TRIP REPORT 2020

BIOVIGILANCE

EXTENDED VERSION

TRIP
Hemo-en biovigilantie

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TRIP report 2020 Biovigilance is published under the responsibility of the TRIP Foundation (Transfusion and Transplantation Reactions in Patients).

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INTRODUCTION

In this 2020 Biovigilance Report, TRIP presents all reports of adverse reactions and events that occurred in the chain of procurement, processing and application of human tissues and cells. It also gives a picture of the numbers of available and applieded cell and tissue products for transplantation and of tissue and healthcare establishments participating in the national biovigilance network.

The COVID-19 pandemic hit the health sector hard in 2020. As a result of the measures surrounding the pandemic, there was a temporary drop in the number of donations and applications of human tissues and cells. In 2020, TRIP received 99 reports of adverse reactions and events involving human tissue, in line with previous years. The ratio of adverse event reports to adverse reaction reports (5.7:1) and the number of serious reports (43) have also remained constant over the last few years. There were 14 late reports from 2019, which will also be discussed in this report.

The COVID-19 pandemic had a major impact on fertility care in the Netherlands by temporarily halting fertility programmes. The largest number of reports was in the category 'Loss of tissues or cells'. For the first time since 2012, no case of 'Incorrect product transplanted/applied' associated with assisted reproduction was reported in 2020. Half of the late reports concerned cases in the category 'congenital abnormality'. This can be explained by the fact that investigation of a congenital abnormality takes time, so the report can not be completed before the final submission date for reports for the annual biovigilence report.

In 2020, TRIP received 28 reports concerning hematopoietic stem cells (2019: 36), including two serious adverse reactions. A total of 11 reports concerned 'Bacterial contamination of product', seven of which involved bone marrow. As in 2019, this was the largest category of reports concerning hematopoietic stem cells. There was an increase in the number of units distributed compared to 2019, while the number of applications remained the same. This may be explained by the COVID-19 pandemic, during which more frequent use was made of cryopreservation of transplants, with the transplants being divided and distributed in smaller units.

As regards tissues and other cells, an increase in reports concerning musculoskeletal tissue was seen in 2020 (from 8 to 20), eight of which concerned the culturing/processing of human cells into ATMPs (Advanced Therapy Medicinal Products). As in 2019, some institutions voluntarily reported the application of ATMPs in the sectors of musculoskeletal tissue, haematopoietic stem cells and other therapeutic cells. However, there are still legal gaps regarding the reporting of adverse occurrences or the reporting of activity data. This is further explained in this report.

There is a minimal decrease in the distribution and application of bone, other musculoskeletal tissue and ocular tissue. This is partly explained by the temporarily reduction in surgeries due to the COVID-19 pandemic, which led to fewer elective (including orthopaedic) operations and fewer corneal donations.

The TRIP foundation would like to express appreciation for the indispensable contributions of all those who contributed to the production of this report. Through the careful monitoring, through the analyses and cooperation, this report can contribute to mapping out and improving the safety and quality of the entire chain from donation to transplantation of human tissue.

FINDINGS AND

MAIN 2020

1 The participation of tissue establishments (defined as the number of establishments providing annual activity data) was 99% (111 out of 112 establishments) and that of transplanting facilities 94% (147 out of 156 establishments).

2 TRIP received 99 reports in 2020, 41 of which concerned serious events or adverse reactions. These numbers are in line with the reports from previous years.

3 After the final submission date for reports for the 2019 Biovigilance report, TRIP received 14 more reports. Twelve of these late reports concerned human reproductive cells and tissues and two concerned bone and other musculoskeletal tissues.

4 During the COVID-19 pandemic, (elective) healthcare was scaled down for several months. A decrease was observed in the figures for processing and application in medicallyassisted reproduction.

5 For the first time since 2012, no case of 'Incorrect product transplanted/ applied' was reported with assisted reproduction in 2020.

6 There was an increase in the number of distributed units of allogeneic peripheral blood stem cells in 2020. This is due to the temporary cryopreservation of these transplants because of the COVID-19 pandemic. With cryopreservation, a stem cell transplant is split into smaller portions than is the case with fresh administration of a transplant.

7 The total number of stem cell transplant recipients in 2020 was similar to that reported in 2019.

8 The number of establishments reporting the use of CAR T/TCR cells increased from four in 2019 to seven in 2020 (reporting is on a voluntary basis). Three reports were received regarding these therapeutic cells, which fall under Advanced Therapy Medicinal Products (ATMPs).

9 Due to the COVID-19 pandemic, there were fewer tissue donations in the Netherlands during the first half of 2020. Regarding solid tissues, a minimal decrease in the application of femoral heads and corneas was observed. Application of other types of tissues was similar to 2019.

10 Despite the limited downscaling of orthopaedic interventions due to the COVID-19 pandemic, there was a significant increase in the number of reports concerning bone tissue. Since 2016, reports relating to this tissue type have been limited to adverse events.

11 There is an increase in the number of reports concerning other musculoskeletal tissues. A number of these relate to cases where autologous chondrocytes were cultured, and there was too much by-product, resulting in the need to obtain a new biopsy.

Recommendations

1 The completeness and accuracy of annual reports from tissue establishments, organ banks and transplanting establishments should be improved. TRIP should support this process by clarifying definitions, providing training courses and adapting and optimizing the annual report forms.

2 For users of new products and medicines prepared from human tissue, such as ATMPs, unambiguous and clear instructions for the criteria and routes for reporting adverse reactions and events should be drawn up in consultation with IGJ, the pharmacovigilance agency Lareb and VWS.

3 In order to determine the seriousness of the loss of body tissue, definitions of scarcity of tissue or cell types should be agreed. This makes it possible to assess whether the loss that occurred leads to (potentially) serious consequences for the intended recipients.

Actions and developments following recommendations in the 2019 TRIP report

In the 2019 TRIP Biovigilance report, three recommendations were made. The recommendations and developments, if any, are reported below.

1 In order to promote the completeness of the application figures, supporting materials and training courses should be developed and provided.
Development: In 2020, due to the COVID-19 pandemic, there was no training in application data reporting.

2 Attention to identification errors in the transplantation chain remains as necessary as ever. These errors also include left-right mix-ups. It is relevant to investigate whether and how the risk of identification errors can be reduced by using a barcode system.
Development: In 2020, there were three reports of 'Incorrect product transplanted/applied' (ocular and musculoskeletal tissue). None of these involved identification errors. The three reports of identification errors in 2020 were registered/received in the categories of 'Near miss' and 'Loss of cells or tissues' (gametes and embryos and musculoskeletal tissue, respectively).

3 The impact of an event involving the loss of human tissue partly depends on scarcity. It is therefore important to gain insight into the availability of tissues and cells. In addition, there is a need for objective criteria against which scarcity can be assessed.
Development: Due to the COVID-19 pandemic, the year 2020 is not a representative year as far as the determination of scarcity is concerned. See Recommendation 3.

1 REPORTS IN 2020

1.1 Registered reports in 2020

Figure 1 shows that the number of reports of adverse events and reactions associated with the donation, procurement, testing, processing, storage, distribution and application of human tissues and cells is similar to the numbers reported in the past five years (99 on average). There were 84 adverse events (85%) and 15 adverse reactions (15%), including four donation complications. Most events and adverse reactions (43%, 43 out of 99 reports) were reported in association with assisted reproduction (see Figures 2a and b). Of the total number of reports, 41 reports (41%) were assessed as serious (criteria: see Annex 3). These serious reports are included in the annual overview for the European Commission (see Annex 4). The final submission date for reports for the 2020 Biovigilance report and the annual overview for the EU was 1 March 2021. Table 1 gives an overview of the number of reports in 2020, according to the type of tissue and severity.

Table 1 Overview of reports per tissue or cell type in 2020

Tissue or cell type	Total	Serious	Adverse events	Reactions	Donation complications
Human reproductive cells and tissues	43	25	38 (20 serious)	2 (2 serious)	3 (3 serious)
Hematopoietic stem cells and therapeutic cells	28	2	18 (0 serious)	9 (2 serious)	1 (0 serious)
Bone and other musculoskeletal tissue	20	8	20 (8 serious)	0	
Skin	0	0	0	0	
Ocular tissue	7	6	7 (6 serious)	0	
Cardiovascular tissue	1	0	1 (0 serious)	0	
Other tissues and cells	0	0	0	0	
Total	**99**	**41**	**84 (34 serious)**	**11 (4 serious)**	**4 (3 serious)**

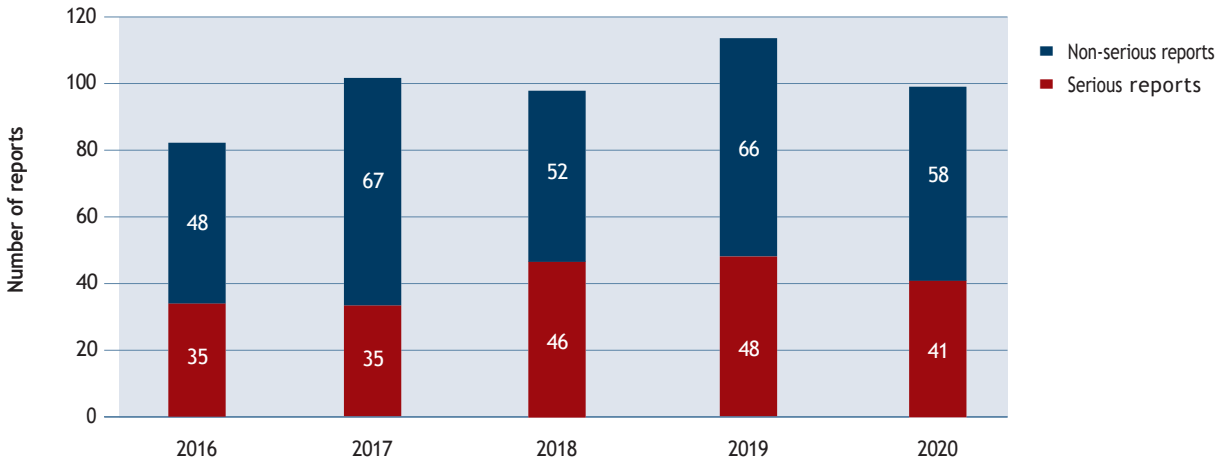

Figure 1 Number of reports received, 2016-2020

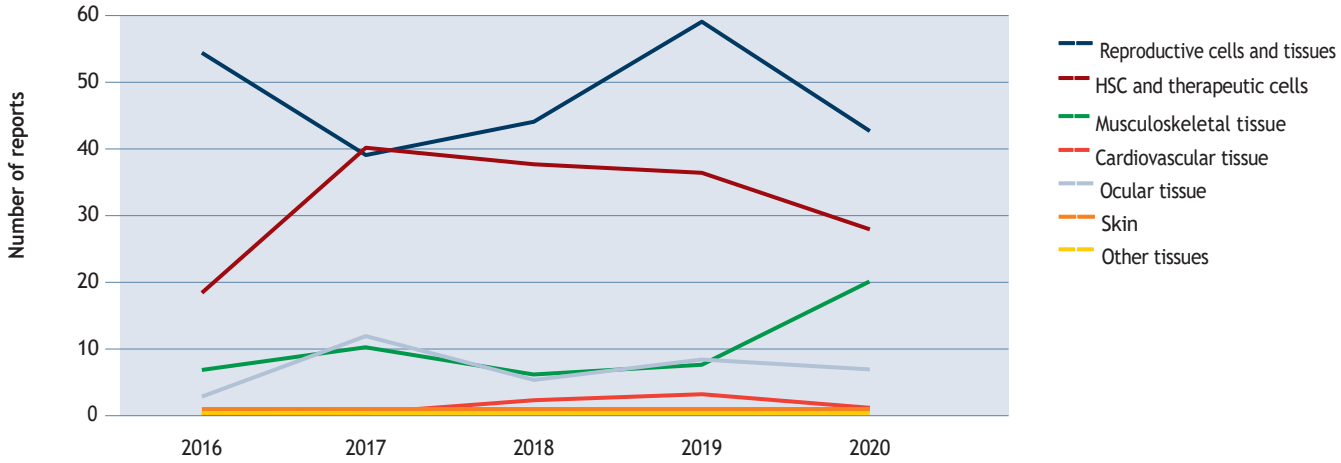

Figure 2a Number of reports per tissue/cell type per reporting year, 2016-2020

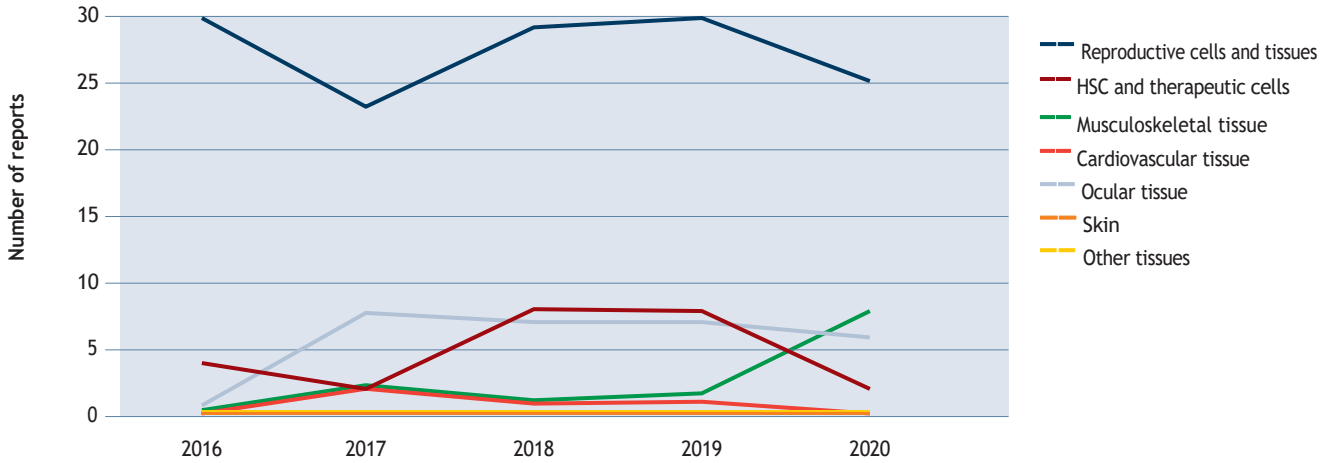

Figure 2b Number of serious adverse events and reactions per reporting year, 2016-2020

1.2 Late reports

After the final submission date for reports for the 2019 Biovigilance report, TRIP received 14 more reports from 2019. Table 2 shows an overview of these reports. The late reports have been incorporated into all relevant tables and figures in this report and are described in the relevant sections in Chapter 2.

Table 2 Late 2019 reports included in the 2020 Biovigilance report

Tissue or cell type	Reporting category	Total	Serious
Donor semen	Congenital abnormality	6	3
Partner semen	Near miss	1	1
Donor semen	Other incident	1	0
Testicular tissue	Other incident	1	1
Embryo	Other incident	1	0
Embryo	Loss of cells	1	1
Oocytes	Other incident	1	0
Bone and other musculoskeletal tissue	Loss of tissue	2	1

2 TISSUES AND CELLS

2.1 Human reproductive cells and tissues

In 2020, 15 IVF laboratories with organ bank accreditation are registered in the Netherlands. Here, intrauterine insemination (IUI), as well as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) operations are performed. In addition, 47 semen laboratories licensed as tissue establishments, most being clinical chemistry laboratories, where only semen for intrauterine insemination (IUI) with partner semen is processed. In addition, four semen laboratories are accredited as organ banks and are therefore authorised to receive (donor) semen after procurement as well as processing and storing it.

Processing, distribution and application

Tables 3 and 4 show figures for processing, distribution and application of reproductive tissues and cells, based on the establishments' annual activity reports. During the analysis of the annual data, it became apparent that there are differences between institutions in the interpretation of the definitions of processing, distribution and application of reproductive tissues. This has led to recommendation 1.

Table 3 a-b-c Processing and distribution of reproductive tissues and cells in 2020

Type of semen and testicular tissue	Tissue establishments	Unit	Processed			Distributed		
			From NL	From EU	Outside EU	In NL	In EU	Outside EU
Partner semen, fresh and cryo	66	Sample	36,281	378	0	29,689	451	0
Donor semen fresh and cryo	20	Sample/straws	5,480	5,478	0	9,931	35	0
Partner semen, MESA/PESA or TESE, fresh and cryo	10	Puncture/biopsy	767	1	0	584	98	0
Donor semen, MESA/PESA or TESE, fresh and cryo	0	Puncture/biopsy	0	0	0	0	0	0
Testicular tissue	1	Graft	5	0	0	0	0	0

Type of oocyte or ovarian tissue	Tissue establishments	Unit	Processed			Distributed*		
			From NL	From EU	Outside EU	In NL	In EU	Outside EU
Own oocytes, fresh and cryo	15	Oocyte	100,924	0	0	N/A	N/A	N/A
Donor oocytes fresh and cryo	12	Oocyte	1,842	0	0	N/A	N/A	N/A
Ovarian tissue	4	Graft	497	0	0	21	0	0

Type of embryo	Tissue establishments	Unit	Processed			Distributed		
			From NL	From EU	Outside EU	In NL	In EU	Outside EU
Embryos, own oocyte - partner semen	15	Embryo	40,802	0	16	22,210	27	16
Embryos, own oocyte - donor semen	15	Embryo	3,503	20	0	1,861	4	0
Embryos, donor oocyte - partner semen	12	Embryo	411	0	0	206	0	0
Donated embryos	5	Embryo	390	0	0	112	0	0

** Oocytes are not distributed for direct human application; distribution figures for oocytes are therefore not provided*

Table 4 Application of reproductive tissues and cells in 2020

Type	Hospitals/ clinics	Recipients	Unit	Grafts From NL	From EU	From non-EU	Total
Partner semen, fresh and cryo	66	10,017	Insemination	23,196	3	0	23,199
Donor semen, fresh and cryo	21	2,966	Insemination	5,551	5,919	0	11,470
Embryos, own oocyte with partner semen	15	11,921	Embryo	21,858	10	1	21,869
Embryos, own oocyte with donor semen	15	1,023	Embryo	1,864	4	0	1,868
Embryos, donor oocyte with partner semen	11	121	Embryo	195	0	0	195
Embryos, donor oocyte with donor semen or donated	3	27	Embryo	117	0	0	117
Ovarian tissue	2	4	Graft	21	0	0	21
Testicular tissue	0	0	Graft	0	0	0	0

COVID-19 pandemic

In 2020, fertility care was greatly affected by the COVID-19 pandemic. On 11 March 2020, the Dutch Federation of University Medical Centres (NFU) issued an advisory report on scaling down non-emergency care. This was done with the aim of making capacity available for the ICU and clinical care of COVID-19 patients and to reduce the risk of infection for other patients and healthcare staff. An additional reason for scaling down fertility care in particular was the unfamiliarity with the effects of SARS-CoV-2 on pregnancy and fertility treatments. For fertility care, this meant that no new fertility treatments and donations were started and only ongoing treatments were completed. Fertility preservation in oncology patients did go ahead. On 14 March, the European Society of Human Reproduction and Embryology (ESHRE) issued a statement saying that assisted pregnancy in fertility patients should be prevented. In April, it was explained that with the exception of urgent fertility preservation, medically assisted reproductive care should not be initiated, reasons including the prevention of potential SARS-CoV-2 related pregnancy complications and reduction of the risk of vertical transmission in COVID-19 positive patients[1].

