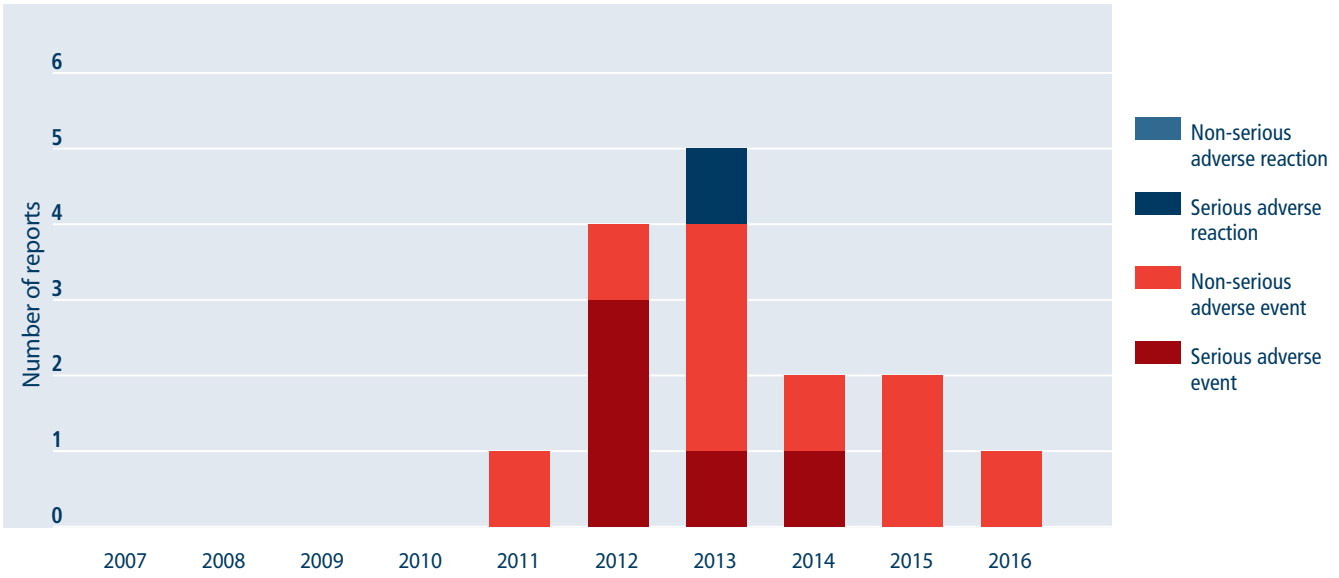

Figure 23. Overview of reports concerning tendons, ligaments and fascia, 2007-2016

2.4 Ocular tissue

In The Netherlands cornea and sclera are harvested from post-mortem donors by enucleation of the complete eyeball which is then processed by one of the two eye banks. The shelf life of a cornea is limited: a cornea is in optimal condition in culture medium for up to four weeks after donation while sclera has a shelf life of one year. Corneas and scleras are also exported and imported.

Processing, distribution and application

In Table 23 the numbers of processed and distributed units of ocular tissue are shown. Table 24 presents the numbers of transplanted ocular tissue units as provided by the contacted hospitals and clinics. Twenty-one hospitals and clinics transplant ocular tissue. Out of these, seven are exclusively corneal transplant centres and four only apply sclera. The gap between distribution and application numbers for sclera is smaller than in 2015; it may be explained by relatively long storage times for sclera. For cornea the discrepancy is very small, all corneal transplant centres provided application data. Figure 24 presents an overview of distributed corneas and sclera in the period 2007-2016.

Table 23. Processing and distribution of ocular tissue in 2016

Type of tissue	Tissue establishment	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Cornea	2	2971	Complete or lamella	1537	181	34	1752
Sclera	1	518	Complete or quadrant	1462	32	0	1494

Table 24. Application of ocular tissue in 2016

Type of tissue	Hospitals/ clinics	Recipients	Transplants				
			Unit	Uit NL	From EU	From non EU	Total
Cornea	17	1504	Complete or lamella	1510	0	0	1510
Sclera	15	1248	Complete or quadrant	1226	22	0	1248

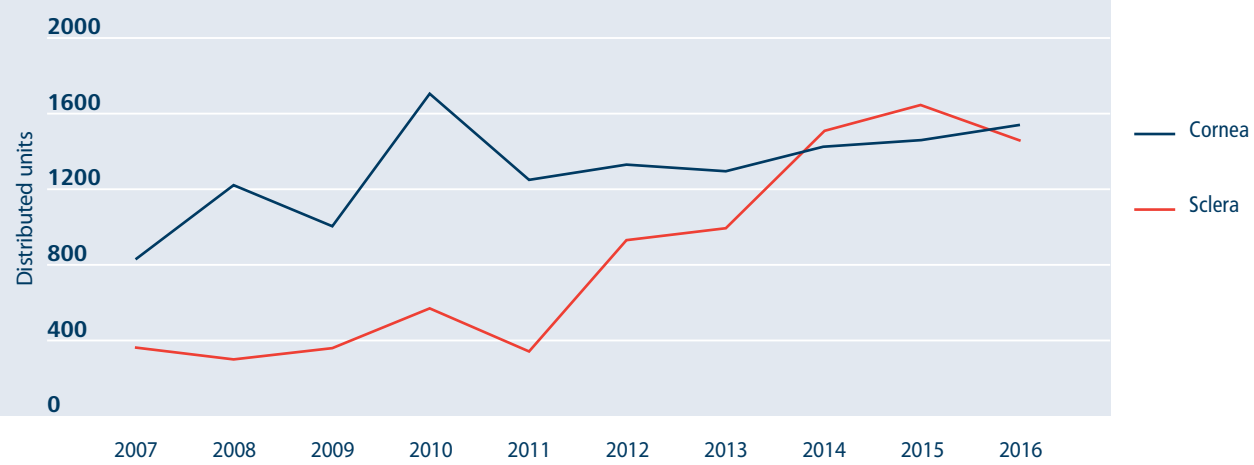

Figure 24. Distributed corneas and sclera, 2007-2016

Reports

In 2016 there were three adverse event reports, out of which one was classified as serious. In Figure an overview is shown of reports concerning ocular tissue in 2007-2016. The 2016 adverse events were reported by two tissue establishments and are summarised in Table 25.

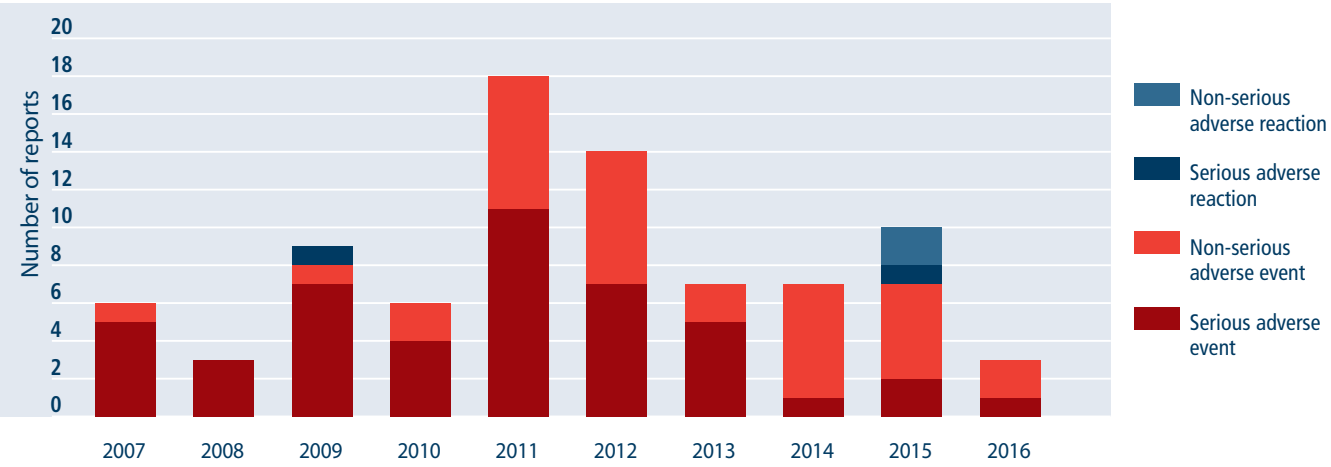

Figure 25. Reports concerning ocular tissue, 2007-2016

Table 25. Overview of adverse events concerning ocular tissue in 2016

Adverse event category	Description
Bacterial contamination of product	• Bacterial contamination of transport medium of 12 corneas by Stenotrophomonas maltophilia, tissue discarded. Ophthalmologist reported the same microorganism in medium of a transplanted cornea, the patient had to have a second transplant due to corneal rejection. No bacterial typing performed, imputability possible. Other corneal transplants uneventful. Analysis: cultures of self-produced medium were false-negative due to incorrect sample taking. Procedure has been corrected. Commercially available medium considered but judged to have negative impact on tissue quality*
Other infection of product	• Yeast (penicillin species) cultured in transport medium by tissue establishment. No adverse consequences for cornea recipient
Loss of tissues or cells	• Blood sample for virology testing left behind in coolbox in lab. Two bulbi discarded. Various measures implemented to prevent recurrence

