

2024 TRIP REPORT

# BIOVIGILANCE

EXTENDED VERSION



# 2024 TRIP REPORT BIOVIGILANCE EXTENDED VERSION



The TRIP 2024 Biovigilance report, extended version, is published under the responsibility of the TRIP (Transfusion and Transplantation Reactions in Patients) Foundation.

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# 1 INTRODUCTION

In this 2024 Biovigilance Report, TRIP presents reports on events and adverse reactions that occur in the chain from the donation to the clinical application of human tissues and cells. The report also provides activity data on the processing, distribution and application of human tissues and cells and the number of recipients. Throughout the report, the processing figures specify the origins of the processed material, stating whether it derives from the Netherlands, from the EU (Europe excluding the Netherlands), or from outside the EU. The report's distribution and application figures state whether the material was distributed in the Netherlands or in the EU (excluding the Netherlands), or exported outside the EU. The activity data was submitted by tissue establishments and healthcare institutions participating in the national biovigilance network.

As from August 2027, Regulation (EU) 2024/1938 on standards of quality and safety for substances of human origin intended for human application, known as Substances of Human Origin (SoHO), will enter into force. This Regulation repeals the EU Directives 2002/98/EC and 2004/23/EC. As stated previously, all human blood products, tissues, cells and substances such as breast milk and faecal microbiota will be subject to the same regulation and thus become Substances of Human Origin (SoHO). All organisations in the Netherlands who are involved in donor care, the procurement, processing, storage, releasing, distributing, importing and exporting of SoHO and/or applying SoHO, must register as a SoHO entity or institution. All organisations already recognised or designated based on the Dutch Body Material (Safety and Quality) Act (Wet veiligheid en kwaliteit lichaamsmateriaal, Wvkl) are automatically registered as SoHO entities or institutions. More information can be found on Farmatec's website.

This year, all tissue establishments known to TRIP which are active in the field of reproductive tissue and cells, hematopoietic stem cells and cells for therapeutic purposes have reported their activities for 2024. Almost all tissue establishments that process, store and/or distribute other tissues and cells, have reported activity for 2024. However, 89% of the institutions that apply other tissues and cells have reported their activities. Given the differences in distribution quantities and application figures, it can be stated that not all of the healthcare institutes are known to TRIP, and also that the specified quantities are not always complete. As stated in last year's report, the reporting of activity data will become mandatory under the forthcoming European regulation on substances of human origin, in order to improve the traceability of SoHO. Given the application figures received, there are still challenges to be faced. TRIP will, as far as possible, support organisations in their steps towards compliance with the European regulation by 2027.

TRIP would like to thank all professionals who contributed to the preparation of this report.

Lastly, we would like to draw your attention to the death of the TRIP Foundation's patroness, Eveline Six – Baroness Van Voorst to Voorst, professor Emeritus in Clinical Chemistry on 15 August 2024. She played an important role in the founding of TRIP. Please refer to the TRIP website for an 'in memoriam'.

# 2 BIOVIGILANCE IN 2024 AND RECOMMENDATIONS

## 2.1 Biovigilance in 2024

Similar to the last year, all tissue establishments known to TRIP which are active in the field of reproductive tissue and cells, hematopoietic stem cells and cells for therapeutic purposes reported their activities in 2024. Of the 23 tissue establishments known to TRIP who process, store and/or distribute other tissues and cells, 22 reported activities for 2024. Of the 139 healthcare institutes known to TRIP, 124 institutes submitted information on the application of other tissues and cells.

In 2024, a total of 111 reports (94 in 2023) were submitted to TRIP before the cut-off date for this report, 1 March 2025. Four reports were assessed as definitely not related to the transplantation chain; these have further been excluded from the report. Sixteen reports from an earlier reporting year were completed in 2024. Of the 107 reports in 2024, 40 reports were assessed as serious, based on the EU criteria. Last year, there were 37 (including the late serious reports received, which were completed in 2024). The six late reports that were assessed as serious are discussed in the relevant chapters.

- In 2024, there were 14 serious events involving reproductive tissues and cells. Besides, eight serious donation complications after treatment in the context of a fertility programme were also reported.
- In 2024, eight reports of serious adverse reactions were received, and three serious events were registered relating to hematopoietic stem cells. In addition, two serious donation complications have been reported.
- In the other tissues and cells category, three serious events relating to ocular tissue were registered. Twice, a serious donation complication relating to bone tissue was registered.

## 2.2 Recommendations

Recommendations	Who
1 Emphasis on the obligation under the European regulation that every organisation that applies substances of human origin must be registered as a SoHO entity via Farmatec	Executive Boards of institutions
2 Taking note of the obligation to submit activity data to TRIP and to ensure the traceability of SoHO as described in the European regulation.	Executive Boards of tissue establishments and healthcare institutes

## 2.3 Follow-up to previous years

- 1 Taking note of the European regulation on substances of human origin for application on humans (Substances of Human Origin – SoHO) and to identify the consequences for future SoHO entities.

### Development:

TRIP is in the process of identifying the consequences of the legislation amendments and has provided information on this at various meetings. The forthcoming regulation was also discussed during the 2024 Biovigilance Symposium.

- 2 Emphasise that, following the finalisation of the European regulation on substances of human origin for application in humans (Substances of Human Origin – SoHO), the traceability and reporting of activity figures will be mandatory for all entities and institutions in the SoHO chain.

**Development:**

TRIP participates in several European projects subject to SoHO regulations. Discussions also take place with new SoHO parties, such as the donor faeces bank and the breast milk bank, to involve them in SoHO vigilance, the TRIP network and TRIP reporting system. Furthermore, a new reporting system will be developed in the coming years that aligns with the preferences of the SoHO entities and the requirements of the European regulation.

# 3 REPRODUCTIVE TISSUE AND CELLS

## 3.1 Institutions involved

In 2024, there were 16 registered IVF laboratories with an organ bank accreditation in the Netherlands. Furthermore, 49 semen laboratories had a tissue establishment or organ bank accreditation. Establishments with an organ bank accreditation are also authorised to receive donor semen after procurement. All IVF laboratories and semen laboratories provided data on the processing, distribution and application of reproductive tissue and cells in 2024. In 2024, one semen bank in the field of fertility ceased its activities and one merged with another semen laboratory.

## 3.2 Activities in 2024

Tables 1 and 2 show the figures for processing, distribution and application of reproductive tissue and cells based on the annual activity reports for 2024. Reproductive tissue and cells can be processed several times, not only after collection but also at a later stage, when processing cryopreserved tissue. The number of processing operations may therefore exceed the unit quantities distributed or applied. The processing figures specify the origins of the processed material and show whether material is derived from the Netherlands, from the EU (Europe excluding the Netherlands), or from outside the EU. The columns under Distributed indicate whether material was distributed in the Netherlands or in the EU (excluding the Netherlands), or exported outside the EU.

Based on the European definition in current legislation, transport between tissue establishments is not considered distribution. Units that were transported and delivered for use in the tissue establishment's own institution are included under Distributed.

Table 1a shows no significant shift in the figures for the processing and distribution of semen and testicular tissue. Where a decrease in the processing of donor semen from Europe was observed in the last two years, slightly more semen from Europe and less from the Netherlands was processed in 2024. More than twice as much donor semen from the Netherlands compared to (non-NL) European donor semen has been processed (2024: 2.4; 2023: 2.8). The difference between applications (Table 2) and distributions (Table 1a) of donor semen is explained by the fact that institutes can use donor semen without intervention from the tissue establishment. Table 1b and Figure 1c show an increase in the processing and application of ovarian tissue after a decrease in 2023. There was noticeably fewer processing of embryos (own oocyte and partner semen) whereas the reduction in distribution is less evident. The decrease is not determined by a single institution. A new aspect in Table 1c is the processing of embryos (donor oocyte and partner semen) derived from Europe.

**Table 1a** Processing and distribution of semen and testicular tissue in 2024

Type of semen or testicular tissue	Tissue establishments	Unit	Processing			Distribution		
			From NL	From EU	From non EU	In NL	In EU	Export outside EU
Partner semen, fresh and cryo	63	Sample/straws	39,213	0	0	24,226	0	0
Donor semen, fresh and cryo	17	Sample/straws	9,604	3,995	0	8,321	0	0
Partner semen MESA/PESA/TESE	11	Puncture/biopsy	1,283	1	0	n/a	n/a	n/a
Donor semen MESA/PESA/TESE	2	Puncture/biopsy	2	0	0	n/a	n/a	n/a
Testicular tissue	2	Graft	35	0	0	0	0	0

**Table 1b** Processing and distribution of oocytes and ovarian tissue 2024

Type of oocytes or ovarian tissue	Tissue establishments	Unit	Processing			Distribution		
			From NL	From EU	From non EU	In NL	In EU	Export outside EU
Own oocyte, fresh and cryo	16	Oocyte	146,655	0	0	n/a	n/a	n/a
Donor oocyte, fresh and cryo	13	Oocyte	3,051	0	0	n/a	n/a	n/a
Ovarian tissue	4	Graft	127	0	0	17	0	0

**Table 1c** Processing and distribution of embryos 2024

Type of embryos	Tissue establishments	Unit	Processed			Distribution in NL	
			From NL	From EU	From non EU		
Embryos, own oocyte and partner semen	16	Embryo		57,797	0	1	26,145
Embryos, own oocyte and donor semen	14	Embryo		5,173	0	0	2,145
Embryos, donor oocyte and partner semen	14	Embryo		695	280	0	354
Embryos, donor oocyte and donor semen or donated	6	Embryo		778	0	0	253

**Table 2** Application of reproductive tissue and cells 2024

Type	Recipients	Unit	Application
Partner semen	10020	Insemination	24,493
Donor semen	3,333	Insemination	9,085
Embryos, own oocyte and partner semen	13,926	Embryo	26,139
Embryos, own oocyte and donor semen	1236	Embryo	2,143
Embryos, donor oocyte and partner semen	199	Embryo	353
Embryos, donor oocyte and donor semen or donated	133	Embryo	253
Ovarian tissue	2	Graft	17
Testicular tissue	0	Graft	0

Figures 1a, 1b and 1c show the application figures for the period 2020-2024.

