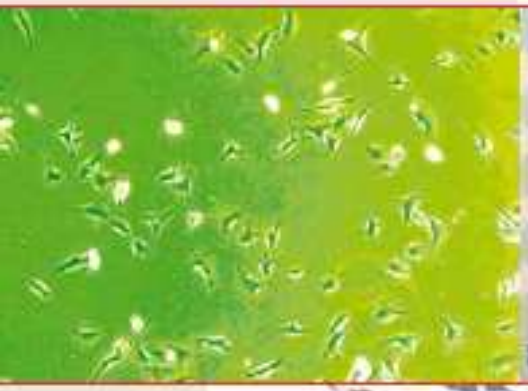
TRANSFUSIE REACTIES IN PATIËNTEN

TRIP

TRIP report 2010
Tissuevigilance



The TRIP report 2010 regarding tissue vigilance reports in The Netherlands in 2010 is published under responsibility of the TRIP (Transfusion Reactions in Patients) Foundation.

ISBN 978-90-78631-08-8

Members of TRIP Governing Board	On behalf of
J.A. Bekkers	Dutch Society for Thoracic Surgery (from January 2010)
M.R. van Bohemen-Onnes	Verpleegkundigen & Verzorgenden Nederland (nurses and nursing care professionals)
A. Brand	Dutch Society of Specialists in Internal Medicine
J.L.P. van Duijnhoven	Dutch Society for Clinical Chemistry and Laboratory Medicine
F.J.L.M. Haas	Society for Hematological Laboratory Advisor (till February 2011)
P.C. Huijgens	Dutch Hematological Society (till January 2010)
I.L. van Kamp	Dutch Society for Obstetrics and Gynaecology (till February 2011)
A.W.M.M. Koopman-van Gemert	Dutch Society for Anaesthesiology and Intensive Care Medicine
M.G.J. van Kraaij	Sanquin Blood Supply (from February 2011)
J.H. Marcelis	Dutch Society for Medical Microbiology
V.M.J. Novotny	Dutch Society for Hematology (from January 2010)
M.A.M. Overbeeke	Dutch Society for Blood Transfusion (till April 2011)
C.L. van der Poel	Sanquin Medical Adviser (till February 2011)
J. Schipper	Dutch Society for Obstetrics and Gynaecology (from February 2011)
J.W.P.H. Soons	Society for Hematological Laboratory Investigation
E.L. Swart	Dutch Society of Hospital Pharmacists
R.Y.J. Tamminga	Dutch Pediatric Society (till December 2010)
R.R.P. de Vries	Transfusion Medicine in University Hospitals
A.J. Willemze	Dutch Pediatric Society (from January 2011)

Advisory Board

R.M.Y. Barge	Dutch Federation of University Hospitals (till January 2010)
J.M.M. Hansen (reading member)	IGZ (Healthcare Inspectorate)
R. Treffers	Dutch Association of Hospitals
H.J.C. de Wit	Sanquin Blood Supply

Patroness

E.J.G.M. Six – Baroness van Voorst tot Voorst

Advisory Committee

J.A. Bekkers, W.M.J. Bodha, A.G. Bokhorst, M. van den Bosch, J.J. Cornelissen, J.H.F. Falkenburg, D.J. van Rhenen, D.B.F. Saris, I.Schipper, C. Voermans, R.R.P. de Vries, S.M. Weima

TRIP Office

M.R. Schipperus	Director
J.C. Wiersum-Osselton	National coordinator
A.J.W. van Tilborgh- de Jong	Senior hemovigilance physician
P.Y. Zijlker-Jansen	Hemovigilance and tissue vigilance physician
M.J. Happel-van 't Veer	Tissue vigilance coordinator
K. Spijker	Scientific officer
I.C. van Veen-Rottier	Secretary

Table of content

Foreword

I am pleased to present you with the TRIP Tissue vigilance Report 2010. This is the third report dedicated to tissue vigilance. From 2008 onwards the annual reports on hemovigilance and tissue vigilance have been separated as the medical professionals concerned with tissue vigilance differ substantially from those concerned with hemovigilance. From the year 2011 tissue vigilance that started off in 2006 as a pilot project will be a regular task for the TRIP Office.

The number of reports of adverse reactions and events with transplantation of human tissues and cells has increased from 46 in 2009 to 77 in 2010. In November 2010 the Healthcare Inspectorate sent a circular to all Boards of hospitals, clinics and tissue establishments to point out the legal requirements with regard to reporting of adverse reactions and events associated with transplantation of substances of human origin to TRIP along with figures for processing, distribution and applications for EU and national reporting. This has led to the implementation of tissue vigilance in growing numbers of institutions and increased awareness of the legal requirements of tissue vigilance. The number of participating hospitals and clinics has risen further this year. There is now complete participation of independent tissue establishments.

The data for 2010 show an increase in reports regarding cartilage and hematopoietic stem cells. Two hospitals that expand and implant autologous cartilage submitted reports. Four institutions transplanting hematopoietic stem cells, one more compared to 2009, submitted reports of reactions and events. As in previous years the majority of reports concern reproductive cells. The numbers of applications of gametes and embryos are much larger than those for other cells and tissues of human origin.

I warmly recommend this report to you and again hope it will provide a stimulus to structurally implement tissue vigilance in order to contribute to the improvement of quality and safety of transplantation of human tissues and cells.

Prof. Dr. René R.P. de Vries
President, TRIP Foundation

Executive summary

The TRIP (Transfusion Reactions in Patients) National Hemovigilance Office introduced tissue vigilance in 2006 at the request of the Ministry of Health with the aim of registering reports of adverse reactions and adverse events and reporting publicly on safety of human tissues and cells. On behalf of the Healthcare Inspectorate TRIP provides the yearly mandatory overview of serious adverse reactions and events to be submitted to the European Commission under the mandatory reporting requirement of the European Directive 2004/23/EC.

Findings

Participation of transplanting institutions of tissues and cells (hospitals and clinics) by submission to TRIP of numbers of processed, distributed and transplanted units and/or the sending of reports, shows a continuous rise from 51,5% in 2009 to 79,4% in 2010. An increasing number (73,2%) has appointed a tissue vigilance officer or coordinator. The independent tissue establishments, including organ banks, show 100% participation. The closing date for inclusion in the 2010 report was April 1 2011.

Concerning the reporting year 2010 a total of 77 reports were received, out of which 46 were assessed as serious and these were included in the overview for the European Commission. Subdivided according to implicated type of cells or tissue there were 49 reports regarding reproductive cells, 13 reports regarding hematopoietic stem cells, seven concerning cartilage transplantation, six concerning ocular tissue, one regarding bone transplantation and one regarding heart valves. There were seven reports of adverse reactions and 70 adverse events, out of which 48 concerned gametes and embryos. The high number of reports concerning reproductive cells reflects the large number of applications, fairly good participation by fertility clinics and a clear professional guideline on reporting of serious adverse reactions, adverse events and calamities in assisted reproductive technology. In 2010 nine IVF laboratories (2009: 7) and four semen laboratories (2009: 1) submitted reports.

