TRIP REPORT 2022

BIOVIGILANCE

EXTENDED VERSION

TRIP
Hemo- en biovigilantie

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1 INTRODUCTION

In this 2022 Biovigilance Report, TRIP presents reports of incidents and adverse reactions that occur in the chain from the donation to the clinical application of human tissues and cells. The report also provides an overview of the activities of tissue establishments and healthcare centres that participate in the national biovigilance network in the field of processing, distribution and application of human tissues and cells.

In 2022, the European Commission published a proposal for the Regulation of the European Parliament and of the European Council on quality and safety standards for substances of human origin (SoHOs) intended for human application. After adoption of the final text and after the implementation period, this regulation will replace the existing directives for blood, tissues and cells. While drawing up this report, we are therefore on the eve of important and, in some respects, far-reaching changes in European legislation on the procurement and application of blood, tissues and cells and other substances from human substances, such as breast milk or faeces. Organs are excluded from the upcoming EU SoHO Regulation. This new regulation aims, among other things, to better protect donors and patients, and to make the EU more self-sufficient in the field of SoHOs. The final text is expected to be adopted in 2024 following the conclusion of discussions between the European Commission, the European Parliament and the European Council. An important change is the introduction of the concept of SoHO entity, which includes organisations that, among other things, procure, process, store and/or apply human substances to patients. Organisations that exclusively apply human substances (healthcare centres) are also included. All SoHO entities must be registered and annually declare their activities concerning human substances. You can find a reference to the change in the regulation on the TRIP website.

TRIP thanks all professionals who contributed to the preparation of this report.

2 BIOVIGILANCE IN 2022 AND RECOMMENDATIONS

2.1 Biovigilance in 2022

All tissue establishments and healthcare centres known to TRIP that are active in the field of reproductive tissues and cells, hematopoietic stem cells and therapeutic cells declared their activities in 2022. All 24 tissue establishments that process, store and/or distribute other tissues and cells have also reported their activities for the year 2022. Of the 129 healthcare centres , 121 submitted information on the application of other tissues and cells.

In 2022, a total of 113 reports were submitted to TRIP before the deadline, 1 March 2023. Forty-four reports were assessed as serious, based on the EU criteria.

— In 2022, there were eight serious incidents involving reproductive tissues and cells. One serious adverse effect and 15 serious donation complications after treatment in the context of a fertility programme were also reported.
— In 2022, four serious incidents related to hematopoietic stem cells were recorded. In addition, four reports of serious reactions were received, two of which concerned circulatory overload after stem cell transplantation.
— Eleven serious incidents were recorded in the category other tissues and cells, involving ocular or musculoskeletal tissue, or a combination of tissue types. One report concerned eight femoral heads, which were released over a period of five years, while the microbiological results were abnormal. There have been no indications of infections among the recipients. One centre indicated that it was impossible to trace what happened to one of the femoral heads. One serious donation complication was also reported after a chondrocyte donation.

2.2 Recommendations

	Recommendation	Who
1	Attention to the development of circulatory overload concerning stem cell transplantation, so that risk factors can be identified	Clinicians in healthcare centres, TRIP
2	Attention to the assurance of the traceability of human substances in healthcare centres	Biovigilance officers and Boards of healthcare centres Directors of hospitals
3	In anticipation of the new European regulation: take note of the impending changes in legislation and their consequences for future SoHO entities	Boards of Directors, tissue establishments, healthcare centres, TRIP

2.3 Follow-up to previous years

1 Working towards clear, simple and usable measures for the activity within a tissue establishment or healthcare centre, and thus towards denominators for incidents and adverse effects in the tissue and cell transplantation chain, in consultation with the supervisory authorities and the tissue establishments establishment.

Development:

In 2022, TRIP discussed the existing differences in interpretation of the term 'distribution' with the Ministry of Health, Welfare and Sport (VWS) and the Healthcare and Youth Inspectorate (IGJ). The definition of distribution is expected to change under the upcoming SoHO Regulation. Until then, the number of units procured at the tissue establishment's own clinic and distributed in the Netherlands is stated separately, to provide unambiguous distribution figures for the EU overview. The definitions regarding the usable measures for activities are further elaborated and explained in the annual figure forms. The forms have been adapted to improve completeness and clarity.

2 Drawing up guidelines for reporting incidents and adverse effects associated with new therapies that are not yet covered by current legislation, so that vigilance is covered from donation up to and including clinical application.

Development:

In consultation with Lareb, a proposal for a vigilance system has been developed that covers the entire chain of registered ATMPs based on human substances. Prior to implementation, the proposal is submitted to the various parties involved in the ATMP chain, IGJ and VWS.

3 REPRODUCTIVE TISSUES AND CELLS

3.1 Establishments and centres involved

In 2022, there were 16 registered IVF laboratories with an organ bank accreditation in the Netherlands. Furthermore, 52 semen laboratories had a tissue institution or organ bank accreditation. Establishment 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 tissues and cells in 2022.

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 for 2022. 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 material (from the Netherlands, from the EU, or from outside the EU). The columns under Distributed indicate whether material was distributed in the Netherlands or in the EU, or exported outside the EU.

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

Table 1a Processing and distribution of semen and testicular tissue

Type of semen or testicular tissue	Tissue establishment	Unit	Processed			Distributed		
			From NL	From EU	From Outside EU	In NL	In EU	Export Outside EU
Partner semen fresh and cryo	66	Sample/straws	39,007	9	0	25,546	0	0
Donor semen fresh and cryo	17	Sample/straws	6,770	5,872	0	8,793	0	0
Partner semen MESA/PESA/TESE	9	Puncture/biopsy	1,087	1	0	n/a	n/a	n/a
Donor semen MESA/PESA/TESE	1	Puncture/biopsy	1	0	0	n/a	n/a	n/a
Testicular tissue	2	Transplant	17	0	0	0	0	0

Table 1b Processing and distribution of oocytes and ovarian tissue

Type of oocytes or ovarian tissue	Tissue establishment	Unit	Processed			Distributed		
			From NL	From EU	From Outside EU	In NL	In EU	Export Outside EU
Own oocytes, fresh and cryo	16	Oocyte	127,091	0	0	n/a	n/a	n/a
Donor oocytes, fresh and cryo	12	Oocyte	2,441	0	0	n/a	n/a	n/a
Ovarian tissue	4	Transplant	278	0	0	18	0	0

Table 1c Processing and distribution of embryos

Type of embryo	Tissue establishment	Unit	Processed			Distributed in NL
			From NL	From EU	From Outside EU	
Embryos, own oocytes and partner semen	16	Embryo	58,245	5	4	23,308
Embryos, own oocytes and donor semen	14	Embryo	4,694	0	0	1,330
Embryos, donor oocytes and partner semen	12	Embryo	1,135	0	0	512
Embryos, donor oocytes and donor semen or donated	6	Embryo	483	0	0	99

Table 2 Application of reproductive tissues and cells

Type	Recipients	Unit	Application
Partner semen	10,739	Inseminaton	25,525
Donor semen	3,042	Insemination	9,047
Embryos, own oocytes and partner semen	13,202	Embryo	23,308
Embryos, own oocytes and donor semen	821	Embryo	1,330
Embryos, donor oocytes and partner semen	266	Embryo	512
Embryos, donor oocytes and donor semen or donated	87	Embryo	99
Ovarian tissue	3	Transplant	18
Testicular tissue	0	Transplant	0

Figures 1a, 1b and 1c show the application data for the period 2018-2022.