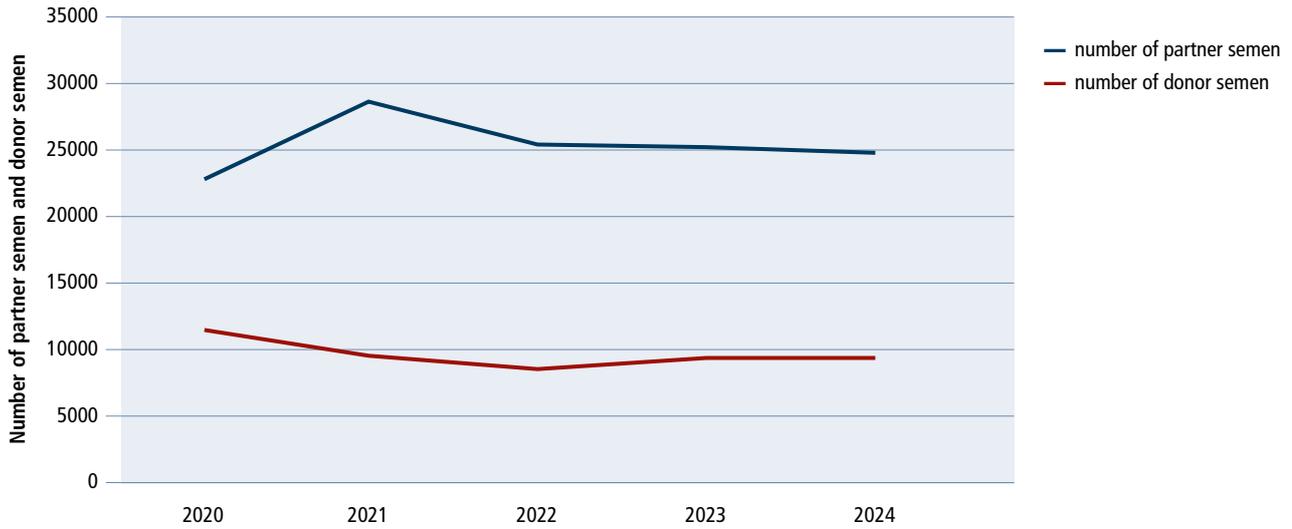


Figure 1a Number of inseminations with partner semen and donor semen, 2020-2024

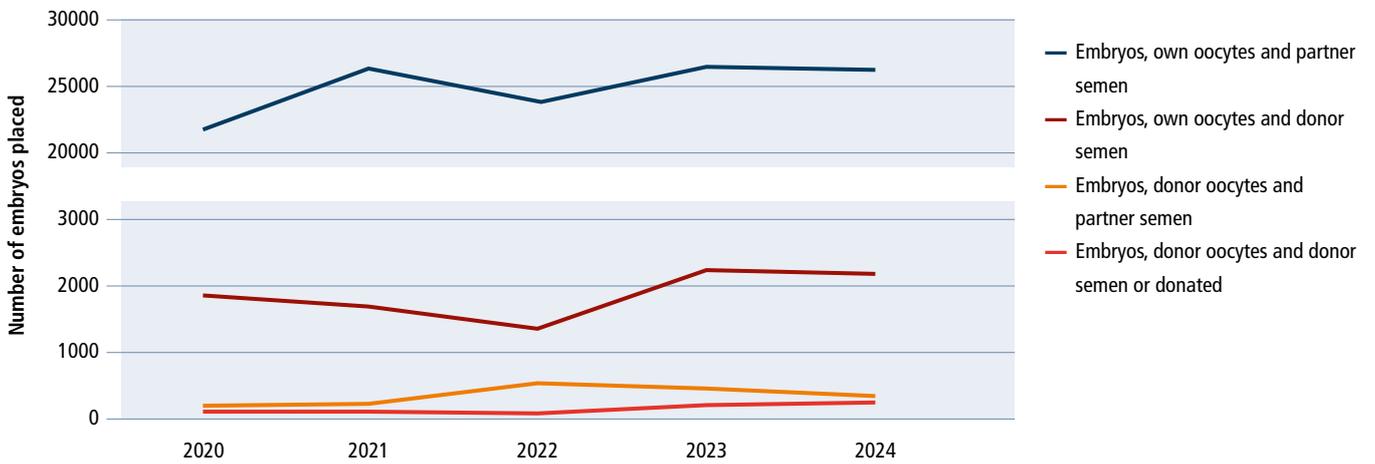


Figure 1b Number of embryos placed, 2020-2024

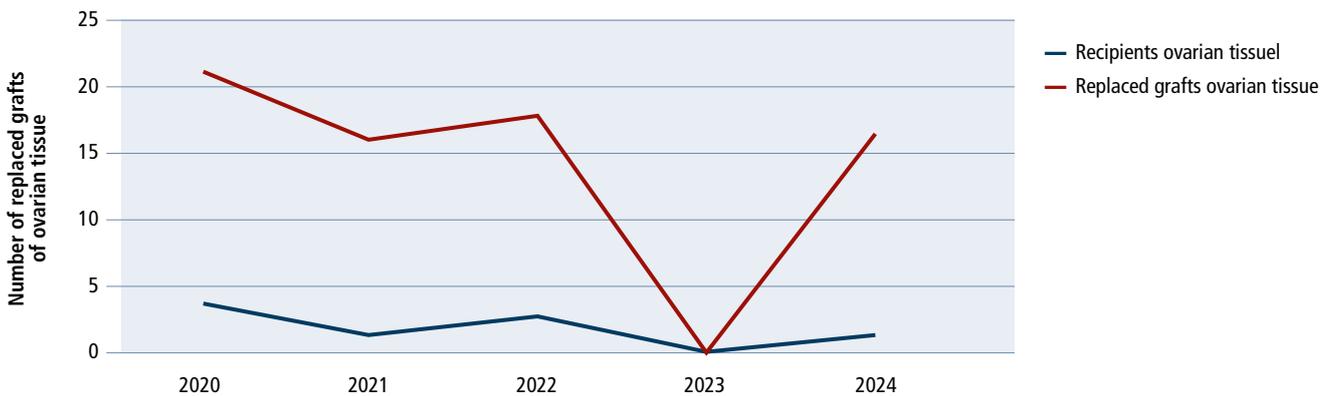


Figure 1c Number of replaced grafts of ovarian tissue 2020-2024

### 3.3 Reports

TRIP received 54 reports on the processing and application of gametes and embryos in medically assisted reproduction for 2024. Four reports were assessed as definitely not related to the medically assisted reproductive process and are not further considered in this biovigilance report.

The 50 reports can be subdivided into 39 events with or without adverse reactions and one with adverse reactions, as well as 10 donation complications (Table 3). Fourteen events and eight donation complications are classified as serious in accordance with EU criteria. Six late reports were also received of events that occurred before 2024 (Table 4) as well as three late donation complications. Of these, two events and three donation complications were classified as serious according to EU criteria. Late reports were included in the figures for the years in which they occurred.

Figure 2 summarises all reports of events, adverse reactions and donation complications with an imputability of unlikely or 'higher', submitted in the period 2020-2024. The seriousness of events and the associated reporting obligation to the EU are determined based on pre-established EU criteria (see TRIP website).

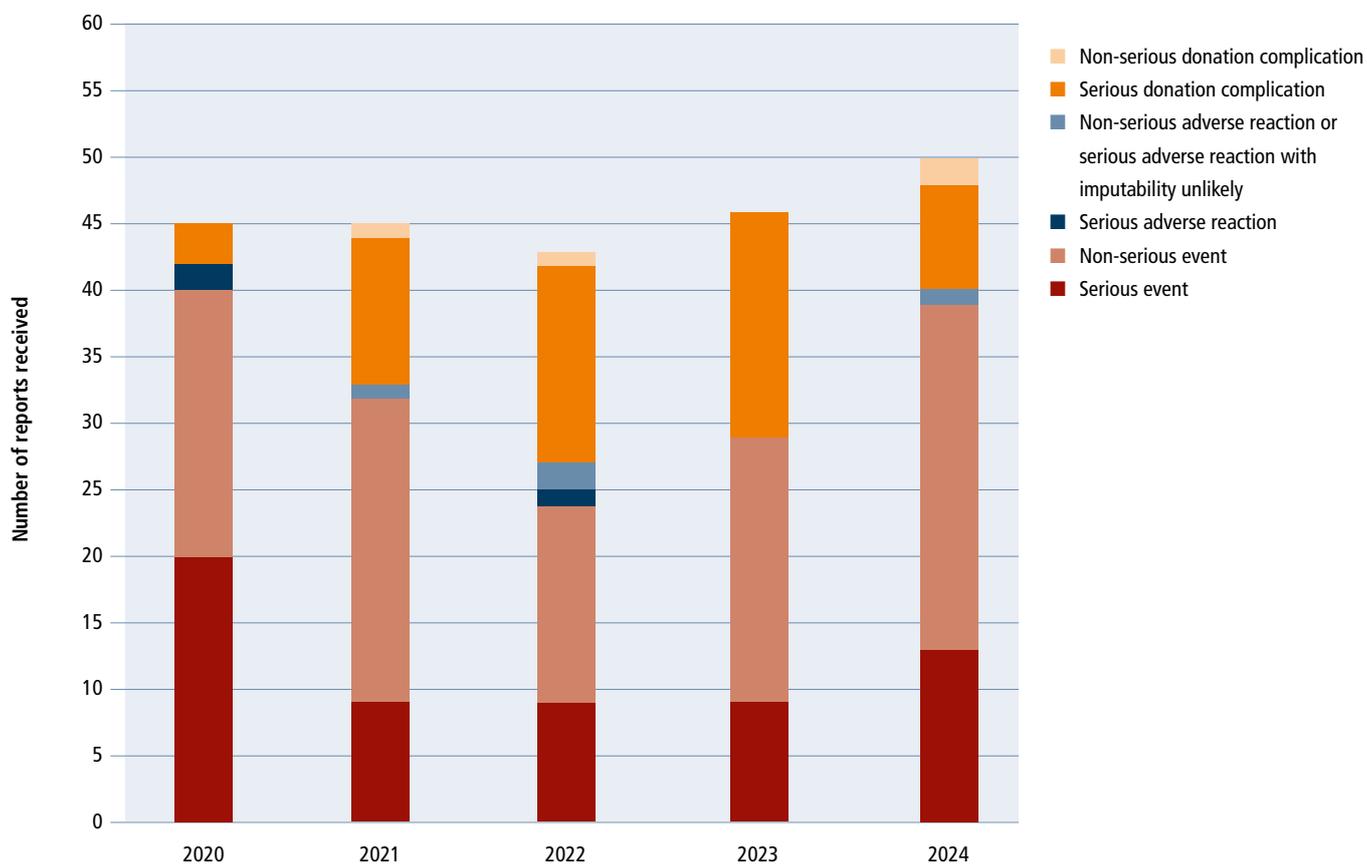
**Table 3** Reports of events and adverse reactions\* concerning reproductive tissue and cells per type of fertility lab in 2024

Fertility laboratories	No. of institutions	Reporting institutions	Total number of reports (serious EU)	Events (serious EU)	Adverse reactions (serious EU)	Donation complications (serious)
IVF laboratories	16	12	39 (21)	29 (13)	0	10 (8)
Semen laboratories	49	4	11 (1)	10 (1)	1 (0)	0
<b>Total</b>	<b>65</b>	<b>16</b>	<b>50 (22)</b>	<b>39 (14)</b>	<b>1 (0)</b>	<b>10 (8)</b>

\* adverse reactions with an imputability of definite, probable, possible, or unlikely

**Table 4** Late reports of events involving reproductive tissue and cells per type of fertility laboratory

Year of occurrence	Type of tissue	Reporting category	Events (serious EU)	Description of serious event
2022	Donor semen	Congenital anomaly	1 (1)	Donor has not been tested, hence carrier status cannot be excluded
2023	Donor semen	Congenital anomaly	3 (0)	
2023	Partner semen	Loss of cells or tissues	1 (0)	Embryo from other prospective parents was placed, but failed to lead to pregnancy
2023	Embryo	Incorrect product transplanted/ applied	1 (1)	
<b>Total</b>			<b>6 (2)</b>	



**Figure 2** Reports of events and adverse reactions with an imputability of definite, probable, possible, or unlikely, concerning reproductive tissues and cells, classified in accordance with the EU seriousness categories, 2020-2024

## Events

Table 5 provides an overview of all events reported per type of tissue or cells. Figures 3a and 3b show the distribution of serious events in the period 2020-2024. Serious events are discussed in the following sections.