** serious*

2.5 Cardiovascular tissue

Processing, distribution and application

In Tables 26 and 27 processing, distribution and application data for cardiovascular tissue are presented. In The Netherlands there is one tissue establishment that processes cardiovascular tissue. Seven health-care institutions transplant cardiovascular tissue and one additional hospital applies vascular patches. Figure 26 shows data on the transplantation of cardiovascular tissue in the past ten years.

Table 26. Processing and distribution of cardiovascular tissue in 2016

Type of tissue	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Aortic valve	1	202 *	Graft	8	10	0	18
Pulmonary valve	1	202 *	Graft	67	8	0	75
Vessel	1	30	Graft	0	5	0	5
Patches	1	71	Graft	19	18	0	37

** Donor hearts*

Table 27. Application of cardiovascular tissue in 2016

Type of tissue	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Aortic valve	2	11	Graft	8	6	0	14
Pulmonary valve	5	68	Graft	67	27	0	94
Vessels	0	0	Graft	0	0	0	0
Patches	4	28	Graft	19	12	0	31

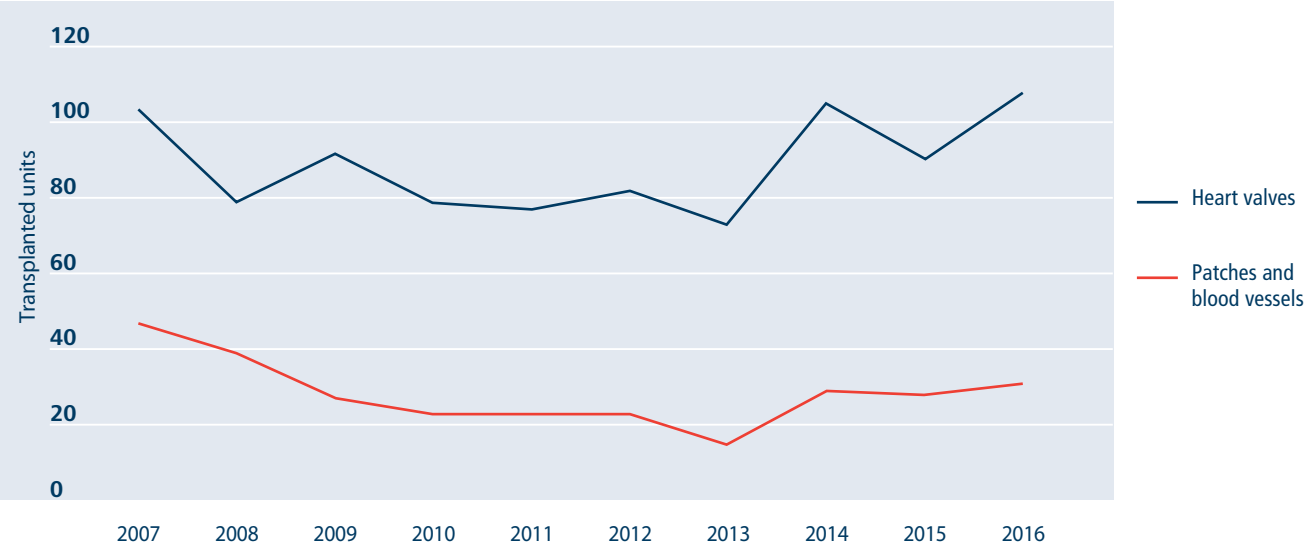

Figure 26. Numbers of transplanted units of cardiovascular tissue, 2007-2016

Data collated from Dutch Transplantation Foundation and TRIP reports

Reports

As in 2015 there were no reports concerning cardiovascular tissue in 2016. An overview of registered reports in 2007-2016 is shown in Figure 27. All reports concerning cardiovascular tissue involved heart valves, both aortic and pulmonary valves. .

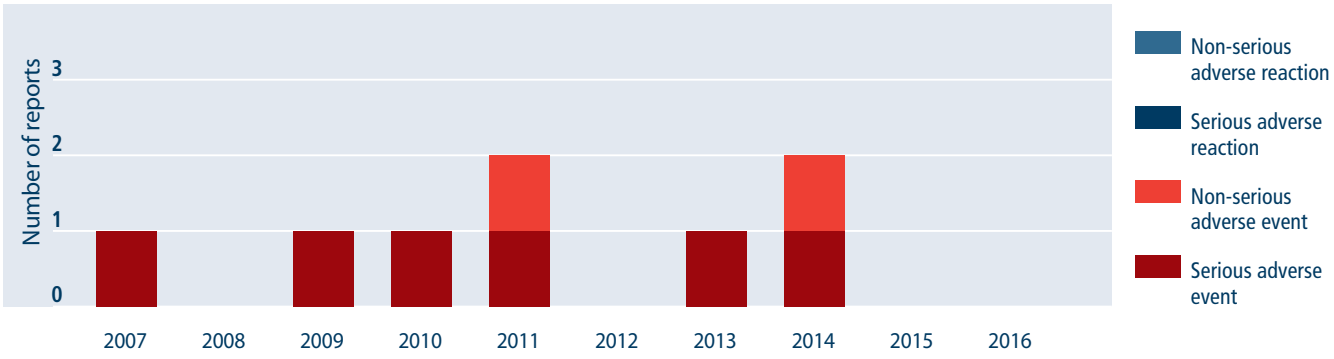

Figure 27. Reports concerning cardiovascular tissue, 2007-2016

2.6 Skin

Processing, distribution and application

In Table 28 data on processed and distributed skin in 2016 are shown. In The Netherlands there is one large organ bank licensed for post-mortem skin processing, storage and distribution. Skin tissue can be subdivided in three categories: donor skin, autologous skin and acellular dermis. The largest category is donor skin that is applied as a temporary dressing in burn patients. The majority of donor skin units is distributed outside The Netherlands. Another three tissue establishments are licensed for the distribution of imported skin products in The Netherlands. In Table 29 the numbers of applied skin units are presented. Hospitals and burn centres will keep a number of some skin units in stock which contributes to the difference between numbers of distributed and transplanted units. Figure 28 gives an overview of the numbers of distributed skin and skin products over the past ten years.

