TRIP REPORT 2018

Biovigilance

Extended version

TRIP
Hemo-en biovigilantie

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Extended version

The TRIP report 2018 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 2018 Biovigilance report, TRIP presents an overview of all reports of adverse reactions and events that occurred in association with application of human tissue and cells or in any of the steps leading up to it, as well as of the biovigilance participation of tissue establishments and healthcare institutions involved in the chain of tissue and cell transplantation. This is the twelfth TRIP biovigilance report.

In 2018, TRIP received 96 reports, of which 44 were serious reports. This number of reports aligns with that of previous years (2017: 101, 2016: 83, including late reports). However, the number of serious reports has increased from the average of 36 reports (35% of all reports) and stands at 44 reports in 2018 (45% of all reports). An explanation for this increase can be found in the increase in serious adverse events and serious adverse reactions occurring with assisted reproduction and in the transplant chain of hematopoietic stem cells. The 2018 reports will be discussed in this report. In addition, TRIP received 14 late reports, relating to transplant procedures that occurred between 2013 and 2017. Seven of these late reports concern congenital abnormalities occurring with the application of donor gametes. The large number of late reports concerning congenital abnormalities is partly due to the fact that congenital abnormalities are often diagnosed at a later time, but there has also been an increase in awareness of the obligation to report congenital abnormalities to the competent authority (the Healthcare Inspectorate). The participation of tissue establishments, hospitals, and clinics has remained stable and is nearly complete.

Out of all reports associated with assisted reproduction, the largest subgroup of reports received by TRIP concerned 'Loss of tissues or cells', as was the case in all previous years of collecting data with the exception of 2017. Out of 19 reports concerning 'Loss of tissues or cells', 13 were assessed as serious. Furthermore, TRIP received 12 reports registered in the category 'congenital abnormality', of which nine were assessed as serious.

On 27 April 2017, the Single European Code (SEC) was introduced. In 2018 TRIP received three reports concerning cases in which tissues and/or cells (musculoskeletal tissue and peripheral blood stem cells) were not correctly coded according to the SEC.

Chapter 3 presents an overview of all reports related to hematopoietic stem cells and therapeutic cells that TRIP has received since it started collecting reports concerning these cells in 2006. Over the years, TRIP has received a wide range of reports of different adverse events and adverse reactions. Over the years a number of small clusters of similar reports have been observed, and when they come from different institutions it may be only because of the national collation of data that they become apparent. Even though it has been twelve years since TRIP has started collecting data on hematopoietic stem cells, the annual number of reports concerning these cells is still increasing. The number of reports of bacterial contaminations in particular has contributed to the most recent increase in reports. For the upcoming years, this issue warrants closer study. The Working Party of Dutch Stem Cell Laboratories will carry out a nation-wide review of the sampling procedures.

The classification in reporting categories of the reports discussed in Chapter 3 highlights the relatively large numbers of reports are registered as 'other reaction' or 'other incident'. TRIP will focus on evaluating these reports and the current reporting categories. Biovigilance reporting categories and criteria are under review in ongoing European projects and this could lead to updated definitions and criteria.

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 to increase safety and quality in the chain that deals with human cells and tissues.

Findings and recommendations

2018 Findings

1 The participation has remained high for tissue establishments (100%), hospitals (98%), clinics (93%) and oral implantology practices (91%).

2 TRIP received 96 reports in 2018, in line with the average number of reports in the previous five reporting years (100 reports).

3 The proportion of reports assessed as serious has increased from an average of 36 reports (35%) in the past five years, to 44 reports in 2018 (45%).

4 After a declining trend in the past two years, both the reports concerning 'Loss of tissues or cells' in assisted reproduction and the serious adverse events concerning hematopoietic stem cells show an increase this year.

5 The largest subgroup of reports are those relating to assisted reproduction (44 out of 96, 46%). Among these reports, 19 concerned a 'Loss of tissues or cells' and 12 concerned a 'Congenital abnormality'.

6 Twelve reports concerning 2018 and seven late reports were categorized as a 'Congenital abnormality'. The large number of late reports of congenital abnormalities is due to several reasons. Congenital abnormalities may be diagnosed some time after birth; there has been an increase in awareness of the obligation to report congenital abnormalities, even if they are detected at a later time, and the competent authority has issued a request that congenital abnormalities related to the use of donated gametes be reported.

7 TRIP received three reports concerning cases (concerning musculoskeletal tissue and peripheral blood stem cells) in which tissues and/or cells were not coded according to the Single European Code (SEC). In one of these cases, only the barcode was incorrect.

8 TRIP received two reports concerning assisted reproduction that were categorised as 'Incorrect product transplanted'. In both cases, staff performed (double) checks of the product, but read what they expected to read on the product, instead of what was actually written. In both cases, pregnancy was prevented.

9 In 2018, TRIP received 15 reports concerning contaminated stem cell products. The number of reports concerning 'Bacterial contamination of product' with hematopoietic stem cells has shown an increasing trend in the last two years.

10 After multiple positive culture results in a short period of time, one stem cell laboratory reviewed their methods of product freezing and of sampling for bacterial cultures to reinforce a sterile process. The Working Party of Dutch Stem Cell Laboratories will carry out a nation-wide review of the sampling procedures.

11 TRIP's compiled registration of reports related to hematopoietic stem cells and therapeutic cells shows that there is a large number of reports categorized as 'Other reaction' or 'Other incident'.

2018 Recommendations

1 The validation of the Single European Code generation by a tissue establishment should be based on verification of both the eye-readable code and the bar or QR code

2 Identification errors in the process of the application of gametes and embryos can probably be further reduced by electronic verification of the correspondence between product and recipient or by an independent second check performed by a staff member who is not involved in the treatment of the recipient.

3 Reports of congenital abnormalities after assisted reproduction should be considered over a period of several years. This review should take into account the distinction between genetic and non-genetic abnormalities.

4 Reports of bacterial contaminations of hematopoietic stem cell products warrant additional consideration from TRIP as well as from professionals, in order to reduce the number of adverse events leading to loss of tissues or cells and additional apheresis procedures.

5 The reports concerning hematopoietic stem cells and therapeutic cells that are categorized as 'Other reaction' or 'Other incident' require further examination by TRIP, with a view to classifying them in specific subcategories where possible.

Actions and developments following recommendations from the 2017 TRIP report

In the 2017 TRIP Biovigilance report, four recommendations were made. The recommendations concerning situations in which relevant developments have occurred are reported below.

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.

Development: In 2018, TRIP received 12 reports concerning congenital abnormalities related to the use of donated gametes. In addition, TRIP received seven late reports of congenital abnormalities, related to transplants that occurred between 2013 and 2017. The awareness of the obligation to report these events has increased.

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.

Development: In 2018, TRIP received only one report of a bacterial contamination detected in an embryo culture. This contamination was a consequence of contamination of the semen, which resulted from a urinary tract infection in the male partner.

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.

Development: In 2018, TRIP received one report of transplantation of bone and tendon products that were past their expiration date.

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.

Development: In 2018, TRIP received six reports of donation complications, one of which was a late report of an event that occurred in 2016. Four of these reports concern complications related to the procurement or donation of oocytes for the donors' own IVF-treatment. One of the reports concerned a donation complication that occurred with the donation of peripheral blood stem cells by an unrelated donor.
The late report concerned a complication that occurred with allogeneic, related bone marrow donation.

Implementation of the Single European Code: Current situation, TRIP survey 2018

In 2018, TRIP surveyed organisations on the implementation (2017) of the Single European Code (SEC). The response rate among tissue establishments was 31% (10 IUI laboratories, 5 IVF laboratories, 7 bone banks, 6 stem cell laboratories and 5 other tissue establishments). Among hospitals and clinics it was 25% (23 hospitals, 2 clinics). The study showed the following:

a The most commonly used coding system in the Netherlands is ISBT 128
b Cooperation between organisations in relation to the SEC is satisfactory, both between tissue establishments and between tissue establishments and the institutions that apply products
c SEC codes are generally provided both in eye readable format and as a bar or QR code
d The SEC is generally recorded in the patient's Electronic Health Record, either by using the bar or QR code or by manually recording the information
e Institutions that apply products often see more added value in the use of the SEC than tissue establishments
f The traceability of products is considered the most important advantage of the SEC
g In the Netherlands, the TRIP website is the source most commonly consulted for information on the SEC.
h Some respondents indicate misgivings about the use of the SEC for stem cell products because this may allow the possibility of tracing the donor.

The full study can be found (in Dutch) via www.tripnet.nl, Biovigilance-Symposia-Report 2018-Presentation Marjan Happel.

CHAPTER 1

Reports to TRIP

1.1 Reports in 2018

In the 2018 reporting year, TRIP received 96 reports of adverse events and adverse reactions that occurred in relation to donating, procuring, testing, storing, distributing and applying human tissues and cells. The reports concern 82 adverse events (85%) and 14 adverse reactions (15%), five of which were donation complications. Out of all reports, 44 (46%) were classified as serious (see Annex 3). These serious reports were included in the annual overview for the European Commission (see Annex 4). Reports included in the 2018 report and the EU overview had to be submitted by March 1st 2019.

The total number of reports received in 2018 is similar to the number received per year in the previous five years (100 on average), but the number of serious reports has increased, from an average of 36 to 44 this year. An explanation for this increase can be found in the increase in serious adverse events and serious adverse reactions occurring with assisted reproduction and in the transplant chain of hematopoietic stem cells. The largest subgroup of adverse events and adverse reactions (46%, 44 of 96 reports) is related to assisted reproduction, which was not the case in 2017 (see Figure 2). The declining trend in the number of reports related to assisted reproduction that was observed in previous years has been broken by a slight rise.
Figure 1 and Figure 2 show the total number of reports received over the past six 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 gives an overview of the serious and non-serious reports in 2018, according to the type of tissue.

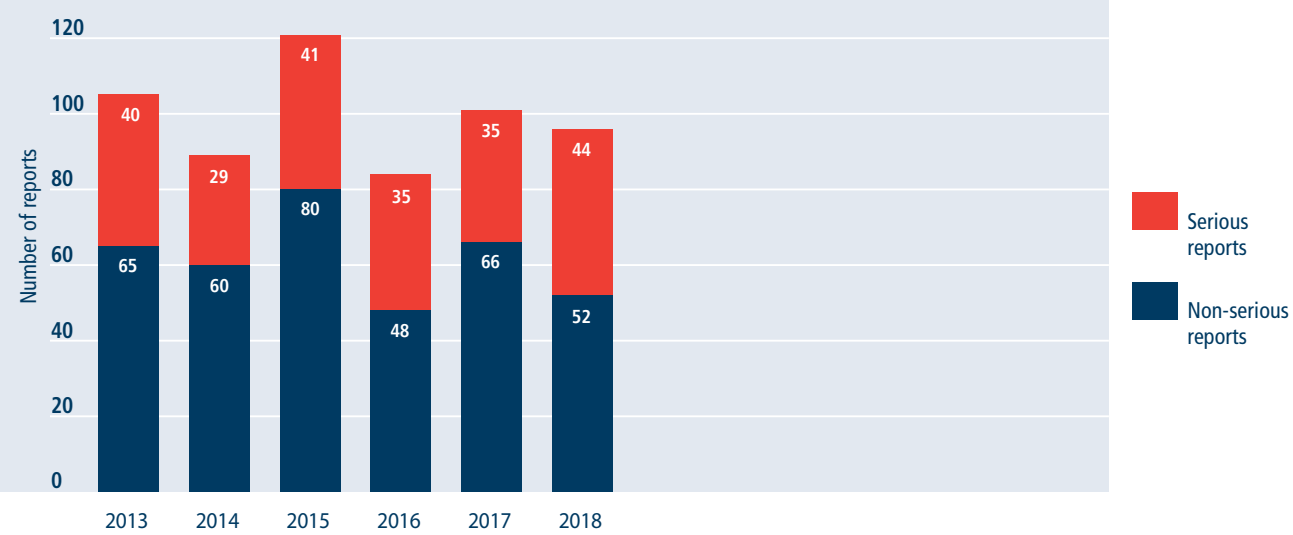

Figure 1. Number of reports received, 2013-2018

Table 1. Overview of reports per tissue or cell type in 2018

	Total	Non-serious	Serious
Gametes, embryos and gonadal tissue	44	15	29
Hematopoietic stem cells and therapeutic cells	38	31	7
Bone and other musculoskeletal tissue	6	5	1
Skin	0	0	0
Ocular tissue	6	0	6
Cardiovascular tissue	2	1	1
Other tissues and cells	0	0	0
Total	**96**	**52**	**44**

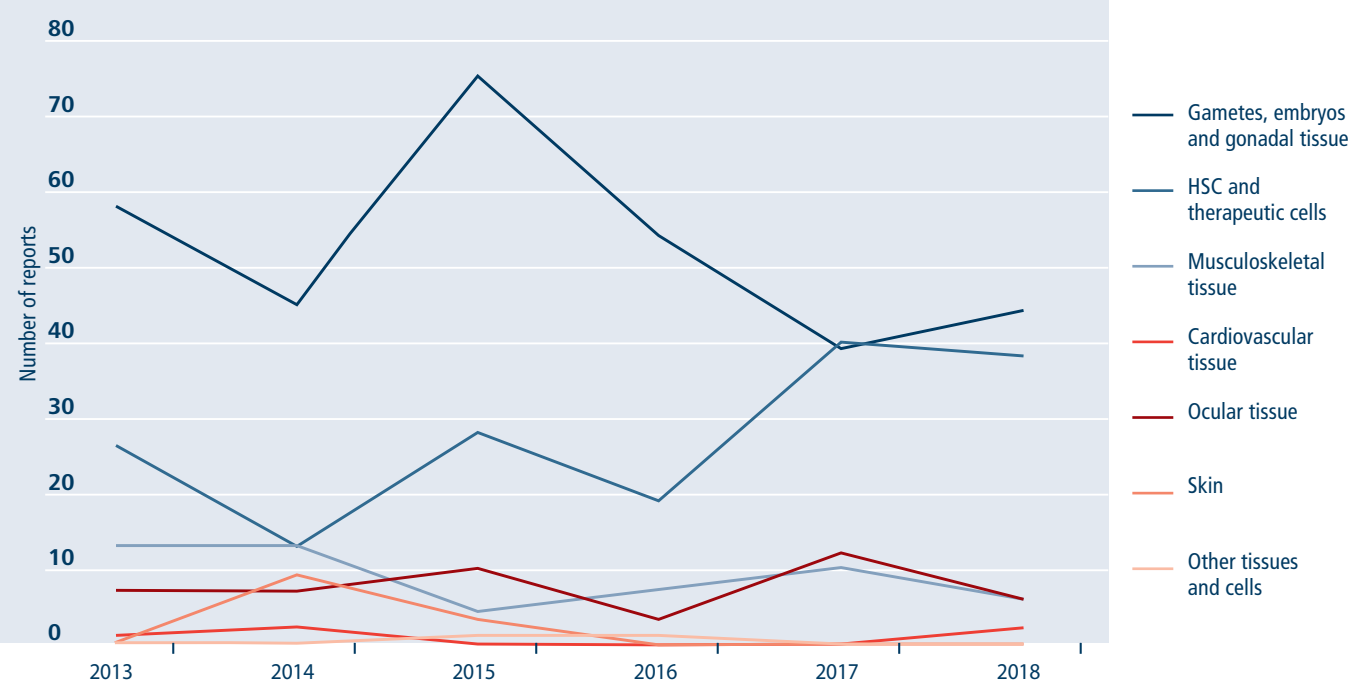

Figure 2. Number of reports received annually per tissue or cell type, 2013-2018

1.2 Late reports

After the final submission date for reports for the 2017 Biovigilance report TRIP received 14 more reports, two from 2013, one from 2015, three from 2016, and eight from 2017. Table 2 provides an overview of these reports. Seven of the late reports are of congenital abnormalities occurring with the application of donor gametes. The large number of late reports concerning congenital abnormalities is partly due to the fact that congenital abnormalities are often diagnosed at a later time, but there has also been an increase in awareness of the obligation to report congenital abnormalities and this has been specifically requested by the competent authority (the Healthcare Inspectorate). One of the late reports concerned a donation complication that occurred with related bone marrow donation; a fractured sacrum, the after-effects of which have not yet resolved. All information presented in the late reports has been incorporated into the relevant tables and figures in this year's biovigilance report.

Table 2. Late reports from 2013-2017, received in 2018

Tissue or cell type	Reporting category	2013	2015	2016	2017
Donor semen	Congenital abnormality	2 *	1	1 *	3 ***
Semen	Other incident				2
Semen	Bacterial contamination of product			1 *	
Bone marrow	Donation complication			1 *	
Bone, femoral head	Incorrect product transplanted				1
Bone, whole	Loss of tissues or cells				1
Cornea	Other incident				1 *

* *indicates the number of serious reports*

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 2018 adverse event and reaction reports are briefly described and analysed. Some reports are highlighted as case descriptions.

2.1 Reproductive tissues and cells

In 2018 in the Netherlands, 15 IVF laboratories (tissue establishments) processed human cells and tissues for the performance of intrauterine inseminations (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injections (ICSI). In 2018, two clinics obtained a license to perform IVF. Furthermore, the Netherlands has 54 licensed tissue establishments, primarily hospital biomedical laboratories, which only 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. Three laboratories have obtained this license.

Processing, distribution, and application

Table 3 and Table 4 respectively, show the figures for processing and distribution, and for application of gametes, embryos and gonadal tissue in 2018. 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 only distributed 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 3 a-b-c. Processing and distribution of gametes, embryos, and gonadal tissue in 2018

Type of semen or 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	39238	5	Sample	28780	12	20	28812
Donor semen, fresh and cryo	18	6840	4500	Sample	9578	21	0	9599
Partner semen, MESA/PESA or TESE, fresh and cryo	9	842	1	Aspiration or biopsy	650	34	0	684
Donor semen, MESA/ PESA or TESE, fresh and cryo	2	2	0	Aspiration or biopsy	0	0	0	0
Testicular tissue	2	5	0	Graft	0	0	0	0

Type of oocyte or 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	15	115043	13	Oocyte	417	0	0	417
Oocytes for donation, fresh and cryo	10	2073	0	Oocyte	174	0	0	174
Ovarian tissue	3	300	0	Graft	7	0	0	7

Type of embryo	No. of tissue establishments	Processed		Distributed				
		From NL	From EU	Unit	In NL*	In EU	Outside EU	Total
Embryos, own oocyte with partner semen	14	48991	9	Embryo	25866	61	0	25927
Embryos, own oocyte with donor semen	13	2753	54	Embryo	1140	0	0	1140
Embryos, donor oocyte with partner semen	12	543	0	Embryo	252	0	0	252
Donated embryos	4	265	4	Embryo	65	0	0	65

** Including distributions within the same clinic*

In 2018 TRIP chose to report the data on processing, distributing and transferring embryo's that were formed (in part) using donated gametes in a more extensive way to the European Commission. The present way of reporting meets the minimum requirements for reporting to the EU.

Table 4. Application of semen, embryos and gonadal tissue in 2018

Type	Hospitals/ clinics	Recipients	Applications				
			Unit	From NL	From EU	From non-EU	Total
Partner semen, fresh and cryo	74	12306	Insemination	27236	0	0	27236
Donor semen, fresh and cryo	17	2967	Insemination	8616	172	0	8788
Embryos, own oocyte with partner semen	12	13913	Embryo	25671	0	0	25671
Embryos, own oocyte with donor semen	13	503	Embryo	1134	0	0	1134
Embryos, donor oocyte with partner semen	12	145	Embryo	243	0	0	243
Donated embryos	4	58	Embryo	65	0	0	65
Ovarian tissue	2	2	Graft	7	0	0	7
Testicular tissue	0	0	Graft	0	0	0	0

TRIP has received sufficiently complete annual data on IUI (both with partner semen and with donor semen) since 2011. The number of patients inseminated using partner semen hovers around 10.000 per year. In 2016 the number of IUI treatments showed a dip and it has subsequently increased to 12.000

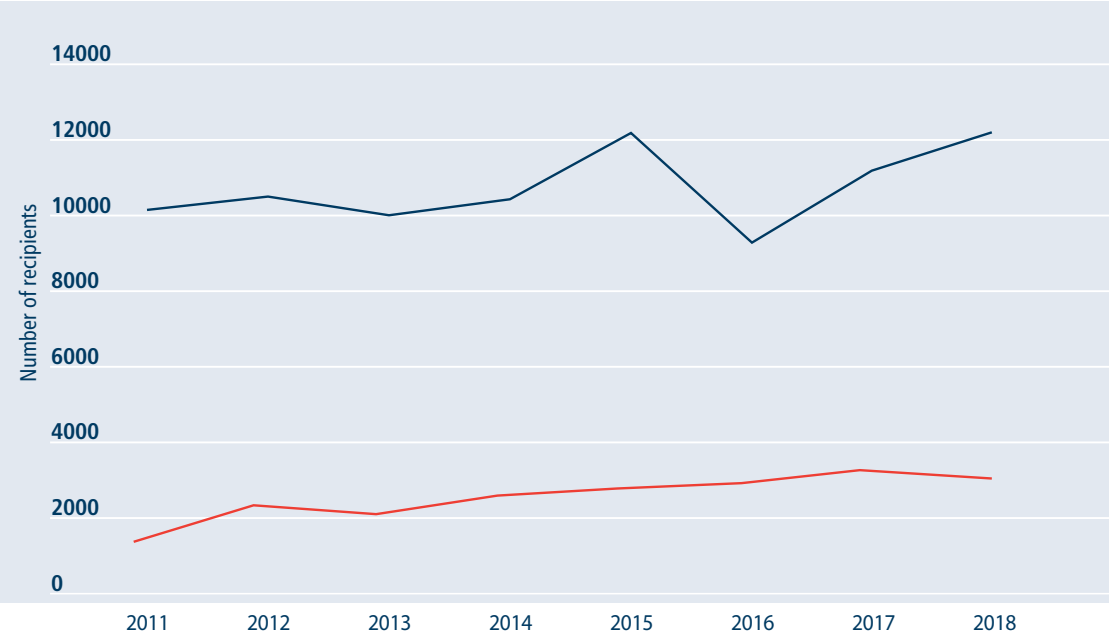

Figure 3. Number of recipients of partner semen and donor semen, 2011-2018

The number of embryos transferred annually decreased from 33,000 in 2012 to approximately 25,000 in 2014. Since 2014, the number of embryos transferred annually has been increasing slowly (Figure 4). However, the number of recipients has remained fairly stable. The discrepancy between these two statistics can be explained by the decrease in transfers using two embryos at the same time and the improvement in pregnancy results.