**Table 5** Overview of events in reproductive tissue and cells in 2024 and late reports

Type of tissue or cells	Event category	Number of reports of events (serious EU)	Late reports (serious EU)
Semen	Bacterial contamination of product	3 (0)	
	Near miss	1 (0)	
	Congenital anomaly	13 (3)	4 (1)
	Other event	2 (1)	
	Risk of transfer of condition	2 (0)	
	Loss of tissue or cells	1 (0)	1 (0)
Oocytes	Near miss	2 (0)	
	Loss of tissue or cells	7 (6)	
Embryos	Bacterial contamination of product	5 (4)	
	Other event	1 (0)	
	Loss of tissue or cells	1 (0)	
	Incorrect product transplanted/applied		1 (1)
Testicular tissue	Near miss	1 (0)	

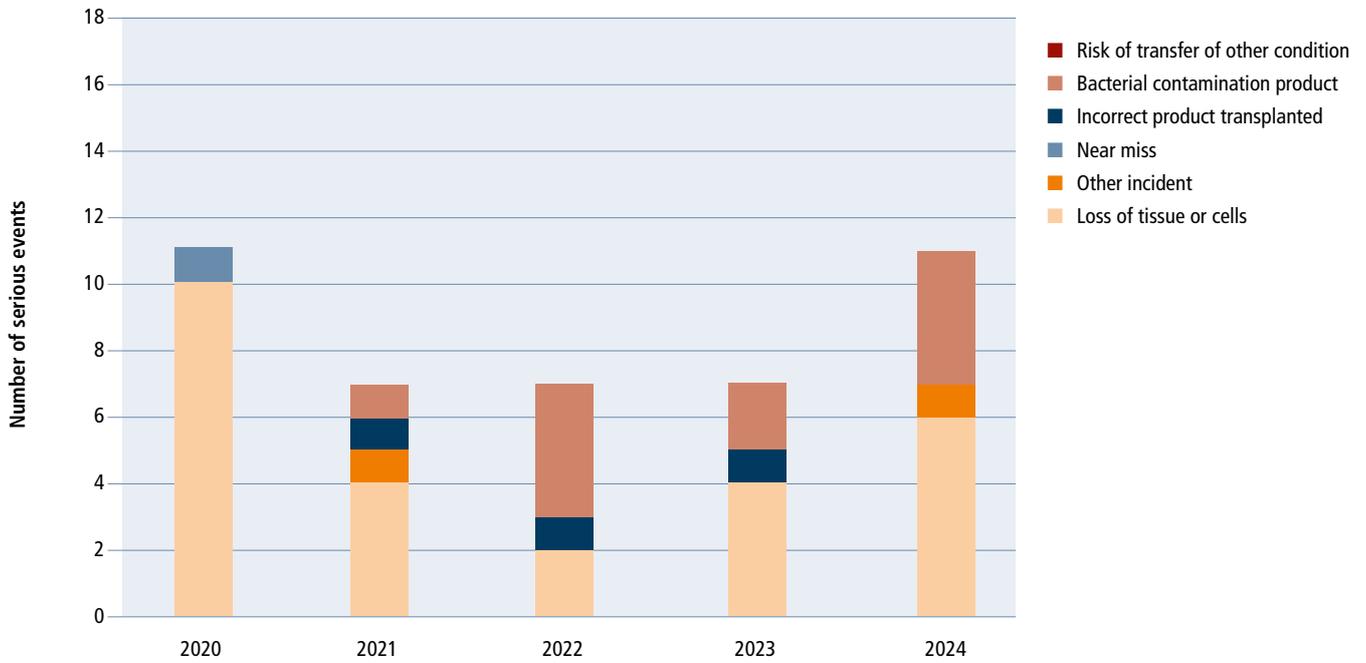


Figure 3a Number of reports of serious events per event category concerning reproductive tissue and cells, 2020-2024

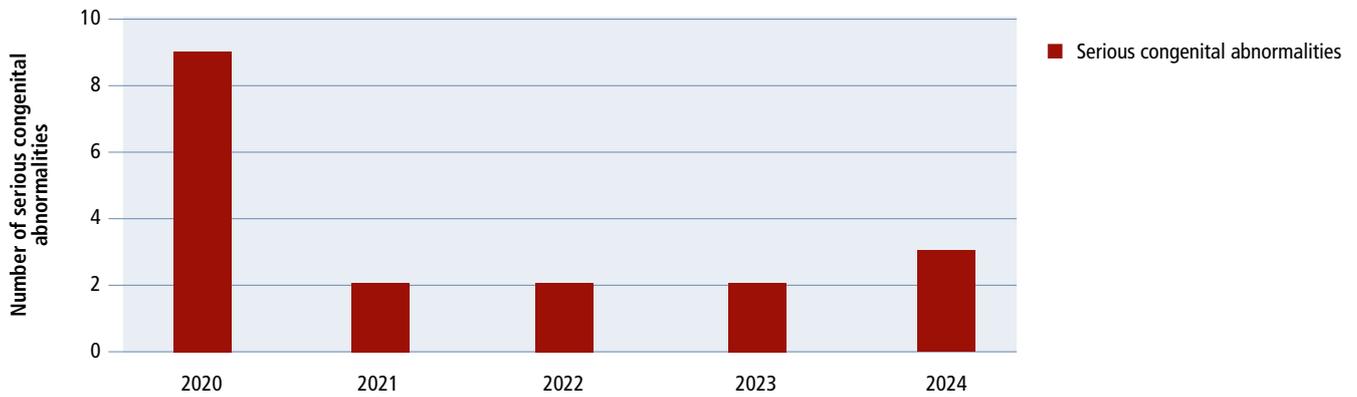


Figure 3b Number of reports of serious congenital anomalies, 2020-2024

*Loss of tissue or cells*

In 2024, TRIP received six reports of serious events leading to the loss of oocytes. This involved the loss of a complete reproductive cycle (Table 6).

**Table 6** Description of serious reports of loss of tissues or cells in 2024

Type of gamete or embryo	Phase in procedure	Description of event
Oocyte	Processing	At the start of the ICSI procedure it was found that no oocytes were present in the petri dish. On searching, the oocytes had, in all probability, not been placed in the petri dish. The cells were not retrieved.
Oocyte	Processing	During oocyte denudation, the oocyte got stuck and the pipette broke when trying to release it.. The oocyte was lost. In all, a single ovum was present for the ICSI procedure.
Oocyte	Processing	During oocyte denudation, the oocyte got stuck and the oocyte was lost. In all, a single ovum was present for the ICSI procedure.
Oocyte	Processing	During transfer from one petri dish to another, the oocyte came out of the pipette and was lost. In all, a single oocyte was present for the ICSI procedure.
Oocyte	Processing	Oocytes that were correctly inseminated via IVF were used again the same day for an ICSI treatment for another prospective couple. As a result, these previously inseminated oocytes have also been injected with semen from another prospective couple. The oocytes were lost.
Oocyte	Processing	In deciding on IVF or ICSI, treatment history was not considered. Hence, IVF was chosen based on the quantity and quality of the semen, while the previous treatment had been ICSI, and ICSI was discussed with the prospective couple. The IVF resulted in a total fertilisation failure (TFF).
Oocyte	Processing	During processing of the oocytes, the petri dish fell and the oocytes were lost.

### *Congenital defects*

In 2024, two reports were registered as serious congenital defects following the use of donor semen. In the first case, it was established that a neonate had liver disorders without genetic abnormalities. In 2022, another neonate from the same semen donor, born without a gallbladder, was likewise reported without genetic abnormalities. To be on the safe side, the remaining semen samples from this donor were destroyed. In the second case, an IgG subclass IV deficiency was found in the neonate. On examination, an autosomal dominant mutation (with potentially unclear pathogenicity or a varying degree of penetrance) was found, for which the semen donor appears to be heterozygous. In the third report, posthumous evidence showed that the donor was a carrier of a mutation in the tumour antigen P53. Neonates were offered additional diagnostics. Some were tested. So far, two neonates are known to be carriers. As far as is known, no malignancies have been identified in the neonates.

Figure 3b shows a decrease in the number of reports classified as serious congenital defects since 2021. One contributing factor is that, starting in 2018, imputability became a key factor in classifying the seriousness of congenital anomalies. Reports with an imputability of ‘definitely not’ or ‘unlikely’ are classified as not serious.

### *Bacterial contamination of product*

In 2024, four serious reports of ‘Bacterial contamination of product’ were submitted by two different institutions. All cases relate to bacterial contamination of an embryo. In one case, the source of the infection had been traced back to the patient, and in the other case it was possibly the patient (this was not tested). In the other two cases, the source of infection was traced back to the partner semen. These reports were classified as serious due to a complete loss of the reproductive cycle.

### *Other event*

In 2024, one serious report was received of an other event. During the processing of the gametes for IUI, on transferring the semen sample, no double check was performed for two prospective couples. Hence, it cannot be excluded that the patient was inseminated with the semen of the other prospective couple. The report was classified as serious due to a complete loss of the reproductive cycle.

### *Adverse reactions*

In 2024, TRIP did not receive any reports of serious adverse reactions following the application of reproductive tissues and cells with an imputability of definite, probable, or possible. In 2020, there was one report about an allergic reaction, and in 2022, one report about a post-transplantation bacterial infection was received after application of reproductive tissues and cells with an imputability of definite, probable or possible. In 2021 and 2023, as was the case in 2024, there were no reports of serious adverse reactions.

### *Donation complications*

Under the new EU SoHO regulation (2024/1938) which is mandatory as of August 2027, persons from whom body material was collected for autologous use or within-relationship use, are no longer considered as donors. Protecting their health in the context of procurement of substances of human origin is considered part of their protection as recipients of SoHO, including ensuring informed consent for the entire procedure. In the context of autologous use and 'within-relationship' use, registration of serious adverse events and reactions is only mandatory if these affect the safety and quality of the substances of human origin, as stipulated in the Body Material (Safety and Quality) Act (Wet veiligheid en kwaliteit lichaamsmateriaal, Wvkl). For example, an event involving shared materials such as a defective gamete collection jar, where the event results in loss of gametes. For donations intended for a third party, reporting serious adverse events and reactions remains mandatory under the Wvkl, and reporting serious adverse donation complications is mandatory under the new regulation. The renewal of the Wvkl, i.e. updating legislation on substances of human origin, does not seem to change this. The review of the Wvkl will probably enter into force in 2026.

Of the 65 institutions, only four reported donation complications to TRIP. This suggests that the reported donation complications likely represent underreporting of donation complications in the Netherlands. Consistent with previous years, the most commonly reported donation complication is ovarian hyperstimulation syndrome (OHSS). Six out of eight reports related to OHSS, in all cases leading to hospital admission. The other two cases relate to abdominal pain due to abdominal bleeding following follicular puncture, including one ovarian rupture.

## **3.4 Summary of reproductive tissue and cells**

All IVF and semen laboratories submitted figures to TRIP regarding the processing, distribution and application of reproductive tissue and cells in 2024. After no applications of ovarian tissue in 2023, ovarian tissue was applied again in 2024. The application of other reproductive tissues and cells remained consistent with previous years. Where a decrease in the processing of semen from Europe was observed in the last two years, slightly more semen from Europe and less from the Netherlands was processed in 2024. There was noticeably fewer processing of embryos (own oocyte and partner semen) where the reduction in distribution is less evident. The decrease is not determined by a single institution.

In 2024, TRIP received 50 reports (+ six late reports) on the donation, processing and application of gametes and embryos in medically assisted reproduction, compared to 37 reports last year. Of these, 22 reports were classified as serious according to EU criteria. This is comparable to 2023 (22). In 2024, 14 serious events and eight serious donation complications were reported. In line with last year, no serious adverse reactions were reported in 2024. Among the six late reports of events completed in 2024, two were classified as serious according to EU criteria.

