TRIP REPORT 2017

Biovigilance

Extended version

TRIP
Hemo-en biovigilantie

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The TRIP report 2017 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

In this 2017 Biovigilance report TRIP presents, for the eleventh consecutive year, an overview of all reports of adverse reactions and events that occurred in the application of human tissue and cells, and of the participation in biovigilance reporting of tissue establishments and health care institutions involved in the chain of tissue and cell transplantation.

In 2017, TRIP received 93 reports, of which 31 were serious reports. This number of reports aligns with that of previous years (2016: 80, 2015: 120 reports, including late reports). Additionally, TRIP received three reports concerning events that occurred in 2016. The 2017 reports will be discussed in this report. The participation of tissue establishments, hospitals, and clinics has remained stable and is nearly complete. The participation of oral implantology clinics registered with TRIP has increased to 94%. This combines to make the biovigilance participation level of Dutch institutions the highest in the EU.

Out of all reports associated with assisted reproduction, the largest subgroup of reports received by TRIP concerned congenital abnormalities. Ten of these reports were assessed as severe, because a (possible) genetic factor was involved. In previous years the category of 'Loss of tissues or cells' represented the largest number of reports.

The number of reports of bacterial contamination of stem cell products was higher in 2017. Furthermore, the relatively large number of reports of non-engraftment after transplants concerning cord blood is remarkable. TRIP received only one report concerning a donation complication.

In 2017, out of all reports associated with cornea transplantation, four reports were registered as 'Risk of transmission of an other disease/condition'. Because corneas cannot be preserved for a long period of time (four weeks at the longest), a patient's autopsy findings are often not available until after the transplantation has taken place. An autopsy may show that, in hindsight, there was a contraindication for donation, because the donor had a transmissible disease that is included in the list for contraindications for tissue donation. However, the risk of transmission of a disease through cornea transplantation is practically excluded.

Chapter 3 concerns donor vigilance. According to the 2006 Decree for requirements for substances of human origin, article 1.1, the definition for severe adverse reactions to transplantations includes severe adverse reactions that occur in donors (donation complications). Furthermore, the Common approach for reportable serious adverse events and reactions as laid down in de tissues and cells Directive 2004/23/EC also requests reporting of serious donation complications, including medicinal stimulation and harm to the donor. Over the past years, TRIP has collected reports of donation complications and these will be discussed in Chapter 3 in a multi–year overview. The chapter also includes summary data from the EU report and the NOTIFY Library. Protection for donors and the required vigilance for such protection are an important concern for TRIP within biovigilance.

TRIP foundation would like to express appreciation for the indispensable contributions of all those involved in the production of this report. The foundation hopes this report will help to demonstrate and increase the safety and quality of the chain that deals with human cells and tissues.

Findings and recommendations

2017 findings

1 The largest subgroup of reports concerns hematopoietic stem cells (HSC). A total of 15 reports of bacterial contamination of HSC transplants were received, eight of which occurred in bone marrow. Such a large number of contaminations has not been reported since biovigilance reporting was initiated in the Netherlands in 2006.

2 A total of seven reports were received in the category of "Lack of growth/engraftment", six of which occurred after the administration of cord blood. Five incidents occurred in the same center, but no link between the different cases was found.

3 The largest subgroup ofreports concerning assisted reproduction are those registered as 'Congenital abnormality' (n=14). This is the largest number of reports of congenital abnormalities registered in a single year to date.

4 There is a considerable decrease in the reports of 'Loss of cells or tissues' with oocytes and embryos. Notably the number of processing errors, such as dropping the petri dish, has decreased.

5 Three reports associated with assisted reproduction concerned bacterial contaminations of embryo cultures resulting from contaminated semen. The contaminations originated during the production of the semen, possibly due to insufficiently hygienic conduct by the male partner.

6 Concerning transplantation of musculoskeletal tissues, TRIP received two reports of transplants used after their expiration date.

7 In 2017, TRIP received four reports of 'Risk of transmission of an other disease/condition' with cornea transplantion, three of which concern cases in which the cornea was donated by a donor who was at risk for hematological malignancies. Because corneas cannot be preserved for a long period of time (four weeks at the longest), a patient's autopsy findings are often not available until after the transplantation has occurred.

8 The participation of oral implantology clinics registered with TRIP has increased to 94%. This brings the total participation of tissue establishments, hospitals, clinics and practices to 97%.

2017 recommendations

1 As a result of the increase in use of donated gametes, the number of reports of congenital (genetic) malformations is likely to increase as well. Through reporting congenital abnormalities to TRIP, the risks of (repeated) transmission of genetic conditions can be monitored.

2 To limit bacterial contaminations in embryo cultures, the male partner should take sufficient hygienic precautions for the semen production. To this end, male partners should be clearly instructed and counselled about the process.

3 Hospitals, clinics, and practices that store musculoskeletal tissue should include a step in the process of transplantation, during which the expiration date of the product is checked. Transplants that are past their expiration date should be removed from storage.

4 Proper donor care requires an understanding of possible reactions in the donor and possible events that may occur during the donation (so-called donation complications). All who are involved in caring for living donors should be aware of the importance of reporting donation complications.

Actions and developments following recommendations from the 2016 TRIP report

In the 2016 TRIP Biovigilance report, six recommendations were made. The recommendations concerning situations in which relevant developments have occurred are reported below.

1 Congenital abnormalities in a fetus or newborn that could (possibly) be transmitted genetically 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.

Development: In 2017, TRIP received 15 reports registered in the category 'congenital abnormality'. This is a significantly higher number of reports than in previous years. This increase in reports may have resulted from TRIP highlighting the issue and raised awareness in tissue establishments concerning the mandatory nature of reporting congenital abnormalities after using donated gametes in assisted reproduction.

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 destroyed or returned to the supplier.

Development: In 2017, TRIP did not receive any reports of use of materials or equipment used in processing or storage of substances of human origin after a recall had occurred.

3 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.

Development: In 2017, TRIP did not receive any reports concerning the rupture of tendons.

CHAPTER 1

Reports to TRIP

1.1 Reports in 2017

In the 2017 reporting year, TRIP received 93 reports of events and adverse reactions that occurred in relation to donating, procuring, testing, storing, distributing and applying human tissues and cells. The reports concern 83 adverse events (89%) and ten adverse reactions (11%), one of which was a donation complication. To be included in the 2017 report and the EU overview, reports had to be submitted by March 1st 2018. Out of all reports, 31 (33%) were classified as serious (see Annex 3). These serious reports were included in the annual overview for the European Commission (see Annex 4). The 2017 data show an increase in the number of reports when compared to 2016, but the number is similar to the number of reports received annually in the years before. In particular, TRIP received a large number of reports in 2017 concerning hematopoietic stem cells (43%, 40 out of the total of 93 reports). The 2017 data also show an increase in the number of reports concerning adverse events and adverse reactions related to ocular tissue. The decrease in the number of reports related to assisted reproduction continues in 2017. Figure 1 and Figure 2 show the total number of reports received over the past ten years. In Figure 1, the reports are subdivided into serious and non-serious reports; in Figure 2, the reports are subdivided according to the type of the tissue or cells related to the report. Table 1 shows a categorization of all reports received in 2017, subdivided into serious and non-serious reports and according to the type of tissue related to the report.

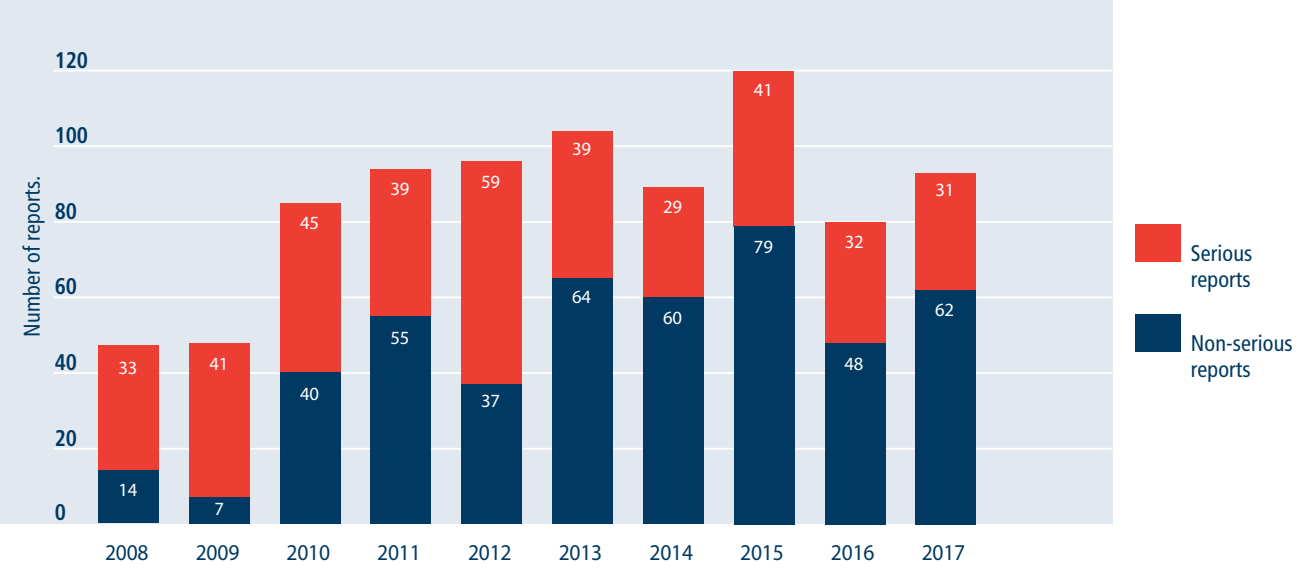


Figure 1. Number of reports received annually, 2008-2017

Table 1. Overview of reports per tissue or cell type in 2017

	Total	Non-serious	Serious
Gametes, embryos and gonadal tissue	34	14	20
Hematopoietic stem cells and therapeutic cells	40	38	2
Bone and other musculoskeletal tissue	8	6	2
Skin	0	0	0
Ocular tissue	11	4	7
Cardiovascular tissue	0	0	0
Other tissues and cells	0	0	0
Total	**93**	**62**	**31**

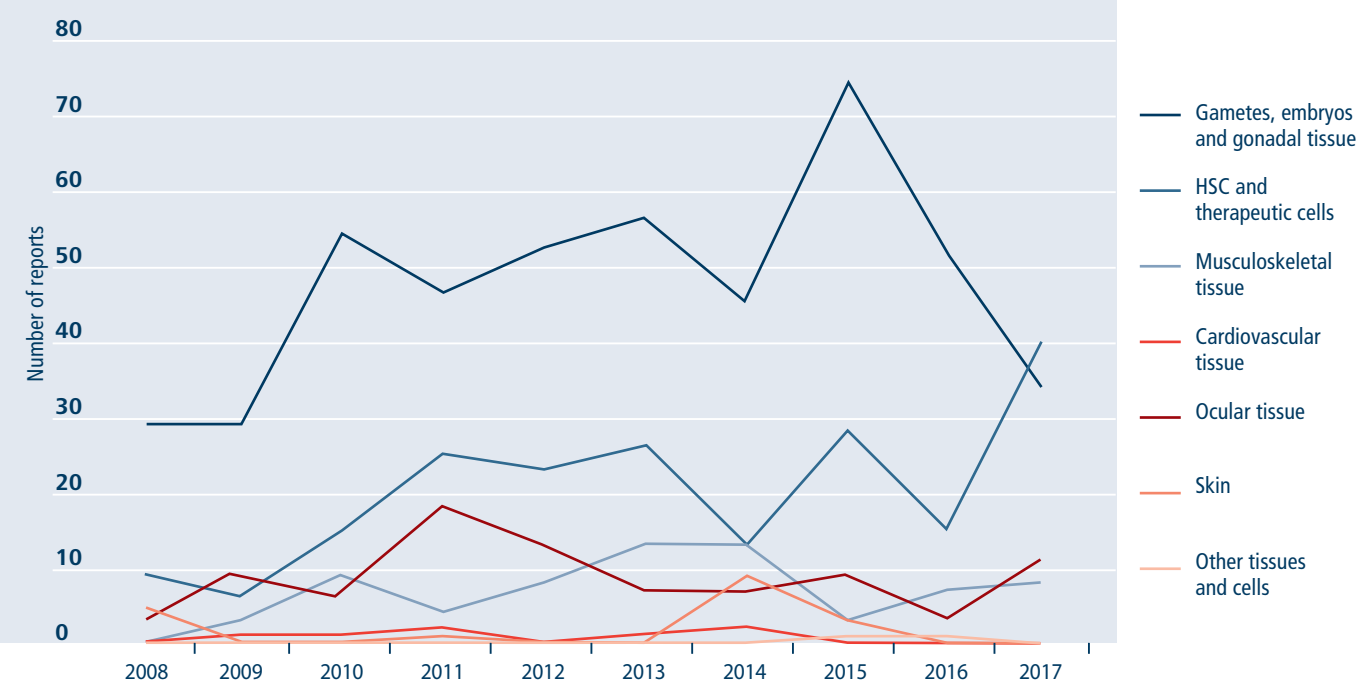


Figure 2. Number of reports received annually per tissue or cell type, 2008-2017

1.2 Late 2016 reports

After the final submission date for reports towards the 2016 Biovigilance report had passed, TRIP received three more reports. All three reports were judged to be serious. One report concerned a serious adverse event involving loss of autologous peripheral blood stem cells, which eliminated the possibility of a second trans-plantation. The second report concerned a genetic condition in a neonate after using donated semen. The third late report concerned bacterial contamination of semen, because of which IUI treatment could not take place, after hormonal stimulation had already occurred. After including these late reports, the total number of reports that TRIP received over the 2016 period is 80, of which 32 reports (40%) concerned serious events or adverse reactions.

Figure 3 shows the annual number of late reports that TRIP received in the previous ten years. In 2013, TRIP successfully addressed the issue of late reports, and now reporters are reminded annually to report events and adverse reactions in a timely manner.

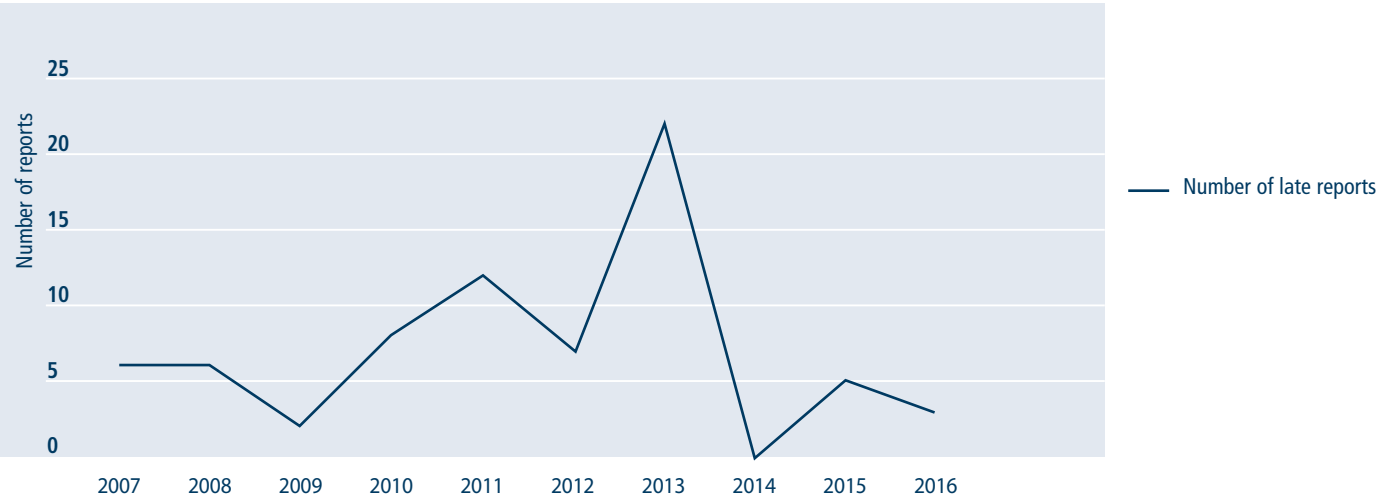


Figure 3. Number of late reports, 2007-2016

CHAPTER 2

Tissues and cells

This chapter describes the processing and distribution data and application data for each type of human tissue and cell. The 2017 adverse event and reaction reports are briefly described and analyzed. Some reports are highlighted as case descriptions.

2.1 Gametes, embryos and gonadal tissue

In 2017 in the Netherlands, 13 fertility laboratories processed human cells and tissues for the performance of intrauterine inseminations (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injections (ICSI): these tissue establishments are licensed as IVF laboratories. In addition to gametes from their own clinic, these laboratories often also process gametes from patients from other clinics (so-called transport clinics). Previously, one of these clinics was licensed for storing and processing semen and oocytes, but did not carry out the insemination process for IVF and ICSI; it used to be a so-called IVF preparatory laboratory. In 2017, this clinic obtained a license to perform all steps in the IVF-process. Furthermore, the Netherlands has 57 licensed tissue establishments, primarily hospital biomedical laboratories, which merely process semen for IUI: the semen laboratories. If a semen laboratory has obtained a license as a so-called organ bank, the laboratory is also allowed to store (donor) semen. Five laboratories have obtained this license (see Table 4).

Processing, distribution and application

Table 2 and Table 3 show, respectively, the figures for processing and distribution, and for application of gametes, embryos and gonadal tissue in 2017. The difference between the numbers for processed and distributed semen and the numbers for applied semen mostly results from the fact that semen that is used for IVF/ICSI is not considered to be distributed and the fact that some cryopreserved semen remains in storage. Oocytes are considered to be distributed only if they are transported to a different fertility laboratory or if they are thawed after cryopreservation. The difference between the number of cryo-embryos distributed and the number of cryo-embryos applied stems from the fact that not all cryo-embryos are viable after thawing, and only viable embryos are transferred.

Table 2 a-b-c. Processing and distribution of gametes, embryos and gonadal tissue in 2017

Type of semen and testicular tissue	No. of tissue establishments	Processed		Distributed				
		From NL	From EU	Unit	In NL	In EU	Outside EU	Total
Partner semen, fresh and cryo	69	39291	0	Sample	27740	68	0	27808
Donor semen, fresh and cryo	17	6733	2760	Sample	7239	17	0	7256
Partner semen, MESA/ PESA/ TESE, fresh and cryo	11	1174	6	Aspiration or biopsy	655	35	0	690
Donor semen, MESA/ PESA/ TESE, fresh and cryo	2	12	0	Aspiration or biopsy	4	0	0	4
Testicular tissue	2	30	0	Graft	0	0	0	0

Type of oocyte and ovarian tissue	No. of tissue establishments	Processed		Distributed				
		From NL	From EU	Unit	In NL	In EU	Outside EU	Total
Oocytes for own treatment, fresh and cryo	13	99762	9	Oocyte	600	7	0	607
Oocytes for donation, fresh and cryo	11	1378	0	Oocyte	206	0	0	206
Ovarian tissue	3	710	0	Graft	18	0	0	18

Type of embryo	No. of tissue establishments	Processed		Distributed				
		From NL	From EU	Unit	In NL	In EU	Outside EU	Total
Embryos, fresh and cryo	13	58723	2	Embryo	28737	24	5	28766

In 2017, in consultation with transplant professionals, TRIP chose to simplify the reporting of the distribution and transfer of the number of embryo's that (partly) originated from donated gametes. In previous years, semen was subdivided into fresh and cryo and according to the type of treatment it was used for (IUI or IVF/ICSI). Oocytes were subdivided into fresh and cryo. Embryos were divided into fresh and cryo, and according to origin (own with partner, donor gamete or gametes). The 2017 level of reporting meets the requirements for reporting to the EU.

Table 3. Application of semen, embryos and gonadal tissue in 2017

Type	Hospitals/ clinics	Recipients	Applications				
			Unit	From NL	From EU	From outside EU	Total
Partner semen, fresh and cryo	75	11373	Insemination	26540	0	0	26540
Donor semen, fresh and cryo	18	3285	Insemination	5854	2516	0	8370
Embryos, fresh and cryo	13	13280	Embryo	27866	0	0	27866
Ovarian tissue	2	3	Graft	18	0	0	18
Testicular tissue	0	0	Graft	0	0	0	0

Trip has received sufficiently complete data on IUI (both with partner semen and with donor semen) since 2011. The number of women inseminated using partner semen hovers around 10.000 per year. The number of women inseminated using donor semen has increased from 1400 in 2011 to over 3200 in 2017 (Figure 4).

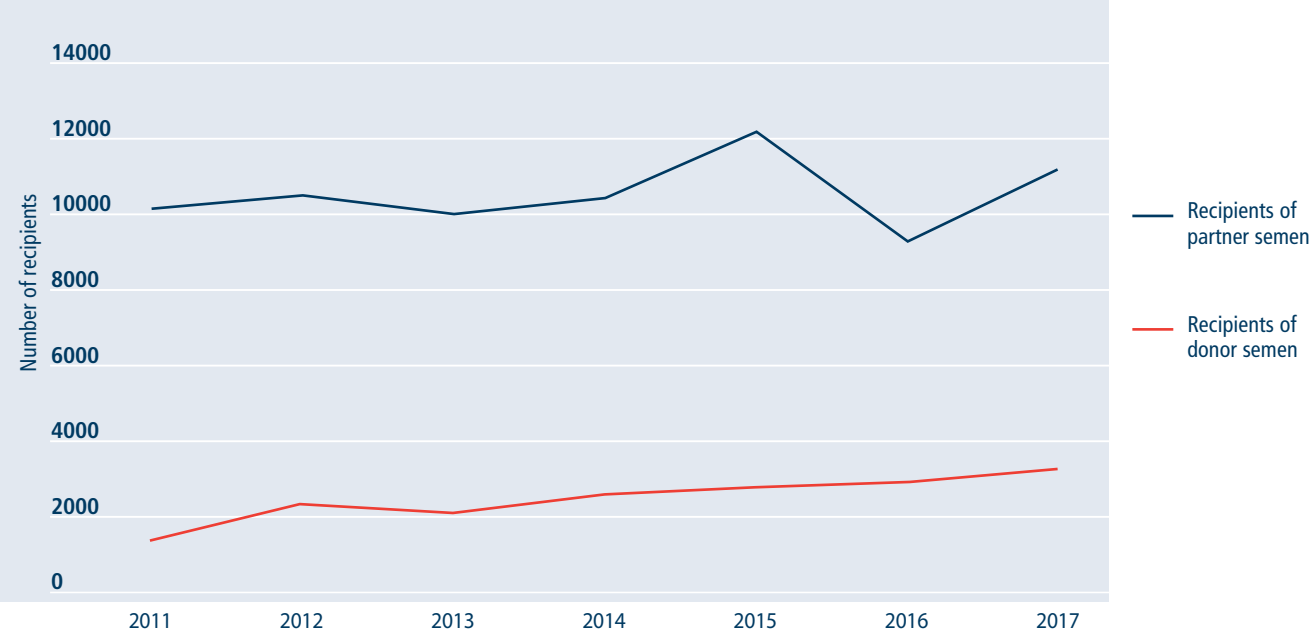


Figure 4. Number of recipients of partner semen and donor semen, 2011-2017.