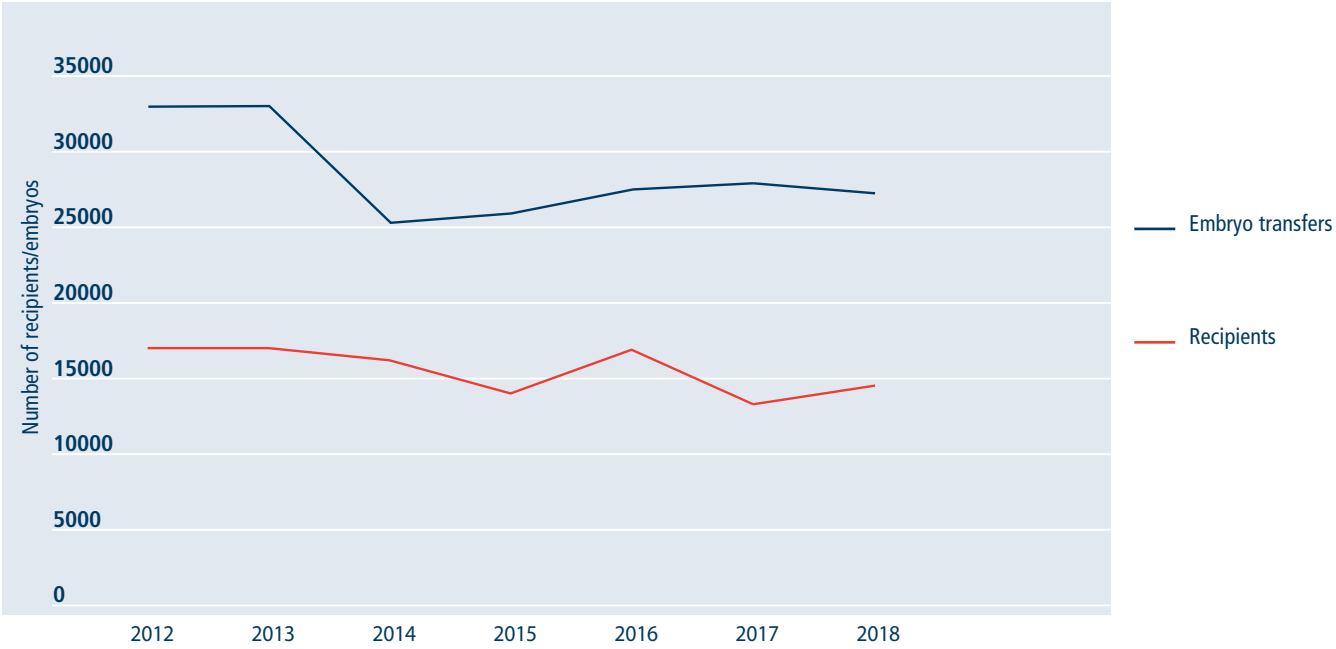

Figure 4. Number of embryo transfers and recipients, 2012-2018

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

Reports

In 2018, TRIP received 44 reports related to procedures related or applications of gametes, embryos and/or gonadal tissue in medically assisted reproduction. Five of these reports concern adverse reactions, and 39 concern adverse events. The number of reports is stable in comparison to previous years (Figure 2). Table 5 provides an overview of the number of reports received from the different fertility laboratories in 2018. Five IVF laboratories and 45 semen laboratories indicated that no (serious) events or adverse reactions occurred in 2018.

Table 5. Overview of 2018 reports from fertility laboratories

Type of fertility laboratory	No. in NL	Reports submitted by	No. of 2018 reports	Number of late reports
IVF laboratories	15	10 (67%)	29 (21 serious)	8 (6 serious)
Semen laboratories	54	9 (17%)	15 (8 serious)	2 (1 serious)
Total	**69**	**19 (28%)**	**44 (29 serious)**	**10 (7 serious)**

Adverse reactions

In 2018, TRIP received five reports of adverse reactions, of which four concerned donation complications. All adverse reactions reported were classified as serious. Over the past five years, TRIP has received 22 reports of adverse reactions (20 of which were donation complications) associated with medially assisted reproduction. Table 6 provides an overview of these reports. Table 7 provides an overview of the reports of donation complications related to the procurement of oocytes for both patients' own fertility treatments and oocyte donation.

The adverse reaction that occurred in a recipient was a post-transplantation bacterial infection after IUI, which caused Pelvic Inflammatory Disease. The partner's semen was cultured, but this culture came up negative. All four donation complications occurred with the procurement of oocytes for patients' own IVF-treatments. In two cases, the procedure led to severe cases of Ovarian Hyperstimulation Syndrome (OHSS). In the third case, ovarian torsion occurred, which was treated laparoscopically. The fourth report of a donation complication concerned a case in which the patient suffered severe abdominal pains after aspiration for the procurement of the oocytes, which led to hospitalisation.

Table 6. Reports of adverse reactions associated with medically assisted reproduction, 2014-2018

Category of reaction	2014	2015	2016	2017	2018	Total
Post-transplantation bacterial infection	1	0	1	0	1	3
Donation complication*	0	11	5	0	4	20
Total	**1**	**11**	**6**	**0**	**5**	**23**

** Donation complications have been reported since 2015*

Table 7. Overview of reports of donation complications related to the procurement of oocytes in the Netherlands, 2015-2018

Donation complication	Autologous oocyte donation	Allogeneic oocyte donation	Total
OHSS*	10	0	10
Pain	1	0	1
Bladder injury	2	1	3
PID**	0	3	3
Ovarian rupture	0	1	1
Ovarian torsion	1	0	1
Hemorrhage	1	0	1

* *Ovarian hyperstimulation syndrome*

** *Pelvic inflammatory disease*

Adverse events

In 2018, TRIP received 39 reports of events associated with gametes and embryos. Of these reports, 24 (62%) were classified as serious. Specific criteria have been set for the assessment of the seriousness

of adverse reactions and events associated with medically assisted reproduction. Events leading to loss of a complete fertility cycle or transmission of a (possibly) congenital disorder through donated gametes or embryos are classified as serious, and thus must be reported.

Figure 5 shows all reports of events related to gametes, embryos and gonadal tissue from 2009 to 2018, classified according the seriousness criteria set out by the European Commission (EC). The number of serious events that occurred in 2018 (24) is higher than the number of serious events in previous years (18 on average). From 2017 onwards, the criteria for reporting serious adverse events and adverse reactions set out in 'Quality norms for laboratory practices for in vitro fertilisation' of the Dutch Association of Clinical Embryologists have been followed. These criteria match the criteria 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.

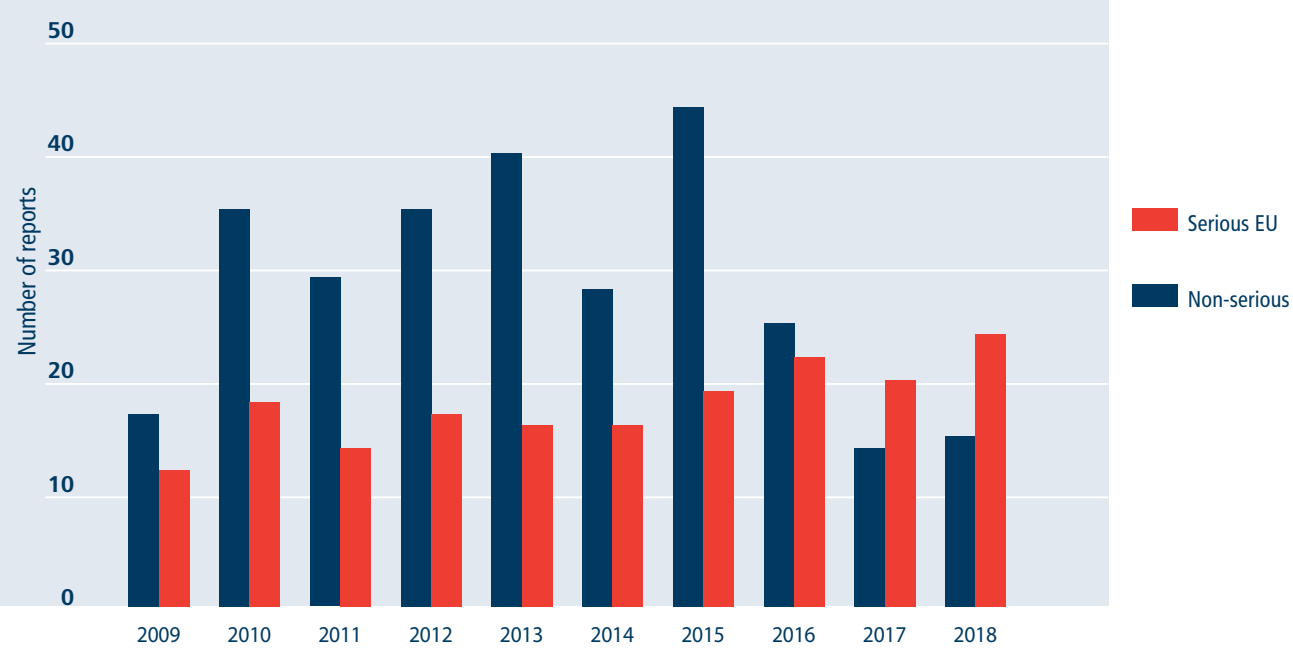

Figure 5. Number of reports of adverse events concerning gametes, embryos and gonadal tissue, 2009-2018

Table 8 provides an overview of the reports classified according to the type of reproductive cell or tissue, type of event and severity. Figure 6 shows the event types of all reports from 2009 to 2018. Before 2017, the category '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'. In 2018, TRIP received 13 reports concerning a 'Loss of tissues or cells' and 12 concerning a 'Congenital abnormality'. The larger number of reports concerning congenital abnormalities may be due to the increase in the use of donated gametes and in the awareness of having to report these adverse events.

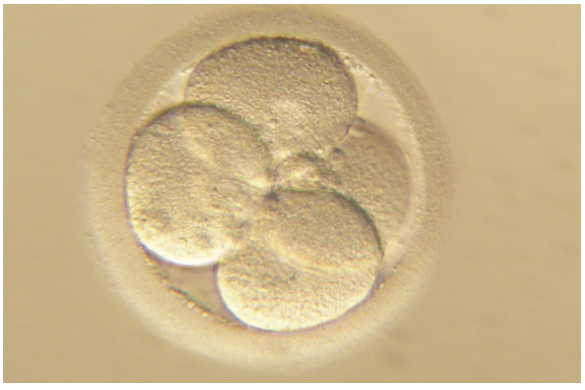

Image 1. Embryo

Table 8. Overview of adverse events concerning gametes, embryos and gonadal tissue in 2018

Type of tissue	Type of event	Total	Serious (EU guidelines)
Semen	Loss of tissues or cells	9	4
	Other incident	4	0
	Incorrect product transplanted	1	1
	Congenital abnormality	12	8
	Near miss	1	0
Oocytes	Loss of tissues or cells	5	5
Embryos	Loss of tissues or cells	5	4
	Bacterial contamination of product	1	1
	Incorrect product transplanted	1	1
Total		**39**	**24**

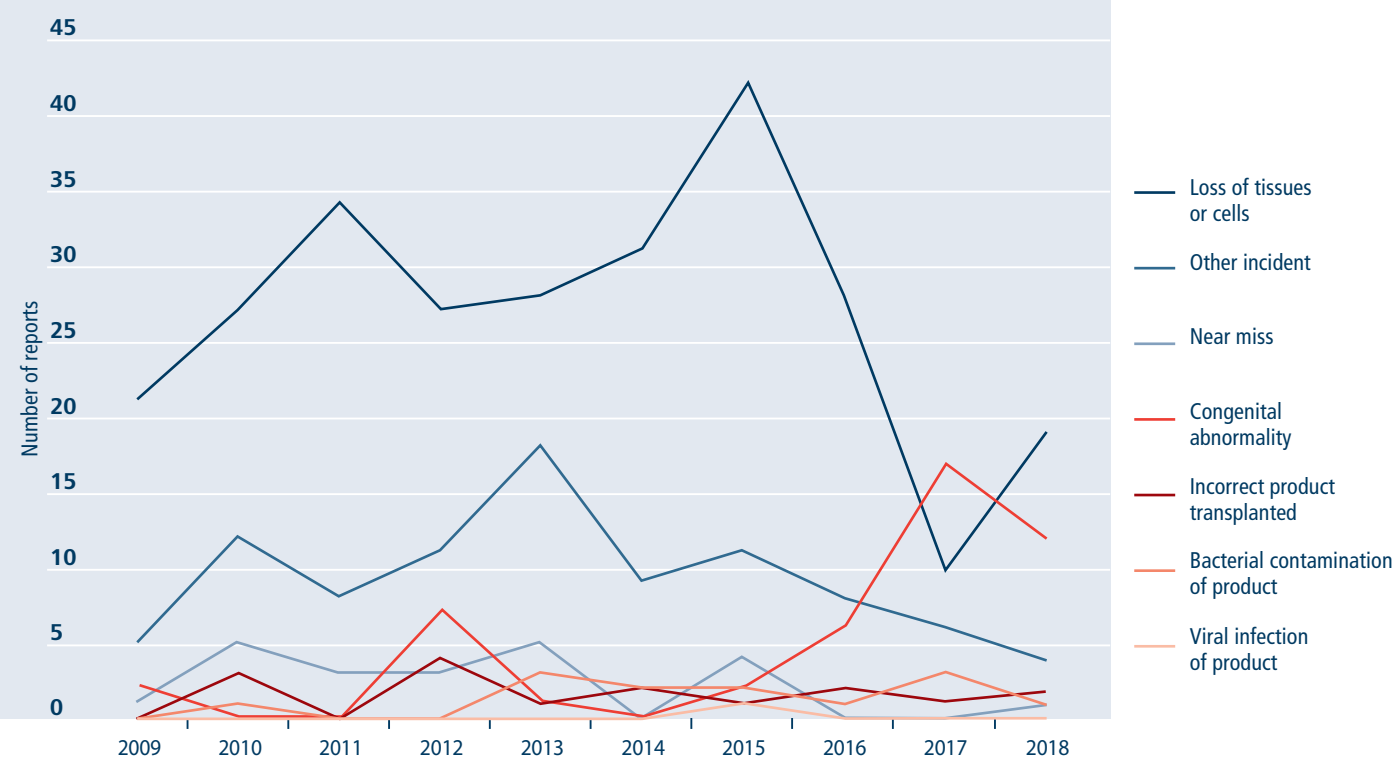

Figure 6. Number of reports per adverse event category concerning gametes, embryo's and gonadal tissue, 2009-2018

Loss of tissues or cells

In 2018, 19 reports were classified as 'Loss of tissues or cells'. The number of reports in this category had decreased in 2017, especially the number of reports classified as not serious. In 2018, as in 2017, the reports TRIP received in the category 'Loss of tissues or cells' were mostly serious (13 of 19). Loss of gametes, embryos or gonadal tissue may, in some cases, 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. Up to 2016, guidelines for the classification for events concerning loss of cells or tissue 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. As of 2017, only the numbers of events classified as serious according to the current guidelines have been displayed in tables and figures.

Figure 7 provides an overview of the number of reports in the category 'Loss of tissues or cells' from 2009 to 2018.

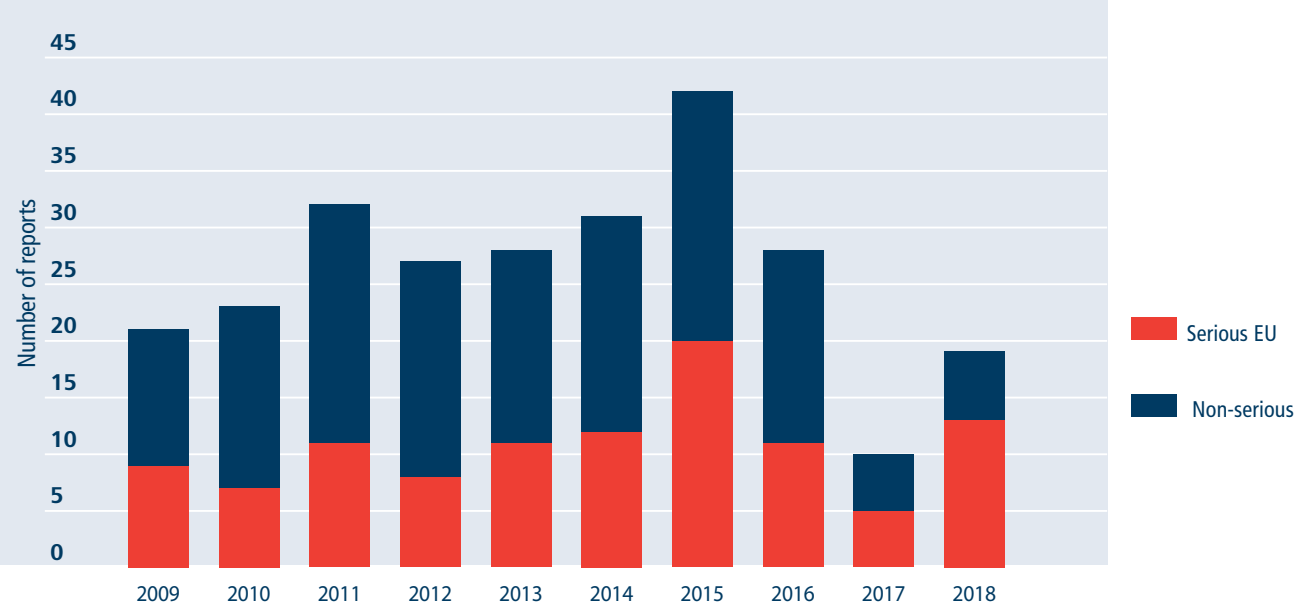

Figure 7. Reports of loss of tissues or cells concerning gametes, embryos or gonadal tissue, 2009-2018

The largest number of adverse events (8) involve processing errors concerning semen, oocytes, and embryos. In 2018 there were no reports of identification errors in this category. There were three reports of communication errors and one report of an administrative error. In addition, two storage errors were reported, as well as one technical error, one error of judgement and three other errors. Forgetting a step remains the most common processing error, as in previous years. Case 1 describes a an event in which semen was lost.

Case 1: Loss of donor semen

A patient ordered semen from a Danish semen bank and it was delivered to her home in a container with liquid nitrogen, that she kept at home. Because the interval between the time of receiving the semen and the patient's ovulation turned out to be longer than expected, the liquid nitrogen tank needed to be topped up. The refill was done at the hospital where the patient was receiving treatment. In order to do so, the container with the straw of semen was taken out of the nitrogen tank. After the tank had been refilled, the container was put back.

When the patient came in for her insemination, it turned out the straw was no longer in the tank.

The area where the tank had been refilled was searched and the straw was found there. The product had thawed and was discarded.

As of July 1st 2018, patients are no longer allowed to receive donor semen from a semen bank themselves. In this case, the gynaecology department had a license to order semen, but no storage facilities in the hospital. Subsequent to this event the protocol at this hospital was changed and donor semen units are stored at a different tissue establishment that has a license to do so.

Congenital abnormality

In the 2018 reporting year, 12 reports were registered as 'Congenital abnormality'. If donation of gametes or embryos by non-partner donors results in the birth of a neonate or in the termination of a pregnancy with a fetus with a (possible) genetic abnormality, the event is classified as a serious adverse event. When a genetic abnormality is detected in a non-partner donor after donation of gametes or embryos, this is also classified as a serious adverse event. The reports concerning congenital abnormalities are summarized in Table 9. Eight of the reports in which a genetic factor was certain or possible have been

classified as serious. In addition, one report where a primary infection in the mother during pregnancy led to congenital abnormalities, was assessed as serious. The imputability in this case is: excluded.