Table 28. Processed and distributed skin units in 2016

Type of tissue	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Donor skin	1	525 *	Pack	2830	6097	6351	15278
Acellular dermis	2	10	Graft	67	26	132	225

* *Donors*

Table 29. Applied skin units in 2016

Type of tissue	Hospitals/ clinics/ practices	Recipients	Applications				
			Unit	From NL	From EU	From non EU	Total
Donor skin	7	77	Pack	1492	7	0	1499
Autologous skin	2	25 *	Graft	25	0	0	25
Acellular dermis	6	162	Graft	161	1	0	162

* *Processed away from the patient outside the healthcare institution's operating theatre*

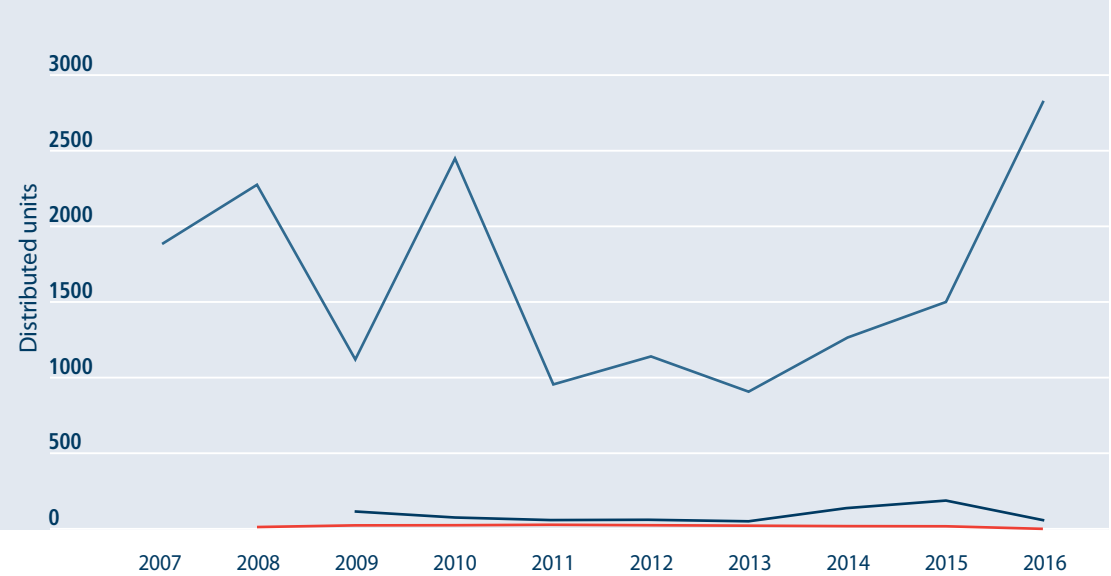

Figure 28. Number of distributed units of skin or skin products, 2007-2016

Reports

In 2016 there were no reports concerning skin tissue. The numbers of reports concerning skin tissue from year to year are shown in Figure 29. The relatively high number of reports in 2014 is explained by reports concerning complications following application of cultured autologous skin in patients with a chronic ulcer. The complications were judged not to be related to the transplanted products.

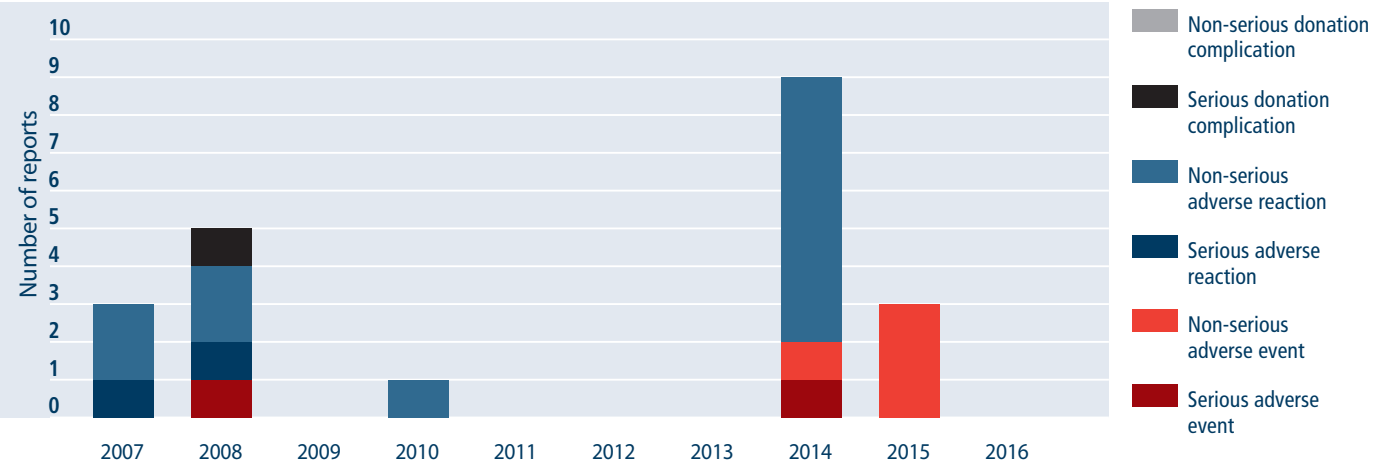

Figure 29. Reports concerning skin tissue or keratinocytes, 2007-2016

2.7 Other tissues and cells

A variety of tissues and cells are ranked in this category, including amniotic membrane, Langerhans' islets, umbilical cord tissue, adipose tissue and (autologous) radioactively labelled erythrocytes and leukocytes for diagnostic purposes.

Processing, distribution and application

Tables 34 and 35 show numbers of processed and distributed units and applied units of other tissues and cells.

Table 30. Processing and distribution of other tissues and cells in 2016

Type of tissue	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Amnion	2	4*	Pack	150	0	0	150
Langerhans' islets	1	48	Graft	6	0	0	6
Umbilical cord tissue	1	2582	Graft	0	0	0	0
Glioma tumour tissue	1	28	Graft	22	0	0	22
Erythrocytes**	1	42	Bag	42	0	0	42
Leukocytes**	1	164	Bag	145	0	0	145

* *Placentae*

***Radioactively labelled for diagnostic purposes*

Table 31. Application of other tissues and cells in 2016

Type of tissue	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Amnion	8	73	Pack	79	0	0	79
Langerhans' islets	2	5	Graft	6	0	0	6

Reports

In 2016 there were no reports involving other tissues and cells. In the past ten years only two reports have been submitted for other tissues and cells: loss of amnion tissue and loss of a granulocyte product.

2.8 Multi-tissue donor

Report involving donation (Law on organ donation)

For a patient who had not registered consent for donation in the Dutch Donor Registry, consent was obtained from the partner with whom the donor had a long-term 'living apart together' (LAT) relationship. The law does not provide for a partner a partner who does not reside at the same address to give consent for donation. The Law on donation was incorrectly interpreted at donor screening and the donor went on to donate ocular, cardiovascular and bone tissue. In consultation with the Ministry of Health, Welfare and Sport clarification of the legal text regarding special long-term partner relationships (e.g. LAT relations) will be sought.

CHAPTER 3

Ten years of biovigilance

By now ten years have lapsed since TRIP Foundation, in cooperation with the Dutch hospitals and tissue establishments, first implemented a national biovigilance system. In 2006 the Ministry of Health, Welfare and Sport requested TRIP to carry out the vigilance tasks laid down in European Directive 2004/23/EG, that stated that all EU Member States must have a system in place for the registration of serious adverse reactions and events concerning human tissues and cells. The legislation aims to set criteria for quality and safety of substances of human origin in order to safeguard good quality healthcare for the patients. Ten years on, the European Commission (Directorate General SANTE) recently started an evaluation of the implementation of the Directives on blood, tissue and cells. This evaluation will focus on quality improvement, effects on transparency and availability of safe products of human origin and effective competent authority oversight.

Ten years of biovigilance are the occasion for TRIP to briefly review what has been accomplished by cooperation the Dutch healthcare institutions and tissue establishments in the area of biovigilance and how this relates to quality monitoring of tissues and cells in the EU. This milestone also offers the opportunity to present an overview of the Dutch contributions to international collaborative work to improve European vigilance effectivity and safety of tissues and cells for patients.

3.1 Ten years of Dutch biovigilance

Network

During the past ten years TRIP has established an extensive network of contacts in tissue establishments, hospitals and clinics and medical professional bodies involved in the transplantation of substances of human origin. Contact persons are biovigilance officers and coordinators, quality officers and responsible persons in the tissue establishments. Through the good cooperation biovigilance in The Netherlands was adopted effectively. Advice and support for reporters is provided for the analysis and reporting of adverse events and reactions, among others by the online reporting system. TRIP can be contacted for informal discussion and advice about the reporting procedures.

Within this network of tissue establishments and healthcare institutions that apply human tissues and cells there are opportunities for mutual support and collaboration when exploring new developments like the implementation of the Single European Code. A biovigilance seminar is organised annually where experiences may be shared. In addition TRIP contributed to the setting up of an online biovigilance platform and is a partner in a national working party on biovigilance protocols.