When no evidence was found that COVID-19 infection would affect the foetus and the first wave of the pandemic subsided, fertility services were restarted[1]. The graphs below, which were presented at the TRIP Biovigilance symposium in January 2021, show the decline in fertility care (Image 1). The numbers 1 to 12 represent the 12 institutions that provided data on the procedures performed. Figure 2 shows the comparison of the number of oocyte punctures between 2019 and 2020. This shows that the second wave in autumn 2020 had no effect on the number of punctures.

[1] ESHRE COVID-19 Working Group, Vermeulen N, Ata B, Gianaroli L, Lundin K, Mocanu E, Rautakallio-Hokkanen S, Tapanainen JS, Veiga A. A picture of medically assisted reproduction activities during the COVID-19 pandemic in Europe. Hum Reprod Open. 2020 Aug 17;2020(3):hoaa035.

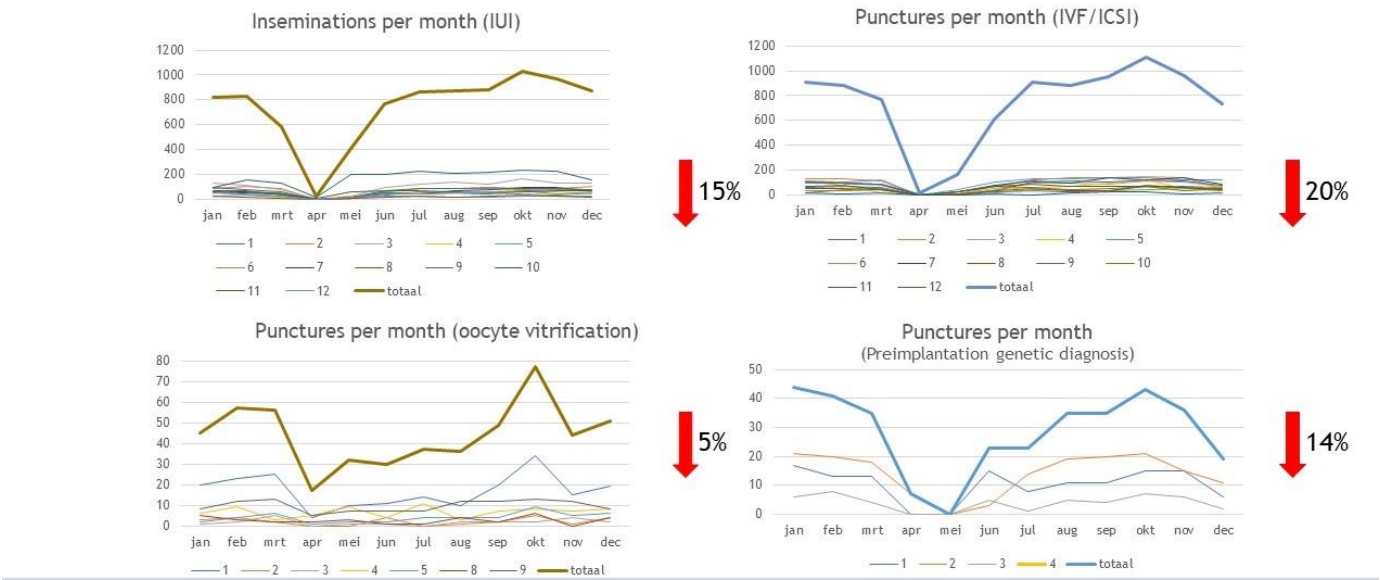

Image 1 Number of inseminations and punctures per month performed for MAR in 12 different institutions in 2020. Source: Presentation at TRIP Biovigilance symposium in January 2021, PowerPoint-presentation (tripnet.nl)

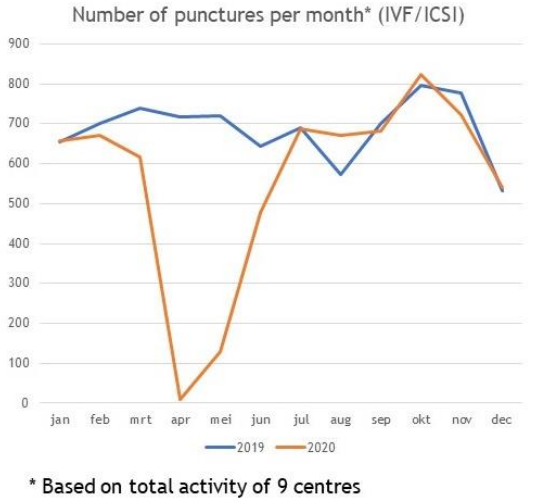

Image 2 Number of oocyte punctures per month for IVF or ICSI in nine different institutions in 2019 and 2020. Source: Presentation at TRIP Biovigilance symposium in January 2021, PowerPoint-presentation (tripnet.nl)
**Based on the combined output of nine centres*

The TRIP data shows that there were fewer applications in 2020. Figure 3 shows the number of inseminations of partner semen and donor semen in 2020 and Figure 4 the number of embryos replaced, broken down by source of origin. The number of recipients of ovarian tissue in 2020 was similar to the number reported in previous years (Figure 5). Recipients of ovarian tissue may receive multiple grafts at the same time.

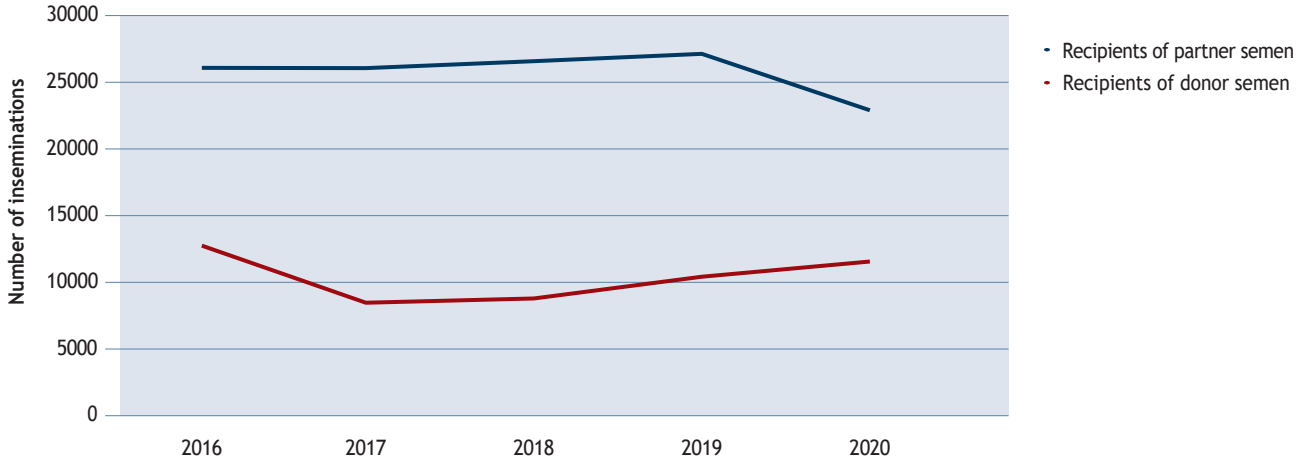

Figure 3 Number of recipients of partner semen and donor semen, 2016-2020

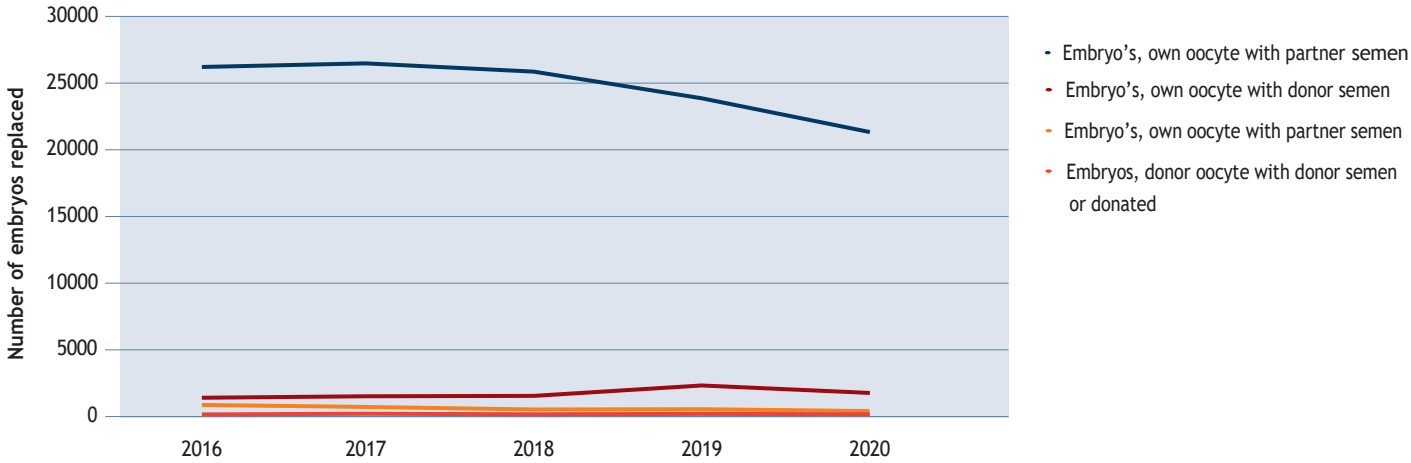

Figure 4 Number of embryos replaced, 2016-2020
2017: In this reporting year, only the total number of embryos replaced was reported, without a breakdown by source of origin. Representation by origin based on average distribution in 2016 and 2018.

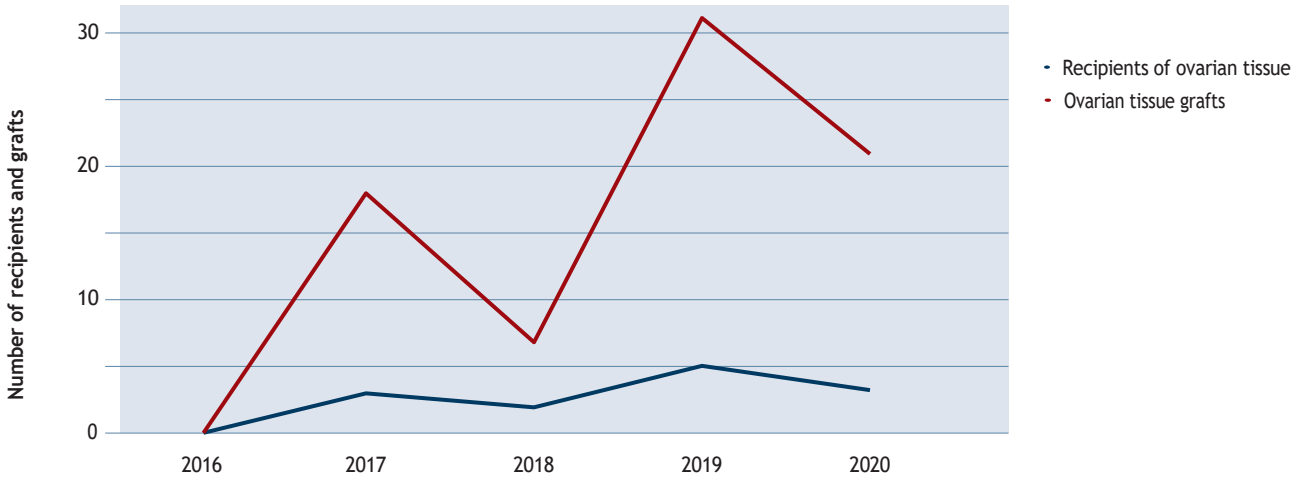

Figure 5 Number of recipients and ovarian tissue grafts replaced, 2016-2020
Corrected data for 2019 by revised report

Reports

In 2020, TRIP received 43 reports related to procedures or applications of gametes, embryos and/or gonadal tissue in medically assisted reproduction. The reports concerned 38 adverse events and five adverse reactions, three of which were donation complications. Figure 6 shows the reports of adverse reactions and events received in the period 2016-2020, classified according to the seriousness criteria set out by the European Commission (EC). These criteria can be found in Annex 3. The number of reports is similar to that of previous years.

In addition to the reports from 2020, 12 late reports of incidents from 2019 were received. These reports are included in the descriptions of the various reporting categories and have been incorporated into all figures and tables. Table 5 provides an overview of the number of reports received in 2020 and the late reports from 2019 from the various fertility laboratories. Four IVF laboratories and 45 semen laboratories indicated that no (serious) adverse events or adverse reactions occurred in 2020.

Table 5 Overview of reports received in 2020 and late reports from 2019 per type of fertility

Fertility laboratories	Number of reports in NL	Number of establishments reporting in 2020	Number of reports in 2020	Number of late reports from 2019
IVF laboratories	15	11 (73%)	33 (21 serious)	11 (5 serious)
Semen laboratories	51	6 (12%)	10 (4 serious)	1 (1 serious)
Total	**66**	**17 (26%)**	**43 (25 serious)**	**12 (6 serious)**

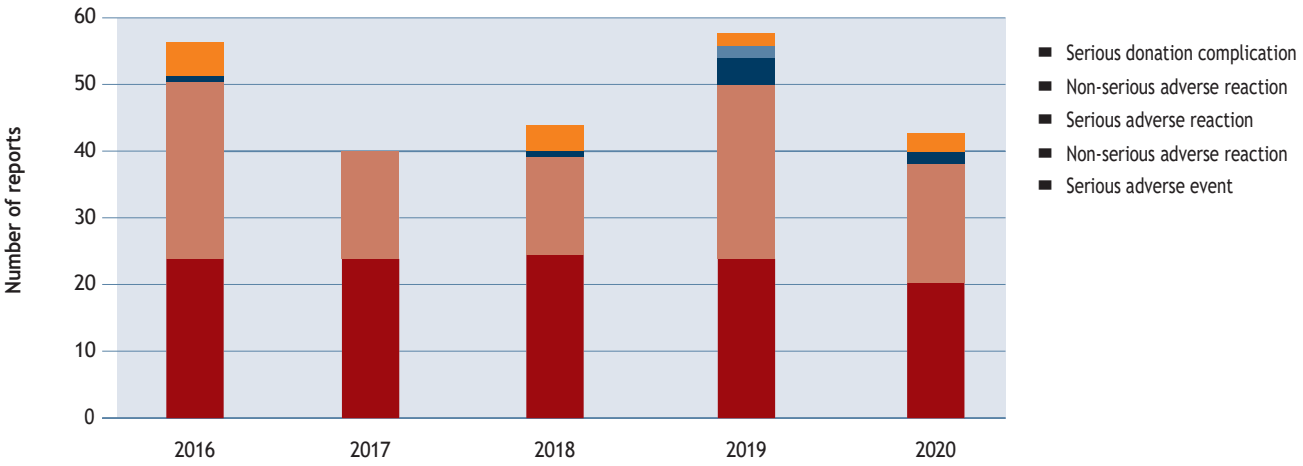

Figure 6 Reports concerning human reproductive cells and tissues, 2016-2020

Adverse reactions

In 2020, TRIP received five reports of adverse reactions associated with medically assisted reproduction, three of which were donation complications related to the collection of oocytes for autologous use (Table 6). All adverse reactions reported were classified as serious. Figure 7 provides an overview of the adverse reactions reported in the last five years. Donation complications have been reported to TRIP since 2015. Reporting of donor side effects to the EU is currently not mandatory, but the European Commission requests that these reports be made on a voluntary basis. Figure 8 provides an overview of the reports of donation complications in obtaining oocytes for both patients' own fertility treatment and oocyte donation received by TRIP since 2015.