Conclusions and recommendations

Participation of hospitals and clinics rose by 28% compared to 2009. However one fifth of hospitals and clinics did not participate in 2010. Therefore numbers of applications are incomplete and possibly there is underreporting of complications at transplantation of tissues and cells. Participation still needs to be improved. The hospital boards need to ensure that their institutions keep a comprehensive registry of numbers of transplanted products of human origin, of transplantation procedures and numbers of recipients as well as of adverse reactions and events.

Nine reports of identification errors show that identification of donors, recipients and tissues needs to be carried out according to protocol and with utmost care at every step of the process. Introduction of new techniques may possibly carry a higher risk of avoidable incidents. This needs to be addressed by clear standard operating procedures and by careful guidance and training of personnel. Extra alertness is required on starting up essential equipment after maintenance or repair in order to prevent avoidable adverse events.

1. Introduction and TRIP working methods

As in the previous two years TRIP has compiled a separate report concerning tissue vigilance for reporting year 2010. Up to the year 2007 tissue vigilance reporting was included in a combined TRIP annual report concerning hemovigilance and tissue vigilance. As the medical professionals in the field of transplantation of human tissues and cells differ from the professionals involved in blood transfusion the decision was then taken to publish two dedicated reports.

Tissue vigilance is the systematic monitoring of adverse events and adverse reactions throughout the chain from tissue or cell donor to recipient, and all other activities which can lead to safer and more effective use of tissues and cells.

In 2005 at the request of the Ministry of Health TRIP initiated preparations for a reporting system for serious adverse events and serious adverse reactions associated with transplantation of human tissues and cells in accordance with the EU Directive 2004/23/EG that came into force in April 2006. The Directive defines standards for safety and quality for donating, procuring, testing, processing, storage and distribution of tissues and cells of human origin. Article 11 of this Directive is dedicated to reporting of serious adverse events and reactions and decrees that all member states should implement a reporting system.

In August 2006 all medical professional bodies, hospitals and clinics, tissue establishments and tissue banks were informed about the launch of a pilot reporting system. A paper form for reporting serious adverse events and serious adverse reactions was developed. Reporters were also asked to report non-serious reactions and events in order to provide insight in possible types of reactions and events in the field of human tissues and cells. Only serious reactions and events that meet the definition of the EU Directive are included in the overview of serious adverse events and reactions for the Ministry of Health and the Healthcare Inspectorate.

In January 2007 the Dutch Law on Safety and Quality of Substances of Human Origin (2003) was updated and adjusted to the EU Directive 2004/23/EG and the Decree on Requirements for Substances of Human Origin (2006) was added. This states that a tissue establishment should appoint a responsible person whose tasks include the reporting of serious adverse reactions and events, which is no longer voluntary with the coming into force of this legislation. Healthcare institutions are obliged to report to the tissue bank/tissue establishments any serious adverse reaction or serious adverse event that could possibly affect the safety and quality of human tissues and cells.

In 2010 the pilot phase of the reporting system was concluded. TRIP prepared for the structural incorporation of tissue vigilance and the corresponding reporting system for serious adverse reactions and events in the TRIP Office activities. From 2011 onwards tissue vigilance will be a regular task of the TRIP Foundation.

In 2007 an Advisory Committee was formed to guide the TRIP staff and board members in the setting up and consolidation of tissue vigilance. The members of the Advisory Committee are experts in the field of human tissues and cells representing various medical professional bodies and tissue establishments. The Advisory Committee assesses all reports before inclusion in the TRIP annual report and the annual overview for the European Commission.

On the TRIP website (www.tripnet.nl) forms for reporting of reactions and events are available. In January 2010 an online pilot reporting system similar to that for hemovigilance was launched. The majority of 2010 reports were submitted online. Also during 2010 continued efforts were made to further implementation of tissue vigilance and to promote reporting in order to improve quality and safety in the use of substances of human origin. The tissue vigilance implementation project for hospitals that was started in 2009 has been concluded; model documents, different models of tissue vigilance systems in hospitals and a roadmap for tissue vigilance for hospitals are available on request. These documents are used regularly in hospitals.

In November 2010 the Boards of all Dutch hospitals and tissue establishments received a circular from the Healthcare Inspectorate. This circular explained the roles of the Healthcare Inspectorate and TRIP regarding reports of serious adverse reactions and events relating to substances of human origin.The circular seems to have had a positive effect on participation in the reporting system for adverse reactions and events as well as on the provision of numbers of processed, distributed and transplanted tissues and cells.

Figure 1 shows reporting communication lines. On behalf of the Healthcare Inspectorate TRIP drafts the annual mandatory overview of serious adverse events and reactions to be forwarded to the European Commission.

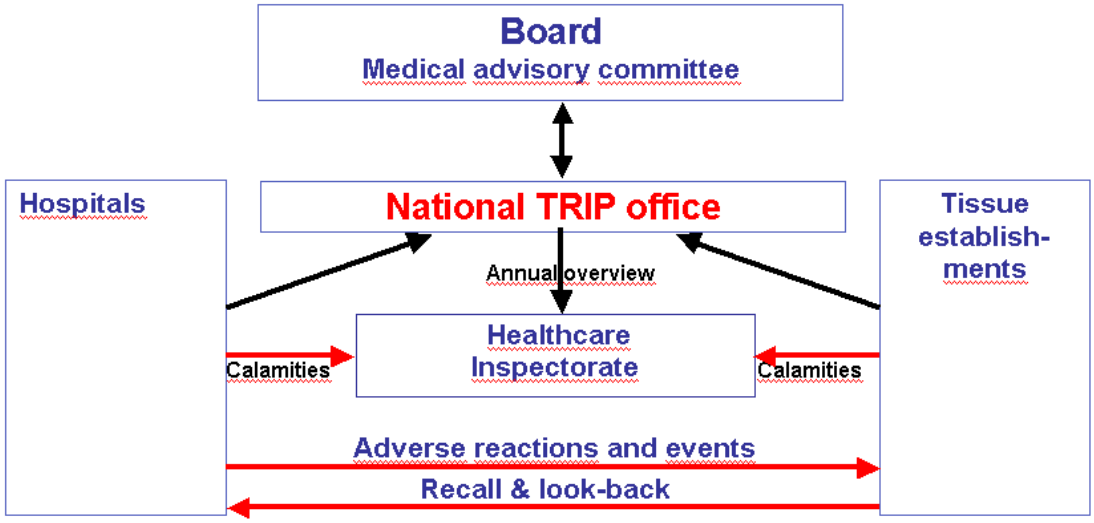


Figure 1. Flowchart of tissue vigilance reporting

2. Participation

The participation of hospitals and tissue establishments in a reporting system for adverse reactions and events associated with transplantation of human tissues and cells is paramount for optimal registration and thus obtaining a clear picture of quality and safety of human tissues and cells. Also the comprehensiveness of reports is a determining factor. Participation is determined on the one hand by submission of reports to TRIP and – if relevant – to the tissue establishment involved and/or the Healthcare Inspectorate. On the other hand yearly numbers of distributed or transplanted human tissues and cells need to be submitted along with the numbers of recipients.

In calculating participation rates TRIP distinguishes two categories of institutions: firstly suppliers of human tissues and cells i.e. independent tissue establishments which are separate from hospitals or clinics, and secondly the transplanting institutions i.e. hospitals and clinics.