TRIP report

TRIP publishes an annual public report that provides transparency on side effects as well as data on the extent of processing, distribution and application activities relating to substances of human origin. These are accompanied by explanations stressing the importance and mandatory nature of adverse reaction and event reporting, ensuring traceability of tissues and cells and proper protocols and procedures. The findings and recommendations in the annual TRIP report can stimulate the various medical professional groups and institutions to develop activities for safety improvement. Certainly in this area there is room for improvement, especially in healthcare institutions that apply substances of human origin in patients. Some of these safety themes are presented in Table 32. Participation of healthcare institutions and tissue

establishment is almost complete. Meanwhile annual adverse event and reaction reporting is stable (approx. 90 reports per year). Noteworthy clusters of reports are listed in Table 33.

Table 32. Selected themes from TRIP annual recommendations, 2007-2016

Years	Theme
2007, 2008 and 2011	• Appointment of biovigilance staff
2009 and 2011-2013	• Participation in the TRIP registration
2012 and 2013	• Alarm systems for and validation of critical equipment (e.g. incubators, cryopreservation devices, transportation boxes, storage vats or storage freezers)
2010 and 2013	• Recommissioning of essential equipment after maintenance or repair
2011, 2013 and 2015	• (Timely) reporting of adverse events, reactions and donation complications
2014	• Temporary storage of substances of human origin in transplanting institutions
2013 and 2016	• Home produced medium or additive solution
2011, 2012 and 2016	• Follow-up of transplanted patients and living donors
2012 and 2016	• Congenital malformation in assisted reproductive techniques following the application of donor gametes
2011 and 2014	• Importation and exportation of substances of human origin

Table 33. Clusters among the biovigilance reports, 2007-2016

Years	Clusters
2007-2016	• Identification and selection errors
2007-2016	• Loss of gametes and embryos
2010-2016	• Leaking units for hematopoietic stem cells
2011-2012	• Corneal haze after transplant
2015-2016	• Pipette issues in IVF laboratories

3.2 Biovigilance in the European Union

In 2006 the legal provisions of EU directive 2004/23/EG regarding vigilance of tissues and cells came into force; the annual mandatory submission of a national overview of serious adverse reactions and events (SARE) to the European Commission commenced in 2008 (2007 data). The aims of the directive were to lay down conditions for free cross-border traffic of substances of human origin and provide for quality and safety assurance within the member states.

The Directorate General for Health Food and Safety (SANTE) maintains contacts with network of national competent authority representatives who meet approximately twice a year to exchange experiences and oversee the implementation of the directives. Here relevant issues are discussed, such as new epidemiological risks or the legal status of new products (e.g. human faeces for transplantation) are discussed. For a few years a Rapid Alert system has been available through which the competent authorities can quickly disseminate information in the case of serious health risks for recipients of human tissues and cells in more than one Member State. In The Netherlands the Healthcare Inspectorate is responsible for receiving and assessing the impact of such rapid alerts and will alert others as necessary. In 2017 a working party of national biovigilance and hemovigilance experts was instated to advise the competent authorities regarding the implementation of the mandatory European vigilance; TRIP staff are members of this group on behalf of The Netherlands.

The results of the collated EU Member State biovigilance reports are published annually. As can be expected in a starting reporting system the number of SARE reports increases year on year. The 2014 EU summary report shows aggregated results of four annual SARE reporting exercises (Figure 30) subdivided into four categories: tissue/cell defect, equipment failure, human error and other. It can be seen that over 40% of reports are attributed to human errors. The data may also be related to the phase where an error occurred, but offer no information on the type of error or the proposed or implemented system improvements to reduce errors. Also, at EU level there is no insight into the types of problems that are reported in the other categories.

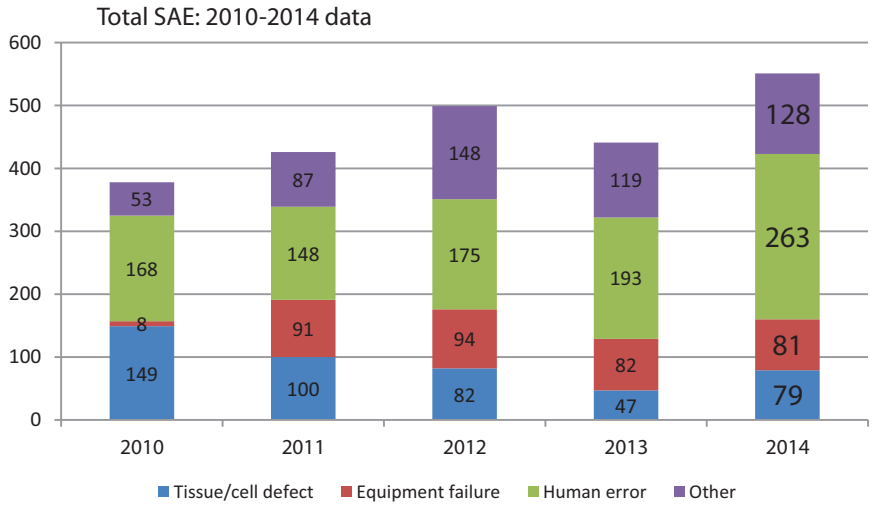

Figure 30. Total number of serious adverse events (SAE): 2010-2014 comparative data
(From Summary of the 2015 annual reporting of serious adverse events and reactions for Tissues and Cells, data from 01/01/2014 to 31/12/2014; SANTE B4/IPK ARES(2016)

In addition to SARE numbers the data on organ, tissue and cell donation and transplantation are also collected and registered by Eurocet. These figures may also support exchange and availability of human tissues and cells within the EU.

3.3 International collaboration in optimising biovigilance

Widespread practice of transplantation of tissues and cells is possible in part due to international exchange of substances of human origin between countries. Due to the extensive knowledge of application of human transplantion and contacts with the organisations involved in procurement of human tissues and cells TRIP has been able to make valuable contributions in European projects that are important for future development and streamlining of biovigilance in Europe.

3.3.1 EUSTITE

EUSTITE (European Union Standards and Training in the Inspection of Tissue Establishments) was the first EU collaborative project in the field of human tissues and cells. EUSTITE aimed to develop supporting materials for biovigilance implementation in EU Member States and for training inspectors of tissue establishments. The project's goal was to promote standardisation of the reporting procedure for serious adverse reactions and events and of inspections of tissue establishments in the EU.

The Netherlands (and 12 other EU Member States) took part in the EUSTITE project from 2007 to 2009. TRIP shared the Dutch methods for adverse reaction imputability assessment and the severity or impact of an adverse event. This led to the development of the Impact assessment tool. Reports to TRIP were used to test the Impact assessment tool for practicability.

Publications:

- Communication and Investigation of Serious Adverse Events and Reactions associated with Human Tissues and Cells
- Inspection of tissue and cell procurement and tissue establishments

3.3.2 SoHO V&S

The SoHO V&S (Vigilance and Surveillance of Substances of Human Origin) project was initiated in 2010 as a follow-on and extension of the EUSITITE project. TRIP was involved from the beginning of this EU project that aimed to harmonise terminology and investigations of SARE. It resulted in several practical guidelines for inspection agencies (competent authorities), vigilance and professionals: the SoHO deliverables. Particularly for assisted reproductive techniques adjustments and additions were made to the EUSTITE deliverables.

Publications:

- Guidance for Competent authorities: Communication and investigation of serious adverse events and reactions associated with human tissues and cells
- Guidance on Vigilance & Surveillance in Assisted Reproductive Technologies in the European Union
- Guidance for healthcare professionals on vigilance and surveillance of human tissues and cells
  Part 1: Tissues
  Part 2: Haematopoietic stem cells

3.3.3 NOTIFY

In February 2011 a global congress was organised by SoHO V&S in cooperation with WHO. This congress was attended by 113 experts from 36 different countries. Based on examples of reports of serious adverse events and reactions reporting categories were agreed. Following this congress the NOTIFY library was developed, a database of educational and well documented SARE reports. Anonymous reports may be submitted by competent authorities and recognised biovigilance systems. The database can be consulted by the public. This database also includes SARE reports concerning organ transplantation and blood transfusion.