Table 9. Reports of congenital abnormalities involving gametes and embryos in 2018

Type of gamete or embryo	Description
Donor semen	Intra-uterine death in 37th week of pregnancy, caused by a Cytomegalovirus (CMV) infection in the mother. Multiple congenital abnormalities were present. The semen donor turned out to be CMV-negative. Primary infection occurred in the mother during pregnancy*
	Child born with imperforate anus. Donor not deferred*
	Autism diagnosed when child is one year old. Donor deferred*
	Child born with hypospadias. Donor deferred*
	Two reports of cases in which trisomy 21 was detected during pregnancy. Both pregnancies were terminated. Donors did not have balanced chromosomal translocation. Donors not deferred
	Teratoma detected at 20-week ultrasound. Caesarean section in 35th week of pregnancy. Tumor removed surgically in two operations. The bladder did not develop properly. Donor not deferred
	Child born with Cystic Fibrosis, detected through neonatal heel prick. Donor found to be a carrier and deferred*
	Child born with tuberous sclerosis. Likely to be a de novo mutation, but a genetic mosaicism cannot be excluded. Donor deferred*
	Child born with Alpers-Huttenlocher syndrome (two POLG mutations). Mother found to be a carrier. Donor deferred for new families*
	Child born with a congenital heart defect, with dilated thoracic aorta. Donor deferred*
	Semen donor turns out to have PDK2 mutation (see Case 2)*

* *Serious*

Case 2 describes a report of a congenital abnormality that was detected in the semen donor after many years.

Case 2.

At 38 years old, a woman contacts her donor father. He turns out to have a polycystic disease of the kidney, PDK2 mutation (autosomal dominant). After investigation, she too turns out to have this mutation, which can cause development of cysts in the liver and kidneys. As the number and size of these cysts increases, this condition may eventually lead to failure of these organs, after which transplants may be necessary.

There were no signs of this genetic defect in the donor's family at the time of donation. Only later in life, many years after his donation procedure, did the condition manifest itself in the donor. It is not known whether other offspring of this donor have also inherited this condition.

Figure 8 provides an overview of all reports in the category 'Congenital abnormality' from 2009 to 2018. Table 10 provides an overview of the different kinds of congenital abnormalities diagnosed from 2007 to 2018.

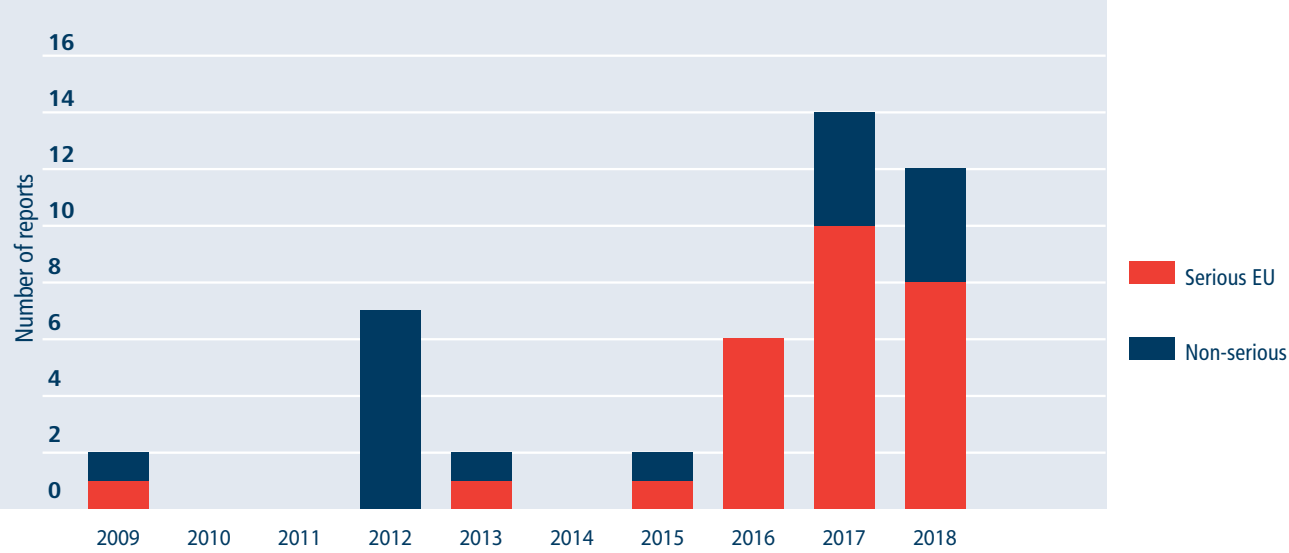

Figure 8. Reports in the category 'Congenital abnormality', 2009-2018

Image 2. Donor semen in storage

Table 10. Overview of reports of congenital abnormalities from 2007 to 2018

Transfer of congenital abnormality after artificial insemination with donated semen (AID), carrier donor		Reports
Cystic Fibrosis	Autosomal recessive	3
Spinal Muscular Atrophy	Autosomal recessive	1
Congenital defect of glycosylation	Autosomal recessive	1
Oculocutaneous albinism	Autosomal recessive	2
Sickle cell trait	Autosomal recessive	1
Alpha thalassemia, heterozygous	Autosomal recessive	1
Cowden syndrome	Autosomal dominant	1
Alpers-Huttenlocher Syndrome	Autosomal recessive	1
Wilson disease (ATP7B mutation)	Autosomal recessive	1
PDK2 mutation	Autosomal dominant	1
SETBP1 mutation	Autosomal recessive	1
Duarte Galactosemia	Autosomal recessive	1
Reduced hearing (DFNB1)	Autosomal recessive	1
Polydactyly	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 AID, possible donor carrier status		
22q11 deletion		1
Chromosomal abnormality after AID, donor not a hereditary carrier		
Trisomy 21		6
Triploidy		1
Congenital abnormality after AID or IVF with donated semen and/or oocyte, genetic 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
Congenital heart defect with dilated the thoracic aorta.		1
Orofacial cleft		1
Hip dysplasia		1
Unilateral renal agenesis		2
Duplicated ureter		1
Spina Bifida		1
Imperforate anus		1
Trigonocephaly (Craniosynostosis of the metopic suture)		2
Congenital deafness		1
Dysmorphic features, hypospadias, omphalocele and diaphragmatic hernia		1
Hypospadias		1
Tuberous sclerosis		1
Congenital abnormality after AID or IVF with donated semen and/or oocyte, congenital factor ruled out		
Dilated renal pelvis left and right, enlarged bladder and imperforate anus		1
Open Spina Bifida		1
Multiple congenital abnormalities after primary CMV infection in mother during pregnancy.		1
Teratoma		1
Congenital abnormality after pre-implantation genetic diagnostics (PGD), result possibly erroneous		
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 when donated gametes are used, the number of reports concerning congenital (genetic) abnormalities has increased. The risk of a genetic abnormalies 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 that occur after use of donor gametes may contribute to insight into 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 in this category varies from 8% to 27%. In 2018 it was 10%. Figure 9 provides an overview of the number of reports registered as 'other incident' from 2009 to 2018. In 2018, TRIP received four such reports, none of which was classified as serious. Table 11 summarizes the reports of 'other incident'.

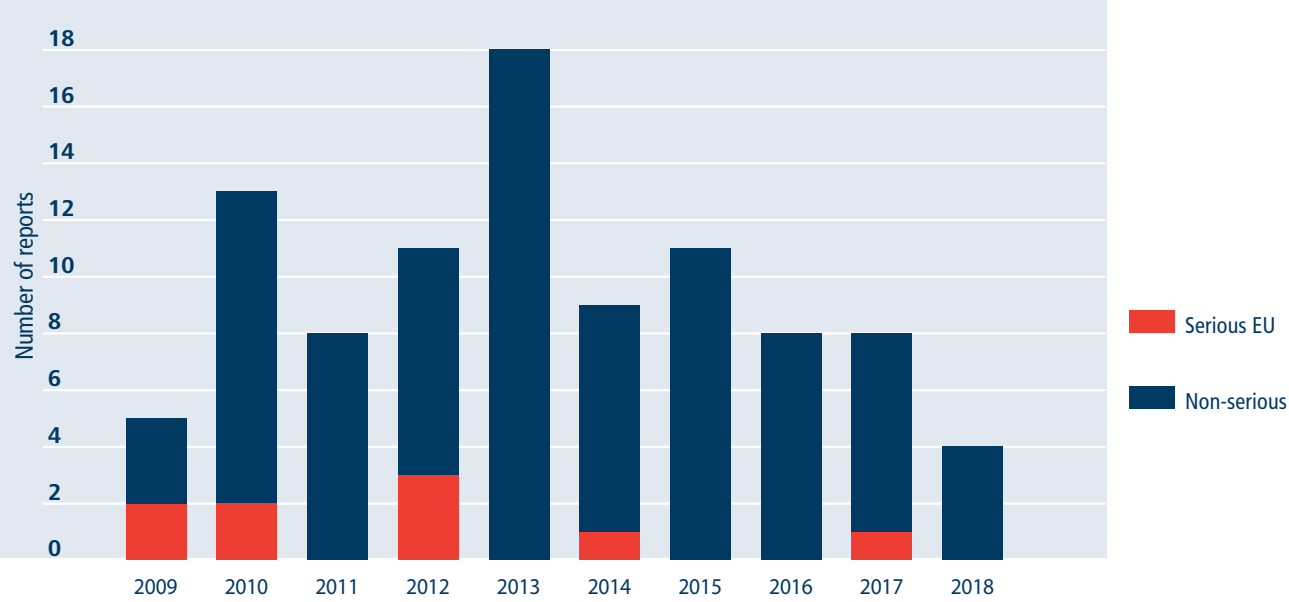

Figure 9. Reports in the category 'Other incident' concerning gametes, embryos and gonadal tissue, 2009-2018

Table 11. Reports in the category 'Other incident' concerning gametes, embryos and gonadal tissue in 2018

Type of error	No. of reports	Type of gamete or embryo	Phase in procedure	Description
Storage error	2	Semen	Donation	Expired semen container provided
				Incorrect semen container provided by gynaecologist
Other	2	Semen	Procurement	Retrograde ejaculation. Insufficient production for IUI
				Inability to ejaculate. Not possible to carry out IUI-treatment

Incorrect product transplanted

In 2018, TRIP received two reports concerning cases in which an incorrect product was transplanted. Reports in this category are always assessed as serious. One report concerned an insemination with semen that did not come from the requested donor, but a different donor. Because the patient's partner had already had a child after assisted reproduction with semen from the requested donor, a pregnancy from semen from a different donor was unwelcome. Emergency contraception (morning-after pill) was prescribed to prevent pregnancy. The other report concerned a case in which a different couple's embryo was transferred, despite double checking of the product. This pregnancy was also prevented. In both cases, the staff involved in the procedure saw what they expected to read on the product, rather than the information that was actually written on it.

Figure 10 provides an overview of all reports in the category 'Incorrect product transplanted' from 2008 to 2018.

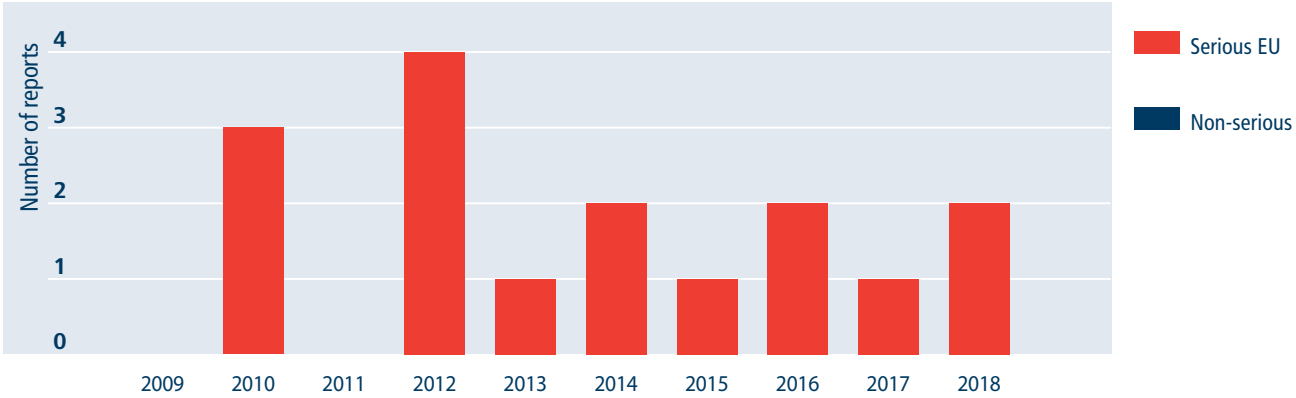

Figure 10. Reports in the category 'Incorrect product transplanted' related to gametes and embryos, 2009-2018

Near miss

In 2018, TRIP received one report classified as a 'Near miss'. Figure 11 provides an overview of all reports of near misses that TRIP has received from 2009 to 2018. Reports of 'Near miss' concern mix-ups or errors that would have led to the transfer or insemination of (an) embryo(s) or semen in the wrong recipient if they had not been detected.

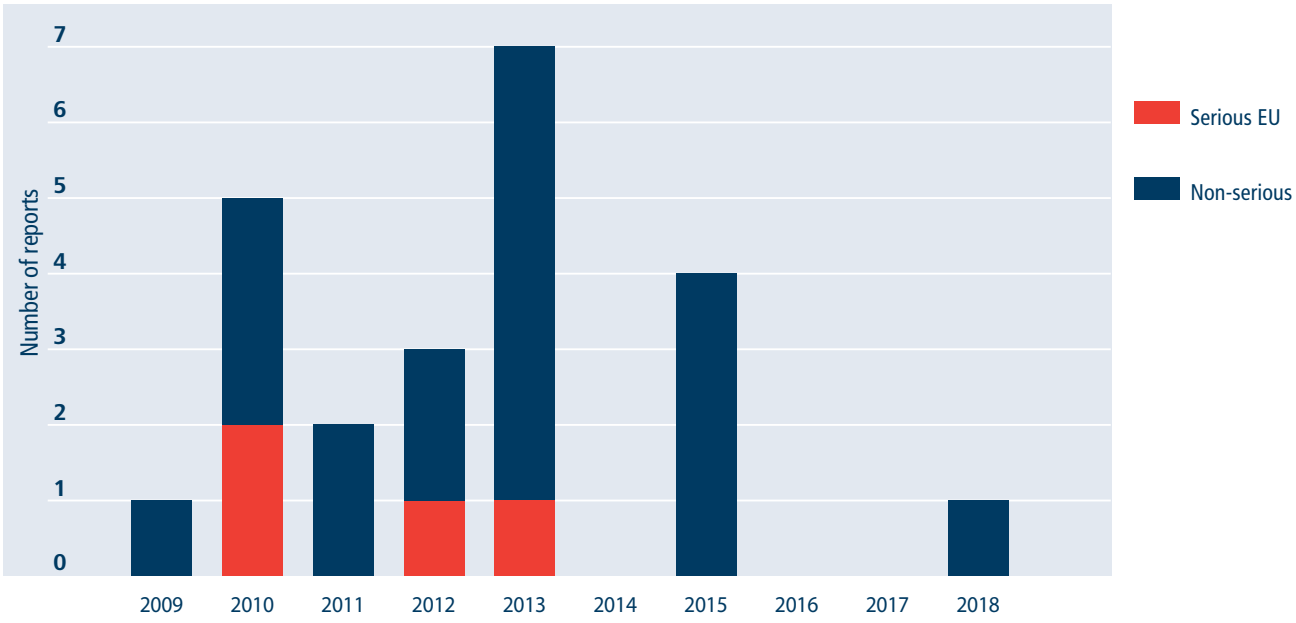

Figure 11. Reports in the category 'Near miss' concerning gametes, embryos and gonadal tissue, 2009-2018

Bacterial contamination of product

In 2018, one report was classified as 'bacterial contamination of product'. In this case, an infection in the embryo culture was detected on the second day. Both the embryos and the semen were cultured, and turned out positive for Pseudomonas aeruginosa. The treatment cycle was lost. The numbers of reports categorized as 'bacterial contamination of product' from 2009 to 2018 are shown in Figure 12.

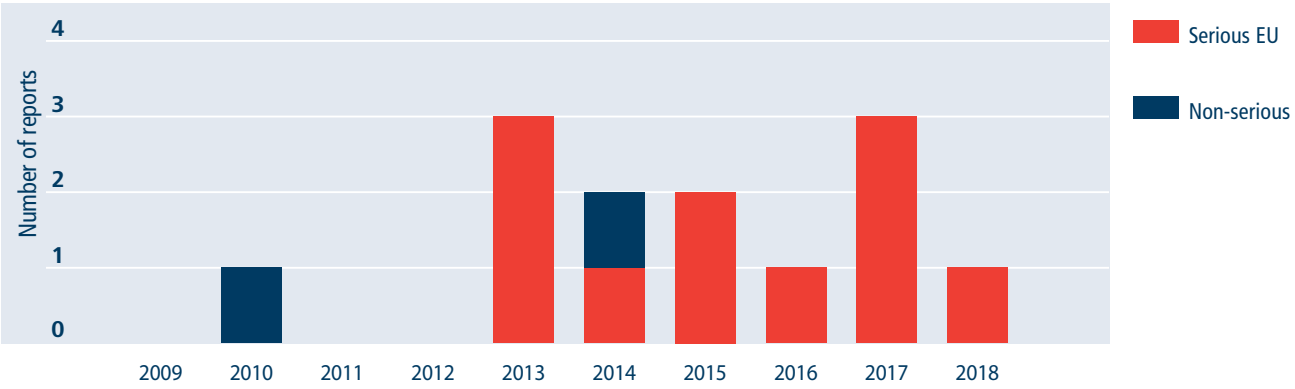

Figure 12. Reports in the category 'Bacterial contamination of product' involving gametes and embryos, 2009-2018

Gametes, embryos and gonadal tissue - summary

In 2018, TRIP received 44 reports related to assisted reproduction. After a decrease in the number of reports related to assisted reproduction in previous years (2015: 75, 2016: 51, 2017: 39), the 2018 data show an increase in the number of reports. TRIP received 39 reports of adverse events, and five reports of adverse reactions, of which four concerned donation complications. All adverse reactions reported were classified as serious. Of the 39 adverse events, 24 were classified as serious. The largest subgroup of reports concerns 'Loss of tissues or cells' (19 reports, 13 classified as serious), which has been the largest subgroup every year, except in 2017. There was also large subgroup of reports concerning 'Congenital abnormality' (12 reports, 9 classified as serious). The one adverse reaction that was not a donation complication concerned a post-transplantation bacterial infection after IUI. The donation complications were: two reports of OHSS, one report of ovarian torsion and one report of severe stomach pains that led to hospitalisation. All donation complications occurred as a result of procedures for donation of tissues or cells for the patients' own treatment.

2.2 Hematopoietic stem cells and therapeutic cells

As of 2018, 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 (as of mid-2018, seven centres due to a merger) 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.

A total of 1717 patients received a HSC transplant in 2018, 58.2% being autologous, 12.3% allogeneic from related donors and 29.5% from unrelated donors.

Cord blood donated by donors from the Netherlands and intended for transplantation to patients unrelated to the donor is processed and stored by Sanquin and subsequently selected for patients inside and outside the Netherlands through Matchis. Additionally, two private blood banks store cord blood for possible future autologous applications.

Processing, distribution, and application

Tables 12, 13, and 14 provide an overview of the number of units of HSC that were processed in stem cell laboratories in the Netherlands and were distributed within the Netherlands, to the EU or outside of the EU and/or were applied in the Netherlands.

Table 12. Processing of hematopoietic stem cells in 2018

Type of cells	Stem cell laboratories	Transplants processed*			
		From NL	From EU	From non-EU	Total
HSC autologous					
Bone marrow	4	23	0	0	23
PBSC	11	2124	0	0	2124
Cord blood	2	1397	0	0	1397
HSC related					
Bone marrow	6	49	0	0	49
PBSC	8	170	0	2	172
Cord blood	1	1	0	0	1
HSC unrelated (column 'From NL' includes units procured through Matchis for distribution outside NL)					
Bone marrow	5	14	31	5	50
PBSC	7	116	254	39	409
Cord blood	5	40	49	17	106

* *If a transplant product is reprocessed in the receiving stem cell laboratory, this is counted a second time. This may cause discrepancies between the numbers shown in the tables..*

Table 13. Distribution of hematopoietic stem cells in 2018

Type of cells	Stem cell laboratories	Bags distributed*			
		From NL	In EU	In non-EU	Total
HSC autologous					
Bone marrow	2	7	0	0	7
PBSC	11	3523	2	0	3525
Cord blood	0	0	0	0	0
HSC related					
Bone marrow	6	47	0	0	47
PBSC	8	169	0	0	169
Cord blood	1	1	0	0	1
HSC unrelated (distribution outside NL per graft)					
Bone marrow	5	50	10	5	65
PBSC	7	416	39	40	495
Cord blood	5	75	1	0	76

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

Table 14. Application of hematopoietic stem cells in 2018

Type of cells	Transplantation centres	Recipients	Bags applied			
			From NL	From EU	From non-EU	Total
HSC autologous						
Bone marrow	2	3	7	0	0	7
PBSC	12	997	3532	0	0	3532
Cord blood	0	0	0	0	0	0
HSC related						
Bone marrow	6	47	47	0	0	47
PBSC	8	163	167	0	0	167
Cord blood	1	1	1	0	0	1
HSC unrelated						
Bone marrow	5	39	41	0	0	41
PBSC	8	414	392	39	7	438
Cord blood	4	53	35	36	2	73

Figure 13 a-b-c shows the numbers of transplants of PBSC, bone marrow and cord blood per year, from 2012-2018. A multiple year overview of the number of patients that received autologous, allogeneic related and unrelated stem cell transplants can be found in Chapter 3, Table 36, 37 and 38.

