TRIP REPORT 2021

BIOVIGILANCE

EXTENDED VERSION

TRIP
Hemo- en biovigilantie

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TRIP Report 2021 Biovigilance is published under the responsibility of the TRIP
(Transfusion and Transplantation Reactions In Patients) Foundation.
This report was produced with the help of a grant from the Dutch Ministry of Health, Welfare and Sport.

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1 INTRODUCTION

1.1 General

In this 2021 Biovigilance Report, TRIP presents all reports of adverse events and reactions that occurred in association with the procurement, processing and application of human tissues and cells. It also provides a picture of the numbers of available and used cell and tissue products for transplantation and of tissue and healthcare establishments participating in the national biovigilance network. This is the fifteenth TRIP biovigilance report.

To determine the impact of the reports of adverse events and reactions, it is crucial to know how many tissues and cells have been processed, distributed and applied. Tissue establishments and organ banks, which receive, store, process and distribute body material, are legally obliged to report their activities. Transplant centres applying tissues and cells, such as hospitals and implantology practices, are not legally obliged to declare their use of human body material. Over the years, TRIP has learned that it is sometimes rather difficult for transplant centres to collect complete data and that it is not always clear what information TRIP wishes to receive.

Partly because of this, TRIP exerted itself in 2021 to help improve the completeness and accuracy of the annual reports from tissue establishments, organ banks and transplanting centres. TRIP has further clarified the terms 'processing', 'distribution' and 'application' (see Section 1.2). This further clarification of definitions, as well as of the routes for reporting adverse reaction and event reports, has led us to revise the structure of the annual biovigilance report.

1.2 Clarification of definitions

The term 'processing' means all operations of a tissue establishment involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications. A distinction is made between material procured at the tissue establishment's own clinic, from the Netherlands (NL, originating from a tissue establishment in the Netherlands other than the clinic's own), from the European Union (EU, originating from a tissue establishment in a EU member state other than the Netherlands), or from outside the EU in the case of import of tissues or cells from countries outside the EU.

The term 'distribution' means transport and delivery of tissues or cells intended for direct human application by a tissue establishment to the organization responsible for direct human application. A distinction is made between distribution within the Netherlands, within the EU (transport and delivery of tissues or cells to an organization outside the Netherlands and within the EU), and outside the EU (export: transport and delivery of tissues or cells to an organization outside the EU). Important for tissue establishments delivering units for use in patients in their own clinic is that, for international reporting, these units should be factored in under 'distribution within the Netherlands'.

Transport and delivery of tissues or cells to another tissue establishment, where, for example, reprocessing takes place, is not considered distribution. Distribution figures are gathered only by the tissue establishment delivering to the establishment applying the tissues or cells. If tissue is transported outside the EU for processing under contract and subsequently returned to the Netherlands, this also does not fall under the definition of distribution according to the EU Directive (2004/23/EC).

Finally, the definition 'transplantation/human application' was also reviewed. Transplantation/human application means the use of tissues or cells in a human recipient. The classification of the origin of the applied material is determined by the country of residence (accreditation) of the tissue establishment delivering the tissue to the clinic for human application. The tissue may come from a hospital's own tissue establishment, from the Netherlands (NL, distributed by a tissue establishment in the Netherlands other than the hospital's own) or from the EU (distributed by a tissue establishment outside the Netherlands but within the EU). Under current legislation it is not permitted to use tissues and/or cells from outside the EU directly for human application. This always requires the agency of an EU-based tissue establishment (very few and urgent cases excepted).

1.3 Main findings in 2021

1. The number of serious adverse events involving reproductive tissues or cells in 2021 was 2.03/100,000 processing operations. In addition one serious congenital abnormality related to the application of donor semen was reported this year.

2. The number of reported serious adverse events related to hematopoietic stem cells was 0.75/1,000 grafts processed in 2021. One serious complication of autologous stem cell donation and one serious adverse event related to the application of cord blood were reported this year.

3. There were seven serious adverse events involving other tissues and/or cells, in one case in combination with an adverse reaction. One event involved a femoral head (0.4 cases per 1,000 units processed), three events involved ocular tissue (0.7 case per 1,000 units processed) and another three events involved the risk of transfer of a condition.

4. Stricter application of the definitions of 'processing' and 'distribution' has led to shifts in the annual figures received.

5. Data on other tissues and cells were lacking from the data of five organisations responsible for human application and data on the number of recipients from the data of several institutions. Consequently, the overall picture of the number of patients treated with human tissues and/or cells in the Netherlands is still incomplete.

6. In some reports, the interval between the observation and reporting of an event or adverse reaction was several months. A large interval between observation and reporting may result in not all relevant information being retrievable.

7. In 2021, the Inspectorate for Healthcare and Youth (IGJ) revoked the accreditation of the last tissue establishment processing and storing autologous stem cells from cord blood (CBUs). There is no longer any activity in The Netherlands in the field of autologous cord blood processing.

2 RECOMMENDATIONS

2.1 Recommendations

	Recommendations	Who?
1	Give shape to biovigilance within the healthcare institution so that there is clarity about the use of human body material, and adverse events and reactions are reported through the appropriate channels; all this with the aim of improving the safety and quality of the application of human body material.	Boards and professionals involved in the application of human tissues and cells in hospitals and clinics.
2	In consultation with supervisory authorities and tissue establishments, work towards clear, simple and usable measures for activities within tissue establishments or transplant centres, and thus towards denominators for adverse events and reactions in the tissue and cell transplantation chain.	TRIP in consultation with the regulatory authorities and tissue establishments
3	Draft guidelines for reporting adverse events and reactions associated with new therapies that are not yet covered by current legislation, so that vigilance is covered from donation up to and including application.	TRIP in consultation with regulatory authorities and relevant institutions
4	Ensure more timely reporting of adverse events and reactions so that complete and adequate analysis of the cause and circumstances is possible.	Biovigilance staff and officers

2.2 Follow-up to previous recommendations

1 Tissue establishments, organ banks and transplant centres should improve the completeness and accuracy of their annual reports. TRIP should support this process by clarifying definitions, providing training courses and adapting and optimizing annual report forms. (Recommendation in the 2020 TRIP Biovigilance Report)
Development: In consultation with VWS and IGJ, TRIP further elaborated the definitions of distribution and processing in 2021 (see Section 1.2) and adapted the annual report forms. As a result of the collection of annual data in 2021, it became clear that more attention should be given to further elaborating and explaining the definitions and quality criteria the annual reports should meet.

2 For users of new products and medicines prepared from human tissue such as ATMPs, TRIP should, in consultation with IGJ, Lareb and VWS, draw up unambiguous and clear instructions for the criteria and routes for reporting adverse events and reactions. (Recommendation in the 2020 TRIP Biovigilance Report)
Development: Discussions with IGJ, Lareb and VWS started in early 2022.

3 REPRODUCTIVE TISSUES AND CELLS

3.1 Institutions involved

In 2021, there were 16 IVF laboratories with organ bank accreditation registered in the Netherlands. One of these centres opened in 2021. Furthermore, 51 semen laboratories had tissue establishment or organ bank accreditation. These institutions are mostly clinical chemistry laboratories, where partner semen is processed for intrauterine insemination (IUI). Institutions with organ bank accreditation are also authorized to receive donor semen after procurement.

All IVF laboratories and semen laboratories provided data on the processing, distribution and application of reproductive tissues and cells in 2021.

3.2 Activities

Tables 1 and 2 show the figures for processing, distribution and application of reproductive tissues and cells based on the annual activity reports in 2021. The definitions of 'processing', 'distribution' and 'application' have been explained in Chapter 1.

Reproductive tissues and cells can be processed several times, not only after collection but also at a later time when processing cryopreserved tissue. The number of processing operations is therefore higher than the number of units distributed or applied. The processing figures below specify the origins of the tissues (from the Netherlands, from the EU, or from outside the EU).

TRIP adheres to the European definition of distribution, in which transport between tissue establishments is not regarded as distribution. In line with the definition, units transported and delivered for use at the institution itself were recorded as distribution. Differences from previous years are therefore partly explained by increased uniformity in data collection. Most notable here is the decrease in distribution of partner and donor semen to other countries, and the reduction of embryo distribution outside the Netherlands to zero.

Table 1a Processing and distribution of semen and testicular tissue

Type of semen or testicular tissue	Tissue establishments	Unit	Processed			Distributed		
			From NL	From EU	Outside EU	In NL	In EU	Outside EU
Partner semen fresh and cryo	67	Sample/straws	41193	1	0	28893	17	0
Donor semen fresh and cryo	18	Sample/straws	4810	5779	0	9611	21	0
Partner semen MESA/PESA/TESE	9	Puncture/biopsy	1089	1	0	n/a	n/a	n/a
Donor semen MESA/PESA/TESE	1	Puncture/biopsy	3	0	0	n/a	n/a	n/a
Testicular tissue	3	Graft	13	0	0	0	0	0

n/a = not applicable

Table 1b Processing and distribution of oocytes and ovarian tissue

Type of oocytes or ovarian tissue	Tissue establishments	Unit	Processed			Distributed		
			From NL	From EU	Outside EU	In NL	In EU	Export Outside EU
Own oocytes, fresh and cryo	16	Oocyte	130142	17	0	n/a	n/a	n/a
Donor oocytes fresh and cryo	12	Oocyte	2608	0	0	n/a	n/a	n/a
Ovarian tissue	4	Graft	654	0	0	16	0	0

Table 1c Processing and distribution of embryos

Type of embryo	Tissue establishments	Unit	Processed			Distributed in NL
			From NL	From EU	Outside EU	
Embryos, own oocytes and partner semen	16	Embryo	53387	0	0	26778
Embryos, own oocytes and donor semen	14	Embryo	5207	0	0	1654
Embryos, donor oocytes and partner semen	12	Embryo	1051	0	0	408
Embryos, donor oocytes and donor semen or donated	6	Embryo	745	0	0	109

Table 2 Application of reproductive tissues and cells

Type	Recipients	Unit	Application
Partner semen	12521	Insemination	28679
Donor semen	3173	Insemination	9840
Embryos, own oocyte with partner semen	13990	Embryo	26770
Embryos, own oocyte with donor semen	883	Embryo	1654
Embryos, donor oocyte and partner semen	238	Embryo	408
Embryos, donor oocyte with donor semen or donated	92	Embryo	109
Ovarian tissue	2	Graft	16
Testicular tissue	0	Graft	0

Figures 1a, 1b and 1c show the application data over the period 2017-2021. After the COVID-19-related decline in 2020, the year 2021 saw an increase in the number of inseminations with partner semen. The number of placed embryos from own oocytes and partner semen is also higher than in previous years.