# 4 HEMATOPOIETIC STEM CELLS AND OTHER CELLS FOR THERAPEUTIC PURPOSES

## 4.1 Institutions involved

In 2024, 15 tissue establishments in the Netherlands were authorised to sample, process, store and/or distribute hematopoietic stem cells (HSCs) and other cells for therapeutic purposes. In 2024, one institution reported having performed no applications of hematopoietic stem cells. These 15 tissue establishments include 12 institutions that, besides the required accreditation as a tissue establishment, also hold accreditation as an organ bank, allowing them to receive human tissues or cells after procurement elsewhere. Three of the 15 tissue establishments are exclusively active in the field of processing cells obtained from bone marrow, or peripheral blood, or umbilical cord blood for purposes of further processing into medicinal products. All tissue establishments active in the field of hematopoietic stem cells submitted a report of their activities in 2024.

Stem cell transplants are performed in 11 transplant centres in the Netherlands. In three institutions, this only concerned autologous stem cell transplants. Stem cell products from unrelated donors are delivered to seven academic transplant centres through the Matchis foundation, mostly via the stem cell laboratories of the respective hospitals. Peripheral blood stem cells (PBSCs), bone marrow and donor lymphocytes from unrelated Dutch donors are collected at two academic hospitals in the Netherlands. There is one tissue establishment that processes, stores and distributes unrelated transplants of umbilical cord blood (cord blood units).

## 4.2 Activities in 2024

Table 7 shows the number of processed hematopoietic stem cell transplants obtained from peripheral blood, bone marrow, umbilical cord blood and donor lymphocytes for the purpose of DLI (Donor Lymphocyte Infusion). Processing of a transplant takes place around the time of collection (e.g. by apheresis or bone marrow aspiration) and may also involve subsequent processing (e.g. after delivery of the transplant at the transplant centre). As a result, transplants may be counted several times in the processing figures. In the processing of hematopoietic stem cells and donor lymphocytes, a downward trend can be seen in the treatment of allogeneic related peripheral blood stem cells. This could possibly be explained by new insights of donor criteria in definite pathologies (young unrelated vs older related). This trend will be followed up. Table 8 shows the distribution and application of stem cell transplants and donor lymphocytes. Reporting by one institution was incomplete for the number of PBSC units applied, which largely explains the discrepancy between distributed and applied units.

For the other cells for therapeutic purposes, the cells, in many cases, are obtained for processing into medicinal products: the production of Advanced Therapy Medicinal Products (ATMPs). Donation, procurement and testing of human tissue and cells that serve as starting material for these ATMPs, fall under the Body Material (Safety and Quality) Act (Wvkl). The manufacturing process is covered by Good Manufacturing Practices legislation (GMP, Eudralex Volume 4) and the product is covered by the Medicines Act (Geneesmiddelenwet, Gmw). Due to the responsibilities under the Wvkl (refer to Table 9), TRIP intends to monitor activities related to the procurement of starting material in the coming years. The submission of data on distribution and final application of ATMPs (medicinal product) is optional, as this is not covered by the Wvkl. This year, eight institutions have reported this application, refer to Table 10. A discrepancy can be seen here between units applied and quantities distributed. This is partly due to the number of units distributed not always being specified. Reporting serious events and complications related to the procurement of substance of human origin, without this affecting the safety or quality of the tissues or cells, is not yet covered by legislation. TRIP intends to receive these reports pending additional regulations.

**Table 7** Processing of hematopoietic stem cells and donor lymphocytes in 2024

Type of cells	Reporting tissue establishments	Processing of transplants			Total
		From NL	From EU	From non EU	
<b>PBSC</b>					
autologous	11	1,430	0	0	1,430
related	8	97	0	0	97
unrelated	8	352	185	33	570
<b>Bone marrow</b>					
autologous	2	7	0	0	7
related	7	40	0	0	40
unrelated	7	115	19	3	137
<b>Umbilical cord blood</b>					
related	1	2	0	0	2
unrelated	5	29	11	16	56
<b>Donor lymphocytes</b>					
related	8	65	0	1	66
unrelated	8	125	65	13	203

**Table 8** Distribution and application of hematopoietic stem cells and donor lymphocytes in 2024

Type of cells	Reporting tissue establishments	Distributed/delivered bags <sup>a</sup>	Reporting transplantation centres	Transplanted bags <sup>a</sup>	Recipients
<b>PBSC<sup>b</sup></b>					
autologous	11	4,069	11	3,663	952
related	8	137	8	135	108
unrelated	8	450	8	469	435
<b>Bone marrow</b>					
autologous	1	2	1	2	1
related	7	43	7	40	40
unrelated	7	58	7	58	57
<b>Umbilical cord blood</b>					
related	0	0	0	0	0
unrelated	5	40	3	31	26
<b>Donor lymphocytes</b>					
related	8	110	8	102	61
unrelated	8	278	8	276	205

<sup>a</sup> One tissue establishment reported the number of transplants rather than number of bags, 1 transplant counted as 1 bag

<sup>b</sup> Reporting by one institution was incomplete for the number of PBSC units applied

**Table 9** Processing of other cells for therapeutic purposes in 2024

Type of cells	Reporting tissue establishments	Processing of collected samples			Total
		From NL	From EU	From non EU	
Mesenchymal stem cells allogeneic	1	1	0	0	1
Mononuclear cells from peripheral blood	7	138	0	828	966
Cells from umbilical cord blood	1	0	0	16	16
CAR T-/TCR cells, autologous	2	52	0	0	52
Tumour tissue and cells	2	47	0	0	47
CD34+cells from HPC	2	4	1	0	5
Virus-specific lymphocytes	1	4	0	0	4

**Table 10** Distribution and application of other cells for therapeutic purposes in 2024

Type of cells	Reporting tissue establishments	Distribution (unit = bags)	Reporting treatment centres	Units applied	Number of recipients
Mesenchymal stem cells allogeneic	2	2	2	2	2
Dendritic cells, autologous	1	6	0	0	0
Mononuclear cells	4	144	2	21	21
Tumour-infiltrating lymphocytes, autologous	1	18	2	57	57
CAR T-/TCR cells, autologous	6	103	8	182	182
Expanded cells from umbilical cord blood	3	20	3	20	4
CD34+cells from HPC	2	5	2	3	2
Virus-specific lymphocytes	2	5	2	5	2

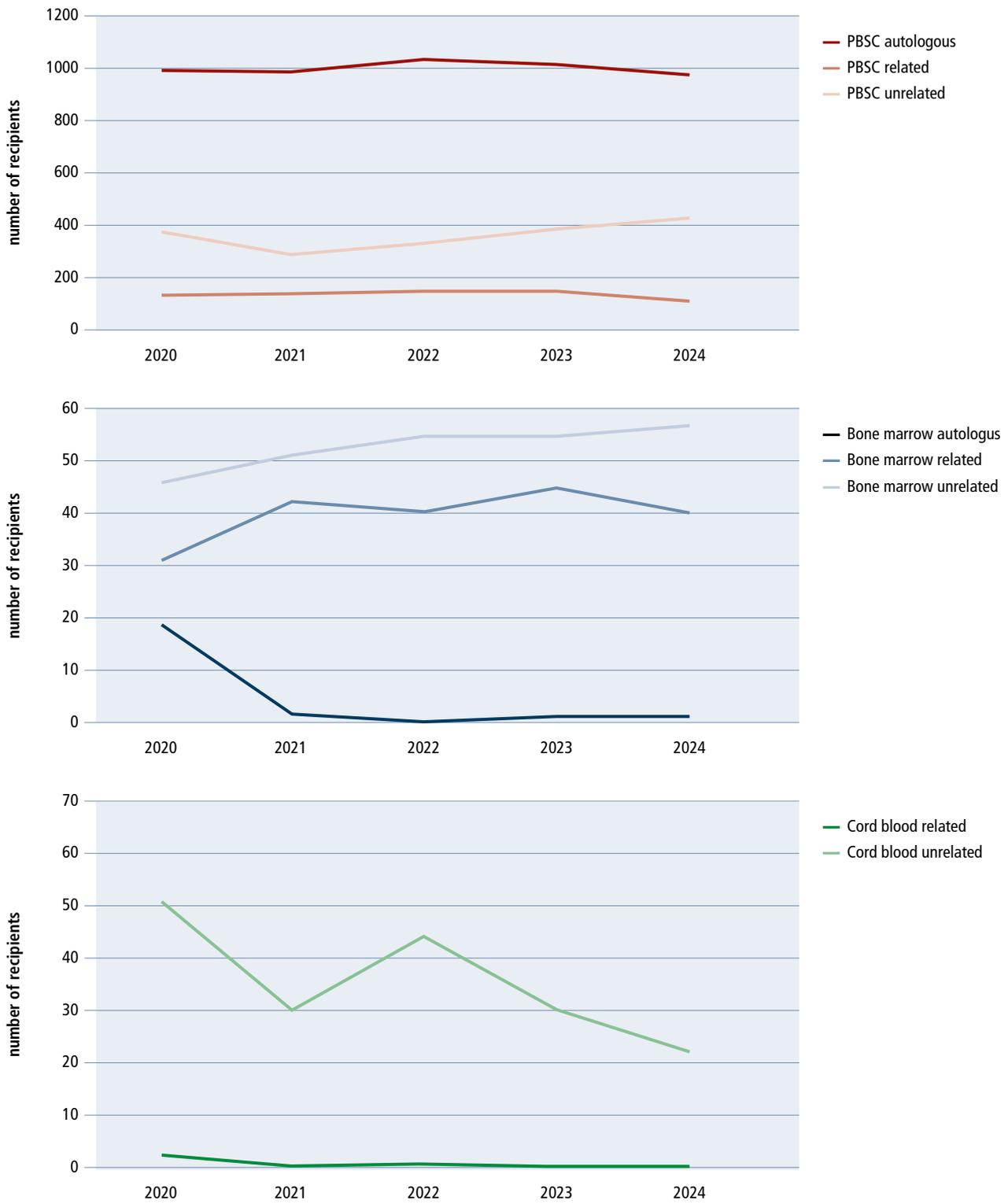


Figure 4a-b-c Number of hematopoietic stem cell transplant recipients per transplant type, 2020-2024.

## 4.3 Reports

In 2024, five out of a total of 32 reports relating to hematopoietic stem cells or other cells for therapeutic purposes were received. Furthermore, seven late 2023 reports were received, all of which were donation complications, one of which was serious. All reports have an imputability of unlikely, possible, probable or definite. The reports include 13 events, 10 adverse reactions, and 16 donation complications. In 2024, eight reports of adverse reactions have a high seriousness ( $\geq 2$ ), an imputability of possible, probable, or definite, and are serious according to EU criteria. In 2024, 14 reports including late reports (with eight adverse reactions, three events, and three donation complications) were assessed as serious in accordance with EU criteria and therefore mandatory to report to the competent authority, the Health and Youth Care Inspectorate (IGJ) (Figure 10). These reports can be made available to the IGJ via the TRIP reporting system. Fewer reports were registered at TRIP than in 2023 (32 vs 42), but a doubling in the number of serious adverse reactions (excluding donation complication), 2023: 4 and 2024: 8. In the following years, it will be assessed whether this represents an outlier or a trend.

Refer to Table 11 for specifications of the reports. Figure 6 shows a multi-year overview of reports on hematopoietic stem cells and other cells for therapeutic purposes. The events defined as serious according to EU criteria (refer to TRIP website for criteria) and the adverse reactions with a seriousness of 2 or higher, as well as an imputability of definite, probable, or possible are described in Tables 12 and 13.