Figure 2 shows participation of independent tissue establishment from 2007 to 2010.
Figure 3 shows participation of hospitals and clinics in the same years.

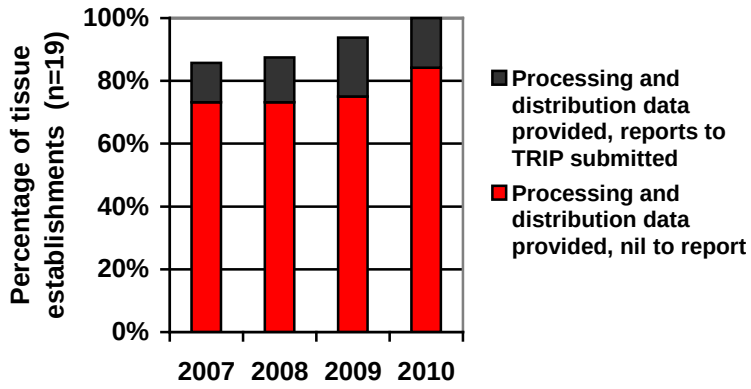


Figure 2. Participation by independent tissue establishments

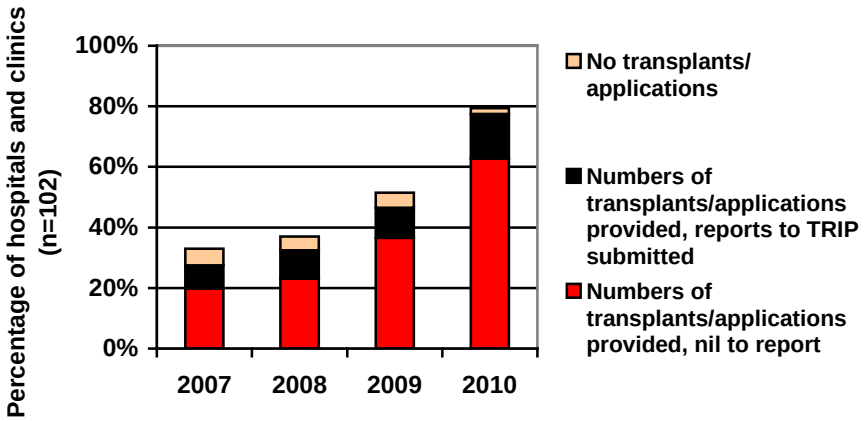


Figure 3. Participation by hospitals and clinics

Hospitals mainly transplant tissues and cells. In some cases a hospital also has a licence as a tissue establishment if it pursues activities in preserving, processing, storage and distribution of human tissues and cells. For these activities a licence is mandatory. A list of licensed hospitals and clinics according to tissue/cell type can be found on the website www.farmatec.nl. Many hospitals perform intrauterine insemination (IUI); the processing of semen also requires a licence from the Ministry of Health.

The total number of hospitals and clinics rose from 101 to 102 by the addition of a specialist eye clinic. The number of licensed independent tissue establishments rose from 16 to 19: three new tissue establishments obtained a licence for processing and distribution of tissues and/or cells.

Many hospitals and tissue establishments now have appointed a tissue vigilance officer or coordinator. This is the case in 73.2% (75/102) of hospitals and clinics. TRIP has a contact in another 15.7 % (16/102) of hospitals and fertility clinics, however this person has not been formally appointed as a tissue vigilance officer. All 19 independent licensed tissue establishments and banks have appointed tissue vigilance officers; in most cases the appointed tissue vigilance officer is also the responsible person as set down in EU Directive 2004/23/EG.

All 19 independent tissue establishments and tissue banks participated in the TRIP registry in 2010. They all submitted processing and distribution data; three sent reports to TRIP and 16 indicated they had nil to report.

Participation by organisations responsible for human application of tissues and cells shows a distinct increase. In 2010 81 out of 102 (79.4%) participated in the registration by providing data on transplanted tissues and cells, recipients and/or by submitting reports of adverse reactions and events. In 2009 participation was 51.5%, so this constitutes an (absolute) increase of 28%. Out of these 81 transplanting institutions 66 stated they had nil to report and 15 sent reports to TRIP. Only two hospitals stated they did not transplant tissues or cells.

Unfortunately it is still not clear for all hospitals if they actually apply human tissues and cells. Sixteen hospitals (15.7%) have never provided numbers despite yearly repeated requests in writing addressed to the Board of these hospitals. Seven of these hospitals do hold a licence for processing or storage of semen and one holds a licence for gametes, embryos and ovarian tissue. Probably data are available but have not been submitted to TRIP. Twelve hospitals submitted incomplete data: exact numbers were lacking or data on specific types of tissues and cells were missing. Often the number of recipients was not submitted. Only if a hospital can provide annual figures or state that it is not transplanting human tissue or cells can the board be sure that the hospital of clinic is meeting its legal obligations with regard to licence, traceability and tissue vigilance reporting.

3. Processing, distribution and transplantation

All hospitals, clinics and tissue establishments/tissue banks in The Netherlands were requested to submit data on distributed products and/or applications/transplantations of tissues and cells in 2010 for the overview for the European Commission. TRIP also requested numbers of recipients and separate data for distribution in The Netherlands, in the European Union and outside the European Union. These data are mandatory for each EU member state to submit to the European Commission according to directive 2004/23/EC and 2006/86/EC.

Figure 4 shows the type(s) of tissues and cells transplanted in the 81 (out of 102) Dutch hospitals and clinics that submitted information to TRIP in 2010.