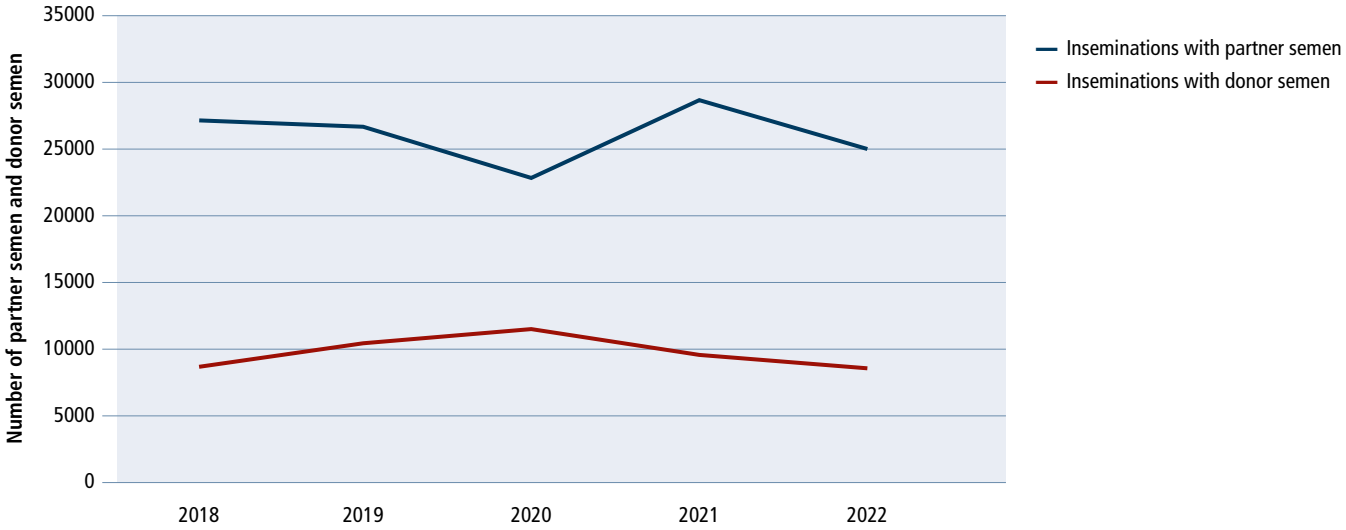

Figure 1a Number of inseminations with partner semen and donor semen, 2018-2022

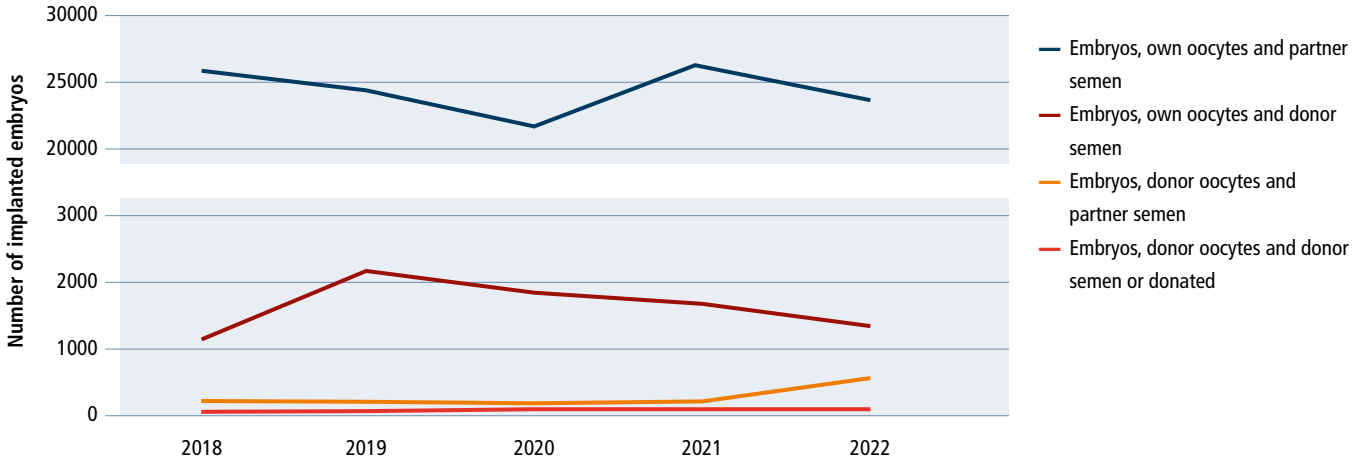

Figure 1b Number of implanted embryos, 2018-2022

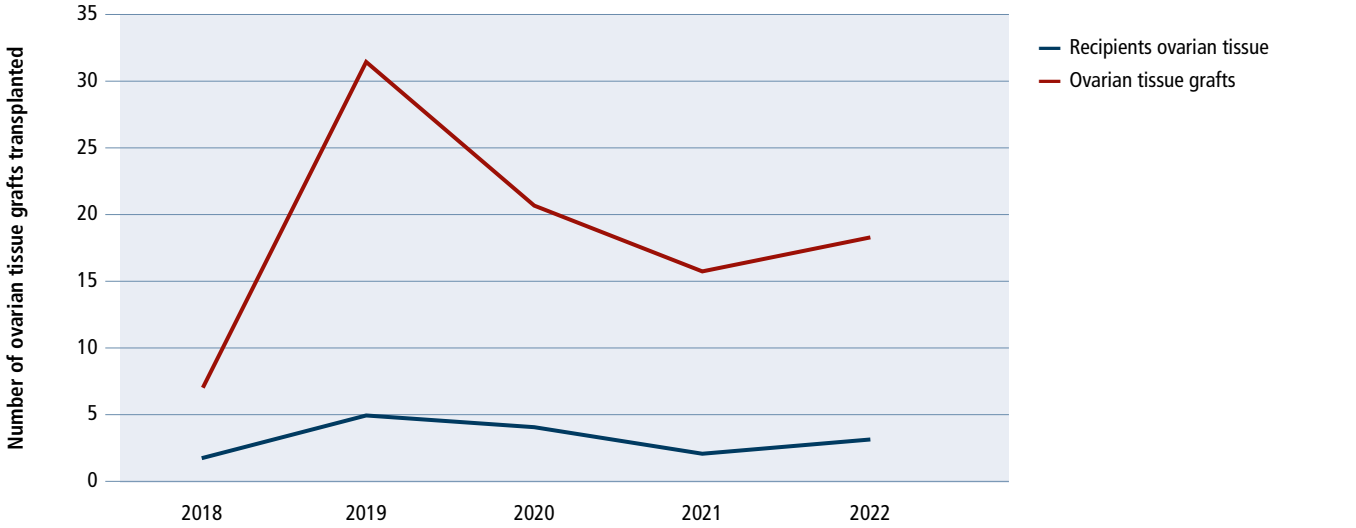

Figure 1c Number of ovarian tissue grafts transplants 2018-2022

3.3 Reports

In 2021, TRIP received 45 reports about adverse reactions during the processing and application of gametes and embryos in medically assisted reproduction. Five reports were assessed as definitely not related to the medically assisted reproductive process and are not further considered in this biovigilance report. The 40 reports with higher imputability can be subdivided into 21 incidents with or without adverse effects, 3 adverse effects, and 16 donation complications (Table 3).

Eight late reports were also received of incidents that occurred before 2022 (Table 4). Where relevant, these reports were included in the figures for the years in which they occurred.

Figure 2 summarises all reports of incidents, adverse reactions and donation complications with unlikely or higher imputability, submitted in the period 2018-2022. Adverse effects with severity grade 2 or higher and definite, probable or possible imputability are reported to the EU, and are shown as 'serious EU'. The severity of incidents and the associated reporting obligation to the EU are determined on the basis of pre-established EU criteria (see TRIP website).

Table 3 Reports of incidents and adverse reactions with definite, probable, possible or unlikely imputability concerning reproductive tissues and cells per type of fertility lab in 2022

Fertility laboratories	Number of centers	Establishment reporting	Total number of reports (serious EU)	Incidents (serious EU)	Adverse effects (serious EU)	Donation complications (serious)
IVF laboratories	16	11	25 (15)	16 (7)	0	9 (8)
Semen laboratories	52	6	15 (8)	5 (1)	3 (1)	7 (7)
Total	**68**	**17**	**40 (24)**	**21 (8)**	**3 (1)**	**16 (15)**

Table 4 Late reports of incidents involving reproductive tissues and cells per type of fertility laboratory

Year of occurrence	Type of tissue	Reporting category	Incidents (serious EU)	Description of serious incident
2017	Donor semen	Congenital defect	1 (0)	
2019	Partner semen	Loss of tissues or cells	1 (0)	
2021	Donor semen	Congenital defect	3 (1)	Postnatally, serious neurological abnormalities are diagnosed in the neonate, caused by an autosomal recessive disorder of which the donor turns out to be a carrier.
	Partner semen	Loss of tissues or cells	1 (0)	
	Embryos	Loss of tissues or cells	1 (0)	
		Incorrect product transplanted	1 (1)	Due to a series of missed checks and incomplete administration, an embryo was placed with a low chance of success..
Total			**8 (2)**	

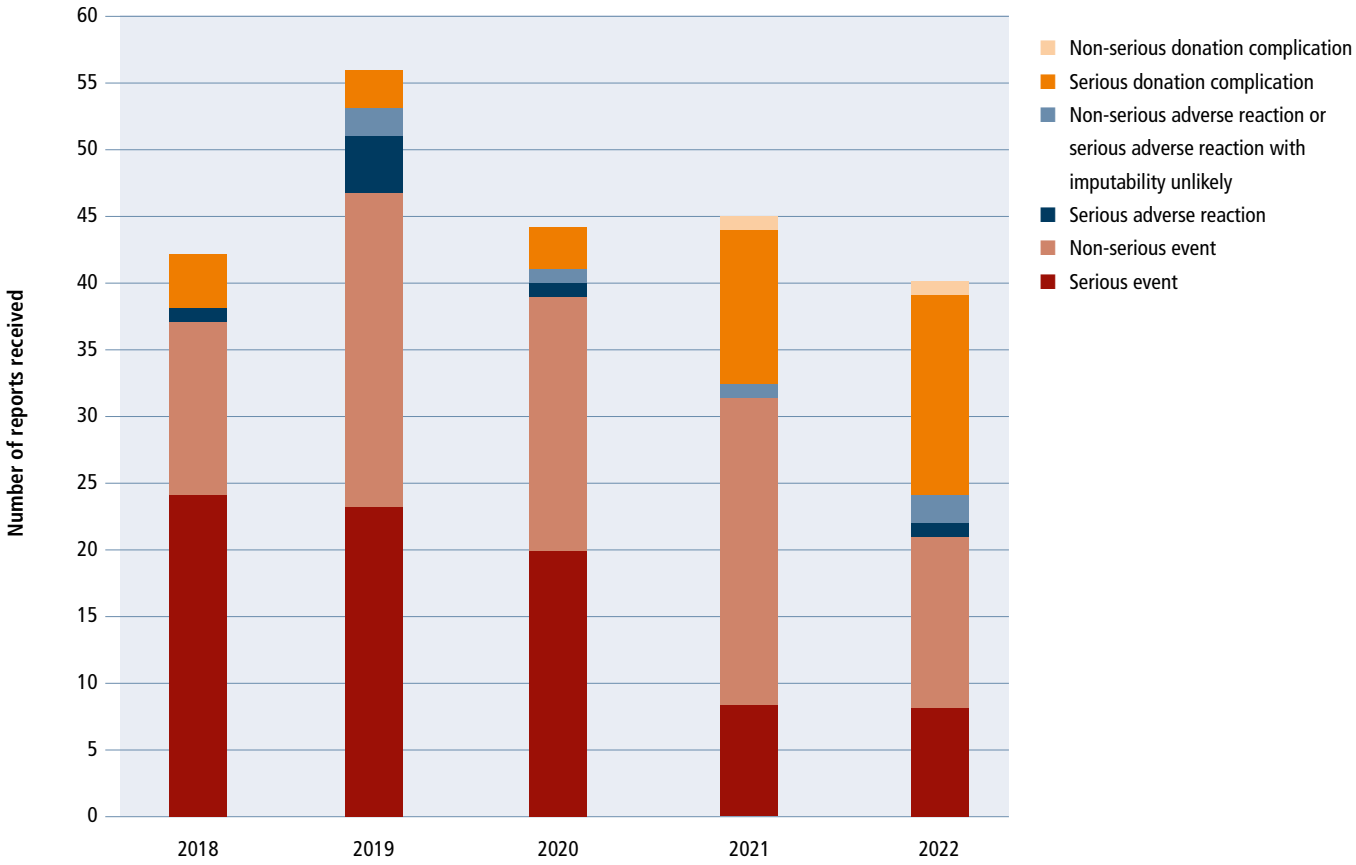

Figure 2 Reports of incidents and adverse reactions with definite, probable, possible or unlikely imputability concerning reproductive tissues and cells, classified by EU severity category 2018-2022

Incidents

Table 5 provides an overview of all incidents reported per type of tissue or cell. Figure 3 shows the distribution of serious incidents in the period 2018-2022. Serious incidents are discussed in the following sections.