**Table 11** Reports per tissue type, reporting category and seriousness (according to EU criteria), 2024 and seven late reports from 2023

Type of tissue or cells	Event category	Number of reports (serious) <sup>a</sup>
Peripheral blood stem cells	Bacterial contamination of product	1 (0)
	Other contamination of product	1 (0)
	Loss of cells or tissues	3 (0)
	Other event	2 (2)
Bone marrow	Bacterial contamination of product	4 (0)
	Other event	2 (1)
Type of tissue or cells	Adverse reaction category	Number of reports (serious) <sup>a</sup>
Peripheral blood stem cells	Post-transplantation febrile reaction	1 (0)
	Other reactions	2 (1)
	Donation complications <sup>b</sup>	13 (2)
Bone marrow	Other reactions	3 (3)
	Circulatory overload	1 (1)
	Donation complications <sup>b</sup>	2 (1)
DLI	Donation complications <sup>b</sup>	1 (0)
Umbilical cord blood	Other reactions	3 (3)

<sup>a</sup> Serious events according to EU criteria, serious adverse reactions  $\geq$  grade 2 with an imputability of definite, probable or possible.

<sup>b</sup> Including 7 late reports from 2023 received

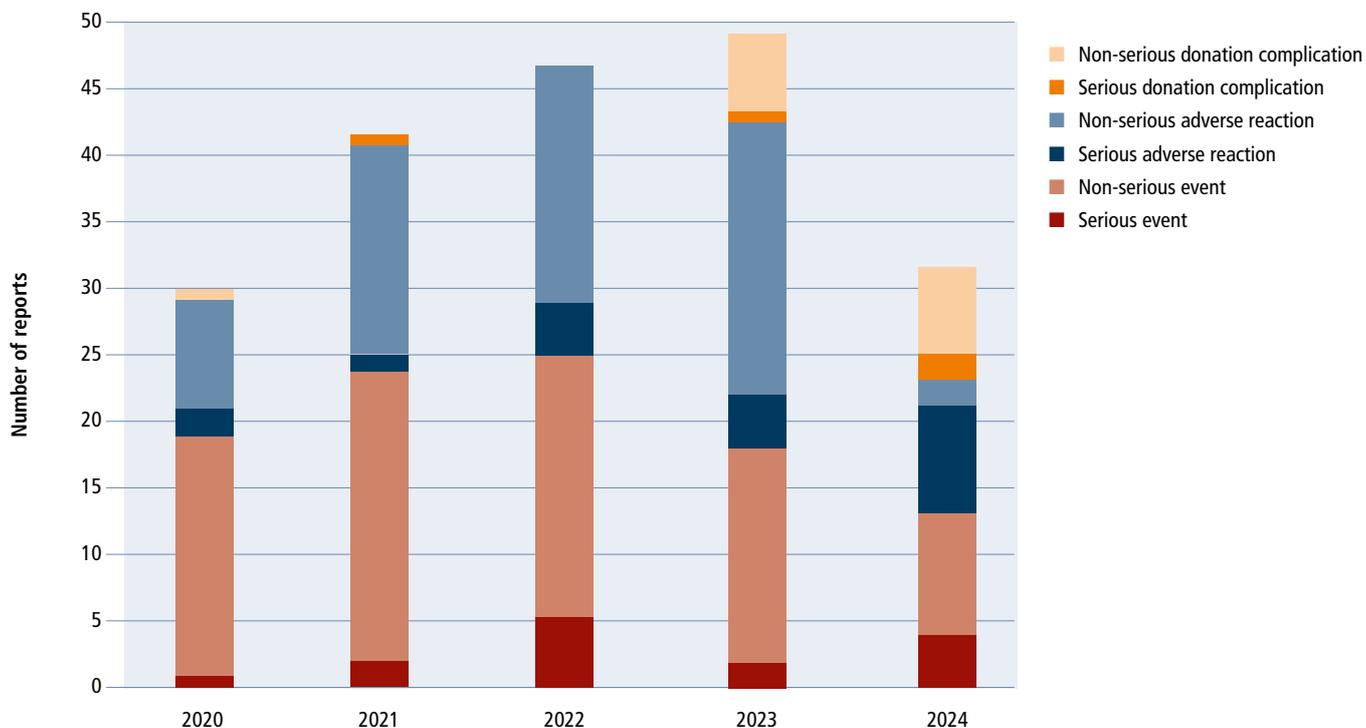


Figure 5 Total reports of hematopoietic stem cells and other cells for therapeutic purposes, 2020-2024

Table 12 Events (serious according to EU definition) relating to hematopoietic stem cells and other cells for therapeutic purposes in 2024

Type of HSC	Event (description)	Reporting category
PBSC, autologous	Test error on testing An urgent determination of CD34 <sup>+</sup> cells was carried out for two patients. Due to these results, a decision was made for another apheresis of both patients. The final results show that a second apheresis was not necessary for both. The cause of the deviating result is not known.	Other event
PBSC, autologous	Identification error on testing Due to a mix-up of patient samples in the results of the leukapheresis, both patients underwent a second procedure, which may have been unnecessary. It is unknown at which point the mix-up occurred.	Other event
Bone marrow, allogeneic related	Assessment error at donation Too much product was collected from a donor, because the collection bag expanded during the procedure. This made it difficult to read the quantity. This resulted in a vasovagal syncope in the donor. The procedure has been modified to allow for a more accurate determination of the quantity collected in future.	Other event

**Table 13** Adverse reactions (seriousness  $\geq 2$ , with an imputability of definite, probable, or possible) relating to hematopoietic stem cells in 2024

Type of HSC	Adverse reaction (description)	Interval in respect of transplantation	Imputability	Seriousness
PBSC, autologous	Post-transplantation febrile reaction Supplementary medical treatment, patient recovered completely	During infusion	Probable	2
Bone marrow, allogeneic unrelated	Circulatory overload Acute respiratory failure. Supplementary medical treatment (oxygen and dehydration), patient recovered completely	After infusion	Possible	3
Bone marrow, allogeneic unrelated	Other reaction – hypertension Supplementary medical treatment, patient recovered completely	During infusion	Probable	2
Bone marrow, allogeneic unrelated	Other reaction– hypertension Supplementary medical treatment, patient recovered completely	After infusion	Definite	2
Bone marrow, allogeneic unrelated	Other reaction– hypertension Supplementary medical treatment, patient recovered completely	During infusion	Possible	2
Umbilical cord blood, allogeneic, related	Other reaction – hypertension Supplementary medical treatment, patient recovered completely	During infusion	Possible	2
Umbilical cord blood, allogeneic, related	Other reaction – hypertension Supplementary medical treatment, patient recovered completely	During infusion	Probable	2
Umbilical cord blood, allogeneic, related	Other reaction – hypertension Supplementary medical treatment, patient recovered completely	During infusion	Probable	2

**Table 14** Donation complications (seriousness  $\geq 2$ , with an imputability of definite, probable, or possible) relating to hematopoietic stem cells in 2024

Type of HSC	Donation complication (description)	Interval in respect of donation	Imputability	Seriousness
PBSC, autologous	Ruptured spleen, for which surgery and ICU admission post OR	During stem cell mobilisation phase	Definite	3
PBSC, allogeneic, related	Deep venous thrombosis and pulmonary embolisms in sickle cell carrier requiring medication, and patient recovered completely	Days after apheresis	Possible	2
Bone marrow, allogeneic, unrelated	Thrombophlebitis in arm after IV (anaesthetics for bone marrow aspiration). Treated with medication, patient recovered completely	During procurement	Probable	2

#### 4.4 Summary of hematopoietic stem cells and cells for therapeutic purposes

In 2024, TRIP received activity data from all tissue establishments that are active in the field of hematopoietic stem cells.

In 2024, three serious events were reported compared to an average of three reports per year in the last five years (2019-2023: range 1-5). Eight serious adverse reactions were registered compared to an average of 2.8 per year in the last five years (2019-2023: range 1-4). There is a doubling in the number of adverse reactions compared to 2022 and 2023. In the following years, it will be assessed whether this represents an outlier or a trend. In 2024, 10 donation complications were reported, of which three were serious. One serious donation complication had been reported in 2023.

One serious adverse reaction is a post-transplant febrile reaction during transplantation of peripheral blood stem cells. Four serious adverse reactions concerned reactions during or after bone marrow aspirations, in which there were three hypertensive reactions and once a circulatory overload. Three serious adverse reactions concerned a hypertensive reaction during umbilical cord blood transplantation. In all cases, supplemental medical treatment was needed to normalise blood pressure or fever, or the recipient was dehydrated and received respiratory support. All recipients recovered completely from the adverse reactions.

# 5 OTHER TISSUES AND CELLS

## Institutions involved

In all, there are 71 hospitals and independent treatments centres, as well as 68 implantology practices that apply other human tissues and cells in the Netherlands, known to TRIP. In 2024, 65 hospitals reported application figures, of which five hospitals reported partially (number of patients could not be traced). Of the implantology practices known to TRIP, 59 reported application figures, six of which indicated that no substance of human origin had been applied in 2024. It is not mandatory for institutions to report application figures, as the use of other tissues and cells is currently not a recognised activity under the Body Material (Safety and Quality) Act (Wvkl). The 2006 Dutch Body Materials Decree states that an institution “passes on all relevant information to the organ centre or tissue establishment from which the body material originates, in order to facilitate traceability and to guarantee quality assurance and safety”. The institutions that provide information about possible reports and application figures will receive a participation statement from TRIP, which the Health and Youth Care Inspectorate may request during an inspection.

In the Netherlands, 23 tissue establishments are authorised to collect, process, store and/or distribute other tissues and cells, of which 22 of them have reported their annual figures. One tissue establishment in the field of other tissues and cells ceased its activities in 2024. There are 13 registered institutions that, besides the required accreditation as a tissue establishment, also hold an accreditation as an organ bank, allowing them to receive tissues or cells directly after procurement. Twelve organ banks reported activity figures in 2024 (Figure 6).

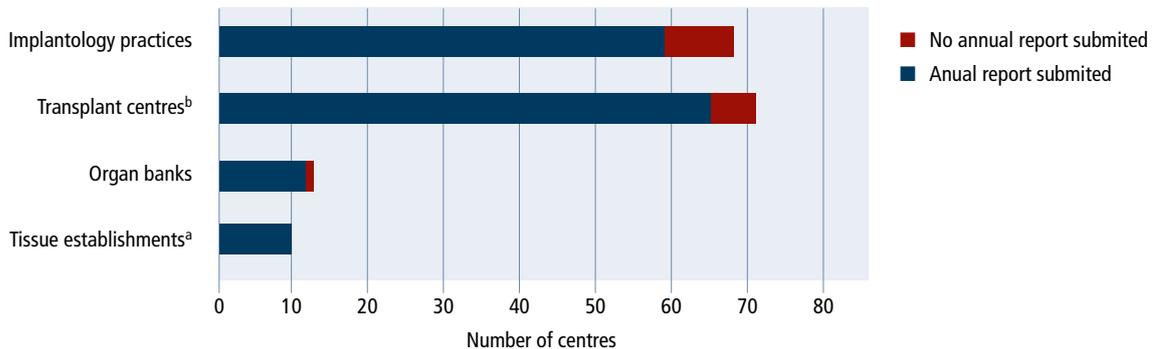


Figure 6 Participation relating to other tissues and cells in 2024

<sup>a</sup> Tissue establishments without accreditation as an organ bank

<sup>b</sup> 65 institutions have submitted reports (5 partially), 6 not at all

## 5.1 Bone and other musculoskeletal tissue and cells

### 5.1.1 Institutions involved

Bone and other musculoskeletal tissue includes femoral heads from living and post-mortem donors, mineralised and demineralised bone filler, whole bones, cranial bones (autologous), tendons, bone-tendon-bone grafts, fascia, cartilage, (autologous) chondrocytes and menisci. In all, 139 institutions/implantologists registered at TRIP have submitted reports on applications of musculoskeletal tissues. One hundred and twenty-four submitted annual figures, of which six indicated that no musculoskeletal tissue had been applied in 2024.