Figure 13 a-b. Number of recipients of HSC transplants per type of transplant, 2012-2018

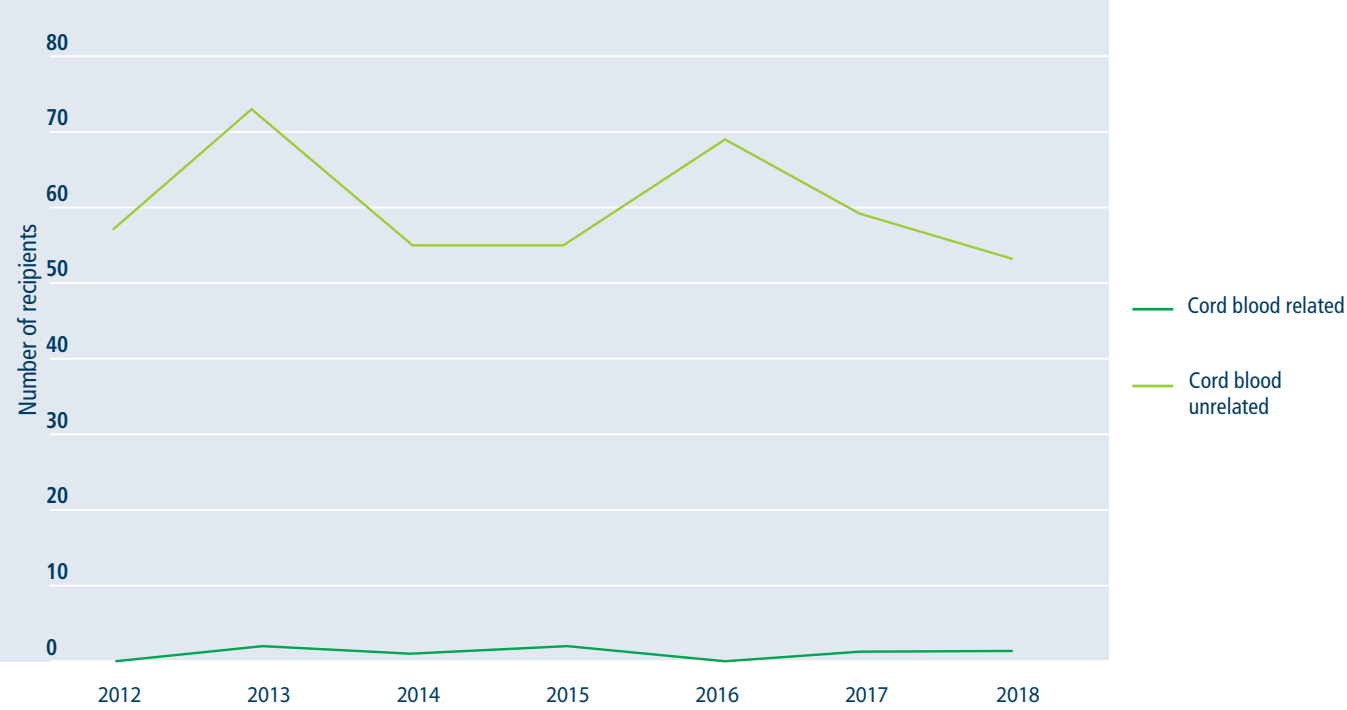

Figure 13 c. Number of recipients of HSC transplants per type of transplant, 2012-2018

In addition to processing hematopoietic stem cells for transplant purposes, several laboratories also process, distribute, and apply cells for therapeutic purposes. The numbers of therapeutic cells processed, distributed and applied in 2018 can be found in Tables 15 and 16. Apart from donor lymphocyte infusions (DLIs), most application of therapeutic cells occurs on a small-scale and in experimental settings. After extensive processing and release for human application, such cells should be considered as ATMPs (Advanced Therapy Medicinal Products).

Donor Lymphocyte Infusion (DLI)

After a allogeneic stem cell transplantation, lymphocytes from the stem cell donor can be applied if some of the patient's own hematopoietic stem cells (malignant or otherwise) can still be found in the patient's body.

Mesenchymal stem cells (MSC)

MSCs are cells that develop into supporting tissues, such as cartilage, bone and adipose tissue, within a patient's body. They play an important role in suppressing the immunologic rejection between the recipient's body and the donor's peripheral blood stem cells/ bone marrow cells. They can be applied for patients with Graft versus Host Disease (GvHD) that does not respond sufficiently to high dose corticosteroids.

Dendritic cells

Dendritic cells are produced by culture and differentiation of monocytes that are procured through an apheresis procedure. Dendritic cells are used for a type of immunotherapy, in which they are stimulated to recognise certain (cancerous) cells, so that they target and clear these after reinfusion.

Tumor infiltrating lymphocytes (TIL)

T-cells are procured from a patient's tumour after it has been removed from the body. These cells are cultured, after which they are transplanted back into the patient's body in order to mount an immune response against the tumorous cells.

Chimeric Antigen Receptor T-cell (CAR-T) / Modified T-cell receptor T-cells (TCR)

For these applications, T-cells are procured from patients through apheresis procedures. The cells are then isolated in a laboratory, activated, and altered genetically so that they are able to recognize specific antigens of the patient's malignancy. After reinfusion, these modified cells can recognize malignant cells with this specific antigen on their surface and eliminate them. Modified TCR cells, in contrast to CAR-T cells, are not modified to recognize antigens on the surface of cells, but tumour-specific peptides that are presented through a Major Histocompatibility Complex (MHC).

Table 15. Processing and distribution of therapeutic cells in 2018

Type of cells	Laboratories	Transplants processed*			Laboratories	Bags distributed		
		From NL	From outside NL	Total		In NL	In EU	Total
Lymphocytes (DLI) related	8	74	1	75	7	87	0	87
Lymphocytes (DLI) unrelated	7	12	136	148	7	62	32	94
Mesenchymal stem cells autologous	2	154	0	154	1	18	0	18
Mesenchymal stem cells unrelated	2	8	2	10	2	57	0	57
Dendritic cells autologous	1	87	0	87	1	87	0	87
Dendritic cells unrelated	1	1	1	2	1	2	0	2
TC-Til cells autologous	2	16	19	35	1	10	0	10
CAR-T/TCR cells	3	6	14	20	2	7	1	8
Mononuclear cells autologous	1	1	0	1	0	0	0	0

* *If a transplant product is reprocessed in the receiving stem cell laboratory, this is counted a second time. This may cause discrepancies between the numbers shown in the tables.*

Table 16. Application of therapeutic cells in 2018

Type of cells	Transplantation centres	Recipients	Units applied		
			From NL	From Outside NL	Total
Lymphocytes (DLI) related	9	83	123	3	126
Lymphocytes (DLI) unrelated	8	91	83	54	137
Mesenchymal stem cells autologous	1	7	18	0	18
Mesenchymal stem cells unrelated	2	20	57	6	63
Dendritic cells autologous	1	87	87	0	87
Dendritic cells unrelated	2	16	12	4	16
TC-Til cells autologous	2	8	10	0	10
CAR-T/TCR cells	3	8	7	3	10
Mononuclear cells autologous	0	0	0	0	0

Reports

In 2018, TRIP received 38 reports of adverse events (29), adverse reactions (8), and donation complications (1) related to HSC and therapeutic cells. Chapter 3 provides a multi-year overview of the reports related to HSC and therapeutic cells. Of the 29 adverse events TRIP received in 2018, six were classified as serious. These reports are described in Table 17. The 23 adverse events that were not classified as serious are summarised in Table 18.

Table 17. Serious adverse events related to HSC in 2018

Type of HSC	Adverse event (category and description)	Reports
Bone marrow, allogeneic, unrelated	Bacterial contamination of product • Positive culture results, *Cutibacterium acnes* (formerly *Propionibacterium acnes*), after procurement, after administration and in reference sample. Increased fever in recipient, more severe than expected for febrile neutropenia	1
PBSC autologous	Bacterial contamination of product • 1x Product discarded after culture showing *Staphylococcus aureus*, new mobilization and apheresis carried out • 1x Product discarded after culture showing *Staphylococcus epidermidis*, new mobilization and apheresis carried out	2
	Other contamination • Product discarded after positive culture for Candida glabrata following procurement, new mobilization and apheresis carried out	1
	Loss of cells • Clot in product because an insufficient amount of ACDA was added, the line was not attached correctly, 1 bag lost, good engraftment	1
Cord blood allogeneic, unrelated	Near miss • Mix-up and temporarily untrackable product during transport because of incorrect labelling by the carrier; it arrived two days later in good condition	1
Total		**6**

Table 18. Non-serious adverse events related to HSC in 2018

Type of HSC	Adverse event (category)	Reports
PBSC autologous	• Bacterial contamination of product • Loss of tissue or cells • Other incident	6 1 2
Bone marrow related	• Bacterial contamination of product • Other incident	1 1
Bone marrow unrelated	• Bacterial contamination of product • Other incident	4 1
PBSC unrelated	• Other incident	4
Cord blood unrelated	• Loss of tissue or cells • Other incident	1 2
Total		**23**

In two cases, a loss of cells occurred (once during the distribution phase, once during the processing phase, due to leakage from the bag). Three of the ten other incidents also concerned cases in which leakage from the bag occurred. Chapter 3 gives an overview (Figure 30) concerning leagage of bags and containers in 2006-2018. Two other incidents related to the Single European Code (SEC) (see box). TRIP did not receive any reports concerning insufficient growth/engraftment in 2018.

Two other incidents related to the SEC

- An allogeneic bone marrow donation is delivered with an incorrect SEC (errors in both the donation code and the product identification code). The Tissue Establishment (TE) number of Matchis is used for is used for the application of the product. The laboratory involved in this incident had not optimised the SEC at the time of the events described in this report.
- An unrelated allogeneic peripheral blood stem cell product is delivered with a missing digit in the donation identification code. The Matchis TE number is used for the application of the product.

Both reports concern events occurring during the first months of 2018. The use of the Matchis identification number, among available documentation enabled the product to be unambiguously identified as the correct product.

TRIP received eight reports concerning adverse reactions, one of which was classified as serious. This report concerned a severe reaction to DMSO during reinfusion of autologous PBSC, as described in Table 19.

Table 19. Overview of adverse reactions in 2018, subdivided according to the type of hematopoietic stem cell

Type of HSC	Reaction (category and description)	Reports
PBSC autologous	Anaphylactic reaction • Hypotension and decrease of oxygen saturation as a result of the use of DMSO Post-transplant febrile reaction • Severe chills and fever 1 hour after reinfusion Other reaction • Serious reaction to DMSO with hypotension and decrease of oxygen saturation* • Vomiting after severe coughing at the start of the reinfusion, transplant continued	1 1 2
PBSC related	Anaphylactic reaction • Nausea and vomiting, back pain, chills and rise in temperature with administration of major ABO incompatible product, no hemolysis Other reaction • Nausea, vomiting, chills/discomfort, decrease in oxygen saturation with administration of major ABO incompatible product, no hemolysis	1 1
PBSC unrelated	Other reaction • Fever without focus, several hours after infusion	1
Cord blood unrelated	Other reaction • After infusion of 90% of the product: vasovagal reaction, and later increase in BP, ascribed to hypertension as a result of DMSO	1
Total		**8**

* *Serious*

TRIP received one report concerning a donation complication. This report concerned a non-serious citrate reaction in combination with a vasovagal reaction and hyperventilation with an unrelated PBSC donation. The apheresis procedure was not resumed after the reaction had been treated; the product was applied and engraftment occurred. Table 35, in Chapter 3, gives a multi-year overview of donation complications.

Bacterial contamination of product and other contamination of product

In 2018, as in 2017, TRIP received 15 reports registered in the categories 'Bacterial contamination of product' and 'Other contamination of product'. These reports are summarised in Table 20.

Table 20. Reports of Bacterial contamination and Other contamination of product in 2018

Type of HSC	Agent	Impact on product	Impact on recipient	Serious	Engraftment
Bone marrow related	*Paenibacillus spp*	Units already infused	None	No	Unknown
Bone marrow unrelated	*Staphylococcus sacharolyticus*	Units already infused	None, preventive administration of antibiotics based on antibiogram	No	Unknown
	Cutibacterium acnes	Units already infused	None, patient was already receiving prophylactic antibiotics	No	Sufficient
	Staphylococcus epidermidis en *Cutibacterium acnes*	Units already infused	None, patient was already receiving prophylactic antibiotics (i.a. against Gram-positive cocci)	No	Sufficient
	Cutibacterium acnes	Units already infused	Fever present before transfusion, patient already receiving broad-spectrum antibiotics, symptoms increased, imputability: possible	Yes	Sufficient
	Staphylococcus caprae (CNS)	Units already infused	None, no additional treatment	No	Sufficient
PBSC autologous	*Staphylococcus epidermidis*	Units not yet administered	Would have been administered without extra precautions. However, patient's morbidity progressed and a different treatment plan was adopted	No	Not applicable
	Parvimonas micra	Discarded	Different treatment plan, patient not suitable for autologous transplantation due to osteomyelitis	No	Not applicable
	Staphylococcus aureus	Discarded	New apheresis	Yes	Not applicable
	Bacteroides spp.	Units administered	None, antibiotics according to protocol	No	Sufficient
	Staphylococcus warneri	Units administered	Antibiotics	No	Sufficient
	Rothia dentocarios en *Streptococcus mitis* en *Streptococcus vestibulans*	Units administered	Antibiotics	No	Sufficient
	Moraxella nonliquefaciens	Units not yet administered (potential 2nd transplant)	Not applicable	No	Not applicable
	Staphylococcus epidermidis	Discarded	New apheresis	Yes	Not applicable
	Candida glabrata	Discarded	New apheresis	Yes	Not applicable

Remarkably, different approaches were taken after three contaminations involving Staphylococcus epidermis. In one case, the product was discarded, in another case the product would have been administered without extra precautions, and in the third the product had already been administered to the patient, who did not show any symptoms, but had been receiving prophylactic antibiotics.

Hematopoietic stem cells and therapeutic cells - summary

The number of applications of stem cells has been increasing, especially the number of PBSC transplants. The number of reports related to HSC in 2018 (38) was similar to the number of reports in 2017 (40). There were seven serious reports, six concerning serious adverse events and one concerning an adverse reaction. A single non-serious donation complication was reported. As in 2017, TRIP received 15 reports of contaminated HSC products, three of which were classified as serious because of a loss of cells which meant new mobilization and apheresis procedures were necessary. In 2018, TRIP did not receive any reports relating to therapeutic cells.

2.3 Bone and other musculoskeletal tissues

There are six bone banks in the Netherlands, situated in hospitals and orthopaedic centres. These banks process, store and distribute bone from living donors (allogeneic femoral heads and autologous cranial bone). Additionally, there is one bone bank that is licensed as an organ bank that is not affiliated with a hospital or a clinic. This bone bank also processes, stores, and distributes post-mortem musculoskeletal tissues, in addition to femoral heads and (autologous) cranial bone from living donors. Furthermore, there are ten tissue establishments in the Netherlands that import (post-mortem) musculoskeletal tissues (mainly from the United States) and distribute these around Europe. One of these tissue establishments also processes allogeneic bone products from EU hospitals, to deliver them back to the tissue establishments of the hospitals after processing.

Bone

Processing, distribution, and application

Table 21 shows the number of units of bone processed and distributed in 2018. Table 22 shows the number of units of bone applied in 2018. These data were supplied by 18 tissue establishments, four independent treatment facilities, 47 oral implantology practices and 62 hospitals. In 2018, the number of post-mortem femoral heads processed and distributed in the Netherlands was lower than in 2017 (Figure 14).

Table 21. Processing and distribution of bone tissue in 2018

Type	Tissue establishments*	Processed			Distributed					
		From on-site clinic	From NL	From EU	Unit	In on-site clinic	In NL	In EU	Outside EU	Total
Bone, whole	3	0	131	12	Bone	0	106	15	16	137
Bone filler, mineralised	8	0	1459	0	Pack	0	6204	4080	3102	13386
Femoral head, living donor	6	751	2832	147	Bone	499	1640	533	0	2672
Femoral head, post-mortem donor	3	0	10	0	Bone	0	39	20	0	59
Bone filler, demineralised	8	0	231	0	Pack	0	1198	15678	14349	31225
Auditory ossicles	0	0	0	0	Graft	0	0	0	0	0
Cranial bone (autologous)	3	47	82	0	Graft	23	57	0	0	80

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

Table 22. Application of bone tissue in 2018

Type	Hospitals/ clinics/ practices	Recipients	Applications					
			Unit	From on-site clinic	From NL	From EU	From non-EU	Total
Bone, whole	14	80	Bone	0	80	0	0	80
Bone filler, mineralised	72	2402	Pack	0	2028	523	0	2551
Femoral heads (whole or halved)*	58	1546	Bone	477	1193	4	0	1674
Bone filler, demineralised	38	671	Pack	0	605	86	0	691
Auditory ossicles	1	1	Graft	0	0	1	0	1
Cranial bone (autologous)	6	49	Graft	23	28	0	0	51

* *Combined data on living and post-mortem donors, as hospitals do not always distinguish between these sources.*

Figure 14 shows the number of bone products used as bone filler that were distributed in the Netherlands from 2009 to 2018. The distribution of mineralised bone filler has continued to increase. Many hospitals choose to request bone chips that have already been ground, rather than grinding femoral heads themselves. The distribution of demineralised bone filler does not show any further decrease. The number of femoral heads, which will be ground by healthcare facilities themselves, shows a slight decrease in 2018.

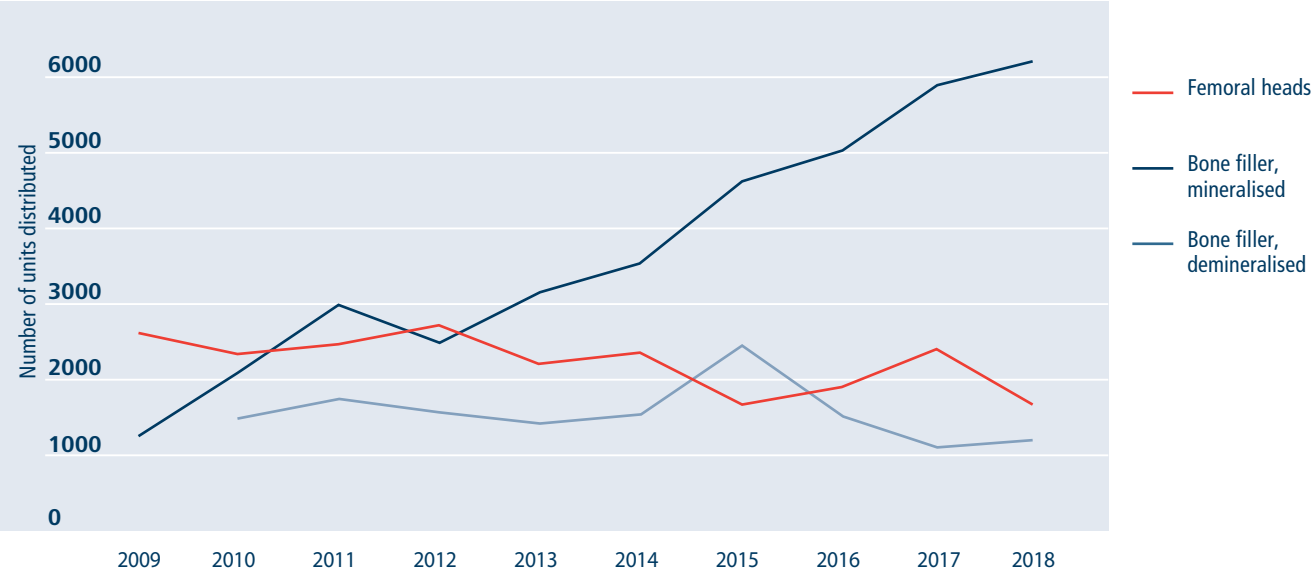

Figure 14. Number of units of bone filler distributed in the Netherlands, 2009-2018

Reports

In 2018, TRIP received four reports of adverse events concerning bone tissue, one of which was classified as serious. The events were reported by one tissue establishment and one hospital. Figure 15 provides an overview of the numbers of adverse reactions and events from 2009 to 2018. Table 23 summarised the adverse events that occurred in 2018.