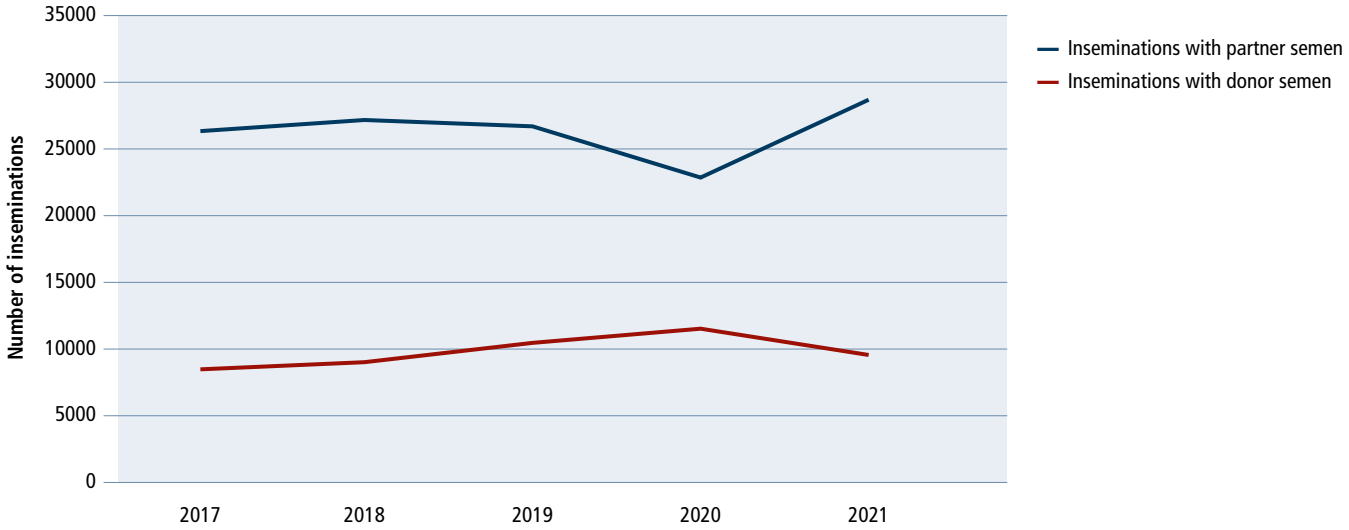

Figure 1a Number of inseminations with partner semen and donor semen, 2017-2021

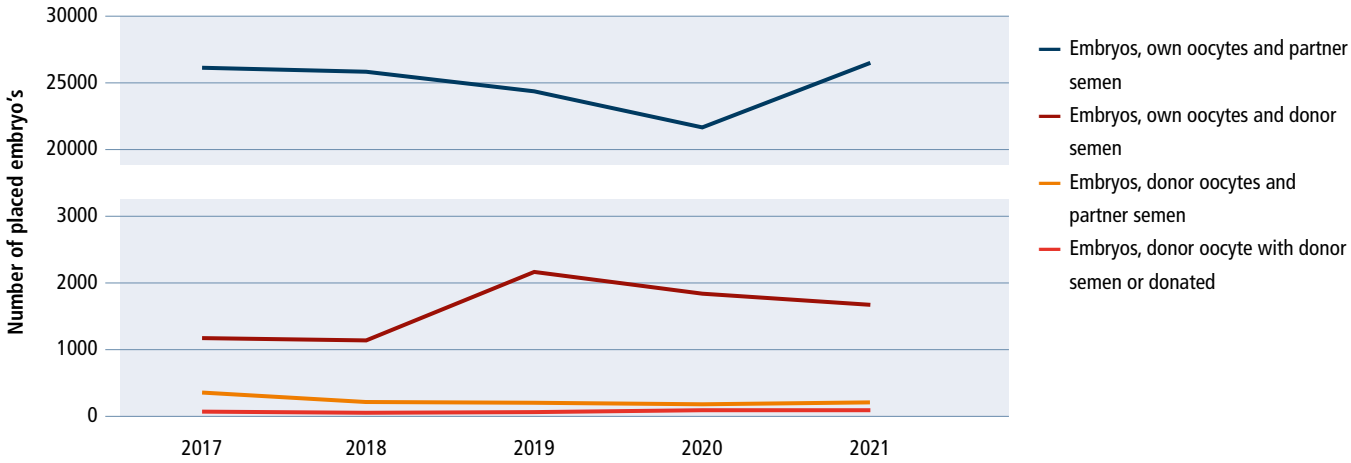

Figure 1b Number of embryos placed, 2017-2021

In reporting year 2017, only the total numbers of placed embryos were reported, with no breakdown by origin. The current breakdown by origin is an estimate based on average distributions in 2016 and 2018.

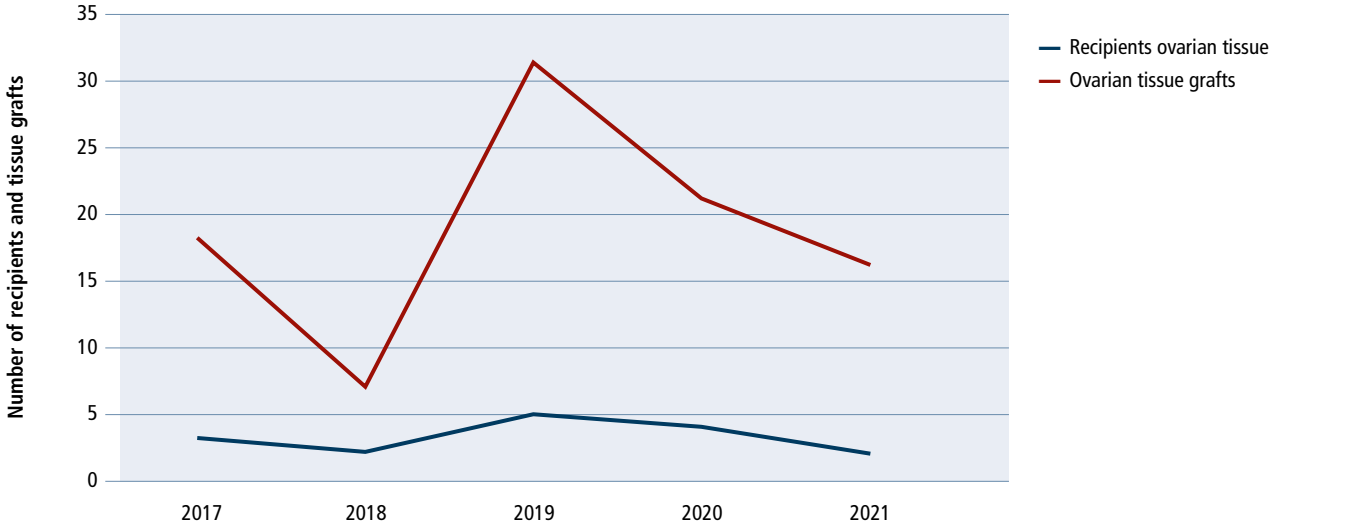

Figure 1c Number of tissue grafts replaced, 2017-2021

3.3 Reports

In 2021, TRIP received 45 reports about adverse events or reactions during the processing and application of gametes and embryos in medically assisted reproduction. Six reports were assessed as definitely not related to the medically assisted reproductive process and are not further considered in this biovigilance report. The 39 reports with higher imputability can be subdivided into 26 adverse events with or without adverse reactions, one adverse reaction, and 12 donation complications (Table 3). One of these reports concerns a late report of a non-serious event which occurred in 2020. This report is where relevant included in the figures.

Figure 2 summarizes all reports of adverse events, adverse reactions and donation complications with imputability unlikely or higher, submitted in the period 2017-2021. Adverse events with severity grade 2 or higher and imputability certain, probable or possible are reported to the EU, and are shown as 'serious EU'. The EU criteria for a serious adverse event are used to assess whether an event should be reported to the EU.

Table 3 Reports of adverse events and adverse reactions with imputability certain, probable, possible or unlikely concerning reproductive tissues and cells by fertility lab type in 2021 and a late report from 2020

Fertility laboratories	Number of institutions	Institutions reporting	Total number of reports (serious EU)	Events (serious EU)	Adverse reactions (serious EU)	Donation complications (serious)
IVF laboratories	16	8 (50%)	24 (12)	15 (4)	1 (0)	8 (8)
Semen laboratories	51	8 (16%)	15 (5)	11 (2)	0	4 (3)
Total	**67**	**16 (24%)**	**39 (17)**	**26 (6)**	**1 (0)**	**12 (11)**

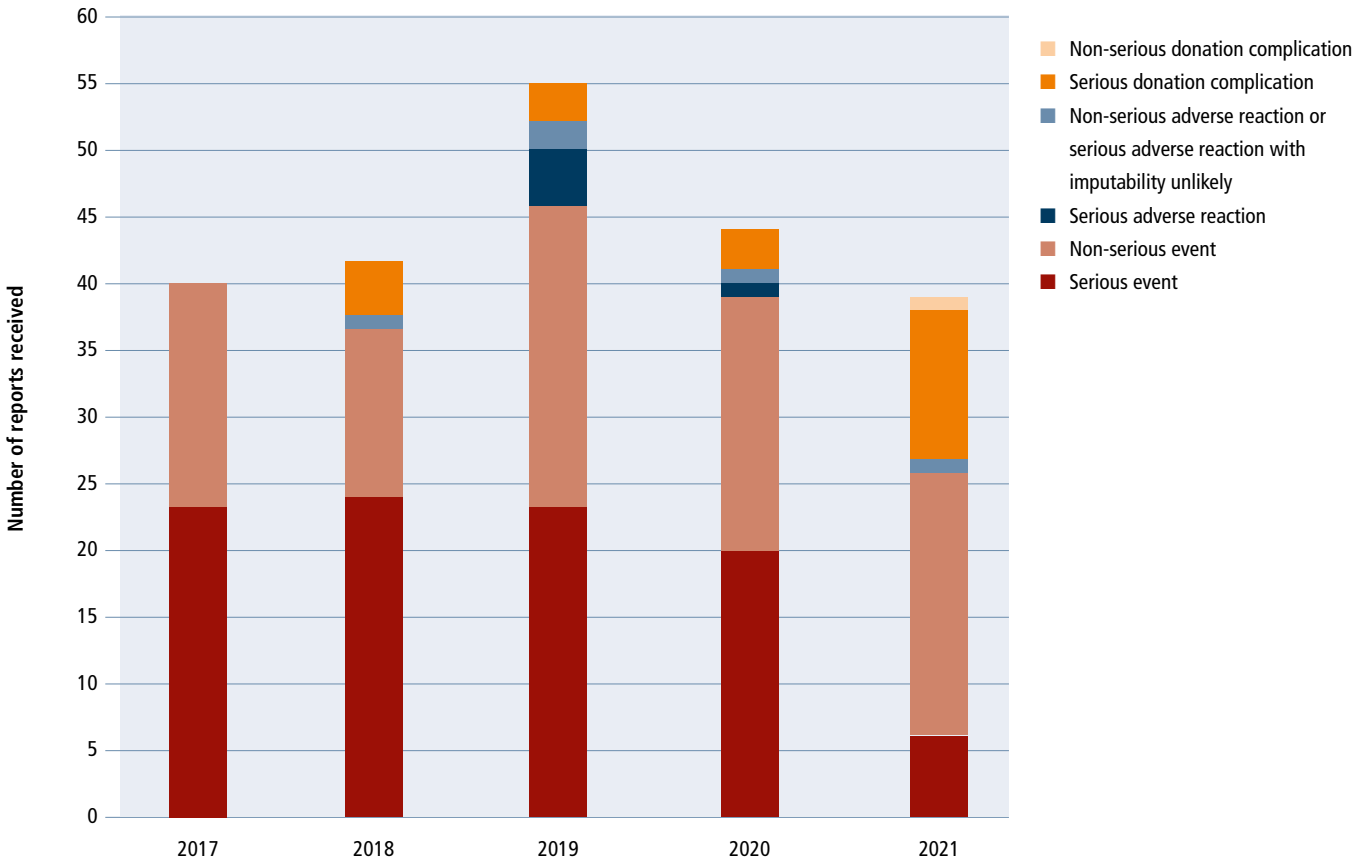

Figure 2 Reports* of events and adverse reactions with imputability certain, probable, possible or unlikely concerning reproductive tissues and cells
* Serious adverse events according to EU criteria and serious adverse events ≥grade 2 with imputability certain, probable or possible

Events

In 2021, TRIP received 26 reports of adverse events relating to the processing and application of reproductive tissues and cells, including a late report from 2020. Six reports were classified as serious according to EU criteria. Table 4 provides an overview of all occurrences reported by tissue or cell type.