The number of embryos transferred annually decreased from 33.000 in 2012 to approximately 25.0000 in 2014. Since 2014, the number of embryos transferred annually has been increasing slowly (Figure 5). However, the number of recipients has remained fairly stable. The cause for the discrepancy between these two statistics may be the decrease in the number of transfers that use two embryos at the same time and/or the improvement in the success of the procedure in leading to pregnancy.

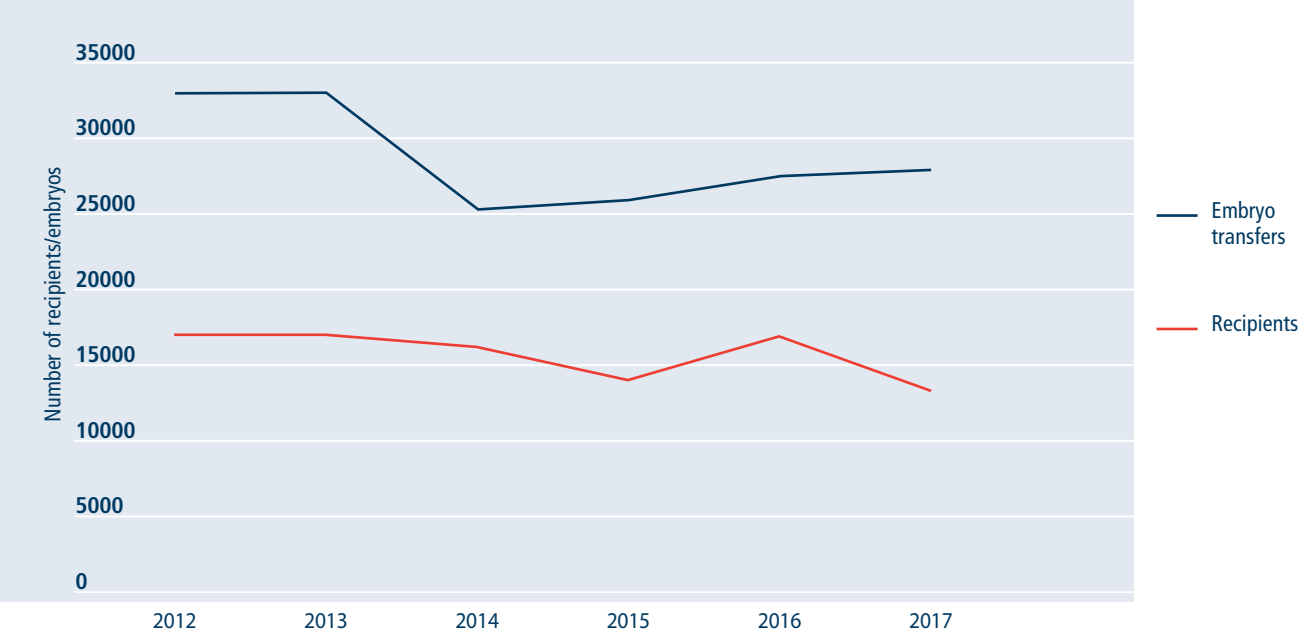


Figure 5. Number of embryo transfers and recipients, 2012-2017

Note: From 2012 onwards, IVF laboratories have provided sufficiently complete data.

2016 IVF data: Record number of children, but only slight increase in number of treatment cycles and number of multiple births

The overall pregnancy rate after IVF has never been as high in the Netherlands as it was in 2016. Moreover, the number of multiple births, which is considered a complication of IVF/ICSI treatment, has only increased slightly. The overall success rate of IVF per treatment cycle increased from 32.6% in 2015 to 34.2% in 2016. The number of multiple births did also increase from 3.5% to 3.8%, but this rate is still low in comparison to the rest of Europe.

In 2016, the number of 'fresh' IVF/ICSI treatments has increased by 3% to 14584, and the number of babies born, 5,174 (+8%) was higher than ever before. In all, in 2016, one in 30 babies was born out of IVF treatment.

According to Dr Jesper Smeenk, a gynaecologist at the Elisabeth Twee Steden Hospital in Tilburg, who compiled the report, the increase in chance of pregnancy is mostly due to the increase in success rate for procedures that use cryopreserved embryos. The total number of pregnancies from so-called cryo-cycles has increased by 10% and now accounts for about 40% of pregnancies resulting from IVF or ICSI. Because the hormonal impact and risks for a woman are far lower in this type of cycle, the increase in success in the cryo-cycle also produces health benefits.

Source: Website of the Dutch Society for Obstetrics and Gynaecology, published December 1st, 2017.

Reports

In 2017, TRIP received 34 reports related to procedures or applications of gametes, embryos and/or gonadal tissue in medically assisted reproduction. All 34 reports concern adverse events, of which 20 (59%) were serious events. The number of reports is stable in comparison to previous years with the exception of

2015, when a one-off increase in reports occurred (Figure 2). Table 4 provides an overview of the number of reports received from the different fertility laboratories in 2017. Three IVF laboratories and 46 semen laboratories indicated that no (serious) events occurred in 2017.

Table 4. Overview of 2017 reports from fertility laboratories

Fertility laboratory	No. in NL	Reports submitted by	No. of 2017 reports	Number of late 2016 reports
IVF laboratories	13	10 (77%)	20	1
Semen laboratories	57	10 (18%)	14	1
Total	**70**	**20 (29%)**	**34**	**2**

Adverse reactions

In 2017, TRIP did not receive any reports of adverse reactions or donation complications. Over the past ten years, TRIP has received 21 reports of adverse reactions (16 of which were donation complications) associated with assisted reproductive techniques. Table 5 provides an overview of these reports.

Table 5. Reports of adverse reactions associated with assisted reproductive techniques, 2008-2017

Adverse reaction	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Other reaction	1	0	1	0	0	0	0	0	0	0	2
Post-transplantation bacterial infection	0	0	0	1	0	0	1	0	1	0	3
Donation complication*	0	0	0	0	0	0	0	11	5	0	16
Total	**1**	**0**	**1**	**1**	**0**	**0**	**1**	**11**	**6**	**0**	**21**

** Donation complications have been reported since 2015*

Chapter 3 provides further information about donor vigilance and donation complications related to medically assisted reproduction.

Adverse events

In 2017, TRIP received 34 reports of events associated with gametes and embryos. 20 of these reports were classified as serious. Specific criteria have been set for the assessment of the severity of adverse reactions and events associated with assisted reproductive techniques. Events concerning loss of a complete fertility cycle or transmission of a congenital disorder through donated gametes or embryos are classified as serious, and thus must be reported. These guidelines have followed since 2017, and as of 2017, only those events classified as serious according to the current guidelines are displayed in tables and figures. Up to 2016, guidelines set out by the Dutch Association of Clinical Embryologists were adhered to, which used a significant decrease in the chance of pregnancy as a criterion for seriousness.

Figure 6 shows all reports of events related to gametes, embryos and gonadal tissue from 2008 to 2017, classified according the criteria set out by the European Commission (EC). The number of serious events occurring in 2017 is similar to the number of serious events in previous years. In 2017, for the first time, the number of reports concerning events classified as serious was higher than the number of reports concerning events not classified as serious. The new 2017 'Quality norms for laboratory practices for in vitro fertilisation' follow the criteria set out in the 'Common approach for reportable serious adverse and reactions as laid down in the tissues and cells Directive 2004/23/EC', published by the EU, for the guidelines concerning the reporting of serious events and adverse reactions.

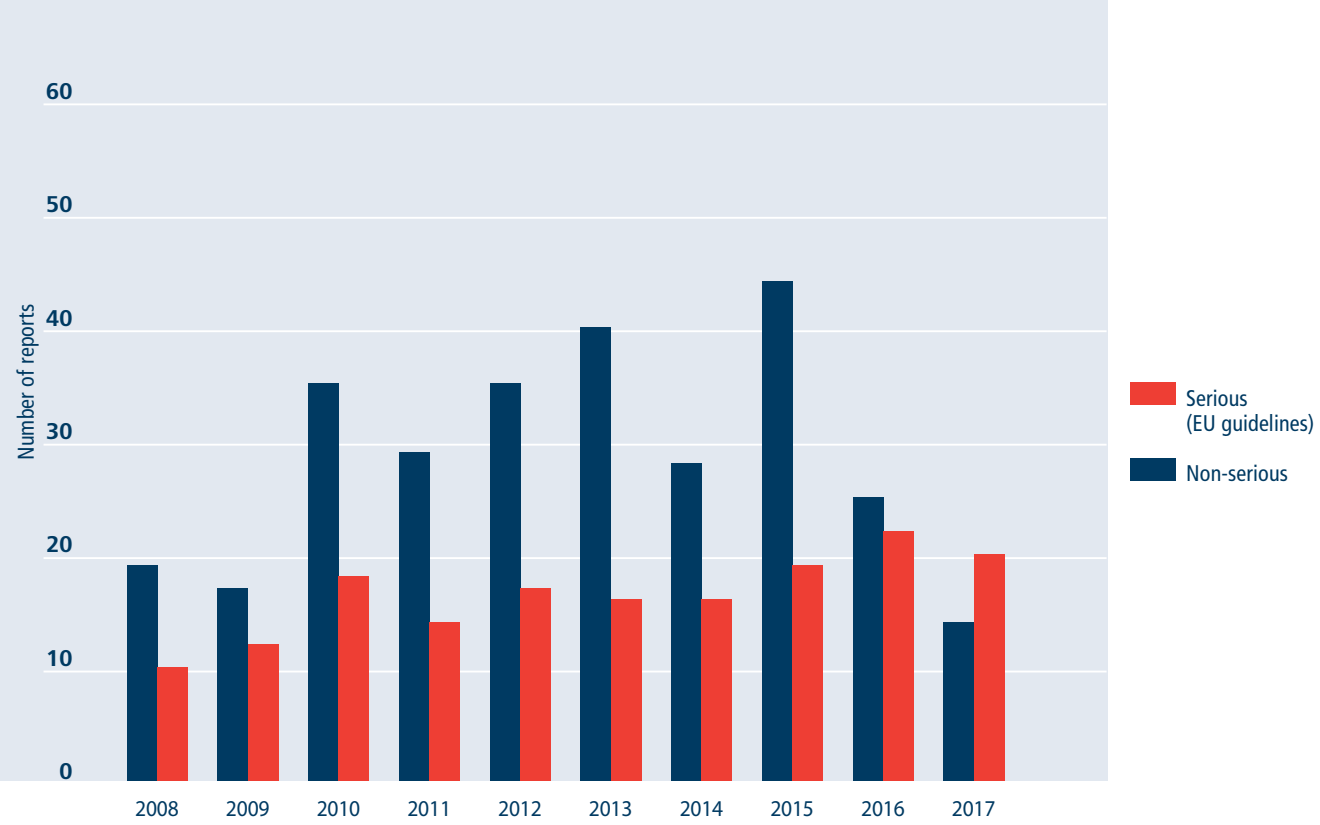


Figure 6. Number of reports of adverse events concerning gametes, embryos and gonadal tissue, 2008-2017

Table 6 provides an overview of the 2017 reports classified according to the type of tissue, type of event and severity. Figure 7 shows the classification of all reports from 2008 to 2017 according to type of incident. Before 2017, the category for events concerning 'Loss of tissues or cells' accounted for the largest number of reports. In 2017, for the first time, the largest number of reports was classified as 'Congenital abnormality'. This change may be due to the increase in the use of donated gametes and an increase in the awareness of having to report these adverse events.

Table 6. Overview of adverse events concerning gametes, embryos and gonadal tissue in 2017

Type of tissue	Type of event	Total	Severe (EU)
Semen	Loss of tissues or cells	5	2
	Other incident	5	0
	Incorrect product transplanted	1	1
	Congenital abnormality	12	9
Oocytes	Loss of tissues or cells	3	3
	Other incident	1	1
	Congenital abnormality	1	0
Embryos	Loss of tissues or cells	2	0
	Bacterial contamination of product	3	3
	Congenital abnormality	1	1
Total		**34**	**20**

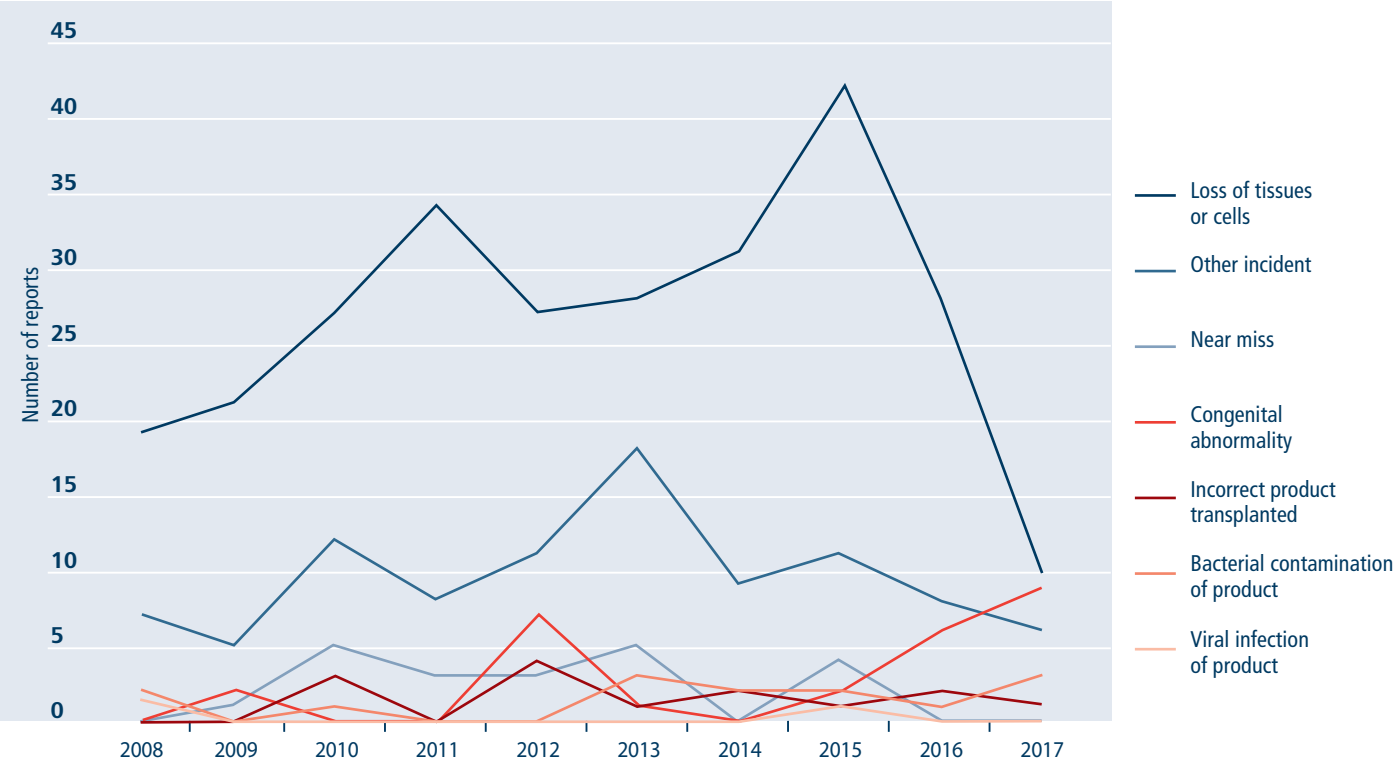


Figure 7. Number of reports per adverse event category concerning gametes, embryo's and gonadal tissue, 2008-2017

Loss of tissues or cells

In previous years, the number of reports in this category ranged from 19 to 42 (see Figure 7). In 2017, only ten reports were classified as 'Loss of tissues or cells'. The number of reports in this category was lower in 2017, especially the number of reports classified as not serious. Loss of gametes, embryos or gonadal tissue may lead to loss of a complete fertility cycle or to inability to store or process reproductive tissue or cells for fertility preservation. In such a case, the event will be classified as serious. Out of the ten reports, five were classified as serious. Figure 8 provides an overview of the number of reports in the category 'Loss of tissues or cells' from 2008 to 2017.

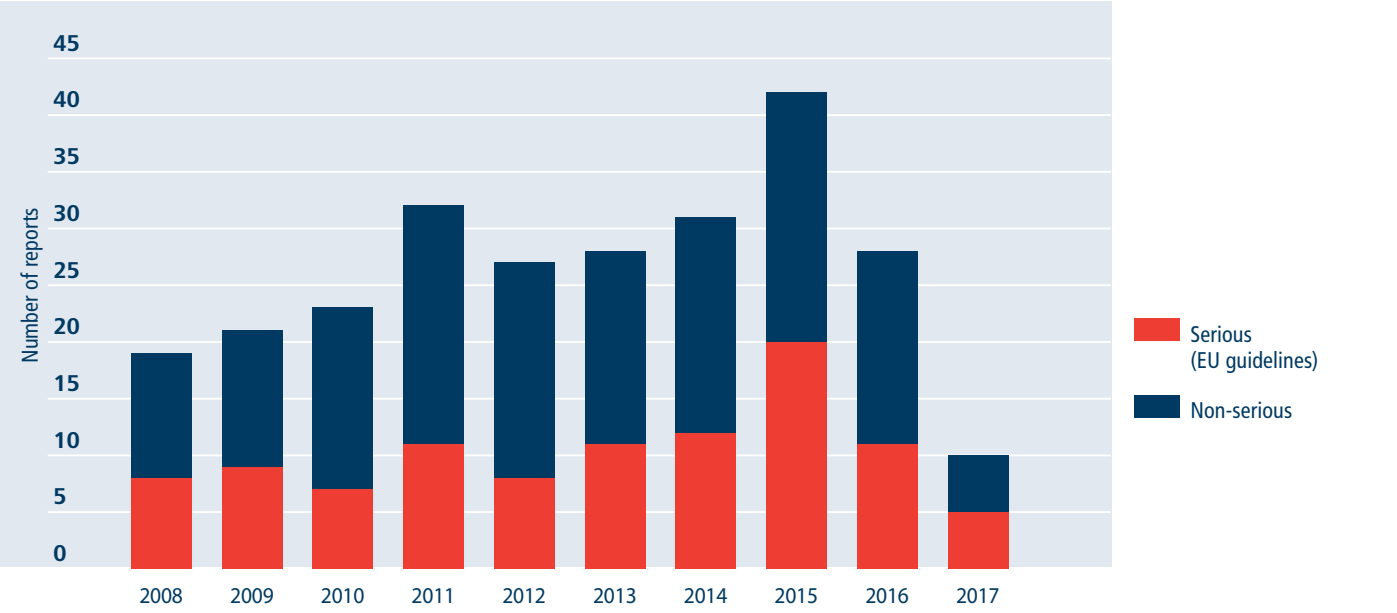


Figure 8. Reports of loss of tissues or cells concerning gametes, embryos or gonadal tissue, 2008-2017

The largest number of adverse events (n=5) involve processing errors concerning semen, oocytes, and embryos. The number of processing errors concerning embryos in particular is considerably lower than in previous years. In 2017 there were no reports of selection errors or assessment errors leading to loss of reproductive tissues or cells. TRIP received one report of a selection error concerning oocytes. Remarkably, in 2017, TRIP did not receive any reports of loss of oocytes or embryos from accidentally dropping a petri dish or other material. In previous years, several recommendations were published suggesting taking preventive measures towards avoiding this type of adverse event. Forgetting a step remains the most common processing error, as in previous years. Case 1 describes a technical error that occurred during semen processing.

Case 1: Cracked centrifuge tube

In the course of processing partner semen for IUI treatment, during the first separation step, one of two centrifuge tubes cracks, which causes a leakage. The crack is observed once the tube is removed from the centrifuge (see Image 1). The tube had not cracked at the start of the centrifugation. The decision is made not to use any more tubes from this batch of tubes, and not to inseminate the semen from the cracked tube.

That day, the IUI treatment for the couple involved took place, using one rather than two tubes of semen, which contained enough semen for the procedure. Another couple that was to receive an IUI treatment that day was referred to another hospital nearby. A third couple's treatment was postponed to the next day, when a new batch of centrifuge tubes had been received.

All three planned IUI treatments were carried out. Thus, this event was not classified as serious. If the execution of any of these treatments had been preventedby this event, it would have been classified as serious.

Image 1. Picture of the cracked centrifuge tube from Case 1.

Congenital abnormality

Fourteen reports in 2017 were registered as 'Congenital abnormality'. If donation of gametes or embryos by donors who are not partners results in the birth of a neonate with a congenital abnormality or in the termination of a pregnancy with a fetus with a (possible) congenital abnormality, the event is classified as a serious adverse event. When a genetic abnormality is detected in a donor (who is not a partner) after donation of gametes or embryos, this is also classified as a serious adverse event. The reports concerning congenital abnormalities are summarized in Table 7. Ten of the reports in which a (possible) genetic factor is involved have been classified as serious.