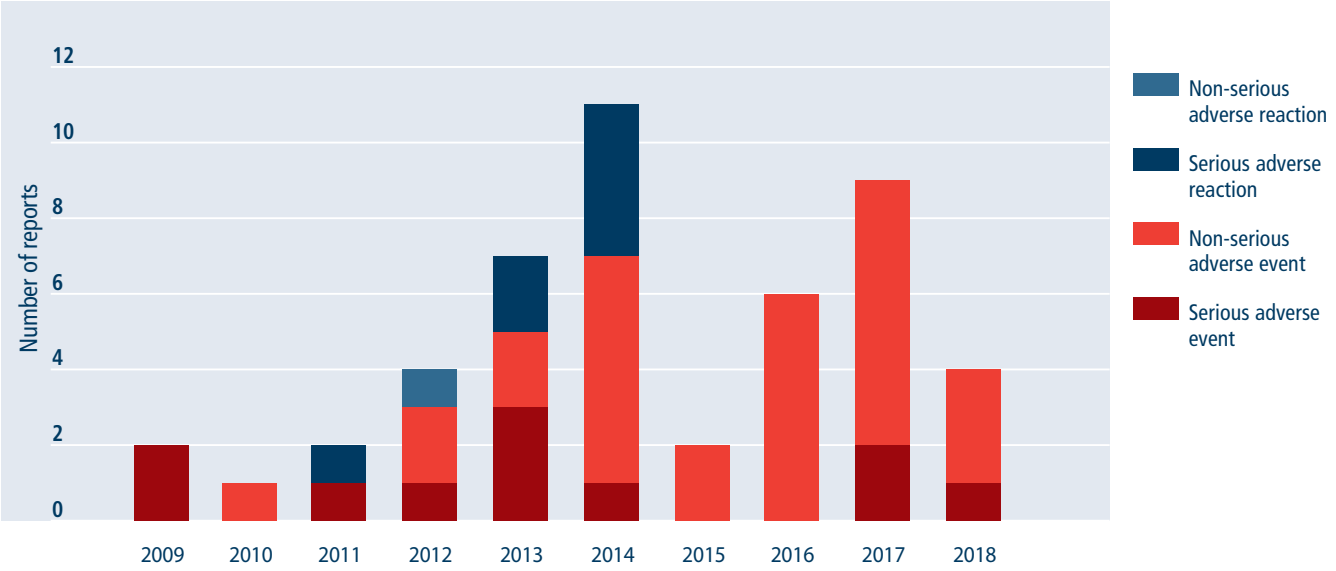

Figure 15. Reports related to bone tissue, 2009-2018

Table 23. Overview of adverse events involving bone tissue in 2018

Category of event	Reports	Type of bone tissue	Description
Loss of tissue or cells	2	Femoral head	When the femoral head is received in the hospital, the packaging turns out to be damaged, and the product is no longer sterile. Femoral head not used
		Bone chips	In the process of moving jars of frozen bone chips in a freezer, six jars were not returned to the freezer. The contents thawed and were lost
Other incident	2	Bone chips and halves of femoral heads	It is recognised that during one step of processing, the sterility of the outside of the bone jar cannot be guaranteed. This could result in contamination of the sterile area of an operating theatre. A recall procedure for 955 products is carried out. Investigation and lookback procedures do not indicate that any contaminations or transmissions to recipients took place*
		Bone chips, bone wedges and whole bones, in addition to tendon tissue and fascia	The bar code of the product identification sequence of the SEC is found to have an error. The year in the expiry date is displayed incorrectly. The eye-readable SEC is correct

* *Serious*

Other musculoskeletal tissues

Processing, distribution, and application

Table 24 shows the number of tendons, ligaments, fascia, cartilage units and menisci that were processed and distributed in the Netherlands in 2018. Table 25 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 partly due to hospitals storing these units. At -80°C, tendons may be stored for up to five years. The discrepancies between the distribution and application figures for cartilage show that the applying establishments are not taking sufficient care in registering these figures.

Table 24. Processing and distribution of other musculoskeletal tissues in 2018

Type	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Tendons	2	895	Graft	537	50	0	587
Bone-tendon-bone grafts	2	30	Graft	28	5	0	33
Ligaments	0	0	Graft	0	0	0	0
Fascia	3	80	Graft	1093	0	0	1093
Cartilage	2	1	Graft	123	0	0	123
Menisci	1	20	Graft	12	6	0	18

Table 25. Application of other musculoskeletal tissues in 2018

Type	Hospitals/ clinics	Recipients	Applications				
			Unit	From NL	From EU	From non-EU	Total
Tendons	46	315	Graft	335	0	0	335
Bone-tendon-bone grafts	8	48	Graft	46	2	0	48
Ligaments	1	1	Graft	1	0	0	1
Fascia	20	339	Graft	346	8	0	354
Cartilage	5	46	Graft	43	3	0	46
Menisci	2	15	Graft	13	2	0	15

Figure 16 shows the numbers of tendons, ligaments, fascia, cartilage and menisci distributed in the Netherlands from 2009 to 2018. The figure shows that the distribution of cartilage remains relatively stable. For 2018, it also shows a slight decrease in the number of tendons distributed and an increase in the number of fascia distributed. Since 2017, no chondrocytes have been distributed. Since they have been classified as Advanced Therapy Medicinal Products (ATMP), they will not be considered in this report.

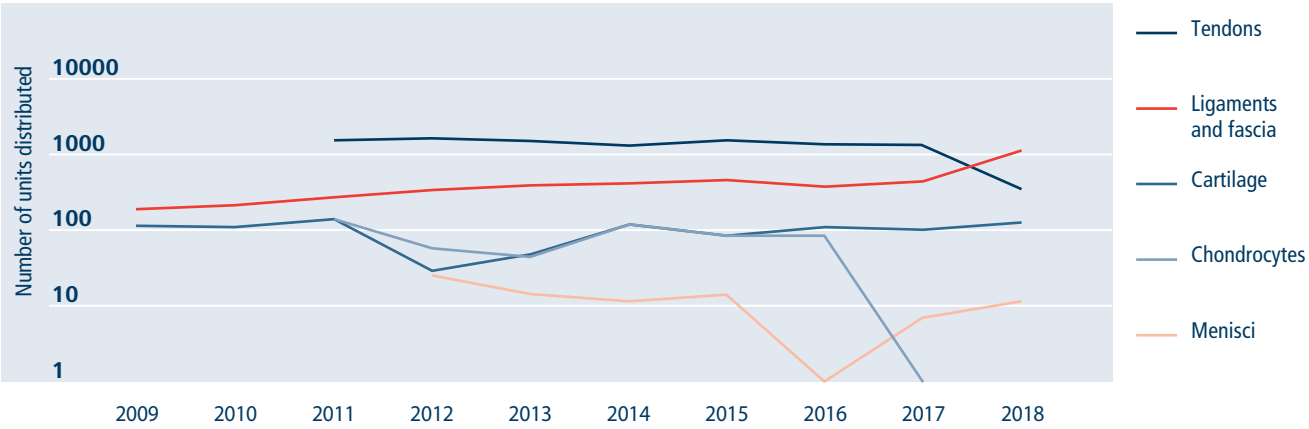

Figure 16. Number of units of other musculoskeletal tissues distributed in the Netherlands, 2009-2018

Reports

In 2018, TRIP received two reports related to other musculoskeletal tissues. Neither of them was classified as serious. One of the reports concerned a product problem with a cartilage graft. The cartilage could not be used during surgery. The other adverse event concerned a selection error with a bone-tendon-bone graft: a graft of which the expiry date had passed was selected. The tendon tore when it was put under tension. A different bone-tendon-bone graft was in stock.

Figure 17 provides an overview of all reports involving other musculoskeletal tissues that TRIP received from 2009-2018. All 2010 reports concern adverse events involving culturing autologous chondrocytes. The procurement and processing of chondrocytes is subject to the Dutch Law on safety and quality of substances of human origin. In 2010, two tissue establishments reported seven adverse events to TRIP, six of which were classified as serious. Both of these tissue establishments have ceased their activities involving culturing chondrocytes.

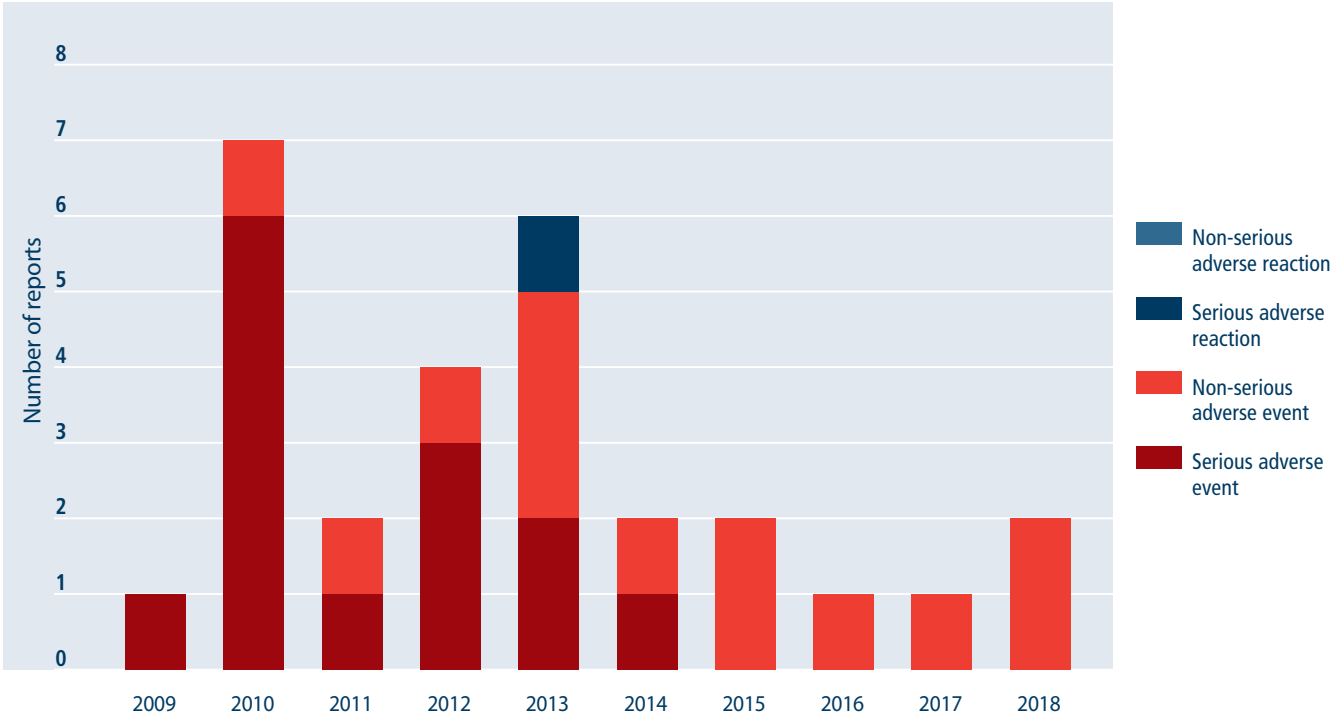

Figure 17. Overview of reports involving other musculoskeletal tissues, 2009-2018

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 (one eye bank has two tissue establishment licenses). Corneas have a limited shelf life: stored in a culture medium, a cornea remains in optimal condition for approximately four weeks. Sclera may be stored for up to a year. Corneas are distributed within the EU and exported to countries outside the EU. In 2018 no scleras were exported. Dutch hospitals and clinics can purchase sclera from tissue establishments licensed in the EU.

Processing, distribution, and application

Table 26 shows the number of units of ocular tissue processed and distributed in the Netherlands in 2018. Table 27 shows the number of units of ocular tissue applied in the Netherlands in 2018, as provided by the hospitals, clinics and independent treatment facilities. Twenty-one Dutch hospitals and clinics transplant ocular tissue. Seventeen hospitals and clinics transplant corneas and ten of them also transplant sclera.

Four transplant sclera only. The difference between the number of units of sclera distributed and the number applied has not decreased in comparison to 2017; the gap may be explained by the fact that scleras can be stored longer. The figures for corneas show only a slight discrepancy. There was significant increase in the numbers of corneas processed (2017: 2717, 2018: 4405), distributed outside the Netherlands (2017: 217, 2018: 605) and transplanted. The number of tissue donors saw a 59% increase, from 1501 in 2017 to 2398 in 2018. The most significant reason for the increase is the change in the criteria for donation of ocular tissue. As of 1 January 2018, bacterial bloodstream infection (sepsis) is no longer a contraindication for cornea donation. As a result of this change, 17% more transplants of corneas occurred in the Netherlands, 244 more than in 2017. The waiting list decreased by 12%. Figure 18 presents the numbers of corneas and of units of sclera distributed from 2009 to 2018.

Table 26. Processing and distribution of ocular tissue in 2018

Type	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Cornea	3	4405	Complete or lamella	1720	533	72	2325
Sclera	1	434	Complete or quadrant	1570	40	0	1610
Limbal stem cells	1	7	Graft	0	7	0	7

Table 27. Application of ocular tissue in 2018

Type	Hospitals/ clinics	Recipients	Applications				
			Unit	From NL	From EU	From non-EU	Total
Cornea	14	1396	Complete or lamella	1410	0	0	1410
Sclera	17	871	Complete or quadrant	872	10	0	882

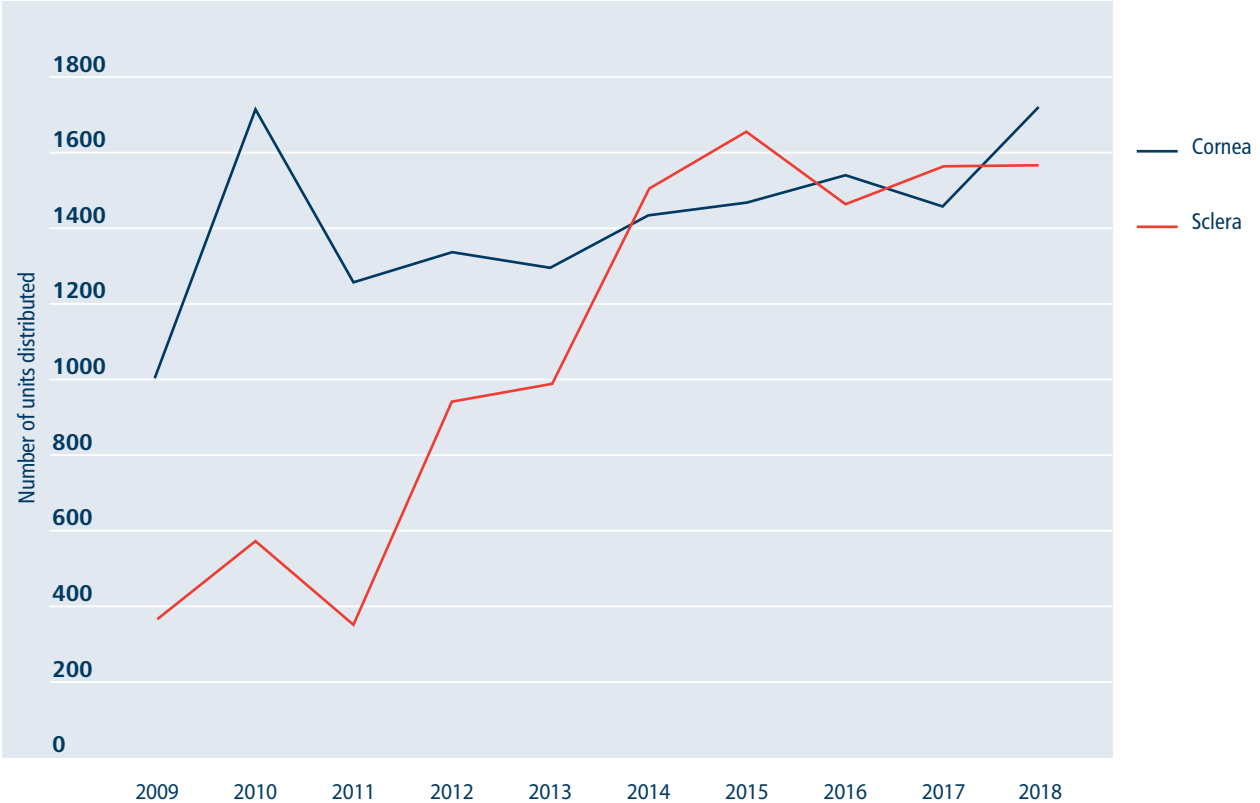

Figure 18. Numbers of units of cornea and sclera distributed in the Netherlands, 2009-2018

Reports

In 2018, TRIP received six reports of adverse events related to ocular tissue. These were all classified as serious. TRIP did not receive any reports of adverse reactions related to ocular tissue. The reports were submitted by three tissue establishments. A brief description of the reports can be found in Table 28. Figure 19 shows an overview of all reports involving ocular tissue from 2009 to 2018.

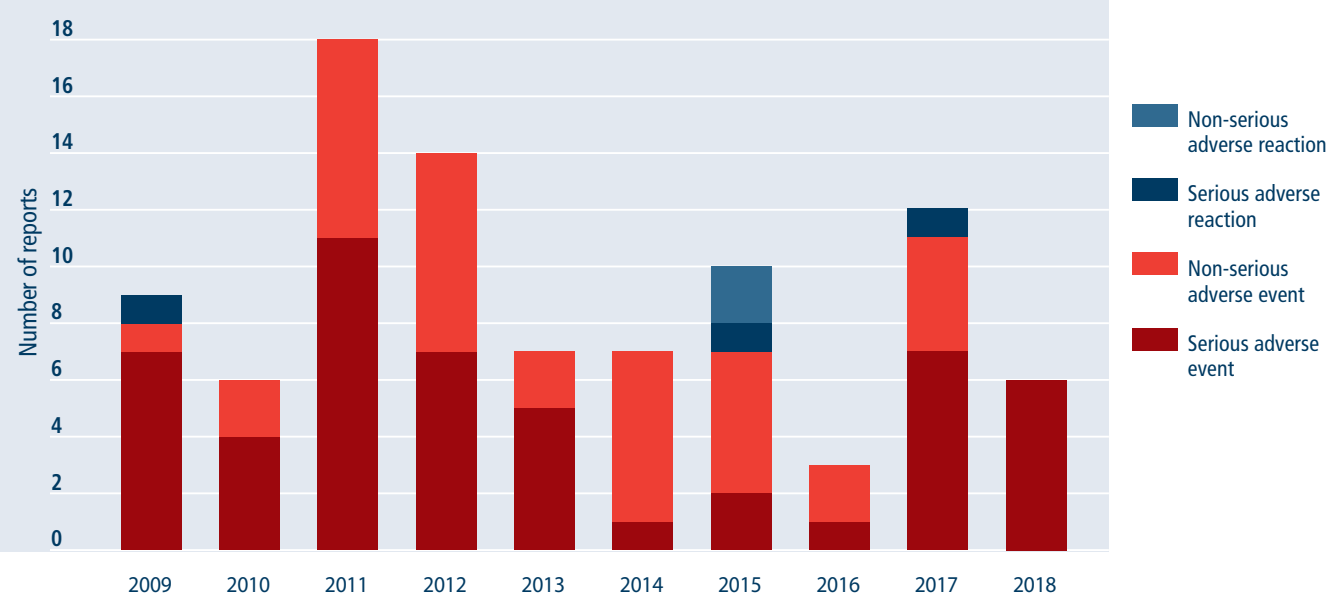

Figure 19. Reports involving ocular tissue, 2009-2018

Table 28. Overview of adverse reactions and events involving ocular tissue in 2018

Category of event	Reports	Description
Incorrect product transplanted	3	Autopsy of the donor reveals viral myocarditis. A systemic viral infection cannot be ruled out. This is a general contraindication for donation. One of the two corneas had already been transplanted. There was no reaction in the recipient*
		Cornea (DMEK**) had not been marked correctly. After the transplantation, the cornea does not become clear. The patient receives a new transplant*
		A risk of cross contamination arose, because the laboratory used a bottle of culture medium that had already contained a cornea when two cornea lamellas were cut. This was not discovered until after the transplant had taken place. The recipient did not show any symptoms*
Viral infection of product	1	Transmission of HSV-1 to two recipients. Cross contamination during one DMEK**-preparation process*
Loss of tissue or cells	1	Mix-up of a DMEK** and a pre-cut lamella. Pre-cut lamella is lost after manipulation in the OR. A transplant is cancelled*
Other incident	1	Autopsy of the donor shows findings suggestive of lysosomal storage disease. There is no kidney tissue available to test for cystinosis. Cystinosis may lead to crystal deposition in the cornea. Both corneas have already been transplanted. No fFollow-up information of recipients available*

* *Serious*

** *Descemet Membrane Endothelial Keratoplasty*

2.5 Cardiovascular tissue

Processing, distribution, and application

Tables 29 and 30 show the processing, distribution, and application figures for cardiovascular tissue in 2018. The Netherlands has one cardiovascular tissue bank. Five healthcare institutions performed heart valve transplantations in 2018. Furthermore, two hospitals applied vascular patches and two hospitals applied pericardium. Figure 20 shows the number of transplanted cardiovascular tissues from 2009 onwards.