Table 6 Overview of adverse reactions related to human reproductive cells and tissues in 2020

Category of reaction	Type of tissue	Description
Allergic reaction	Donor semen	Itching due to gentamicin in medium*
Donation complication	Oocytes	Bleeding after ovum pick-up*
	Oocytes	Full-blown infected necrotising myoma after ovum pick-up*
	Oocytes	Ovarian hyper stimulation syndrome (OHSS)*
Other reaction	Partner semen	Fever, chills, fatigue, pain in abdomen due to Mycoplasma genitalium after IUI*

**Serious*

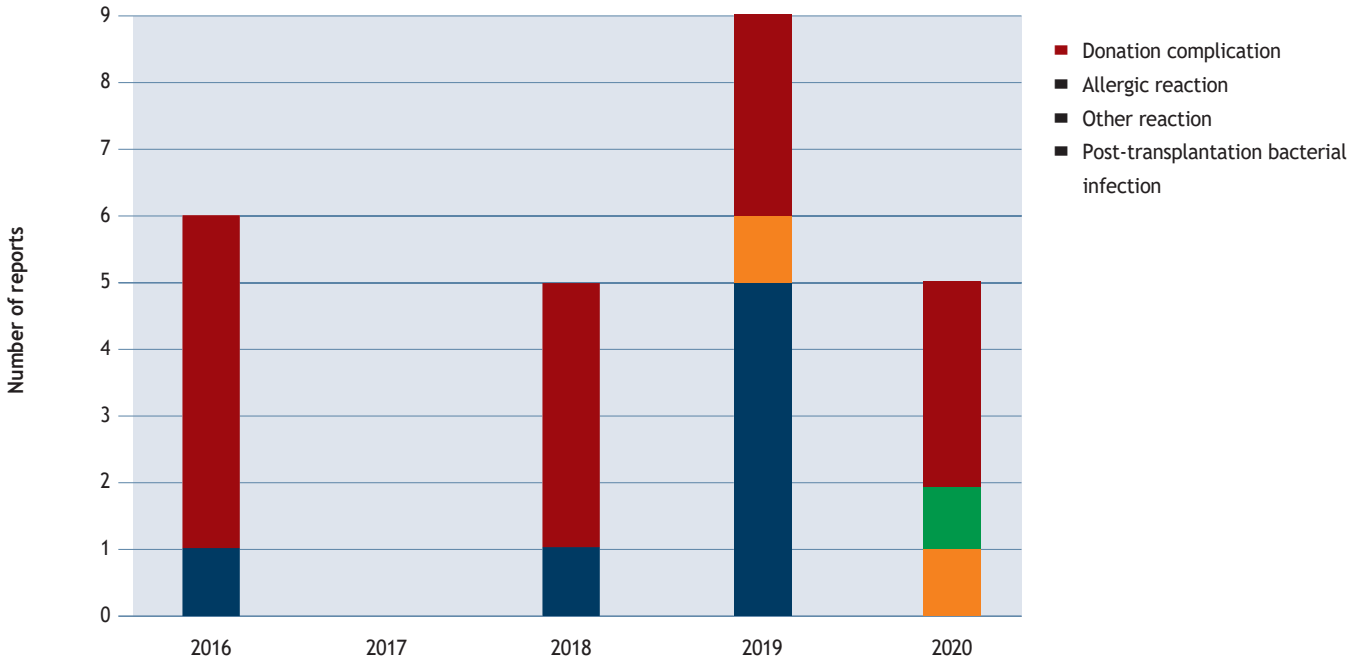

Figure 6 Reports concerning human reproductive cells and tissues, 2016-2020

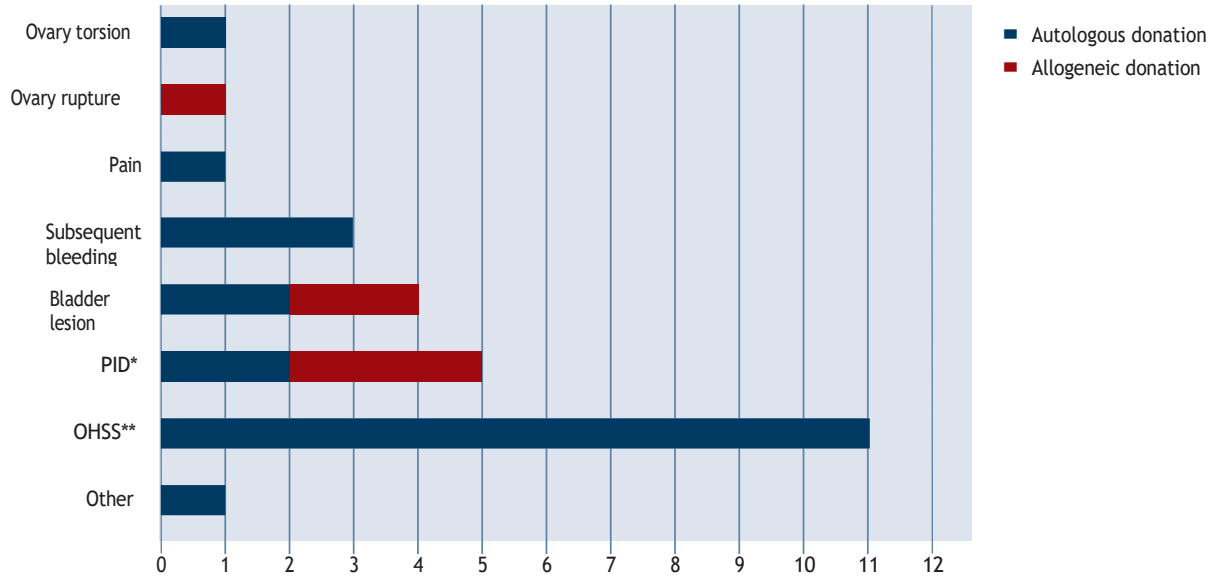

Figure 8 Reports of donation complications related to the procurement of oocytes in the Netherlands, 2015-2020
Donation complications have been reported to TRIP since 2015
** Pelvic inflammatory disease*
*** Ovarian hyper stimulation syndrome*

Events

In 2020, TRIP received 38 reports of adverse events relating to reproductive cells and tissues. Of these, 20 reports (53%) were assessed as serious adverse events (Figure 6). The percentage of serious adverse events is similar to that of the previous years (52% over the last 5 years). Furthermore, 12 adverse events from 2019 were reported. Of these, 6 reports (50%) were assessed as serious adverse events.

Table 7 shows the adverse events by type of reproductive cells and tissues, adverse event category, and severity. Figure 9 shows the distribution of adverse events in the period 2016-2020. The categories 'Loss of cells or tissues' and 'Congenital abnormality' accounted for the largest number of reports. In 2020, TRIP received 20 reports concerning a 'Loss of cells or tissues' and 15 concerning a 'Congenital abnormality'. The larger number of reports concerning congenital abnormalities received since 2017 may be due to the increase in the use of donated gametes and in the awareness of having to report these adverse events.

Table 7 Overview of adverse events related to reproductive cells and tissues in 2020 and late reports from 2019

Type of tissue or cells	Adverse event category	Total 2020	Serious 2020	Late reports from 2019	Late reports of serious adverse events from 2019
Semen	Loss of cells or tissues	3	0	0	0
	Other incident	1	0	1	0
	Congenital abnormality	15	9	6	3
	Near miss	1	1	1	1
Oocytes	Loss cells or tissues	7	5	0	0
	Other incident	0	0	1	1
Embryos	Loss cells or tissues	10	5	1	0
	Other incident	1	0	1	0
Testicular tissue	Other incident	0	0	1	1
Total		**38**	**20**	**12**	**6**

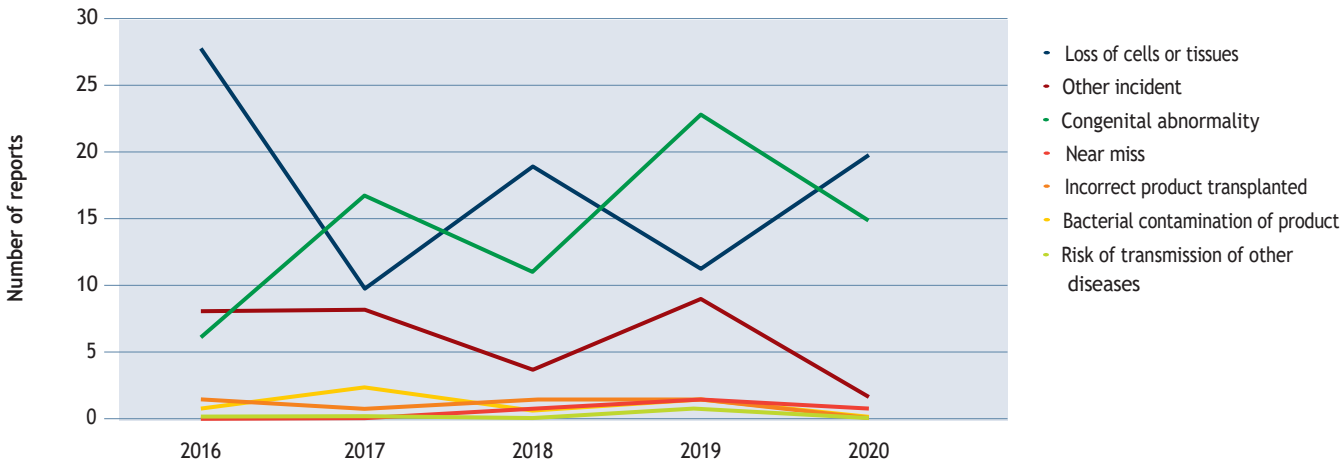

Figure 9 Number of reports per adverse event category concerning reproductive cells and tissues, 2016-2020

Loss of cells or tissues

In 2020, 20 reports were registered as concerning 'Loss of cells or tissues'. Ten cases involved the loss of a complete reproductive cycle or the loss of irreplaceable tissues or cells. These reports have been classified as serious. TRIP also received one late report from 2019. Figure 10 provides an overview of the number of reports in the category 'Loss of cells or tissues' in the period 2016-2020.

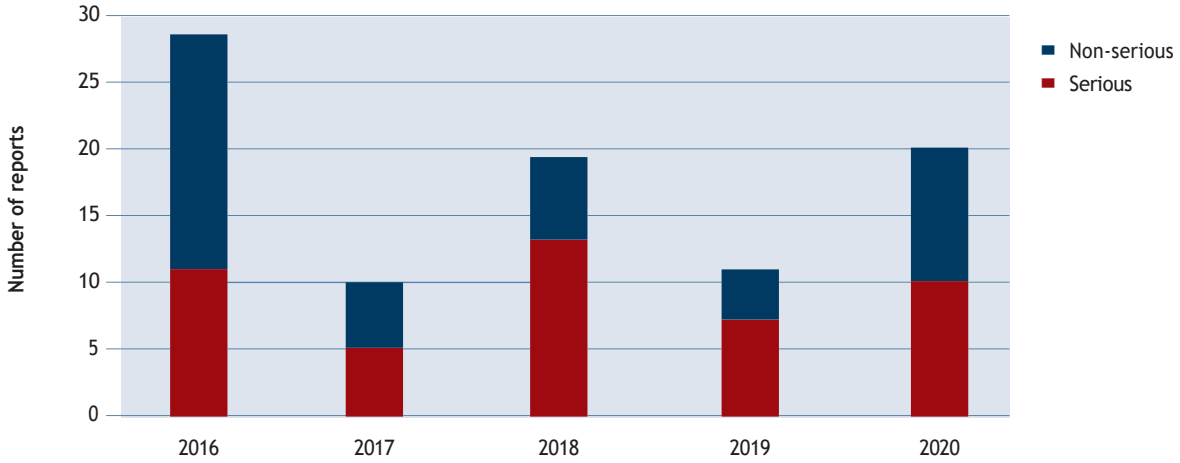

Figure 10 Reports in the category 'Loss of cells or tissue(s)' concerning reproductive cells and tissues, 2016-2020

Of the reports in the category 'Loss of cells or tissues', 15 involved an error during the processing of oocytes or semen or during the processing and transplantation of embryos. There was also a clerical error, as well as an identification error and technical error. Three other errors were reported in the procurement, processing and transplantation phases.

Congenital abnormality

In the 2020 reporting year, 15 reports and six late reports from 2019 were registered as concerning 'Congenital abnormality' (Table 8). 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 foetus with a (possible) genetic abnormality, the event is classified in this category. This is a serious adverse event for the foetus or neonate. Twelve reports in which a genetic factor is definitely or possibly involved have been assessed as serious. Case 1 describes a hereditary form of hypertrophic cardiomyopathy after IUI-D from an anonymous donor before 2004. Figure 11 provides an overview of reports in the category 'Congenital abnormality' in the period 2016-2020. Table 9 gives an overview of the different congenital abnormalities in the period 2007-2020.

Table 8 2020 reports and late reports from 2019 in the category 'Congenital abnormality' relating to the use of donor semen

Year	No. of reports	Description	Donor deferred
2019	1	Child born with metabolic disease Medium-chain acyl-CoA dehydrogenase deficiency. Donor and mother found to be both carriers.*	Donor deferred.
	1	Long QT syndrome suspected of causing neonatal death (2 weeks old). Final diagnosis was sudden infant death syndrome.	Donor was temporarily deferred and became eligible again after it had been established that no hereditary disease was involved.
	1	Developmental delay in donor child based on 16p11.2 deletion syndrome. Deletion not found in donor.	Donor remained available for families with children from previous donations.
	1	Child born with West syndrome based on abnormalities in KIAA1109 genes. Donor and mother found to be carriers.*	Donor remained available for families with children from previous donations.
	1	CHD8 syndrome in a donor child (autosomal dominant). CHD8 gene mutation was not found in the donor. Likely to be a *de novo* mutation.	Donor remained available for families with children from previous donations.
	1	Child born with nystagmus and oculocutaneous albinism. Two mutations in OCA2-gen. Donor and mother found to be carriers.*	Donor deferred. Other pregnancy from this donor underway.

Table 8 2020 reports and late reports from 2019 in the category 'Congenital abnormality' relating to the use of donor semen

Year	No. of reports	Description	Donor deferred
2020	1	Donor child of the same donor as in report mentioned above has nystagmus. Carrier donor.*	Donor deferred.
	1	Donor child has Joubert syndrome. Donor and mother found to be carriers.*	Donor deferred.
	2	Child born with schisis. A genetic component may be involved.*	One donor was already deferred. Two donor deferred.
	1	Child was born with clubfeet, without other forms of dysmorphia.	Donor not deferred.
	1	Trisomy 21 was diagnosed during pregnancy. Increased risk based on the mother's age.	Donor not deferred.
	1	Trisomy 21 was diagnosed during pregnancy. A hereditary variant is not excluded.*	Donor deferred.
	1	Hydrops foetalis associated with trisomy 21 with structural heart defect. Pregnancy aborted. No donor translocation.*	Donor not deferred.
	1	Turner syndrome with severe heart defect diagnosed during pregnancy.2	Donor not deferred.
	2	Boy born with hypospadias. No other abnormalities.	Donors not deferred.
	1	A donor child was diagnosed with celiac disease. A genetic component may play a role in celiac disease.*	Donor is no longer used.
	1	Donor child was diagnosed with Rett syndrome (mutation of the MECP2 gene on the X chromosome). Usually *a de novo* mutation.*	Donor remains available to families with children from a previous donation.
	1	Child born with Cystic Fibrosis. Donor and mother are carriers.*	Donor deferred.
	1	Man dies of a hereditary form of hypertrophic cardiomyopathy. Described in Case 1.*	Donor is no longer used.

Total 15 + 6 late

**Serious*

Case 1

An adult died of an inherited form of hypertrophic cardiomyopathy, a condition in which the heart muscle is thickened and can lead to sudden death at a young age. This condition is usually an autosomal dominantly inherited disease or arises after a mutation. The person concerned was conceived with donor semen at the time. The mother is not a carrier, the brother (offspring of the same semen donor) also appears to be a carrier of the defect. Therefore, it is very likely that the semen donor is a carrier of this heart defect. The semen was donated anonymously before 2004, which makes it difficult to trace the donor.

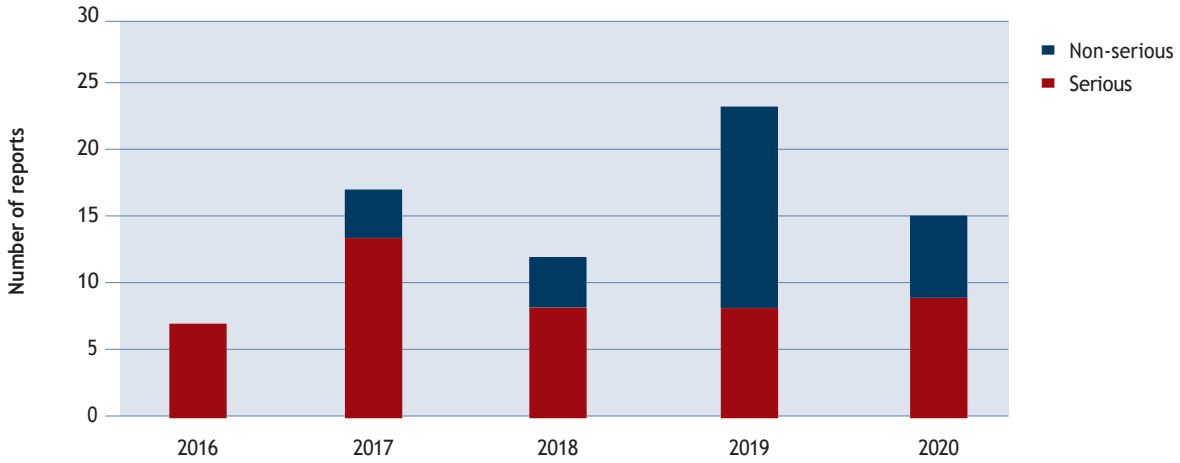

Figure 11 Reports in the category 'Congenital abnormality', 2016-2020

Table 9 Overview of congenital anomalies reported after gamete or embryo donation from non-partner donor(s) or after pre-implantation genetic diagnosis (PGD), in the period 2007-2020

Transmission of genetic disorder, carrier donor	**Number**
Autosomal recessive	20
Autosomal dominant	4
***De novo* mutation**	
Autosomal dominant	5
X-linked recessive	1
Transmission of genetic disorder through mother, donor not a hereditary carrier	
Autosomal dominant	1
Chromosomal abnormality, possible donor carrier status	
Trisomy	1
Deletion	1
Chromosomal abnormality, donor not a hereditary carrier	
Trisomy	13
Triploidy	1
45X	2
47XYY	1
Congenital abnormality, genetic factor not ruled out	
Cardiac	5
Neurological	3
Urogenital	4
Musculoskeletal	3
Gastrointestinal	2
Sensory	3
Craniofacial	3
Multi-system	1
Oncological	1
Congenital abnormality, genetic factor ruled out	
Cardiac	1
Neurological	1
Urogenital	2
Musculoskeletal	2
Multi-system	5
Oncological	1
Congenital abnormality after PGD, result possibly erroneous	
Neurological	1
Unbalanced translocation	1
Neonatale sterfte met verdenking op congenitale afwijking	
Long QT syndrome	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 genetic abnormalities in a donor is assessed through a donor's medical history. Autosomal recessive abnormalities that do not manifest themselves in the donor are usually not detected using this method. However, by consistently reporting congenital abnormalities when using donor gametes, the occurrence in multiple offspring can indicate the need for screening and/or exclusion of the donor, so that similar abnormalities in future offspring can be prevented.

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. In the category 'Other Incident', TRIP received two 2020 reports and four late reports from 2019 (Table 10). Figure 12 provides an overview of the number of reports registered as 'Other incident' from 2016 to 2020. The nature of two 'Other incident' reports is classified as 'Other'. Initially, a congenital disease was suspected, but after ancillary investigation, no indication for this was found.