Table 7. Reports of congenital malformation involving gametes and embryos in 2017

Type of gamete or embryo	Description
Donor semen	Child born with dilated renal pelvis left and right, enlarged bladder and imperforate anus. No genetic factor in donor. Donor not deferred.
	Child born with a right-side duplicated ureter. Donor deferred.*
	Child born with mono-kidney. Donor deferred.*
	20-week ultrasound showed congenital heart defect with VSD, PDA, PFO. Donor deferred.*
	Two children born with Trigonocephaly (Craniosynostosis of the metopic suture) from two different donors. Initially both donors were deferred, later deferral was reversed for one. Genetic factor not completely ruled out, however (see Case 2).*
	Child born with congenital deafness. Donor deferred.*
	Child born with Cystic Fibrosis. Detected through neonatal heel prick. Donor turns out to be hereditary carrier (autosomal recessive). Donor deferred.*
	Child bron with Cowden syndrome[1]. Donor turns out to be hereditary carrier (abnormality in PTEN gene, autosomal dominant). Donor deferred.*
	Child (boy) born with Duchenne muscular dystrophy. Mother is not a hereditary carrier. Turns out to be a spontaneous mutation (X-linked recessive). Donor not deferred.
	Child born with 22q11 deletion. Donor deferred* Trisomy 21 detected in FCMB test**. Pregnancy terminated. Donor does not have balanced chromosomal translocation. Donor not deferred.
Partner oocyte and donor semen	After IVF with oocyte from female partner and donated semen, ultrasound shows Spina bifida myelomeningocele. The defect was treated trough fetoscopic patchingof the spine at 24 weeks of amenorrhea. Possible folic acid metabolic disorder. Donor not deferred.
Embryo	Child born with unbalanced translocation, out of a pregnancy for which PGD was carried out beforehand. Unclear whether it was an erroneous diagnosis, genetic mosaicism or a spontaneous pregnancy.*

* *Serious*
** *Testing of fetal cells in maternal blood for trisomy 13, 18 and 21*
*** *Pre-implantation genetic diagnosis*

[1] Cowden syndrome is a rare congenital condition which is characterized by the occurrence of both benign and malignant tumours in different parts of the body throughout the patient's lifetime.

Case 2 describes the two reports concerning the birth of two children with trigonocephaly.

Case 2. Trigonocephaly

A child is born after AI with donated semen. The child falls out of its cradle at a young age, after which it is brought to a pediatrician for a check-up. During physical examination, a prominent ridge in the front of the skull is observed. Further examination shows this is a sign of craniosynostosis of the metopic suture. This defect results in a triangular skull: Trigonocephaly. The pediatric neurosurgeon decides to plan an operation for when the child turns 1 year old. A report is made to TRIP, because a genetic factor cannot be ruled out (10% chance). The donor is initially deferred, but after exclusion of a genetic factor this deferral is reversed.
Two months later, TRIP receives a second report of a child born with Trigonocephaly after AI with donated semen. The children's birthdays are 3.5 months apart. Checks establish that the donated semen in this case comes from a different donor. This donor is also deferred.

Figure 9 provides an overview of all reports in the category 'Congenital abnormality' from 2007 to 2017. Table 8 provides an overview of the different kinds of congenital abnormalities diagnosed from 2007 to 2017.

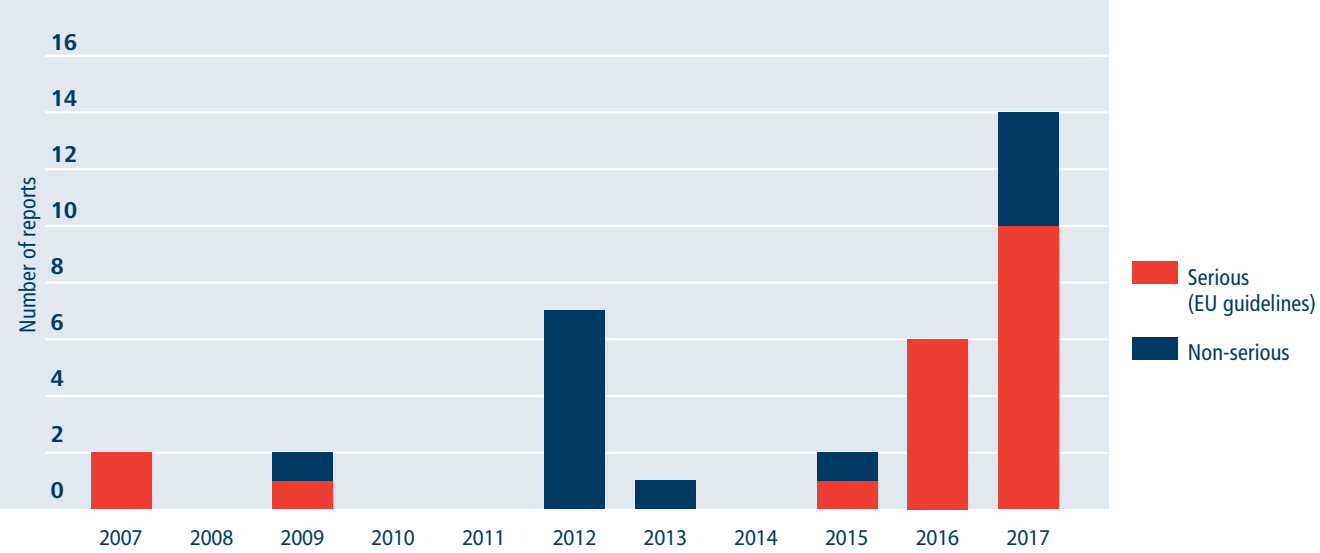


Figure 9. Reports in the category 'Congenital abnormality', 2007-2017

Tabel 8. Overview of reports of congenital abnormalities from 2007 to 2017

Transfer of congenital abnormality after AI with donated semen, donor hereditary carrier		No.
Cystic Fibrosis	Autosomal recessive	2
Spinal Muscular Atrophy	Autosomal recessive	1
Congenital defect of glycosylation	Autosomal recessive	1
Oculocutaneous albinism	Autosomal recessive	1
Sickle cell trait	Autosomal recessive	1
Cowden syndrome	Autosomal dominant	1
De novo mutation, AID		
Achondroplasia	Autosomal dominant	1
Neurofibromatosis	Autosomal dominant	1
Tuberous sclerosis complex	Autosomal dominant	1
Duchenne muscular dystrophy	X-linked recessive	1
Chromosomal abnormality after AI with donated semen, donor possibly hereditary carrier		
22q11 deletion		1
Chromosomal abnormality after AI with donated semen, donor not a hereditary carrier		
Trisomy 21		4
Triploidy		1
Congenital abnormality after AI with donated semen or IVF with donated semen and/or oocyte, congenital factor not ruled out		
Congenital abnormality in aortic valve		1
VSD and ASD (in combination with trisomy 21)		1
Complex congenital heart defect with VSD, PDA, PFO		1
Orofacial cleft		1
Hip dysplasia		1
Unilateral renal agenesis		2
Duplicated ureter		1
Spina Bifida		1
Trigonocephaly (Craniosynostosis of the metopic suture)		2
Congenital deafness		1
Dysmorphic features, hypospadias, omphalocele and diaphragmatic hernia		1
Congenital abnormality after AI with donated semen or IVF with donated semen and/or oocyte, congenital factor ruled out		
Dilated renal pelvis left and right, enlarged bladder and imperforate anus		1
Spina Bifida myelomeningocele		1
Congenital abnormality after PGD, possibly erroneous diagnosis		
Ponto-cerebellar hypoplasia (PCH) type 2 mutation		1
Unbalanced translocation		1

Due to the increase in the use of donated gametes and the awareness of the obligation to report congenital abnormalities in processes in which donated gametes are used, the number of reports concerning congenital (genetic) abnormalities has increased. The risk of a congenital abnormality occurring in a donor is assessed through a donor's medical history. Autosomal recessive abnormalities that do not manifest themselves in the donor are not detected using this method. Thus, the reporting of congenital abnormalities may contribute to estimating the risk of (repeated) transmission of congenital abnormalities.

Other incident

The category "other incident" mostly encompasses reports concerning adverse events that do not lead to the loss of tissue or cells, but to possible deterioration of the quality of tissue or cells. From year to year, the proportion of reports concerning assisted reproduction that are registered as other incident varies from 8% to 27%. In 2017, 17% of reports concerned other incidents. Figure 10 provides an overview of the number of reports registered as other incident from 2008 to 2017. In 2017, TRIP received six reports, one of which was classified as serious. Table 9 summarizes the reports classified as other incident.

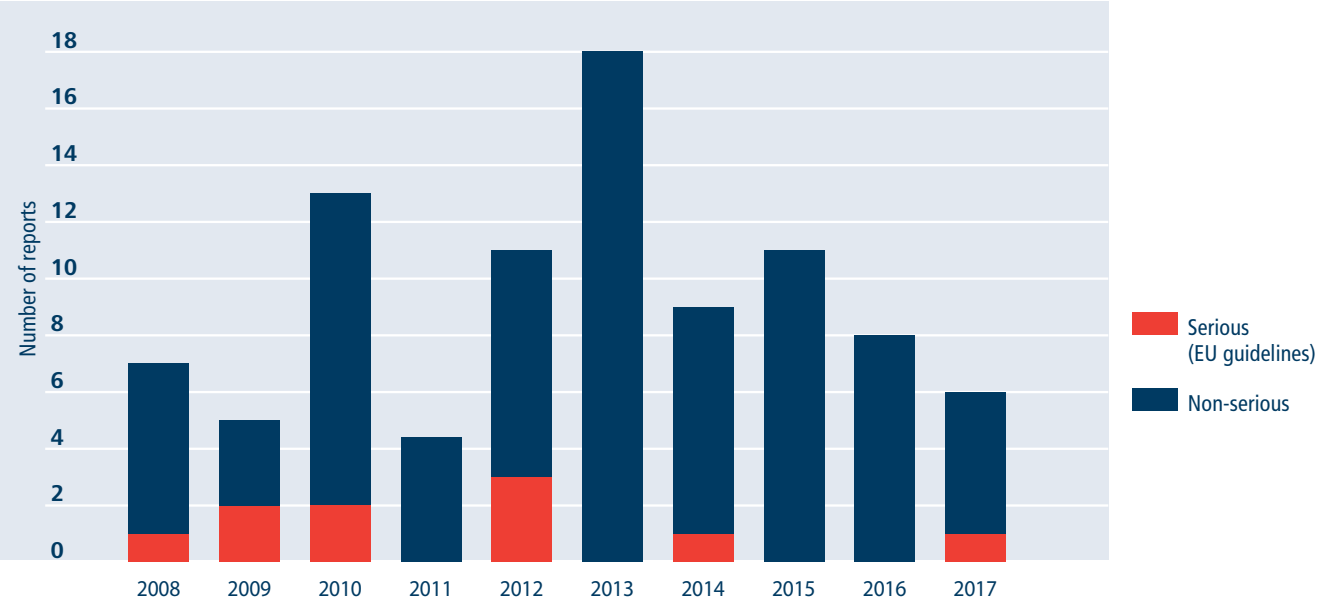


Figure 10. Reports in the category 'Other incident' concerning gametes, embryos and gonadal tissue, 2008-2017

Table 9. Reports in the category 'Other incident' concerning gametes, embryos and gonadal tissue from 2008 to 2017

Type of error	No. of reports	Type of gamete or embryo	Phase in procedure	Description
Storage error	2	Semen	Donation	Expired semen container provided
			Procurement	Semen container not properly sealed
Processing error	1	Oocytes	Insemination	Failed to inseminate oocytes. ICSI carried out the next day.* (see Case 3)
Assessment error	1	Semen	Processing	Processing was carried out using expired tubes 9 times.
Administrative error	1	Semen	Processing	Colour coding of materials changed during processing. No mix-up. Distress in treated couple. DNA test for confirmation.
Other	1	Semen	Retrieval	Blood of donor mixed with semen due to cut sustained on the edge of the semen container

* *Serious*

Case 3 describes the processing error concerning the insemination of oocytes in detail.

Case 3. Oocytes not inseminated, ICSI the next day

In one IVF treatment, the laboratory staff forgot to inseminate 11 oocytes. The dish with the oocytes was placed in the incubator. The next day, staff discover that the oocytes have not been inseminated and that there are no spermatozoa present in the culture droplets. The laboratory decides to inseminate the oocytes using ICSI. A day later, two of the 11 oocytes turn out to have been fertilized. These zygotes developed into an 8-cell type A embryo and a 6-cell type B embryo. Both embryos were transferred.
A root cause analysis was carried out, which has led to the introduction of a time-out moment in the process of insemination during which extra checks are carried out. Although the error in this case did not lead to the loss of an entire fertility cycle, the event was nevertheless been classified as serious, due to the possible reduction and deterioration in quality.

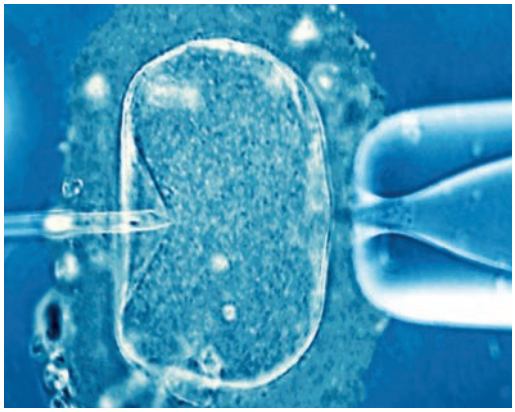


Image 2. ICSI

Incorrect product transplanted

In 2017, TRIP received one report concerning a case in which an incorrect product was transplanted. Reports in this category are always assessed as serious. This report concerned the insemination of donated semen from a donor who had been deferred by a semen bank in another EU member state. The donor had been deferred after a congenital heart defect was detected in a pregnancy from the same donor. This deferral was known, but was overlooked due to a communication error. Emergency contraception (morning-after pill) was prescribed to prevent pregnancy in the recipient of the semen.

Figure 11 provides an overview of all reports in the category 'Incorrect product transplanted' from 2008 to 2017.

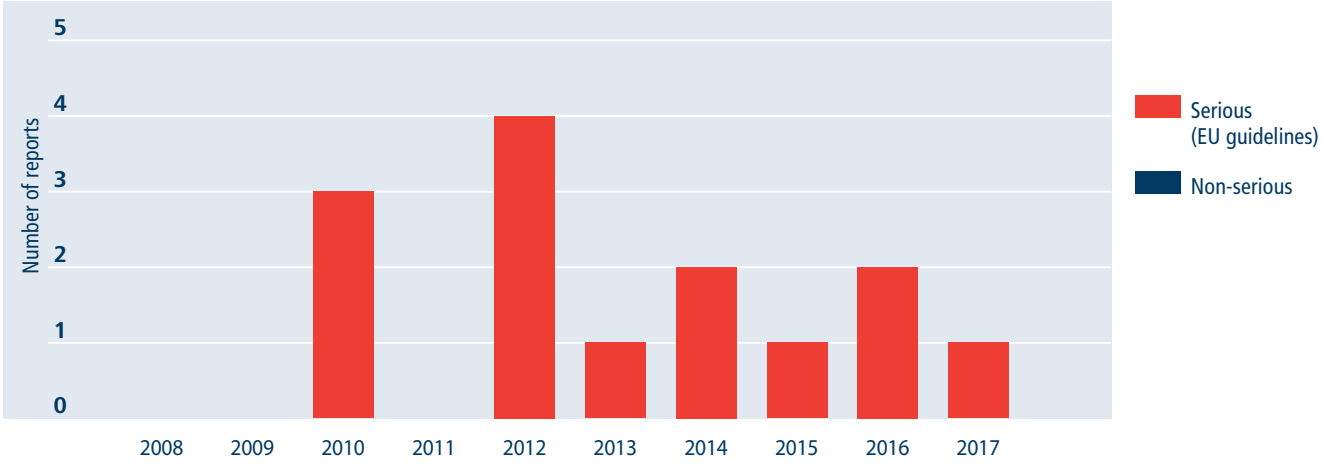


Figure 11. Reports in the category 'Incorrect product transplanted', 2008-2017.

Bacterial contamination of product

In 2017, three reports were classified as 'bacterial contamination of product'. The numbers of reports in this category from 2008 to 2017 are shown in Figure 12. Table 10 summarizes the three reports concerning adverse events in 2017. At least two of these three reports may be attributed to inadequate hygiene during the production and collection of semen. Since 2007, TRIP has received six reports of embryo cultures having been contaminated with enteric bacteria. In four cases, the (partner) semen had been contaminated with these bacteria.

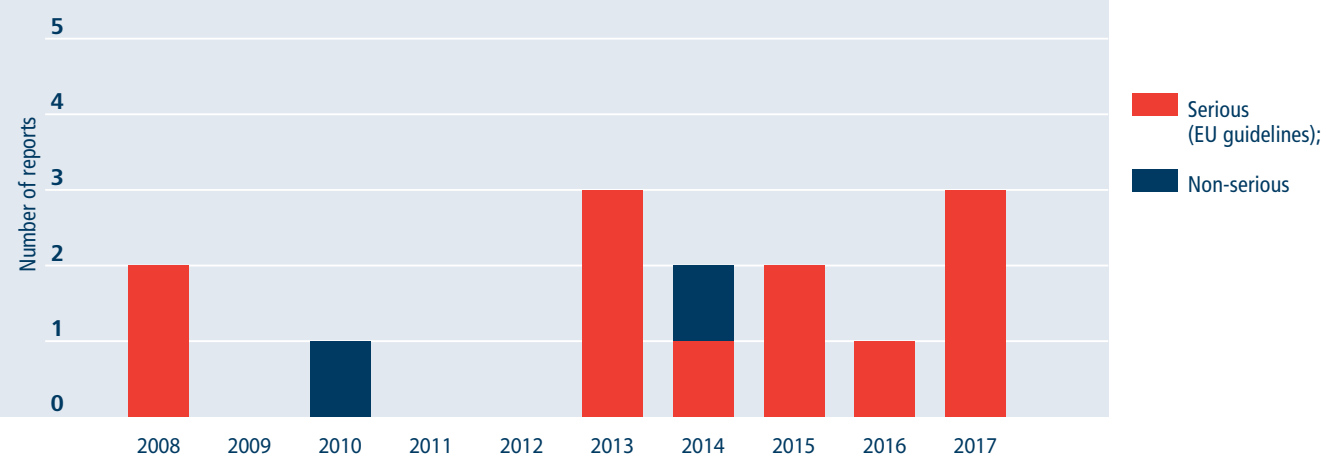


Figure 12. Reports in the category 'Bacterial contamination of product' involving gametes and embryos, 2008-2017

Table 10. Reports in the category 'Bacterial contamination of product' involving gametes and embryos, 2008-2017

Type of error	No. of reports	Phase in procedure	Type of gamete or embryo	Description
Production error	3	Culturing	Embryos	Bacterial contamination involving E. coli, Staphylococcus and Streptococcus. Originated from partner semen.*
				Bacterial contamination involving E, coli, Enterococcus fecalis and Klebsiella pneumoniae. Originated from partner semen.*
				Bacterial contamination involving Enterococcus fecalis. Originated from partner semen.*

* *Serious*

Summary gametes, embryos and gonadal tissue

The total number of reports related to assisted reproduction in 2017 is lower than in 2016. However, the number of serious reports remains around 20, despite an increase of the number of applications. In contrast to previous years, the category 'Loss of tissue or cells' (ten reports, five of which serious) no longer accounts for most reports. Particularly the number of processing errors involving oocytes and embryos has decreased. In 2017, TRIP received the largest number of reports in the category 'Congenital abnormalites' (14 reports, ten of which were serious), including nine reports of serious congenital abnormalities related to the use of donated semen. In addition, TRIP received one report related to pre-implantation genetic diagnosis (PGD). Furthermore, TRIP received three serious reports concerning bacterial contamination of embryo cultures involving enteric bacteria originating from the (partner) semen and one report of a serious incident categorized as 'Incorrect product transplanted'. In 2017, TRIP did not receive any reports of adverse reactions related to assisted reproduction, which include donation complications related to oocyte donation.

2.2 Hematopoietic stem cells and therapeutic cells

As of 2017, there are 13 stem cell laboratories in the Netherlands that are licensed to collect, process, store, and distribute hematopoietic stem cells (HSC) and therapeutic cells donated by autologous and related donors. The distribution of stem cell products donated by unrelated donors (including cord blood) for specific patients to the Netherlands' eight academic transplantation centres is mediated by Matchis, usually through the stem cell laboratory of the hospital involved. Bone marrow and peripheral blood stem cells (PBSC) donated by unrelated donors from the Netherlands are collected in two academic hospitals, which have hemapheresis units and stem cell laboratories, in cooperation with Sanquin, the organisation responsible for the blood service in the Netherlands. A total of 1759 patients received a HSC transplant in 2017, 60% being autologous, 12% allogeneic from related donors and 28% allogeneic from unrelated donors. Approximately 11% of the allogeneic products applied in the Netherlands are donated by Dutch donors (Table 13). Cord blood for transplantation to patients unrelated to the donor is processed and stored by Sanquin and is distributed worldwide for allogeneic transplantation in cooperation with Matchis. Additionally, two private blood banks store cord blood for autologous applications.

Processing, distribution, and application

Tables 11, 12, and 13 provide an overview of the numbers of bags of HSC and therapeutic cells processed, distributed and/or applied in the Netherlands in 2017.