3.3.4 Council of Europe / EDQM-steering committee on organ transplantation CD PT O

EDQM is the Council of Europe's advisory body regarding quality of medicines and healthcare and it has the following goals concerning organ transplantation:

- Solving issues concerning organ, tissue and cell transplantation, in particular quality and safety standards
- Monitoring practices in the EU in this area and risk monitoring
- Supporting Member States in improving and promoting organ transplantation and the principle of voluntary unpaid donations
- Setting of ethical quality and safety standards
- Investigation of organ shortage
- Contribution to public awareness of organ, tissue and cell donation

On behalf of The Netherlands TRIP is a member of this committee due to its expertise in the field of tissues and cells.

3.3.5 Economic landscapes of human tissues and cells for clinical application in the EU

Recently the report 'Economic landscapes of human tissues and cells for clinical application in the EU' was published on the European Commission's website. In the chain of voluntary and largely unpaid donation and transplantation of substances of human origin both private and public organisations are involved. The resulting conflicts of interest led the European Commission to commission this study that presented an overview of the organisation in the EU of the three most important sectors:

- Replacement tissues: bone, cornea, skin and cardiovascular tissue
- Hematopoietic stem cells from bone marrow, peripheral blood and cord blood
- Reproductive tissues and cells: semen, oocytes and embryos

The three domains were charted in collaboration with the 28 EU Member States to provide an overview of the legal frameworks, cost structures, technological developments and the most relevant trends in ethical and sociological issues. The results of this research will enable European Member States to optimise the organisation and regulation of safe and reliable procurement of human transplants in the context of technological innovations and increasing globalisation. TRIP contributed to this project by charting organisations involved in replacement tissues and hematopoietic stem cells and their importation and exportation. In addition the results will be meaningful for future developments of ATMPs of human origin.

3.3.6 ECDC: Risk assessment of transmission of bacterial and vector borne infections through SoHO

This project was initiated by the European Centre for Disease Prevention and Control (ECDC) in order to obtain an overview of infection transmission risk from donor to recipient following the application of substances of human origin. TRIP is involved as tissue expert and co-author. In this project the available scientific evidence is collected by means of a systematic literature review. In the first part of the project (2014-2015) the focus was on the transmission risk of vector-related infectious diseases like Chagas and Dengue. In the next stage the risk of transmission of bacterial infections like Staphylococcus aureus from donor to recipient is the object of study.

3.3.7 VISTART

The EU project VISTART (Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation), running till October 2018, aims to assist EU Member States in the development and improvement of oversight and control in the field of application of blood and tissues and cells. TRIP is involved as an expert member and collaborating partner. VISTART's goal is to promote and facilitate harmonisation of inspection, authorisation and vigilance systems concerning blood, tissues and cells and to extend cooperation between EU Member States.

3.3.8 Euro GTP II: Good Tissue & cell Practices

In the Euro GTP II project (Good Practices for demonstrating safety and quality through recipient follow-up) a method is being developed for safeguarding the desired safety and effectiveness of new human tissue and cell products using validation and targeted follow-up in patients. In order to assess the risk of a new product in advance of application, tools have been developed, that are being tested among others by clinicians and that also survey the requirements for acceptability of a new product for transplantation or infusion. In addition the project will survey the organisation of current methods for evaluation of clinical applications (e.g. clinical trials) and patient follow-up. A progress update may be found in a combined EU newsletter.

3.4 Conclusion

Over the last ten years all involved groups have put in a lot of hard work to build a robust biovigilance system, that is able to provide transparency about risks of tissue and cell transplantation. The system makes it possible to issue recommendations concern e.g. protocols, traceability and process organisation. The quality of information in biovigilance reports in The Netherlands is satisfactory by now; through highlighting of clusters of adverse events and reactions enable medical professionals to critically review their chain and perform additional analyses if necessary. At EU level the desired level of quality and quantity of reports has not yet been reached but the current EU projects will lead to improved harmonisation and quality of vigilance data. In addition the correct analysis of the provided data will also contribute to improving quality and safety of substances of human origin within the EU and preventing adverse consequences in patients. The challenges for the next ten years will be to obtain uniform information and improve the analyses leading to optimisation of recommendations and regulations. At the same time there is a need for harmonisation in the field of organ vigilance and hemovigilance. TRIP will continue to promote an efficient and effective biovigilance system in the interests of all patients and also in the interest of donors of substances of human origin: a commitment that will certainly find support from professionals in the field of transplantation and transfusion.

CHAPTER 4

Participation

Participation of all stakeholders in the TRIP reporting system is essential for the quality of the biovigilance system. Participation is defined on the basis of both submission of reports to TRIP and provision of annual numbers of all types of processed, distributed and transplanted units of human tissues and cells along with the number of recipients. The quality and completeness of the submitted figures as well as of reports are also important; the processing, distribution and application data are used as denominator for reports to provide insight in incidence.

In looking at participation rates TRIP distinguishes two categories of institutions:

1 the tissue establishments (this includes so-called "organ banks", see below) that procure, process, store and/or distribute human tissues and cells; and
2 the hospitals, clinics and oral implantology practices that apply or transplant human tissues and cells.

4.1 Tissue establishments

According to the definition in the Law on safety and quality of substances of human origin (Wvkl), article 1.1.k, a tissue establishment is a tissue bank, hospital department or other institution that performs activities in connection with processing, storage or distribution of human tissues and cells. A hospital can be a user of human tissues and cells and can also harbour one or more tissue establishments.

A tissue establishment cannot receive tissues and cells after procurement without an additional licence. Tissue establishments which receive human tissues and cells after harvesting of human tissues and cells must be licensed as so-called organ banks. Organ banks according to article 1.1.l of the Law on safety and quality of substances of human origin are also 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 activities determines whether a licence as an organ bank or tissue establishment is necessary.

Table 34 presents an overview of licensed tissue establishments and organ banks in The Netherlands in 2016 (source: Farmatec). Some hospitals house several tissue establishments and/or organ banks.

Table 34. Licensed tissue establishments and organ banks in 2016

	Tissue establishment	Organ banks	Total
Independent institution	9	11	20
Located in hospital or clinic	56	36	92
Total	**65**	**47**	**112**

Figure 31 shows the number of licences issued by Farmatec for each type of human tissue or 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. Some tissue establishments and organ banks hold several licences. Figure 32 shows the annual percentages of tissue establishments that provided data on processing and distribution and those submitting biovigilance reports. All tissue establishments submitted data on processing and distribution in 2016. Participation by tissue establishments in 2016 was 100% (112 out of 112).