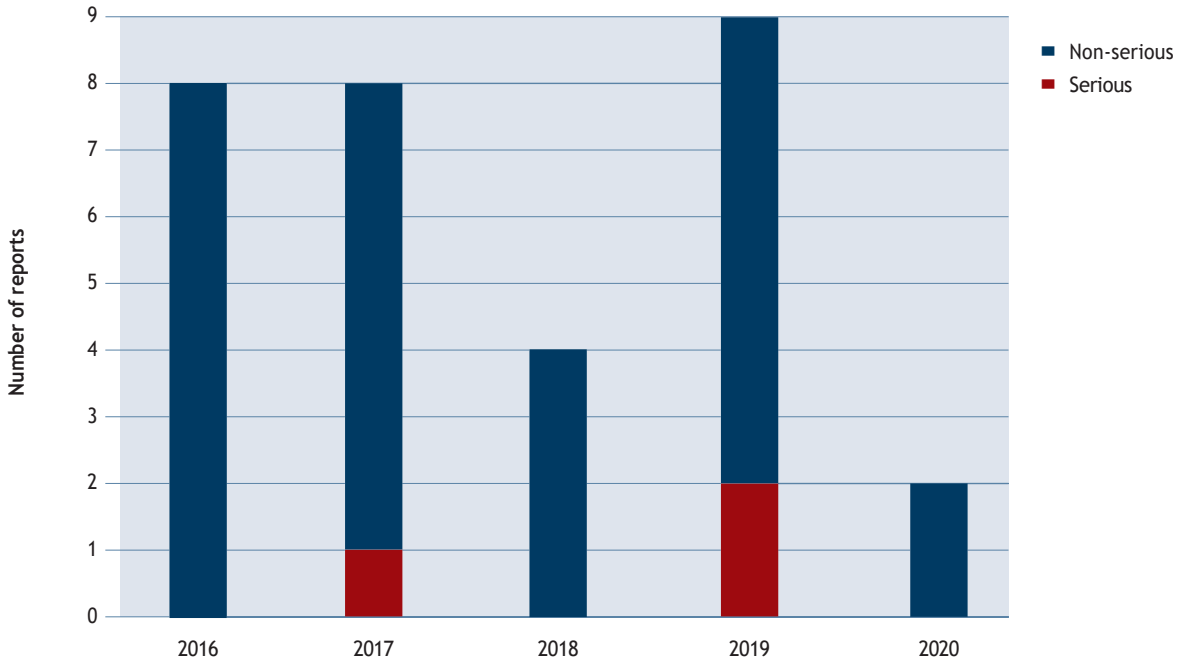

Figure 12 Reports in the category 'Other incident' concerning human reproductive cells and tissues, 2016-2020

Table 10 2020 reports and late reports from 2019 in the category 'Other incident' concerning human reproductive cells and tissues

Type of error	Type of gamete or embryo	Phase	Description
Storage error	Partner semen	Processing	Upon receipt, the semen sample was placed in the refrigerator, which caused the motility to be lower than normal. Insemination took place using this sample and a new sample.
Clerical error	Embryo(s)	Storage	Status of the embryos in the cryo bank was not sufficiently clear to the treating doctor, so that no up-to-date information could be given to patients.
Identification error	Oocyte(s)	Procurement	Jars containing follicular fluid were not labelled after follicular puncture. Following correct identification, IVF treatment took place.
Identification error	Testicular tissue	Procurement	Material from the outpatient department was delivered bearing the sticker of another patient. The correct identity of the material could be established.
Other	Semen donor	Donation	Intrauterine foetal death after 30 weeks of pregnancy.
Other	Semen donor	Donation	Low motor development in child born, no evidence of underlying disease.

Incorrect product transplanted/applied

In 2020, in contrast to previous years, no reports were received concerning the transplantation of an incorrect product. Reports in this category are always assessed as serious. Figure 13 provides an overview of reports of 'Incorrect product transplanted/applied' in the period 2016-2020.

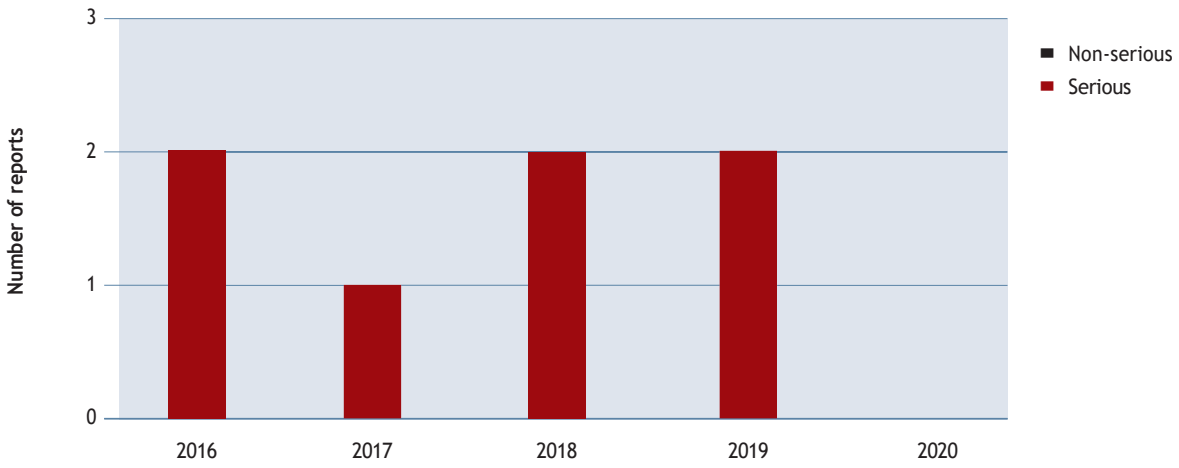

Figure 13 Reports in the category 'Incorrect product transplanted/applied' related to human reproductive cells and tissues.

Near miss

In 2020, TRIP received one report classified as a 'Near miss' and one late report from 2019 (Table 11). Figure 14 provides an overview of all reports of near misses that TRIP received in the period 2016-2020. Reports of 'Near miss' concern mix-ups or errors that could have led to the transfer or insemination of (an) embryo(s) or semen in the wrong recipient if they had not been detected.

Table 11 2020 reports and late reports from 2019 in the category 'Near miss' concerning human reproductive cells

Type of error	Year	Type of tissue or cells	Description
Identification error	2019	(Partner) semen	During processing two semen samples were neither identified nor double-checked. Both destroyed. New samples were provided, allowing IVF treatments to go ahead.
	2020	(Donor) semen	Sticker on form for handing in semen proved to be from another patient. Discovered by partner. Error corrected. IUI could be performed.

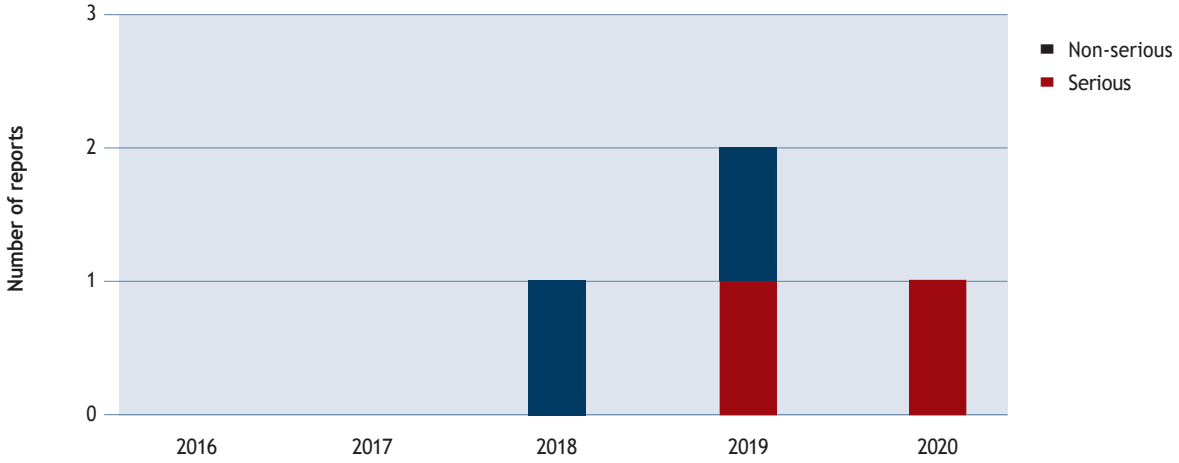

Figure 14 Reports in the category 'Near miss' concerning human reproductive cells and tissues, 2016-2020

Human reproductive cells and tissues - summary

Fertility care in 2020 was greatly affected by the COVID-19 pandemic. A decrease in the number of applications in almost all fertility treatments has been observed since March 2020. However, the number of reports received by TRIP is in line with previous years. In 2020, TRIP received 43 reports from 17 different fertility laboratories. Five adverse reactions relating to reproductive cells and tissues were reported, three of which were donation complications. Thirty-eight adverse events were reported. The largest number of reports was in the category 'Loss of tissues or cells'. (20, ten of which were serious). For the first time since 2012, TRIP did not receive any report in the category 'Incorrect product transplanted/applied'. Half of the 12 late reports were reports of congenital abnormalities in the application of donor gametes. The investigation of a congenital abnormality usually takes a considerable amount of time, which may explain the delay between discovery and completion of a report.

2.2 Hematopoietic stem cells and other therapeutic cells

As of 2020, there are 12 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 provision of stem cell products donated by unrelated donors (including cord blood) for specific patients to the Netherlands' eight academic transplantation centres is mediated by Matchis, usually through the stem cell laboratory of the hospital involved. Unrelated stem cell products for Dutch patients are mostly from foreign donors (477/510=94% of transplants in 2020). Bone marrow and peripheral blood stem cells (PBSC) donated by unrelated donors from the Netherlands are collected by Matchis in two academic hospitals with hemapheresis units and stem cell laboratories. A minority of these donations are used for Dutch patients (33 transplants in 2020); the majority are distributed to foreign transplant centres (189 transplants in 2020). A total of 1658 patients received an HSC transplant in 2020, 61% being autologous, 10% allogeneic from related donors and 29% from unrelated donors (see Table 14).

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 available for requests for patients inside and outside the Netherlands through Matchis. Additionally, one private blood bank stores cord blood for possible future autologous applications. These units were not distributed or applied in 2020. Because of the COVID-19 pandemic, stem cell transplants from unrelated donors were not administered immediately, but were temporarily stored using cryopreservation. This was done to avoid harm from possible transport problems; the recipient was not conditioned until the transplant had actually arrived. In addition, if necessary, there was time to perform additional tests or wait for a symptom-free period in the case of symptoms of COVID-19 in either donor or recipient. For this reason, the transplants were split into smaller portions and distributed, and there was an increase (from 348 to 786) in the number of transplanted bags of PBSC from unrelated donors, while the number of recipients in 2020 remained approximately the same as in 2019 (Figure 15).

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 the EU and/or were applied in the Netherlands.

Processing of a transplant takes place around the time of collection (e.g. apheresis or bone marrow extraction) and there may also be subsequent processing (e.g. after receipt of the transplant at the transplant centre). As a result, transplants may be counted several times in the processing figures; this may explain apparent discrepancies between the tables. Distribution is the issuing of a unit by the stem cell laboratory for (direct) application. According to the definition, the transport of a transplant from one laboratory to another does not formally fall under distribution; however, the numbers of unrelated transplants transported to other EU countries and outside the EU are listed in Table 13. Not all establishments reported the distribution and application figures in numbers of bags (but in transplants instead). This may explain discrepancies between the tables. Figure 15 a-b-c shows the annual numbers of PBSC, bone marrow and cord blood transplants.

Table 12 Processing of hematopoietic stem cells in 2020

Type of cells	Stem cell laboratories	Processing of transplants			
		From NL	From EU	From non-EU	Total
HSC autologous					
PBSC	11	1344	0	0	1344
Bone marrow	3	21	0	0	21
Cord blood	1	1400	0	0	1400
HSC related					
PBSC	8	181	0	0	181
Bone marrow	5	31	0	0	31
Cord blood	1	4	0	0	4
HSC unrelated*					
PBSC	7	283	246	31	560
Bone marrow	4	68	22	6	96
Cord blood	6	32	44	12	88

*'From NL' column includes units requested through Matchis and collected for application outside NL

Table 13 Distribution of hematopoietic stem cells in 2020

Type of cells	Stem cell laboratories	Bags distributed*			
		In NL	In EU	In non-EU	Total
HSC autologous					
PBSC	11	3359	0	0	3359
Bone marrow	2	20	0	0	20
Cord blood	0	0	0	0	0
HSC related					
PBSC	8	292	0	0	292
Bone marrow	5	31	0	0	31
Cord blood	1	3	0	0	3
HSC unrelated					
PBSC	7	721	103	61	885
Bone marrow	4	123	11	14	148
Cord blood	6	79	4	2	85

*Number distributed in NL per bag, number distributed outside NL per transplant

Table 14 Application of hematopoietic stem cells in 2020

Type of cells	Transplantation centres	Recipients	Bags applied			
			From NL	From EU	From non-EU	Total
HSC autologous						
PBSC	12	991	3323	0	0	3323
Bone marrow	2	19	20	0	0	20
Cord blood	0	0	0	0	0	0
HSC related						
PBSC	8	132	292	0	0	292
Bone marrow	5	31	31	0	0	31
Cord blood	1	3	3	0	0	3
HSC unrelated						
PBSC	8	386	391	330	65	786
Bone marrow	5	45	41	4	0	45
Cord blood	7	51	36	37	3	76

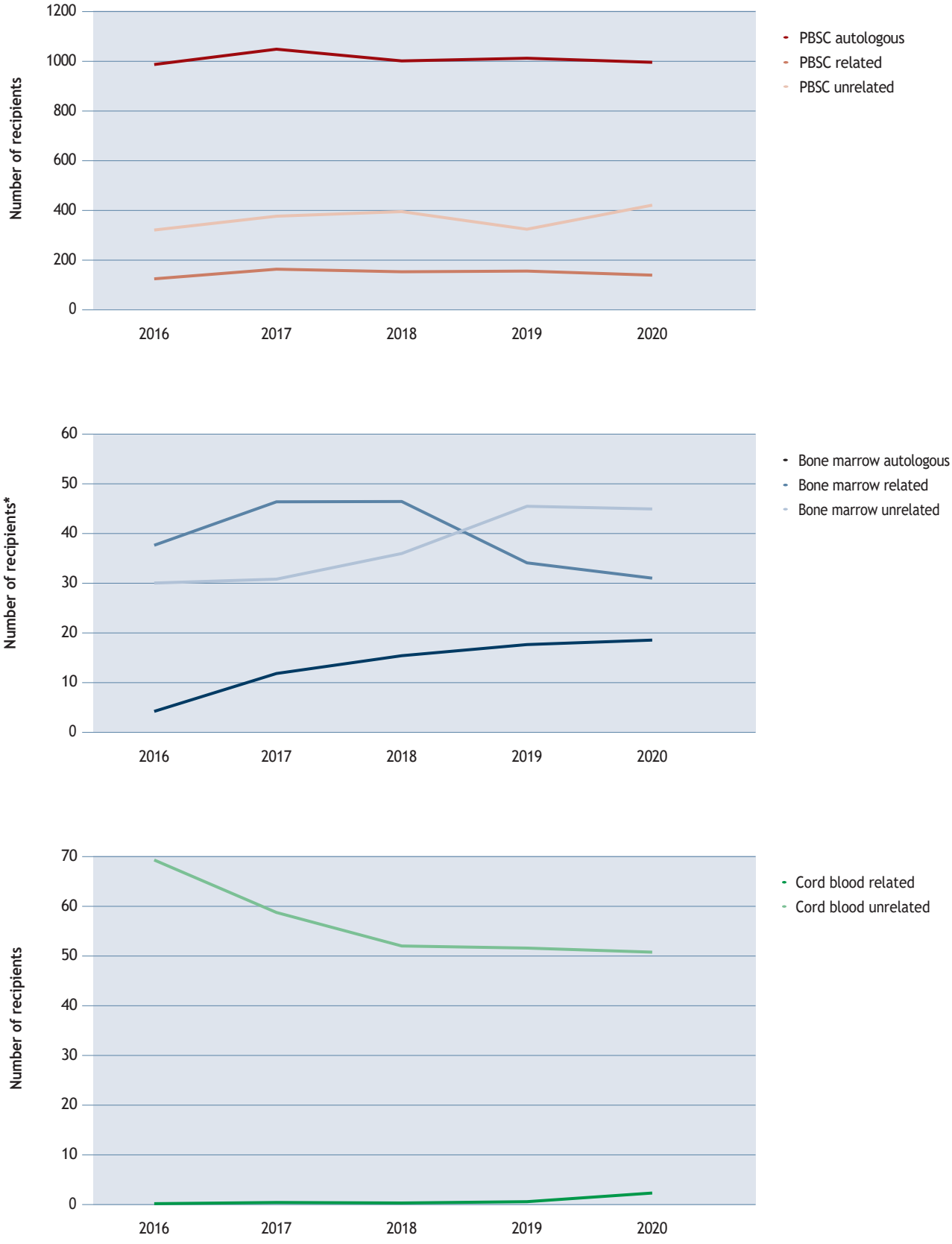

Figure 15 a-b-c Number of recipients of hematopoietic stem cell transplants by type of transplant, 2016-2020
** Corrected data for Bone Marrow autologous recipients 2017 to 2019, Bone Marrow unrelated recipients data based on number of distributed Matchis transplants*

In addition to processing hematopoietic stem cells for transplant purposes, several laboratories also process, distribute, and apply cells for other therapeutic purposes. The numbers of therapeutic cells processed, distributed and applied in 2020 can be found in Tables 15 and 16. Apart from donor lymphocyte infusions (DLIs), most applications of therapeutic cells occur on a small-scale and in experimental settings. If advanced processing is performed, such cells should be considered ATMPs (Advanced Therapy Medicinal Products). Seven centres provided figures for application of CAR T/TCR- cells in 2020 (2019: 4). The reporting of adverse events relating to the procurement, donation and testing of human body tissue is covered by biovigilance. Adverse events in the preparation of ATMPs fall within the GMP reporting system. Once an ATMP has been registered as a medicine, it falls under the responsibility of the pharmacy (which explains the difference between processing and distribution figures) and adverse reactions must be formally reported under pharmacovigilance.