Table 11. Processing of hematopoietic stem cells and therapeutic cells in 2017

Type of cells	No. of tissue establishments	Transplants processed*			
		From NL	From EU	From non-EU	Total
HSC autologous					
Bone marrow	4	14	0	0	14
PBSC	11	1877	0	0	1877
Cord blood	2	1282	1743	129	3154
HSC related					
Bone marrow	7	45	0	0	45
PBSC	9	195	0	1	196
Cord blood	1	3	0	0	3
HSC unrelated					
Bone marrow	8	35	16	2	53
PBSC	8	102	193	26	321
Cord blood	6	200	36	18	254
Therapeutic cells					
Lymphocytes (DLI) related	8	66	0	0	66
Lymphocytes (DLI) unrelated	8	36	115	16	167
Mesenchymal stem cells autologous	1	17	0	0	17
Mesenchymal stem cells unrelated	2	34	7	0	41
Dendritic cells autologous	1	64	0	0	64
Dendritic cells unrelated	1	0	3	0	3
TC-Til cells autologous	1	4	0	0	4
Granulocytes irradiated	1	5	0	0	5
CAR-T/TCR cells	2	6	0	0	6

* *If a transplant product is reprocessed in the receiving stem cell laboratory, this is counted a second time*

Compared to 2016, the number of autologous bone marrow and PBSC products processed has decreased and the number of allogeneic bone marrow and PBSC products processed has increased (both related and unrelated). Furthermore, the number of cord blood products shows a 41% decrease in comparison to 2016. The number of autologous cord blood products from the Netherlands processed by private blood banks shows a 30% decrease. Developments in the field of biotechnology are reflected in the Netherlands in the application of TC-Til (Tumor-infiltrating lymphocytes) cells and CAR-T cells (Chimeric antigen receptor T cells). For the time being, these applications are carried out using autologous cells.

Table 12. Distribution of hematopoietic stem cells and therapeutic cells in 2017

Type of cells	No. of tissue establishments	Units distributed*			
		From NL	From EU	Outside EU	Total
HSC autologous					
Bone marrow	3	12	0	0	12
PBSC	11	3674	0	0	3674
Cord blood	1	0	0	1	1
HSC related					
Bone marrow	7	52	0	0	52
PBSC	9	187	0	0	187
Cord blood	1	1	0	0	1
HSC unrelated					
Bone marrow	7	52	13	11	76
PBSC	7	346	41	17	404
Cord blood	7	77	1	2	80
Therapeutic cells					
Lymphocytes (DLI) related	8	68	0	0	68
Lymphocytes (DLI) unrelated	8	117	3	1	121
Mesenchymal stem cells autologous	1	12	0	0	12
Mesenchymal stem cells unrelated	2	34	7	0	41
Dendritic cells autologous	1	4	0	0	4
Dendritic cells unrelated	1	5	0	0	5
TC-Til cells autologous	1	5	0	0	5

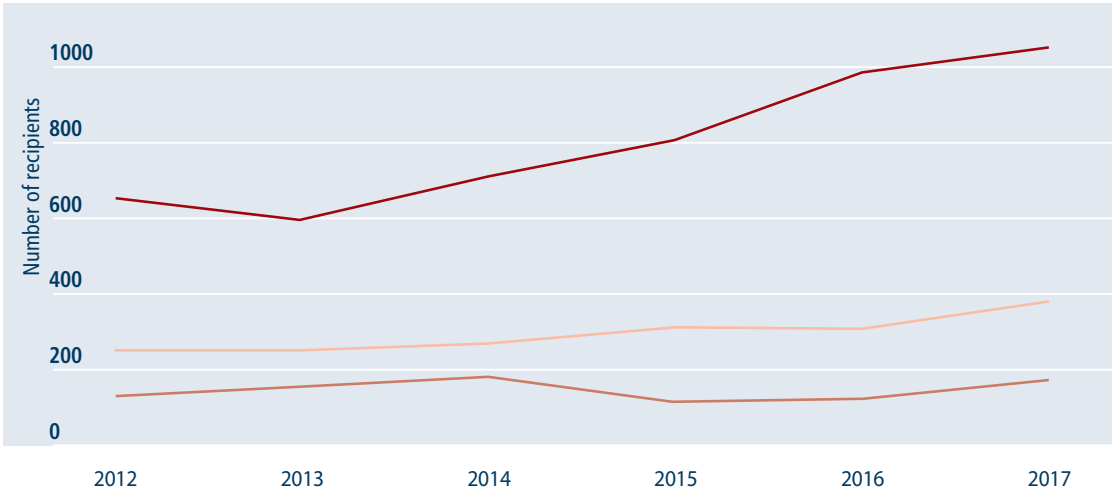
* *Distribution refers to products destined for transplantation or other therapeutic purposes*

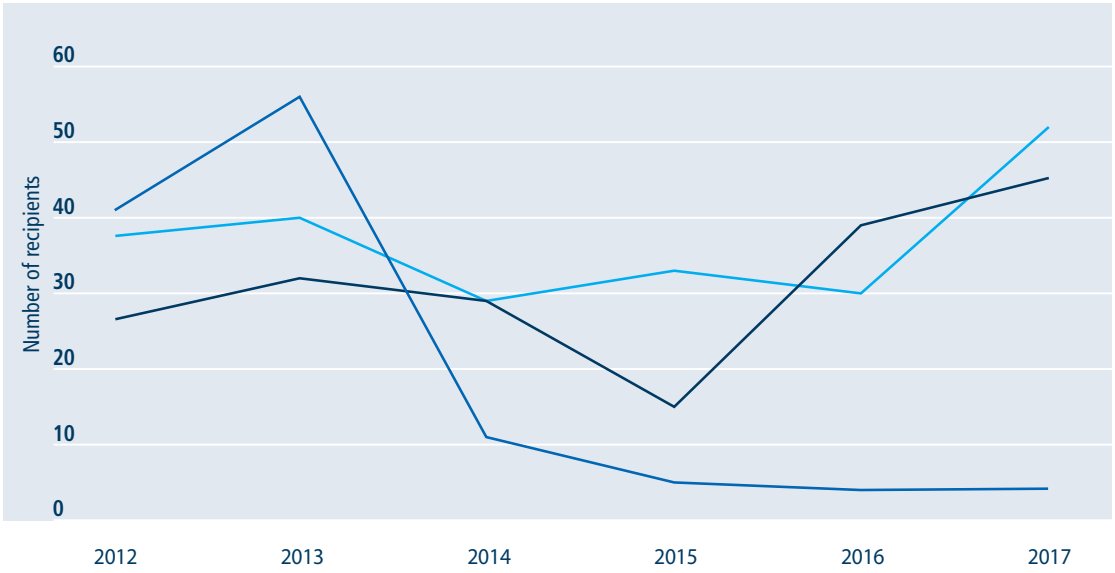
Table 13. Application of hematopoietic stem cells and therapeutic cells in 2017

Type of cells	No. of tissue establishments	No. of recipients	No. of bags applied			
			From NL	From EU	From non-EU	Total
HSC autologous						
Bone marrow	3	4	12	0	0	12
PBSC	14	1051	3711	0	0	3711
Cord blood	0	0	0	0	0	0
HSC related						
Bone marrow	8	45	57	0	0	57
PBSC	9	170	201	0	0	201
Cord blood	1	1	1	0	0	1
HSC unrelated						
Bone marrow	8	52	52	4	0	56
PBSC	10	377	257	148	20	425
Cord blood	8	59	55	27	2	84
Therapeutic cells						
Lymphocytes (DLI) related	10	67	79	0	0	79
Lymphocytes (DLI) unrelated	9	94	89	28	3	120
Mesenchymal stem cells autologous	1	4	12	0	0	12
Mesenchymal stem cells unrelated	2	26	73	0	0	73
Dendritic cells autologous	1	2	5	0	0	5
Dendritic cells unrelated	1	16	16	0	0	16
TC-Til cells autologous	1	7	7	0	0	7

The number of patients that received an allogeneic transplant from a related or an unrelated donor, went up by 24% in comparison to 2016. The largest increase was in the number of recipients of allogeneic bone marrow (41%) and PBSC (27%). The number of recipients of allogeneic cord blood shows a 13% decrease.

As Figure 13-a-b-c shows, the number of autologous PBSC transplants has increased, whereas the number of autologous bone marrow transplants has remained stable in comparison to 2016. Allogeneic transplants of PBSC (related and unrelated) have increased, but not as significantly as allogeneic transplants of bone marrow. The number of related and unrelated allogeneic bone marrow transplants show respectively a15% and a 73% increase in 2017. The increase in the number of related bone marrow transplants may be ascribed to the increase in the number of haploidentical stem cell transplants, of which the success rate has increased due to a new transplant method. The number of unrelated donor lymphocyte infusions (DLIs) shows a 68% increase, whereas the number of related DLIs has remained stable.





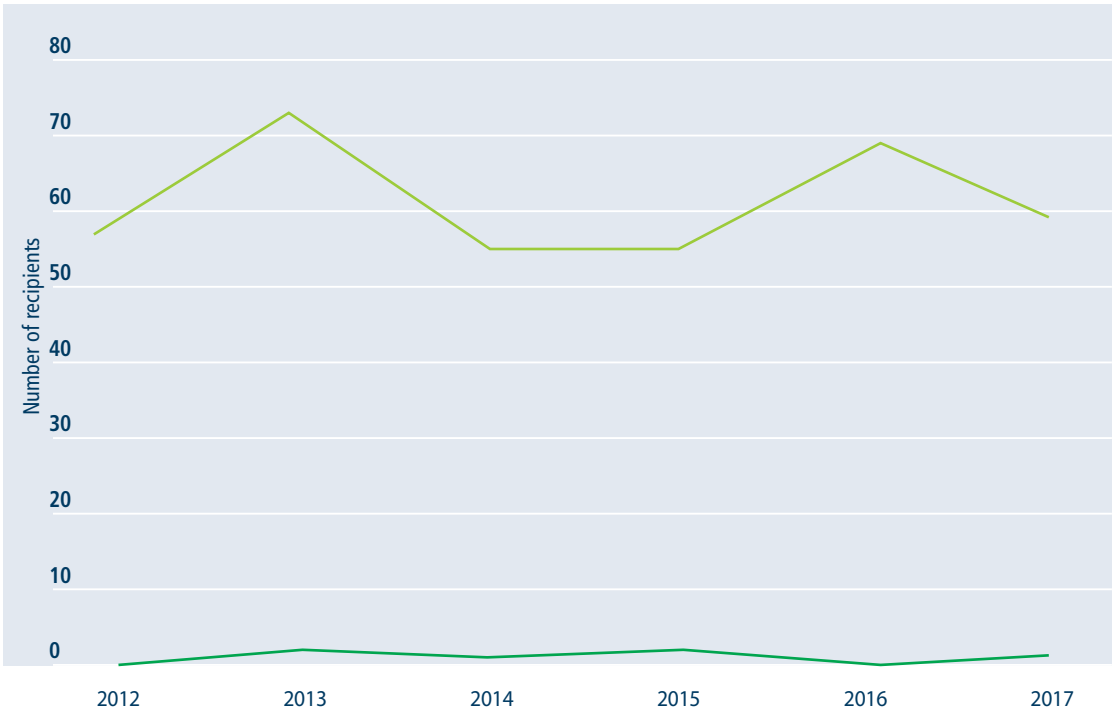


Figure 13 a-b-c. Number of recipients of HSC transplants per type of transplant, 2012-2017

Reports

In 2017, TRIP received 40 reports of adverse events and reactions related to transplants of HSC and therapeutic cells. For an overview of the donation complications reported, turn to chapter 3: The challenge of donor vigilance.

In 2017, 32 adverse events were reported, one of which has been classified as serious. TRIP received eight reports of adverse reactions, none of which have been classified as serious. The serious adverse event concerns a bacterial contamination of an autologous PBSC product, which resulted in having to redo the process of mobilisation and collection. Figure 14 displays an overview of all reports of related to HSC and therapeutic cells TRIP has received over the past ten years. The number of non-serious adverse events and the number of non-serious adverse reactions have increased significantly in comparison to previous years. The events and reactions reported are summarized in Tables 14 and 15, subdivided according to the type of HSC or type of therapeutic cell involved in the transplant.

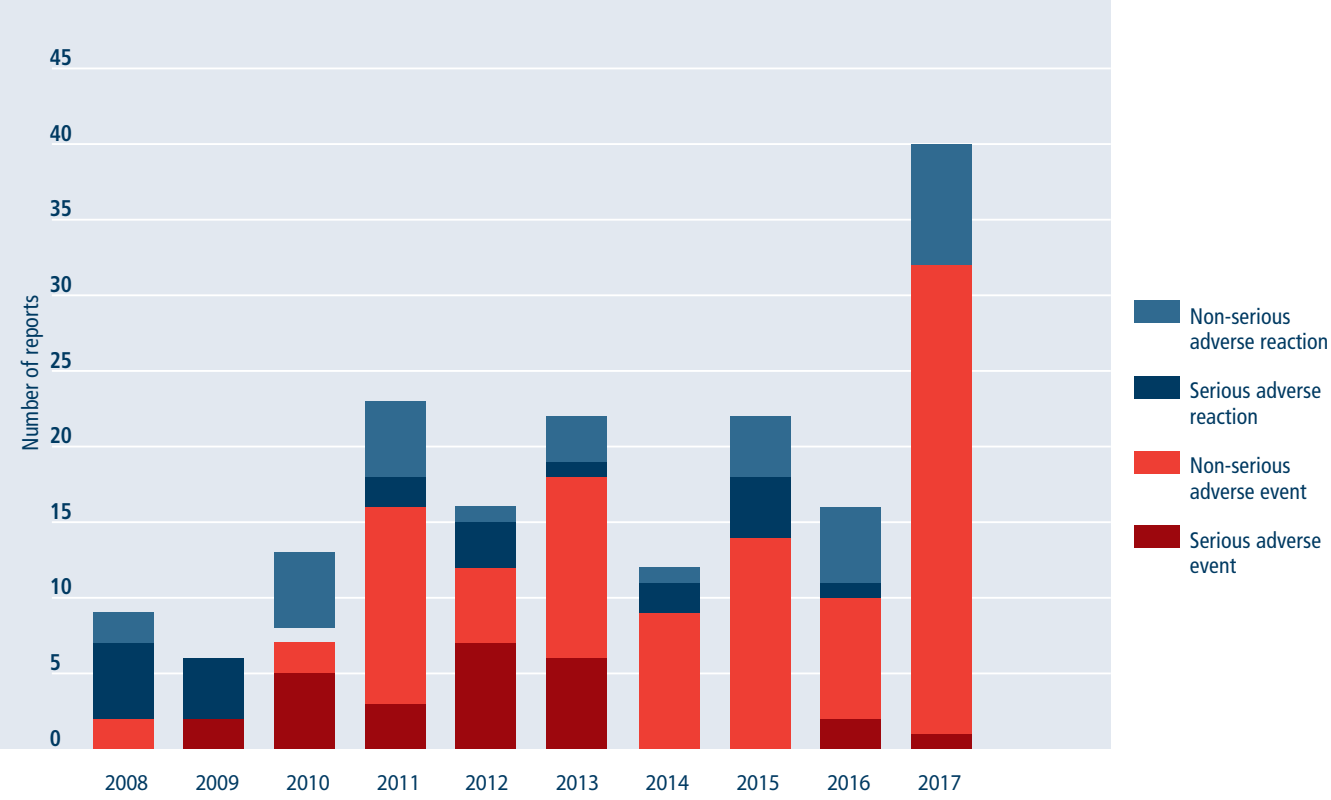


Figure 14. Reports related to HSC and therapeutic cells, 2008-2017

Adverse events

Table 14 summarizes the adverse events reported in 2017. The number of 'bacterial contaminations' (15, 47% of all adverse events) is striking, the number involving bone marrow as well as the number involving PBSC. The cause for these bacterial contaminations can be found in the collection (8), processing (6), testing (1) of the products. One case, in which a product was discarded after a contamination with Staphylococcus Aureus, has been assessed as serious by the Biovigilance advisory board (loss of cells), as it led to the patient having to redo the mobilization and apheresis processes. In the remaining cases, the product was infused despite the bacterial contamination.

TRIP received six reports of insufficient engraftment after the administration of cord blood, five of which came from the same establishment. A thorough investigation was carried out, but no causal relation between the processing of the products and the insufficient engraftment could be established. After 2016, TRIP has not received any more reports of leakage from bags.

Table 14. Overview of adverse events in 2017, subdivided according to the type of hematopoietic stem cell or therapeutic cell

Type of HSC or therapeutic cell	Adverse event (category and description)	Number
Bone marrow autologous	Bacterial contamination of product • Concerns a contamination of rescue bone marrow	1
Bone marrow allogeneic	Bacterial contamination of product • Bacterial contamination of bone marrow was reported 8 times; one time in a product donated by a related donor, seven times in a product donated by an unrelated donor. In four cases, the bacterial contamination involved Gram positive rod bacteria (Propionibacterium acnes), in the remaining cases it involved coagulase negative staphyolococcus bacteria	8
Bone marrow allogeneic	Other incident • Atypical cells and macrophages observed in bone marrow morphology of an unrelated allogeneic donor	1
PBSC autologous	Bacterial contamination of product • In all cases, the bacterial contamination involved staphylococcus epidermidus, in two cases additional bacteria were also found (streptococcus orali and staphylococcus warneri). In four cases, the patient receiving the transpant product was preventively given prophylactic antibiotics prior to administration. In one case, the product was discarded after staphylococcus aureus was detected and new mobilisation and apheresis procedures had to be undertaken*	5
	Insufficient growth/engraftment • No indication of poor vitality detected in cultures of reference ampoules, re-infusion of autologous cells carried out	1
	Other incident • During defrosting, the donation tube turns out to have broken off the opening; contact between product and environment • During processing, the collection tube spontaneously disconnected from the product bag (see Image 3) • Product has normal aspect after defrosting, but is cloudy during infusion, thus infusion time was elongated. Unable to determine cause (protein/cell aggregates, clotting?) • When initiating the culture, clotting is observed. Heparin preventively added to product before infusion (no further clotting observed)	4
	Loss of cells • Clotting in product due to technical malfunctioning in apheresis machine; product free of clotting cryo-preserved (30% of collected material lost). Sufficient amount of product left for transplant • After cryopreservation, one bag of product was left behind in the preservation machine. Sufficient number of cells yielded for transplant	2
Cord Blood allogeneic	Insufficient growth/engraftment • In three cases a new transplant of cord blood took place, after which sufficient engraftment occurred • One patient received a new transplant of PBSC, after which repopulation occurred • In once case, quality control showed that, after the washing procedure, the CD34+ cells were low and the vitality was poor • In one case delayed engraftment (day +33) occurred after a new transplant with cord blood	6
	Other incident • Data logger not connected properly, which inhibited the receiving center's ability to read out the temperature during transport. Transplantation postponed	1
Donor Lymphocytes	Bacterial contamination of product • CNS** cultured after damage to the bag after puncturing went unnoticed	1
	Other incident • Abnormal aspect (red aggregates) in cold product. Normal aspect at room temperature	1
Total		**31**

* *Serious*
** *Coagulase negative Staphylococcus bacteria*

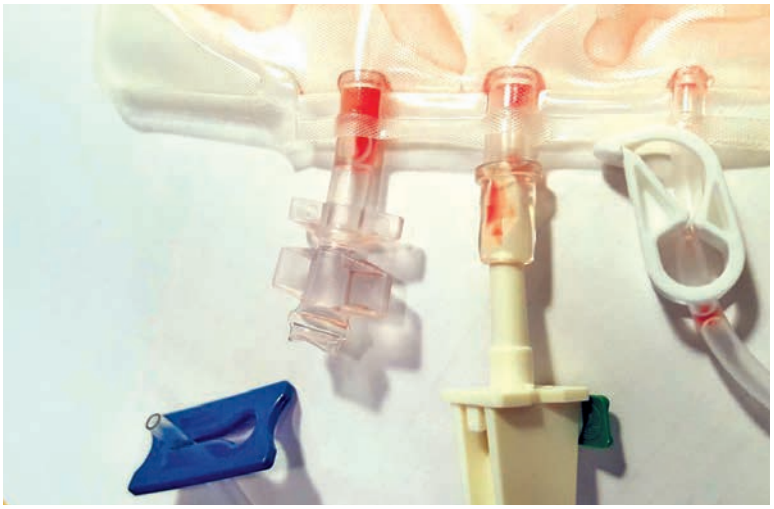


Image 3. Spontaneously disconnected collection tube and newly attached spike in HSC bag

Adverse reactions

Table 15 summarizes the eight reports TRIP received concerning adverse reactions related to HSC, subdivided according to type of HSC. None of these adverse reactions have been classified as serious.

Table 15. Overview of adverse reactions in 2017, subdivided according to the type of hematopoietic stem cell

Type of HSC	Reaction (category and description)	Number
PBSC autologous	Other reaction • Hypotension and nausea post-transplant; supplementation of fluid and administration of prednisolone. Symptoms disappeared after 24 hours. DMSO levels in product within norm • Fever without focus on the day of the transplant • Neurological symptoms ten minutes after infusion is started (impaired vision, confused speech, tingling). Infusion terminated; consultation with neurologist and CT-scan of skull. No evident abnormalities	3
PBSC allogeneic	Anaphylactic reaction • Dyspnea (decrease in saturation) and hypotension during infusion; after interruption and administration of antihistamines transfusion was completed. • Dyspnea, hypotension, and laryngeal edema; improvement after administration of antihistamines, product administered in full	2
	Post-transplant febrile reaction • Fever and chills after administration, no indications for haemolysis	1
	Other reaction • Fever, chills and pain in legs after administration. Attributed to incompatibility of major blood group	1
Cord blood allogeneic	Other reaction • Abdominal pain during infusion. Neutropenic fever after infusion, possibly due to urinary tract infection	1
Total		**8**

In 2017, TRIP received one report of a serious donation complication, which was related to autologous stem cell apheresis, which caused a pulmonary embolism. This report is discussed in the 10-year overview of donation complications provided in chapter 3 (see Chapter 3, Table 24).

Summary hematopoietic stem cells and therapeutic cells

In 2017, TRIP received 40 reports of adverse events and reactions related to HSC and therapeutic cells, which means this number has increased significantly in comparison to 2016 (150%). One of these reports has been assessed as serious. Only one of the reports of donation complications TRIP has received has been assessed as serious. There were no reports of serious adverse reactions in recipients. A remarkable statistic is the high number of reports concerning bacterial contamination of bone marrow and PBSC and the high number of reports concerning non-engraftment after a transplant involving cord blood. The extent of the application of allogeneic hematopoietic stem cells from bone marrow and peripheral blood has increased significantly. Chapter 3 will discuss the importance of donor vigilance in more detail.