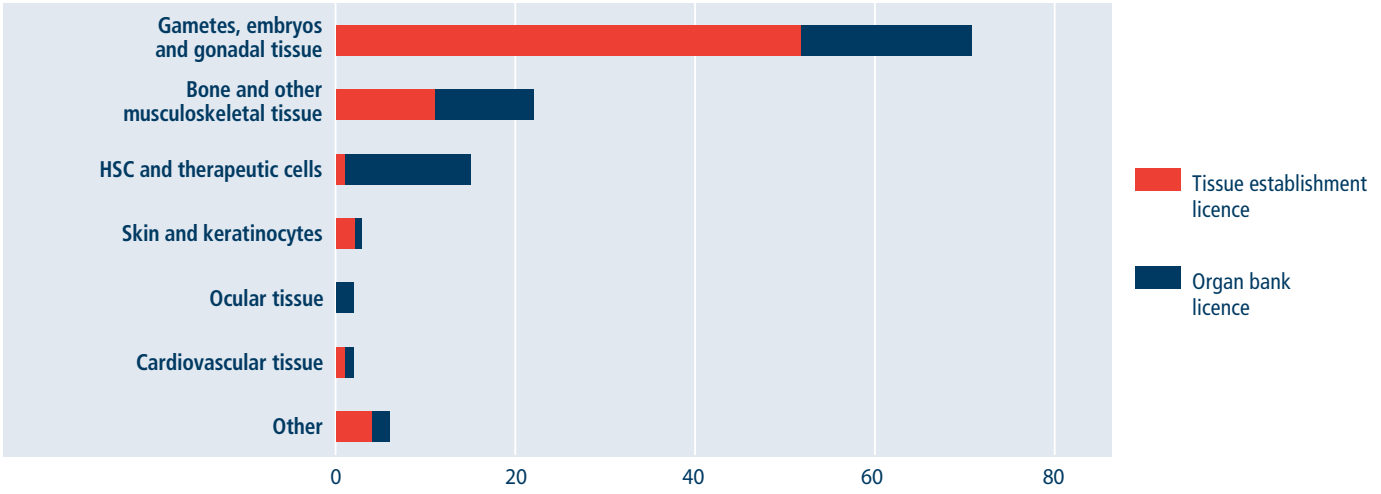

Figure 31. Number of licensed tissue establishments and organ banks in 2016

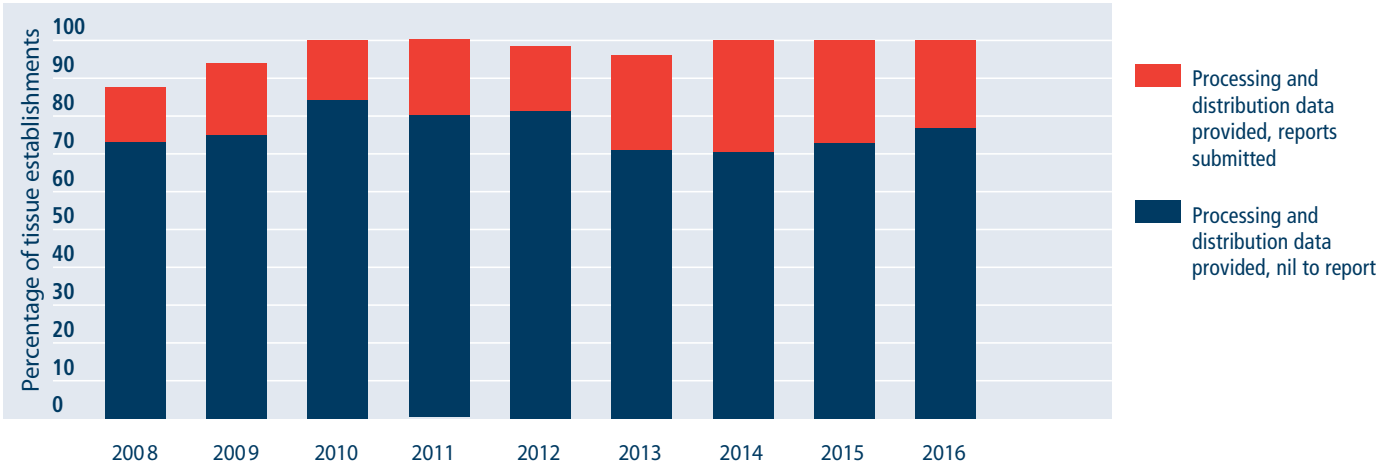

Figure 32. Participation of tissue establishments (period 2008-2011: n=20, 2012-2016*: n=112-120)

* *Up to 2012 tissue establishments located in hospitals or clinics were not considered under participation of tissue establishments.*

4.2 Organisations responsible for human application of tissues and cells

In 2016 89 hospitals, 20 clinics and 46 oral implantology practices were contacted for information on numbers of applied tissues and cells, the number of recipients and the reporting of adverse events and reactions. The clinics and oral implantology practices that indicated in a survey in 2013 that they applied human tissues and cells were added to the database of applying institutions. Participation by hospitals and clinics in 2016 was 100% (109 out of 109). In four cases the data were incomplete. The implantology practices were contacted for the fourth time in 2016 and their participation was 87% (40 out of 46), an 8% increase compared to 2015. In all, eight independent healthcare institutions and seven oral implanto-

logy practices replied they did not apply tissues or cells in 2016. The overall participation of organisations responsible for human application of tissues and cells in 2016 was 96% (149 out of 155). In Figures 33 and 34 participation rates are shown from 2008 onwards.

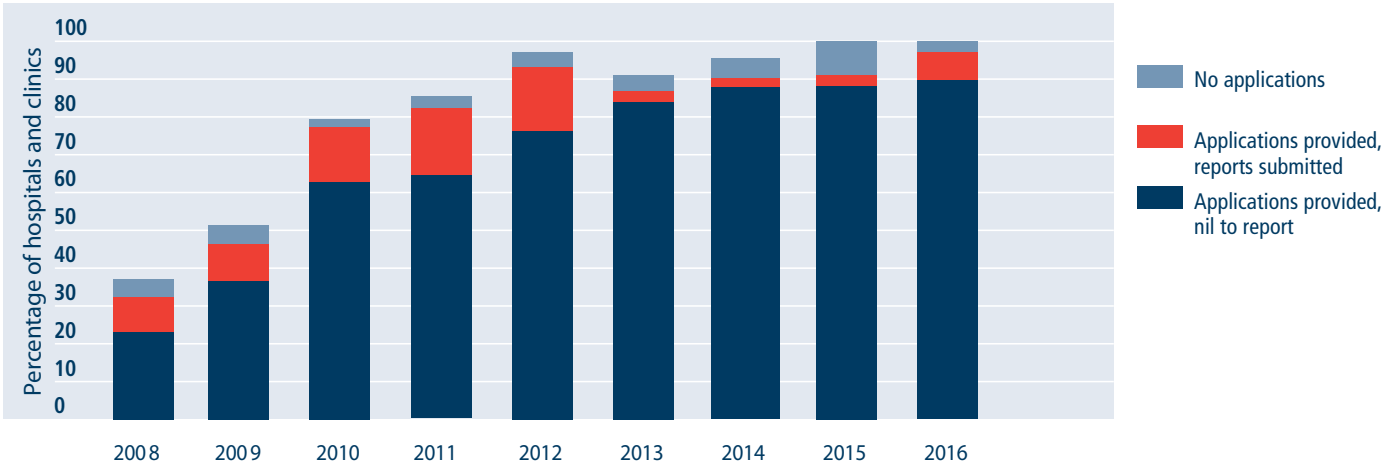

Figure 33. Participation by Dutch hospitals and clinics (n=101-115)

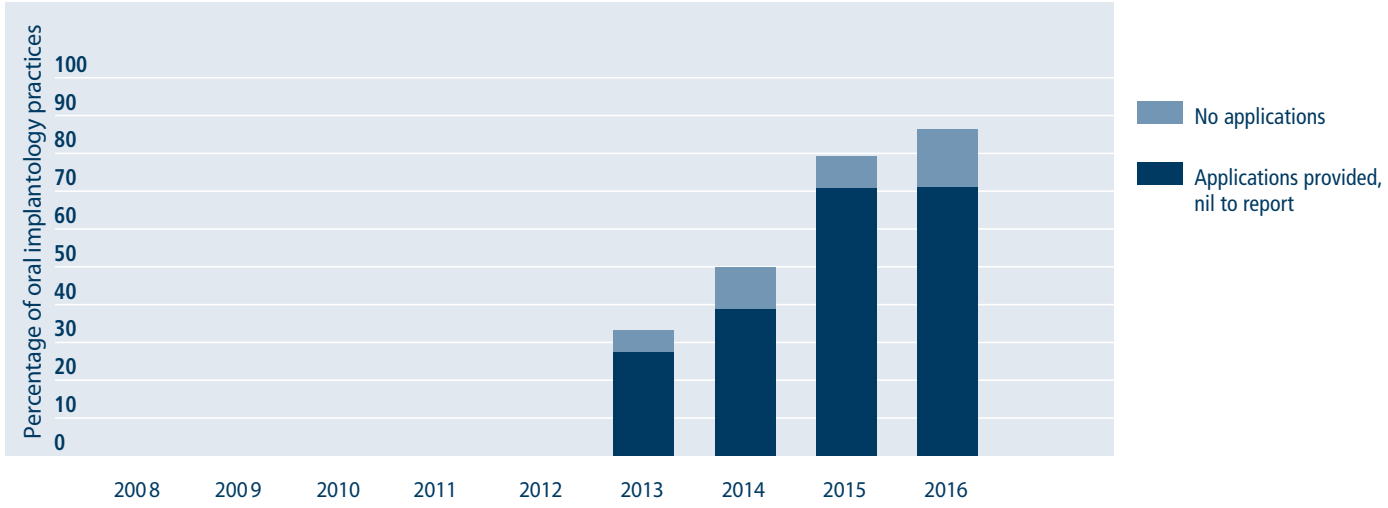

Figure 34. Participation by Dutch implantology practices* (n=36-48)

** Practices that previously indicated they applied substances of human origin*

ANNEX 1

About TRIP

TRIP (Transfusion and Transplantation Reactions in Patients) Foundation was created in 2001 for the purpose of establishing a national hemovigilance system. 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.