Table 15 Processing and distribution of therapeutic cells in 2020

Type of cells	Laboratories	Transplants processed			Laboratories	Bags distributed		
		From NL	From outside NL	Total		In NL	Outside NL	Total
Lymphocytes (DLI) related	8	70	0	70	8	90	0	90
Lymphocytes (DLI) unrelated	5	57	108	165	5	187	10	197
Mesenchymal stem cells autologous#	1	5	0	5	1	8	0	8
Mesenchymal stem cells unrelated#	2	20	0	20	2	77	0	77
Dendritic cells autologous#	1	7	0	7	0	0	0	0
Dendritic cells unrelated#	0	0	0	0	0	0	0	0
TC-Til cells autologous#	1	16	0	16	1	8	0	8
CAR T/TCR cells#	2	46	0	46	4	71	0	71
Mononuclear cells#	4	50	56	106	2	23	0	23
Expanded cells from cord blood#	1	1	0	1	2	2	0	2

No compulsory reporting of distribution under the Dutch law on quality and safety of body material (ATMPs and processed cells in clinical studies).

Table 16 Application of therapeutic cells in 2020

Type of cells	Treatment centres	Recipients	Units applied		
			From NL	From outside NL	Total
Lymphocytes (DLI) related	8	84	90	0	90
Lymphocytes (DLI) unrelated	6	179	134	49	183
Mesenchymal stem cells autologous	1	4	8	0	8
Mesenchymal stem cells unrelated	2	42	77	0	77
Dendritic cells autologous	0	0	0	0	0
Dendritic cells unrelated	1	1	5	0	5
TC-Til cells autologous	2	9	9	0	9
CAR T/TCR cells	7	92	45	46	91
Mononuclear cells	1	15	15	0	15
Expanded cells from cord blood	2	2	1	2	3

Reports

In 2020, TRIP received 28 reports relating to hematopoietic stem cells or other therapeutic cells: 18 adverse events and ten adverse reactions including one donation complication (Figure 16). Table 17 describes the adverse events; no events concerning HSC or other cells were assessed as serious in 2020. The nine adverse reactions, including two serious ones, are described in Table 18. Because of the COVID-19 pandemic, products that would normally have been administered fresh (allogeneic PBSC) were now also cryopreserved because of additional testing and care planning options. This has not led to an increase in the number of reports of potentially DMSO-related adverse reactions. In Table 19 the donation complication is described.

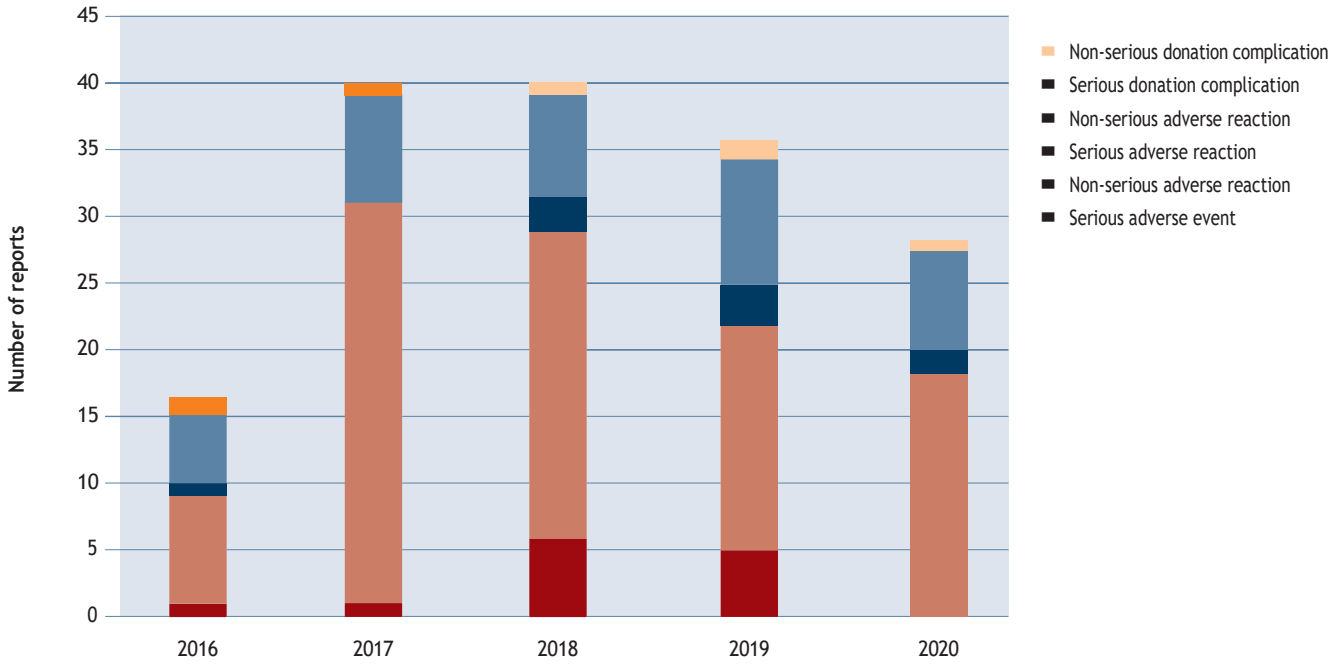

Figure 16 Reports concerning HSC and therapeutic cells, 2016-2020

Table 17 Adverse events relating to hematopoietic stem cells in 2020

Type of HSC	Adverse event (category and description)	Reports
PBSC autologous	Bacterial contamination of product • Positive culture of product, Lactobacillus species, no additional measures, uncomplicated reinfusion, adequate engraftment	1
PBSC allogeneic unrelated	Bacterial contamination of product • Positive culture of product, *Bacillus cereus*, preventive antibiotics, adequate engraftment • Positive culture of product, *Fusobacterium nucleatum*, preventive antibiotics, engraftment sufficient Other incident • Clots in product to be processed, depletion set blocked despite additional filtration step, ultimately sufficient recovery and product with sufficient cells after cryopreservation (becayse of SARS-CoV-2) uncomplicated administration, adequate engraftment • Repeat positive donor screening for HTLV, see case 2	2 2
Bone marrow allogeneic related	Bacterial contamination of product • Positive culture of product, *Actinomyces oris*, repeat culture negative, no additional antibiotics, adequate engraftment • Positive culture of product, *Propionibacterium acnes*, also found in donor centre, no additional antibiotics, adequate engraftment	2
Bone marrow allogeneic unrelated	Bacterial contamination of product • Positive culture of product, Gram-positive cocci, no positive cultures in transplantation centre, no additional antibiotics, uncomplicated administration • Positive culture of product, *Propionibacterium acnes*, preventive antibiotics, no particular problems reported by transplantation centre (elsewhere) • Positive culture of product, *Staphylococcus epidermidis*, also found in donor centre, no additional antibiotics, adequate engraftment • Positive culture of product, *Staphylococcus capitis*, also found in donor centre, no additional antibiotics, adequate engraftment • Positive culture of product before cryopreservation, Pseudomonas species, culture after cryopreservation negative, preventive antibiotics, adequate engraftment Loss of cells • During processing, when stripping the line, tube detached from the collection bag: several ml of graft lost, additional sterility test remained negative, adequate engraftment • Clots detected during filtration of product causing filter jamming: manual filtration, patient received fewer cells than requested, adequate engraftment. Donor centre adds lower amount of heparin	5 2
Lymphocytes, allogeneic unrelated	Bacterial contamination of product • Positive culture product before cryopreservation (residual fraction of administered product), *Staphylococcus epidermidis*, culture after cryopreservation negative, released for possible use.	1
T-cells, autologous for ATMP	Loss of cells • Temperature overshoot during transport of processed product, product lost, patient undergoing new apheresis procedure • TILT incident during transport of apheresis product, resulting in breakage, half of the bags unusable, sufficient cells for ATMP production • During the production process, the product was found to be out of specification, the product was returned as a back-up and the apheresis procedure was repeated for new production.	3
Total		**18**

Table 18 Overview of adverse reactions in 2020, by type of hematopoietic stem cells

Type of HSC	Adverse event (category and description)	Reports
PBSC autologous	Other reaction • Dyspnoea during reinfusion with drop in saturation, for which oxygen and hydrocortisone were administered, rapid recovery, imputability probable • Increase in nausea after reinfusion for which anti-emetics were given, imputability unlikely.	2
PBSC related	Other reaction • Vomiting several hours after transplantation, imputability unlikely	1
PBSC unrelated	Anaphylactic reaction • Chills, fever, hypotension and vomiting 15 minutes after transplantation, for which clemastine and IV fluids were administered, recovery within a few hours, imputability certain*.	1
	Post-transplantation bacterial infection • Chills and fever two hours after transplantation for which antibiotics were initiated. Positive blood culture of patient with coagulase-negative staphylococcus (CNS) and *Staphylococcus epidermidis* after administration through an infected line. Product cultures remained negative, patient recovered within 24 hours, imputability unlikely	1
	Other reaction • Hypotension one day after transplantation for which antihypertensive drugs were discontinued and IV fluids were administered, imputability unlikely. • Hypotension and tachycardia approx. 8 hours after transplantation, spontaneous recovery, imputability possible	2
Mesenchymal stem cells, unrelated	Other reaction •Vomiting, hypertension and tachycardia following administration of ATMP with spontaneous recovery, imputability possible	1
Bone marrow, related	Other reaction • Baby with hypertension, dyspnoea and seizures following transplantation, treated with paracetamol, diuretics, antiepileptic drugs and antihypertensive drugs. Admission to ICU and postponement of 2nd part of graft until next day. Imputability likely*.	1
Total		**9**

* *Serious*

Table 19 Donation complication with hematopoietic stem cells in 2020

Type of HSC	Donation complication	Interval from donation	Imputability	Seriousness
PBSC allogeneic unrelated	Donor with a history of tinnitus experiences tinnitus again the night before donation without incidental phenomena. PBSC donation proceeded without further complications, symptoms had improved at follow-up.	During G-CSF mobilisation	Possible	1

Case 2

On the day before starting conditioning a patient who was to receive a stem cell transplant from an unrelated donor, the transplanting establishment was informed of a positive screening result for the donor. The donor's HTLV 1/2 screening test was repeat positive on the day of collection, whereas it was negative at screening 2.5 weeks earlier. The patient's conditioning of the recipient had to be postponed while awaiting additional tests. The PCR and immunoblot proved negative six days after donation and the patient underwent transplantation 14 days later than initially planned. The collection centre has a standard policy of repeating full viral serology on the day of collection.

Hematopoietic stem cells and therapeutic cells - summary

The number of stem cell applications in 2020 (1658 recipients) remained stable compared to 2019 (1642 recipients). Due to the COVID-19 pandemic, there was an increase in the number of distributed and applied PBSC units from allogeneic donors. This can be explained by the temporary change in procedure (cryopreservation instead of fresh administration), for which grafts are split into smaller units. The total number of reports relating to HSC in 2020 (28) was lower than in 2019 (36). Two adverse reactions were assessed as serious and none of the adverse events, compared to three serious adverse reactions and five serious adverse events in 2019. There were 11 reports of bacterial contamination of products in 2020, seven of which involved bone marrow (two related, five unrelated donors), compared to 14 reports in 2019, nine of which involved bone marrow (four related, five unrelated donors), making this the largest reporting category again.

The number of establishments reporting the use of ATMPs has increased from four to seven. Despite the fact that there are no conclusive regulations on the reporting of adverse events in relation to application of these products, three reports concerning other therapeutic cells were submitted on a voluntary basis in 2020. These reports concerned adverse CAR T-cell events, where in two cases the patient needed to undergo a new apheresis procedure. The cases underline the importance of monitoring adverse events with this form of treatment, which is currently not seamlessly covered by legislation (pharmaco-, hemo- and/or biovigilance).

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 throughout Europe. One of these tissue establishments stopped processing and distributing tissues in 2020, but stores tissues for another tissue establishment.

Bone

Processing, distribution and application

Tables 20 and 21 show the number of processed and distributed units of bone and the number of applied units of bone tissue, respectively. These data were supplied by 14 tissue establishments, two independent treatment facilities, 46 oral implantology practices and 67 hospitals. The discrepancy between distribution and application figures might be explained by the fact that the figures from the applying establishments are still incomplete. The numbers of applied femoral heads and units of bone filler have decreased, possibly due to the scaling down of care in 2020 as a consequence of the COVID-19 pandemic, which led to fewer elective orthopaedic operations. Figure 17 shows how many units of bone filler and femoral heads were distributed in the Netherlands from 2016 to 2020.

Table 20 Processing and distribution of bone tissue in 2020

Type	Tissue establish-ments*	Processed			Distributed					
		From on-site clinic	From NL	From EU/non-EU	Unit	In on-site clinic	In NL	In EU	Outside EU	Total
Femoral head, living donor	7	532	1719	98	Bone, whole or halved	468	1290	539	13	2310
Fem. head, post-mortem donor	2	0	19	2	Bone	0	25	34	2	61
Bone filler, mineralized	8	0	2125	3	Pack	0	4967	3602	1859	10428
Bone filler, demineralized	5	0	256	5	Pack	0	1652	12757	11337	25746
Bone, whole	2	0	179	27/1	Bone	0	146	1	35	182
Cranial bone autologous	3	69	110	2	Graft	16	64	0	0	80

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

Table 21 Application of bone tissue in 2020

Type	Hospitals/ clinics/practices	Recipients	Applications					
			Unit	From on-site tissue establishment	From NL	From EU	From non-EU	Total
Femoral heads (whole or halved)*	46	1251	Bone	487	842	10	0	1339
Bone filler, mineralized	74	2693	Pack	0	2348	534	0	2897
Bone filler, demineralized	21	354	Pack	0	289	76	0	366
Bone, whole	16	73	Bone	0	73	0	0	73
Cranial bone autologous	5	46	Graft	16	30	0	0	46

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

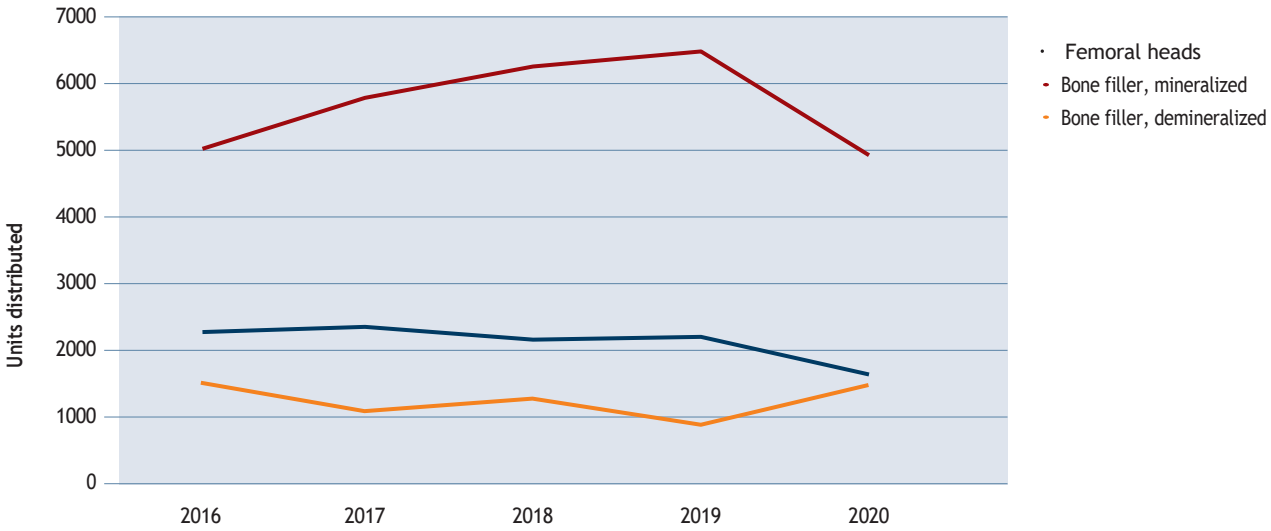

Figure 17 Number of units of bone filler and femoral heads distributed in the Netherlands from 2016 to 2020

Reports

In 2020, TRIP received ten reports concerning bone tissue in 2020 and one late report from 2019. All are reports of adverse events, five reported by hospitals and six by tissue establishments (see Table 22). Of the 11 reports, three are serious (see Figure 18). There has been a notable increase in the number of reports (one in 2019 to 11 reports in 2020). Seven reports involved multiple tissues. Twice there was a freezer malfunction. Two reports concerned damaged packaging. The variety of adverse events described below show that bone banking is a complex process.