Figure 3a shows the number of serious events per 100,000 processing operations broken down by event category, over the period 2017 to 2021. The congenital anomalies assessed as serious according to EU classification over the period 2017 to 2021 are plotted against the number of donor gamete applications in Figure 3b. Serious events are discussed in the following sections.

Table 4 Overview of events in reproductive tissues and cells in 2021 and a late report from 2020

Type of tissue or cells	Adverse event category	Number of reports of events (serious EU)	Late report from 2020 (serious EU)
Semen	Other incident	5 (0)	
	Congenital abnormality	10 (1)	
	Near miss	1 (0)	1 (0)
	Bacterial contamination of product	1 (0)	
Oocytes	Loss of tissues or cells	4 (3)	
	Near miss	1 (0)	
Embryos	Loss of tissues or cells	2 (1)	
	Near miss	1 (0)	
	Bacterial contamination of product	1 (1)	

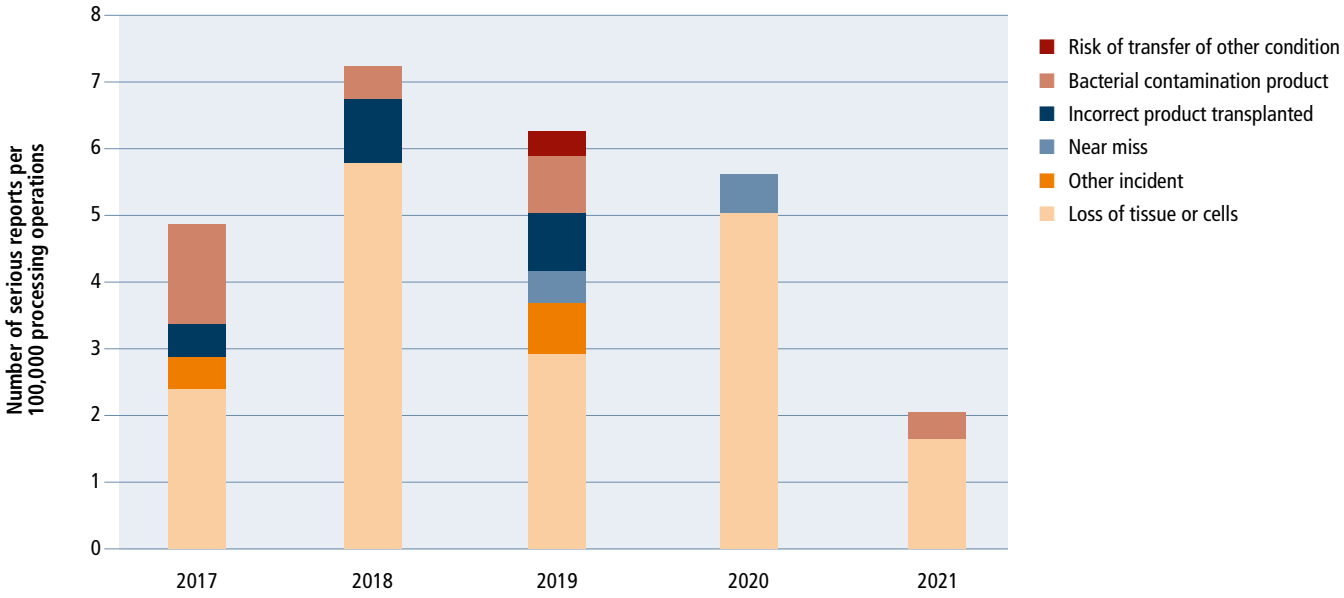

Figure 3a Number of reports per adverse event category concerning reproductive tissues and cells per 100,000 processing operations, 2017-2021

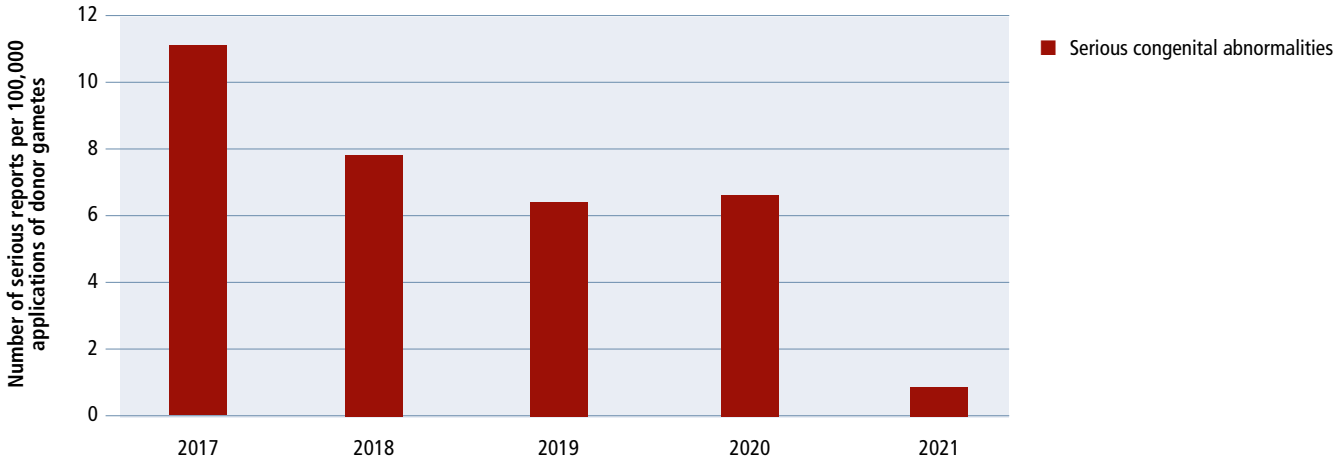

Figure 3b Number of serious congenital abnormalities per 100,000 applications of donor gametes, 2017-2021

Loss of tissues or cells

In 2021, TRIP received four serious reports concerning loss of oocytes or embryos, involving the loss of a complete reproductive cycle (Table 5). In one report, the loss was related to temperatures during the transport of oocytes in a transport box (see Case 1). In the remaining three serious loss cases, the loss of the material occurred during processing. The number of adverse events with loss of tissues and/or cells fluctuates over the years, reaching 1.63 cases per 100,000 processing operations in 2021 (Figure 3a).

Table 5 Description of serious reports of loss of tissues or cells in 2021

Type of gamete or embryo	Phase in process	Description of event
Oocyte	Transport	See Case 1. During the transportation of oocytes, the temperature in the transport case rose to almost 50 ˚C. The transport box was not equipped with an independent temperature logger, so temperatures during transportation could not be monitored. The oocytes were lost.
Oocyte	Processing	Because of abnormal aspects of the oocyte, the quality of the gamete after puncture was determined immediately in the first wash dish rather than in the final culture dish. The oocyte and wash dish were discarded.
Oocyte	Processing	When a patient's oocytes were placed in liquid nitrogen, the tube was found not to fit into the canister, which was already full. When the tube was removed, carriers from two other patients came up with it and fell out of the canister.
Embryo	Processing	During embryo freezing, when additional liquid nitrogen was added, there was a malfunction in the freezing device, which accelerated the programme. The embryos did not survive the thawing process.

Case 1

After a routine transport of oocytes in the context of IVF treatment, the temperature in the transport box was almost 50 ˚C on arrival at the clinic. The tube of water that had been added to check the temperature confirmed this reading. On departure, a temperature of 36 ˚C was measured. However, the transport box was not equipped with an independent temperature logger. The temperature during transport could therefore not be monitored. The follicle tubes were refrigerated. Due to denaturation of proteins at elevated temperatures, it was decided not to use the oocytes.

The transport box was immediately taken out of circulation and checked by the supplier. No abnormalities were found. Periodic checks of the box had been carried out as agreed. Prior to the incident, the transport box had been used several times without any problems. Since this incident, the temperature in each and every transport box is measured before transport and recorded in the EHR.

Congenital abnormality
In the reporting year 2021, one report was registered as a serious congenital abnormality, which occurred several years ago. In this case, it was found that the semen donor was a carrier of a recessive gene mutation, which combined with the mother's carrier status led to the birth of a neonate with an autosomal recessive metabolic disorder. Two children of this donor with different mothers have been diagnosed with the same disorder.

In 2021, fewer reports were assessed as relating to serious congenital abnormality compared to previous years, both in absolute terms and plotted against the number of applications of donated gametes or embryos. Part of the explanation is the fact that, in 2018, imputability began to play a role in assessing the severity grade of congenital anomalies, with reports with imputability excluded or unlikely being assessed as not serious.

Bacterial contamination of product
TRIP received only one serious report of bacterial contamination. It concerns an adverse event involving several pairs; the follow-up of these pairs was ongoing at the time this report was written.

Adverse reactions
In 2021, TRIP did not receive any reports of serious adverse reactions following the application of reproductive tissues and cells with imputability certain, probable or possible. Figure 4 shows reports of serious adverse reactions with imputability possible or higher over the period 2017-2021.

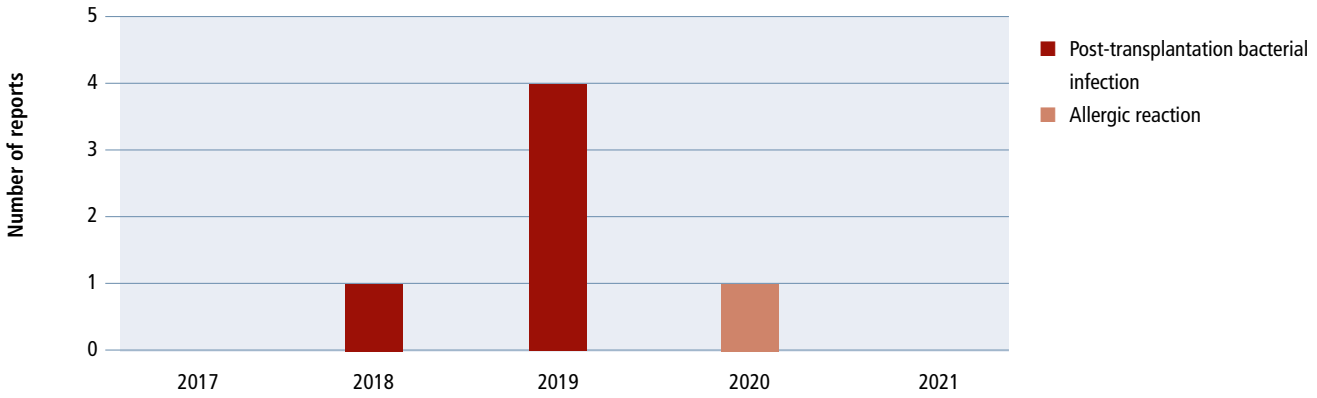

Figure 4 Reports of serious adverse events in medically assisted reproduction with imputability certain, probable or possible, 2017-2021

Donation complications
Donation complications are attracting increasing international attention. Monitoring donation complications leads to better information for patients and donors and contributes to safety in the chain of procurement and clinical application of human tissues and cells. Donation complications have been reported to TRIP since 2015. Under the Dutch Body Material Safety and Quality Act (WVKL), reporting complications during procurement of human tissues and cells is mandatory when the complication has an impact on the safety and quality of the donated tissues and cells. Central reporting of donation complications that do not affect the safety and quality of the material is not included in the Act. The reports TRIP receives are therefore not a reflection of the total number of donation complications occurring in the Netherlands.