Table 29. Processing and distribution of cardiovascular tissue in 2018

Type	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Aortic valves	1	217 *	Graft	8	4	0	12
Pulmonary valves	1	217 *	Graft	81	21	0	102
Vessels	1	16	Graft	0	0	0	0
Patches	1	88	Graft	42	20	0	62
Pericardium	1	0	Graft	143 **	0	0	143

* *Donor hearts*
** *Originating from outside the EU and distributed by a tissue establishment in NL*

Table 30. Application of cardiovascular tissue in 2018

Type	Hospitals/ clinics	Recipients	Applications				
			Unit	From NL	From EU	From non-EU	Total
Aortic valves	5	18	Graft	8	10	0	18
Pulmonary valves	5	96	Graft	81	15	0	96
Vessels	0	0	Graft	0	0	0	0
Patches	4	42	Graft	40	3	0	43
Pericardium	4	41	Graft	37	4	0	41

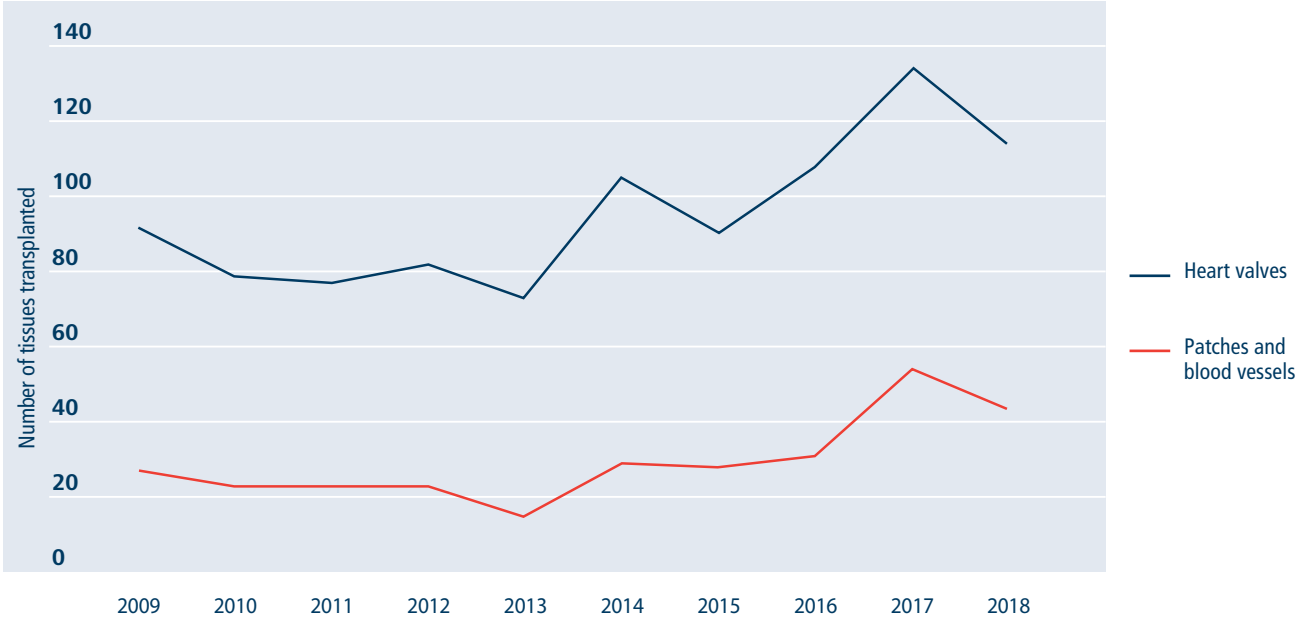

Figure 20. Number of cardiovascular tissues transplanted in the Netherlands, 2009-2018
Data from Dutch Transplantation Foundation and, from 2013 onwards, TRIP reports

Reports

In 2018, TRIP received two reports related to cardiovascular tissue, one of which was classified as serious. Bacterial contamination with *Cutibacterium acnes* was detected in a peroperative culture of a pulmonary valve. Sampling during the surgical procedure is not part of the protocol of this tissue establishment. There is a serious risk of the culture being contaminated in the operating theatre. The patient was treated prophylactically with antibiotics, which prolonged hospitalization. The other report concerned a non-serious adverse event. An incorrectly sized patch was ordered because of a mistake (selection error) in the establishment carrying out the transplant. A substitute patch was available in time, so the patient's surgery was not postponed.

Since 2009, TRIP has received nine reports related to cardiovascular tissue, six of which were classified as serious. The reports are shown in Figure 21.

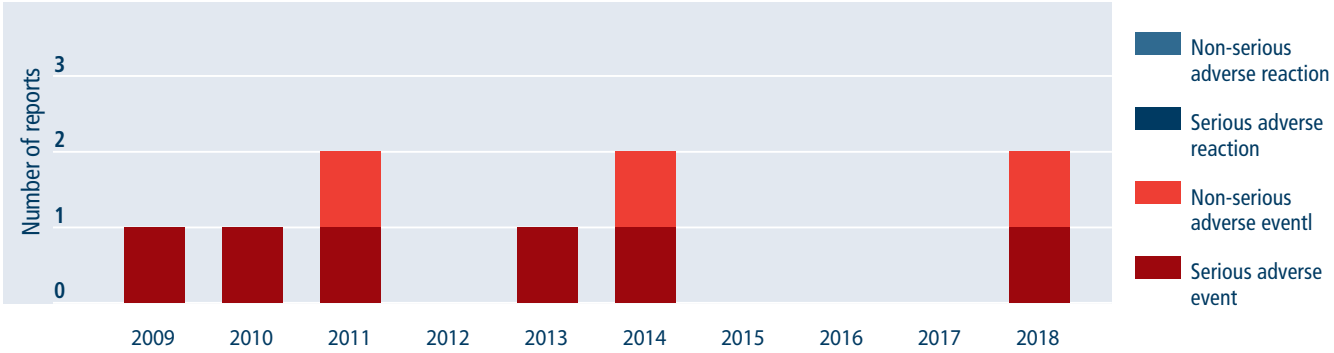

Figure 21. Reports related to cardiovascular tissue, 2009-2018

2.6 Skin

Processing, distribution, and application

The Netherlands has one large skin bank, which processes, stores and distributes skin donated post-mortem. Skin tissue is subdivided into donor skin, autologous skin and acellular dermis. Table 31 shows the number of units of skin tissue processed and distributed in 2018. Donor skin is applied most often, particularly in burn patients as a temporary wound cover. Much of the donor skin is distributed outside the Netherlands. Furthermore, the Netherlands has two distributors of acellular dermis originating from outside the Netherlands. Table 32 shows the number of units of skin that were applied in 2018. The difference between the number of units distributed and the number of units applied can be attributed to the fact that hospitals and burn centres store units of donor skin. Figure 22 shows the number of units of skin and skin products distributed from 2011 to 2018. The data from 2016 show a one-off increase in the number of distributed units of donor skin. That year, one burn centre ordered more donor skin than usual because of an increase in the number patients and several clinical studies.

Table 31. Number of units of skin processed and distributed in 2018

Type	Tissue establishments	Processed NL / EU	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Donor skin	1	367* / 51*	Pack	1626	8625	5053	15304
Acellular dermis	3	17* / 0	Graft	422	117	127	666

* *Donors*

Table 32. Number of units of skin applied in 2018

Type	Hospitals/ clinics/ practices	Recipients	Applications				
			Unit	From NL	From EU	From non-EU	Total
Donor skin	6	87	Pack	1421	0	0	1421
Autologous skin*	2	31 *	Graft	31	0	0	31
Acellular dermis	8	139	Graft	176	1	0	177

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

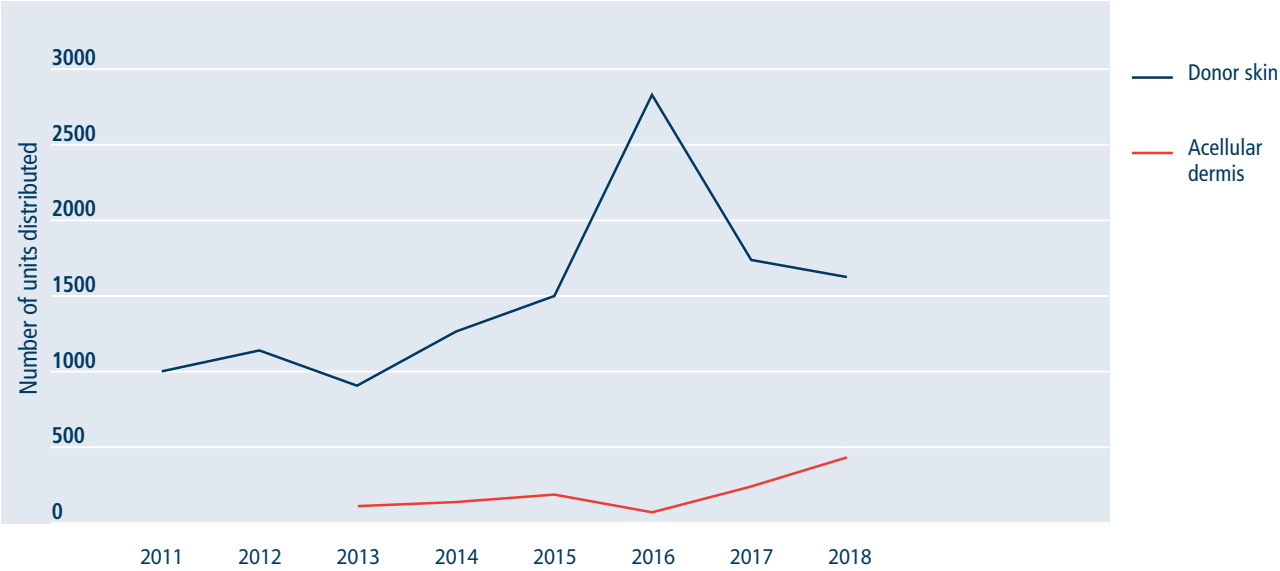

Figure 22. Units of skin and acellular dermis distributed in the Netherlands, 2011-2018

Reports

In 2018, TRIP did not receive any reports involving skin tissue.

2.7 Other tissues and cells

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

Processing, distribution, and application

Tables 33 and 34 below show, the number of units of other tissues and cells processed and distributed, and the number of units of other tissues and cells applied, respectively, The data show a significant increase in the number of amniotic membranes distributed in the EU. The majority of these amniotic membranes was distributed by a single tissue establishment that merely distributes and does not perform any processing. The distributed amniotic membranes originate from inside the EU. In comparison to 2017, twice as many tissue establishments reported use of amniotic membrane in 2018. In the Netherlands, amniotic membrane is chiefly used to cover damaged cornea in anticipation of further treatment.

Table 33. Processing and distribution of other tissues and cells in 2018

Type	Tissue establishments	Processed NL / EU / non-EU	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Amnion	3	1* / 6* / 0	Pack	200	691	11	902
Pancreatic islets	1	43** / 4** / 0	Graft	13	0	0	13
Umbilical cord tissue	1	142 / 0 / 0	Graft	0	0	0	0
Tumour tissue	1	0 / 6 / 13	Graft	0	0	0	0
Red blood cells***	1	18 / 0 / 0	Bag	17	0	0	17
Leukocytes***	1	119 / 0 / 0	Bag	118	0	0	118

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

Table 34. Application of other tissues and cells in 2018

Type	Hospitals/ clinics	Recipients	Applications				
			Unit	From NL	From EU	From non-EU	Total
Amnion	10	114	Pack	118	0	0	118
Pancreatic islets	1	9	Graft	12	0	0	12
Red blood cells***	1	2	Graft	2	0	0	2
Leukocytes***	1	2	Graft	2	0	0	2

*** *Radioactively labelled for diagnostic purposes*

Reports

In 2018, TRIP did not receive any reports involving other tissues or cells. Throughout TRIP's years of collecting data, there have been only two reports involving this group of tissue types: one report concerning loss of a granulocyte product and one report concerning amniotic membrane.

CHAPTER 3

Vigilance regarding hematopoietic stem cells and therapeutic cells, 2006-2018

3.1 Introduction

After an initial ramp-up period (2006-2009), in 2010 to 2018, TRIP has received a fairly constant number of reports (83-121) each year regarding adverse events and reactions related to human tissues and cells. The participation rate in tissue establishments, hospitals, and clinics is generally good, as further discussed under 'findings and recommendations'. Figure 23 shows the number of reports per year.

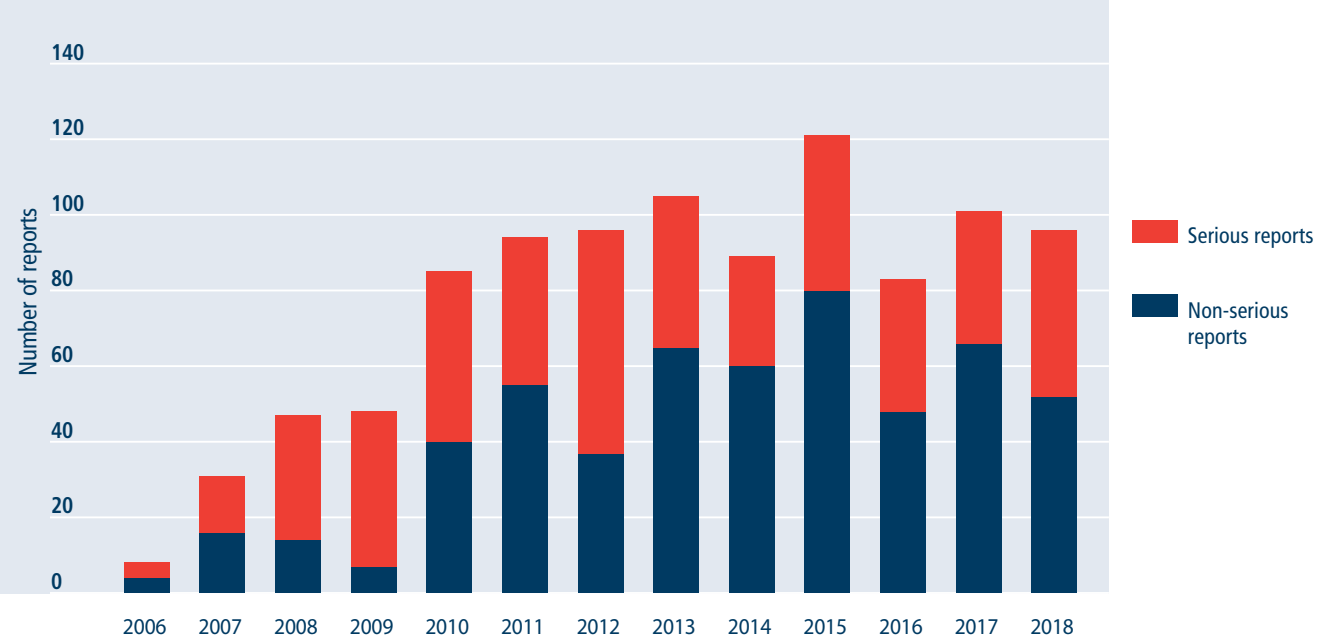

Figure 23. Number of biovigilance reports per year, all tissues and cells

This chapter will discusses the reports of adverse reactions and events in relation to the related to the numbers of processed and applied units of the different types of hematopoietic stem cells (HSC). Additionally, specific clusters of reports related to HSC and other therapeutic cells will be described. These clusters are donation complications, contaminated products, leakage from bags and insufficient engraftment.

3.2 Number of reports

From 2006 to 2018, TRIP received 258 reports related to hematopoietic stem cells (peripheral blood stem cells, bone marrow, and cord blood) and therapeutic cells. Figure 24 gives an overview of these reports.

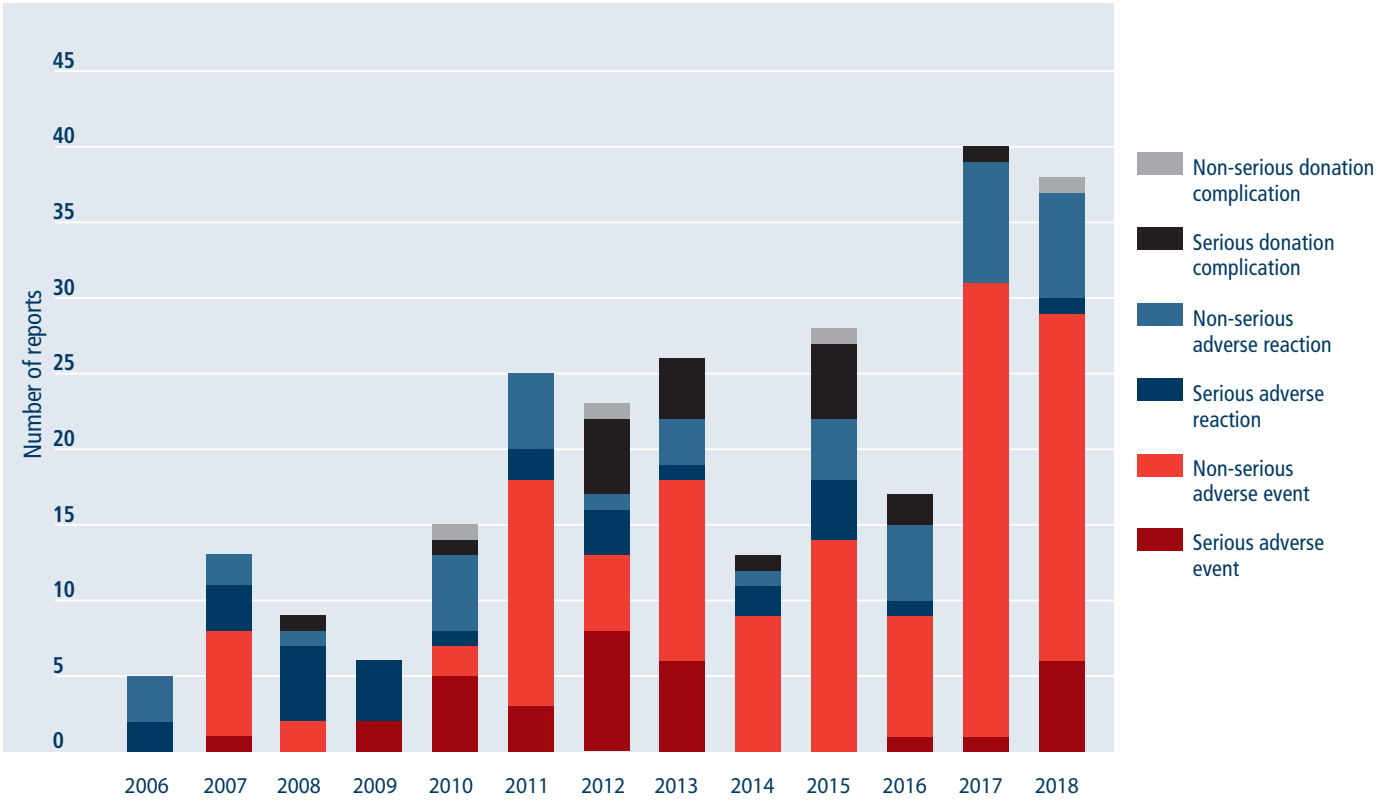

Figure 24. Reports related to HSC and therapeutic cells, 2006-2018

In total, TRIP received 160 reports of adverse events, 74 reports of adverse reactions and 24 reports of donation complications. Figures 25 and 26 below show the numbers of reports in each reporting category. Figure 27 shows the reports of Other reaction as they would be subdivided according to the new EU subcategories. Table 35 summarizes the donation complications.