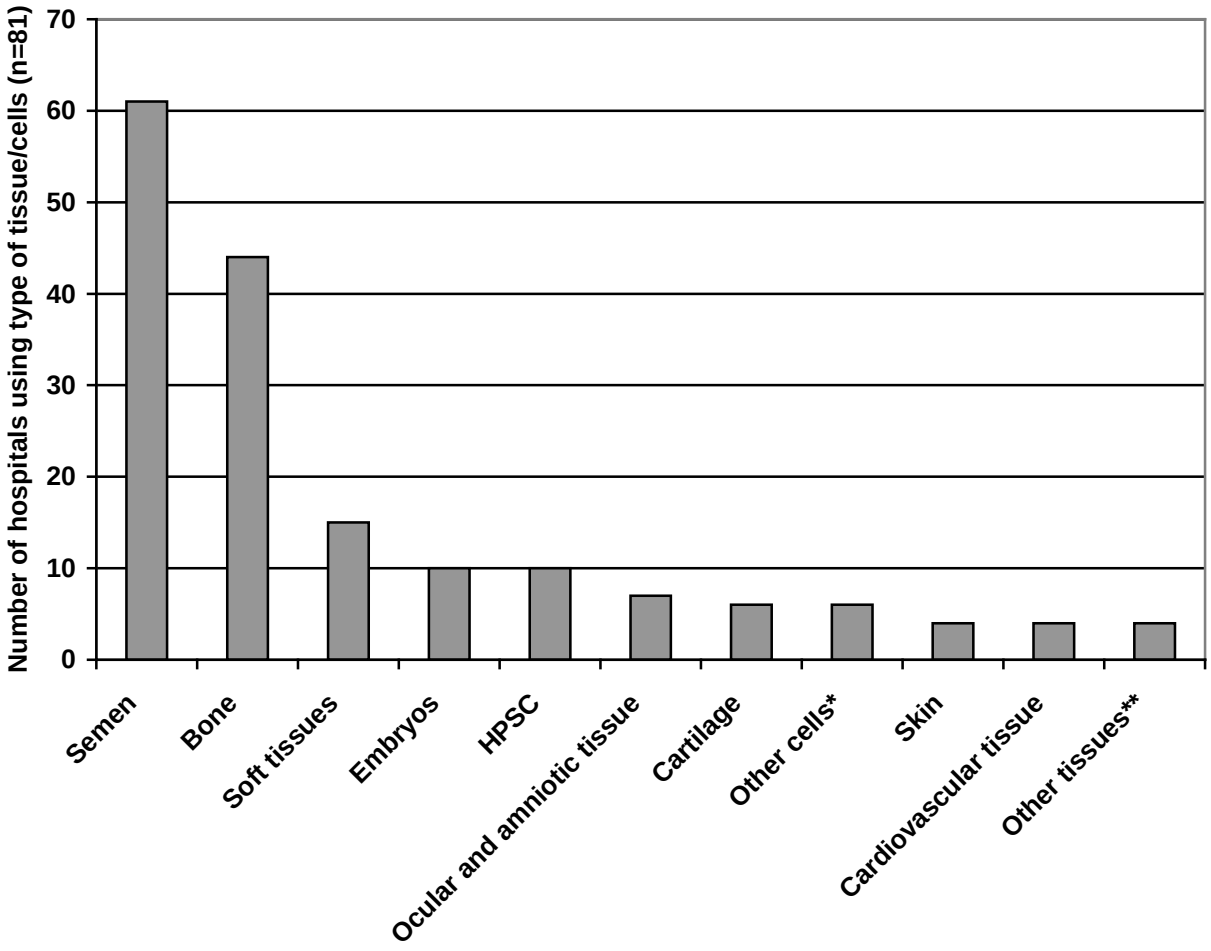


Figure 4. Number of hospitals using type of tissue/cells

* Other cells include: mesenchymal stem cells, lymphocytes and dendritic stem cells.

** Other tissues include: testicular and ovarian tissue, Langerhans' islets, umbilical cord tissue and adipose tissue.

Table 1 shows submitted numbers of processed, distributed and transplanted human tissue and cells within The Netherlands in 2010. There is a discrepancy between numbers of distribution and transplantation for some types of tissues and cells. This is due to incomplete data as a third of the hospitals failed to submit data or sent incomplete information. The reproductive cells account for the largest numbers by far. Here also the data are incomplete; ten out of 13 (78%) laboratories for in vitro fertilisation (IVF) provided data to TRIP.

Table 1. Overview of processed, distributed and transplanted units of human tissues and cells within The Netherlands in 2010

Type	Hospital and clinics*		Independent tissue establishment**		Transplanted**	Recipients****
	Processed / distributed		Processed/ distributed			
Skin						
Donor skin (cm^2 /containers)	-	-	2140000	24480	431	unknown
Cultured skin	unknown					
Keratinocytes	14	12			12	12
Bone						
Bone, whole	3	-	168	78	89	83
Bone chips or fragments	7	50	959	2025	740	589
Femoral heads (halved)	-	31	96	85	43	43
Femoral heads (whole)	738	560	762	1660	1396	1268
Cranial bone (autologous)	19	9			53	53
Auditory ossicles			-	99	2	2
Demineralised bone			-	1431	unknown	
Miscellaneous			-	12	19	18
Cartilage	184	184	11	109	176	173
Soft tissues						
Tendons	-	3	-	133	70	54
Fascia	12	12	-	1230	112	68
Other			-	166	12	12
Ocular tissue						
Cornea			2707	1111	300	272
Sclera			569	353	25	25
Amnion			1 placenta	43	5	5
Cardiovascular tissue						
Heart valves	-	-	246	75	43	43
Vessels and patches	10	10	23	23	30	30
Hematopoietic stem cells (unrelated donors)						
Bone marrow	37	35	-	12	48	48
Peripheral blood stem cells	134	134	90	67	250	188
Cord blood	29	45	130	7	58	33
Hematopoietic stem cells (related donors)						
Bone marrow	15	15			21	20
Peripheral blood stem cells	126	138			156	122
Hematopoietic stem cells (autologous)						
Bone marrow	88	51			75	57
Peripheral blood stem cells	1829	1522	812	642	1536	438
Cord blood			24494	7		
Other cells						
Mesenchymal stem cells	39	43			88	40
Lymphocytes	150	92	-	3	100	67
Dendritic cells	26	26			54	28
Reproductive cells						
Semen (donor)	11360	6663			6456	1698
Semen (partner)	37771	25643			22029	8851
Oocytes	106059	34				
Embryos	30447	23540			21295	11576
Other tissues						
Testicular tissue	401	198			104	78
Ovarian tissue	149	-			-	-
Langerhans' islets	41	6			6	4
Umbilical cord tissue			11115	-		
Adipose tissue			24	-		

* Data submitted by 63 hospitals and clinics (62%), internal distribution by hospitals/clinics with licence for tissue establishment
** Data submitted by 19 independent tissue establishments/tissue banks (100%)
*** Data submitted by 81 out of 102 hospitals/clinics (79%)
**** Data submitted by 72 out of 102 hospitals/clinics (71%)

The processing figures of independent tissue establishments/banks are much higher than the distribution figures. The reasons for this include processing and storage as precaution (e.g. autologous cord blood or peripheral blood stem cells), inventory management and distribution outside The Netherlands. The figures for processing and distribution of hematopoietic stem cells are quoted as transplants, whereas infusion is recorded in units. The processing of skin is given in cm^2 whereas the distribution and application figures are expressed as numbers of containers. The data on the number of recipients (provided by 71% of hospitals) are less complete than those for applications (provided by 79%of hospitals).

Table 2 shows numbers of human tissues and cells distributed outside The Netherlands. These data are relevant, as the law requires reporting of serious adverse reactions and events in the country of origin of the transplants.

Table 2. Human tissues and cells distributed outside The Netherlands in 2010

Type	Distributed within EU *	Distributed outside EU *
Skin		
Donor skin	8838	5450
Bone		
Bone, whole	10	2
Bone chips or fragments	822	-
Femoral heads (halved)	81	-
Femoral heads (whole)	212	-
Demineralised bone	6847	1299
Soft tissues		
Tendons	88	-
Fascia	-	-
Other	23	-
Ocular tissue		
Cornea	200	16
Sclera	4	-
Amnion	4	-
Cardiovascular tissue		
Heart valves	39	1
Vessels and patches	11	-
Hematopoietic stem cells (unrelated donors)		
Bone marrow	8	7
Peripheral blood stem cells	12	5
Cord blood	12	7
Other cells		
Lymphocytes	1	-
Reproductive cells		
Semen (donor)	604	-
Semen (partner)	528	-
Oocytes	4750	-

* Data provided by 19 independent tissue establishments outside hospitals and clinics (100%)

4. Reports 2010

By the closing date for this report, April 1 2011, TRIP had received 77 reports of adverse reactions and events related to tissues and cells in 2010. This constitutes an increase of 64% compared to 2009. In total 70 adverse events and 7 adverse reactions were reported by two independent tissue establishments and 16 hospitals/clinics (2009: three independent tissue establishments, nine hospitals/clinics). Five hospitals submitted reports for the first time. The increase in number of reports is probably caused by a so-called registration effect and improved awareness of tissue vigilance. The number of reports per reporting institution varied from one to 12.