The majority of donation complications reported to TRIP involve ovarian hyperstimulation syndrome (OHSS). OHSS is a potentially life-threatening complication that can occur after hormonal stimulation of the ovaries in the context of medically assisted reproduction. In 2021, TRIP received nine reports of OHSS after oocyte puncture for autologous application, all of which involved hospitalization. Furthermore, one case was reported in which OHSS occurred, followed by adnexal torsion. In addition, an infected cyst, detected after oocyte puncture in the context of an IVF procedure, led to ICU admission in one patient.

3.4 Conclusion

Adherence to the definitions of 'processing', 'distribution' and 'application' as presented in the European directive has led to a change in the annual reports, affecting in particular the distribution figures.

After the COVID-19-related decline in 2020, 2021 saw a higher number of applications of reproductive tissues and cells. More inseminations with partner semen were performed, and the number of placed embryos from own oocytes and partner semen was also higher than in previous years.

The pick-up in fertility care is not reflected in the number of reports TRIP received. There were fewer serious reports in 2021, both in absolute terms and plotted against the number of processing operations.

4 HEMATOPOIETIC STEM CELLS AND OTHER THERAPEUTIC CELLS

4.1 Institutions involved

In 2021, 14 tissue establishments in the Netherlands were authorized to collect, process, store and/or distribute hematopoietic stem cells (HSCs) and other therapeutic cells. These institutions include nine laboratories that, besides the required tissue establishment license, also have an organ bank license, with which they are also authorized to receive human tissues or cells after procurement. Two of the tissue establishments are exclusively active in the field of processing cells obtained from bone marrow or peripheral blood for the production of medicinal products. In 2021, the Healthcare and Youth Inspectorate (IGJ) revoked the accreditation of one tissue establishment, which processed and stored autologous stem cells from umbilical cord blood. The body material stored was deemed unsuitable for human application by IGJ due to critical shortcomings in the quality and safety of the stem cells. As a result, there's no activity in processing of autologous cord blood in the Netherlands. TRIP received no report (on possible activities in 2021) from the tissue establishment concerned. One tissue establishment submitted an incomplete report, which did include the figures for the total number of units, but did not provide any data on the number of recipients and the origins of the grafts. This brings the participation of tissue establishments using stem cells to 86% (12/14) in 2021, i.e. below 100% for the first time since 2014. One new accreditation was granted to an organization that further processes cord blood stem cells for the production of medicinal products, keeping the total number of tissue establishments at 14.

Stem cell products from unrelated donors are delivered to eight academic transplant centres through Matchis, mostly via the stem cell laboratories (tissue establishments) of the respective hospitals. Peripheral blood stem cells (PBSCs), bone marrow (BM) and donor lymphocyte infusions (DLIs) from unrelated Dutch donors are collected, by Matchis, at two academic hospitals in the Netherlands. There is one tissue establishment that processes, stores and distributes unrelated cord blood units (CBU). Figure 5 shows the national and international flows of unrelated stem cell transplants to and from Dutch donors and recipients.

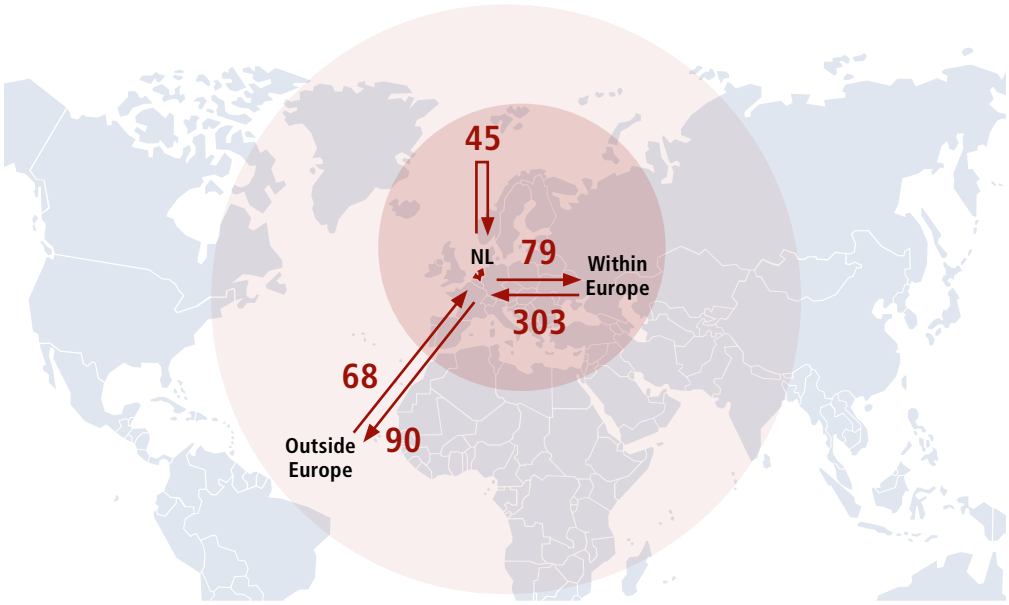

Figure 5 Number of unrelated stem cell transplants (peripheral blood stem cells, bone marrow and umbilical cord blood units) from and to Dutch donors and recipients in 2021, based on reports received from Matchis and the Cord Blood Bank.

4.2 Activities in 2021

Table 6 shows the number of processed hematopoietic stem cell transplants obtained from peripheral blood, bone marrow and cord blood. 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 have been counted several times in the processing figures. (See Chapter 1 for the definition of 'processing'.) One tissue establishment was unable to submit data on the origin of the processed stem cells. This is why these transplants were only included in the total numbers in the report of processed PBSC units from unrelated donors.

The distribution and application of stem cells is shown in Table 7. The European definition of distribution as explained in Chapter 1 has been adhered to more strictly this year. Transport between two tissue establishments is not included in the definition; the distribution figures are therefore lower. This applies especially to unrelated units as these are first sent to other tissue establishments prior to administration. The report of one tissue establishment was not included in the number of recipient figures. Its figures for transplanted units were, however, included in the total.

Cells for other therapeutic purposes, donor lymphocyte infusions excepted, are in many cases procured for the production of advanced therapy medicinal products (ATMPs). Donation, procurement and testing of human tissues and cells that serve as starting material for these ATMPs fall under the Dutch Body Material (Safety and Quality) Act (WVKL). The manufacturing process falls under Good Manufacturing Practices (GMP) legislation and the product after registration under the Medicines Act. Because of the responsibilities under the WVKL, TRIP wants to get a complete picture of the reporting of activities related to the procurement of the starting material in the coming years (see Table 8). The submission of data on distribution and final application for medicines is optional, but has been increasing in recent years (see Table 9). Reports of serious adverse events and complications related to the procurement of body material that do not affect the quality of the material, are not yet regulated by legislation, but TRIP would like to receive them pending additional regulations. Reports of known adverse reactions in the application of medicines are not TRIP's responsibility. TRIP is consulting with bodies such as Lareb, VWS and parties in practice to arrive at an unambiguous route for reporting.

Table 6 Processing of hematopoietic stem cells in 2021

Type of cells	Stem cell laboratories	Processing of transplants			
		From NL	From EU	From non-EU	Total
PBSCs					
PBSCs, autologous	11	1424	0	0	1424
PBSCs, related	8	209	0	0	209
PBSCs, unrelated	8	272	197	26	520*
Bone marrow					
Bone marrow, autologous	2	21	0	0	21
Bone marrow, related	7	54	0	0	54
Bone marrow, unrelated	5	52	23	1	76
Cord blood					
Cord blood, autologous	0	0	0	0	0
Cord blood, related	1	1	0	0	1
Cord blood, unrelated	4	26	32	6	64

* Total PBSCs unrelated, including 25 units of unknown origin

Table 7 Distribution and application of hematopoietic stem cells in 2021

Type of cells	Stem cell laboratories	Bags distributed/ delivered*	Transplant centres	Bags applied*	Recipients#
PBSCs					
PBSCs, autologous	11	4096	12	4091	985
PBSCs, relative	8	370	8	370	146
PBSCs, unrelated	8	714	8	714	298
Bone marrow					
Bone marrow, autologous	2	5	2	5	2
Bone marrow, related	7	58	7	58	42
Bone marrow, unrelated	5	57	5	57	51
Cord blood					
Cord blood, autologous	0	0	0	0	0
Cord blood, related	0	0	0	0	0
Cord blood, unrelated	3	52	3	51	30

* Two stem cell laboratories reported the number of transplants rather than the number of bags, 1 transplant was counted as 1 bag

\# One institution did not report the number of recipients of PBSCs and BM allogeneic related.

Table 8 Processing of other therapeutic cells in 2021

Type of cells	Laboratories	Transplants processed			
		From NL	From EU	From non-EU	Total
Lymphocytes (DLIs) related	8	68	0	0	68
Lymphocytes (DLIs) unrelated	7	80	82	14	176
Mesenchymal stem cells, autologous	0	0	0	0	0
Mesenchymal stem cells, unrelated	2	18	0	0	18
Mononuclear cells	10	194	0	299	493
Expanded cells from cord blood	1	5	0	0	5

Table 9 Application of other therapeutic cells in 2021

Type of cells	Laboratories	Distribution (unit = bags)	Treatment centres	Units applied	Number of recipients
Lymphocytes (DLIs) related	8	82	8	82	52*
Lymphocytes (DLIs) unrelated	7	220	7	220	151*
Mesenchymal stem cells, autologous	0	0	0	0	0
Mesenchymal stem cells, unrelated	2	39	1	24	22
Dendritic cells, autologous	1	7	1	171	46
Mononuclear cells	3	25	2	23	20
TC-TIL cells, autologous	1	5	2	14	13
CAR T/TCR cells	8	149	8	125	118
Expanded cells from cord blood	1	4	1	4	4

* Number of recipients missing for DLIs related and unrelated from one laboratory.