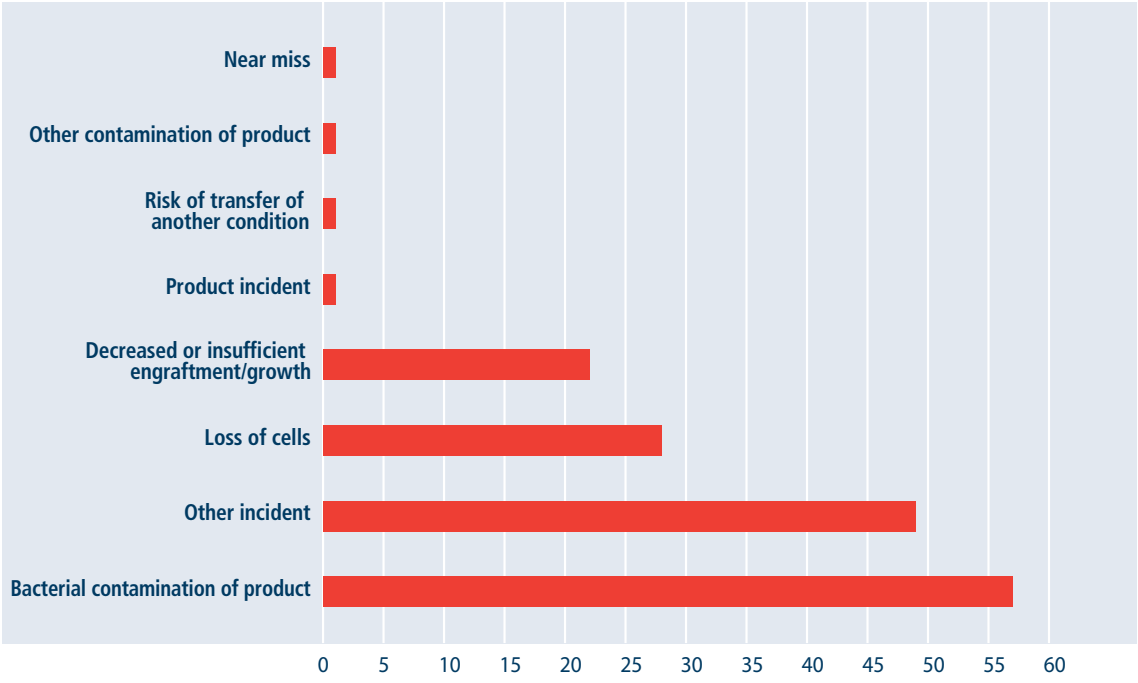

Figure 25. Adverse events reported to TRIP, 2006-2018 (n=160)

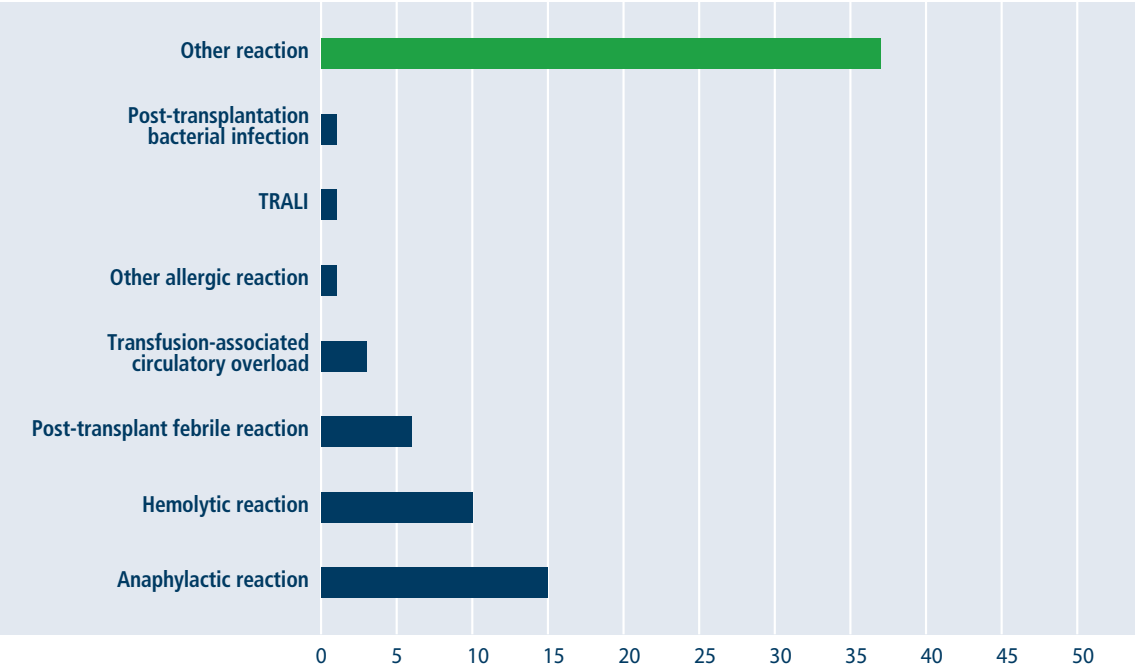

Figure 26. Adverse reactions reported to TRIP, 2006-2018 (n=74)

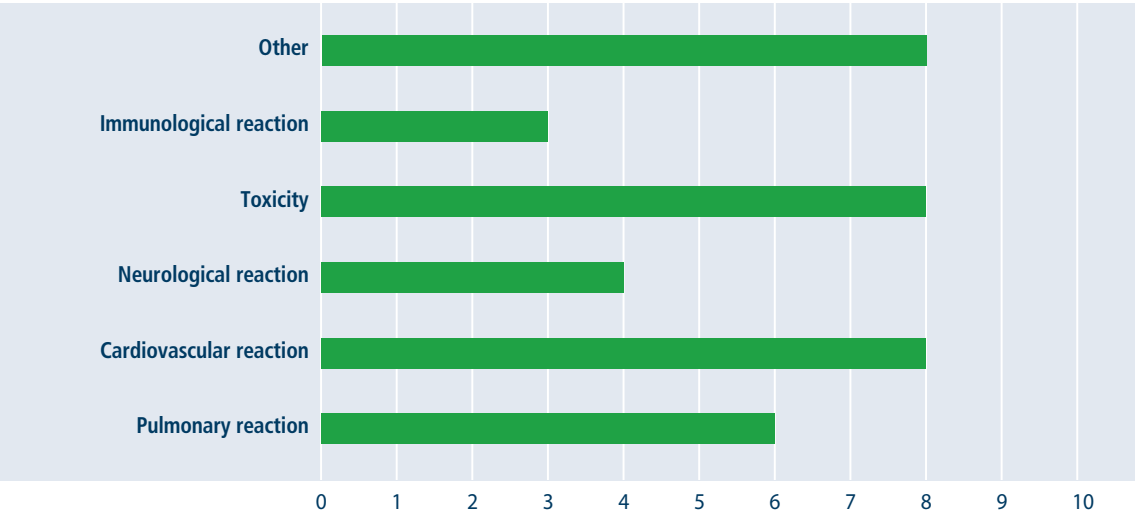

Figure 27. Other reactions, 2006-2018, subdivided according to new EU subcategories (n=37)

The adverse events reported in the category Other incident (n=49) included leakage of bags that did not result in loss of cells (15x), abnormalities in the product, such as too few or too many cells (12x), agglutinations in the product (5x), administrative errors (4x) and transport and/or storage errors (3x). The 37 reports categorized as 'other reaction' encompass all adverse reactions in recipients of HSC or therapeutic cells that do not fit the criteria for any of the other categories.

Table 35. Overview of donation complications related to hematopoietic stem cells and therapeutic cells, 2006-2018

Type of cells	Reports	Donation complication	Interval from donation	Imputability
PBSC allogeneic, unrelated	8	IgA nephropathy	During GCSF# stimulation	probable
		Tetany and laryngospasm due to hypocalcaemia*	During apheresis	certain
		Hypocalcaemia, hyperventilation and vasovagal reaction	During apheresis	probable
		Phlebitis	Not stated	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 vertigo*	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
Granulocytes, related	1	Vitiligo	6 months	possible
Bone marrow unrelated	2	TIA*	8 months	unlikely
		Breast cancer*	2 years	unlikely
Bone marrow related	1	Fractured sacrum*	2 weeks	probable
Total	**24**			

** Serious*
 # Granulocyte colony stimulating factor

The majority of long-term complications concern diagnoses of conditions that also regularly occur in the general population. Thus, the imputability of these complications is often deemed unlikely or, at most, possible. According to current working arrangements, these long-term complications are reported, because a connection to the use of stimulating factors is not unthinkable and cannot be ruled out. Long-term complications are reported most often in unrelated donors, in part due to the longer follow-up. The imputability of short-term complications is often judged to be higher, and they are often of a more temporary nature.

3.3 Incidence of serious adverse events, adverse reactions and donation complications with HSC, 2010-2018

In Tables 36, 37, and 38, the number of serious reports with HSC is shown in relation to the number of transplants (recipients) of HSC, bone marrow, and cord blood. The tables show, respectively, the reports related to transplants of HSC from unrelated donors, from related donors and autologous HSC.

Table 36. Reports related to unrelated hematopoietic stem cell donation and transplantation, 2010-2018

HSC (not including therapeutic cells)	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
No. of recipients	269	292	349	326	353	392	407	463	506	3357
No. of adverse events	2	4	5	7	3	2	4	15	14	56
No. of serious adverse events	2	1	2	2	0	0	0	0	2	9
No. of serious adverse events per 1000 recipients	7.4	3.4	5.7	6.1	0.0	0.0	0.0	0.0	4.0	2.7
No. of adverse reactions	3	4	3	1	2	4	3	2	2	24
No. of serious adverse reactions	1	1	2	0	1	1	0	0	0	6
No. of serious adverse reactions per 1000 recipients	3.7	3.4	5.7	0.0	2.8	2.6	0.0	0.0	0.0	1.8
No. of donations	51	26	35	24	44	41	52	95	134	502
No. of donation complications	1	0	3	3	0	2	0	0	1	10
No. of serious donation complications	1	0	3	3	0	2	0	0	0	9
No. of serious donation complications per 1000 donations*	19.6	0.0	85.7	125.0	0.0	48.8	0.0	0.0	0.0	17.9

** The imputabillity of six of the nine serious donation complications that were reported was deemed unlikely, see Table 35*

Table 37. Reports related to related hematopoietic stem cell donation and transplantation, 2010-2018

HSC (not including therapeutic cells)	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
No. of recipients	142	156	174	187	210	130	162	190	210	1561
No. of adverse events	1	0	2	1	0	4	0	1	2	11
No. of serious adverse events	0	0	1	0	0	0	0	0	0	1
No. of serious adverse events per 1000 recipients	0.0	0.0	5.7	0.0	0.0	0.0	0.0	0.0	0.0	0.6
No. of adverse reactions	1	1	0	1	0	1	1	3	2	10
No. of serious adverse reactions	0	0	0	0	0	0	0	0	0	0
No. of serious adverse reactions per 1000 recipients	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
No. of donation complications	0	0	3	1	1	2	1	0	0	8
No. of serious donation complications	0	0	2	1	1	2	1	0	0	7
No. of serious donation complications per 1000 transplants*	0.0	0.0	11.5	5.3	4.8	15.4	6.2	0.0	0.0	4.5

** Three of the seven serious donation complications concerned long-term complications, of which the imputability was deemed possible, see Table 35. The number of donation complications is related to the number of recipients in this table, because different establishments reported their data regarding donations/transplants (vs. bags) in different ways.*

Table 38. Reports related to autologous hematopoietic stem cell donation and transplantation, 2010-2018

HSC (not including therapeutic cells)	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
No. of recipients of autologous stem cell transplants	553	537	633	643	722	812	990	884	1000	6774
No. of adverse events	4	12	5	6	6	7	5	13	13	71
No. of serious adverse events	3	2	4	2	0	0	1	1	4	17
No. of serious adverse events per 1000 recipients	5.4	3.7	6.3	3.1	0.0	0.0	1.0	1.1	4.0	2.5
No. of adverse reactions	2	2	1	2	1	3	2	3	4	20
No. of serious adverse reactions	0	1	1	1	1	3	1	0	1	9
No. of serious adverse reactions per 1000 recipients	0.0	1.9	1.6	1.6	1.4	3.7	1.0	0.0	1.0	1.3
No. of donation complications	1	0	0	0	0	1	1	1	0	4
No. of serious donation complications	0	0	0	0	0	1	1	1	0	3
No. of serious donation complications per 1000 transplants*	0.0	0.0	0.0	0.0	0.0	1.2	1.0	1.1	0.0	0.4

* *The number of donation complications is related to the number of recipients in this table, because TRIP did not receive uniform data regarding the number donations/transplants vs bags.*

Over the years, the data related to HSC donations from related donors, and in particular the data related to autologous HSC, has been expressed variably either as donations/transplants or as bags. For this reason the number of recipients is used as a denominator in Tables 37 and 38, as a measure for the general volume of autologous HSC-transplantation.

3.4 Bacterial contamination of product, 2006-2018

From 2006 to 2018, TRIP received a total of 58 reports of contamination of product, of which 57 concerned bacterial contamination and one was an other contamination. Among these reports, seven were classified as serious (see Figure 28).

The reports concerned contamination of PBSC (29x), bone marrow (22x), cord blood (3x), and lymphocytes (4x). Figure 29 provides an overview of the most common bacterial contaminations and the steps taken following the detection of contamination and/or the consequences (if any) after infusion of a contaminated product.

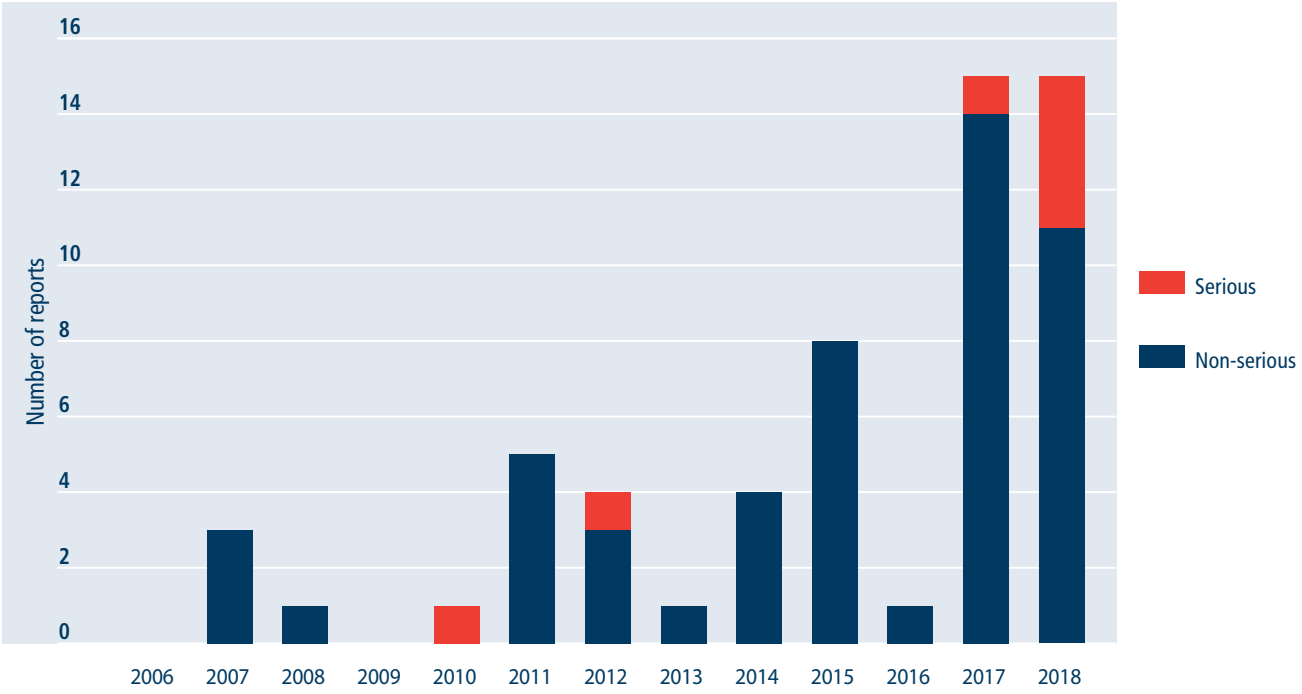

Figure 28. Bacterial contamination of product and other contamination of product, 2006-2018

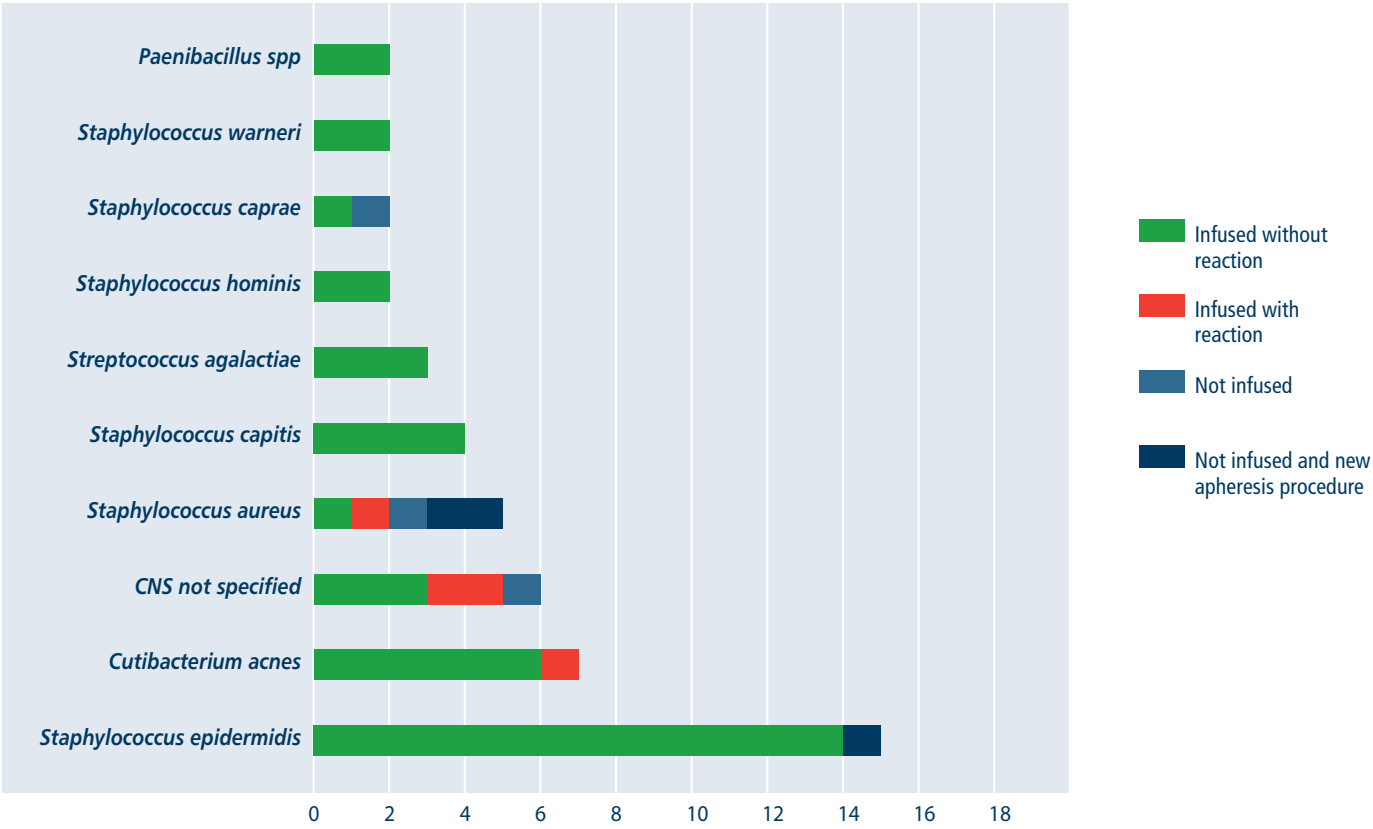

Figure 29. Commonest bacterial contaminations and outcome, 2006-2018

Bacterial contamination of a product is assessed as serious if the contamination caused symptoms in the recipient or led to the loss of a transplant after which a new apheresis procedure became necessary. The number of reported bacterial contaminations shows a significant increase in 2017 and 2018. Remarkably, this increase is mainly due to an increase in non-serious reports from two specific establishments. The Working Party of Dutch Stem Cell Laboratories is undertaking a nationwide review of the sterility check methodologies and the occurrence of contaminations.

3.5 Loss of cells, 2006-2018

From 2006 to 2018, TRIP received a total of 28 reports of loss of cells. Loss of cells means loss of unique material, which can have serious consequences for a recipient. In 18 of the reports the loss of cells was caused by leakages in the collection and storage materials used for HSC and other therapeutic cells. The other ten reports concerned a human error during collection or processing (8x), a mechanical issue (1) and an unknown cause (1). In addition, TRIP received 15 reports of other incidents in which leakage of a bag occurred. In these cases, (in some cases after intervention) the product was salvaged and there was no loss of cells. Figure 30 shows the number of reports concerning leakage of bags per reporting year. A report is assessed as serious if the incident led to loss of irreplaceable autologous cells or recipient-specific cells. The reasons for the leakages in the equipment are shown in Table 39, to the extent that they are known. It should be noted that all these incidents involved products with a cryo-preservation step in the process.

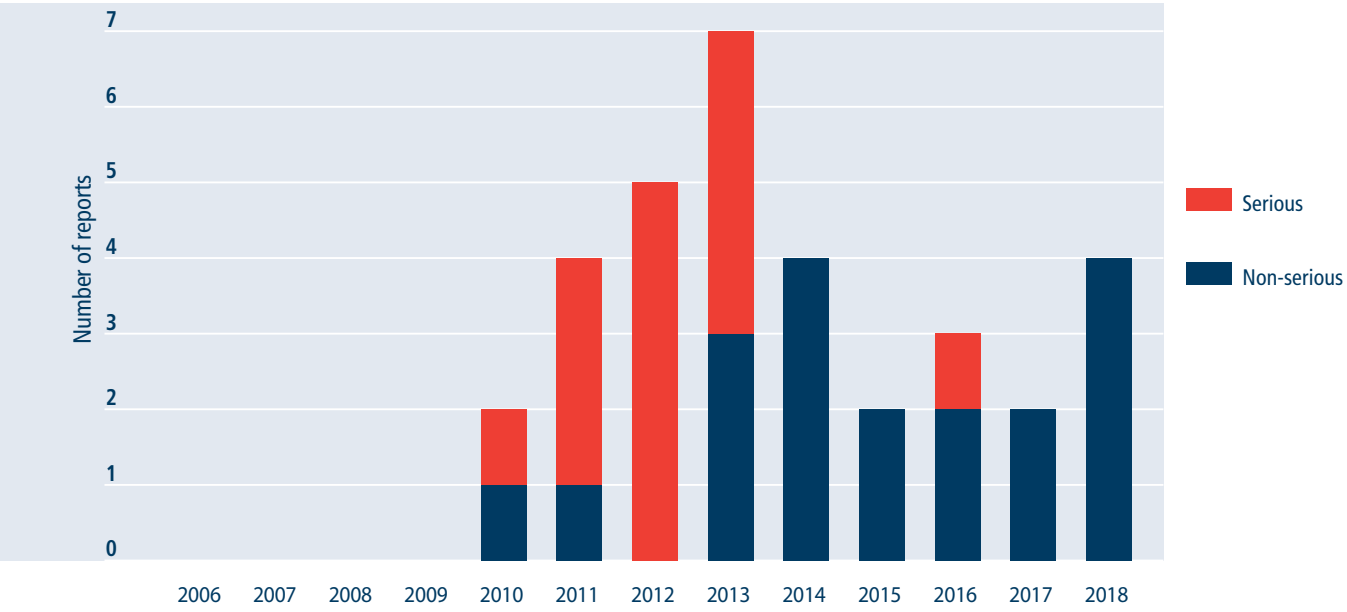

Figure 30. Number of reports of leakages in collection and storage equipment for HSC and other therapeutic cells, 2006-2018

Table 39. Reports of leakages in collection and storage materials, subdivided according to cause

	Total	Serious
Issue with disposable during apheresis	6	3
Tear in bag	13	7
Tubing or connection port that tears loose	7	3
Rupture after dropping bag	2	0
Cause unclear, leakage of bag detected during defrosting	5	1
Total number of reports of leakage of materials	**33**	**14**

3.6 Insufficient engraftment, 2006-2018

From 2006 to 2018, TRIP received 22 reports of insufficient engraftment after a stem cell transplant, three of which were classified as serious. The extent of engraftment is considered insufficient if the graft or transplanted material does not show the expected growth or increase in number of cells.