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 associated with 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) unintended adverse reactions and events throughout the transplantation chain from donor to recipient of substances of human origin with the aim of achieving safer and more effective use of tissues, cells and organs.

The TRIP reporting system for adverse reactions and events related to the application and transplantation of substances of human origin meets the requirements laid down in Dutch and European legislation. The online reporting system allows those reporting to TRIP to simultaneously submit serious reactions and events to the Healthcare Inspectorate. The Healthcare Inspectorate is the competent authority on behalf of the Ministry of Health. The mandatory reporting of adverse reaction and events to the Healthcare Inspectorate applies to tissue establishments according to the Law on safety and quality of substances of human origin and the Decree on requirements for substances of human origin (2006). The Decree on requirements for substances of human origin was updated in 2012 in accordance with EU directive 2010/53/EG. Figure 35 presents a flowchart of serious and non-serious biovigilance reports in Dutch healthcare.

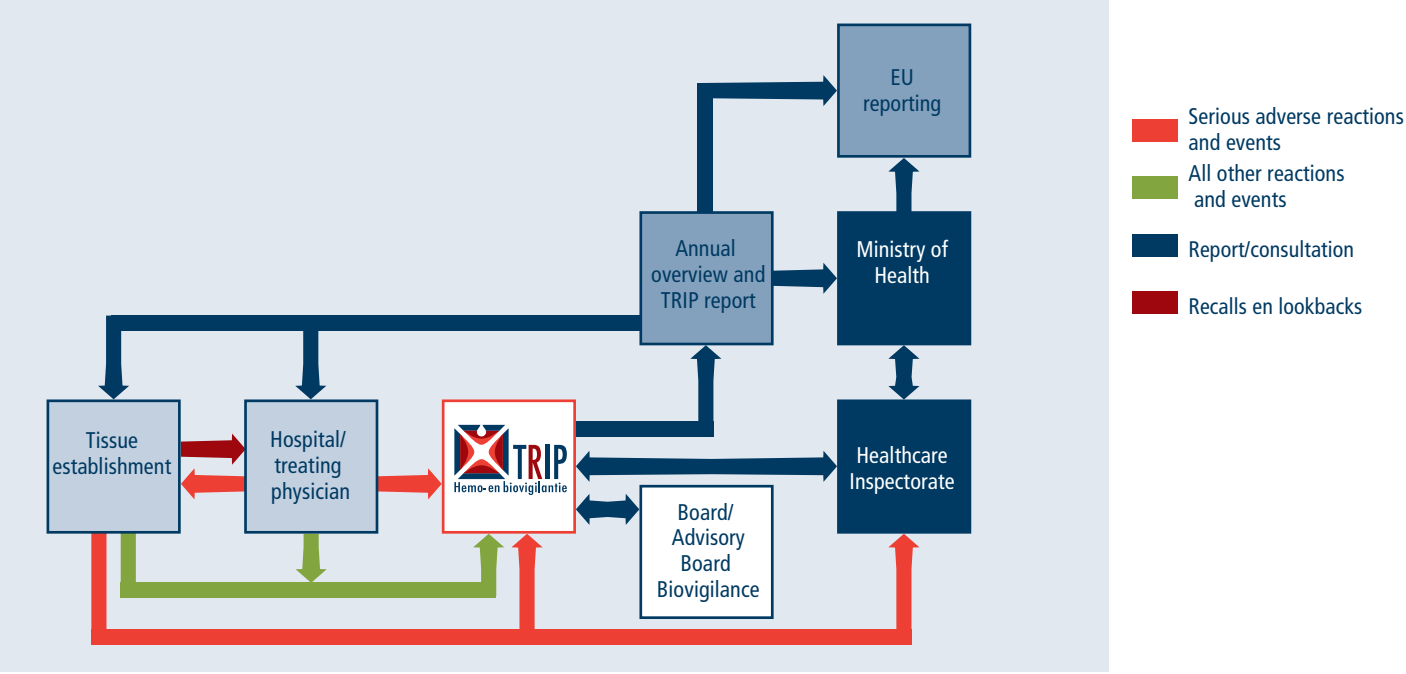

Figure 35. Flowchart of biovigilance reporting

The scope of the Law on safety and quality of substances of human origin includes all substances of human origin (from living as well as deceased 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. The Law on safety and quality always applies to allogeneic application (derived from a human donor).

TRIP working method

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 from hospitals, clinics and licensed tissue establishments since 2006 and serves to support the monitoring and improvement 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 collects data annually on 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 the annual mandatory data submission to the European Commission. On behalf of the Healthcare Inspectorate TRIP complies the annual mandatory overview of serious adverse events and reactions to be forwarded to the European Commission.

Tissue establishments, hospitals and other institutions that provide processing, distribution and/or application figures and submit reports on adverse reactions and/or events to TRIP receive an annual participation certificate. This participation certificate contributes to safety awareness in the application of substances of human origin and to the safety management system. The participation certificate may also be formally reviewed by the Healthcare Inspectorate as part of licensing procedures or licence renewal for tissue establishments.

TRIP is guided by a Biovigilance Advisory Board representing relevant medical professional bodies and specialties as well as tissue establishments. The Biovigilance Advisory Board provides medical professional and strategic guidance with regard to biovigilance, reviews all reports anonymously and advises with regard to the annual report. If a report is judged to be serious by the Advisory Committee but has not been submitted to the healthcare inspectorate, TRIP will remind the reporter about the mandatory nature of reporting to the competent authority (see Annex 2, Reporting to the Healthcare Inspectorate).

ANNEX 2

Reporting of adverse events and reactions

Tissue establishments

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 (see Annex 3). 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. Adverse reactions and events should be reported to TRIP and also to the Healthcare Inspectorate if necessary.

Hospitals, clinics and practices

Organisations responsible for human application of tissues and cells should report (possible) product-related serious adverse reactions and events to the supplying tissue establishment and may also report to TRIP. TRIP checks for duplicate reports and if any are found, merges them in consultation with the reporters. If a calamity has occurred which (possibly) has been caused by human tissue or cells the hospital must also report this to the Healthcare Inspectorate according to the Dutch law on quality, complaints and disputes in healthcare.

Reporting to the Healthcare Inspectorate

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. In agreement with the Healthcare Inspectorate TRIP takes care of registration of all adverse reactions and events. The TRIP digital reporting system facilitates the forwarding of serious adverse reaction and event reports to the Healthcare Inspectorate: reporters can select the option of forwarding the report to the Healthcare Inspectorate so that they only need to submit information once. The reporting of serious adverse reactions and events is different from the reporting of a calamity according to the Dutch law on quality, complaints and disputes in healthcare. The Healthcare Inspectorate has a definition for a calamity (see Annex 3) and has specific procedures for this.

In November 2015 the Healthcare Inspectorate sent a letter to all tissue establishments clarifying the reporting of adverse reactions and events to the Healthcare Inspectorate and TRIP. Figure 36 shows the reporting routes in a flowchart.