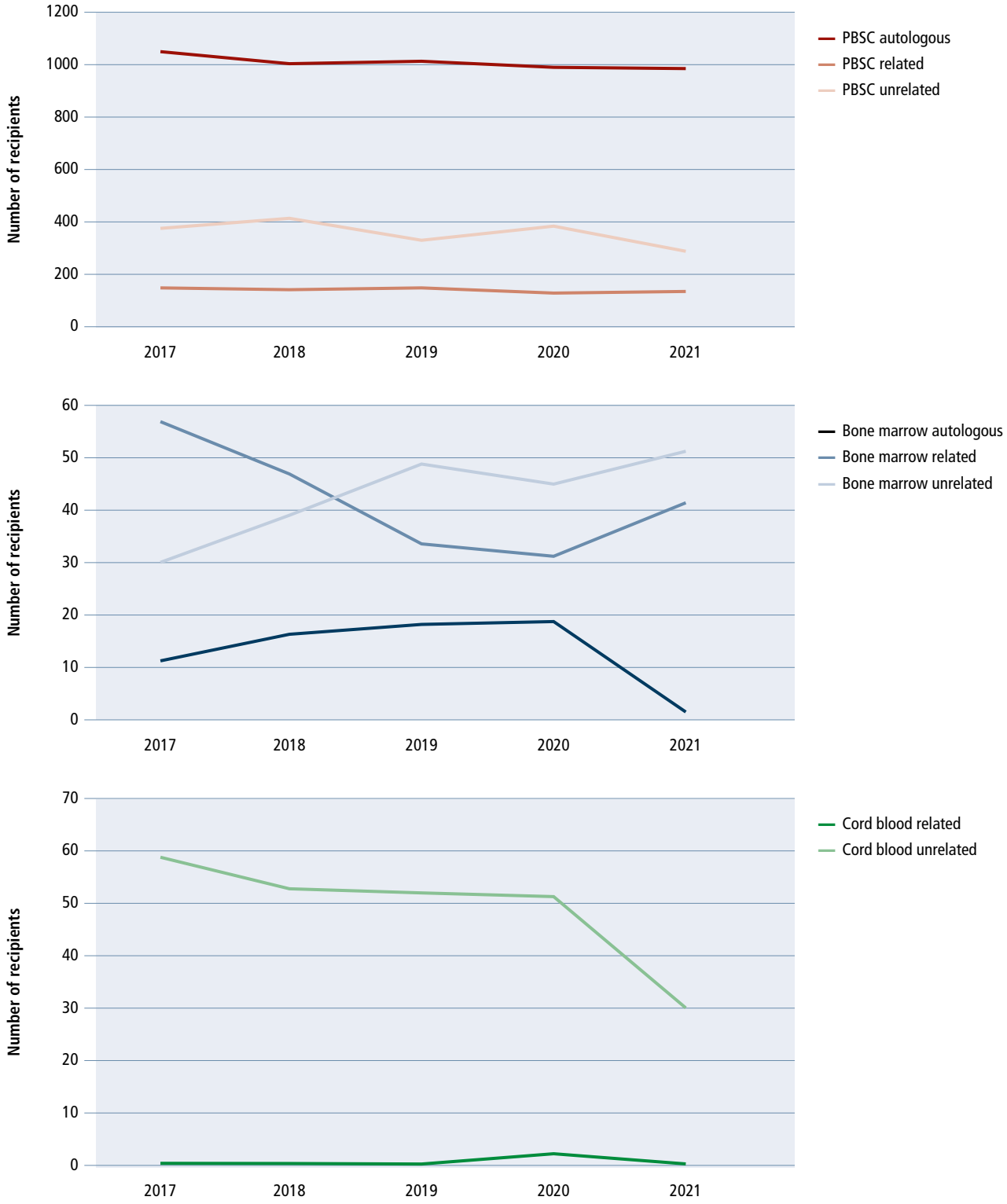

Figure 6a-b-c Number of hematopoietic stem cell transplant recipients by transplant type, 2017-2021.
One institution did not report the number of recipients of PBSCs and BM allogeneic related in 2021.

4.3 Reports

In 2021, TRIP received 44 reports relating to hematopoietic stem cells or other therapeutic cells; two of them were late reports from 2020. The reports mainly concern low-grade adverse reactions and events that are not serious according to EU criteria. Not all tissue establishments report these non-serious adverse reactions and events to TRIP.See Table 10 for specifications of the reports. Figure 7 shows a multi-year overview of reports of HSCs and other cells. The three events defined as serious according to EU criteria (see TRIP website for criteria) and the two adverse reactions with a severity grade of 2 or higher and imputability certain, probable or possible are described in Tables 11, 12 and 13. In Figures 8, 9 and 10, these reports are plotted over time in relation to the numbers processed or number of recipients over the period 2017 to 2021.

Table 10 Reports by tissue type, reporting category and severity (according to EU criteria)

Type of tissue or cells	Category of adverse event	Reports (serious)*	
PBSCs	Bacterial contamination of product	3 (0)	
	Loss of cells or tissues with consequences	1 (1)	see Table 11
	Incorrect product transplanted	1 (1)	see Table 11
	Other incident	5 (0)	
Bone marrow	Bacterial contamination of product	12 (0)	
	Other incident	1 (0)	
Mononuclear cells	Bacterial contamination of product with other consequences	1 (1)	see Table 11
Leucocytes	Other incident	1 (0)	
Type of tissue or cells	**Category of adverse reaction**	**Reports (serious)***	
PBSCs	Donation complication	1 (1)	see Table 13
	Post-transplantation bacterial infection	1 (0)	
	Other reaction	14 (0)	
Bone marrow	Other reaction	1 (0)	
Cord blood	Other reaction	2 (1)	see Table 12

* Serious events according to EU criteria, serious adverse events ≥ grade 2 with imputability certain, probable or possible.

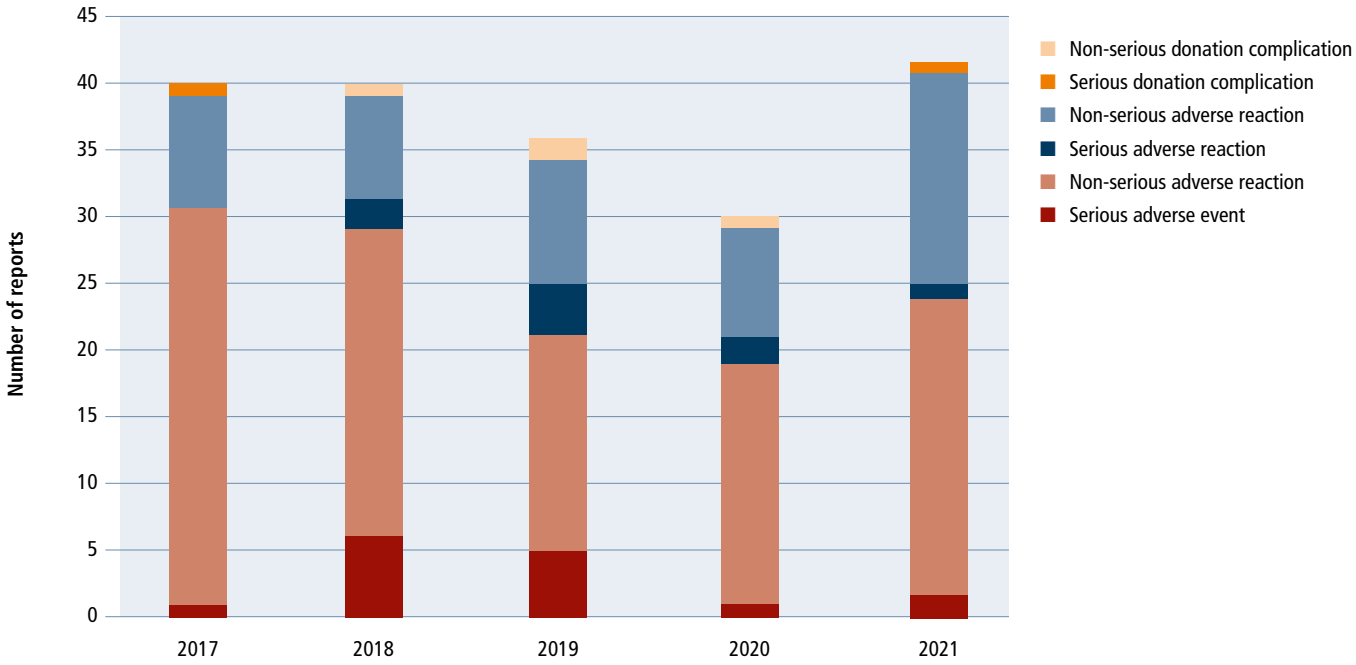

Figure 7 Total reports of hematopoietic stem cells and other therapeutic cells, 2017-2021

Table 11 Adverse events (serious according to EU definition) relating to hematopoietic stem cells in 2021, including one late report* (2020)

Type of HSC	Adverse event (description)	Report category
PBSCs, allogeneic, related*	Product error during procurement. Stem cell product started clotting after collection, resulting in unsuccessful donation. Laboratory tests showed no abnormalities in donor. A unit of cord blood was found for the recipient. In the resulting waiting period to transplantation, the recipient was seriously ill. Procedural error during apheresis was untraceable. Concerns a late report > 1 year after the incident was observed.	Loss of cells + Other consequences
PBSCs, allogeneic, related	Assessment error during issue. After infusion, the graft was found to still have a status with which it should not have been issued because test for West Nile virus was not yet performed. Afterwards, this turned out to be an unfairly assigned classification. The risk of transfer was subsequently deemed nil and the product was released after all.	Incorrect product transplanted
Mononuclear cells, autologous	Product error during procurement. Positive sterility testing of a T-cell apheresis product for ATMP production. The cellular starting material was found to be contaminated with *Staph. epidermidis* and *Staph. haemolyticus*. The material was rejected even before ATMP production and patient underwent new T-cell apheresis.	Bacterial contamination of product + Other consequences

Table 12 Adverse reaction (severity grade ≥2, imputability certain, probable or possible) relating to hematopoietic stem cells in 2021

Type HSCs	Adverse reaction (description)	Interval vs transplant	Imputability	Severity
Cord blood, allogeneic, unrelated	Child with acute lymphoblastic leukemia. Hypertension with headache during transplantation, for which treatment was given using two antihypertensive drugs. Other reaction - Full recovery	During procedure	Possible	2

Table 13 Donation complication (severity ≥2, imputability certain, probable or possible) relating to hematopoietic stem cells in 2021

Type of HSCs	Donation complication (description)	Interval vs donation	Imputability	Severity
PBSCs, autologous	Myocardial infarction on the evening after uncomplicated stem cell apheresis. Cardiac catheterization shows coronary stenosis in patient with history of vascular disease (CVA).	Evening after apheresis	Possible	2

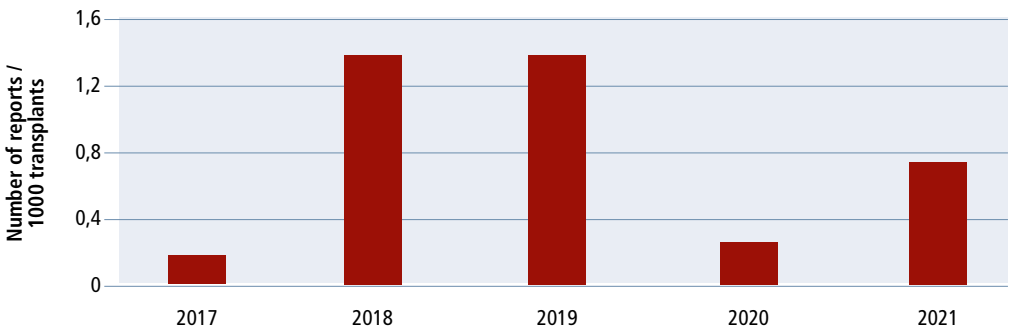

Figure 8 Number of adverse events (serious according to EU criteria) per 1000 processed grafts, 2017-2021

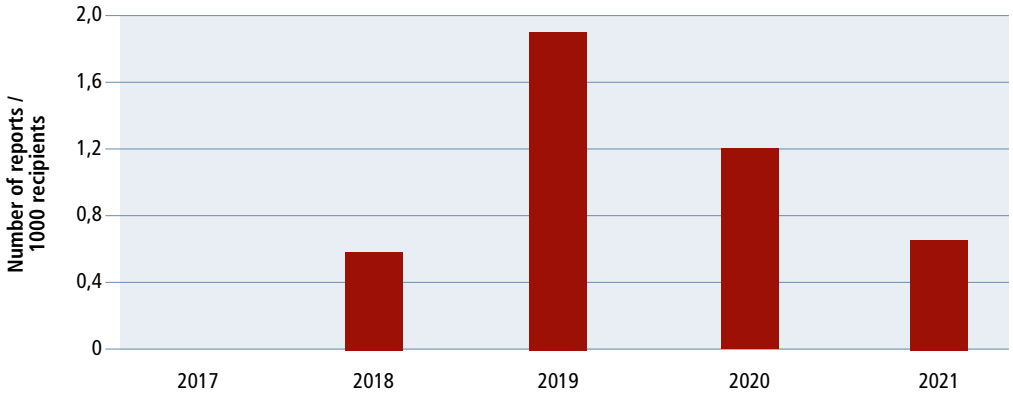

Figure 9 Number of serious adverse events (≥grade 2 and imputability certain, probable or possible) per 1000 recipients, 2017-2021

Figure 10 Number of serious donation complications (≥grade 2 and imputability certain, probable or possible) per 1000 processed grafts (PBSCs and BM collected in NL, as a measure of number of donations), 2017-2021

4.4 Conclusion

In 2021, as far as the reporting of annual figures relating to the processing, distribution and application of stem cells was concerned, participation was incomplete for the first time since 2014. As regards the figures relating to distribution, the European definition was adhered to more strictly (see Chapter 1), and as a result the reported distribution figures are lower. However, this change will make the figures more consistent and hopefully more comparable over the years. However, there is still a discrepancy in the reports in terms of units distributed and applied, number of transplants versus bags. With the revision of the European directive, it is expected that more unambiguous definitions will become available, providing clearer instructions for tissue establishments concerning the reporting of activities. This may in future lead to an internationally comparable denominator for serious adverse events and reactions in the tissue and cell transplantation chain.