TRIP has commissioned an online reporting system for serious adverse events and reactions relating to tissues and cells. This system was available to reporters in pilot form from March 2010; out of 77 reports 64 were submitted online.

The total number of reports from 2006 up to and including 2010 is shown in *Figure 5*. In *Figure 6* the distribution per cell and tissue type is displayed.

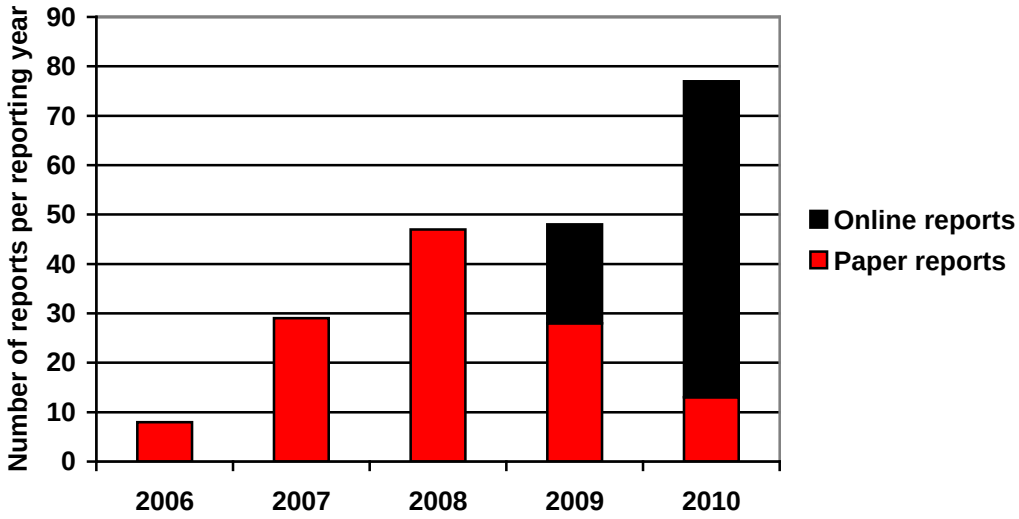


Figure 5. Number of reports per reporting year

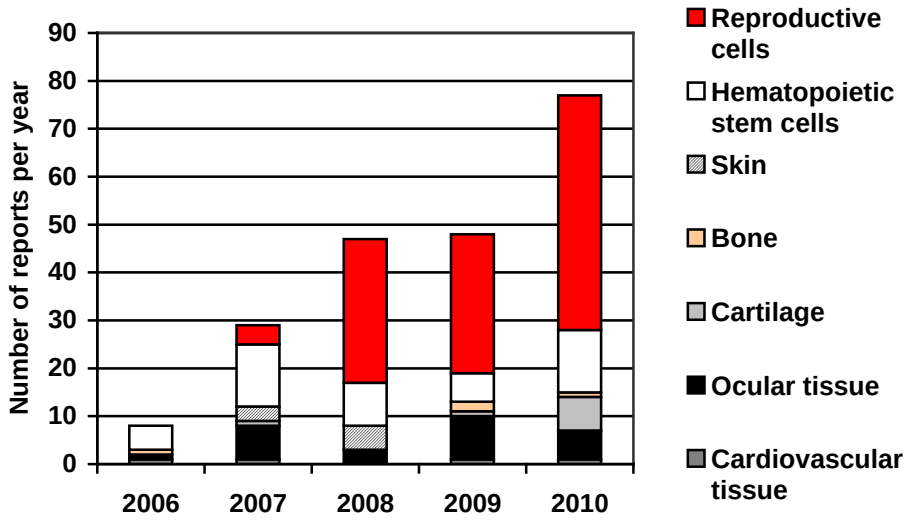


Figure 6. Reports per reporting year per tissue or cell type

The distribution of reports per cell or tissue type in 2010 is shown in *Figure 7*.

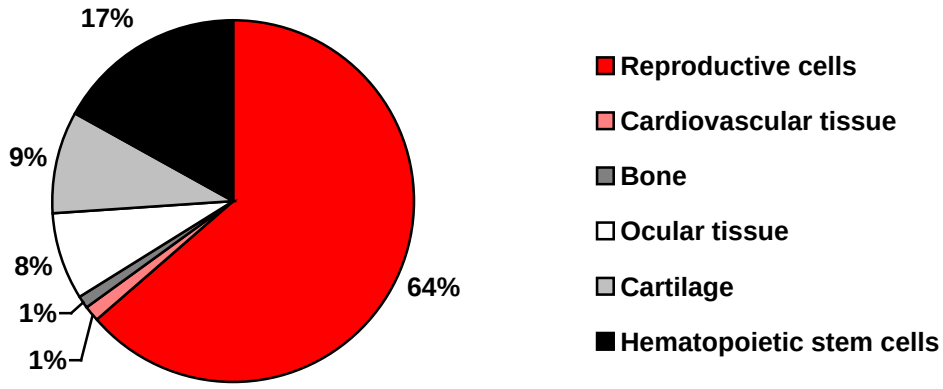


Figure 7. Percentage reports in 2010 per cell or tissue type

The Advisory Committee assessed 44 reports as serious according to the criteria of EU directive 2004/23. In *Table 3* an overview is presented of the serious reports per cell or tissue type compared to the total.

Table 3. Serious reports per tissue or cell type

Tissue/cell type	Total	Serious reports
Cardiovascular tissue	1	1
Bone	1	0
Ocular tissue	6	4
Cartilage	7	7
Hematopoietic stem cells	13	6
Reproductive cells	49	26
Total	**77**	**44 (57%)**

The reports were classified into categories. The definitions of these categories of adverse reactions and events including descriptions of error types are available on the TRIP website www.tripnet.nl. *Table 4* and *5* show the reports of adverse events and adverse reactions categorised per cell and tissue type.

Table 4. Adverse events per tissue/cell type

Adverse event	Cardio vascular	Bone	Ocular	Cartilage	HPSC	Reproductive cells	Total
Bacterial contamination of product	1	1	1	1	1	1	6
Loss of tissues or cells			2	3	2	27	34
Poor/failure of engraftment/growth				1	2		3
Incorrect product transplanted				1		3	4
Near miss						5	5
Other incident			3	1	2	12	18
Total	**1**	**1**	**6**	**7**	**7**	**48**	**70**

Table 5. Adverse reactions per tissue/cell type

Reaction	Cardio vascular	Bone	Ocular	Cartilage	HPSC	Reproductive cells	Total
Circulatory overload					1		**1**
Other reaction					4	1	**5**
Donation complication					1		**1**
Total	**0**	**0**	**0**	**0**	**6**	**1**	**7**

Cardiovascular tissue

Relating to cardiovascular tissue one report was submitted in the category bacterial contamination of product: a Staphylococcus aureus was isolated in rinsing fluid from a pulmonary valve. The patient had no adverse reaction. However the cultures were not performed according to protocol of the tissue establishment. Cultures should have been taken from valve remnants instead of the rinsing fluid. The aortic valve of this post mortem donor was sacrificed to obtain further cultures, which all were negative.