2.3 Bone and other musculoskeletal tissues

There are eight bone banks in the Netherlands as part of hospitals and orthopedic centers. These banks process, store and distribute bones from living donors (allogeneic femoral heads and autologous cranial bone). Additionally, there are two bone banks that are licensed as organ banks that are not affiliated with a hospital or a clinic. One of these banks processes, stores and distributes post-mortem musculoskeletal tissues. Furthermore, there are eight tissue establishments in the Netherlands that import (post-mortem) musculoskeletal tissues (mainly from the United States) and distribute these around Europe. Lastly, there is one tissue establishments that is licensed to cultivate autologous chondrocytes, but no such activity took place in this establishment in 2017.

Bone

Processing, distribution and application

Table 16 shows the number of units of bone processed and distributed in 2017. Table 17 shows the number of units of bone applied in 2017. These data were supplied by 18 tissue establishments, two independent treatment facilities, 42 oral implantation clinics and 65 hospitals.

Table 16. Processing and distribution of bone tissue in 2017

Type of tissue	Tissue establishments*	Processed		Distributed					
		From on-site clinic	From NL	Unit	In on-site clinic	In NL	In EU	Outside EU	Total
Bone, whole	2	0	183	Bone	0	102	22	0	124
Bone filler, mineralized	10	0	2378	Pack	0	5885	4234	1643	11762
Femoral head, living donor	6	343	2687	Bone	351	1950	45	0	2346
Femoral head, post-mortem donor	4	0	101	Bone	0	89	375	8	472
Bone filler, demineralized	8	0	3364	Pack	0	1087	16330	18234	35651
Auditory ossicles	0	0	0	Graft	0	0	0	0	0
Cranial bone (autologous)	4	34	101	Graft	25	54	0	0	79

** Including bone banks in hospitals (amongst which cranial bone banks) and tissue establishments of which the sole purpose is distribution*

Table 17. Application of bone tissue in 2017

Type of tissue	Hospitals/ clinics/ practices	Recipients	Applications					
			Unit	From on-site clinic	From NL	From EU	From non-EU	Total
Bone, whole	15	78	Bone	0	79	0	0	79
Bone filler, mineralized	78	2827	Pack	0	2484	580	0	3064
Femoral heads (whole or halved)*	60	1365	Bone	351	1390	0	0	1741
Bone filler, demineralized	26	412	Pack	0	338	96	0	434
Auditory ossicles	1	1	Graft	0	1	0	0	1
Cranial bone (autologous)	7	40	Graft	25	29	0	0	54

** Data concerning both living and post-mortem donors, as hospitals do not always register whether the source is the one or the other*

Figure 15 shows the number of bone products used as bone filler that were distributed in the Netherlands from 2008 to 2017. It shows an increase in the distribution of mineralized bone filler. On the other hand, the distribution of demineralized bone filler is decreasing. The number of femoral heads, which are grinded by the transplantation facilities, has remained approximately stable over the course of the previous ten years.

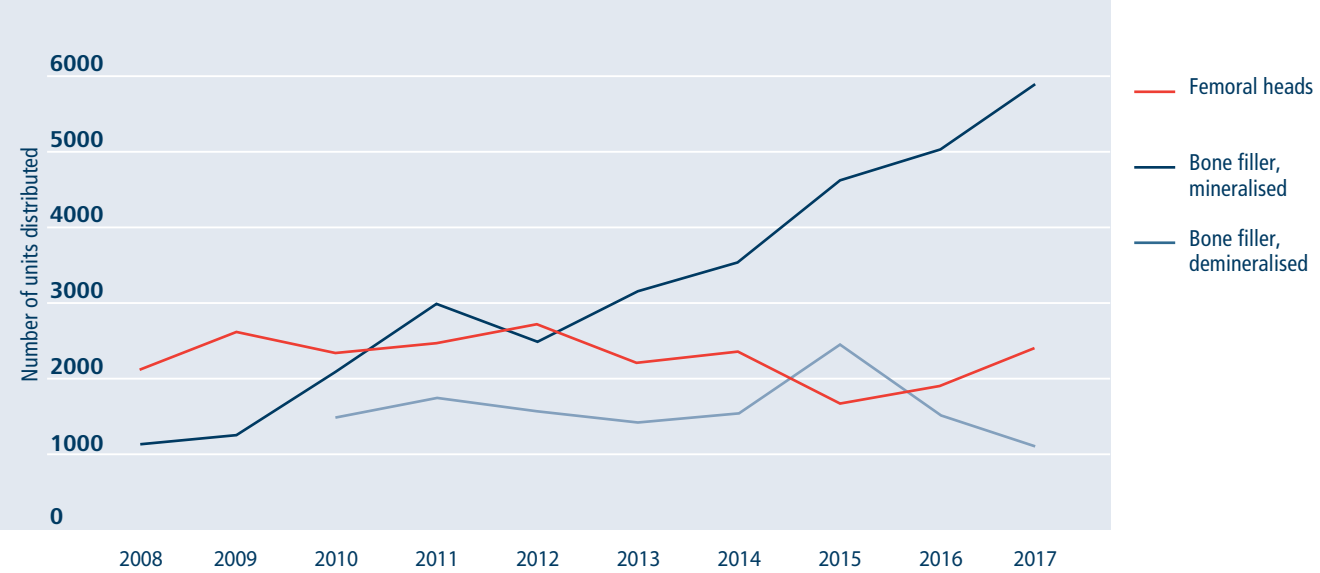


Figure 15. Number of units of bone filler distributed in the Netherlands, 2008-2017

Reports

In 2017, TRIP received seven reports concerning bone tissue, two of which have been classified as serious. One of the most serious complications that is feared for a bone transplant is the transfer of pathogens, as bone infections are difficult to treat. This year, TRIP did not receive any reports concerning a bacterial infection after a bone transplant. Figure 16 provides an overview of the number of adverse reactions and events from 2008 to 2017. Table 18 summarizes the adverse events that occurred in 2017.

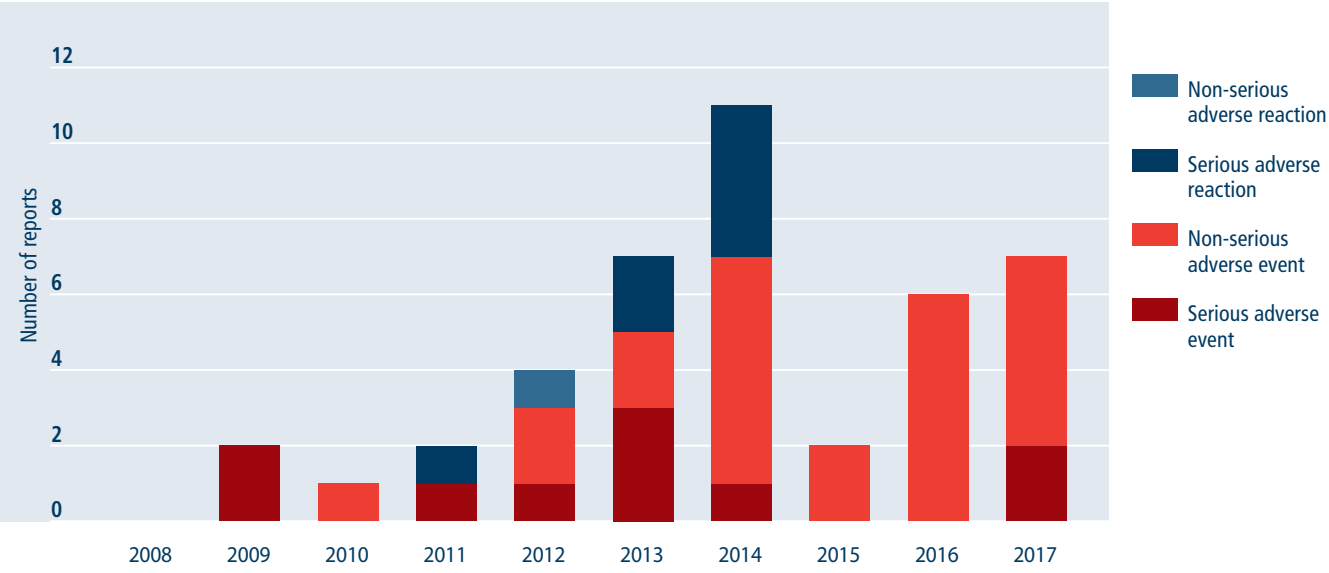


Figure 16. Reports involving bone tissue, 2008-2017

Table 18. Overview of adverse events involving bone tissue in 2017

Category of event	No. of reports	Type of bone tissue	Description
Bacterial contamination of product	1	Bone chips	Positive result in culture done before operation. Staphylococcus Aureus cultured. Results came in after operation for which the bone chips were used. No reaction in recipient*
Loss of tissue or cells	2	Bone chips	As a result of an administrative error, four units of bone chips were labelled incorrectly. Error was discovered before the units were distributed and the units were discarded
		Femoral head	Femoral head disappeared from temporary storage in a transplantation centre. Traceability not ensured.
Incorrect product transplanted	2	Bone chips	Expired unit of bone chips used for an operation. Discovered by bone bank after receiving follow-up form. No reactions in recipient
		Proximal tibia	Expired bone tissue used as an emergency solution, because the tissue that was initially supposed to be used did not fit. Surgeon was aware of expiration. No reaction in recipient
Other incident	1	Femoral head	Femoral head intended for use as bone filler turns out be full of cysts during operation. Donor selection did not adhere to guidelines. Different femoral head used for operation.
Near miss	1	Femoral head (living donor)	Previous risky behaviour discovered prior to donation of second femoral head. Recall of previously donated femoral head. This femoral head turns out not to have been transplanted but discarded.*

* *Serious*

Other musculoskeletal tissues

Processing, distribution and application

Table 19 shows the number of tendons, ligaments, fascia, cartilage and menisci that were processed and distributed in the Netherlands in 2017. Table 20 shows the number of applications of these musculoskeletal tissues. For tendons, ligaments and fascia, there is a considerable difference between the number of units distributed and the number of units applied. This discrepancy could be attributed to hospitals storing these units. At -80°C , tendons may be stored for up to five years. The discrepancy in the processing and application figures for cartilage show that the applying establishments are not taking sufficient care in registering these figures.

Table 19: Processing and distribution of other musculoskeletal tissues in 2017

Type of tissue	No. of tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Tendons	2	911	Graft	577	109	0	686
Bone-tendon-bone grafts	2	49	Graft	27	34	0	61
Ligaments	0	0	Graft	0	0	0	0
Fascia	3	48	Graft	1346	86	0	1432
Cartilage	3	34	Graft	102	0	0	102
Chondrocytes	1	0	Graft	0	0	0	0
Menisci	1	14	Graft	7	5	0	12

Table 20. Application of other musculoskeletal tissues in 2017

Type of tissue	No. of clinics/ hospitals	Recipients	Applications				
			Unit	From NL	From EU	From non-EU	Total
Tendons	44	340	Graft	353	4	0	357
Bone-tendon-bone grafts	7	33	Graft	14	0	0	14
Ligaments	3	7	Graft	0	7	0	7
Fascia	18	390	Graft	353	51	0	404
Cartilage	6	15	Graft	13	2	0	15
Chondrocytes	0	0	Graft	0	0	0	0
Menisci	1	13	Graft	7	7	0	14

Figure 17 displays the development of the number of tendons, ligaments, fascia, cartilage and menisci distributed in the Netherlands from 2008 to 2017. After initially decreasing until 2013, the number of units of cartilage distributed has stably remained around 100 units per year since 2014. In 2017, there was no distribution of cultured chondrocytes as ATMP.

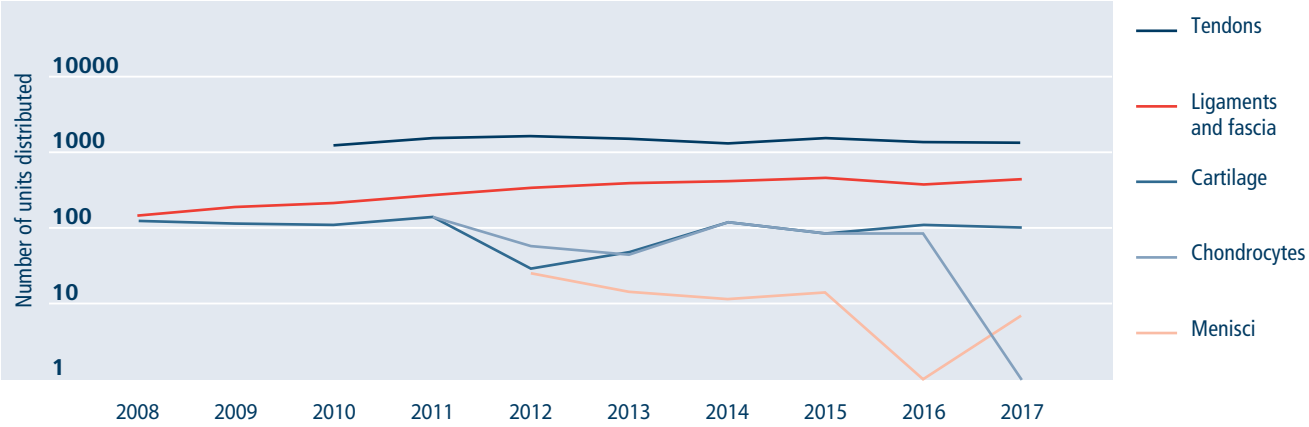


Figure 17. Number of units of other musculoskeletal tissues distributed in the Netherlands, 2008-2017

Reports

In 2017, TRIP received one report concerning a non-serious adverse event involving tendon tissue. This report from 2017 concerns a semitendinous tendon that was delivered to a health care facility, but not used for the recipient. The tendon was not stored in the freezer and thus defrosted. The tendon tissue was lost. As in the previous three years, TRIP did not receive any reports involving cartilage. TRIP has never received any reports involving menisci since it started collecting reports. Figure 18 provides an overview of all reports involving other musculoskeletal tissues that TRIP received from 2008-2017. All reports from 2010 concern adverse events involving culturing autologous chondrocytes. The collection and processing of chondrocytes is subject to the Dutch Law on safety and quality of substances of human origin. That year, two tissue establishments reported seven adverse events to TRIP, six of which were classified as serious. One of these two tissue establishments ceased its practices involving culturing chondrocytes in 2012. The other establishment did not process or distribute any chondrocytes in 2017.

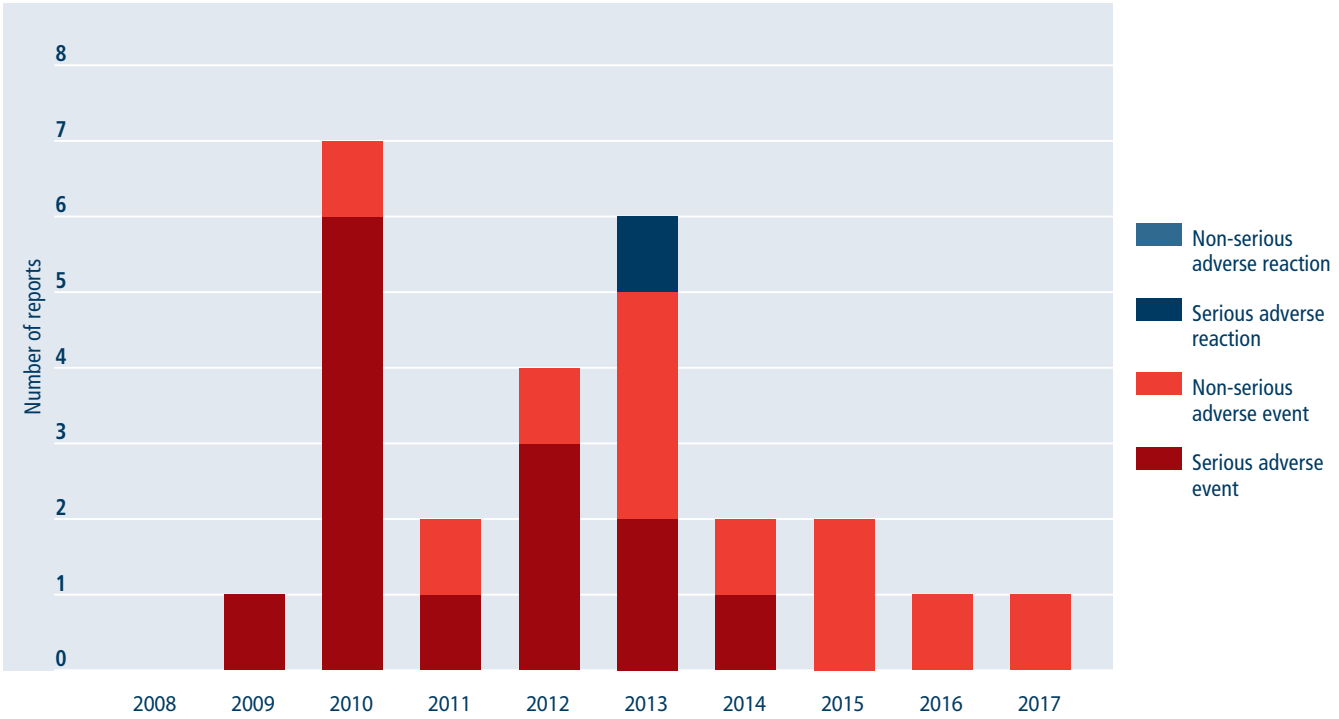


Figure 18. Overview of reports involving other musculoskeletal tissues, 2008-2017

2.4 Ocular tissue

In the Netherlands, cornea and sclera are obtained from post-mortem donors through enucleation of the entire eyeball, which is then processed by one of two eye banks. Corneas have limited shelf life: when stored in a culture medium, a cornea can only remain in optimal condition for up to four weeks. Sclera may be stored for up to a year. Cornea are distributed within the EU and are exported outside the EU. Sclera are not exported. Dutch hospitals and clinics can purchase sclera from tissue establishments licensed by the EU.

Processing, distribution, and application

Table 21 displays the number of units of ocular tissue processed and distributed in the Netherlands in 2017. Table 22 displays the number of units of ocular tissue applied in the Netherlands in 2017, as indicated by hospitals, clinics and independent treatment facilities. Twenty Dutch hospitals and clinics transplant ocular tissue. Sixteen hospitals and clinics transplant cornea, ten of which also transplant sclera. Four transplant sclera only. The difference between the number of units of sclera distributed and the number applied has, again, decreased in comparison to previous years. The numbers concerning corneas do not show a discrepancy. Figure 19 displays the number of units of cornea and the number of units of sclera distributed from 2008 to 2017.

Table 21. Processing and distribution of ocular tissue in 2017

Type of tissue	No. of tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside Eu	Total
Cornea	2	2717	Complete or lamella	1453	179	38	1632
Sclera	1	448	Complete or quadrant	1560	47	0	1607

Table 22. Application of ocular tissue in 2017

Type of tissue	No. of tissue establishments	Recipients	Applications				
			unit	From NL	From EU	From non-EU	Total
Cornea	16	1448	Complete or lamella	1450	16	0	1466
Sclera	14	1185	Complete or quadrant	1185	1	0	1186

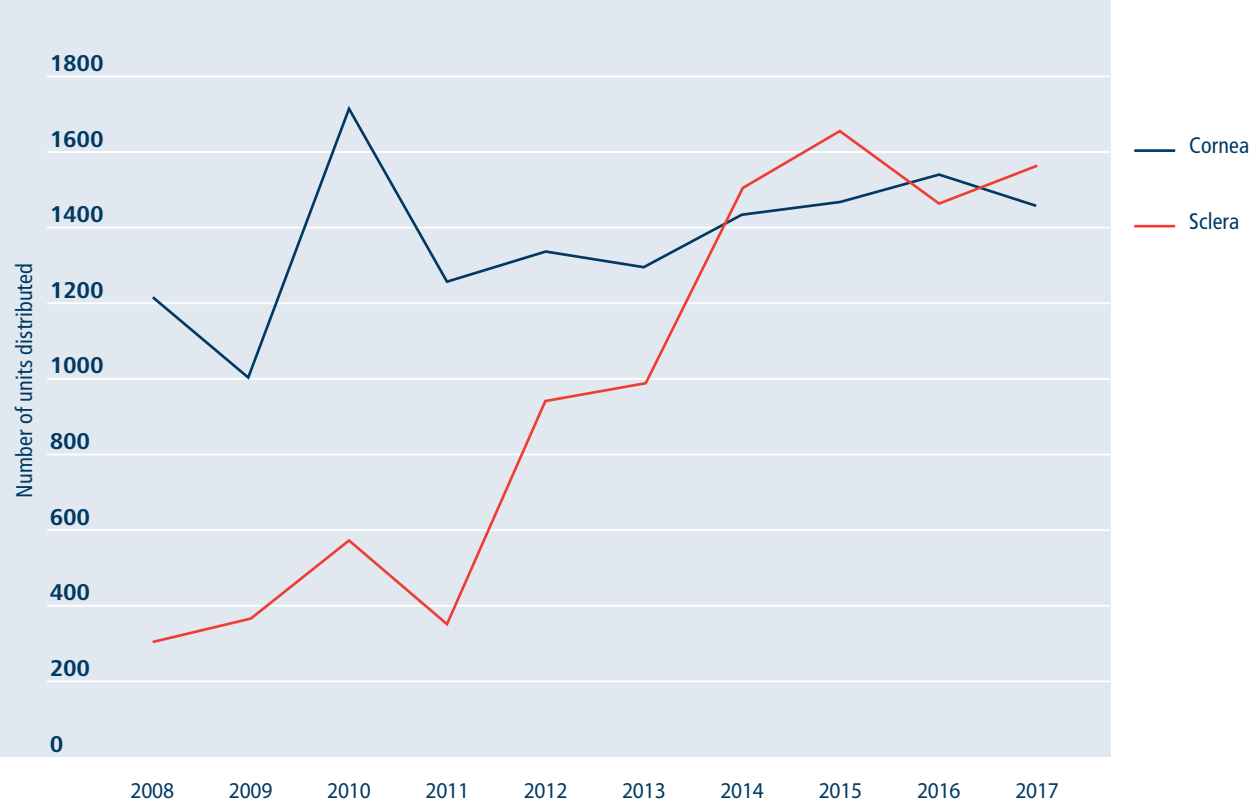


Figure 19. Numbers of units of cornea and sclera distributed in the Netherlands, 2008-2017

Reports

In 2017, TRIP received 11 reports involving ocular tissue. Ten reports concerned adverse events, of which six were classified as serious, one report concerned an adverse reaction, which was also classified as serious. The reports were made by two tissue establishments and one transplant center. The reports are summarized in Table 23. Figure 20 displays an overview of all reports involving ocular tissue received from 2008 to 2017.