One of the reports concerned a patient who also had a serious infection and showed insufficient engraftment after an autologous bone marrow transplant. In one year, TRIP received six reports of insufficient engraftment after cord blood transplantation, five of which came from the same transplantation centre. A thorough investigation was carried out by the establishment but no causal relation between the processing of the products and the insufficient engraftment could be established. All other reports of insufficient engraftment related to autologous PBSC.

3.7 Summary

Since TRIP started collecting biovigilance reports in 2006, a wide variety of adverse events and adverse reactions related to HSC and other therapeutic cells has been reported. A number of small clusters of similar reports have been observed, even though they came from different institutions, in part because of the centralised data collection by TRIP. Even though it is twelve years since TRIP started collecting data on HSC, the number of reports concerning these cells still shows an increasing trend. The number of reports concerning bacterial contamination of products in particular has contributed to the most recent increase in reports. Because there have also been five serious reports concerning bacterial contamination, this issue warrants closer attention in the upcoming years. Currently, the Working Party of Dutch Stem Cell Laboratories is undertaking further investigation regarding the issue. Review of the separate reporting categories highlights the large numbers reports registered as 'other reaction' or 'other incident'. TRIP will focus on evaluating these reports and the current reporting categories. There are also some ongoing European projects concerning biovigilance reporting categories and criteria. Results of these projects may lead to future revision of the definitions and criteria used for biovigilance in the Netherlands.

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 transplantation 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 non-profit 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 40 provides an overview of the number of licensed tissue establishments and organ banks in the Netherlands in 2018 (source: Farmatec). A number of Dutch hospitals houses multiple tissue establishments and/or organ banks. The number of tissue establishments housed in hospitals decreased in 2018 because some hospitals merged. The number of independent tissue establishments increased because several new ones were authorised.

Table 40. Licensed tissue establishments and organ banks in the Netherlands in 2018

	Tissue establishments	Organ banks*	Total
Independent establishments	14	13	27
Housed in a hospital or clinic	48	30	78
Total	**62**	**43**	**105**

* *Organ banks are also licensed as tissue establishments*

Figure 31 shows the number of licenses issued by Farmatec per type of tissue and/or cells. Farmatec is an executive body that grants licences and permits with regards to pharmaceuticals, medical devices, blood components, and human tissues and cells on behalf of the Dutch Ministry of Health. Some tissue establishments are licensed for multiple types of tissues and/or cells. Figure 30 shows the percentages of tissue establishments that have 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 provided data on the number of units processed and distributed in 2018. The participation of tissue establishments in 2018 was 100% (105 out of 105).

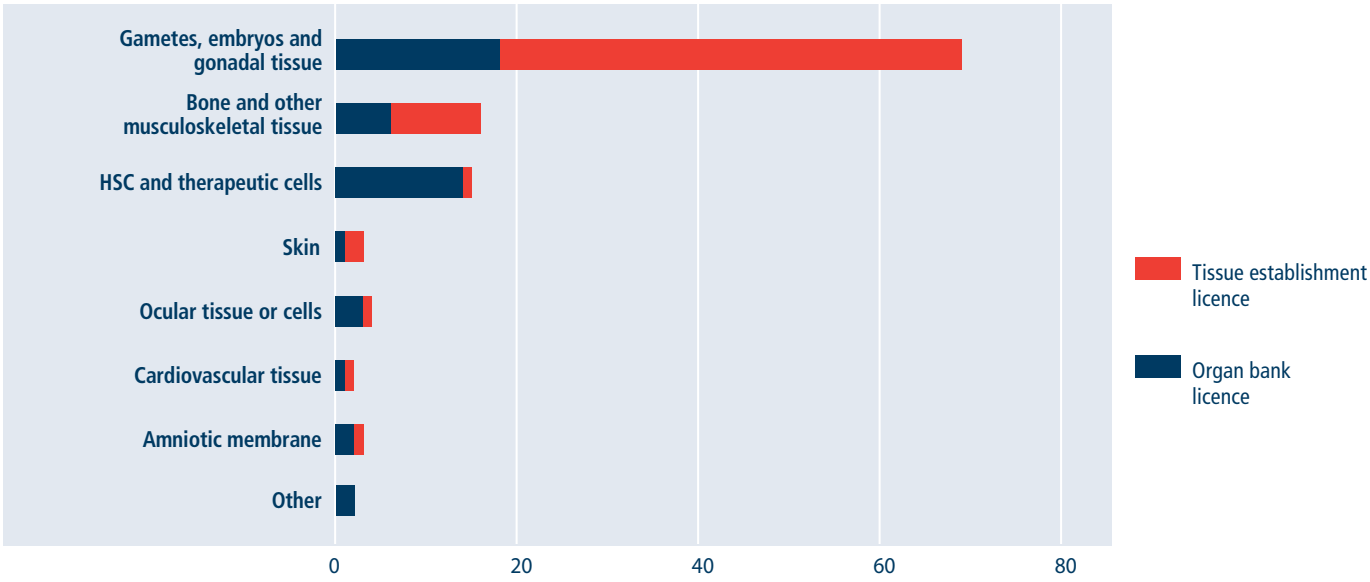

Figure 31. Number of licensed tissue establishments and organ banks in 2018 by type of human tissue or cells

4.2 Organisations responsible for human application of tissues and cells

In 2018, 81 hospitals, 15 clinics and independent healthcare institutions, and 57 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. Two hospitals were closed in 2018. In 2018, the participation rate of hospitals was 98% (79 out of 81). The participation rate of clinics and independent tissue establishments was 93% (14 of 15). Four healthcare establishments were unable to submit complete data. The participation rate of oral implantology practices which apply human tissues was 91% (52 out of 57) in 2018. Two independent healthcare institutions and four oral implantology practices indicated that they had not applied any human tissues or cells in 2018. The participation of all establishments responsible for human application of tissues and cells combined is 95% (145 out of 153). Figure 30 shows the percentages of establishments and practices that supplied data on the number of transplanted or applied tissues and/or cells.

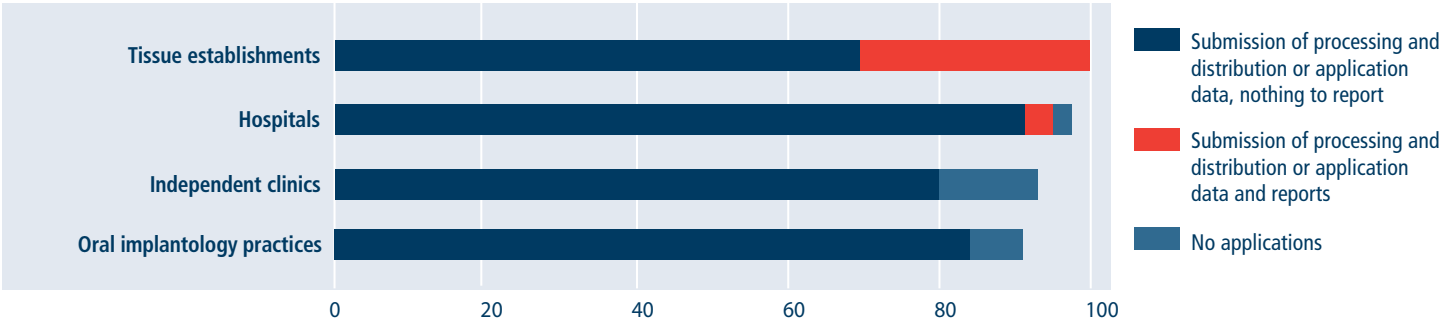

Figure 32. Participation of establishments and practices involved in biovigilance in 2018

Tissue establishments n=105
Hospitals n=81
Independent clinics n=15
Oral implantology practices that have indicated that they apply substances of human origin n=57

Image 3. Femural struts

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 33 presents a flowchart of serious and non-serious biovigilance reports in Dutch healthcare.

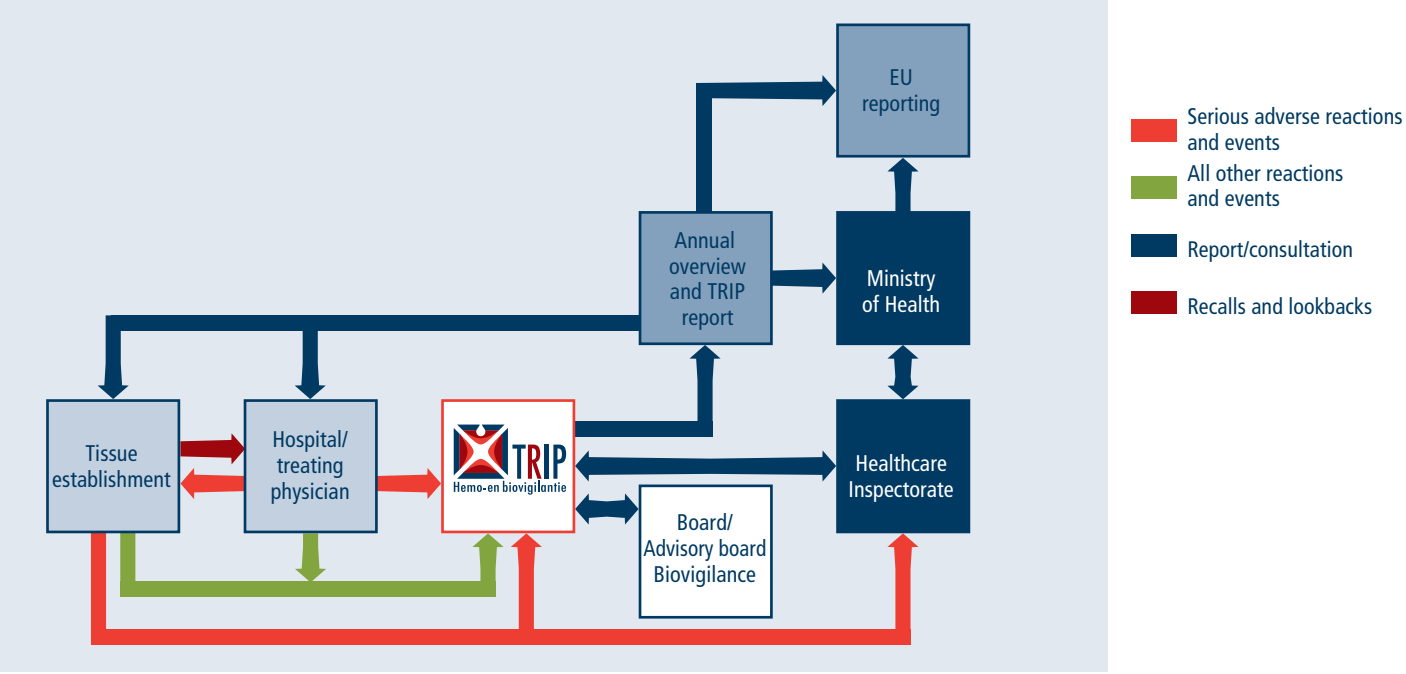

Figure 33. Flow chart of reports concerning substances of human origin

The scope of the Law on safety and quality of substances of human origin includes all human tissues and cells (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). The Law on safety and quality does not apply to organs and thus TRIP does not register adverse events and reactions related to the donation, processing, storing (during transport) and transplantation of organs.

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 annually collects data on the numbers of processed, distributed and applied human tissues and cells 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 to the board and staff members of TRIP. The Biovigilance Advisory Board also anonymously reviews all reports 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 must 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 reactions and event reports to the Healthcare Inspectorate: reporters can choose to 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.

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 34 shows the reporting routes in a flowchart.

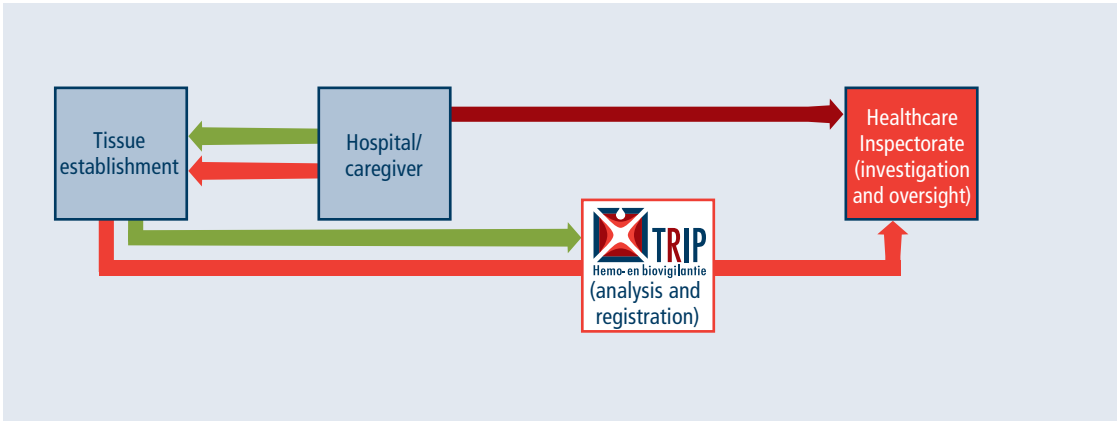

Figure 34. Flow chart of reports concerning substances of human origin

Serious adverse reactions or events within the scope of the Law on safety and quality of substances of human origin are best submitted to the Healthcare Inspectorate via the TRIP online reporting system. This channels the reports to the inspectors involved in enforcement of the Law on safety and quality of substances of human origin and reduces the likelihood of reports being (possibly incorrectly) treated as lying within the scope of the Law on quality, complaints and disputes 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 event or reaction is solely reported to the Healthcare Inspectorate, the inspectors will ask reporters to also submit the report to TRIP.

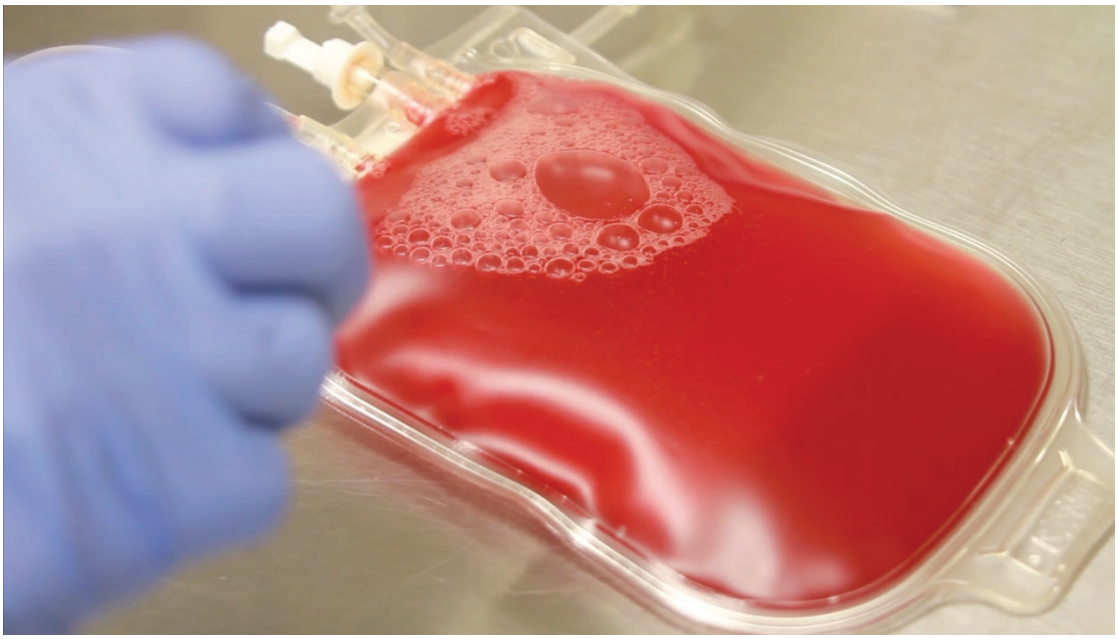

Image 4. Cord blood unit

ANNEX 3

Definitions and reporting criteria

Definitions of categories of adverse reactions and adverse events

All definitions of the categories used for adverse reactions and adverse events can be found on the TRIP website (www.tripnet.nl)

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 hospitalization or morbidity.

The criteria used by the European Commission are presented in Table 41. 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 41. Criteria for a 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 termination of a pregnancy of a fetus with a transmitted genetic disease following medically reproduction 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 42 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 42. 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, minor clinical effects without (prolongation of) need for hospital admission and without invalidity, incapacity or long-term consequences for the recipient. Not life-threatening. of consequenties voor de ontvanger of donor. Geen levensgevaar.
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 way as adverse reactions in recipients. Serious donation complications are not yet subject to mandatory reporting to the EU. The EC does 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 2.7 (2018)', stating:

It is noted that many EU Member State competent authorities collect information on donor adverse reactions not influencing the quality and safety of tissues and cells. These reactions fall outside the scope of the tissues and cells Directive 2004/23/EC and should be reported elsewhere as appropriate (e.g. to pharmacovigilance systems). They include:

- Ovarian hyperstimulation syndrome (OHSS) as an exaggerated response to the use of ovarian induction medications
- Reactions to Granulocyte Colony-Stimulating Factor (GCSF) following peripheral blood stem cell collection
- Reactions which result in harm to the donor (i.e. cardiac or neurological episodes)

Nevertheless, the European Commissionrecognises the value of these data in the context of tissue and cells regulation, and invites MS to submit an annual report concerning donor reactions reported to the competent authorities 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 43 shows the number of serious adverse reactions and events related to substances of human origin reported in 2018. In total, 44 reports were assessed as serious. These 44 reports concern 38 serious adverse events, two serious adverse reactions and four serious donation complications.

Table 43. Overview of serious reports in 2018

Type	Serious adverse reaction	Serious adverse event	Serious donation complication	Total serious reports
Semen	1	13	0	14
Oocytes	0	5	4	9
Embryos	0	6	0	6
Ocular tissue	0	6	0	6
HSC and therapeutic cells	1	6	0	7
Musculoskeletal tissues	0	1	0	1
Cardiovascular tissue	0	1	0	1
Total	**2**	**38**	**4**	**44**

ANNEX 5

List of terms and abbreviations

AID	Artificial insemination with donor semen
Allogeneic	Originating from a donor (genetically non-identical person)
AML	Acute myeloid leukemia
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
ASD	Atrial septal defect
ATMP	Advanced Therapy Medicinal Product
Autologous	Originating from a person's own body
CAR-T	Chimeric Antigen Receptor T-cell
Chondrocytes	Cartilage cells
Clinic	Specialised institution committed to one area of health care
CNS	Coagulase-negative staphylococci
Cryopreservation	The process of freezing and subsequent storage of frozen tissues and cells
Cutibacterium acnes	Formerly Propionibacterium acnes
Distribution	Transportation and delivery to end users
DLI	Donor lymphocyte infusion
DMSO	Dimethyl sulfoxide (cryoprotectant)
EC	European Commission
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
GCSF	Granulocyte colony stimulating factor
Gonadal	Relating to sex glands
Healthcare Inspectorate	Healthcare Inspectorate
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	Intrauterine insemination
IVF	In vitro fertilisation
KLEM	Association of clinical embryologists
Matchis	Dutch registry for stem cell donors
MESA	Microsurgical epididymal sperm aspiration
Morbidity	Extent of disease
Mortality	Death
NL	The Netherlands
OHSS	Ovarian hyperstimulaton syndrome
Oocytes	Egg cells

Organ bank	Tissue establishment with licence to receive substances of human origin after procurement
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
Retrieval	Process whereby donated substances of human origin become available
Sanquin	Sanquin (Foundation charged with operating the Dutch national blood establishment)
Semen	Sperm
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
Tissue establishment	A tissue bank, a hospital department or other institution that holds a licence for processing, preserving, storage and/or distribution of substances of human origin
VSD	Ventricular septum defect
Wkkgz	Law on Quality, Complaints and Disputes in Healthcare
Wvkl	Dutch Law on safety and quality of substances of human origin

TRIP Hemovigilance and biovigilance office
Schuttersveld 2
2316 ZA Leiden
Email: info@tripnet.nl
www.tripnet.nl