Bone

One report of bacterial contamination relating to a femoral head was registered. One out of six cultures taken at the time of transplantation grew a coagulase negative staphylococcus. The recipient was treated with prophylactic antibiotics and experienced no untoward symptoms. As all cultures taken at processing and freezing were negative, the positive result was assessed as most likely due to accidental contamination when taking the culture sample.

Ocular tissue

Six adverse events were reported relating to ocular tissue: one concerning sclera and five relating to corneas. Two reports were submitted in the category loss of tissues or cells. After complaints from two end users about blue spots on donor sclera the tissue establishment checked all stored scleras. Forty scleras (54% of the stock) had to be disposed of due to blue spots, which probably originated from disposable materials used at processing. The tissue banks modified its procedures. The second report concerned the loss of an HLA-matched cornea. At the opening of the transplant container the cornea accidentally dropped on the non-sterile thumb of an operating theatre team member. Even though the recipient was already anaesthetised, the operation was deferred because of risk of contamination of the donor cornea. The patient had to be placed on the waiting list again for another HLA-matched cornea.

Three reports were submitted in category of other incident. All reports concerned product incidents that cannot be eliminated, as only the definitive autopsy report revealed a contraindication for donation. The first report related to a donor who was diagnosed at autopsy with a systemic infection of unknown origin. The recipients of two corneas from this donor had no complications. Stored tissues of this donor were disposed of. A second report related to a donor with small lesions in the heart valves suggestive of chronic active endocarditis and pericarditis; one corneal recipient showed no symptoms, while no follow up information was available on the other recipient who was transplanted abroad. The third report regarded a donor with mucin deposits in the heart valves suggesting connective tissue disease, however without any clinical sign of connective tissue disease. The tissue establishment had noted no abnormalities when processing the corneas. Transplantation was uncomplicated in one recipient. The abnormality was not relevant for the other recipient who only had an endothelial transplant.

Concerning corneal transplantation one report involved bacterial contamination of the product. One out of six cultures of medium (taken at transfer of the cornea to transport medium) became positive for a Gram-negative rod after transplantation was completed. The recipient did not show any relevant symptoms.

Cartilage

Seven reports concerned the use of autologous chondrocytes. All reports were assessed to be serious. *Table 6* presents an overview; the events are briefly described below.

Table 6. Overview of reports concerning autologous chondrocytes

Category	Number	Type of error
Incorrect product transplanted	1	Identification error
Loss of tissues or cells	3	Communication error
		Technical error
		Other error
Bacterial contamination of product	1	Processing error
Poor/failure of engraftment/growth	1	Other error
Other incident	1	Technical error

One report concerned transplantation of an incorrect product where due to an identification error cultured chondrocytes from another patient were transplanted. The transplanted patient reportedly suffered no adverse consequences, however the operation for the other patient had to be postponed until previously harvested and stored chondrocytes had been cultured.

Three reports were submitted in the category loss of tissues or cells. Due to a communication error only four instead of the intended seven containers of cultured chondrocytes were transplanted. No statement was possible about long-term consequences for the patient. Another report mentioned loss of cultured chondrocytes as the container broke whilst being thawed in a water bath. The patient had to undergo a second operation to harvest more chondrocytes. The third report related to positive endotoxin testing of the product before distribution; the product was withdrawn and destroyed. On further investigation it turned out the test was false positive due to high glucane concentration in the product. This patient also had to have a second procedure for harvesting of chondrocytes.

There was one report in the category of bacterial contamination of product involving positive cultures for a cellumonas species. The operation for the recipient who was already hospitalised had to be postponed until new cultured chondrocytes were available. There was one report of poor growth in culture due to poor quality of patient's cartilage and he was scheduled for a total knee replacement. The last report concerned a technical fault of the procurement kit for chondrocytes. Despite a storage temperature alarm the kit was utilised and the procured cartilage was processed. The cells in fact showed normal expansion and were transplanted.

Hematopoietic stem cells (HPSC)

Concerning peripheral hematopoietic stem cells and cord blood a total of 13 reports were received from four hospitals. In *Table 7* an overview is presented of these reports, which is followed by a summary per report.

Table 7. Reports involving hematopoietic stem cells (HPSC)

HPSC	Adverse reaction	(serious)	Adverse event	(serious)	Total	(serious)
Cord blood	0		2	(2)	2	(2)
HPSC autologous	1	(0)	4	(3)	6	(3)
	1	donation complication				
HPSC allogeneic related	1	(0)	1	(0)	2	(1)
HPSC allogeneic unrelated	3	(1)	0	(0)	3	(1)
Total	**6**	**(1)**	**7**	**(5)**	**13**	**(8)**

Cord blood

Two other incidents were reported: a product fault and a technical fault. A foreign cord blood bank distributed a major incompatible product in three bags. The hospital requested a product containing less than 150 x 10^9 red blood cells. Lab checks after infusion showed 85 x 10^9 erythrocytes per bag (total 255 x 10^9). The product should have been washed before infusion. The patient suffered no clinical consequences; hemolysis parameters were temporarily elevated for one day only. A technical fault was reported involving a rupture in a cord blood bag that could be clamped immediately. Cell loss was minimal and without clinical consequence.

Autologous HPSC

One donation complication was reported with autologous stem cell apheresis: the patient had trombocytopenia that lasted three days. Another report was submitted as other reaction: 10 minutes after the start of infusion the patient suffered dizziness, rigors, shortness of breath and gastrointestinal symptoms, leading to deferral of infusion of the fourth out of four bags. The patient recovered after treatment with oxygen, clemastine and corticosteroids. The fourth bag was administered the next day without any clinical symptoms.

Three reported adverse events concerned poor engraftment (2) and bacterial contamination (1). One patient had delayed engraftment that eventually completely resolved. The other patient failed to engraft and died. The third event reported repeated positive cultures for staphylococcus aureus prior to the freezing procedure. Infusion was done while administering antibiotics, the patient had no symptoms and blood cultures were sterile. A fourth report, registered as loss of tissues or cells, concerned a rupture of one out of six HPSC bags. The event had no sequelae for the patient as the target of infused cells was met.

Allogeneic related HPSC
There was one report of circulatory overload. During infusion the patient became seriously dyspnoeic and chest X-ray confirmed circulatory overload. A second report was registered as an other incident: due to a processing error at selection of CD34+ cells the product did not meet standards. The patient suffered no adverse consequences and there was satisfactory engraftment.

Allogeneic unrelated HPSC
Three adverse reactions were reported as other reactions. At infusion of a DMSO cryopreserved stem cell product the patient developed hypotension, vasodilation, hypoxemia and transient unspecified neurological symptoms. After treatment in the ICU the patient recovered completely. A second report concerned infusion of a fresh product that was followed by hypoxia, nausea, headache and myalgia. The third report described transient hypoxia and chest tightness. It is not known whether a fresh or cryopreserved product was infused.