In terms of reports received, the number has increased to pre-2019 levels. However, the vast majority are reports of non-serious reactions and events, which are not reported by all tissue establishments. In 2021, reports were received from three tissue establishments (1-32 reports per tissue establishment).

The total number of stem cell transplant recipients over the past five years is stable, and stem cell transplantation may be said to be safe. An average of 0.8 serious adverse event per 1,000 recipients was reported over the past five years: Two reports of a serious donation complication were received in the last five years, which amounts to 0.2 per 1000 processed grafts (PBSCs + bone marrow in NL). It is possible that the number of donation complications does not show a complete picture of the situation in the Netherlands. Reporting serious donation complications is not (yet) regulated in the WVKL and reporting is voluntary. As far as reported events are concerned, there is an incidence of 0.7 per 1000 processed grafts.

There are still grey areas in vigilance regarding new advanced treatment methods with drugs manufactured from human cells and tissues. Incidents when obtaining starting material for these drugs, but also adverse events later in the GMP process with consequences for the donor, are considered worth monitoring by TRIP. One example is the report of a bacterial contamination of the autologous cell product procured, which required the donor to undergo a new apheresis procedure. Furthermore, in line with the WVKL, and to find a denominator for these adverse events and reactions, TRIP requests all tissue establishments to report the number of starting materials procured. Presumably, however, these reports to TRIP are not yet complete. Known adverse reactions to registered medicinal products manufactured from human body material do not fall under TRIP's focal area and therefore do not need to be reported to TRIP. Lareb is the body that registers adverse events and reactions relating to medicinal products in the Netherlands. TRIP is in discussion with Lareb and the Ministry of Health, Welfare and Sport to establish an unambiguous reporting route for institutions dealing with adverse events and reactions when obtaining human material and manufacturing medication for these advanced treatments (ATMPs).

5 OTHER TISSUES AND CELLS

Institutions involved

In total, 71 hospitals and independent facilities and 51 implantology practices applying other human tissues and cells in the Netherlands are known to TRIP. Three hospitals did not report application figures this year and one hospital reported application figures only partially. Of the implantology practices known to TRIP, 50 reported application figures.

A total of 26 tissue establishments, including 15 organ banks, process, store and/or distribute other tissues and cells. One organ bank did not report its activities in 2021 (Figure 11).

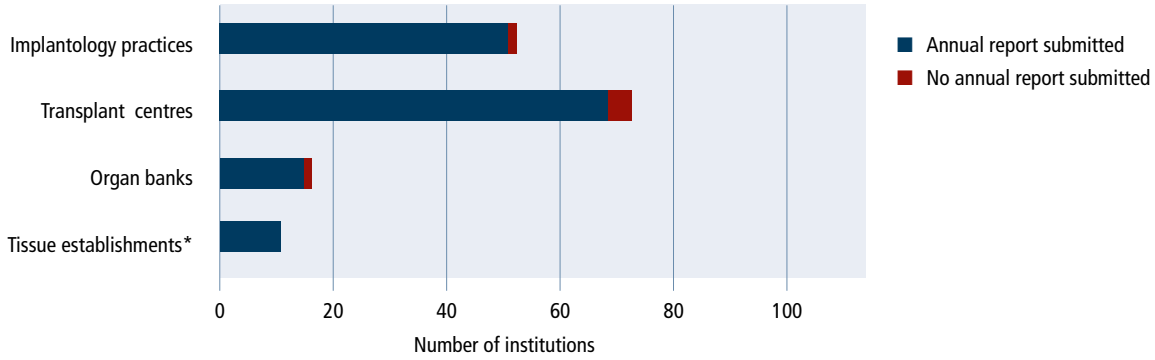

Figure 11 Participation relating to other tissues and cells in 2021

* Tissue establishments without organ bank accreditation

5.1 Bone and other musculoskeletal tissues and cells

5.1.1 Institutions involved

Bone and other musculoskeletal tissues include 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. Autologous chondrocytes are grown and processed into advanced therapy medicinal products (ATMPs). Some institutions report application data to TRIP, but this is not mandatory.

In July 2022, 20 institutions in the Netherlands had tissue establishment or organ bank accreditation for processing, preserving and/or distributing bone and other musculoskeletal tissues. All of them have submitted reports of their activities in 2021.

In total, 120 institutions known to TRIP submitted reports of the application of musculoskeletal tissues, among them were four hospitals and one implantology practice that did not provide figures.

5.1.2 Activities 2021

Table 14 shows the processing of bone and other musculoskeletal tissues in 2021. Compared to 2020, there was a 80% decrease in the processing of demineralised bone filler and a halving of the number of whole bones processed. This is largely explained by the fact that there was enough in stock to distribute in 2021 and, as a result, there was no need to reprocess. The number of processed bone-tendon-bone grafts and fascia compared to 2020 doubled. The distribution of mineralized bone filler also doubled, but there was only a minimal increase in the application.

There was a decrease in the number of recipients of femoral heads, whole bones, bone-tendon-bone grafts and tendons, because not all transplant centres entered the number of recipients on the TRIP form and five transplant centres did not submit a report (Table 15).

Table 14 Processing of bone and other musculoskeletal tissues and cells in 2021

Type of tissue/cells	Tissue establishments	Processed			
		From NL	From EU	From non-EU	Total
Femoral heads, living donor	6	2609	136	0	2745
Femoral heads, post-mortem donor	1	11	0	0	11
Bone filler, mineralized	1	2057	0	0	2057
Bone filler, demineralized	1	50	0	0	50
Bone, whole	1	89	91	0	180
Cranial bone, autologous	3	139	0	0	139
Tendons	1	769	0	0	769
Bone-tendon-bone grafts	1	83	0	0	83
Fascia	1	471	0	0	471
Cartilage	2	40	0	0	40
Chondrocytes, autologous	1	69	0	0	69
Menisci	1	53	0	0	53

Table 15 Distribution and application of bone and other musculoskeletal tissues and cells in 2021

Type of tissue/cells	Tissue establishments	Hospitals/ clinics	Distributed				Units applied (from NL)	Recipients
			In NL	Export		Total		
				In EU	Outside EU			
Bone								
Femoral heads, living donor	7	49	1742	636	5	2383	1343 (1317)	838
Femoral heads, post-mortem donor	2		24	34	0	58		
Bone filler, mineralized	8	70	14504	8135	4223	26862	3037 (2375)	2730
Bone filler, demineralized	8	26	1732	12849	15104	29685	433 (294)	396
Bone, whole	2	18	161	30	11	202	92 (91)	56
Cranial bone, autologous	3	4	82	0	0	82	40 (40)	30
Other musculoskeletal tissues and cells								
Tendons	1	32	454	32	0	486	305 (304)	226
Bone-tendon-bone grafts	1	10	33	2	0	35	24 (24)	16
Fascia	1	2	105	0	0	105	97	97
Cartilage	1	4	36	0	0	36	9	9
Chondrocytes, autologous	1	1	76	0	0	76	24	22
Menisci	1	1	19	7	0	26	7	?

5.2 Cardiovascular tissues

5.2.1 Institutions involved

Cardiovascular tissue includes aortic and pulmonary valves, vessels, patches and the pericardium. There is one institution In the Netherlands that is engaged in processing, preserving and/or distributing cardiovascular tissue. It has submitted its annual report to TRIP.

Of the 10 institutions applying cardiovascular tissue known to TRIP, nine reported the number of applications.

5.2.2 Activities in 2021

There is no notable change in cardiovascular tissue processing (Table 16). As in last year's biovigilance report, no pericardium is processed by or distributed from Dutch tissue establishments. In 2021, 18 vessels were processed but no vessels were distributed or applied. There are no notable shifts within cardiovascular tissue distribution and application (Tables 16 and 17). There were 16 aortic valves distributed in the Netherlands and 21 aortic valves from the Netherlands were applied.

Table 16 Processing of cardiovascular tissues and cells in 2021

Type	Tissue establishments	Processed			
		From NL	From EU	From non-EU	Total
Aortic valves	1	252	0	0	252
Pulmonary valves	1	252	0	0	252
Vessels	1	18	0	0	18
Patches	1	142	0	0	142
Pericardium	0				

Table 17 Distribution and application of cardiovascular tissues and cells in 2021

Type of tissue/cells	Tissue establishments	Hospitals/ clinics	Distributed				Units applied (from NL)	Recipients
			In NL	In EU	Outside EU	Total		
Aortic valves	1	4	16	4	0	20	29 (21)	29
Pulmonary valves	1	4	94	15	0	109	90 (78)	90
Vessels	0	0	0	0	0	0	0	0
Patches	1	4	35	33	0	68	37 (36)	37
Pericardium	0	5	0	0	0	0	183 (0)	129

5.3 Skin

5.3.1 Institutions involved

Skin includes donor skin, acellular dermis, autologous skin and cultured skin. Three institutions in the Netherlands are engaged in the processing, preservation and/or distribution of skin tissue. All three have submitted their annual reports to TRIP.

Of the 14 institutions applying skin known to TRIP, ten are hospitals and four implantology practices. One hospital has not yet reported their appliying figures, but did not report the use of donor skin since 2019.

5.3.2 Activities in 2021

There was a decrease in skin distribution in Europe (34%) and an increase in exports (37%) (Tables 18 and 19). Donor skin applications in the Netherlands halved and there was a 90% decrease in acellular dermis applications, with five hospitals/clinics reporting having applied acellular dermis this year compared to eight in 2020. It is possible that hospitals had acellular dermis from 2020 in stock and that less was applied due to COVID (lock-down and fewer social meetings).

Table 18 Processing of skin in 2021

Type	Tissue establishments	Processed			
		From NL	From EU	From non-EU	Total
Donor skin	1	441	46	0	487
Acellular dermis	3	46	0	0	46
Autologous skin	0	0	0	0	0
Cultured skin	0	0	0	0	0

Table 19 Distribution and application of skin in 2021

Type	Tissue establishments	Hospitals/ clinics	Distributed				Units applied (from NL)	Recipients
			In NL	In EU	Outside EU	Total		
Donor skin	1	8	1328	9536	1768	12632	1011 (994)	92
Acellular dermis	3	5	228	0	425	653	15 (14)	11
Autologous skin	0	1				0	1 (1)	1
Cultured skin	0	0				0	0	0

5.4 Ocular tissues

5.4.1 Institutions involved

Ocular tissue includes corneal, scleral and limbal stem cells. There are four Dutch institutions involved in processing, preserving and/or distributing ocular tissue, all of which submitted their annual reports to TRIP. Of the ten institutions applying ocular tissue known to TRIP, nine reported the number of applications.

5.4.2 Activities in 2021

Noticeably more ocular tissues were processed (increases of 125%, 184% and 175% respectively). As there was also an increase in the number of sclerae processed, the number of processing operations is back to pre-COVID levels (Table 20).