Table 22 Overview of adverse events involving bone tissues in 2020

Adverse event category	Reports	Bone product	Description
Loss of cells or tissues	3	Femoral heads and bone chips	Femoral heads and bone chips lost due to freezer malfunction
		Tibia	Damaged packaging, implantation not carried out (possible contamination). New operation required*
		Femoral heads	Packaging was damaged and considered possibly contaminated
Near miss	2	Whole bone	Donor did not meet the requirements for the use of whole bone. Tissue lost
		Bone chips	The labels on the inner and outer packaging did not match
Other incident	6	Femoral heads, bone chips, fascia and tendons	During preparation of the annual report, for some tissues it was not recorded whether they had been transplanted
		Femoral head	Unlicensed distribution to third parties*
		Femoral heads	Freezer malfunction, no material lost
		Bone chips	Typing error in the SEC code of one batch
		Whole bone (cornea, tendon and cartilage)	Procutement without legal authorization*

* Serious

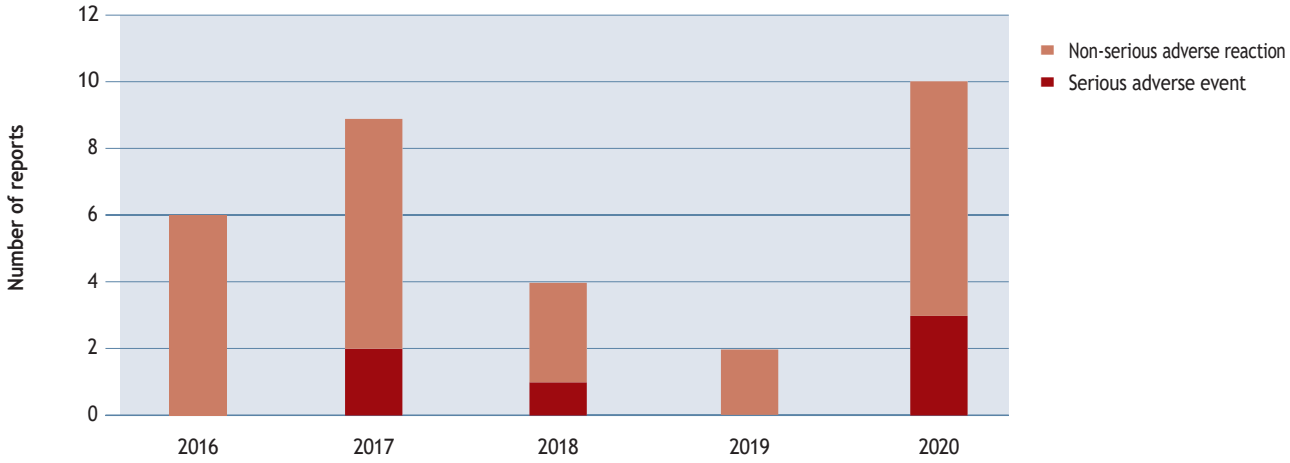

Figure 18 Reports associated with to bone tissue, 2016-2020

Other musculoskeletal tissues

Processing, distribution and application

Tables 23 and 24 present the processing and distribution figures and the application figures for tendons, fascia, cartilage, menisci and chondrocytes respectively. The discrepancy between distribution and application figures might be partly explained by the fact that the figures from the applying establishments are still incomplete. Figure 19 shows the year-on-year trends in numbers of distributed units of tendons, ligaments and fascia, cartilage, autologous chondrocytes and menisci in the period 2016-2020, showing no significant changes. In 2020, as in 2019, there was an increase in autologous chondrocytes which were distributed and reported as applied. Autologous chondrocytes are cultured after donation and are therefore classified as ATMPs. Provision of data reports on distribution and application is therefore on a voluntary basis. Table 26 shows a decrease in the use of other musculoskeletal tissue, which is most notable in the application of fascia (Table 24). Thirteen hospitals/clinics did not report on the use of fascia, whereas they did in 2019. This decrease is partly explained by the temporary scaling down of care in 2020 due to the COVID-19 pandemic, which led to fewer elective operations. One applying establishment indicated that it has partly switched to other materials.

Table 23 Processing and distribution of other musculoskeletal tissues in 2020

Type	Tissue establishments	Processed	Unit	Distributed In NL	Distributed In EU	Distributed Outside EU	Distributed Total
Tendons	1	631	Graft	575	51	0	626
Bone-tendon-bone grafts	1	48	Graft	17	19	0	36
Fascia	1	172	Graft	116	0	0	116
Cartilage	1	48	Graft	41	0	0	41
Menisci	1	11	Graft	9	5	0	14
Chondrocytes, autologous*	2	99	Graft	12	0	0	12

* *ATMPs*

Table 24 Application of other musculoskeletal tissues in 2020

Type	Hospitals/clinics	Recipients	Unit	Applications From NL	Applications From EU	Applications From non-EU	Applications Total
Tendons	39	343	Graft	349	3	0	352
Bone-tendon-bone grafts	8	35	Graft	35	0	0	35
Fascia	6	26	Graft	20	12	0	32
Cartilage	4	25	Graft	26	0	0	26
Menisci	2	10	Graft	9	1	0	10
Chondrocytes, autologous*	1	36	Graft	36	0	0	36

* *ATMPs*

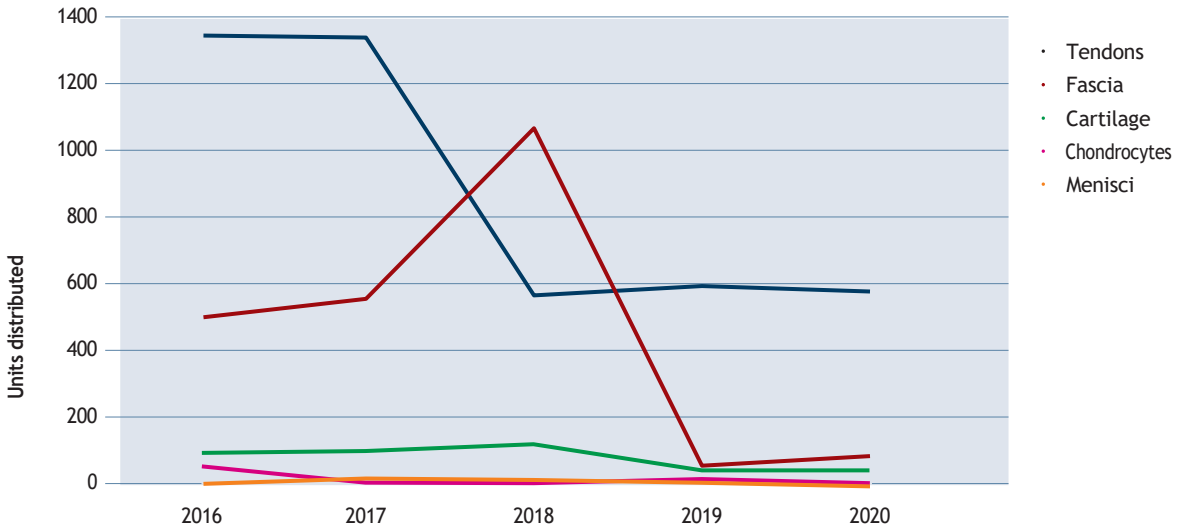

Figure 19 Number of units of other musculoskeletal tissues distributed in the Netherlands, 2016-2020

Reports

In 2020, TRIP received ten reports relating to other musculoskeletal tissues, all adverse events and no adverse reactions (see Figure 20). There was also one late report of a serious adverse event from 2019. Of the 2020 reports, half were assessed as serious and the remaining five as non-serious. The adverse events are summarized in Table 25. Eight of the reports concerned culturing of autologous chondrocytes and processing into ATMPs. Since 2019, these chondrocyte cultures have been taking place again in the Netherlands. Prior to this the last chondrocyte cultures in the Netherlands were performed in 2010. This explains the increase in reports associated with 'Other musculoskeletal tissues'.

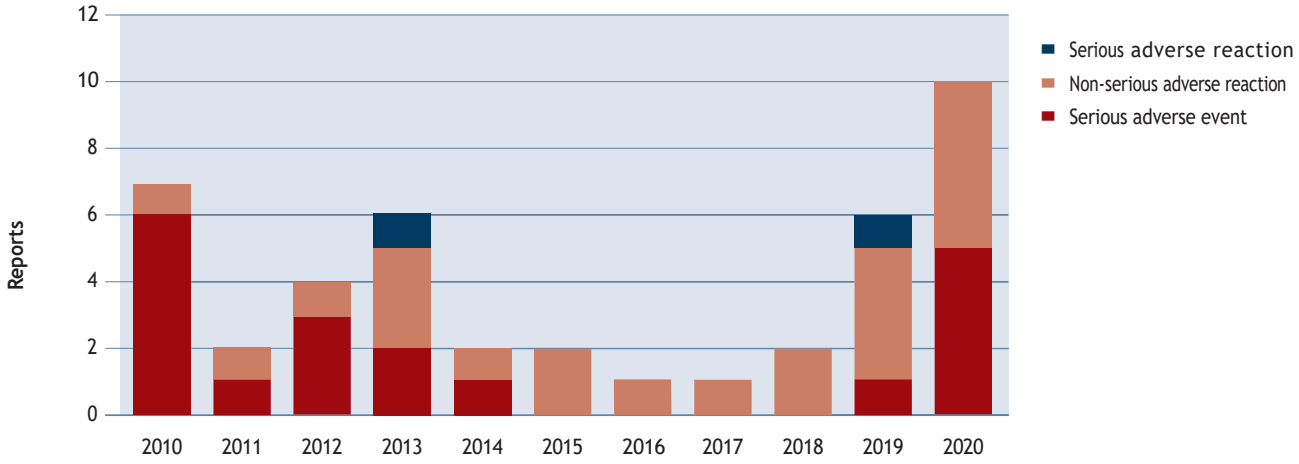

Figure 20 Overview of reports involving other musculoskeletal tissues, 2010-2020*
** Seven reports from 2010 were of adverse events involving culturing autologous chondrocytes, reported by two tissue establishments, both of which have ceased these activities. Since 2019, chondrocytes have again been cultured in a newly accredited establishment*

Table 25 Overview of adverse events involving other musculoskeletal tissues in 2020

Adverse event category	Reports	Product	Description
Loss of tissue or cells	8+1	Cartilage, autologous	Too many synoviocytes in cell culture, therefore not implanted (4/2)
		Cartilage, autologous	Too much or insufficient increase of chondrocytes in cell culture, therefore not implanted (3/3)
		Cartilage, allogeneic	Cartilage discarded due to doubts about the quality of the tissue (1/0)
		Tendons	After preparation, the tendon proved too short and could not be used for surgery (1/0)
Incorrect product transplanted	1	Tendons and bone	Distribution of tissues which had not yet been released (1/1)
Bacterial contamination of product	1	Cartilage	Contamination in biopsy transport fluid, leading to discontinuation of cell culture (1/0)

** Reports (Total/Serious)*

2.4 Ocular tissue

In the Netherlands, cornea and sclera are obtained from post-mortem donors through enucleation of the entire eyeball, which is then processed by one of two eye banks. Corneas have 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 one year.

Processing, distribution and application

Tables 26 and 27 show the number of processed, distributed and applied units of ocular tissue, respectively. Twenty-one hospitals and clinics reported that they transplant ocular tissue: 16 transplant corneas, 10 of these also transplanting sclera, and five transplant sclera only. Figure 21 shows the numbers of corneas and units of sclera distributed in the Netherlands between 2016 and 2020.

There is a decrease in the number of transplanted corneas in 2020, due to the postponement of operations caused by the COVID-19 pandemic and a temporary stop of enucleation in donors in the Netherlands. No distribution or application of limbal stem cells was reported on this year.

Table 26 Processing and distribution of ocular tissue in 2020

Type	Tissue establishments	Processed	Unit	Distributed			
				In NL	In EU	Outside EU	Total
Cornea	3	3564	Complete or lamella	1493	372	45	1910
Sclera	1	336	Complete or quadrant	1777	25	0	1802
Limbal stem cells*	1	4	Graft	0	0	0	0

* Concerns ATMPs

Table 27 Application of ocular tissue in 2020

Type	Hospitals/clinics	Recipients	Unit	Applications			
				From NL	From EU	From non-EU	Total
Cornea	16	1227	Complete or lamella	1243	0	0	1243
Sclera	15	1403	Complete or quadrant	1395	8	0	1403

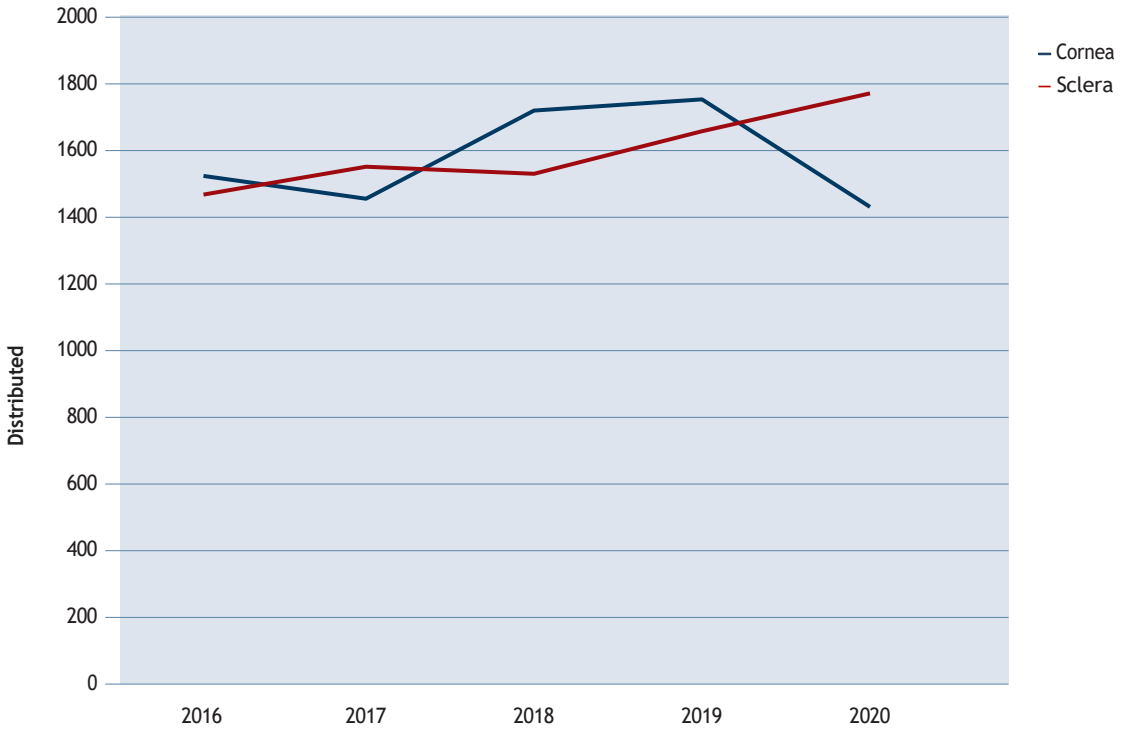

Figure 21 Number of units of cornea and sclera distributed in the Netherlands, 2016-2020

Reports

In 2020, TRIP received seven reports of adverse events. Six were classified as serious, a number similar to that in previous years. The reports are briefly described in Table 28. The reports are all about corneal tissue. In two cases, multiple tissues from the same donor were affected. Due to the limited shelf life (≤ 28 days) of corneas, it is not possible to wait for the results of the microscopic autopsy report before releasing the cornea. Therefore, there is a chance that the autopsy report will show that there was a contraindication for tissue donation, for which there was no indication at the time of screening the suitability of the donor. In 2020, this was the case once. Figure 22 shows an overview of reports concerning ocular tissue in the period 2016-2020.

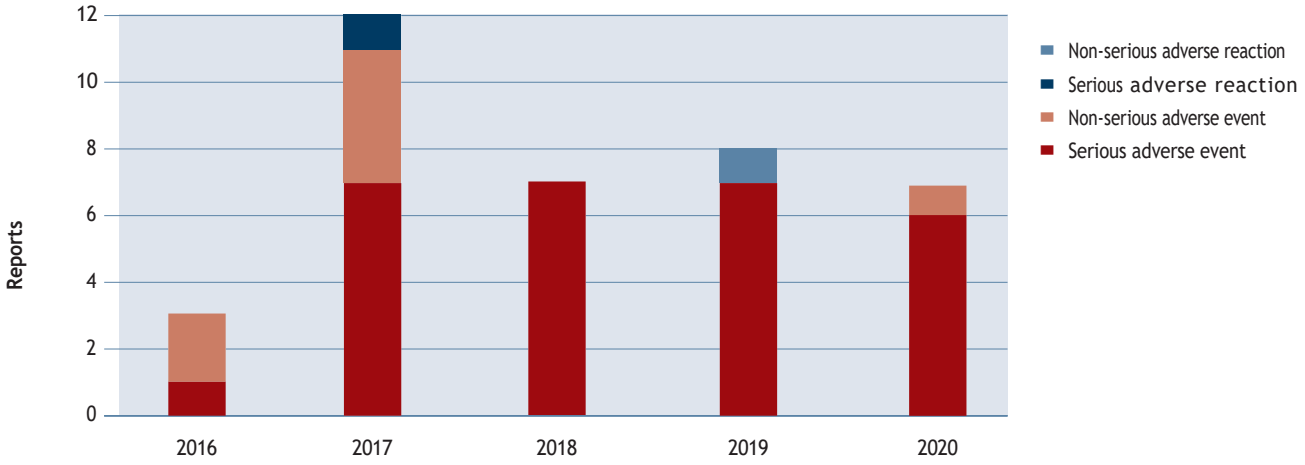

Figure 22 Reports related to ocular tissue, 2016-2020

Table 28 Overview of adverse reactions and events involving ocular tissue in 2020

Adverse event category	Reports	Description
Near miss	2	• Hemodilution noted, making donor virology unreliable. Corneas rejected, as well as a heart valve*. • Cornea incorrectly marked, discovered preoperatively by transplanting physician and corrected*
Other incident	2	• Possible infiltrate on cornea, therefore not implanted* • Because of last-minute change of recipient, the donor cornea was initially wrongly registered as transplanted to a different recipient; this was corrected.
Risk of transmisson of another condition	1	• After the results of the final post-mortem report on the donor became available, contraindication for tissue donation could not be excluded, but corneas had already been transplanted (sclera and skin also rejected).*
Incorrect product transplanted	2	• Microfissures developed during processing, as a result of which the markings were not visible, so probably not correctly placed preoperatively* • Donor previously received donor tissue him or herself; this is a contraindication for tissue donation*
Total	**7**	

** Serious*

2.5 Cardiovascular tissue

Processing, distribution and application

Tables 29 and 30 show the processing, distribution and application of cardiovascular tissue. There is one heart valve bank in the Netherlands. There are four centres that transplanted heart valves in 2020. There are now six hospitals applying pericardium, and this activity has increased in the last few years. However, no tissue establishment in the Netherlands distributed pericardium in 2020. Figure 23 shows the number of human cardiovascular tissues transplanted from 2016.