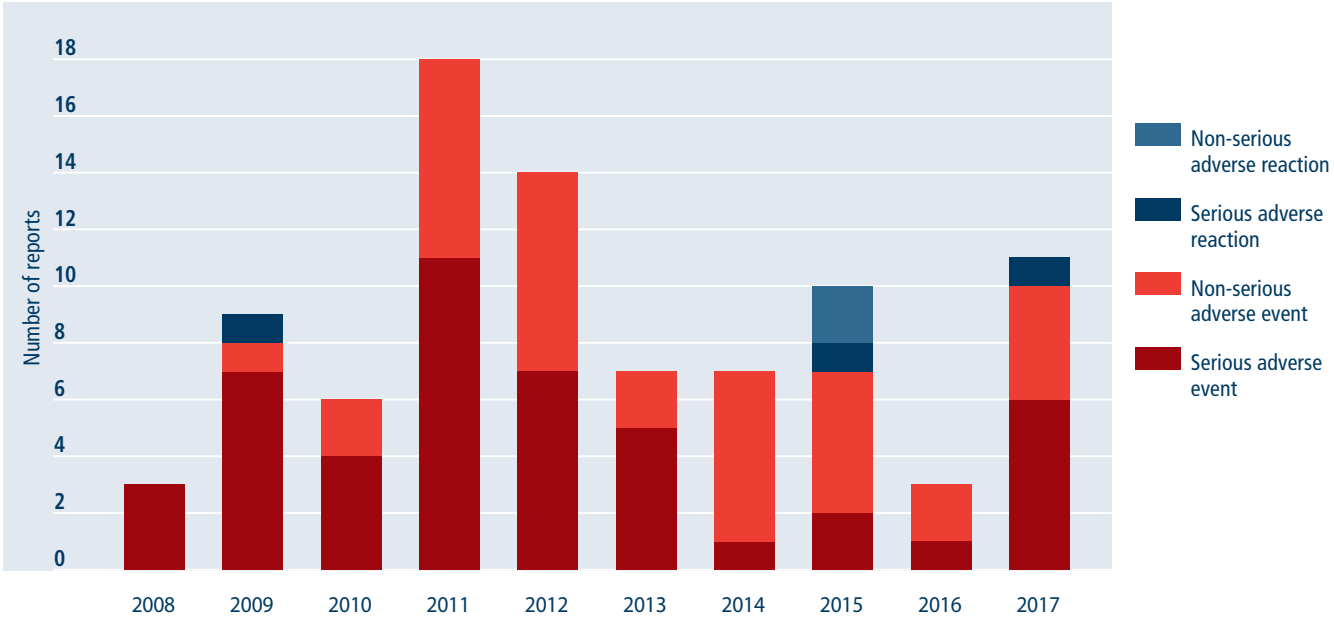


Figure 20. Reports involving ocular tissue, 2008-2017

Table 23. Overview of adverse reactions and events involving ocular tissue in 2017

Category of event	Number of reports	Description
Risk of transfer of other condition	4	In three cases, the donor's autopsy report mentions a haematological malignity after the donor's corneas have already been transplanted. Haematological malignity are contra-indications for donation*
		After a transplant of both corneas, a microscopic study of the brains indicates amyloid angiopathy. Further studies rule out a prion condition
Bacterial contamination of product	1	Positive results indicating the presence of Mycobacterium chelonae-abscessus in preoperative and peroperative cultures of the transplanted cornea lamella (DMEK**). Possible source of contamination is melting icewater from (damaged) bags used for transport of bulbi. After issues arising with the transplant, the decision is made to redo the transplant*
Other incident	3	A fold in a cornea lamella (DMEK**) turns out to be a tear during transplantation. Ophthalmologist applies a different transplantation technique, transplanting only 60% of the lamella. Recipient's vision is sufficiently restored using this technique
		A study of a donated mitral valve indicates acute endocarditis. Both corneas have already been transplanted, without any issues*
		Collagen disease cannot be ruled out in a donor. Sclera should have been discarded. However, sclera are wrongly distributed, despite this information being known. Sclera-units have already been transplanted when error is detected. No issues in recipients reported
Incorrect product transplanted	1	Identification error with the cornea during distribution to the transplanting facility. Cornea turns out to be suitable for transplantation and is transplanted. No consequences for recipient
Loss of tissue or cells	1	Donor blood is sent to an incorrect address, which inhibits carrying out screenings for infection diseases. As a result, the donated corneas cannot be used for transplantation*
Category of reaction		**Description**
Other reaction	1	Clouding of the cornea after transplant (see Image 4). Ahead of the transplant, there were no indications of any abnormalities in the cornea. The transplant is redone*

* *Serious*

** *Descemet Membrane Endothelial Keratoplasty*

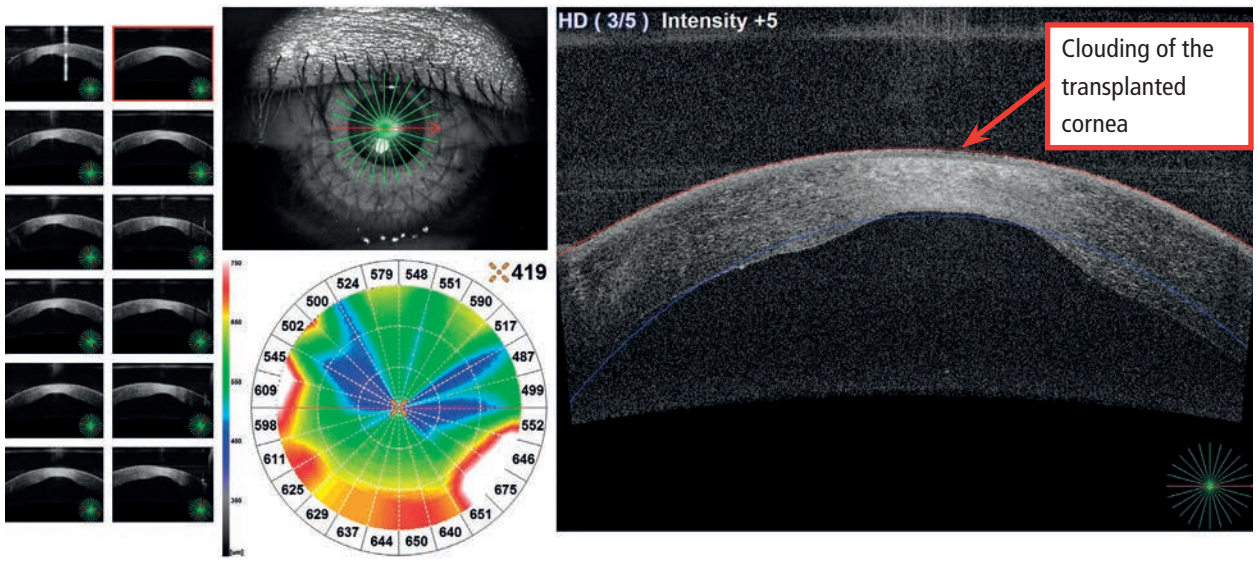


Image 4. Optical Coherence Tomography and pachymetry of cornea showing clouding

2.5 Cardiovascular tissue

Processing, distribution, and application

Tables 24 and 25 show the processing, distribution, and application figures of cardiovascular tissue in 2017. The Netherlands has one cardiovascular tissue bank. Five health care institutions have transplanted heart valves in 2017. Furthermore, two hospitals applied vascular patches and two hospitals applied pericardia. Figure 21 displays the number of transplanted cardiovascular tissues from 2008 to 2017.

Table 24. Processing and distribution of cardiovascular tissue in 2017

Type of tissue	No. of tissue establisments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Aortic valves	1	159 *	Graft	27	4	0	31
Pulmonary valves	1	159 *	Graft	80	9	0	89
Vessels	1	18	Graft	1	4	0	5
Patches	1	65	Graft	28	9	0	37
Pericardia	1	0	Graft	88	0	0	88

* *Donor hearts*

Table 25. Application of cardiovascular tissue in 2017

Type	No. of tissue establisments	Recipients	Applications				
			Unit	From NL	From EU	From non-EU	Total
Aorta kleppen	4	37	Graft	27	10	0	37
Pulmonaal kleppen	4	96	Graft	80	16	0	96
Vaten	1	1	Graft	1	0	0	1
Patches	5	53	Graft	28	25	0	53
Pericard	2	9	Graft	1	8	0	9

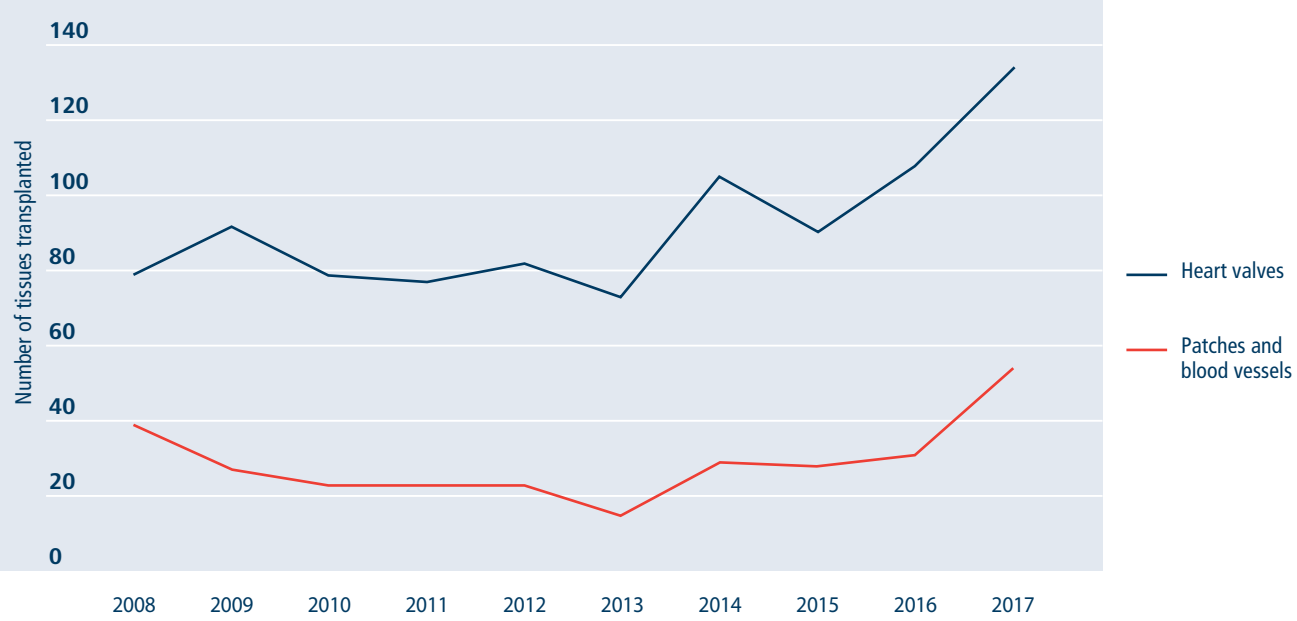


Figure 21. Number of cardiovascular tissues transplanted, 2008-2017

Data collected from Dutch Transplantation Foundation and, from 2013 onwards, TRIP reports

Reports

As in 2015 and 2016, TRIP did not receive any reports involving cardiovascular tissue in 2017. Since 2008, TRIP has received seven reports involving cardiovascular tissue, five of which have been classified as serious. All reports involving cardiovascular tissue concern heart valves (both aortic valves and pulmonary valves).

2.6 Skin

Processing, distribution and application

The Netherlands has one large skin bank, which processes, stores, and distributes donated skin. Skin tissue is subdivided into three categories: donor skin, autologous skin, and acellular dermis. Table 26 displays the number of units of skin tissue processed and distributed in 2017. Donor skin is applied most often, particularly in burn patients as a temporary wound cover. A large part of the distribution of donor skin occurs outside of the Netherlands. Furthermore, the Netherlands has three distributors for acellular dermis, one of which did not distribute any acellular dermis in 2017. Table 27 displays the number of units of skin that were applied in 2017. The difference between the number of units processed and distributed and the number of units applied can be attributed to the fact that hospitals and burn centers store units of donor skin. Figure 22 shows the number of units of skin and skin products distributed from 2008 to 2017.

Table 26. Number of units of skin processed and distributed in 2017

Type of tissue	No. of tissue establishments	Processed NL/EU	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Donor skin	1	362 / 50 *	Pack	1732	7600	5942	15274
Acellular dermis	3	29 / 0 *	Graft	224	186	204	614

* *Donors*

Table 27. Number of units of skin applied in 2017

Type of tissue	No. of clinics/ hospitals/ practices	Recipients	Applications				
			Unit	From NL	From EU	From non-EU	Total
Donor skin	7	64	Pack	1181	11	0	1192
Autologous skin	2	31 *	Graft	31	0	0	31
Acellular dermis	7	77	Graft	74	3	0	77

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

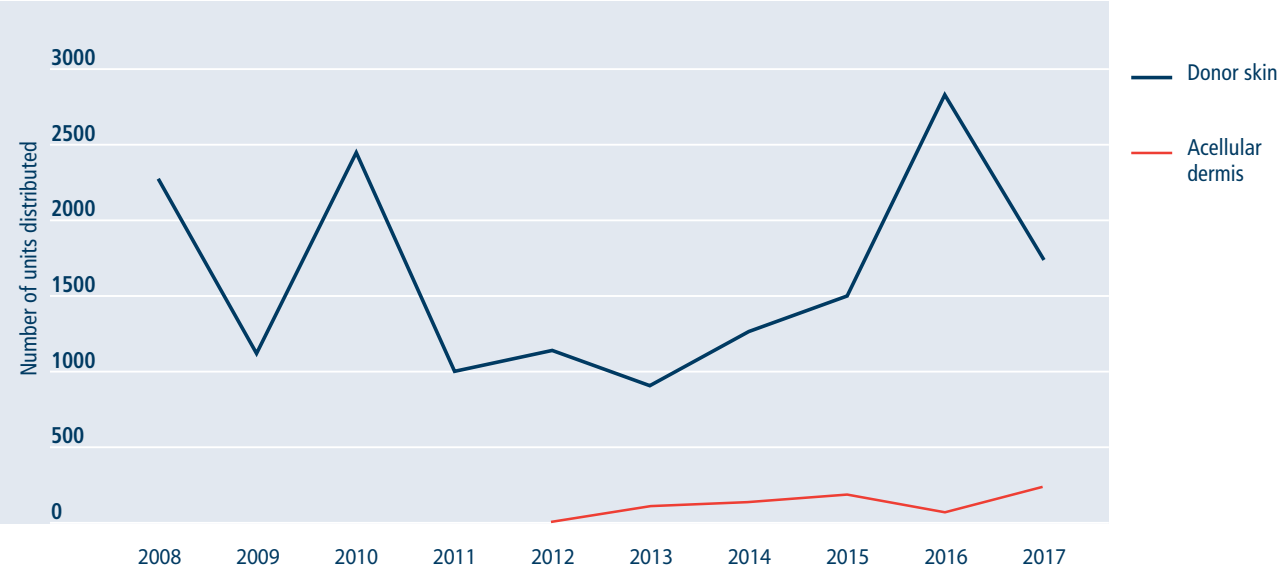


Figure 22. Number of units of skin and acellular dermis distributed, 2008-2017

Reports

In 2017, TRIP did not receive any reports involving skin tissue. The development of the number of reports involving skin tissue from 2008-2017 is shown in Figure 23. The relatively large number of reports in 2014 can be attributed to a number of reports concerning complicated courses of action related to transplants of cultured autologous skin for patients suffering from chronic ulcers, which were not product-related.

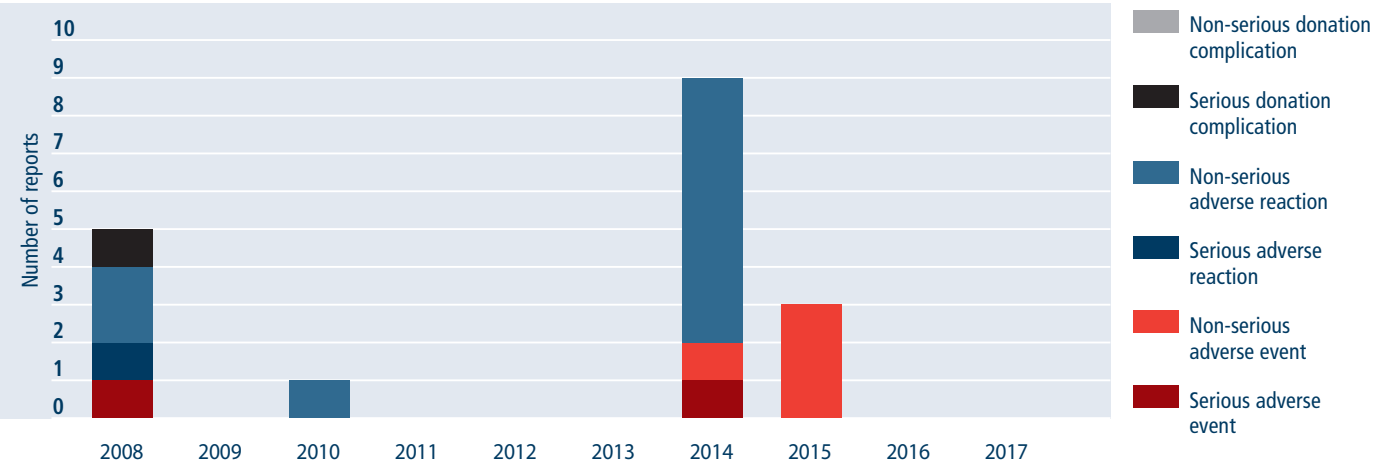


Figure 23. Reports involving skin or skin tissue, 2008-2017

2.7 Other tissues and cells

The category for 'other tissues and cells' encompasses a wide variety of different types of tissues and cells, such as: amnia, pancreatic islets, umbilical cord tissue, adipose tissue, radioactively labelled red blood cells and leukocytes intended for autologous diagnostic purposes.

Processing, distribution and application

Tables 28 and 29 below show, respectively, the number of units of other tissues and cells processed and distributed, and the number of units of other tissues and cells applied.

Table 28. Processing and distribution of other tissues and cells in 2017

Type of tissue	Tissue Establishments	Processed NL / EU / non-EU	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Amnia	2	1* / 4* / 0	Pack	149	260	0	409
Pancreatic islets	1	60** / 2** / 0	Graft	8	0	0	8
Umbilical cord tissue	1	96 / 1125 / 117	Graft	0	0	0	0
Glioma tumour tissue	1	0 / 3 / 11	Graft	0	0	0	0
Red blood cells***	1	32 / 0 / 0	Bag	32	0	0	32
Leukocytes***	1	127 / 0 / 0	Bag	127	0	0	127

* *Placentas*
** *Pancreases*
*** *Radioactively labelled for diagnostic purposes*

Table 29. Application of other tissues and cells in 2017

Type of tissue	Hospitals/ clinics	Recipients	Applications				
			Unit	From NL	From EU	From non-EU	Total
Amnia	5	78	Pack	85	0	0	85
Pancreatic islets	1	8	Graft	8	0	0	8

Reports

In 2017, TRIP did not receive any reports involving other tissues or cells. Throughout TRIP's years of collecting data, it has only received two reports involving this category of tissue types: one report concerning loss of a granulocyte product and one report concerning an amnion.

CHAPTER 3

The challenge of donor vigilance

3.1 Introduction

Without donors donating tissues and cells, transplantation would not be possible. In some cases it is possible for a patient to "donate" their own (autologous) tissues or cells (stem cells, reproductive cells, musculoskeletal tissues and skin). However, in many cases this is not possible and transplants require donated tissues or cells from related or unrelated allogeneic donors. In some cases tissues and cells are donated post-mortem, but other donations come from living donors.

Complications occurring during the donation process do not necessarily impact the safety and quality of the donated tissues or cells. However, donation should always be as safe as possible, aiming to avoid or minimise complications. Donor vigilance may be defined as the systematic monitoring of adverse reactions and incidents throughout the entire chain of care for donors of human tissue and cells, aiming to improve the safety and quality of donation (derived from definition of hemovigiliance in Haemovigilance: an effective tool for improving transfusion practice, R.R.P. de Vries and J.C. Faber (eds), Wiley, 2012).
The Decree on requirements for substances of human origin, article 1.1, part of the Dutch Law on safety and quality of substances of human origin, defines serious adverse reaction as follows:

> An unintended response, including a communicable disease, in **the donor** or in the recipient, associated with the **procurement** or human application of tissues and cells or occurring throughout the chain from **donation** to transplantation in the donor or the recipient, that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity.

This definition shows that serious donation complications should also be considered as serious adverse reactions that are part of the donation chain. In the Netherlands, cells and tissues are donated voluntarily, without monetary compensation. An allogeneic donor has to be healthy. Firstly, the donated material should be safe for the recipient(s) of these tissues or cells. Secondly, but not less importantly, donation must occur safely. Donor vigilance gives us gain insight into the safety of donations, make recommendations to improve safety, and to inform potential future donors of the risks of donation.

The World Health Organisation (WHO) has set out guidelines for protecting the safety of living donors. Also, in collaboration with the Italian National transplant center (CNT), the WHO has set up a world-wide database of didactic examples of reactions and incidents related to blood, human tissues, cells, and organs. This so-called NOTIFY Library provides informative and well-documented case reports of reactions and incidents (www.notifylibrary.org). Competent authorities and recognised biovigilance systems supply anonymized reports to the database and more recently hemovigilance systems have also started to do so. Anyone may consult and search the database. The NOTIFY Library also includes reports of (serious) donation complications. The taxonomy that was developed for these reports is shown in Table 30.