Ocular tissue distribution increased minimally compared to last year, with a decrease in ocular tissue applications (Table 21). There is a discrepancy between the number of corneas and sclerae distributed and their applications. According to annual figures from the Netherlands Transplant Foundation (NTS), 1831 corneal transplantations were performed (using both Dutch and foreign donors). This discrepancy of annual figures received is probably due to one transplant centre not submitting a report and incomplete application figures.

Table 20 Processing of ocular tissues and cells in 2021

Type	Tissue Establishments	Processed			
		From NL	From EU	From non-EU	Total
Cornea	3	4436	0	10	4446
Sclera	1	619	0	0	619
Limbal stem cells	1	7	0	0	7

Table 21 Distribution and application of ocular tissues and cells in 2021

Type	Tissue establishments	Hospitals/ clinics	Distributed				Units applied (from NL)	Recipients
			In NL	In EU	Outside EU	Total		
Cornea	3	13	1819	552	45	2416	1620 (1578)	1591
Sclera	1	17	1951	23	0	1974	1277 (1251)	952
Limbal stem cells	0		0	0	0	0	6 (0)	6

5.5 Other cells and tissues

5.5.1 Institutions involved

Other cells and tissues include amniotic membranes, pancreatic islets and leucocytes for diagnostics.

Of the four Dutch organ banks engaged in the processing, storage and/or distribution of other cells and tissues, one did not submit a report. Of the 15 institutions applying other cells and tissues known to TRIP, 11 reported their activities; two indicated they had not applied other cells and tissues in 2021, and one indicated it was unable to provide exact figures. One hospital did not submit a report.

5.5.2 Activities in 2021

Table 22 describes the processing of other cells and tissues. Table 23 shows the distribution figures. Some of the other cells and tissues are processed into ATMPs. The processing, distribution and application of body material for ATMPs does not need to be reported to TRIP, as there are no conclusive regulations regarding the reporting thereof.

Table 22 Processing of other cells and tissues in 2021

Type	Tissue establishments	Processed			
		From NL	From EU	From non-EU	Total
Amniotic membranes*	3	10	7	0	17
Pancreatic islets&	1	11	0	0	11
Leucocytes for diagnostics	1	7	0	0	7
Tumour tissue	2	10	0	0	10

* placentas
& pancreases

Table 23 Distribution and application of other cells and tissues in 2021

Type	Tissue establishments	Hospitals/ clinics	Distributed				Units applied (from NL)	Recipients
			In NL	In EU	Outside EU	Total		
Amniotic membranes	3	8	206	43	0	249	128 (128)	119
Pancreatic islets	1	1	11	0	0	11	11 (11)	11
Leucocytes for diagnostics	1		6			6	0	0
Tumour tissue	2	0	10	0	0	10	0	0

5.6 Reports related to tissues and cells

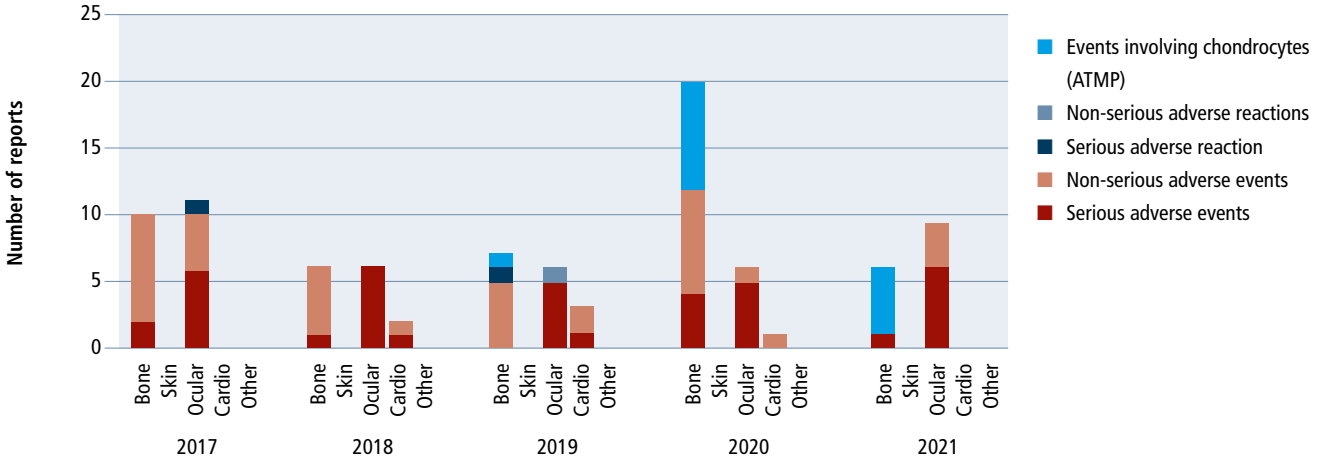

Figure 12 Total reports related to other tissues and cells, 2017-2021
Three late autopsy reports with a contraindication for donation under reports related to bone chondrocytes for ATMP production and under ocular tissue or cells (see below)

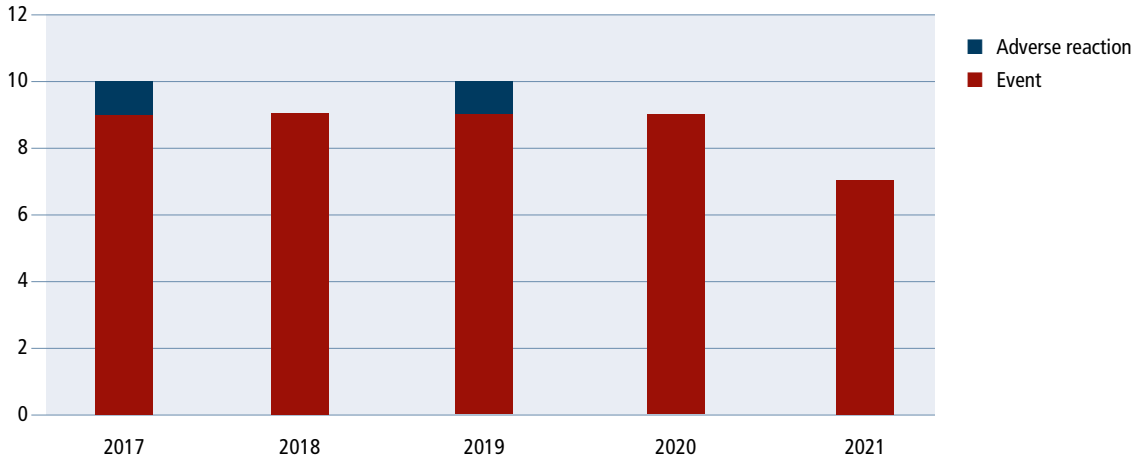

Figure 13 Number of events (serious according to EU criteria) related to other tissues and cells broken down by tissue type, 2017-2021
2021: one ocular adverse event; three late autopsy reports with a contraindication for donation

In 2021, 15 reports were received regarding other tissues and cells, six of which concerned bone and other musculoskeletal tissues and nine were about corneas, including three reports concerning situations in which the corneas had already been issued but subsequent information revealed a contraindication for donation (Figure 12).

Of the 15 reports, five related to the culture of chondrocytes for the production of ATMPs. As has already been mentioned in last year's TRIP biovigilance report, there is no conclusive regulation regarding the reporting (and severity) of adverse events occurring when producing ATMPs using human tissues and cells. These are therefore left out of consideration. They are specified in Figure 12.

The remaining 10 reports are all adverse events, including one involving an adverse reaction. Seven reports were rated as serious (Figure 13). They are summarized in Table 24.

To concretize the safety of other tissues and cells, the adverse events are plotted against the number of processing operations. There was one adverse event involving a femoral head relative to 2620 processed femoral heads (0.4 cases per 1000 units distributed) and there were three adverse events involving corneas relative to 4446 distributed corneas (0.7 cases per 1000 units processed).

Three corneal incidents concerned the risk of transfer of another condition. In these incidents, the screening of the potential donor and the results of the gross autopsy report showed no evidence of a contraindication for donation. Due to the limited shelf life of corneas (≤28 days), it was not possible to wait for the results of the microscopic autopsy report. The corneas were therefore released for application. However, the microscopic autopsy report showed possible evidence of incipient dementia/ cerebral amyloid angiopathy. Despite the fact that the risk in this case is currently a theoretical risk, this microscopic outcome is a contraindication for tissue donation. Because of their shelf life, corneas were already applied. According to the (retrospective) microscopic autopsy report, these corneas did not meet requirements, so these reports were included in the category of serious adverse events. The cases are described in Table 24.

In previous years, adverse reactions or events can involve an unknown quantity of (different) tissues; this is hard to visualize it in a figure.

Table 24 Adverse events (serious according to EU definition, see section C) related to other tissues and cells in 2021, including one adverse event concerning an adverse reaction.

Tissue	Adverse event (category and description)	Number
Bone	Near miss Femoral head for which not all tests were completed (due to insufficient test material) was prepared for issue. Whilst the femoral head was prepared for issue, the error notification was rejected. Upon issue, the notification was noted and the femoral head was rejected and placed in quarantine. Accidentally, the femoral head was issued as part of another series. During the booking out of rejected tissue, the missing femoral head was noticed, retrieved and destroyed. Detected before transplantation.	1
Cornea	Loss of cells or tissues Cornea was not 'pre-cut', despite request. As a result, the cornea could not be used in surgery.	1
Cornea	Other contamination of product and other infection post-transplant Postoperatively, a yeast infection (Candida glabrata) was found in recipient and in the transport medium. The graft had to be removed.	1
Cornea	Loss of cells or tissues During processing, no 'pre-stripping' of DMEK, which therefore could not be used in surgery.	1
Cornea	Risk of transfer of condition Based on the results of the final donor autopsy report, a contraindication for tissue donation could not be ruled out. The corneas were already transplanted by then.	3

5.7 Conclusion regarding other tissues and cells

After assessing the completeness and accuracy of the annual figures (see recommendation 1 of 2020 biovigilance report), it emerged that three hospitals and one implantology practice had not reported their application figures and one hospital had not provided a complete report. In a few reports, the number of recipients had not been reported. One report mentioned that the figures could not be retrieved and were therefore not submitted.

Examination of the annual reports revealed a large discrepancy between the number of units distributed and the number of units applied for some tissue types. Possible cause was that some of the tissues and cells were stored at the transplant centre. However, this might not explain everything. Other options could be that the numbers reported by the tissue establishments are not correct, because it is not clear what data TRIP wishes to receive or because application figures are difficult to retrieve for a biovigilance officer, or that TRIP lacks data from hospitals and clinics that do use human material.

Reports regarding other tissues and cells show no notable shifts compared to previous years. In 2021, the aim was to plot reports against a denominator such as distribution or application. There were seven serious reports in 2021, all concerning adverse events, including one related to bone tissue, three related to ocular tissues and three related to adverse events due to risk of transfer of condition. One adverse event concerned an adverse reaction, during which a recipient developed an infection with Candida glabrata, which was later also found in the transport medium.

A third of all reports regarding other tissues and cells related to the culture of chondrocytes for ATMPs. Adverse events during procurement or processing may have consequences for autologous donors. TRIP considers it essential to keep an eye on this. (See Section 4.4 for more information on ATMPs.)

ANNEXES

A ABOUT TRIP

The TRIP (Transfusion and Transplantation Reactions in Patients) Foundation was established 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.

Biovigilance refers to the systematic monitoring of adverse events and 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 obliges Member States to report serious adverse events and reactions that may be related to the quality and/or safety of these body materials. This Directive was transposed into the Dutch Body Materials (Safety and Quality) Act (WVKL) and the Body Material Requirements Decree 2006. The latter was amended in 2012 based on European Directive 2010/53/EC.