### 5.1.2 Activities in 2024

Table 14 shows the processing of bone and other musculoskeletal tissues in 2024. Table 15 shows the distribution and application of the various tissues after processing.

In 2024, no processing of bone to filler (demineralised) was reported by tissue establishments in the Netherlands. There is more distribution of bone tissue which has been processed in the EU, or that has possibly been imported from third countries. In the Netherlands, there are a number of tissue establishments that only distribute bone filler (both mineralised and demineralised), mainly outside the Netherlands. These distributors already receive processed musculoskeletal tissue from Europe, or possibly from outside the EU, and distribute it to institutions in the Netherlands and the rest of Europe. This could explain the difference between the processing figures in Table 14 and the distribution figures in Table 15. Imported processed tissue products must be allocated a Single European Code (SEC) number in Europe. This is considered as a processing step. The processing of cartilage is similar to that in 2023. The number of recipients this year is very low (there may be missing recipient figures).

In 2024, more bone-tendon-bone grafts and fascia were applied than in 2023. For almost all musculoskeletal tissue, Table 15 shows that there is a big difference between the number of products distributed and the number of recipients, as was also the case in previous years. This could partially be explained because some recipients had received multiple grafts/units, or that tissue was still in stock. The most probable reason is that some institutions may struggle or are completely unable to track their stock and the use of these products, possibly leading to incomplete figures. At least five hospitals indicated that the number of recipients could not be traced. Another possibility is that not all users are known at TRIP as yet.

Autologous chondrocytes are cultivated for preparation into Advanced Therapy Medicinal Products (ATMPs). Only collection of the cartilage biopsy and any processing before it is sent to the manufacturer, such as testing, preservation or storage, are subject to the Wvkl. Application is not reported to TRIP by all institutions due to its non-mandatory nature. Applications of chondrocyte products in patients are subject to the ATMP and medicinal product regulations. There was an increase in the number of cartilage biopsies in comparison to 2023 (was 94 in 2023).

**Table 14** Processing of bone and other musculoskeletal tissue and cells in 2024

Type of tissue/cells	Reporting tissue establishments	Processing tissue from donors from			Total
		NL	EU	non EU	
Femoral heads, living donor	5	2,758	420	0	3,178
Femoral heads, post-mortem donor	1	42	0	0	42
Bone filler, mineralised	1	2,850	0	0	2,850
Bone filler, demineralised	1	0	0	0	0
Bones, whole	2	187	5	0	192
Cranial bone (autologous)	3	125	1	0	126
Tendons	1	274	0	0	274
Bone-tendon-bone grafts	1	19	0	0	19
Fascia	1	83	0	0	83
Cartilage	1	10	0	0	10
Cartilage for chondrocytes, autologous, for ATMP	1	142	0	0	142
Menisci	1	22	0	0	22

**Table 15** Distribution and application of bone and other musculoskeletal tissue and cells in 2024

Type of tissue/cells	Reporting		Distribution units				Units applied	
	tissue establishments	Reporting institutions	In NL	In EU	Export outside EU	Total	(from NL)	Recipients
Femoral heads, living donor*	6	44	1,521	688	3	2,212	836 (835)	803
Femoral heads, post-mortem	1		33	0	0	33		
Bone filler, mineralised	8	83	9,046	4,811	3,028	16,885	3,283 (2,719)	3,207
Bone filler, demineralised	7	12	509	11,765	17,862	30,136	159 (144)	115
Bones, whole	2	16	158	12	0	170	43 (43)	43
Cranial bone, autologous	3	10	63	0	0	63	49 (49)	49
Tendons	1	23	522	44	0	566	224 (224)	206
Bone-tendon-bone grafts	1	10	11	6	0	17	51 (51)	51
Fascia	2	4	211	0	0	211	82 (82)	74
Cartilage	2	1	51	0	0	51	2 (2)	2
Chondrocytes (ATMP)	1	1	n/a	n/a	n/a	n/a	64 (64)	59
Menisci	1	3	26	4	0	30	24 (20)	24

\* one tissue establishment has ceased processing femoral heads, still distributes ex-stock

## 5.2 Cardiovascular tissue

### 5.2.1 Institutions involved

Cardiovascular tissue includes aortic and pulmonary valves, vessels, patches and the pericardium. In the Netherlands, there are two institutions involved in the processing, storage and/or distribution of cardiovascular tissue, and they both submitted their annual reports to TRIP. Of the ten institutions known to TRIP that perform cardiovascular tissue applications, all reported the number of applications in 2024.

### 5.2.2 Activities in 2024

The 2024 activity data is similar to 2023 for cardiovascular tissue (Tables 16 and 17). In 2024, there were 218 post-mortem heart valve donors, which is slightly less than in 2023 (224). The number of aortic or pulmonary valves that were suitable for clinical applications after processing is much lower than the number of donor hearts received for processing. Due to necessary stringent quality requirements (tissue structure and microbiological status), a relatively large part was not approved for application. The distribution figures are therefore much lower for the cardiac valves. Of the 108 applications of pulmonary valves from the Netherlands, 104 were distributed, and the figures provided are probably partly incorrect (Table 17). Given the very stringent storage conditions, the question is whether some cardiac valves kept 'in stock' at institutions, for example because surgery was changed, should be considered as tissue loss. One institution did not report the number of pericardium applications.

**Table 16** Processing of cardiovascular tissue and cells in 2024

Type of tissue	Reporting tissue establishments	Processing tissue from donors from			Total
		NL	EU	non EU	
Aortic valves	1	218	0	0	218
Pulmonary valves	1	218	0	0	218
Vessels	1	4	0	0	4
Patches	1	59	0	0	59

**Table 17** Distribution and application of cardiovascular tissue in 2024

Type of tissue	Reporting		Distribution units				Applied units	
	tissue establishments	Reporting institutions	In NL	In EU	Exports	Total	(from NL)	Recipients
Aortic valves	1	4	5	4	0	9	11 (9)	11
Pulmonary valves	1	3	104	18	0	122	108 (106)	108
Vessels	1	1	0	0	0	0	1 (1)	1
Patches	1	4	37	12	0	49	143 (143)	143
Pericardium*	2	5	1,019	0	0	1,019	102 (62)	79

\* Pericardium is ordered by the institutions from distributors within or outside the Netherlands

## 5.3 Skin

### 5.3.1 Institutions involved

Skin includes donor skin, acellular dermis, autologous skin and cultured skin.

Four institutions in the Netherlands are involved in the processing, storage and/or distribution of skin tissue. All four submitted their annual reports to TRIP.

There are nine institutions known to TRIP that perform donor-skin applications. One hospital did not submit figures in 2024. Furthermore, three hospitals are known to use acellular dermis, two applied acellular dermis to patients in 2024. There is one implantology practice that has submitted figures on the use of acellular dermis. In 2024, there are no longer any hospitals that report the processing or application of autologous skin or cultured skin.

### 5.3.2 Activities in 2024

The number of post-mortem skin donors from the Netherlands increased (this was 389 donors in 2023). Fewer skin grafts were processed from EU donors (157 in 2023). The number of distributed packages containing skin in the Netherlands decreased compared to 2023 (2,364 packages). As in previous years, there is a discrepancy between the number of units distributed and the number of units applied. This is partly due to differences in reporting practices between tissue establishments and institutions. Distribution in Europe has decreased by 40%, while exports have shown a slight decrease compared to last year (1,615). There is a slight decrease in the number of package distributions of acellular dermis compared to 2023 (388). Once again, the number of units actually applied differs significantly; it is much lower than the number of units distributed. It is probable that applications of pieces of acellular dermis by implantologists have not been reported to TRIP.

**Table 18** Processing of skin in 2024

Type of tissue	Reporting tissue establishments	Processing of skin from donors from <sup>a</sup>			Total
		NL	EU	Non EU	
Donor skin	1	349	125	0	474
Acellular dermis	1	39	0	0	39

<sup>a</sup> Processing of donor skin and acellular dermis is reported as the number of post-mortem skin donors.

**Table 19** Distribution and application of skin in 2024

Type of tissue	Reporting		Distribution units				Units applied	
	tissue institutions	Reporting institutions	In NL	In EU	Exports	Total	(from NL)	Recipients
Donor skin	1	8	1,203	6,650	1,476	9,329	814 (785)	103
Acellular dermis	3	4	140 <sup>a</sup>	0	226	366	8 (5)	8 <sup>a</sup>

<sup>a</sup> The application of a large number of distributed acellular dermis grafts has not been reported

## 5.4 Ocular tissue

### 5.4.1 Institutions involved

Ocular tissue includes corneal, scleral and limbal stem cells. The limbal stem cells are starting material for further processing into ATMP. Currently, it is not mandatory for tissue establishments to report their annual figures relating to starting material for ATMPs to TRIP, as there is no conclusive legislation yet. There are four institutions in the Netherlands involved in the processing, storage and/or distribution of ocular tissue, three of which submitted their annual reports to TRIP.

Of the 22 institutions known to TRIP that perform ocular tissue applications, 20 institutions have been able to provide figures in 2024.

### 5.4.2 Activities in 2024

There is a discrepancy between the number of corneas and sclerae distributed and their applications. According to the annual figures of the Dutch Transplantation Foundation (NTS), 2,056 corneas were allocated in 2024. TRIP received reports from 13 institutions detailing 1,764 cornea applications. This distribution-to-application discrepancy is probably due to the fact that some institutions may have incomplete application figures. There is also a significant difference between the number of units of sclera distributed and applied. Some institutions do provide figures of their orders, but the data on the tissue actually applied is missing.

**Table 20** Processing of ocular tissue and cells in 2024

Type of tissue/cells	Reporting tissue establishments	Processing of ocular tissue from donors from			Total
		NL	EU	non EU	
Cornea	2	5,156	0	0	5,156
Sclera	1	657	0	0	657
Limbal stem cells	2	0	0	0	0

**Table 21** Distribution and application of ocular tissue and cells in 2024

Type of tissue/cells	Reporting		Distributed transplants				Applied units	
	tissue establishments	Reporting institutions	In NL	In EU	Exports	Total	(from NL)	Recipients
Cornea	2	13	2,094	702	101 <sup>a</sup>	2,897	1,764 (1,764)	1,764
Sclera	1	16	1,931	77	0	2,008	1,511 (1,501)	1,319
Limbal stem cells	2	2	0	0	0	0	0	0

<sup>a</sup> The number of corneas exported is much lower compared to 2023 (117)

## 5.5 Other tissues and cells

### 5.5.1 Institutions involved

Other tissues and cells include amniotic membranes, pancreatic islets and nervous tissue. The tumour-infiltrating leukocytes isolated from tumour tissue are described in chapter 4. In the Netherlands, three organ banks and one tissue establishment are involved in the processing, storage and/or distribution of these other tissues and cells. TRIP knows 12 institutions that apply other tissues and cells. All institutions have reported their activity.

### 5.5.2 Activities in 2024

Table 22 shows the number of processing operations involving other tissues and cells. Some of the other tissues and cells are applied as starting material for further processing into ATMPs. Table 23 shows the distribution data. Some of these tissues and cells were distributed to an institution outside the Netherlands. Except for the mesenchymal stem cells (MSC) from fatty tissue, no other tissues/cells were applied that were not derived from donors in the Netherlands.