Reproductive cells

In 2010 there were 49 reports concerning procedures or transfer of gametes or embryos at assisted reproductive technology. This represents an increase compared to 2009 (n=29). This increase in number of reports has to be considered in relation to the large number of IVF treatments (2009: ≈15,500 follicle aspirations, see www.nvog.nl). There appears to be better reporting due to the positive attitude of the involved professionals. Notably the 2008 guideline for clinical embryologists regarding reporting of serious adverse events and reactions in assisted reproductive technology has a favourable effect. In 2010 one adverse reaction was reported. The remaining 48 reports involved adverse events. These reports were submitted by nine (out of 13) Dutch IVF laboratories and three hospitals with a licence for the processing of semen. In 2009 seven IVF laboratories and one semen laboratory sent reports to TRIP.

Adverse reaction
One adverse reaction was reported with IUI. It concerned an other reaction: the patient experienced a burning sensation after insemination with a semen sample that was processed with a liquefying medium.

Adverse events
Figure 8 shows the distribution of adverse events in the reporting year 2010. As in 2008 en 2009 the category of loss of tissues or cells was the largest.

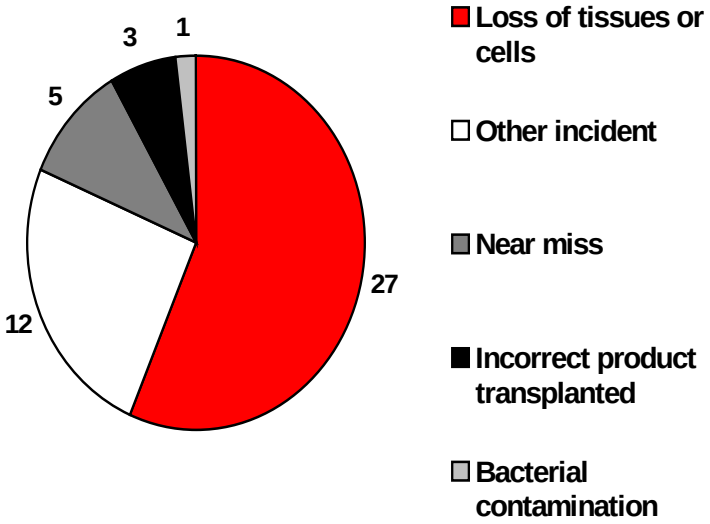


Figure 8. Categories of adverse events relating to reproductive cells

Bacterial contamination of product
One report concerned bacterial contamination of a semen sample of the partner that was inseminated contrary to protocol owing to an error of judgment. The recipient suffered no bacterial complications.

Incorrect product transplanted
Three events were reported in the category incorrect product transplanted. Twice the wrong embryo was transferred. A genetically abnormal embryo was transferred after pre-implantation diagnosis due to a selection error; no pregnancy resulted. The second report concerned the transfer of an embryo of another couple due to an identification error that was facilitated by a language barrier. The recipient was prescribed medication to prevent a pregnancy. The third report in this category related to insemination of incorrect donor semen. Semen from a CMV positive donor was erroneously selected for a CMV negative woman. No seroconversion or infectious complications occurred.

Near miss
Three out of five reports in this category concerned semen. In one the wrong semen container, that of an incorrect partner, was placed next to the ovum dish. The error was duly noted and corrected. In the second report an unlabelled semen sample was received in the lab. After ascertaining identity the sample was used. The third report concerned a man who transported ova to the lab at another fertility clinic and presented himself as the male partner of the patient and produced a second semen sample when it was found that transportation time for the semen sample had been too long. When the referring hospital was informed it transpired the man was not the male partner and he knowingly tried to defraud. Procedures for identification by photograph were implemented.

Two reports related to embryos. The lids of two culture dishes for embryos were mixed up. This was discovered and corrected at the first - planned - double check. Another report mentioned the thawing of an incorrect embryo for a couple with a similar name without checking date of birth. This was discovered just before embryo transfer. The embryo was refrozen.

Other incident
Three reports concerned processing errors. The embryos for six couples were cryopreserved using an aberrant cryopreservation program. This was discovered during the procedure and the straws were transferred to another freezer. After defrosting these embryos appeared normal and pregnancies developed after implantation. The second report describes how a straw containing embryos was found frozen to the container in the freezer and the seal broke when it was removed. The straw was resealed; there was no risk of contamination or degeneration. A third report concerned the accidental dropping of follicle suspension containing two oocytes onto a warm hotplate. Both oocytes were recovered, to prevent contamination they were rinsed.

Three reports concerned technical faults. A semen container broke during centrifugation. Enough semen remained for application. The cryopreservation of twelve embryos had to be stopped as the freezer was found to be malfunctioning after maintenance. All embryos had to be restored to culture conditions and were cryopreserved the following day. A third event reported delay of seeding by ten minutes as the seeding alarm failed. No adverse effects are expected for the embryos.

Two reports arose from administrative errors. Due to a typing error in the waiting list number a letter regarding the maximum storage time was sent to the wrong patient. Due to incorrect diary booking an embryo was defrosted a day early. The patient was able to come to hospital and had the embryo transfer that same day.

Three reports regarded assessment errors. A semen sample in an unapproved container was processed, whereas according to protocol a new sample should have been requested in an approved container. Fertilisation failed even though the semen was found to have normal motility at insemination. The second report concerned bacterial contamination of the semen sample that was inseminated contrary to protocol on the instructions of the attending physician. The recipient had no complications. In a third report the semen erroneously had not been checked for HIV. The IUI treatment had to be deferred although the woman had received hormonal treatment in preparation.

One report concerned a communication error. Three embryos belonging to one patient were frozen in error, as the treating physician did not indicate that the patient was Hepatitis C positive. According to protocol no remaining embryos are to be cryopreserved to avoid possible risks of cross contamination. After risk analysis the chances of contamination were assessed to be nil with the particular type of straw used for cryopreservation. The other embryos stored in the container could be transferred.

One report regarded an other error. After incubator maintenance the temperature was found to be one degree below specification during the complete fertilisation process. Although fertilisation did occur

embryos were judged to be sub optimal. Protocol did not include temperature check after maintenance.

Loss of tissues or cells
The number of reports registered in this category was 27. Figure 9 shows the distribution according to type of error in this category.

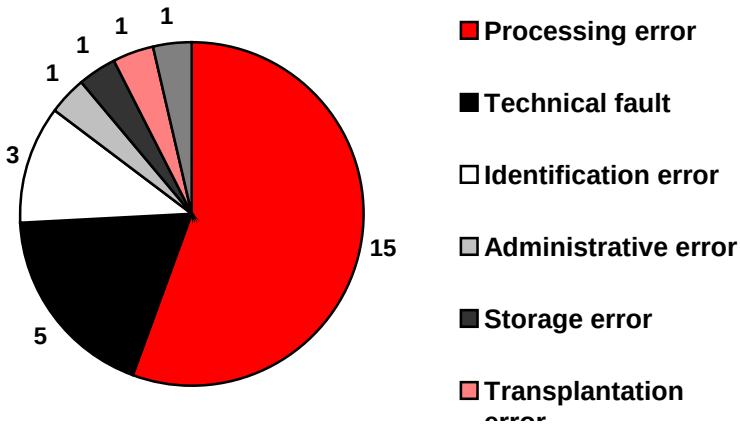


Figure 9. Type of error in category loss of tissues or cells

Processing error
Fifteen reports that were attributed to a processing error are summarized in *Table 8*.