Table 5 Overview of incidents in reproductive tissues and cells in 2022 and late reports

Type of tissue or cells	Incident category	Number of reports of incidents (serious EU)	Late reports (serious EU)
Semen	Bacterial contamination product	1 (1)	
	Congenital defect	10 (1)	4 (1)
	Other incident	1 (0)	
	Loss of tissues or cells		2 (0)
Oocyte	Loss of tissues or cells	2 (2)	
Embryos	Bacterial contamination product	3 (3)	
	Incorrect product applied	1 (1)	1 (1)
	Loss of tissues or cells	2 (0)	1 (0)
	Other contamination product	1 (0)	

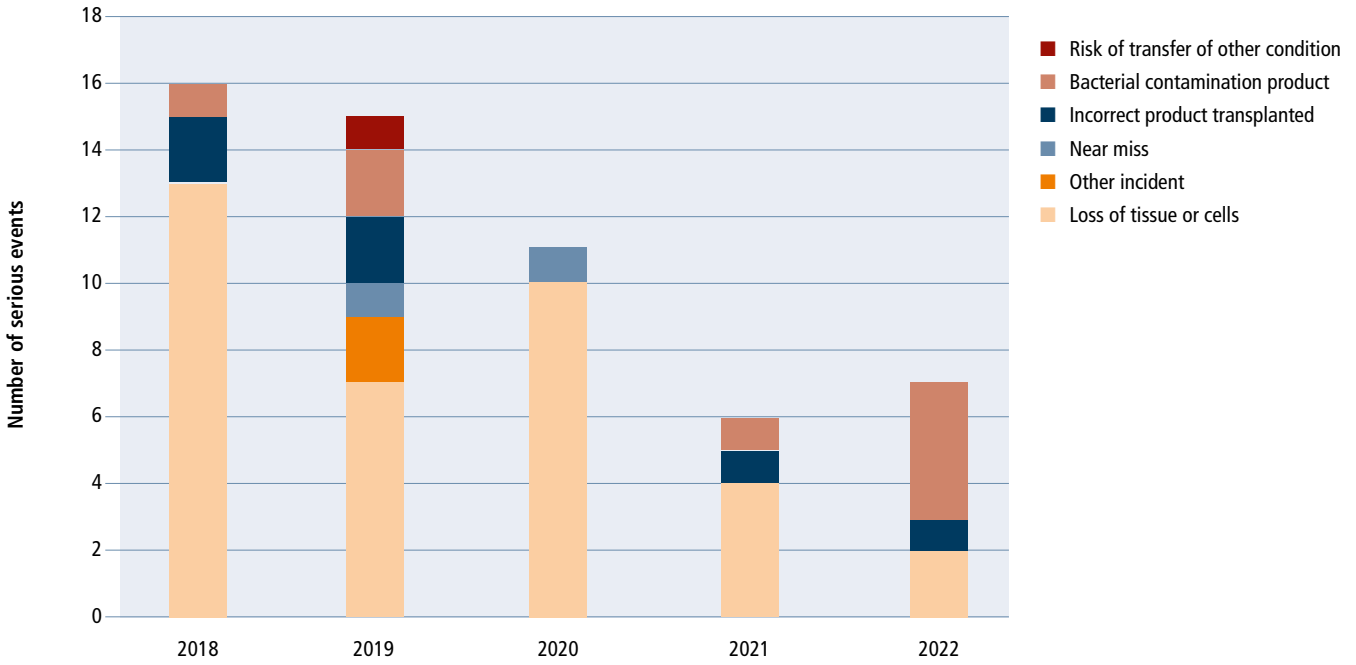

Figure 3a Number of reports of serious incidents per incident category concerning reproductive tissues and cells 2018-2022

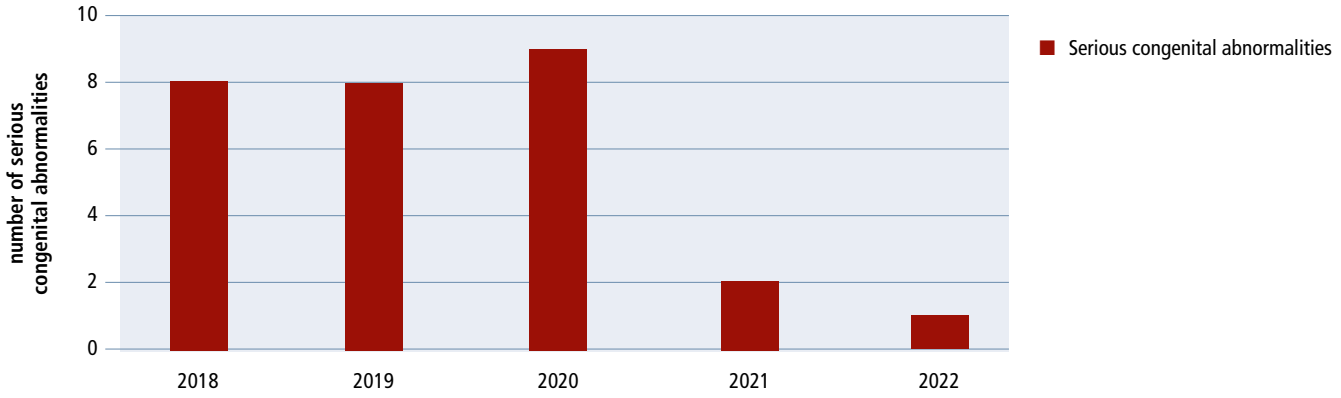

Figure 3b Number of reports of serious congenital abnormalities 2018-2022

Loss of tissues or cells

In 2022, TRIP received two reports of serious incidents 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 2022

Type of gamete or embryo	Phase in process	Description of incident
Oocyte	Processing	At the collection of the oocytes during a puncture, the tube containing the oocytes fell and the oocytes were lost.
Oocyte	Processing	After searching for oocytes, the cells were not transferred from the collection dish to the culture dish, but were mistakenly discarded. The check was subsequently not carried out in accordance to the applicable procedure.

Congenital abnormality

In 2022, one report was registered as a serious congenital abnormality after the use of donor semen, in which a bilateral cleft palate was found in the neonate. In line with 2021, fewer reports were assessed as serious congenital abnormalities compared to previous years. Part of the explanation is the fact that, in 2018, imputability began to play a role in assessing the severity grade of congenital anomalies. Reports with an 'excluded' or 'unlikely' imputability are assessed as not serious according to the EU criteria.

Bacterial contamination of product

In 2022, four cases of bacterial contamination were reported by four different tissue establishments. Three cases involved bacterial contamination of one or more embryos, and the fourth case involved contaminated semen. In all cases, the source of the infection could be traced back to the patient or partner. For all four patient pairs involved, the reproductive cycle was lost and therefore the reports are classified as serious.

Incorrect product applied

In 2022, one unintended transfer of a 3PN embryo, instead of a 2PN embryo, was reported. The 3PN embryo was initially grown outside the culture system and was mistakenly transferred to culture medium in the system. Subsequently, the transfer with the 3PN embryo was carried out. The background to the unintentional transfer of the 3PN embryo to the culture medium in the system was a different method of dripping, which meant that the fertilisation container and blastocyst container could not be clearly distinguished from each other. The method of dripping has been discussed and a mould has been developed to promote proper dripping.

Adverse effects

In 2022, TRIP received one report of a serious adverse reaction following the use of semen (Figure 4). Post-transplant bacterial contamination occurred after IUI in a non-stimulated cycle. An Enterococcus faecalis was found in the urine culture and culture of pus from the cervix. The source of the contamination has not been determined.

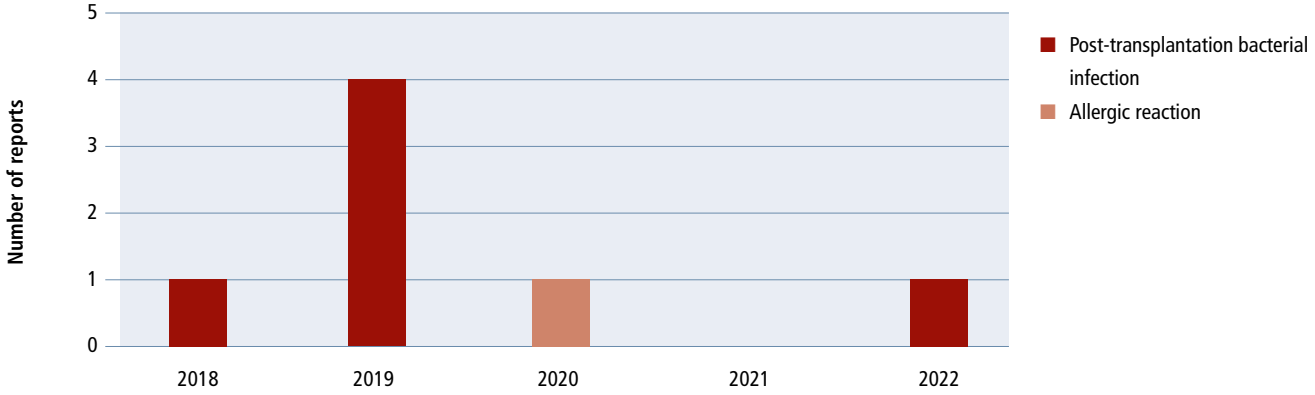

Figure 4 Reports of serious adverse reaction in medically assisted reproduction with definite, probable or possible imputability, 2018-2022

Donation complications

In 2022, 15 serious donation complications were reported. 12 cases involved ovarian hyperstimulation syndrome (OHSS) after oocyte puncture for autologous use, leading to hospitalisation. There were two instances of torsion of one of the adnexa occurred. In addition, one patient was admitted to hospital due to increasing pain after oocyte puncture, probably due to hematoma formation.