**Table 22** Processing of other tissues in 2024

Type of tissue	Reporting tissue establishments	Processing tissue from donors from			Total
		NL	EU	Outside EU	
Amniotic membranes <sup>a</sup>	2	2	8	0	10
Pancreatic islets <sup>b</sup>	1	18	0	0	18
Salivary glands for ATMP	1	2	0	0	2

<sup>a</sup> Retrieved from placenta

<sup>b</sup> Retrieved from pancreas

**Table 23** Distribution and application of other tissues and cells in 2024

Type of tissue/cells	Reporting tissue establishments	Reporting institutions	Distributed transplants				Applied units (from NL)	Recipients
			In NL	In EU	Exports	Total		
Amniotic membranes	2	7	229	51	2	282	115 (115)	115
Pancreatic islets	1	1	18	0	0	18	17 (17)	17
Salivary gland stem cells (ATMP)	1	1	2	0	0	2	2 (2)	2
MSC from fatty tissue		1					4 (0)	1
Nervous tissue	1	1	0	48	0	48	4 (4)	4
Breast milk <sup>a</sup>		1					15,590 ml	

<sup>a</sup> Currently not subject to legislation on substances of human origin

## 5.6 Reports on other tissues and cells

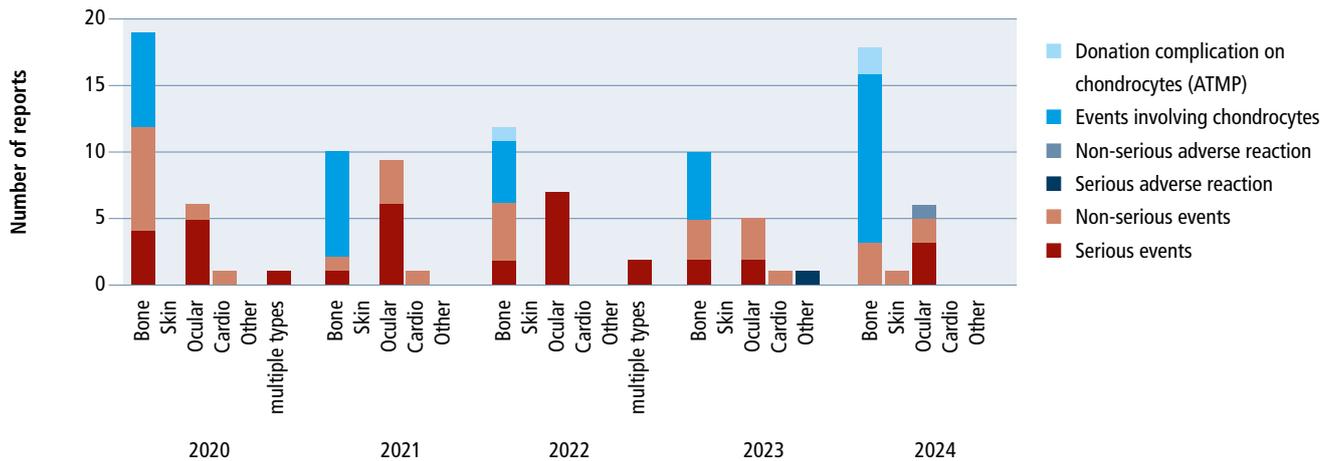


Figure 7 Total reporting on other tissues and cells, 2020-2024

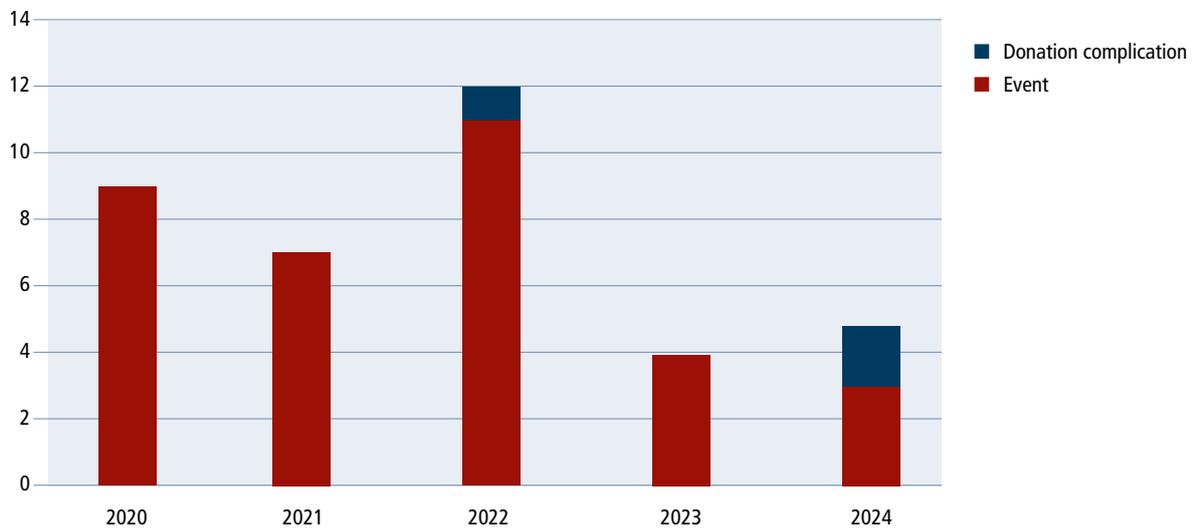


Figure 8 Number of reports (serious according to EU criteria) per year, 2020-2024

In 2024, TRIP received 25 reports concerning other tissues and cells. The reports concern three on musculoskeletal tissue (bone/tendon), six reports on cornea (Figure 7), one on skin and fifteen on chondrocytes. Of the reports on musculoskeletal tissue, two involved loss of tissue (bone) and one near miss (tendon, mix-up of follow-up forms). Of the six reports relating to cornea, three are classified as serious according to the EU definition, due to late information about a contra-indication, refer to Table 24.

Of the 25 reports, 15 are related to a chondrocyte product for the production of an ATMP. The reports show that almost all the cases resulted in the biopsy being lost. For 5-9% of the biopsies do not procure a product for implantation. Two reports concern a donation complication, classified as serious according to the EU definition, refer to Figure 8 and Table 24. Eleven reports concern events in which the cartilage biopsy was lost due to insufficient growth of the correct cells during cultivation, making the preparation for ATMP (chondrocyte products) impossible. This may be due to the biopsy procedure. If a biopsy is not collected from the correct spot, it may contain more synovial cells and fewer chondrocytes. When the biopsy is then cultivated, it is not the chondrocytes that multiply, but the synovial cells. More attention or training in the biopsy procedure for collecting chondrocytes could possibly lead to a reduction in the loss of chondrocyte product. In one report, the biopsy was lost due to bacterial contamination, and

one biopsy due to transportation delay. As a result, in all cases, a biopsy had to be re-taken or another type of treatment had to be started. As mentioned earlier, there is currently no definitive regulation for reporting events during ATMP production involving human tissues and cells. The reports regarding ATMPs are included in Figure 7.

**Table 24** Serious reports (according to EU definition, refer to Annex C) for other tissues and cells in 2024

Type of tissue	Event of donation complications (category and description)
Cornea	Risk of transfer of condition The late microscopic pathology report showed chronic lymphocytic leukaemia (CLL) present in the donor. In macroscopic terms, there was no suspicion; contra-indication for tissue donation; one cornea had already been transplanted
Cornea	Risk of transfer of condition The late pathology report showed that donor may possibly have had neurodegenerative disease; risk of prion disease (contra-indication for tissue donation). One cornea had already been transplanted.
Cornea	Risk of transfer of condition After the results of the final donor autopsy report, a contra-indication (neurodegenerative disease) for tissue donation could not be excluded, but the corneas had already been transplanted.
Chondrocytes	Donation complication — patient 1 experienced bleeding after the biopsy was taken — patient 2 developed a deep venous thrombosis after the biopsy was taken, which required treatment. In both cases seriousness 2, probable, full recovery.

## 5.7 Summary of other tissues and cells

After an assessment of the annual figures, again it reveals gaps in the application figures, not only for musculoskeletal tissue and cornea/sclera in particular, but also for acellular dermis and pericardium. Information has not been received from a number of hospitals and five hospitals reported partially. After closer investigation, the data is not complete for some hospitals. Like last year, an extra 'checkbox' was added to the annual reporting form, allowing institutions to indicate that they did not apply any substances of human origin. Six implantology practices checked this box.

In some reports, the number of recipients was not provided. A number of institutions that apply other tissues and cells reported difficulties in obtaining application data from their administrative records, such as the number of treated patients. The new SoHO regulations now requires SoHO entities to be registered and makes it mandatory for annual figures to be submitted. TRIP will continue to provide support (by way of annual symposiums, workshops, and information on the website).

The number of reports concerning other tissues and cells showed no significant shifts compared to previous years. In 2024, there were a total of five reports classified as serious (according to EU criteria), the same as in 2023.

Fifteen of the reports concerning other tissues and cells, of which two were classified as serious according to the EU definition, related to the cultivation of chondrocytes for ATMPs. Events during procurement or processing can have consequences for the donor, in this case autologous, as a new biopsy must be taken or an additional treatment may be required. The procurement of starting materials is subject to the Wvkl.

# ANNEXES

# A ABOUT TRIP

The TRIP (Transfusion and Transplantation Reactions in Patients) Foundation was established in 2001, with the aim to develop 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.

Biovigilance refers to the systematic monitoring of events and adverse reactions throughout the human body material transplantation chain, with the ultimate goal of achieving safer and more effective use of tissues and cells. European Directive 2004/23/EC makes it mandatory for Member States to report serious adverse events and adverse reactions that may be related to the quality and/or safety of these substances of human origin. This Directive was enshrined in the Dutch Body Material (Safety and Quality) Act (Wvkl) and the Dutch Body Material Decree 2006. The latter was amended in 2012, based on European Directive 2010/53/EC.

The TRIP reporting system for adverse events and adverse reactions related to the use of human body materials meets the requirements laid down in European and Dutch legislation. Figure 9 shows a flowchart of serious and non-serious biovigilance reports in the Dutch healthcare sector. It is plausible that the number of 'non-serious' events and adverse reactions is much higher than the number of serious cases, and that not all institutions submit the less serious reports to TRIP. This is consistent with the high percentage of serious events and reactions in reports to TRIP.

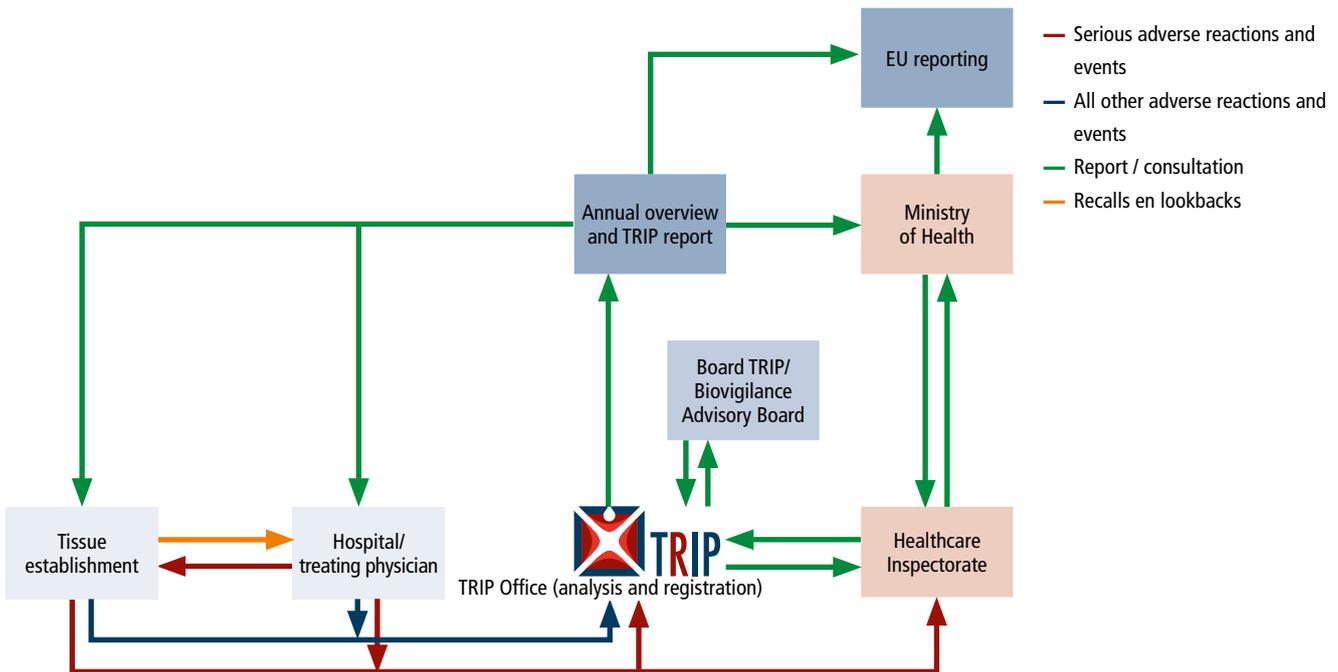


Figure 9 Flowchart of notifications and reports concerning human tissue and cells

All types of human body material from both live and post-mortem donors are subject to the scope of the Wvkl, with the exception of body material that is taken from and returned to the same person in the same surgery procedure. If autologous material is stored or processed in an area other than where the patient stays, the provisions of the Wvkl do apply. Allogeneic applications of tissues are subject to the scope of the Wvkl in all cases.