Table 30. NOTIFY taxonomy 'Harm to a donor'

Level 1	Level 2	Level 3
Harm to a donor (donation complication)	Allergic reaction	Local Systemic/anaphylactic
	Drug related reactions	GCSF-related Ovarian hyperstimulation syndrome
	Embolic complications reactions	Air embolism Fat embolism Thromboembolism
	Excessive collection/removal	
	Infection	
	Malignancy	
	Miscellaneous complications	Anesthetic agents Cardiovascular Catheterization/Intubation Gastrointestinal Immunological Insertion of needle Metabolic Neurological Psychological Pulmonary Surgical site
	Procurement outside legal framework	
	Toxicity	
	Undue exposure to risk/intervention	
	Vasovagal Reactions	
	Other	

3.2 Donor vigilance in the EU

TRIP follows the 'Common approach for reportable serious adverse events and reactions as laid down in the tissues and cells Directive 2004/23/EC' for reporting donation complications. As of version 2.2. (2013), it recommends as followings.

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 hyperstimulation syndrome (OHSS) as an exaggerated response to the use of ovulation induction medications
- Reactions to Granulocyte colony stimulating factor (G-CSF) for 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 on a voluntary basis. An additional non-mandatory section 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.

Figure 24 shows the number of reports of serious donation complications that the European Commission has received from 2010. From 2014 onwards, over 600 serious donation complications have been reported annually, by, on average, 18 of the 28 EU member states and Norway (62%).

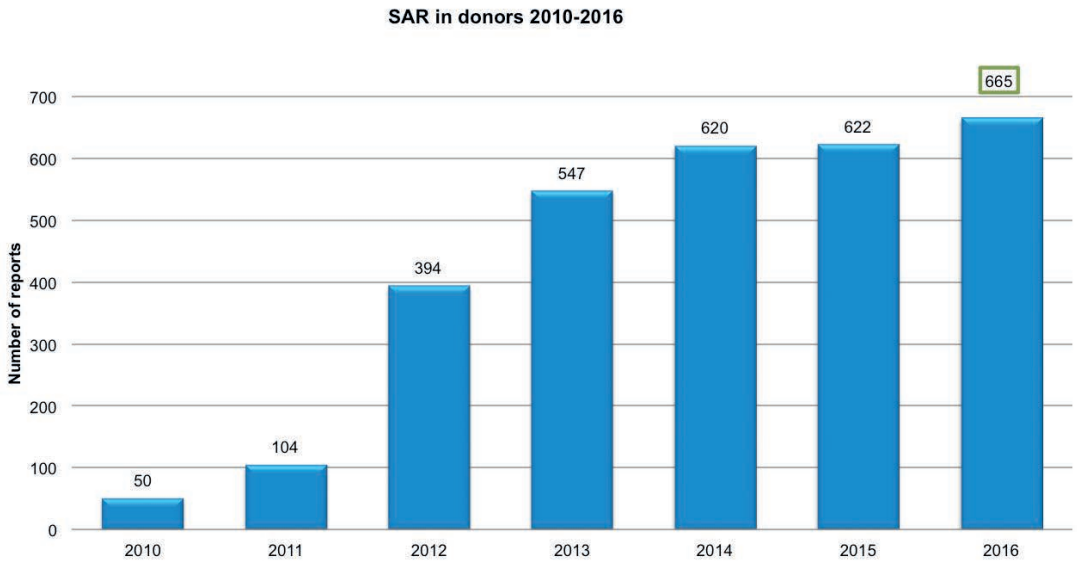


Figure 24. Number of serious donation complications in the EU, 2010-2016
From "Summary of the 2017 annual reporting of serious adverse events and reactions for Tissues and Cells, data from 01/01/2016 to 31/12/2016"

Figure 25 shows the donation complications in the EU from 2010 to 2016, categorized according to the type of donation complication. The first clear guidance for when and how donation complications could be reported was given in the 'Common approach for reportable serious adverse events and reactions as laid down in the tissues and cells Directive 2004/23/EC, version 2.2 (2013)'.

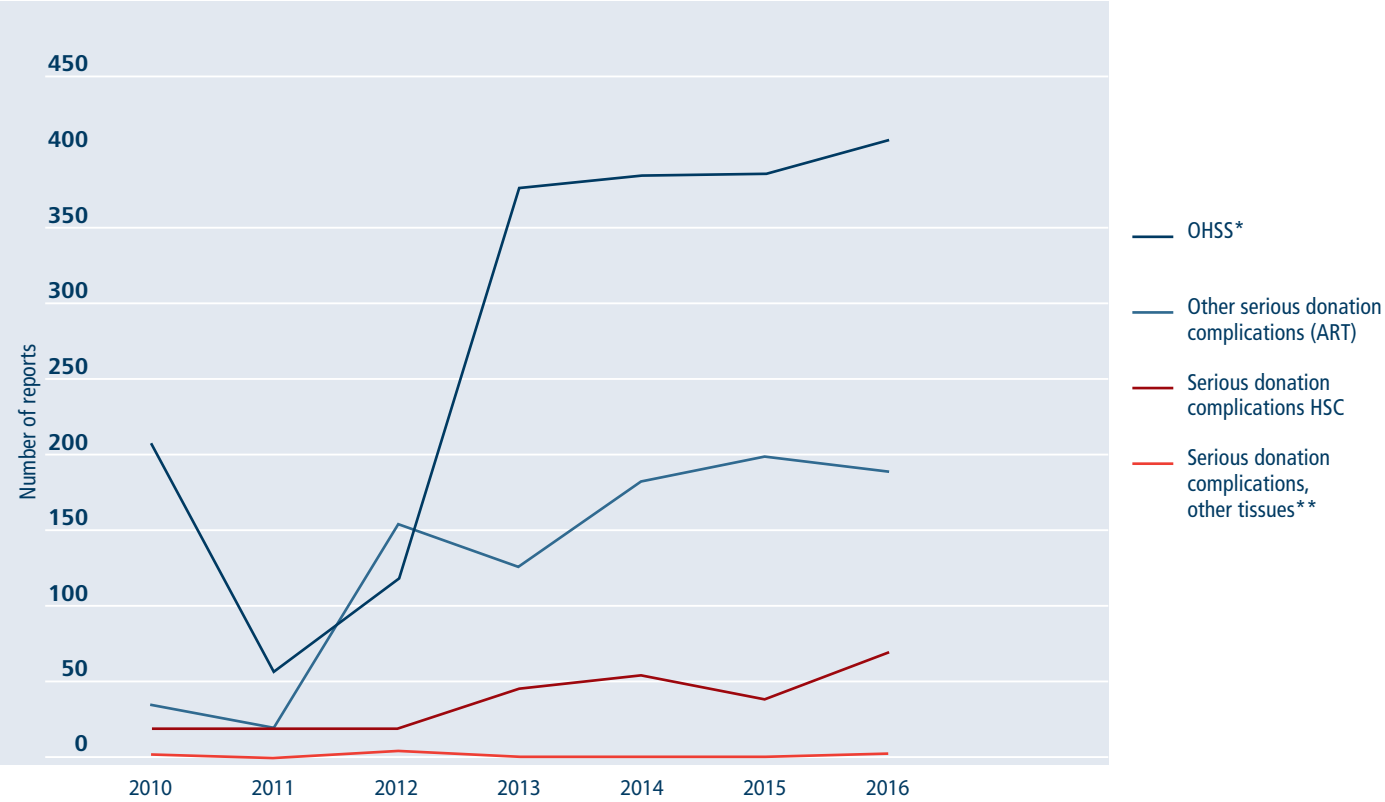


Figure 25. Reports of serious donation complications in the EU, 2010-2016[1]

* *Ovarian hyperstimulation syndrome*

** *Donation complications in donors of skin/keratinocytes, cartilage/chondrocytes or other musculoskeletal tissues*

[1] In 2010, serious reports of ovarian hyperstimulation syndrome (OHSS) were reported as serious adverse reactions, whereas they should have been reported as serious donation complications. Because of a lack of clarity on the reporting of OHSS in 2011, significantly fewer cases of OHSS were reported that year.

In the ongoing evaluation of European legislation, there have been calls to include donor vigilance in the scope of the Directive 2004/23/EC, even though there may be no influence on the quality and/or safety of the donated human tissue.

3.3 Donation of gametes

In some cases, donated gametes are required to fulfil a desire to have children. Knowledge of the use of donated semen is widespread. Donated semen is used for IUI and IVF/ICSI. However, in some cases the cause for reduced fertility or infertility lies with the woman. Women, due to various causes, may not (or no longer) produce oocytes. In such cases, the use of donated oocytes may offer a solution. In the Netherlands, the donation of gametes and embryos is legal. In addition, intra-relational oocyte donation is possible (donation within a lesbian relationship). As with all other donations, donors do not receive any monetary compensation for donating gametes or embryos. Hence, donation occurs out of altruistic motives. For oocyte donation, donors do receive reimbursement for expenses (travelling expenses, day care for children, loss of income, etc.) Outside the EU (for instance in the United States and Ukraine), it is not unusual for women to receive monetary compensation for oocyte donation. For some women this provides an important source of income. However, with multiple successive donations there is an increased risk of donation complications. Furthermore, the possibility of exploitation of women is not inconceivable in this kind of system.

Semen (donated by partners or other donors) is easily procured through masturbation. Only in a very limited number of cases is surgical procurement of semen (PESA/MESA or TESE) or electrostimulation required. During PESA/MESA or TESE, complications may occur, as is possible during any surgical

procedure. The most important complications are hemorrhage or infections in the epididymis or the testicle. There are no known cases of donation complications related to the procurement of semen in the Netherlands, the EU or the NOTIFY library.

Both with the use of autologous oocytes and the use of donated oocytes, complications from stimulation or Ovum Pick Up are classified as donation complications. The classification of the severity of donation complications is based on the same guidelines as the severity assessment of complications in recipients. For the procurement of oocytes, the follicles in the ovaria are aspirated after medicinal ovarian stimulation. This stimulation may result in complications. One of the possible complications is ovarian hyperstimulation syndrome.

Ovarian hyperstimulation syndrome

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication that may occur as a result of treatment of anovulation through ovulation induction or controlled ovarian hyperstimulation as part of medically assisted reproduction. With 0.1-2% of these treatments serious OHSS occurs. OHSS develops during the luteal phase of the menstrual cycle, especially after stimulation using gonadotrophin, in particular in combination with a GnRH agonist. The syndrome almost only occurs if hCG is administered or produced as a result of pregnancy. OHSS is characterized by symptoms such as abdominal bloating, abdominal pain, dyspnea and general discomfort as a result of enlarged ovaria, ascites and reduced organ perfusion. The precise cause of OHSS is not yet known and no causal therapy can be implemented so the focus must be on prevention of the syndrome. Preventive measures could be taken before or during ovulation induction or controlled ovarian hyperstimulation. However, even if all appropriate measures are taken, it is not possible to prevent of OHSS in all cases. Treatment of OHSS consists of supportive care and treatment of its symptoms. If the syndrome occurs, the care for the patient should include looking out for possible complications, in particular for thromboembolic processes. OHSS is subdivided into three levels of severity: light to moderate; serious; and very serious. Hospitalization is indicated for all serious cases.
(Source: Dutch Society for Obstetrics and Gynaecology, Guidelines Ovarian hyperstimulation syndrome, version 2.0, translation by TRIP)

Additionally, the aspiration of oocytes (Ovum Pick Up) presents a risk of complications such as damage to surrounding organs or tissues, hemorrhaging, and infections.

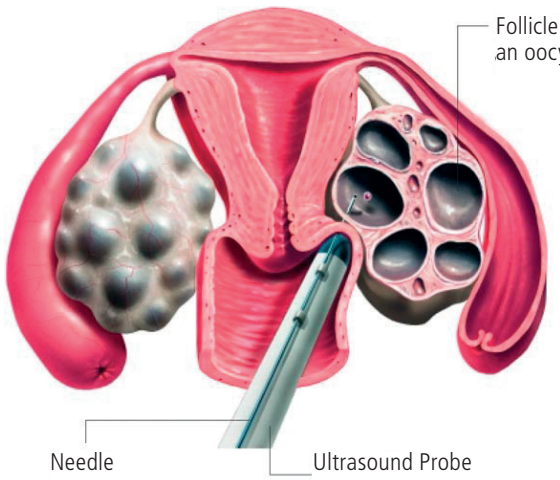


Image 5. Follicle aspiration (Ovum Pick-up)

There is only a small risk of a complication as a result of the procurement of oocytes. However, if complications do occur, these may be severe and can lead to hospitalization and loss of fertility. Hence, the monitoring of donation complications related to the donation of oocytes is valuable.

Table 31 provides an overview of the reports of donation complications related to the procurement of oocytes in the Netherlands that TRIP has received since 2015. Table 32 shows the number and types of serious donation complications that have been reported to the European Commission.

Table 31. Overview of reports of donation complications related to the procurement of oocytes in the Netherlands, 2015-2017

Donation complication	Autologous oocyte donation	Allogeneic oocyte donation	Total
OHSS*	8	0	8
Bladder lesion	2	1	3
PID**	0	3	3
Ovarian rupture	0	1	1
Hemorrhage	1	0	1

* *Ovarian hyperstimulation syndrome*
** *Pelvic inflammatory disease*

In the Netherlands, approximately 14.000 stimulations for the procurement of oocytes take place every year. In three years, 16 serious donation complications have been reported. This equates to one serious donation complication per 2625 stimulations (0.04%).

Table 32. Overview of reports of serious donation complications related to donation of oocytes in the EU, 2012-2016

Year	OHSS*	Infections	Surgical complications (incl. anesthetics)	Other complications	Total
2012	118	32	68	53	271
2013	376	39	49	38	502
2014	384	26	95	50	555
2015	386	27	103	68	584
2016	413	30	90	43	576

* *Ovarian hyperstimulation syndrome*

In the Netherlands, pharmacovigilance (the registration of adverse reactions associated with the use of pharmaceuticals) is carried out by Lareb. This vigilance system has received three reports of OHSS since 1996, which shows that at least some cases of OHSS have (also) been reported to Lareb. In general, pharmacovigilance reports to Lareb primarily concern adverse reactions that are serious, new or less known.

As of July 2018, the NOTIFY Library included five donation complications related to the donation of oocytes. It must be noted that NOTIFY does not aim to include all known cases in its database; rather it aims to register those cases which can provide valuable didactic examples for health care professionals to learn from. Table 33 shows these donation complications, classified according to the Notify taxonomy.

Table 33. Donation complications related to the procurement of oocytes registered in NOTIFY Library (as of July 2018).

Level 2	Level 3	Examples
Drug related reaction	Ovarian hyperstimulation syndrome	
Infection		Pelvic inflammatory disease
Miscellaneous complications	Surgical complication	Hemorrhaging

3.4 Donation of hematopoietic stem cells and therapeutic cells

Hematopoietic stem cells (HSC) are given to patients whose own blood stem cells need replacement because of disease or insufficient functioning. Treatments can be carried out using a patient's own HSC (autologous), HSC from an allogeneic donor with a compatible Human Leukocyte Antigen (HLA) tissue type (a family member or an unrelated donor) or HSC from HLA-compatible cord blood.

Image 6. Peripheral blood stem cell apheresis

Autologous and allogeneic HSC can only be procured from bone marrow or from peripheral blood (peripheral blood stem cells: PBSC). Stem cells are procured from bone marrow through multiple punctures of the pelvic brim while the patient is under general anesthesia. PBSC are collected through apheresis, after a four-day treatment using a granulocyte colony stimulating factor (GCSF). Over the past 20 years, treatment of hematological disorders in adult patients has been increasingly performed using PBSC, in part because the potential number of stem cells that can be harvested using PBSC techniques is larger. Therapeutic cells from a donor (donor lymphocyte infusion, DLI) are often applied as supportive treatment after a stem cell transplantation.

World Marrow Donor Association (WMDA)
Since the harvesting/collecting of hematopoietic stem cells from voluntary non-related donors began, a key prerequisite for all parties involved in the process has been ensuring the safety of donors. Because donating bone marrow or PBSC is not in the interests of the donor's own physical health, donor registries and transplant centres must consider both the medical and ethical aspects of the donation procedure. One of the main purposes of establishing the WMDA was to develop an internationally acknowledged set of Standards for all aspects of care for non-related donors.

Since 2007, TRIP has also received and registered reports concerning complications that occurred during or after donation of both autologous and allogeneic stem cells and of therapeutic cells. Many donation complications which are reported in relation to donation of hematopoietic stem cells concern diagnoses of pathologies that occur regularly in the general population as well, and of which the imputability to the donation is considered unlikely, or at most possible. In total, over the past 11 years, TRIP has received 22 reports of donation complications related to collection of hematopoietic stem cells or therapeutic cells. Table 34 provides an overview of these reports.

Table 34. Overview of donation complications related to hematopoietic stem cells or therapeutic cells in the Netherlands, 2007-2017

Type of stem cell	Number	Donation complication	Interval from donation	Imputability
PBSC allogeneic unrelated	7	IgA nephropathy	During GCSF* stimulation	probable
		Tetany and laryngo-spasm due to hypocalcaemia	During procedure	certain
		Phlebitis	During procedure	probable
		Stroke	2 months	unlikely
		Breast cancer	2 years	unlikely
		Polyarthritis rheumatica	4 years	unlikely
		Rheumatoid arthritis	6 years	unlikely
PBSC allogeneic, related	8	Deep venous thrombosis followed by pulmonary embolism	During procedure	certain
		Transient rise of creatinine level	During procedure	probable
		Benign paroxysmal positional vertigoid	Immediately	probable
		Exacerbation of asthma and back pain	7 days	probable
		Shoulder abscess (S. aureus)	12 days	possible
		Inflammatory bowel disease	6 months	possible
		MDS-RAEB	5 years	possible
		AML	7 years	possible
PBSC autologous	4	Thrombocytopenia	During apheresis	certain
		Pulmonary embolism	During apheresis	probable
		Pulmonary embolism	During apheresis	possible
		Splenic rupture	2 days	certain
Donated lymfocytes, related	1	Vitiligo	6 months	possible
Bone marrow, unrelated	2	TIA	8 months	unlikely
		Breast cancer	2 years	unlikely
Total	**22**			

** Granulocyte colony stimulating factor*

In the Netherlands, Lareb registers adverse reactions related to pharmaceuticals (pharmacovigilance). Since 2001, Lareb has received 327 reports concerning adverse reactions related to the use of a hematopoietic stimulating factor. The European Union collects all data related to donation complications. Table 35 shows the donation complications related to donation of hematopoietic stem cells in each annual report to the EC.

Table 35. Serious donation complications related to donations of hematopoietic stem cells in the EU, 2012-2016

	Malignancies	CCardio-vascular and pulmonary reactions	Neurological reactions	Toxicities (citrate)	Allergic reactions (e.g. to GCSF)	Infections	Other reactions	Total
2012	3	3	0	1	1	0	11	19
2013	4	0	4	7	4	0	27	46
2014	0	3	9	8	6	0	27	53
2015	0	3	9	6	12	3	12	45
2016	4	8	1	14	15	5	21	68
Total	11	17	23	36	38	8	98	231

As of spring 2018, 153 donation complications in donors of HSC are listed in the NOTIFY library; the majority of these complications are short-term complications (during or shortly after the donation process). Table 36 gives an overview of the types of complications described in the NOTIFY library.

Table 36. Complications related to stem cell donation described in the NOTIFY library (as of july 2018)

Level 2	Level 3	Examples
Allergic reaction	Local (atopic dermatitis)	
Drug related reaction	GCSF-related	splenic rupture; TIA; macroscopic hematuria due to IgA nephropathy
Embolic complication	Air embolism	
	Fat embolism	
	Thromboembolism	thrombosis after central venous catheter; pulmonary embolismpneumonie, osteomyelitis, sepsis
Infection		pneumonia; osteomyelitis; sepsis
Malignity		acute myeloid leukemia; Hodgkin lymphoma
Miscellaneous complications	Anesthetic agents	pancreatitis; malignant hyperthermia
	Cardiovascular	pulmonary edema; shock; sudden cardiac death
	Catheterization/intubation	laryngospasm; dysphagia; hemopneumothorax
	Gastrointestinal	ileus; enteritis
	Immunological	sarcoidosis; rheumatoid arthritis; hypo/hyperthyroidism
	Insertion of needle	hematoma; pseudo-aneurysm
	Neurological	epileptic fit; transverse myelitis
	Psychological	suicidal ideation
	Surgical site	iliac fracture; iliac artery injury; nerve injury
Toxicity		citrate-induced hypocalcaemia
Vasovagal reactions		hypotension; nausea; fainting
Other		urolithiasis; transfusion reaction

In contrast to what is the case for unrelated donors, follow up and registration of complications in related donors are not well organised. On the one hand, this stems from the fact that reporting of donation complications in related donors is mandatory only if the donation complication affects the quality of the donated tissues or cells intended for transplantation (and as such may affect the recipient). But in addition there is no long-term follow up for related donors and thus no registration of long-term effects. In order to safeguard the health of donors, for both related and unrelated donors, insight in the occurrence and characteristics of donation complications is important. This insight may contribute to the continuous improvement and high qualityof donor care. Internationally, donation complications in unrelated donors are reported to and registered by the WMDA. In the Netherlands, donation complications in autologous and related donors may, in the same way as donation complications in unrelated donors, be reported to TRIP.

3.5 Donation of other tissues and cells

Tissues are typically donated by post-mortem donors. Some tissues can also be donated by living donors or be procured from patients themselves. The procurement of autologous tissue to be transplanted elsewhere during the same procedure can also result in complications. Mostly, these donations concern musculoskeletal tissues, blood vessels, and skin. Autologous keratinocytes and chondrocytes can be cultured for use at a later time. The procurement of these may also result in complications.

The most frequent tissue donations by living donors are donation of femoral heads donatied after hip replacement surgery. Complications which may arise are not regarded as donation complications, because the removal of the femoral head is part of the hip replacement surgery. Additionally, some living donors donate placentas, which can be used to procure amnion. There are no risks involved in donating placentae.