Table 29 Processing and distribution of cardiovascular tissue in 2020

Type	Tissue establishments	Processed	Unit	Distributed In NL	Distributed In EU	Distributed Outside EU	Total
Aortic valves	1	212 *	Graft	21	0	0	21
Pulmonary valves	1	212 *	Graft	87	9	0	96
Vessels	1	15	Graft	0	4	0	4
Patches	1	112	Graft	37	21	0	58
Pericardium	0	0	Graft	0	0	0	0

* Donor hearts

Table 30 Application of cardiovascular tissue in 2020

Type	Hospitals/clinics	Recipients	Unit	Applied From NL	Applied From EU	Applied From non-EU	Total
Aortic valves	3	20	Graft	17	3	0	20
Pulmonary valves	4	102	Graft	91	11	0	102
Vessels	1	43	Graft	44	0	0	44
Patches	3	38	Graft	36	2	0	38
Pericardium	6	122	Graft	0	123	0	123

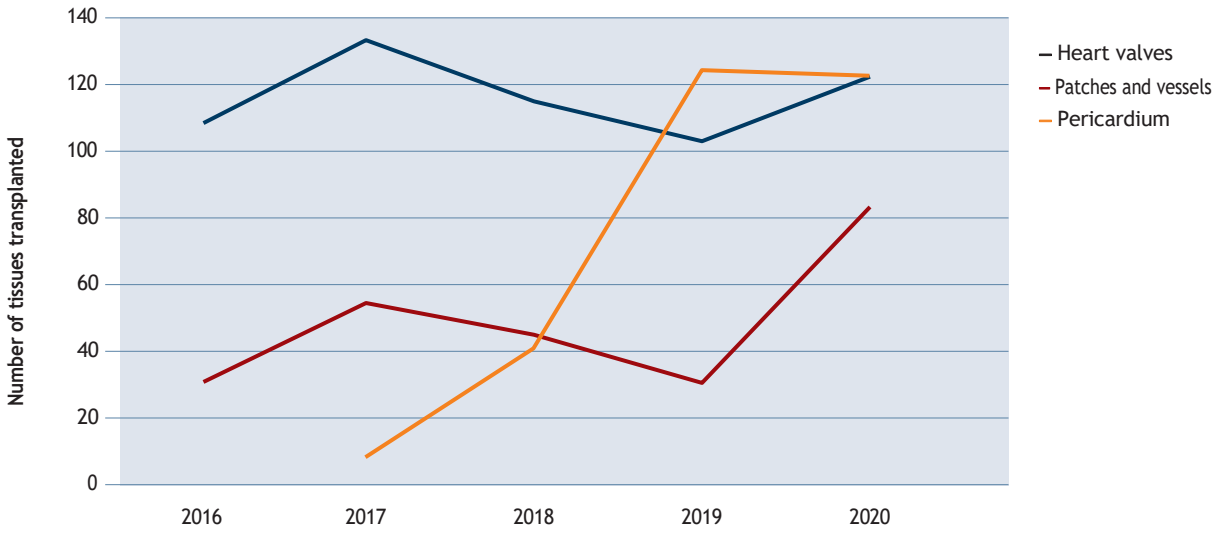

Figure 23 Number of cardiovascular tissues transplanted in the Netherlands, 2016-2020

Reports

One non-serious adverse event was reported concerning cardiovascular tissue (Table 31 and Figure 24).

Table 31 Overview of adverse events related to cardiovascular tissue in 2020

Adverse event category	Reports	Product	Description
Other incident	1	Pulmonary valve	Patient continued to bleed at the anastomosis, which started to tear. The anastomosis site dried up and no additional intervention was required.

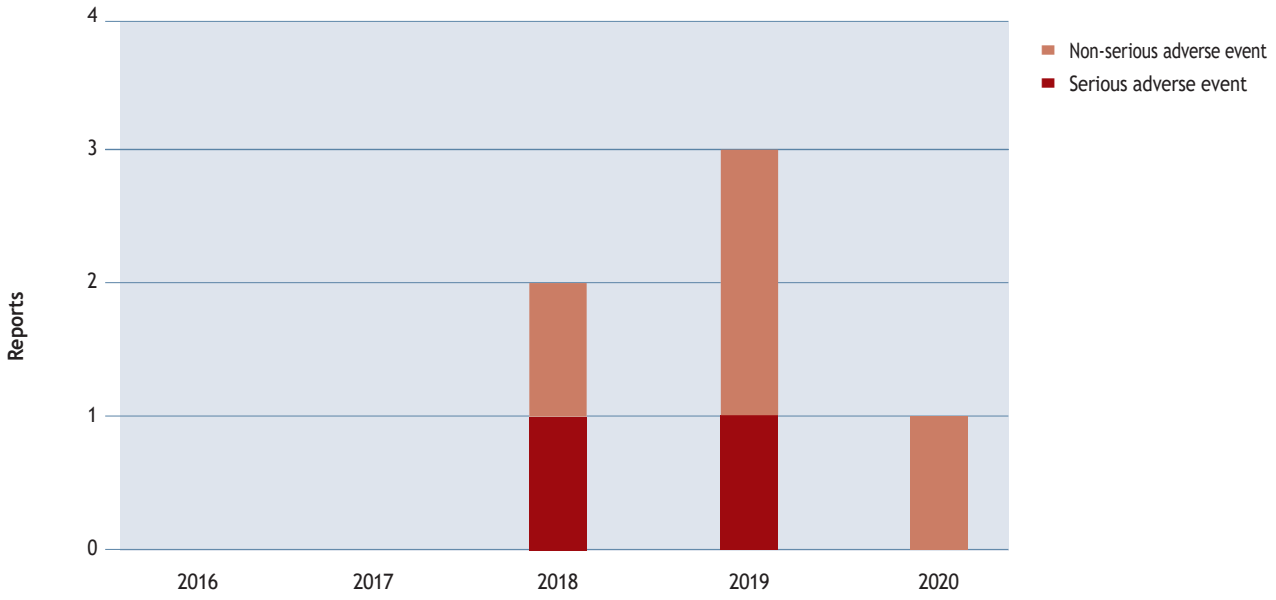

Figure 24 Reports related to cardiovascular tissue, 2016-2020

2.6 Skin

Processing, distribution and application

The Netherlands has one skin bank which processes, stores and distributes post-mortem donor skin. Skin tissue is subdivided into donor skin, autologous skin and acellular dermis. Table 32 shows the number of units of skin tissue processed and distributed in 2020. Much of the donor skin is distributed outside the Netherlands. The Netherlands went into lockdown in the spring of 2020 and scaled down care, causing a notable shift in the distribution of skin to the EU (in countries where there was no lockdown in 2020). There are two distributors of foreign acellular dermis, mainly for dental applications. Table 33 shows the number of units of skin that were applied in 2020. Figure 22 shows the number of units of skin and skin products distributed from 2016 to 2020. In 2020, there was no use of autologous skin (this refers to autologous skin processed outside the operating theatre of a healthcare facility); the number of hospitals/clinics/practices reporting use of acellular skin increased from four in 2019 to eight in 2020.

Table 32 Number of units of skin tissue processed and distributed in 2020

Type	Tissue establishments	Processed NL/EU	Unit	Distributed In NL	In EU	Outside EU	Total
Donor skin	1	377* / 165*	Pack	2113	12783	1107	16003
Acellular dermis	3	34* / 0	Graft	313	50	423	786

* Donations received from NL/other EU countries

Table 33 Number of units of skin applied in 2020

Type	Hospitals/ clinics	Recipients	Unit	Applications From NL	From EU	From non-EU	Total
Donor skin	9	106	Pack	1994	33	0	2027
Autologous skin*	0	0	Graft	0	0	0	0
Acellular dermis	8	162	Graft	167	0	0	167

* If processed outside the operating theatre of a healthcare institution

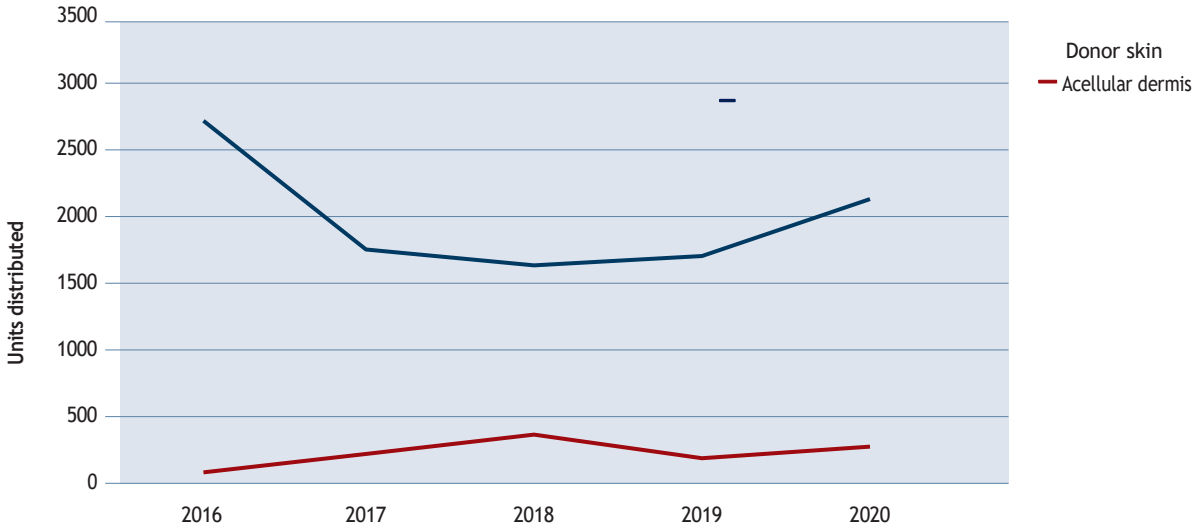

Figure 25 Number of units of donor skin and acellular dermis distributed in the Netherlands, 2016-2020

** The data from 2016 show a one-off increase in the number of distributed units of donor skin because of larger number of patients and several clinical studies in one burns centre.*

Reports

In 2020, as in previous years, no reports were submitted concerning 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: amniotic membranes, pancreatic islets, and radioactively labelled leukocytes intended for autologous diagnostic purposes.

Processing, distribution and application

Tables 34 and 35 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. In 2020, there was no processing of

radioactively labelled red blood cells. For the first time, more units of amniotic membrane were distributed in the Netherlands than abroad due to the discontinuation of one tissue establishment that distributed to foreign countries. Based on the submitted activity data, less tumour tissue was processed and distributed. The processing of human body material into an ATMP is not subject to mandatory reporting.

Table 34 Processing and distribution of other tissues and cells in 2020

Type	Tissue establishments	Processed NL/EU/non-EU	Unit	Distributed In NL	In EU	Outside EU	Total
Amnion	2	2* / 20* / 0	Pack	211	27	0	238
Pancreatic islets	1	5# / 0# / 0	Graft	5	0	0	5
Cells from bone marrow or peripheral blood	1	1 / 0 / 36	Bag	0	0	0	0
Leukocytes$	1	4 / 0 / 0	Bag	4	0	0	4
Tumour tissue+	1	13 / 0 /0	Graft	13	0	0	13

* *Placentas*

\# *Pancreases*

$ *Radioactively labelled for diagnostic purposes*

\+ *Distributed as ATMPs, no mandatory reporting of distribution*

Table 35 Application of other tissues and cells in 2020

Type	Hospitals/ clinics	Recipients	Unit	Applied From NL	From EU	From non-EU	Total
Amniotic membrane	7	97	Pack	105	0	0	105
Pancreatic islets	1	5	Graft	5	0	0	5
Leukocytes$	1	4	Graft	4	0	0	4

$ *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 (2012) and one report concerning amniotic membrane (2015).

Tissues and other cells - summary

As regards tissues and other cells, a decrease in distribution and application is seen. This decrease is particularly seen in bone and other musculoskeletal tissues and ocular tissue. This decrease may be explained by the scaling down of care in 2020 due to the COVID-19 pandemic, which led to fewer elective operations (including orthopaedic operations). Furthermore, due to the COVID-19 pandemic, there was a temporary suspension of donor donations in the Netherlands.

There was an increase in reports involving autologous chondrocytes for processing into ATMPs. There are no conclusive regulations regarding the reporting of these incidents and, so far, they have been submitted to TRIP on a voluntary basis. As with hematopoietic stem cells and therapeutic cells, such adverse events can lead to consequences for the patients (donors) concerned, such as having to undergo an additional procedure to obtain material. These reports/cases underline the importance of monitoring adverse events in this form of treatment, which is currently not fully covered by legislation (pharmaco-, hemo- and/or biovigilance). As emphasized in Recommendation 2 this year, this should be clarified in consultation with the relevant parties.

3 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 the submission of reports to TRIP on adverse events and reactions associated with the application of tissues and cells as well as the provision of annual data on 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 into the occurrence rate of incidents and reactions.

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

1 The tissue establishments (including so-called "organ banks") that procure, process, store and/or distribute human tissues and cells;
2 The hospitals, clinics, independent treatment centres and oral implantology practices that apply or transplant human tissues and cells.

3.1 Tissue

According to the definition in Article 1(1)(k) of the Dutch Body Material (Safety and Quality) Act (Wvkl), a tissue establishment is a tissue bank, hospital department or other institution that performs activities related to the processing, preservation, storage or distribution of body material. 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.

Not every tissue establishment is authorized to receive tissues or cells immediately after procurement (exception: semen laboratories that only process and directly distribute partner semen). Receiving body material - after procurement - is reserved for so-called organ banks. According to legislation, organ banks must not be for profit. According to Article 1(1)(l) of the Body Material (Safety and Quality) Act, organ banks are also licensed to subsequently process, store and distribute body material. The scope of activities determines whether a licence as an organ bank or tissue establishment is necessary.

Figure 26 provides an overview of the number of licensed tissue establishments and organ banks in the Netherlands in 2020 (source: Farmatec). A number of Dutch hospitals houses multiple tissue establishments and/or organ banks.

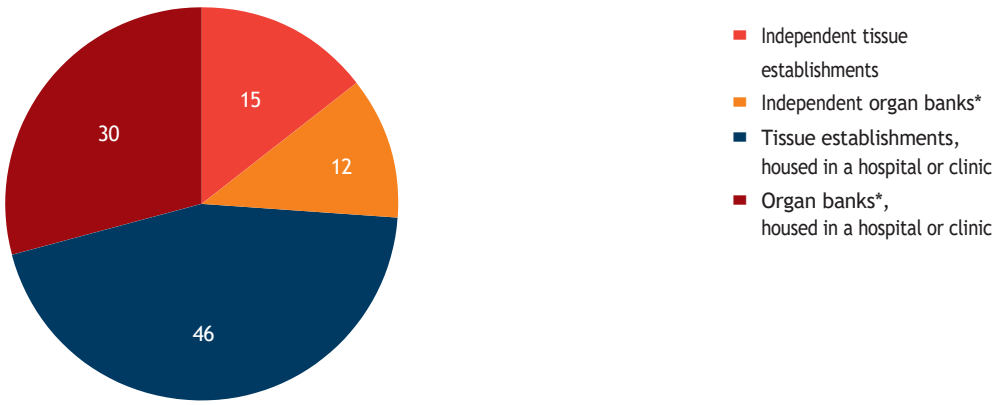

Figure 26 Licensed tissue establishments and organ banks in the Netherlands in 2020

** Organ banks are also licensed as tissue establishments*

Figure 27 shows the number of licenses issued by Farmatec by type of body material. This organization is part of the Central Information Unit on Healthcare Professions (implementing body of the Ministry of Health, Welfare and Sport) and issues licences and accreditations relating to medicines, medical devices, blood products and body material. Some tissue establishments are licensed for multiple types of tissues or cells. Figure 28 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, if applicable, the number of tissue establishments that participated in vigilance reporting.

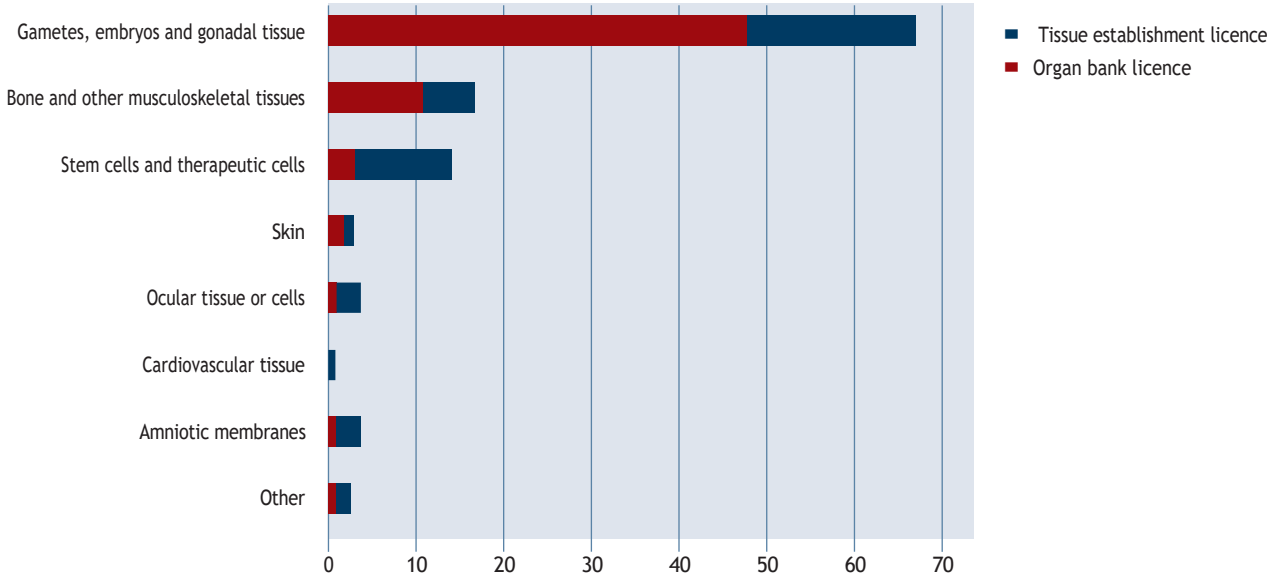

Figure 27 Number of licensed tissue establishments and organ banks in 2020 by type of human body material

3.2 Organisations responsible for the application of human body material

In 2020, 81 hospitals, 10 clinics and independent treatment centres, and 65 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 adverse events and/or reactions that occurred. One hospital, three independent treatment centres and 10 oral implantology practices indicated that they had not transplanted or applied human tissues and/or cells or applied only direct autologous bone tissue in 2020. In 2020, the participation rate of healthcare institutions was 94% (147 of 156). Figure 28 shows the percentages of establishments and practices that supplied data on the number of transplanted or applied tissues and/or cells and submitted vigilance reports (if applicable).