Table 8. Reports in category loss of tissues or cells due to processing error

Step in process	Number of reports	Cell type	Summary
Isolation	1	oocytes	• 1 oocytes accidentally placed in culture dish of another patient
Incubation	3	oocytes and embryos	• covering oil omitted in culture dish • culture dish with embryos thrown away • oocyte dish not placed in culture
Transfer	3	oocytes and embryos	• 3 injected oocytes not transferred after ICSI • capillary broken at transfer of oocytes to culture dish • capillary containing 2 embryos broken
Cryopreservation	6	embryos	• incorrect container used for freezing • seeding accidentally forgotten • visotube with 2 embryos not transferred to LN_2 vat • 1 straw containing 1 embryo left in freezer • 2 straws containing 3 embryos left in freezer • incorrect freezing procedure used after repair
Thawing	1	embryo	• incorrect DMSO dilutions used for thawing
Embryo transplant	1	embryo	• dish and catheter accidentally dropped

Technical fault
In five reports technical faults led to loss of semen or embryos. Due to toxicity of the mineral oil used for covering embryos in culture eleven embryos of three couples were lost. Fifteen embryos belonging to four couples degenerated; this was blamed on the glassware utilised in the process. Nine embryos were lost as the freezer had an extreme fluctuation in temperature between –10 ^{o}C and –100 ^{o}C. After maintenance, incorrect setting of the pressure relief valve gave rise to leakage of liquid nitrogen; the

cryopreservation process had to be discontinued for four embryos belonging to two couples. Due to breaking of the container at centrifugation a semen sample was lost; the man was able to produce a second specimen.

Identification error
Due to marking the date of embryo transfer next to the wrong patient an embryo was thawed two weeks early. A tube with follicle aspirate was incorrectly labelled with two labels identifying two patients and could therefore not be processed; the number of oocytes lost is not known. During an ICSI procedure injected oocytes were not transferred to a culture dish and were accidentally injected a second time. Five oocytes were triploid and unfit for culture.

Administrative error
Due to listing of an incorrect identifying code two straws containing three embryos were not transferred from freezer to storage freezer. This was discovered the next day.

Storage error
A hot pack was placed in a transportation device for follicle aspirate. This was not according to protocol; when it arrived in the fertility laboratory temperature had risen to 42 ^{o}C. One of the two isolated oocytes was fertilised but the embryo showed abnormalities and could not be transferred. Due to insufficient ovarian reserves IVF treatment could not be repeated.

Transplantation error
Only half of the processed semen was inseminated during IUI. A tube containing the other half of the semen was inadvertently left in the transportation box.

Other error
A tube of follicle aspirate containing two oocytes was left behind in the transportation box and was returned to the referring hospital.

Late 2009 reports

After the closing date for the 2009 TRIP Annual Report Tissue vigilance another two reports were registered. This brings the number of reports for 2009 to 48. One report was assessed to be serious; the total number of serious reports in 2009 stands at 41 (85%).

The late reports concerned semen and autologous cartilage. One report was registered in the category of congenital malformation. After donor IUI a baby with cleft palate was born. The other report is an adverse event relating to the expansion of cartilage cells. The medium for bacterial contamination checks was found not to meet the requirements of the tissue establishment as it could produce false negative results. Transplantation had to be postponed for three patients.

5. Overview of mandatory reports of serious adverse reactions and events (in accordance with EU legislation)

Table 9 presents an overview of the number of serious adverse reactions and events reported in 2010.

Table 9 Overview of serious reports in 2010

	Oocytes	Embryos	Semen	Ocular tissue	Cartilage	HPSC	Cardio-vascular	Total
Serious reactions	0	0	0	0	0	1	0	**1**
Serious events	9	14	3	4	7	5	1	**43**
Serious reaction in donor	0	0	0	0	0	0	0	**0**
Total serious reports								**44**

6. Conclusions and recommendations

Actions and developments following the recommendations in the TRIP annual report 2009

1. A joint circular from the Ministry of Health, the Healthcare Inspectorate and TRIP should point out the mandatory nature of tissue vigilance.
   Action: In November 2010 the Healthcare Inspectorate issued a circular to all Dutch hospitals and tissue establishments clarifying the respective responsibilities of TRIP and the Inspectorate.

2. Participation of a healthcare institution requires the submission of information both on serious adverse reactions and events and on distribution and transplantations numbers.
   Action: The above-mentioned circular states that every tissue establishment is required by law to submit data on processing, distribution and transplantation to TRIP.

3. At licensing inspections for tissue establishments and tissue banks the TRIP certificate of participation should be reviewed. This certificate confirms receipt of the mandatory data for inclusion in the national data for the European Commission.
   Action: At the biannual inspection of tissue establishments by the Healthcare Inspectorate the inspectors enquire about TRIP participation.

Conclusions

1. Tissue vigilance implementation has improved in The Netherlands as evidenced by increased participation and a larger number of reports from a growing number of reporting institutions.

2. However there is still underreporting of both the numbers of procedures and of complications, in particular by the hospitals transplanting tissues and cells. One fifth of hospitals and clinics did not participate in 2010.

3. The identification of recipients and donors of tissues or cells is not always carried out completely and according to protocol as was demonstrated by nine reports of adverse events due to identification errors.

4. Newly implemented techniques or types of transplantation possibly may give rise to a higher risk of preventable adverse events.

5. Four adverse events occurred after maintenance or repair of essential equipment.

Recommendations

1. The Boards of Healthcare Institutions should ascertain that the medical specialists involved in transplantation of tissues and cells keep a comprehensive registry of number of transplantation procedures, tissue products, adverse events and reactions.
2. Identification of donors, recipients and tissues and cells should be carried out with the utmost care according to protocol at every step of the process. It can be included in the time-out protocol for an operative procedure.
3. The introduction of new techniques or transplant procedures should be based on a standard operating procedure after careful guidance and training of staff in order to prevent avoidable adverse events.
4. Particular alertness is advised after maintenance or repair of essential equipment. The recommissioning should be laid down in a standard operating procedure.

List of terms and abbreviations

Apheresis	Type of blood donation involving the selective mechanical withdrawal of specific blood components while infusing the remaining components to the donor or patient
Allogeneic	Originating from a donor (genetically non-identical person)
Autologous	Originating from a person's own body
DMSO	Dimethyl sulphoxide
ET	Embryo Transfer
EU	European Union
Farmatec	Organisation resorting under the Dutch Ministry of Health, responsible for accreditation and licensing of pharmaceuticals, medical devices, blood products and substances of human origin
HLA	Human Leukocyte Antigen
HPSC	Hematopoietic stem cells
ICSI	Intra-cytoplasmatic Sperm Injection (type of IVF)
IUI	Intra-uterine Insemination
IVF	In Vitro Fertilisation
SOP	Standard Operating Procedure
TRIP	TRIP Foundation (Transfusion Reactions in Patients)