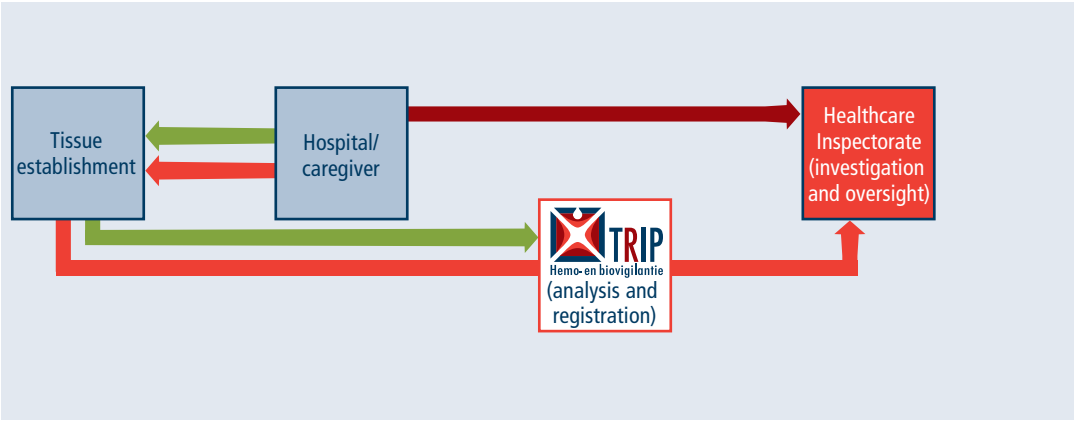

Figure 36. Flow chart of reports concerning substances of human origin

Serious adverse reactions or events within the scope of the Law on safety and quality of substances of human origin are best submitted to the Healthcare Inspectorate via the TRIP online reporting system. This channels the reports to the inspectors involved in enforcement of the Law on safety and quality of substances of human origin and reduced the likelihood of reports being (possibly incorrectly) treated as lying within the scope of the Law on quality in healthcare. However reports will always be assessed on healthcare quality aspects as well and full analysis will be required if an event is judged to be a calamity. If an adverse or reaction is solely reported to the Healthcare Inspectorate, the inspectors will ask reporters to also submit the report to TRIP.

ANNEX 3

Definitions and reporting criteria

Serious adverse event

A serious adverse event is defined as follows (according to EU Directive 2004/23/EC Article 3):

> A 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.

The criteria used by the European Commission are presented in Table 35. These criteria were developed by the EU projects EUSTITE and SOHO V&S and adopted in the "Common approach for reportable serious adverse events and reactions as laid down in the tissues and cells Directive 2004/23/EC".

Table 35. 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
- The event led to birth of a child or abortion of a fetus with a transmitted genetic disease following assisted reproductive technologies with non-partner gametes or donated embryos
- The donor is diagnosed with a genetically transmissible disease after donation of gametes or embryos

Serious adverse reaction

A serious adverse reaction is defined as follows ((EU Directive 2004/23/EC Article 3)

> 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.

Table 36 shows the definitions of severity grades of adverse reactions with explanatory comment. The definition of a serious adverse reaction corresponds to severity grade 2 or higher.

Table 36. Severity grade of adverse reactionsbijwerkingen

Grade 0	• No morbidity. The reaction is only discovered later and/or through laboratory investigation or screening. Full recovery of the recipient or donor
Grade 1	• Minor morbidity, not life-threatening Minor clinical effects without (prolongation of) need for hospital admission and without invalidity, incapacity or long-term consequences for the recipient
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. A living donor or recipient needs medical or surgical intervention following harvesting or transplantation of the tissues or cells (vasopressor medication, intubation, transfer to intensive care) in order to prevent death; or a life-threatening infection is transmitted
Grade 4	• Mortality following a transplantation adverse reaction NOTE Grade 4 does not apply if the patient recovers to a stable clinical condition after a transplantation reaction and subsequently dies of causes unrelated to the tissue or cell transplantation

Serious donation complication

Donation complications can be graded for severity in the same manner. Serious donation complications are not yet subject to mandatory reporting to the EU. The EC however requests submission of these reports on a voluntary basis. TRIP collects donation complications for the annual overview of serious adverse reactions and events for the European Commission. For the reporting of donation complications TRIP follows the 'Common approach for reportable serious adverse events and reactions as laid down in the tissues and cells Directive 2004/23/EC, version 2.3 (2014)', stating:

It is noted that many EU Member State competent authorities collate information on donor adverse reactions not influencing the quality and safety of tissues and cells. Reactions which fall outside the scope of the tissues and cells Directives and should be reported elsewhere as appropriate (e.g. to pharmacovigilance systems) include:

- Ovarian Hyper-Stimulation Syndrome (OHSS) as an exaggerated response to the use of ovulation induction medications
- Reactions to Granulocyte Colony-Stimulating Factor (G-CSF) following peripheral blood stem cell collection
- Reactions which result in harm to the donor (i.e. cardiac or neurological episodes).

Nevertheless, the EU Commission recognizes the value of these data in the context of tissue and cells regulation, and invites Member States to submit an annual report concerning donor reactions reported to the CA on a voluntary basis. An additional non-mandatory category on donor reactions not influencing the quality and safety of tissues and cells has been inserted in the electronic report template.
The reported cases will not be included in the calculation of the total number of SARs.

Calamity

A calamity is defined by the Dutch Law on Quality, Complaints and Disputes in Healthcare 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'.

ANNEX 4

Overview of mandatory reports of serious adverse reactions and events

(IN ACCORDANCE WITH EU LEGISLATION)

Table 37 shows the number of serious adverse reactions and events reported related to substance of human origin in 2016. In all, 29 reports were classified as serious. There were 21 serious adverse events and eight serious adverse reaction, out of which six concerned serious donation complications.

Table 37. Overview of serious reports in 2016

Tissue or cell type	Serious adverse reaction	Serious adverse event	Serious donation complication	Total serious reports
Semen	1	7	0	8
Oocytes	0	6	5	11
Embryos	0	6	0	6
Ovarian tissue	0	1	0	1
Ocular tissue	0	1	0	1
HSC and therapeutic cells	1	0	1	2
Total	**2**	**21**	**6**	**29**

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ANNEX 5

List of terms and abbreviations

Apheresis	Type of blood donation involving the selective mechanical withdrawal of specific blood components while returning (infusing) the remaining components to the donor or patient
Allogeneic	Originating from a donor (genetically non-identical person)
AML	Acute myeloid leukemia
ASD	Atrium septum defect
ATMP	Advanced Therapy Medicinal Product
Autologous	Originating from a person's own body
Cryopreservation	The process of freezing and subsequent storage of frozen tissues and cells
Distribution	Transportation and delivery to end users
DLI	Donor lymphocyte infusion
EC	European Commission
ET	Embryo Transfer
EU	European Union
EUSTITE	European Union Standards and Training in the Inspection of Tissue Establishments (EU project 2007-2009)
Farmatec	Organisation resorting under the Dutch Ministry of Health, responsible for accreditation and licensing of pharmaceuticals, medical devices, blood products and substances of human origin
G-CSF	Granulocyte colony stimulating factor
HLA	Human leukocyte antigen
HSC	Hematopoietic stem cells
HSC-A	Hematopoietic stem cells collected by apheresis
HSC-C	Hematopoietic stem cells cord blood
HSC-M	Hematopoietic stem cells collected by bone marrow biopsy
ICSI	Intra-cytoplasmic sperm injection (type of IVF)
Imputability	Degree to which an adverse reaction can be attributed to applied substance of human origin
IUI	Intra-uterine insemination
IVF	In vitro fertilisation
KLEM	Association of clinical embryologists
Lareb	Dutch national registry for adverse drug reactions
MESA	Microsurgical epididymal sperm aspiration
Monozygotic	Deriving from one fertilised oocyte
NL	The Netherlands
NOTIFY library	International database of examples of adverse reactions and events relating to blood, tissues, cells and organs
NVOG	Dutch Society for Obstetrics and Gynaecology
OHSS	Ovarian hyperstimulation syndrome
OR	Operating room
Organ bank	Tissue establishment with licence to receive substances of human origin after procurement

PCH2	Pontocerebellar Hypoplasia type 2 (Volendam disease)
PCNSL	Primary Central Nervous System Lymphoma
PESA	Percutaneous epididymal sperm aspiration
PGD	Preimplantation genetic diagnosis
Pharmacovigilance	Vigilance of pharmaceuticals
PID	Pelvic inflammatory disease
Processing	All actions necessary for preparing, manipulating, preserving and packaging substances of human origin
Procurement	Process whereby donated substances of human origin become available
SARE	Serious adverse reactions and events
Semen	Sperm
SOHO V&S	Vigilance and Surveillance of Substances of Human Origin (EU project 2010-2013)
TESE	Testicular sperm extraction
TIA	Transient ischemic attack, temporary occlusion of a cerebral blood vessel
Tissue establishment	A tissue bank, a hospital department or another institution that holds a licence for processing, preserving, storage and/or distribution of substances of human origin
Vitrification	Rapid cryopreservation method mainly used for oocytes
VSD	Ventricle septum defect
WHO	World Health Organisation
WMDA	World Marrow Donor Association
Wvkl	Dutch Law on safety and quality of substances of human origin

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