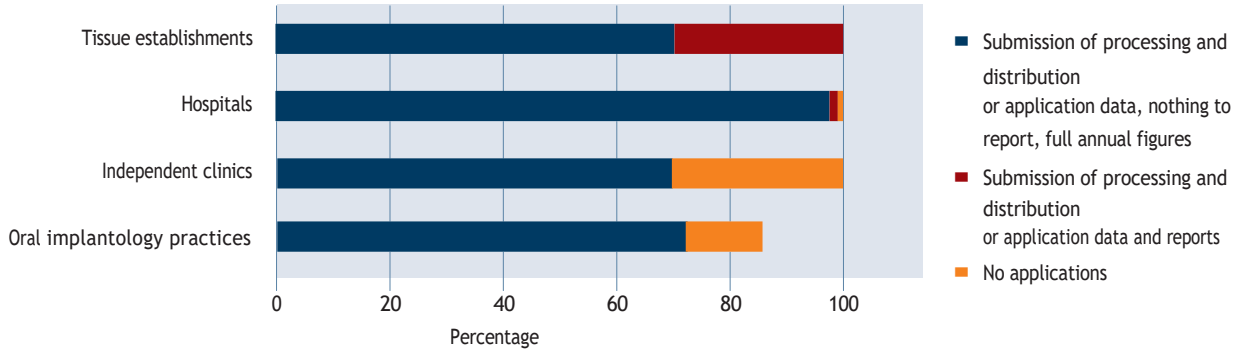

Figure 28 Participation of establishments and practices involved in biovigilance in 2020
Tissue establishments n=112, Hospitals n=81, Independent clinics n=10
Oral implantology practices that in the past stated that they apply human body material n=65

ANNEXES

A About TRIP

The 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, Welfare and Sport (VWS), a pilot project for biovigilance data registration was set up. Since 2012 biovigilance has been a formal task for the TRIP foundation.

European legislation on the quality and safety of human tissues and cells obliges Member States to have a system in place for reporting adverse reactions and events associated with the use of these substances (Directive 2004/23/EC, which was transposed into the Dutch Body Material (Safety and Quality) Act (Wvkl) and the Body Material Requirements Decree 2006 (Eisenbesluit lichaamsmateriaal 2006). This is called biovigilance and refers to the systematic monitoring of (serious) adverse reactions and events throughout the transplantation chain from donor to recipient of human material 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 human body material meets the requirements laid down in Dutch and European legislation. (In the Netherlands, the Healthcare and Youth Inspectorate (IGJ) has been designated as the competent authority for receiving reports of serious adverse events and reactions. The online reporting system also facilitates the mandatory reporting of serious adverse events and reactions to the IGJ under the Body Material (Safety and Quality) Act (see also Annex 2). This statutory duty to report applies to tissue establishments in accordance with the Dutch Body Material (Safety and Quality) Act and the Body Material Requirements Decree 2006. The Body Material Requirements Decree was amended in 2012 in line with European Directive 2010/53/EC. Figure 29 presents a flowchart of serious and non-serious biovigilance reports in Dutch healthcare. It is likely that the number of 'non-serious' adverse reactions and events is much higher than the serious cases and that not all institutions submit the less serious reports to TRIP. The high percentage of serious adverse events and reactions in reports to TRIP (up to 50%) fits in with this.

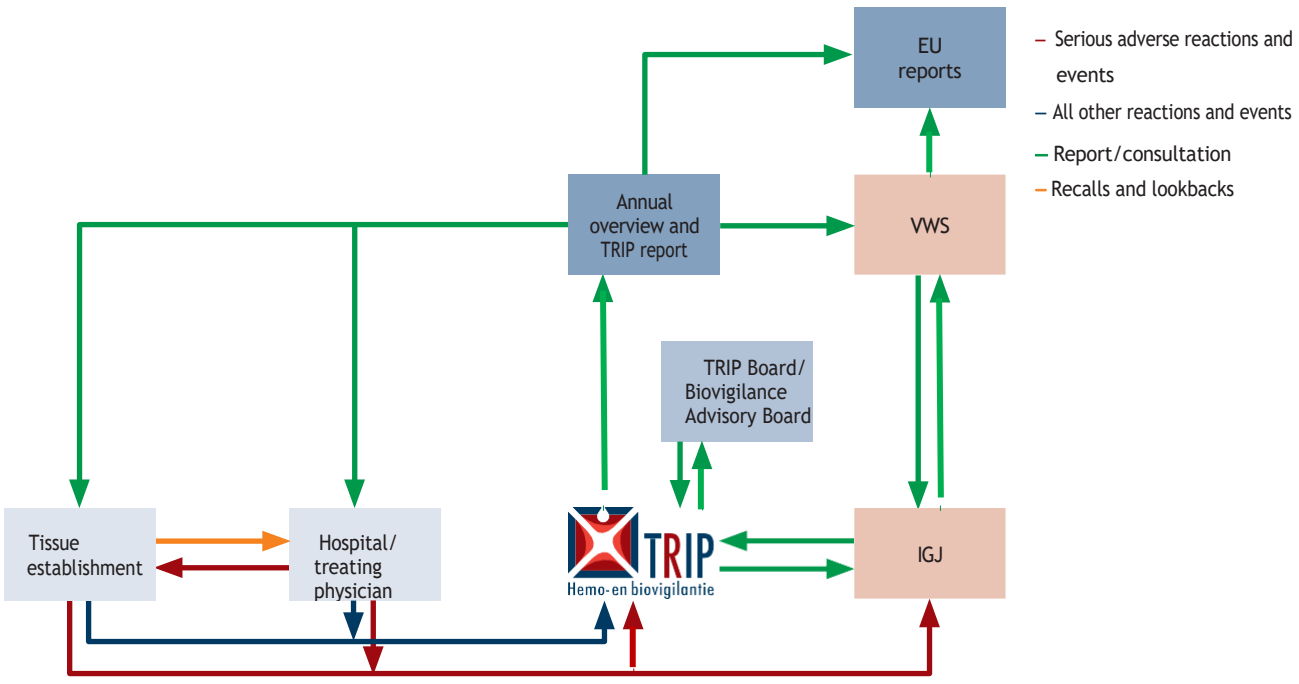

Figure 29 Flow chart of reports concerning human tissues and cells

The scope of the Body Material (Safety and Quality) Act includes all human tissues and cells (from living as well as post-mortem donors) with the exception of autologous material that is obtained from and transplanted in the same person in one and the same procedure. If autologous tissues are preserved or processed (including the preparation or processing in another location, distant from the patient) the Body Material (Safety and Quality) Act does apply. The Act always applies to allogeneic application (derived from a human donor).

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 from all Dutch tissue establishments, hospitals and other healthcare facilities, 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. TRIP compiles the annual mandatory overview of serious adverse events and reactions to be forwarded to the European Commission, through the Ministry of Health, Welfare and Sport.

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 hospitals' safety management system. The participation certificate may also be formally reviewed by the Health and Youth Care Inspectorate as part of licensing procedures or licence renewal for tissue establishments or organ banks.

TRIP is guided by a Biovigilance Advisory Board representing relevant medical professional bodies and specialties. 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 Board, but has not been submitted to the Healthcare and Youth Inspectorate, TRIP will remind the reporter about the mandatory nature of reporting to the competent authority (see Annex B, Reporting to the Healthcare and Youth Inspectorate).

B REPORTING ADVERSE EVENTS AND REACTIONS

Tissue establishments

Reporting of serious adverse reactions and events relating to human body material is laid down in Article 8.1 of the Dutch Body Material Requirements Decree 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 body material or that are detected after application and could be linked to the applied body material. Adverse reactions and events should be reported to TRIP and also to the Healthcare and Youth Inspectorate (IGJ) if they are classified as serious.

Hospitals, clinics and practices

Organizations responsible for application of human tissues and cells must report (possible) product-related serious adverse reactions and events to the supplying tissue establishment. They may also report these to TRIP. TRIP checks for duplicate reports and if any are found, merges them in consultation with the reporters.

In the event of a 'calamity' caused, or possibly caused by human body material, the hospital must also inform the IGJ in accordance with the Quality, Complaints and Disputes Act (Wkkgz).

Reporting to the Healthcare and Youth Inspectorate

In the Netherlands, the Healthcare and Youth Inspectorate (IGJ) has been designated as the competent authority for receiving reports of serious adverse events and reactions. In agreement with the Ministry of Health, Welfare and Sport (VWS) and the Healthcare and Youth Inspectorate, TRIP handles the registration of all adverse reactions and events related to body material. The TRIP digital reporting system facilitates the forwarding of serious adverse reactions and event reports to the IGJ. Reporters can enter the information once and select the option of forwarding the report to the IGJ if applicable.

The reporting of serious adverse reactions and events is different from the reporting of an 'calamity' according to the Quality, Complaints and Disputes in Healthcare Act). A calamity has a different definition (see Appendix C, Definitions and Reporting Criteria); the IGJ follows its own specific procedure for a reported calamity.

In November 2015 the IGJ sent out a letter to all tissue establishments clarifying the reporting of adverse reactions and events to the Inspectorate and TRIP. Figure 30 shows the reporting routes in a flow chart.

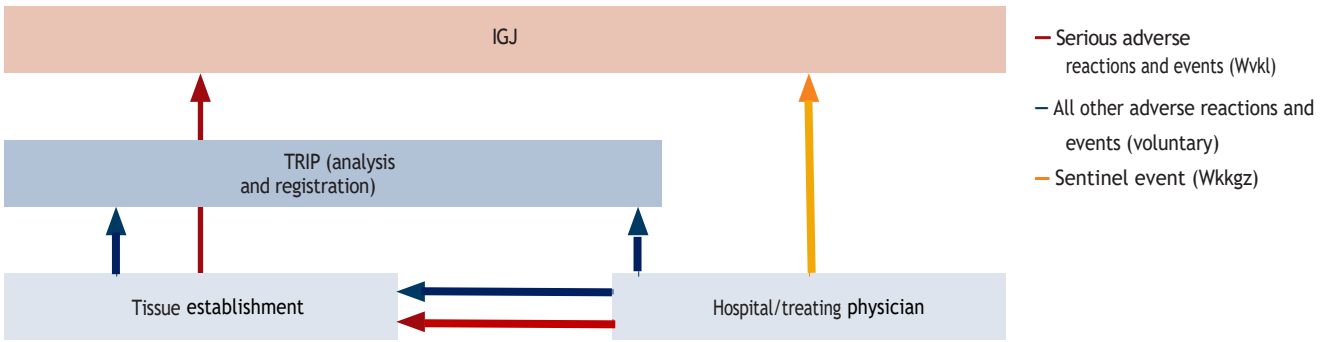

Figure 30 Flow chart of reports concerning human body material

Serious adverse reactions or events within the scope of the Body Material (Safety and Quality) Act are best submitted to the Healthcare and Youth Inspectorate through the TRIP online reporting system. This channels the reports to the inspectors responsible for oversight of the Body Material (Safety and Quality) Act and reduces the likelihood of reports being (possibly incorrectly) dealt with under the Quality, Complaints and Disputes in Healthcare Act. However, reports will always be assessed on healthcare quality aspects as well, and a full investigation will be required if an event is deemed to be a calamity.

C DEFINITIONS AND REPORTING CRITERIA

Definitions of categories of adverse reactions and 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 (in Art. 1.1 of the Body Material Requirements Decree 2006):

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 (Art. 1.1 Body Material Requirements Decree 2006)

The criteria used by the European Commission are presented in Table 36. 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 36 Criteria for a serious adverse event

- Inappropriate tissues/cells were distributed and/or clinically applied
- The event could have implications for other recipients 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 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 a mix-up 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 foetus with a transmitted genetic disease following medically assisted reproduction with non-partner gametes or a donated embryo
- 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 (in Art. 1.1 of the Body Material Requirements Decree 2006):

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 or incapacitating or which results in, or prolongs, hospitalization or morbidity (Art. 1.1 Body Material Requirements Decree 2006).

The definitions for the severity grades of adverse reactions are set out in Table 37. The definition of a serious adverse reaction corresponds to severity grade 2 or higher.

Table 37 Severity grade of adverse

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) hospitalization and without invalidity, incapacity or long-term consequences for the recipient or donor. Not life-threatening
Grade 2	Moderate to serious morbidity, may or may not be life-threatening; or leading to hospitalization or prolongation of hospitalization or illness; or necessitating medical or surgical intervention; or transmission of a serious infection or disease; or associated with chronic disability or incapacity for work.
Grade 3	Serious morbidity, directly life-threatening. A living donor or recipient needs medical or surgical intervention following the harvesting or transplantation of tissues or cells (vasopressors, intubation, ICU admission) 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 European Commission (EC). The EC does however request 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 3.0 (2020)', stating (TRIP paraphrase):

Reporting of serious adverse reactions in donors is MANDATORY if these influence the quality and safety of the donated tissues or cells, and NOT SUBJECT TO MANDATORY REPORTING for adverse reactions that do not influence the quality and safety of the donated material. Many EU Member State competent authorities collect information on donor adverse reactions not influencing the quality and safety of tissues and cells.

Some reactions fall outside the scope of the tissues and cells Directive 2004/23/EC and should formally be reported elsewhere (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) in connection with peripheral blood stem cell collection

Nevertheless, the European Commission recognises the value of these data in the context of tissue and cells regulation, and invites Member States to report annually, on a voluntary basis, any serious donation complications that do not affect the quality and safety of tissues and cells.

Calamity

A calamity is defined by the Dutch Quality, Complaints and Disputes in Healthcare Act as follows:

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

D OVERVIEW OF MANDATORY REPORTS OF SERIOUS ADVERSE REACTIONS AND EVENTS (IN ACCORDANCE WITH EU LEGISLATION)

Table 38 shows the number of serious adverse reactions and events related to human tissues or cells reported in 2020. In total, 41 reports were assessed as serious. These concern 34 serious adverse events, four serious adverse reactions and three serious donation complications.

Table 38 Overview of serious reports in 2020

Type	Serious adverse reaction	Serious adverse event	Serious donation complication	Total serious reports
Semen	2	10	0	12
Oocytes	0	6	3	9
Embryos	0	4	0	4
HSC and therapeutic cells	2	0	0	2
Ocular tissue	0	6	0	6
Musculoskeletal tissues	0	8	0	8
Total	**4**	**34**	**3**	**41**

TRIP classifies events followed by a serious adverse reaction or with a serious consequence as serious events. These reports are submitted to the European Commission (EC) as serious adverse reactions (only). These include proven and possible inheritance of a congenital abnormality when using donated gametes or embryos, post-transplantation infection in a recipient with a micro-organism that requires treatment or prolonged hospitalization, re-transplantation after transplantation with an incorrect product or additional stimulation, apheresis or bone marrow collection for autologous stem cell transplantation(s) and an aborted procedure where the patient is already under anaesthesia or has been conditioned for transplantation.

Late serious reports from 2019 have been added to the 2020 TRIP report to the EC.

E LIST OF TERMS AND ABBREVIATIONS

AD	Amenorrhea duration (gestational age)
A&E	Accident and emergency department
Apheresis	Type of blood donation involving the selective mechanical withdrawal of specific blood components while returning (infusing) the remaining components to the donor or patient
Allogeneic	Originating from a donor (genetically non-identical person)
ATMP	Advanced Therapy Medicinal Product
Autologous	Removed from and applied in the same person
CAA	Cerebral amyloid angiopathy
CAR T	Chimeric Antigen Receptor T-cells
Chondrocytes	Cartilage cells
Cryopreservation	The process of freezing and subsequent storage of frozen tissues and cells
Cutibacterium acnes	Formerly: Propionibacterium acnes
Distribution	Transportation and delivery of tissues and cells intended for human application
DLI	Donor lymphocyte infusion
DMEK	Descemet Membrane Endothelial Keratoplasty
DMSO	Dimethyl sulfoxide
EC	European Commission
U	Unit
ET	Embryo transfer
EU	European Union
EUSTITE	European Union Standards and Training in the Inspection of Tissue Establishments (EU project 2007-2009)
Pharmacovigilance	Vigilance of pharmaceuticals
Farmatec	This organization is part of the Central Information Unit on Healthcare Professions (CIBG; implementing body of the Ministry of Health, Welfare and Sport) and issues licences and authorisations relating to medicines, medical devices, blood products and body material.
GCSF	Granulocyte Colony Stimulating Factor
Gonadal	Relating to sex glands
HSC	Hematopoietic stem cells
ICU	Intensive Care Unit
ICSI	Intra-cytoplasmatic sperm injection (type of IVF)
IGJ	Healthcare and Youth Inspectorate
Imputability	Degree to which an adverse reaction can be attributed to an applied substance of human origin
IUI	Intrauterine insemination
IUI-D	Intrauterine insemination with donor semen
IVF	In vitro fertilization
KLEM	Association of clinical embryologists
Clinic	Specialized healthcare facility committed to one area of healthcare
Matchis	Dutch registry for stem cell donors
MESA	Microsurgical epididymal sperm aspiration
Morbidity	Extent of disease
Mortality	Death
NL	The Netherlands
NTS	Nederlandse Transplantatie Stichting (Dutch Transplantation Foundation)
OHSS	Ovarian hyperstimulation syndrome
OR	Operating room
Oocytes	Egg cells

Organ bank	Tissue establishment with licence to receive substances of human origin after procurement
PBSC	Peripheral blood stem cells
PESA	Percutaneous epididymal sperm aspiration
PGD	Preimplantation genetic diagnosis
PID	Pelvic inflammatory disease
PKU	Phenylketonuria (metabolic disease)
Postpartum	After giving birthy
Sanquin	Foundation charged with operating the Dutch national blood establishment
SAE	Serious adverse event
SAR	Serious adverse reaction
Semen	Sperm
SoHO V&S	Vigilance and Surveillance of Substances of Human Origin (EU project 2010-2013)
TACO	Transfusion associated circulatory overload
TC-TILs	Tumour infiltrating lymphocytes
TCR	T-cell receptor (gene therapy)
TESE	Testicular sperm extraction
TRALI	Transfusion-related Acute Lung Injury
Retrieval	Process whereby donated body material or organs become available
VWS	Dutch Ministry of Health, Welfare and Sport
Tissue establishment	A tissue bank, hospital department or other organisation that holds a licence for processing, preserving, storage and/or distribution of body material
Wkkgz	Quality, Complaints and Disputes in Healthcare Act
Wvkl	Body Material (Safety and Quality) Act