In the Netherlands, there has been one report, in 2008, of thrombosis after an autologous skin donation harvested in order toculture an autologous skin graft. TRIP has received no further reports of complications related to donation of tissues and cells. In the mandatory submission to the EC, nine serious donation complications related to the donation of other tissues and cells were reported: seven reports related to donation of musculoskeletal tissues, one report related to the donation of ocular tissue and one report related to the donation of other tissues.

The NOTIFY Library includes 15 reports of donation complications related to the donation of musculoskeletal tissues (ribs, iliac crests, (proximal) tibia, (part of) a tendon or ligament). Table 37 shows the different types of donation complications registered. Complications related to donations of tissue mostly occur in relation to (autologous) donations of musculoskeletal tissues.

Table 37. Types of donation complications related to donation of other tissues in NOTIFY Library (as of July 2018)

Level 2	Level 3	Examples
Infections	Surgical site	persistent pain; fractures; bleeding; loss of function; injury to surrounding tissues
Miscellaneous complications	Neurological	

3.6 Challenges for the future

The European Commission is currently evaluating the EU legislation concerning tissues and cells (Directive 2004/23/EC). This is the first formal evaluation of this legislation since the basic acts were approved in 2004 (tissues and cells). This evaluation has the objective of assessing whether the legislation has achieved its original objectives, and whether it is still fit for purpose. The evaluation consists of several different phases, conducted following a formal roadmap and including a study an extensive stakeholder consultation. The EU projects VISTART2 and TRANSPOSE3 provide input for possible future revision of the Directive and for harmonization of the legislation concerning blood with that for tissues and cells in the EU. In the evaluation there have been calls to include donor vigilance in the scope of the Directive 2004/23/EC. If so, reporting serious donation complications may become mandatory. The definitive report of the evaluation is expected by the end of 2018.

Awareness of the importance of the safety of donors is an important aspect of biovigilance. Currently, it can be presumed that not all (serious) donation complications are reported (yet). In anticipation of the EC potentially including donor vigilance in the Directive for tissues and cells, TRIP would like to increase awareness of donor vigilance with all institutions and medical staff that are involved in the chain of donating and procuring human tissues and cells. Reporting donation complications can help, as with transplantation, to improve safety of donation of tissues and cells, thus ensuring that donors' willingness to donate is not jeopardized.

[2] VISTART (Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation) aims to promote and facilitate harmonization of inspection, authorization and vigilance systems for blood, tissues and cells and to increase inter-member state collaboration and confidence in each other's inspection and vigilance programs.

[3] TRANSPOSE (TRANSfusion and transplantation PrOtection and SElection of donors) aims to add to harmonizing European donor selection and protection policies related to donations of substances of human origin.

CHAPTER 4

Participation

Participation of all stakeholder organisations in the TRIP reporting system is essential to the quality of the biovigilance system. Participation in the reporting system entails 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 and reports are also important; the processing, distribution and application data are used as the denominator for reports to provide insight in the occurrence rate of incidents and reactions.

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 Dutch 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 related to the processing, storage or distribution of human tissues and cells. Hence, a hospital can, in addition to performing transplants and/or other applications of human tissues and cells, also house 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 procurement of human tissues and cells must be licensed as so-called organ banks. According to article 1.1.l of the Law on safety and quality of substances of human origin, organ banks are also licensed to subsequently process, store and distribute human tissue and cells and must be nonprofit organisations. Thus, all organ banks are also tissue establishments; but 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 38 provides an overview of the number of licensed tissue establishments and organ banks in the Netherlands in 2017 (source: Farmatec). A number of Dutch hospitals houses multiple tissue establishments and/or organ banks. Because of hospitals merging, the total number of tissue establishments decreased in 2017. Mostly this decrease is due to the merging of IUI-laboratories. Additonally, two bone banks in hospitals/clinics ceased their activities.

Table 38. Licensed tissue establishments and organ banks in the Netherlands in 2017

	Tissue establishments	Organ banks	Total
Independent establishments	9	11	20
Housed in a hospital or clinic	51	36	87
Total	**60**	**47**	**107**

Figure 26 shows the number of licenses Farmatec has issued per type of tissue and/or cells. Farmatec is an executive body that grants licenses and permits with regards to pharmaceuticals, medical devices, blood components, and substances of human origin on behalf of the Dutch Ministry of Health. Some tissue establishments have been licensed for multiple types of tissues and/or cells. Figure 27 shows the percentages of tissue establishments that has provided data on the number of units of tissue and/or cells processed and distributed annually and the number of tissue establishments that have participated in vigilance reporting. All tissue establishments have provided data on the number of units processed and distributed in 2017. The participation of tissue establishments in 2017 was 100% (97 out of 97).

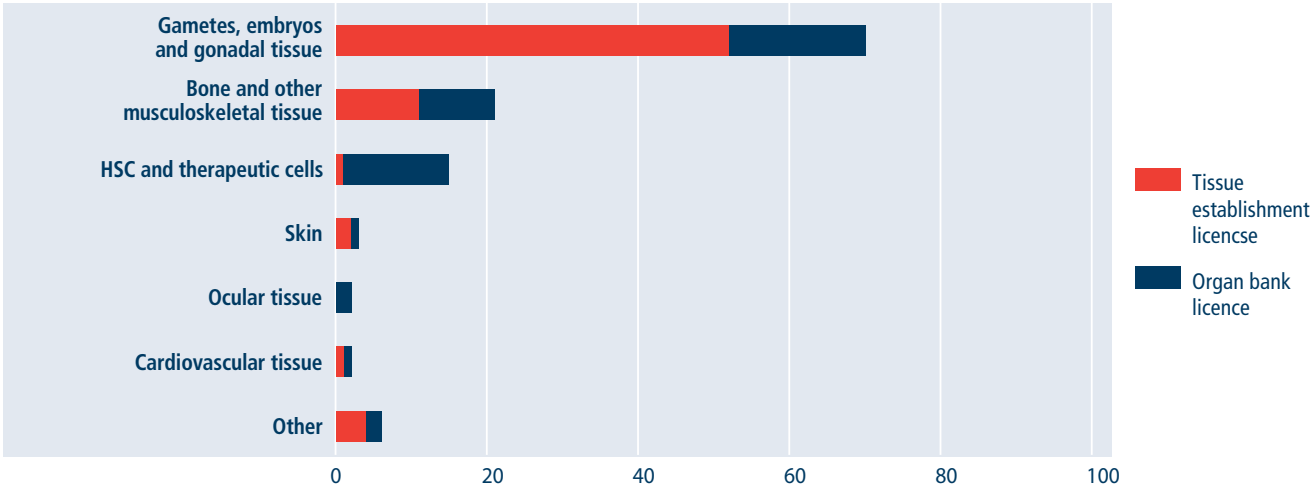


Figure 26. Number of licensed tissue establishment and organ bank in 2017 by type of human tissue or cells

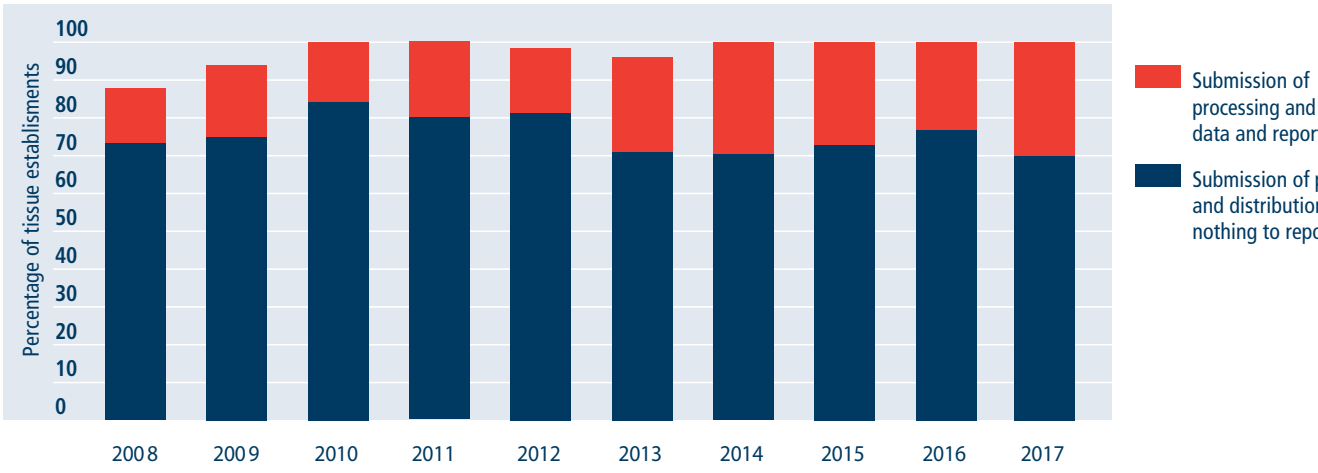


Figure 27. Participation of tissue establishments (2008-2011: n=20; 2012-2017*: n=112-120)

* *Up to 2012, tissue establishments housed in hospitals and clinics were not included in the data on the participation of tissue establishments.*

4.2 Organisations responsible for human application of tissues and cells

In 2017, 83 hospitals, 19 clinics and independent healthcare institutions, and 49 oral implantology practices were approached for submission of their annual data on the application of human tissues and cells, the number of patients that received transplants, and the number of incidents and/or reactions that occurred. The participation rate of hospitals, clinics, and independent treatment centers was 99% (101 out of 102) in 2017. Three of these establishments were unable to submit complete data. The oral implantology practices which apply human tissues were approached for the fifth year in 2017. In 2017,

the participation rate among oral implantology practices was 94% (46 out of 49). Six independent health-care institutions and four oral implantology practices indicated that they had applied no human tissues or cells in 2017. The participation of all establishments responsible for human application of tissues and cells together is 97% (147 out of 151). Figure 28 and Figure 29 show the course of participation rates over the past few years.

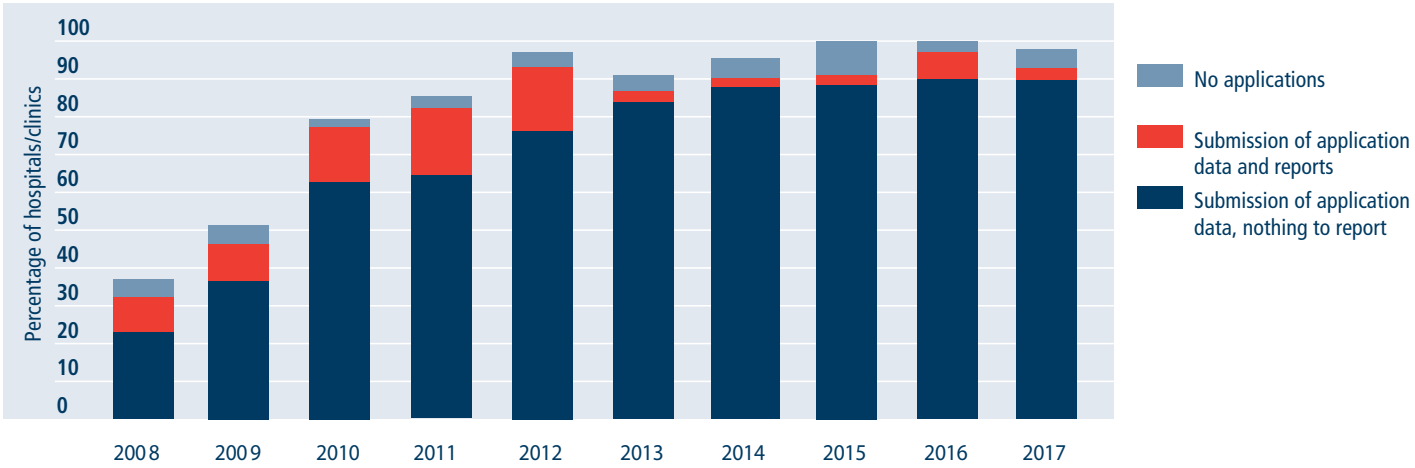


Figure 28. Participation of Dutch hospitals and clinics (n=101-115)

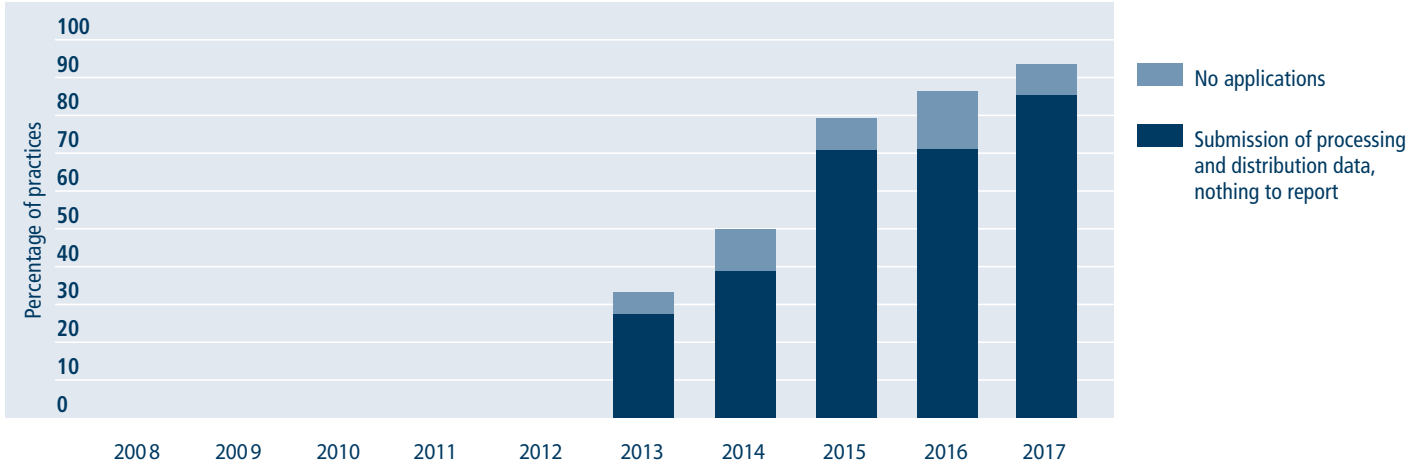


Figure 29. Participation of Dutch oral implantology practices* (n=101-115)

** Practices that have indicated that they apply substances of human origin*

ANNEX 1

About TRIP

TRIP (Transfusion and Transplantation Reactions in Patients) Foundation was founded 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 reactions and events to the Healthcare Inspectorate applies to tissue establishments according to the Dutch 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/EC. Figure 35 presents a flowchart of serious and non-serious biovigilance reports in Dutch healthcare.

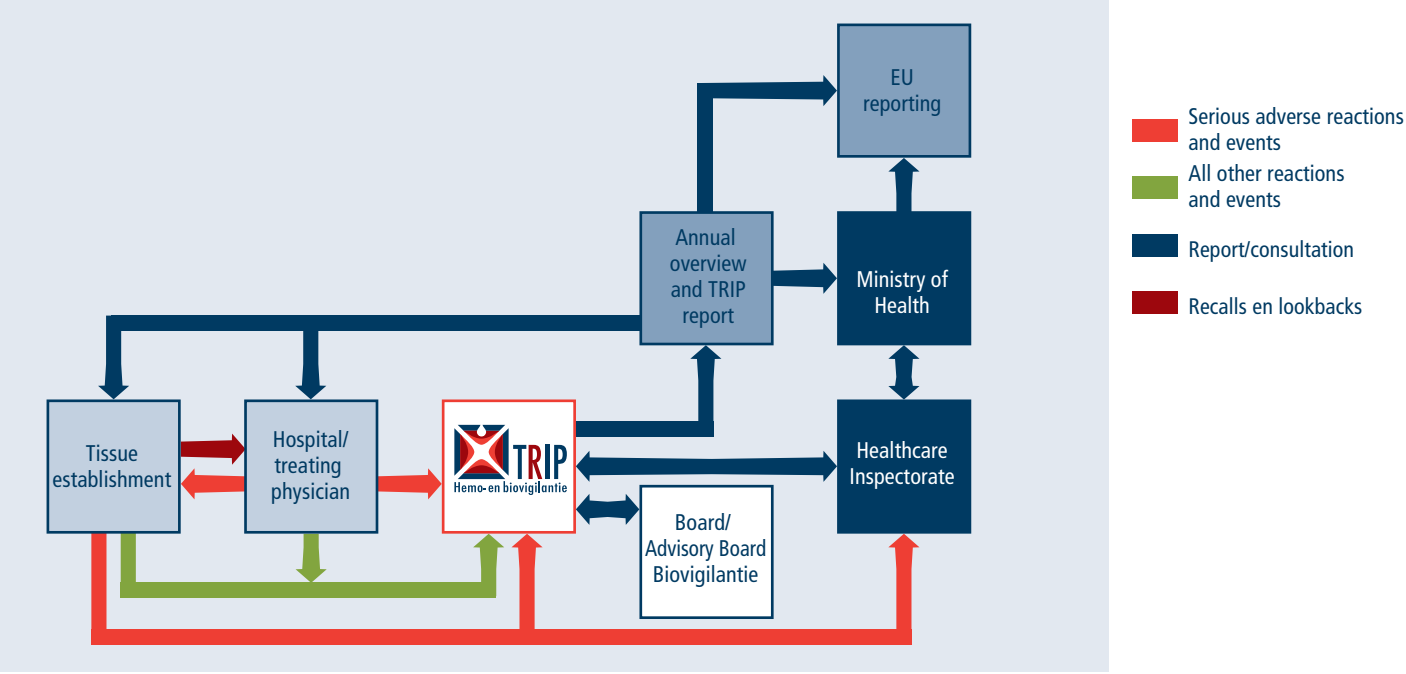


Figure 30. Flowchart of biovigilance reporting

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 post-mortem 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 compiles 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 the reporting, investigation, registration and forwarding of information on serious adverse reactions and events that could influence the quality and safety of substances of human origin or that are detected 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 they are classified as serious.

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 these 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 has (possibly) 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 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.

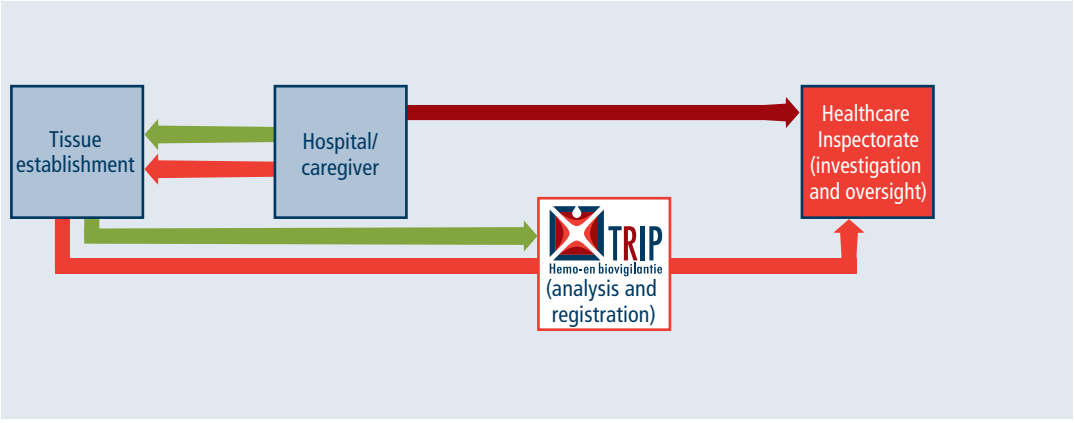


Figure 31. Flow chart of reports concerning substances of human origin

In November 2015 the Healthcare Inspectorate sent out a letter to all tissue establishments clarifying the reporting of adverse reactions and events to the Healthcare Inspectorate and TRIP. Figure 31 shows the reporting routes in a flowchart.

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 reduces 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 a full investigation 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 39. 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 39. 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 40 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 40. Severity grade of adverse reactions

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 hyperstimulation syndrome (OHSS) as an exaggerated response to the use of ovulation induction medications
- Reactions to growth factors (Granulocyte colony stimulating factor, GCSF) used for 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 on a voluntary basis.

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 41 shows the number of serious adverse reactions and events related to substances of human origin reported in 2017. In total, 31 reports were assessed as serious. These 31 reports concern 29 serious adverse events, one serious adverse reaction and one serious donation complication.

Table 41. Overview of serious reports in 2017

Tissue or cell type	Serious adverse reaction	Serious adverse event	Serious donation complication	Total serious reports
Semen	0	12	0	12
Oocytes	0	4	0	4
Embryos	0	4	0	4
Ovarian tissue	1	6	0	7
Ocular tissue	0	1	1	2
HSC and therapeutic cells	0	2	0	2
Total	**1**	**29**	**1**	**31**

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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
Chondrocytes	Cartilage cells
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
Gonadal	Relating to sex glands
HLA	Human leukocyte antigen
HSC	Hematopoietic stem cells
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
Keratinocytes	Skin cells
Lareb	Dutch national registry for adverse drug reactions
Matchis	Dutch center for stem cell donors
MESA	Microsurgical epididymal sperm aspiration
Morbidity	Extent of disease
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 hyperstimulaton syndrome
Oocytes	Egg cell
OPU	Ovum Pick Up, follicle puncturing
OR	Operating room

Organ bank	Tissue establishment with licence to receive substances of human origin after procurement
Pathogens	Infectious agent of organic origin
PBSC	Peripheral Blood Stem Cells
PDA	Patent Ductus Arteriosus
PESA	Percutaneous epididymal sperm aspiration
PFO	Patent Foramen Ovale
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
Sanquin	Sanquin (Foundation charged with operating the Dutch national blood establishment)
Semen	Sperm
SoHo	Substances of Human Origin
SoHO V&S	Vigilance and Surveillance of Substances of Human Origin (EU project 2010-2013)
TC-Til	Tumor infiltrating lymphocytes
TESE	Testicular sperm extraction
TIA	Transient ischemic attack, temporary occlusion of a cerebral blood vessel
TRANSPOSE	TRANSfusion and transplantation PrOtection and SElection of donors
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
VISTART	Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation
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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