The proposal for the Regulation of the European Parliament and of the Council on quality and safety standards for human substances describes the importance of a high level of health protection of donors. The registration of donation complications and adverse effects that occur after pre-treatment with medication in the context of donation will change wne the EU SoHO regulation comes into effect. Currently, registration of serious adverse incidents surrounding donation is only mandatory if they have consequences for the safety or quality of the human substance.

3.4 Summary of reproductive tissues and cells

In 2022, TRIP received 45 reports about incidents or adverse reactions during the processing and application of gametes and embryos in medically assisted reproduction. Twenty-four reports were assessed as serious in accordance with the EU criteria, including eight incidents, one adverse effect and 15 donation complications.

Eight late reports were also received of incidents that occurred before 2022.

4 HEMATOPOIETIC STEM CELLS AND OTHER CELLS FOR THERAPEUTIC PURPOSES

4.1 Tissue establishments involved

In 2022, 16 tissue establishments in the Netherlands were authorised to collect, process, store and/or distribute hematopoietic stem cells (HSCs) and other cells for therapeutic purposes. These establishments include twelve laboratories that, besides the required licence as a tissue institution, also have an organ bank licence, with which they are also authorised to receive human tissues or cells after procurement. Three of the 16 tissue establishments are exclusively active in the field of processing cells obtained from bone marrow or peripheral blood for the production of medicinal products. All tissue establishments active in the field of hematopoietic stem cells declared their activities in 2022.

Stem cell transplantation is performed in 12 transplant centres in the Netherlands. In four centres, this only concerns autologous stem cell transplants. Stem cell products from unrelated donors are delivered to eight academic transplant centres through the Matchis foundation, mostly via the stem cell laboratories of the respective hospitals. Peripheral blood stem cells (PBSCs), bone marrow (BM) and donor lymphocyte infusions (DLIs) from unrelated Dutch donors are collected at two academic hospitals in the Netherlands. There is one tissue institution that processes, stores and distributes unrelated cord blood units (CBU).

4.2 Activities in 2022

Table 7 shows the number of processed hematopoietic stem cell transplants obtained from peripheral blood, bone marrow, cord blood and donor lymphocyte infusions. 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 applying institution). As a result, transplants may have been counted several times in the processing figures. The distribution and application of stem cells and DLIs is shown in Table 8.

For the other cells for therapeutic purposes, the cells are in many cases obtained for processing into medicinal products: 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 falls under the Medicines Act. Because of the responsibilities under the WVKL, TRIP needs to get a complete overview of the reporting of activities related to the procurement of the starting material in the coming years (see Table 9). The submission of data on distribution and final application for medicines is optional, but has been increasing in recent years (see Table 10). Reports of serious incidents and complications related to the procurement of human substances are not yet regulated by legislation, but TRIP prefers to receive them, pending additional regulations. Reports of known adverse effects in the application of medicines are not TRIP's responsibility. TRIP is consulting with Lareb, VWS, IGJ and parties active in the field on a flow chart for a clear reporting route, see Chapter 2.3.

Table 7 Processing of hematopoietic stem cells and DLIs in 2022

Type of cells	Tissue establishments	Processing of transplants			
		From NL	From EU	Outside EU	Total
PBSC					
autologous	11	1,241	0	0	1,241
related	8	188	0	0	188
unrelated	8	350	182	39	571
Bone marrow					
autologous	1	2	0	0	2
related	5	45	0	0	45
unrelated	8	52	19	3	74
Cord blood					
related	2	3	0	0	3
unrelated	5	25	34	25	84
Lymphocytes (DLI)					
related	8	72	0	0	72
unrelated	7	80	44	13	137

Table 8 Distribution and application of hematopoietic stem cells and DLIs in 2022

Type of cells	Tissue establishments	Distributed/ delivered bags*	Reporting Transplant centres	Bags applied*	Recipients
PBSC					
autologous	11	3,350	11	3,346	1,040
related	8	499	8	498	155
unrelated	8	675	8	684	328
Bone marrow					
autologous	0	0	0	0	0
related	5	41	5	41	40
unrelated	8	83	8	83	55
Cord blood					
related	1	1	1	1	1
unrelated	5	66	5	64	44
Lymphocytes (DLI)					
related	8	90	8	87	70
unrelated	7	166	7	161	124

* Three tissue establishments reported the number of transplants rather than the number of bags, 1 transplant was counted as 1 bag.

Table 9 Processing of other therapeutic cells in 2022

Type of cells	Tissue establishments	Transplants processed			
		From NL	From EU	Outside EU	Total
Mesenchymal stem cells unrelated	2	69	0	0	69
Mononuclear cells from peripheral blood	9	193	0	367	560
Cells from cord blood	2	5	0	9	14
Tumour tissue/cells	3	23	0	0	23
Granulocytes	1	30	0	0	30

Table 10 Distribution and application of other therapeutic cells in 2022

Type of cells	Tissue establishments	Distribution (unit = bag)	Treatment centres	Units units	Number of Recipients
Mesenchymal stem cells unrelated	2	31	2	31	26
Dendritic cells, autologous	2	17	2	111	29
Mononuclear cells, autologous	3	39	2	20	18
Tumour infiltrating lymphocytes, autologous	3	22	2	36	34
CAR T/TCR cells, autologous	9	95	8	150	143
Expanded Natural Killer Cells from cord blood	1	5	1	5	5
Granulocytes	1	29	1	29	1

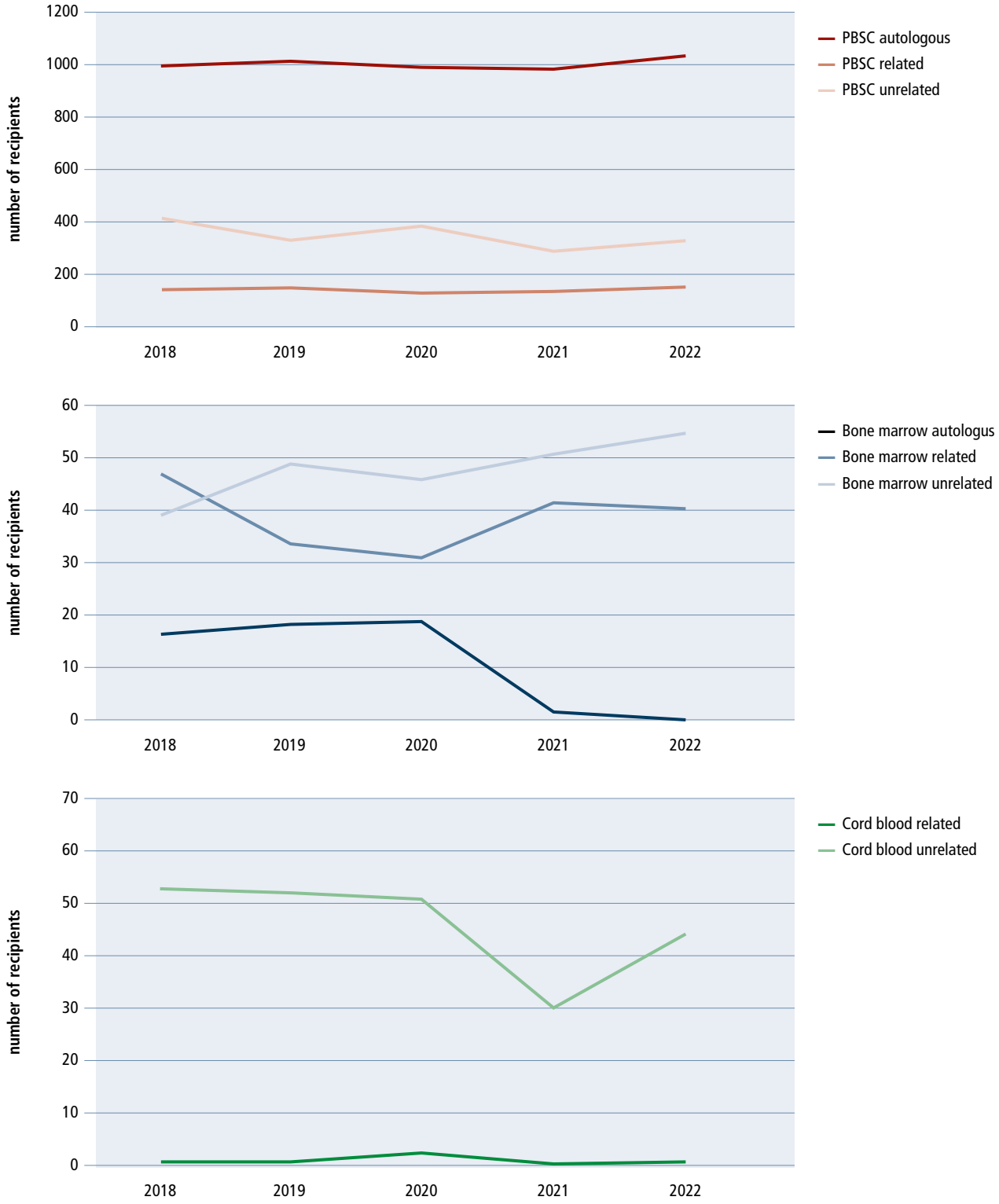

Figure 5a-b-c. Number of hematopoietic stem cell transplant recipients per transplant type, 2018-2022. In 2021, one center did not report the number of recipients of PBSC and BM allogeneic related.

4.3 Reports

In 2022, a total of 47 reports relating to hematopoietic stem cells or other cells for therapeutic purposes were received from seven reporting centres. One report was assessed as definitely not related to the stem cell transplant and is not further considered in this biovigilance report. The reports mainly concern low-grade adverse effects and incidents that are not serious according to EU criteria. Not all tissue establishments report these non-serious adverse effects and incidents to TRIP. In 2022, eight reports (four adverse effects and four incidents) were assessed as serious in accordance with EU criteria and therefore mandatory to report at EU level. These reports can be made available to the IGJ via the TRIP reporting system.

See Table 11 for specifications of the reports. Figure 6 shows a multi-year overview of reports of HSCs and other cells. The incidents defined as serious according to EU criteria (see TRIP website for criteria) and the adverse reactions with a severity grade of 2 or higher and definite, probable or possible imputability are described in Tables 12 and 13.