### **Working method**

TRIP is an independent foundation that cooperates closely with the users of human body materials and tissue establishments. All submitted reports are registered, analysed and reviewed by experts. The results and conclusions are published annually. TRIP additionally collects data annually on the numbers of human body materials processed, distributed and applied at all tissue establishments, hospitals and other relevant healthcare providers in the Netherlands, in accordance with European regulations. The information is aggregated as a denominator for the data collected by TRIP on events and adverse reactions, as well as for the mandatory annual submission to the European Commission. TRIP compiles the required annual overview of serious adverse events and adverse reactions for submission to the European Commission through the Ministry of Health, Welfare and Sport.

Tissue establishments, hospitals and other institutions that provide figures on processing, distribution and/or application, as well as information on events and/or adverse reactions to TRIP, receive an annual participation certificate. TRIP's participation certificate is part of safety awareness in the application of substances of human origin and is therefore consistent with the safety management systems in hospitals. The participation certificate may also be requested during inspections related to obtaining, renewing, or amending an accreditation for tissue establishments or organ banks.

TRIP is supported by a Biovigilance Advisory Committee comprising representatives from relevant medical professional bodies and specialisms. The Biovigilance Advisory Committee provides medical professional and strategic advice with regard to biovigilance to TRIP's board and staff members. The Biovigilance Advisory Committee also anonymously reviews all reports and advises with regard to the annual reports.

# B REPORTING OF EVENTS AND ADVERSE REACTIONS

## **Tissue establishments**

The reporting of serious adverse events and reactions relating to human body materials is laid down in Article 8.1 of the 2006 Dutch Body Materials Decree. This article states that the tissue establishment is responsible for the reporting, investigation, registration and forwarding of information on serious adverse events and reactions that could influence the quality and safety of substances of human origin or that are detected after clinical application and could be linked to the human body materials used. If classified as serious, adverse events and reactions should be reported to TRIP and also to the Health and Youth Care Inspectorate (IGJ). In case a report is assessed as serious by TRIP and has not been reported to the IGJ, the reporting party will be made aware of the obligations regarding reporting to the IGJ.

## **Hospitals, clinics and practices**

Healthcare institutions must report (possible) product-related serious adverse reactions or events to the supplying tissue establishment. In addition, they may also report to TRIP. TRIP checks for duplicate reports from both the reporting healthcare institutions and the tissue establishments, and merges them if any are found.

In the event of a 'calamity', possibly caused by human body material, the hospital must also inform the IGJ in accordance with the Healthcare Quality, Complaints and Disputes Act (Wet kwaliteit, klachten en geschillen zorg, Wkkgz).

## **Reporting to the Health and Youth Care Inspectorate**

In the Netherlands, the IGJ has been designated as the competent authority for receiving reports of serious events and adverse reactions. In agreement with the Ministry of Health, Welfare and Sport (VWS) and the IGJ, TRIP takes care of the registration of all events and adverse reactions related to human body materials. TRIP's digital reporting system facilitates the forwarding of serious events and adverse reaction reports to the IGJ. Reporting parties only need to submit data once and can opt to forward the report to the IGJ at their own discretion.

The reporting of serious events and adverse reactions is different from reporting a calamity in accordance with the Healthcare Quality, Complaints and Disputes Act. Calamities have a different definition and the IGJ has its own specific procedure for dealing with calamities. Figure 10 shows a flowchart of the reporting.

Serious events or adverse reactions within the scope of the Wvkl are best submitted to the IGJ through the TRIP reporting system. This channels the reports to the inspectors involved in enforcement of the Wvkl and reduces the likelihood of reports being (possibly incorrectly) treated as being within the scope of the Healthcare Quality, Complaints and Disputes Act (Wkkgz). However, reports will always be assessed on healthcare quality aspects as well, and can, if required, be handled as a calamity.

## **Reports regarding ATMPs**

In the production of ATMPs from human body materials, human cells or tissues are used as starting material. The quality of this material may lead to adverse reactions in recipients of this type of medicinal product. Events can have consequences for both the patient and donor, e.g. loss of tissues and cells.

Current vigilance systems facilitate part of the chain of tissue donation, ATMP production and product administration, but certain adverse events have not yet been addressed in existing regulations. To promote the safety and quality assurance of ATMPs, it is necessary to design a clear vigilance system that covers the entire ATMP chain from donation up to and including follow-up after administration.

Based on international and national legislation, TRIP is collaborating with Lareb, the designated agency where serious and non-serious adverse reactions of medicinal product are reported subject to the Medicines Act (Geneesmiddelenwet, Gmw), on the design of a comprehensive vigilance framework for ATMPs based on human body materials. This creates a link between biovigilance and pharmacovigilance. After consultations in the field, formalised cooperation between both vigilance systems is necessary to successfully implement the proposal and to increase knowledge of events and adverse reactions in the ATMP chain.

**Definitions of categories of events and reactions and reporting criteria**

All definitions of the categories used for events and reactions, as well as reporting criteria for serious events or reactions, can be found on the TRIP website.

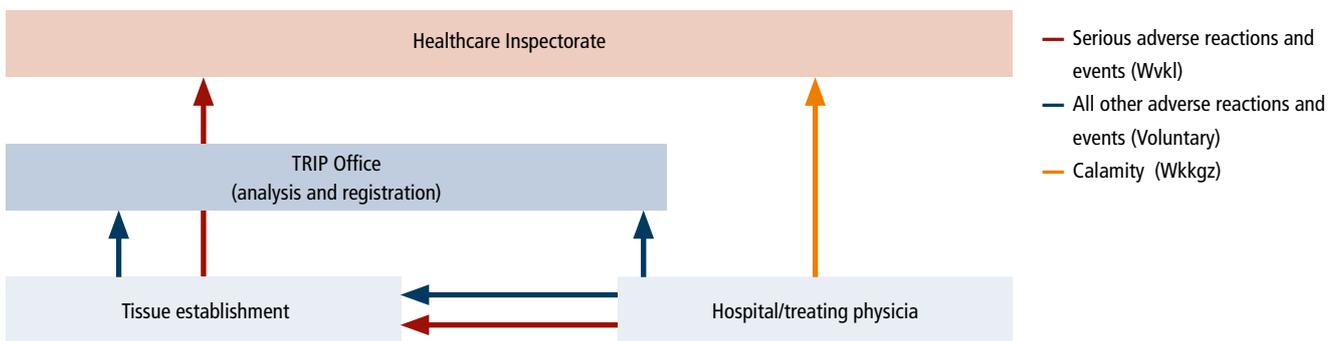


Figure 10 Flowchart of reports regarding human body materials

## C SUMMARY OF EVENTS AND ADVERSE REACTIONS REPORTED TO THE EU

Table 25 shows the number of serious events and adverse reactions related to human tissues or cells reported or completed in 2024. In all, 37 reports (+ six completed in 2024) were assessed as serious. These are serious adverse reactions, serious events and serious donation complications. Three serious reports had not been completed prior to the final submission date and will be included in the overview next year. This explains the discrepancies between the reports by MAR (two reports) and the HSC (one report)

**Table 25** Overview of known or completed serious events and adverse reactions that were reported to the EU in 2024

Type	Serious adverse reaction	Serious event*	Serious donation complication	Total serious reports
Semen	0	4	0	4
Oocytes	0	5	11	16
Embryos	0	5	0	5
HSC and cells for therapeutic purposes	7	3	3	13
Ocular tissue	0	3	0	3
Musculoskeletal tissue	0	0	2	2
<b>Total</b>	<b>7</b>	<b>20</b>	<b>16</b>	<b>43</b>

\* 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. These include proven and possible inheritance of a congenital anomaly when using donor gametes or embryos, post-transplantation contamination of a recipient with a micro-organism that requires treatment or prolonged hospitalisation, re-transplantation after transplantation with an incorrect product or additional mobilisation, apheresis or autologous bone marrow aspirations for stem cell transplant(s) and an aborted procedure where the patient is already under anaesthesia or has been conditioned for transplantation.

# D LIST OF TERMS AND ABBREVIATIONS

Apheresis	Type of blood donation involving the selective mechanical withdrawal of specific blood components while returning the remaining components (by infusion) to the donor or patient
Allogeneic	Originating from a donor
ATMP	Advanced Therapy Medicinal Product
Autologous	Originating from a person's own body or removed from and applied to the same person
CAR T-cells	Chimeric Antigen Receptor T-cells
Chondrocytes	Cartilage cells
Cryopreservation	The process of freezing and subsequent storage of frozen tissues and cells
Distribution	Transport and delivery of body material intended for application on humans
DLI	Donor Lymphocyte Infusion
DMEK	Descemet Membrane Endothelial Keratoplasty
EU	European Union
GMP	Good manufacturing practices
HSC	Hematopoietic stem cells
ICU	Intensive Care Unit
IGJ	Health and Youth Care Inspectorate (Inspectie Gezondheidszorg en Jeugd)
Imputability	Attributability
IUI	Intra-uterine insemination
IVF	In vitro fertilisation
Lareb	Dutch National Registration and Evaluation of Adverse Drug Reactions; reporting and knowledge expertise centre for adverse reactions to medicinal products, vaccines and other health products
Matchis	Dutch registry for stem cell donors
MESA	Microsurgical epididymal sperm aspiration
NL	The Netherlands
NTS	Netherlands Transplantation Foundation (Nederlandse Transplantatie Stichting)
Oocytes	Ova
Organ bank	Tissue establishment with accreditation to receive human body materials after procurement
PBSC	Peripheral blood stem cells
PESA	Percutaneous epididymal sperm aspiration
Procurement	Process by which body material or a donated organ becomes available
Semen	Sperm
SoHO	Substances of Human Origin
TIL	Tumour-infiltrating lymphocytes
TCR	T-cell receptor (gene therapy)
TESE	Testicular sperm extraction
Tissue establishment	A tissue bank, hospital department or other institution that is active in the processing, preservation, storage or distribution of human body material
VWS	Dutch Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport)
Wkkgz	Dutch Healthcare Quality, Complaints and Disputes Act (Wet kwaliteit, klachten en geschillen zorg)
Wvkl	Dutch Body Material (Safety and Quality) Act (Wet veiligheid en kwaliteit lichaamsmateriaal)