The TRIP reporting system for adverse events and reactions related to the application and transplantation of human bodily material meets the requirements laid down in European and Dutch legislation. Figure 14 presents a flowchart of serious and non-serious biovigilance reports in Dutch healthcare. It is likely that the number of 'non-serious' adverse events and reactions 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 fits in with this.

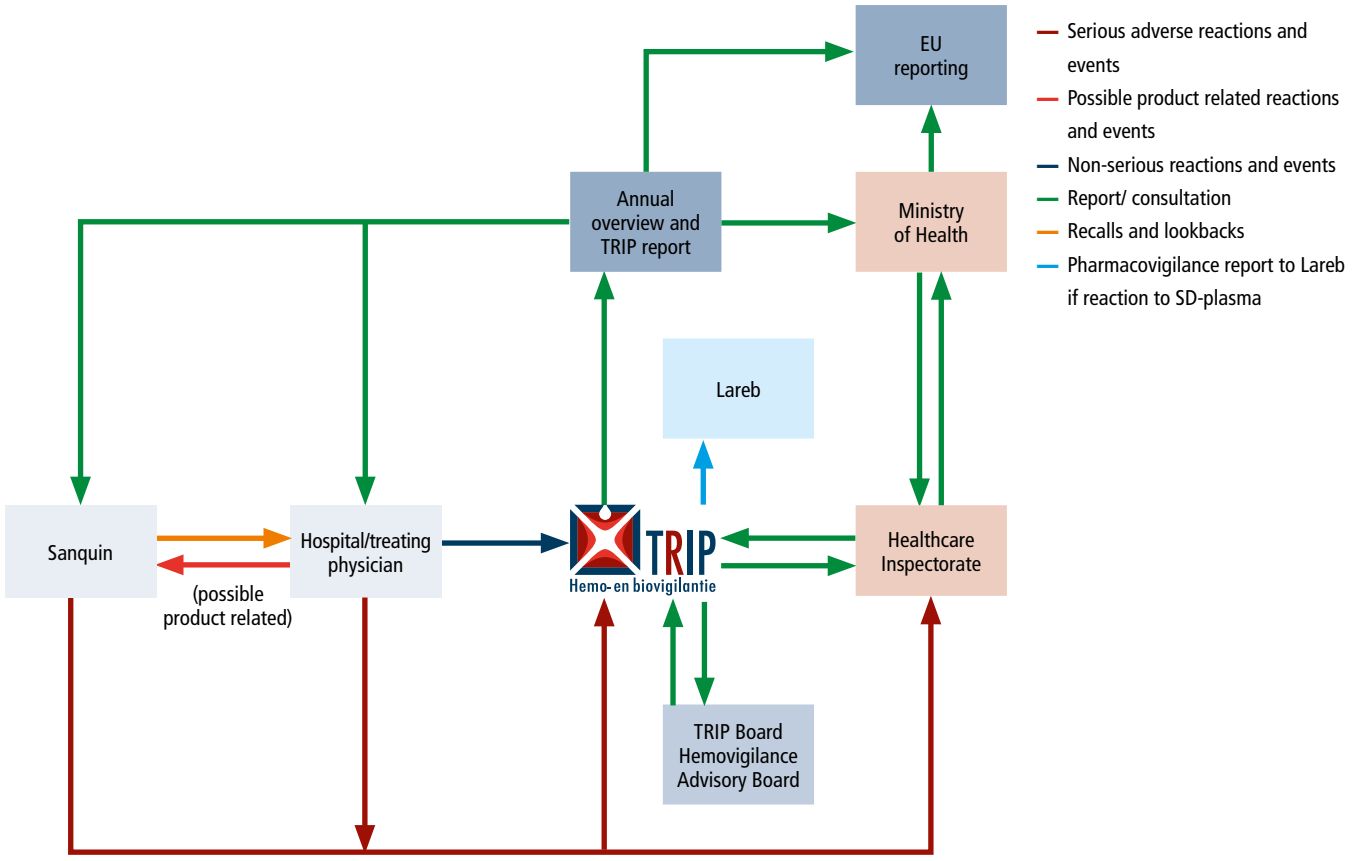

Figure 14 Flowchart of reports concerning human tissues and cells

All types of human body material from both living and post-mortem donors, fall within the scope of the WVKL, with the exception of body material that is removed and returned to the same person in the same operation. If autologous material is stored or processed in an area other than where the patient stays, it does fall under the provisions of the WVKL. Allogeneic applications of tissues fall under the scope of the WVKL in all cases.

Working method

TRIP is an independent foundation that cooperates closely with the users of human substances and tissue establishments. All submitted reports are registered, analysed and reviewed by experts. The results and conclusions are reported annually. TRIP also annually collects data on the numbers of processed, distributed and applied human tissues and cells in all Dutch hospitals, other care providers and tissue establishments, in accordance with European regulations. The information is aggregated as a denominator for the TRIP data on adverse events and reactions 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 reports.

B REPORTING OF ADVERSE EVENTS AND REACTIONS

Tissue establishments

The 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 Health and Youth Care Inspectorate (iJG) if they are classified as serious. If a report is assessed as serious by TRIP and has not been reported to the IGJ, the reporter will be made aware of the obligations regarding reporting to the IGJ.

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 'sentinel event' 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 Health and Youth Care Inspectorate

In In the Netherlands, the Health and Youth Care 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 Health and Youth Care Inspectorate (IGJ), TRIP takes care of 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 choose to select the option of forwarding the report to the IGJ so they only need to submit information once.

The reporting of serious adverse reactions and events is different from the reporting of an emergency according to the Quality, Complaints and Disputes in Healthcare Act. A sentinel event has a different definition and the IGJ has its own specific procedure for dealing with sentinel events.

Figure 15 diagrammatically presents the reporting route.

Serious adverse reactions or events within the scope of the Body Material (Safety and Quality) Act are best submitted to the Health and Youth Care Inspectorate through the TRIP online reporting system. This channels the reports to the inspectors involved in enforcement of the Body Material (Safety and Quality) Act and reduces the likelihood of reports being (possibly incorrectly) treated as lying within the scope of 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 sentinel event.

Reports regarding ATMPs

There are still grey areas in vigilance regarding new advanced treatment methods with drugs manufactured from human cells and tissues. Incidents when obtaining starting material for these drugs, but also adverse events later in the GMP process with consequences for the donor, are considered worth monitoring by TRIP. Donation, procurement and testing of human tissues and cells that serve as raw material for these ATMPs fall under the Body Material (Safety and Quality) Act (WVKL). The manufacturing process falls under Good Manufacturing Practices (GMP) legislation and the product

after registration under the Medicines Act. Reports of serious adverse events and complications related to the procurement of body material that do not affect the safety or quality of the material are not yet regulated by legislation, but TRIP would like to receive them pending additional regulations. Known adverse reactions to registered drugs manufactured from human body material do not fall within TRIP's focus area and therefore do not need to be reported to TRIP. Lareb is the Dutch body that registers adverse events and reactions related to medicinal products. TRIP is in discussion with Lareb and the Ministry of Health, Welfare and Sport to establish an unambiguous reporting route for institutions dealing with adverse events and reactions when obtaining human material and manufacturing medication for these advanced treatments.

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

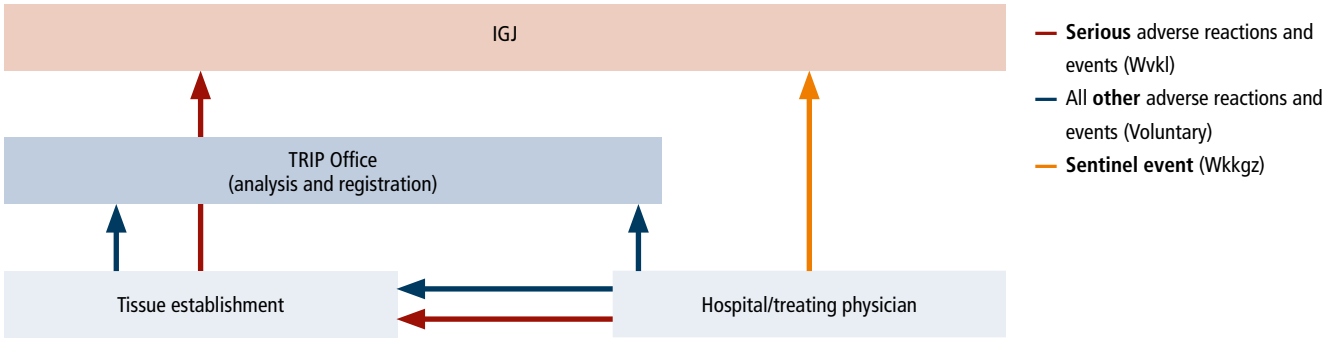

Figure 15 Flowchart of reports regarding human body material

C OVERVIEW OF REPORTS OF SERIOUS EVENTS AND ADVERSE REACTIONS REPORTED TO THE EU

Table 25 shows the number of serious adverse events and reactions related to human tissues or cells reported in 2021, including one late report from 2020. In total, 27 reports were assessed as serious. These concern two serious adverse reactions, 13 serious adverse events and 12 serious donation complications.

Table 25 Overview of serious adverse events and reactions reported to the EU in 2021

Type	Serious adverse reaction	Serious adverse event*	Serious donation complication	Total serious reports
Semen	0	0	0	0
Oocytes	0	3	11	14
Embryos	0	1	0	1
HSCs and therapeutic cells	1	3	1	5
Ocular tissue	1	5	0	6
Musculoskeletal tissues	0	1	0	1
Total	**2**	**13**	**12**	**27**

* The information in two serious reports was not complete at the time of closing EU registration; these reports will be included next year.

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 concerning serious adverse reactions. These include proven and possible inheritance of a congenital abnormality when using donor gametes or embryos, post-transplantation contamination of a recipient with a micro-organism that requires treatment or prolonged hospitalization, re-transplantation after transplantation with an incorrect product or additional mobilisation, apheresis or bone marrow extraction for autologous stem cell transplantation(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 (genetically non-identical person)
ATMP	Advanced Therapy Medicinal Product
Autologous	Originating from a person's own body or removed from and applied to the same person
BM	Bone marrow
CAR T cells	Chimeric Antigen Receptor T-cells
CBU	Cord blood unit
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 human application
DLI	Donor lymphocyte infusion
DMEK	Descemet Membrane Endothelial Keratoplasty
EHR	Electronic health record
EU	European Union
GMP	Good manufacturing practice
HSC	Hematopoietic stem cells
ICU	Intensive Care Unit
IGJ	Dutch Healthcare and Youth Inspectorate
Imputability	Degree to which an adverse reaction can be attributed to an applied substance of human origin
IUI	Intrauterine insemination
IVF	In vitro fertilization
Lareb	Dutch reporting and knowledge centre for adverse reactions to medicines, vaccines and other health products
Matchis	Dutch registry for stem cell donors
MESA	Microsurgical epididymal sperm aspiration
NL	Netherlands
NTS	Nederlandse Transplantatie Stichting (Netherlands Transplantation Foundation)
Oocytes	Egg cells
Organ bank	Tissue establishment with licence to receive substances of human origin
PBSC	Peripheral blood stem cells
PESA	Percutaneous epididymal sperm aspiration
Procurement	Process by which body material or a donated organ becomes available
Semen	Sperm
TCR	T-cell receptor (gene therapy)
TESE	Testicular sperm extraction
Tissue establishment	A tissue bank, hospital department or other institution that holds a licence for the processing, preservation, storage or distribution of body material
VWS	Dutch Ministry of Health, Welfare and Sport
WKKGZ	Quality, Complaints and Disputes in Healthcare Act
WVKL	Body Material (Safety and Quality) Act