Table 11 Reports per tissue type, reporting category and severity (according to EU criteria), 2022

Type of tissue or cells	Incident category	No. of reports (serious)*
Peripheral blood stem cells	Bacterial contamination of product	3 (1)
	Loss of tissues or cells	1 (0)
	Other incident	3 (0)
Bone marrow	Bacterial contamination of product	9 (0)
Donor lymphocytes	Loss of tissues or cells	1 (0)
	Other incident	1 (0)
Mononuclear cells	Bacterial contamination of product	2 (1)
Leukocytes	Other incident	1 (0)
Granulocytes	Loss of tissues or cells	1 (1)
CAR T-cells	Loss of tissues or cells	1 (0)
Tumour infiltrating lymphocytes	Bacterial contamination of product	1 (1)
Type of tissue or cells	**Category of adverse effect**	**No. of reports (serious)***
Peripheral blood stem cells	Post-transplantation febrile reaction	2 (0)
	Post-transplantation bacterial infection	1 (0)
	Circulatory overload	1 (0)
	Other reaction	3 (1)
Bone marrow	Circulatory overload	3 (2)
	Other reaction	3 (0)
Cord blood	Other reaction	7 (1)
Donor lymphocytes	Other reaction	1 (0)
CAR T-cells	Other reaction	1 (0)

* Serious incidents according to EU criteria, serious adverse effects ≥ grade 2 with definite, probable or possible imputability.

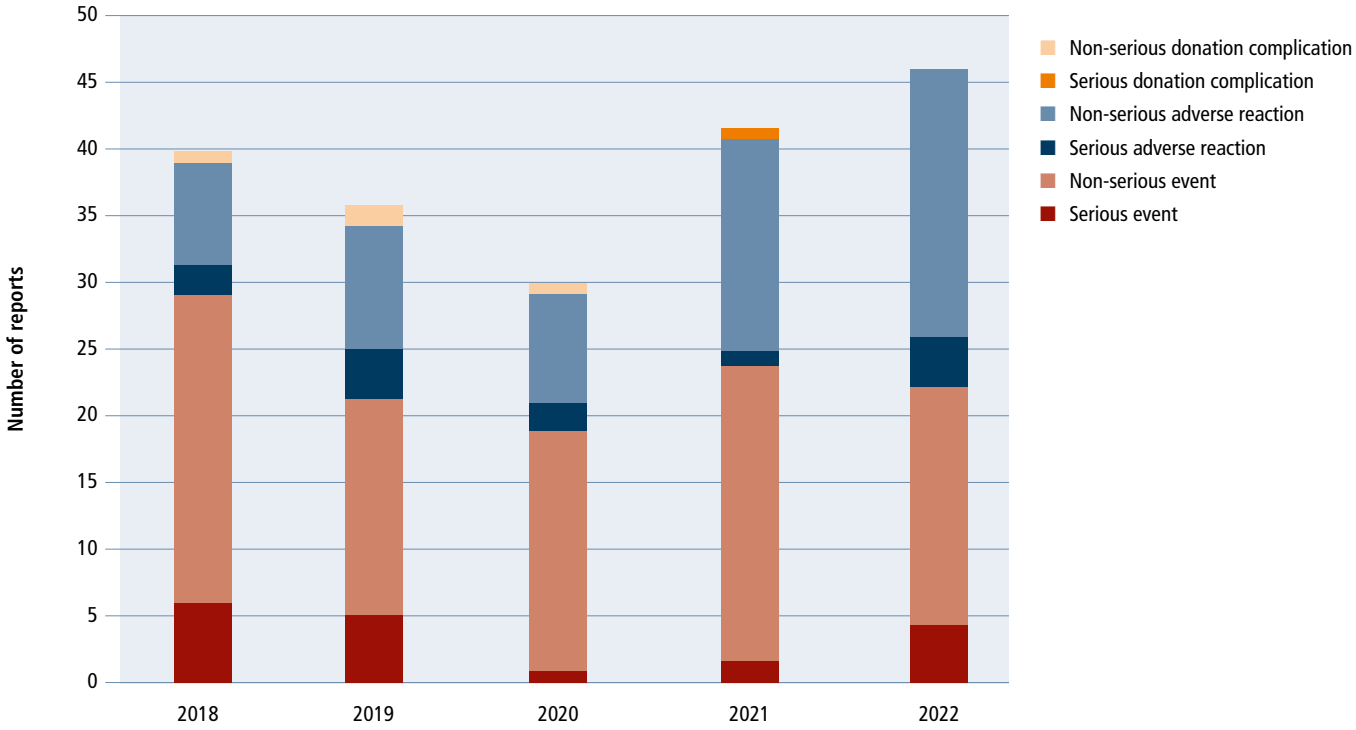

Figure 6 Total reports of hematopoietic stem cells and other cells for therapeutic purposes, 2018-2022

Table 12 Adverse effects (serious according to EU definition) relating to hematopoietic stem cells and other cells for therapeutic purposes in 2022

Type of HSC	Incident (description)	Reporting category
PBSC, autologous	Product error during procurement. On the second day after procurement of the autologous stem cell transplant, temperature increased. The patient's cultures and the apheresis product were positive for Staphylococcus aureus. The patient was treated with antibiotics and subsequently underwent an additional apheresis procedure.	Bacterial contamination product
Mononuclear cells, autologous	Product error during procurement. When processed into ATMP at pharmaceutical company 'production failure', testing product showed presence of Staphylococcus epidermidis Cultures at tissue institution remained negative. However, after the second apheresis, the obtained apheresis product was again contaminated. Patient underwent antibiotic treatment and third apheresis procedure, after which ATMP production and subsequent treatment were successful.	Bacterial contamination product
Tumour infiltrating lymphocytes, autologous	Product error during procurement. Tumour tissue for TIL production received in incorrect, non-sterile container. Also Enterococcus faecium demonstrated in the obtained tissue. The production process was stopped and the patient underwent a second procedure for the procurement of new tissue for ATMP production.	Bacterial contamination product
Granulocytes, allogeneic unrelated	Processing error during procurement. Clots detected in apheresis product, apheresis device and infusion line. Analysis showed that insufficient anticoagulant had been used during the procedure, the pharmacy supplied a different concentration of citrate than before. Donation without complications, but no product. No clinical consequences for intended recipient.	Loss of cells

Table 13 Adverse effect (severity grade ≥2, definite, probable or possible imputability) relating to hematopoietic stem cells in 2022

Type of HSC	Adverse effect (description)	Interval v. transplant	Imputability	Severity
PBSC, autologous	Other reaction Dyspnoea with saturation drop to 92% and erythema. Indicated as toxicity with DMSO where maximum DMSO load has not been exceeded. Full recovery	During procedure 1st unit	Definite	2
Bone marrow, allogeneic related	Circulatory overload Hypertension and saturation drop to 88%. About 300 ml applied product Pre-existing renal dysfunction. Short-term treatment with oxygen and diuretics. Full recovery	During procedure	Probable	2
Bone marrow, allogeneic unrelated	Circulatory overload Transplant with approximately one litre volume. Hypertension, oxygen requirement, bradycardia and neurological symptoms (restlessness, agitation, headache). Treated with diuretics and antihypertensives. Full recovery	During procedure	Definite	2
Cord blood, allogeneic, unrelated	Other reaction Hypertension during transplantation requiring drug treatment. Admission to ICU for observation, recovered without additional treatment. Indicated as response to DMSO. Full recovery	During procedure	Probable	2

4.4 Summary of hematopoietic stem cells and cells for therapeutic purposes

In 2022, TRIP received reports from all tissue establishments and healthcare centres that are active in the field of hematopoietic stem cells. This number of reports (the denominators) is not comparable from year to year due to incomplete participation in 2021, changes in specified units (transplants instead of bags by three establishments) and differences in interpretation of the concepts of processing and distribution. Seven tissue establishments submitted reports of incidents and adverse effects (range 1-33 reports per tissue institution) that occurred in the chain from donor to patient.

The figures regarding patients treated with stem cell transplantation do not show any noticeable changes. However, increasing activity is visible in the processing, distribution and application of other cells for therapeutic purposes, often with the aim of further processing into medicines such as CAR T-cells. This is also reflected in the number of reports. In 2022, seven reports were received regarding other cells with a therapeutic purpose (excluding DLIs), as opposed to two in 2021; these concern cases that are comparable to the reports in the stem cell category.

In 2022, four serious incidents were registered compared to an average of three per year in the last five years (2017-2021: range 1-6). In addition, four reports of serious reactions were received compared to an average of 1.8 per year in the last five years (2017-2021: range 1-3). In 2022, no donation complications were reported to TRIP.

Two serious reactions and two non-serious reactions involved circulatory overload as an adverse effect of stem cell transplantation, three of them in the case of a bone marrow transplant and one in the transplantation of peripheral blood stem cells. Within hemovigilance, this is a known complication of blood transfusion, responsible for the largest number of reactions with serious morbidity. This complication is getting a lot of attention within hemovigilance and recommendations and tools for prevention have also been developed. Attention is drawn to signalling this complication in the clinical care of patients undergoing stem cell transplantation. By structurally reporting this type of reaction to TRIP, insight can be obtained of the occurrence of circulatory overload after treatment with hematopoietic stem cells and risk factors can be identified.

5 OTHER TISSUES AND CELLS

Healthcare centres and tissue establishment involved

In total, 71 healthcare centres and 58 implantology practices applying other human tissues and cells in the Netherlands are known to TRIP. Two centres did not report application figures this year and three centres reported application figures only partially. Of the implantology practices known to TRIP, 55 reported application figures, among them were seven that reported not to have applied human substances in 2022. It is not mandatory for healthcare centres to report application figures. This is because the use of other tissues and cells is not currently a recognised activity under the WWKL. The 2006 Directive on Human Substances states that an applying institution "passes on all relevant information to the organ centre or tissue institution from which the material originates, in order to facilitate traceability and to guarantee quality assurance and safety". The centres that provide information about possible reports and application figures will receive a participation statement from TRIP, which the IGJ may request during an inspection.

In the Netherlands, there are 10 tissue establishments authorised to collect, process, store and/or distribute other tissues and cells. In addition, there are 14 tissue establishments that, besides the required licence as tissue establishment , also have a licence as an organ bank, with which they are also authorised to receive tissue or cell transplants direct after procurement. All have declared their activities in 2022 (figure 7).

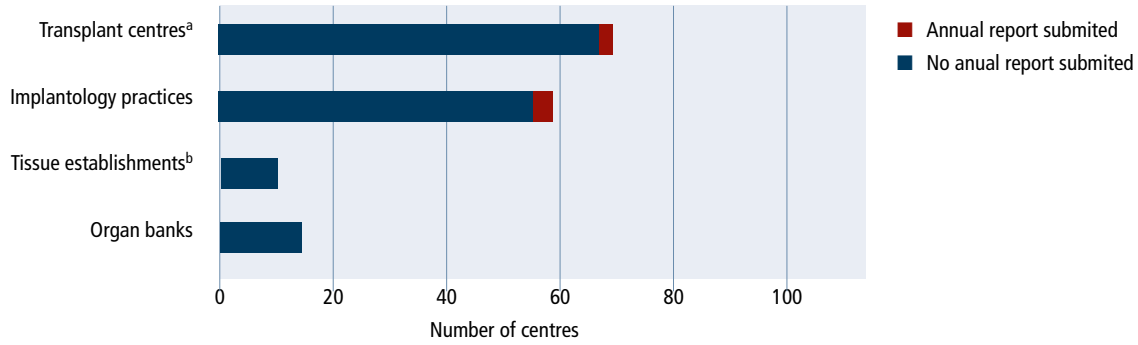

Figure 7 Participation relating to other tissues and cells in 2022
[a] Three centres submitted a partial report
[b] Tissue establishment without organ bank accreditation

5.1 Bone and other musculoskeletal tissues and cells

5.1.1 Establishments and centres 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 establishments reported their application figures to TRIP, but not all do so due to its non-mandatory nature. In May 2023, 17 centres in the Netherlands had a tissue establishment or organ bank accreditation for the processing, preserving and/or distributing of bone and other musculoskeletal tissues. All 17 submitted reports of their activities in 2022.

In total, 122 centres known to TRIP submitted reports of the application of musculoskeletal tissues, among them were two hospitals submitting partial reports and two hospitals and three implantology practices that did not provide figures.

5.1.2 Activities 2022

Table 14 shows the processing of bone and other musculoskeletal tissues in 2022. There is a noticeable increase in the use of cartilage, although no direct increase in its distribution is seen. For femoral heads, bone filler, mineralised and demineralised, and tendons, the number of recipients was not specified several times, two, five, four, and four times, respectively. Apart from the increase in cartilage applications, no noticeable shifts are seen. There remains a striking difference in application and distribution of bone filler, possibly because not all users know / are known to TRIP (Table 15).

Table 14 Processing of bone and other musculoskeletal tissues and cells in 2022

Type of tissues/cells	Tissue establishments	Processing of transplants			
		From NL	From EU	Outside EU	Total
Bone					
Femoral heads, living donor	7	3,053	105	0	3,158
Femoral heads, post-mortem donor	1	12	0	0	12
Bone filler, mineralised	1	2,215	0	0	2,215
Bone filler, demineralised	1	172	8	0	180
Bone, whole	2	100	47	0	147
Cranial bone (autologous)	3	157	0	0	157
Other musculoskeletal tissues and cells					
Tendons	1	573	2	0	575
Bone-tendon-bone grafts	1	29	1	0	30
Fascia	1	107	0	0	107
Cartilage	1	35	2	0	37
Chondrocytes, autologous	1	87	0	0	87
Menisci	1	31	1	0	32

Table 15 Distribution and application of bone and other musculoskeletal tissues and cells in 2022

Type of tissue/cells	Tissue establishment	Healthcare centres	Distributed units				Applied units (from NL)	Recipients
			In NL	Export In EU	Export Outside EU	Totaal		
Bone								
Femoral heads, living donor	8	49	1,696	671	0	2,367	1,243 (1,242)	1,145
Femoral heads, post-mortem donor	2		31	34	0	65		
Bone filler, mineralised	9	75	9,507	7,790	4,339	21,636	3,013 (2,682)	2,553
Bone filler, demineralised	9	31	1,165	11,818	14,580	27,563	1,023 (677)	686
Bone, whole	2	18	195	22	2	219	103 (103)	102
Cranial bone, autologous	3	5	89	0	0	89	48 (48)	48
Other musculoskeletal tissues and cells								
Tendons	1	30	527	48	0	575	360 (360)	306
Bone-tendon-bone grafts	1	7	21	9	0	30	20 (20)	19
Fascia	1	2	105	0	2	107	97 (97)	49
Cartilage	1	8	28	0	0	28	25 (14)	17
Chondrocytes (ATMP)	1	1	81	0	0	81	29 (29)	29
Menisci	1	2	15	1	0	16	16 (16)	16

5.2 Cardiovascular tissues

5.2.1 Establishments and centres involved

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

Of the 10 centres applying cardiovascular tissue known to TRIP, all reported the number of applications.

5.2.2 Activities 2022

There are no notable shifts in figures concerning cardiovascular tissue distribution and application (Tables 16 and 17). 80 pulmonary valves were distributed and 83 applied from the Netherlands, however, in 2021 more pulmonary valves were distributed than applied (Table 17). When using both patches and pericardium, one institution did not specify the number of recipients.

Table 16 Processing of cardiovascular tissues and cells in 2022

Type of tissue	Tissue establishment	Processing of transplants			
		From NL	From EU	Outside EU	Total
Aortic valves	1	215	0	0	215
Pulmonary valves	1	215	0	0	215
Vessels	1	10	0	0	10
Patches	1	108	0	0	108

Table 17 Distribution and application of cardiovascular tissues and cells in 2022

Type of tissue	Tissue establishment	Healthcare centre	Distributed units				Applied units (from NL)	Recipients
			In NL	In EU	Export	Total		
Aortic valves	1	3	5	1	0	6	5 (3)	5
Pulmonary valves	1	4	80	23	0	103	88 (83)	88
Patches	1	3	38	27	0	65	30 (25)	25
Pericardium	0	6				0	193 (0)	97

5.3 Skin

5.3.1 Establishments and centres involved

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

Of the 8 healthcare centres applying skin known to TRIP, 7 are hospitals and 1 is an implantology practice. One hospital has not yet reported their figures for 2022, but has not reported the use of donor skin since 2019.

5.3.2 Activities 2022

More skin grafts were processed from donors outside the Netherlands, from other member states of the EU. More units of skin were distributed and applied to patients in the Netherlands, making the figures comparable to 2020. Distribution in Europe and exports increased slightly compared to last year (Tables 18 and 19). There is a decrease in the distribution of the number of units of acellular dermis, with the distribution number more in keeping with the application rate.

Table 18 Processing of skin in 2022

Type of tissues	Tissue establishments	Processing of transplants/donors*			
		From NL	From EU	Import	Total
Donor skin	1	389	157	0	546
Acellulair dermis	3	42	3	0	45
Autologous skin	0				0

* The processing of donor skin is specified in the number of donations/donors and acellular dermis in the number of grafts

Table 19 Distribution and application of skin in 2022

Type of tissue	Tissue establishment	Healthcare centre	Distributed units				Applied units (from NL)	Recipients
			In NL	In EU	Export	Total		
Donor skin	1	5	2,364	13,915	1,577	17,856	1,924 (1,924)	68
Acellular dermis	3	4	19	0	350	542	10 (10)	8
Autologous skin	0	1				0	2 (2)	2

5.4 Ocular tissues

5.4.1 Establishment and centres 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 Dutch establishments involved in the processing, preserving and/or distributing of ocular tissue, all of which submitted their annual reports to TRIP.

Of the 22 healthcare centres applying ocular tissue know to TRIP, one centre indicated that it would not be able to provide figures this year.

5.4.2 Activities 2022

One tissue establishment indicated that they did not process or distribute ocular tissue this year (Tables 20 and 21). There is a discrepancy between the number of corneas and sclerae distributed and their applications. According to the annual figures of the Netherlands Transplant Foundation (NTS), 1,909 corneas were allocated in 2022. TRIP received reports about 1,766 applications. This discrepancy of annual figures received is probably due to one center not submitting a report and incomplete application figures.

Table 20 Processing of ocular tissues and cells in 2022

Type of tissues/cells	Tissue establishment	Processing of transplants			
		From NL	From EU	Outside EU	Total
Cornea	2	4,370	0	0	4,370
Sclera	1	599	0	0	599
Limbal stem cells	1	1	0	0	1

Table 21 Distribution and application of ocular tissues and cells in 2022

Type of tissue	Tissue establishments	Healthcare centres	Distributed transplants				Applied units (from NL)	Recipients
			In NL	In EU	Export	Total		
Cornea	2	14	1,977	499	47	2,523	1,815 (1,766)	1,796
Sclera	1	16	1,830	22	0	1,852	1,425 (1,396)	1,421

5.5 Other cells and tissues

5.5.1 Establishments and centres involved

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

In the Netherlands, there are three organ banks and one tissue establishment that are engaged in the processing, storage and/or distribution of other cells and tissues. Of the 10 centres applying other cells and tissues known to TRIP, 8 reported their activities; 2 indicated they were unable to provide exact figures for 2022.

5.5.2 Activities 2022

Table 22 shows the numbers for the processing of other cells and tissues (Table 23). Some of the other cells and tissues are used as starting material for further processing into ATMP. One tissue establishment indicated that it did not process or distribute tumour tissue this year, in contrast to previous years.

Table 22 Processing of other cells and tissues in 2022

Type of tissues	Tissue establishments	Processing of transplants			
		From NL	From EU	Import	Total
Amniotic membranes[a]	2	2	11	0	13
Pancreatic islets[b]	1	15	0	0	15

[a] placentas

[b] pancreases

Table 23 Distribution and application of other cells and tissues in 2022

Type of tissues/cells	Tissue establishment	Healthcare centres	Distributed transplants				Applied units (from NL)	Recipients
			In NL	In EU	Export	Total		
Amniotic membranes	3	6	213	158	4	375	128 (128)	110
Pancreatic islets	1	1	15	0	0	15	15 (15)	15
Salivary gland stem cells for ATMP	0	1				0	1	1
Nervous tissue for ATMP	1	0	0	8	0	8		
Tumour tissue for ATMP	1	0	8	0	0	8		

5.6 Reports on other tissues and cells

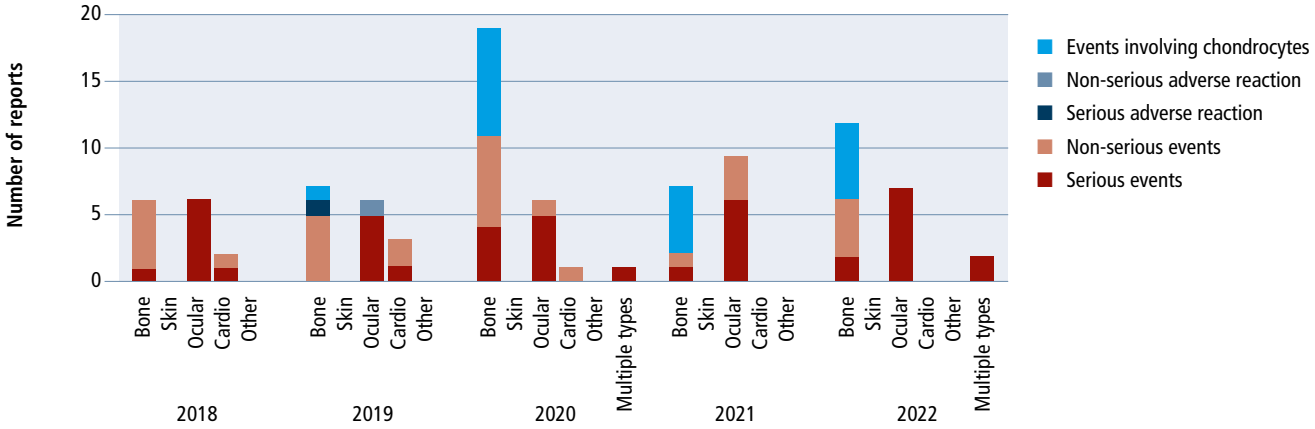

Figure 8 Reports relating to other tissues and cells, 2018- 2022
Under bone chondrocyte reports and under ocular, there were 2 late autopsy reports with a contraindication for donation (see explanation below).

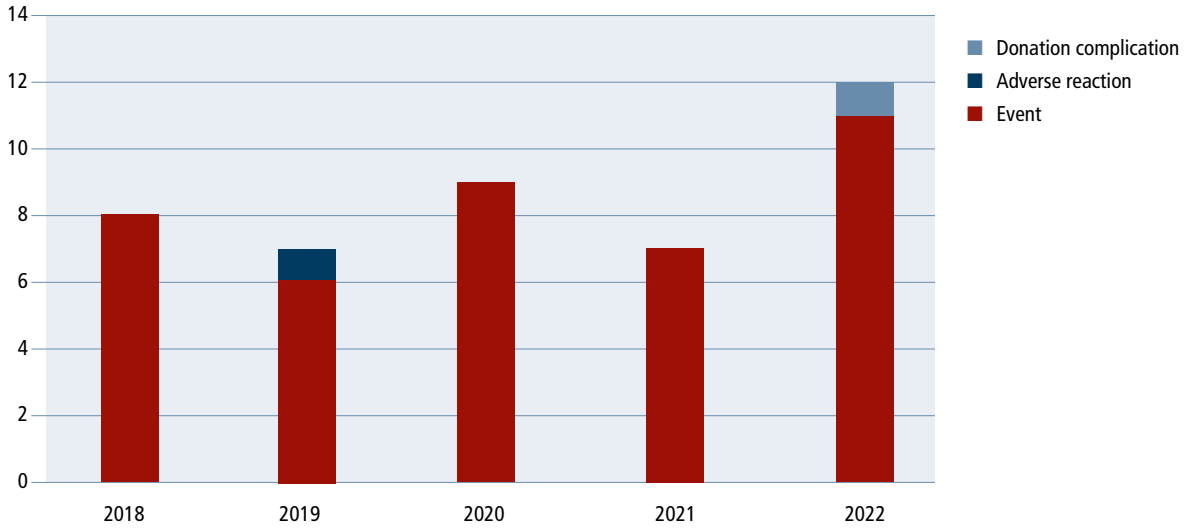

Figure 9 Number of reports (serious according to EU criteria) per year, 2018-2022
2022: 2 late autopsy reports with a contraindication for donation; 1 donation complication for ATMP production

In 2022, TRIP received 21 reports regarding other tissues and cells and one late report from 2021. Five reports concerned bone and eight reports are related to other musculoskeletal tissues; in two reports, the entire donation was lost and there were seven reports concerning (among other things) corneas (Figure 8). Of the seven reports concerning corneas, six reports involved the loss of the entire donation, with three cases in which the corneas had already been distributed and three cases where the corneas were not yet distributed. The 22 reports were submitted by four healthcare centres and four tissue establishments.

Of the 22 reports, six 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 incidents that take place when producing ATMPs using human tissues and cells. One of the reports regarding chondrocytes concerns a donation complication in autologous donation and is summarised in Table 24 below (serious for the EU). Reporting donation complications is currently voluntary (see Chapter 3.3.1, Donation complications). The reports regarding ATMPs are included in Figure 8.

The other 16 reports are all incidents. Of the 22 reports, 12 reports were assessed as serious according to the EU criteria (Figure 9). They are summarised in Table 24.

Two corneal incidents concerned the risk of transfer of another condition. In these reports, 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 and is assessed as serious according to EU criteria. Furthermore, minor localisation of a low-grade B-cell lymphoma was found on microscopic examination, which is also a contraindication for tissue donation.

Table 24 Serious incidents (according to EU definition, see Annex C) related to other tissues and cells in 2022

Type of tissue	Incident (category and description)	Number
Bone	Bacterial contamination of product In the period between 2017 and 2022, 8 femoral heads were released, while the culture result upon donation showed growth (7×) or the serology test result upon donation was positive for Q fever (1×). One centre indicated that the femoral head could not be traced to the recipient (1×). There have been no indications of infections among the recipients.	1
Bone	Risk of transfer of condition Four years after liver donation, a neuroendocrine tumour was diagnosed (coincidental finding after procurement). Regarding the donated bone tissue and tendon tissue, no viable cells remain after treatment, so the chance of tumour cells being transplanted approaches zero. The practitioners were informed as a precaution and any available material was destroyed. As far as we know, there are no complications from bone recipients.	1
Cornea	Near miss During surgery, the DMEK was found to be incorrectly marked and was reoriented and transplanted perioperatively. The tissue probably moved a little during marking, causing the "interpunction" to be off centre.	1
Cornea	Loss of cells or tissue After tissue removal, the corneas fell during transport and were no longer suitable for transplantation.	2
Cornea	Loss of cells or tissue Blood samples were lost after tissue donation, meaning that procured corneas could no longer be used for transplantation.	2
Cornea	Risk of transfer of condition After receiving the results of the final donor autopsy report, a contraindication for tissue donation could not be ruled out, but the corneas were already transplanted.	1
Cornea	Wrong product transplanted/applied During registration for tissue donation, donor did not state their medical history to include a premalignant hematological disorder, which is a general contraindication for tissue donation.	2
Multiple tissues	Loss of cells or tissues Blood samples were lost after tissue donation, meaning that procured corneas could no longer be used for transplantation.	1
Chondrocytes[a]	Donation complication Two weeks after autologous donation of chondrocytes, the patient called the hospital with complaints of pain and an uneasy wound at the same location as the previous biopsy. The symptoms persisted and a septic arthritis developed, requiring several rounds of endoscopic irrigation and antibiotics for several weeks.	

[a] and one donation complication in autologous donation for ATMP.

5.7 Summary of other tissues and cells

After assessing the completeness and accuracy of the annual figures, it was found that two hospitals had not reported their application figures and three hospitals only partially reported application figures. This year, an extra 'box' was added to the form, where healthcare centres could indicate that they had not used humane substances. Seven implantology practices ticked this box. In some reports, the number of recipients was not specified. For a number of healthcare centres using other tissues and cells, it is difficult to estimate whether the application figures are complete. In addition, although this will change due to the new SoHo regulations, it is not mandatory for healthcare centres to report these activities at this moment.

Reports regarding other tissues and cells show no notable shifts compared to previous years. There were 12 serious reports in 2022, most of which were incidents, including two related to bone tissue, two cases where entire donations were lost and seven cases related to ocular tissues, two of which involved a risk of transmission of a condition in the microscopic autopsy report. For the first time, there was a serious donation complication (according to EU criteria) with an autologous donation for ATMP production.

Nearly a third of all reports on other tissues and cells was related to the cultivation of chondrocytes into ATMP. Incidents during procurement or processing may have consequences for the donor, in this case autologous. In 2022, TRIP consulted Lareb regarding the development of a route for the reporting of incidents and reactions in the ATMP production chain.

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 incidents and adverse effects throughout the human substance 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 incidents and adverse reactions that may be related to the quality and/or safety of these human substances. This Directive was transposed into the Dutch Body Material (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 incidents and adverse reactions related to the transplantation of human substances meets the requirements laid down in European and Dutch legislation. Figure 10 presents a flowchart of serious and non-serious biovigilance reports in Dutch healthcare. It is likely that the number of 'non-serious' incidents and adverse reactions is much higher than the number of serious cases, and that not all establishment submit the less serious reports to TRIP. This is consistent with the high percentage of serious incidents and reactions in reports to TRIP.

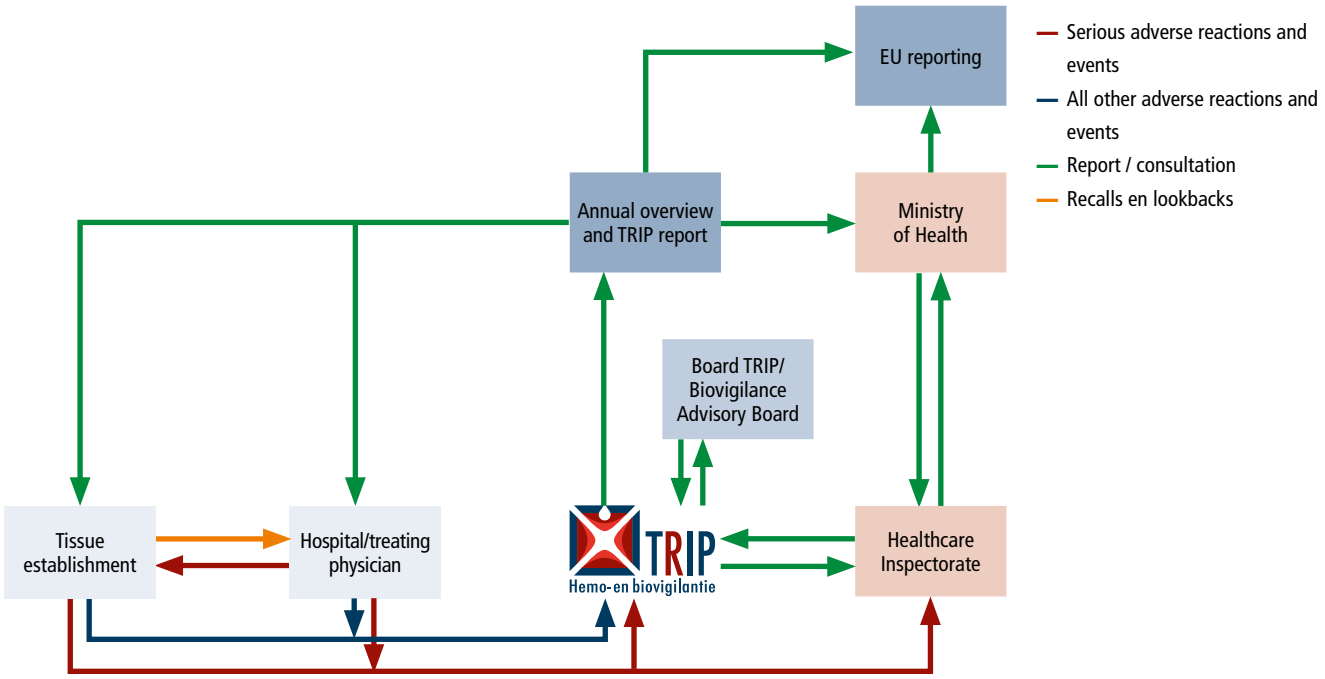

Figure 10 Flowchart of reports concerning human tissues and cells

All types of human substances, from both living and post-mortem donors, fall within the scope of the WVKL, with the exception of human substances removed and returned to the same person in the same surgical procedure. If autologous material is stored or processed in an area other than where the patient stays, he provisions of the WVKL are not applicable. Allogeneic applications of tissues fall under the scope of the WVKL in all cases.

Method

TRIP is an independent foundation that cooperates closely with the users of human substances (healthcare centres) and tissue establishments. All reports submitted 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 substances by all Dutch hospitals, other healthcare providers and tissue establishments, in accordance with European regulations. The information is aggregated as a denominator for the TRIP data on incidents and adverse effects and the annual mandatory data submission to the European Commission. TRIP compiles the annual mandatory overview of serious adverse incidents and adverse reactions to be forwarded to the European Commission, through the Ministry of Health, Welfare and Sport.

Tissue establishments, hospitals and other healthcare centres that provide processing, distribution and/or clinical application figures and submit reports on incidents and/or adverse reactions to TRIP receive an annual participation certificate. This participation certificate contributes to safety awareness in the clinical 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 licencing procedures or licence renewal for tissue establishments or organ banks.

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

B REPORTING OF INCIDENTS AND ADVERSE REACTIONS

Tissue establishments

The Reporting of serious adverse incidents and adverse reactions relating to human substances is laid down in Article 8.1 of the Dutch Body Material 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 incidents and adverse reactions that could influence the quality and safety of human substances or that are detected after application and could be linked to the applied human substance. Adverse incidents and adverse reactions should be reported to TRIP and also to the Health and Youth Care Inspectorate (IJG) if classified as serious. 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.

Healthcare centres; i.e. hospitals, other centres such as implantology practices

Healthcare centres must report (possible) product-related serious adverse reactions or incidents 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 reporting parties.

In the event of a 'calamity' (possibly) caused by human substances, the healthcare centre must also inform the IGJ in accordance with the Healthcare Quality, Complaints and Disputes Act (WKKGZ).

Reporting to the Health and Youth Care Inspectorate

In the Netherlands, the Health and Youth Care Inspectorate (IGJ) has been designated as the competent authority for receiving reports of serious incidents and adverse 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 incidents and adverse reactions related to human substances. The TRIP digital reporting system facilitates the forwarding of serious incidents and adverse reactions reports to the IGJ. Reporting parties 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 incidents and adverse reactions is different from the reporting of calamities under the Healthcare Quality, Complaints and Disputes Act. Calamities have a different definition including a specific procedure. Figure 11 gives a schematic presentation of the reporting route.

Serious incidents or adverse reactions 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 being within the scope of the Healthcare Quality, Complaints and Disputes Act. However, reports will always be assessed on healthcare quality aspects as well, and a full investigation will be required if a case is deemed to be a calamity.

Reports regarding ATMPs

In the production of ATMPs from human substances, 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 medicine. Incidents can have consequences for both patient and donor, for example loss of tissues and cells.

Current vigilance systems provide part of the chain of tissue donation, ATMP production and administration, but certain adverse reactions are not yet 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 to follow-up after clinical application.

Based on international and national legislation, TRIP is collaborating with Lareb, the designated agency where serious and non-serious adverse reactions of medicines are reported under the Medicines Act, on the design of a comprehensive vigilance framework for ATMPs based on human substances. This creates a link between biovigilance and pharmacovigilance. Formalised cooperation between both vigilance systems is necessary to successfully implement the proposal and to increase knowledge of incidents and adverse reactions in the ATMP chain.

Definitions of categories of incidents and adverse reactions and reporting criteria

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

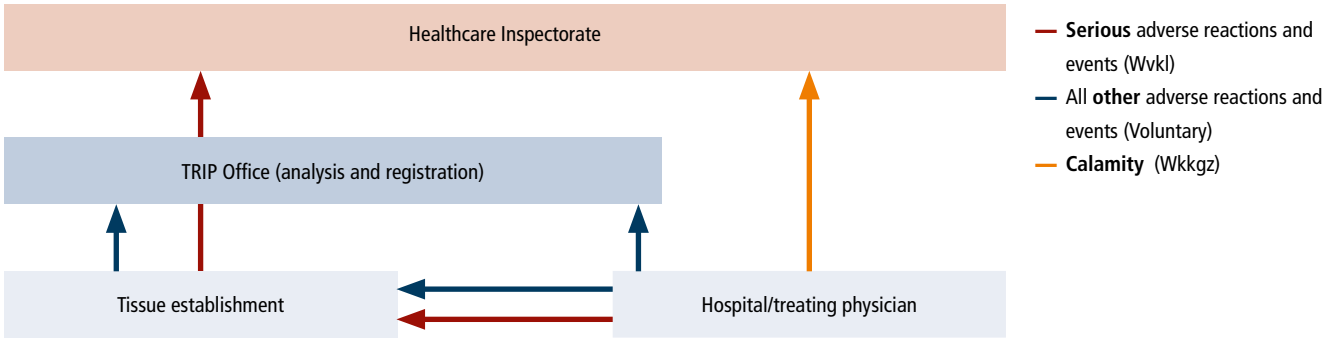

Figure 11 Flowchart of reports regarding human substances

C SUMMARY OF INCIDENTS AND ADVERSE REACTIONS REPORTED TO THE EU

Table 25 shows the number of serious incidents and adverse reactions related to human tissues or cells reported in 2022. In total, 44 reports were assessed as serious. These are serious adverse reactions, serious incidents and serious donation complications.

Table 25 Overview of serious incidents and adverse reactions reported to the EU in 2022

Type	Serious adverse reaction	Serious incident*	Serious donation complication	Total serious reports
Semen	1	2	0	3
Oocytes	0	2	15	17
Embryos	0	4	0	4
HSC and therapeutic cells	4	4	0	8
Ocular tissue	0	5	0	5
Musculoskeletal tissue	0	2	1	3
Multiple types of tissue	0	4	0	4
Total	**5**	**23**	**16**	**44**

* TRIP classifies incidents followed by a serious adverse reaction or with a serious consequence as serious incidents. These reports are submitted to the European Commission (EC) as 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 hospitalisation, re-transplantation after transplantation with an incorrect product or an aborted procedure where the patient is already under anesthesia or has been conditioned for transplantation.

D LIST OF TERMS AND ABBREVIATIONS

Allogeneic	Originating from a donor (genetically non-identical person)
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
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
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
EU	European Union
GMP	Good manufacturing practice
HSC	Hematopoietic stem cells
ICU	Intensive Care Unit
IGJ	Inspectorate for Healthcare and Youth
Imputability	Degree to which an adverse reaction can be attributed to an applied substance of human origin
IUI	Intrauterine insemination
IVF	In vitro fertilisation
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	The Netherlands
NTS	Nederlandse Transplantatie Stichting (Netherlands Transplantation Foundation)
Oocytes	Human egg cells
Organ bank	Tissue establishment with licence to receive substances of human origin
PBSC	Peripheral blood stem cells
PESA	Microsurgical epididymal sperm aspiration
Procurement	Process by which body material or a donated organ becomes available
Semen	Sperm
TCR	T-cell receptor (gene therapy)
TC-TIL	Tumour infiltrating lymphocytes
TESE	Testicular sperm extraction
Tissue establishment	A tissue bank, hospital department or other centre that holds a licence for the processing, preservation, storage or distribution of human substances
VWS	Dutch Ministry of Health, Welfare and Sport
WKKGZ	Healthcare Quality, Complaints and Disputes Act
WVKL	Body Material (Safety and Quality) Act