EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Unit D2 – Medical Products: quality, safety, innovation

ANNUAL SARE REPORT 2024
Tissues & Cells

(Data collected from 01/01/2023 to 31/12/2023 and submitted to the European Commission in 2024)

Co-funded by the European Union

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COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

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Contents

INTRODUCTION

The transplantation of human tissues and cells significantly improves the quality of life and health outcomes for thousands of EU citizens each year, offering vital therapeutic options across a range of medical conditions. Despite these considerable benefits, the use of human-derived biological materials inherently carries potential risks, including the transmission of infectious diseases or other adverse reactions in recipients. To effectively mitigate these risks, robust safety and quality standards have been established within EU legislation, emphasising the importance of vigilant oversight and surveillance.

Central to maintaining these high safety and quality standards are the vigilance and surveillance systems designed to promptly detect and respond to Serious Adverse Reactions (SAR) and Serious Adverse Events (SAE), collectively termed SARE. A SAR refers to an unintended response, observed in a donor during or after procurement, or in the recipient of tissues or cells, which is fatal, life-threatening, disabling, incapacitating or results in or prolongs hospitalisation or morbidity. A SAE describes any unexpected occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells (T&C) that could lead to a SAR.

As mandated by EU legislation[1], Member States (MS) annually report their national SARE data to the European Commission (EC). Compiled by the respective national competent authorities (NCAs), these reports are essential tools in the continual improvement of tissue and cell safety across Europe. In alignment with recommendations from the EU co-funded project "*Harmonising Activity Data Collection Exercises in the Field of Tissues and Cells in Europe*" (2018)[2], this report categorises T&C into three distinct categories: Replacement T&C, Haematopoietic Stem Cells (HSC) and Reproductive T&C.

This report presents an analysis of SARE data for the year 2023 submitted to the EC by 31 European countries, highlighting the ongoing commitment to safeguarding public health. It introduces several refinements to the methodology and data presentation, aimed at enhancing clarity, comparability and overall insight into trends across Europe.

[1] Article 7 and Annexes III, IV and V of Directive 2006/86/EC

[2] https://www.edqm.eu/documents/52006/162284/tissues-and-cells-conclusions-and-recommendations-harmonising-activity-data-collection-exercises.pdf/b53fa49e-180e-c4ec-daaf-648f087da606?t=1629883980927

EXECUTIVE SUMMARY

31 Reporting Countries

27 EU MS plus Iceland, Liechtenstein, Norway and the UK (Northern Ireland)

Units processed

Replacement T&C
446,497 *(n = 26)*

HSC
89,371 *(n = 23)*

Reproductive T&C
2,561,020 *(n = 21)*

Units distributed

Replacement T&C
449,719 *(n = 29)*

HSC
43,943 *(n = 25)*

Reproductive T&C
533,967 *(n = 23)*

Number of recipients

Replacement T&C
177,327 *(n = 24)*

HSC
33,383 *(n = 24)*

Reproductive T&C
175,290 *(n = 20)*

Serious Adverse Reactions (SAR)

42
Replacement T&C
(n = 7)

52
HSC
(n = 12)

293
Reproductive T&C
(n = 16)

Total SAR incidence rate per 10,000 recipients *(or per 10,000 units distributed)*

Replacement T&C 2.4 *(0.9)*

HSC 15.6 *(11.8)*

Reproductive T&C 16.7 *(5.5)*

SAR in donors

Replacement T&C 0 | **HSC** 49 *(n = 6)* | **Reproductive T&C** 678 *(n = 17)*

Fatalities in recipients or offspring

0
Replacement T&C

5
HSC
(n = 2)

12
Reproductive T&C
(n = 4)

Fatalities in donors

0

Serious Adverse Events (SAE)

187
Replacement T&C
(n = 14)

299
HSC
(n = 19)

333
Reproductive T&C
(n = 17)

Total SAE incidence rate per 10,000 units processed

Replacement T&C 4.2

HSC 33.5

Reproductive T&C 1.3

METHODOLOGY

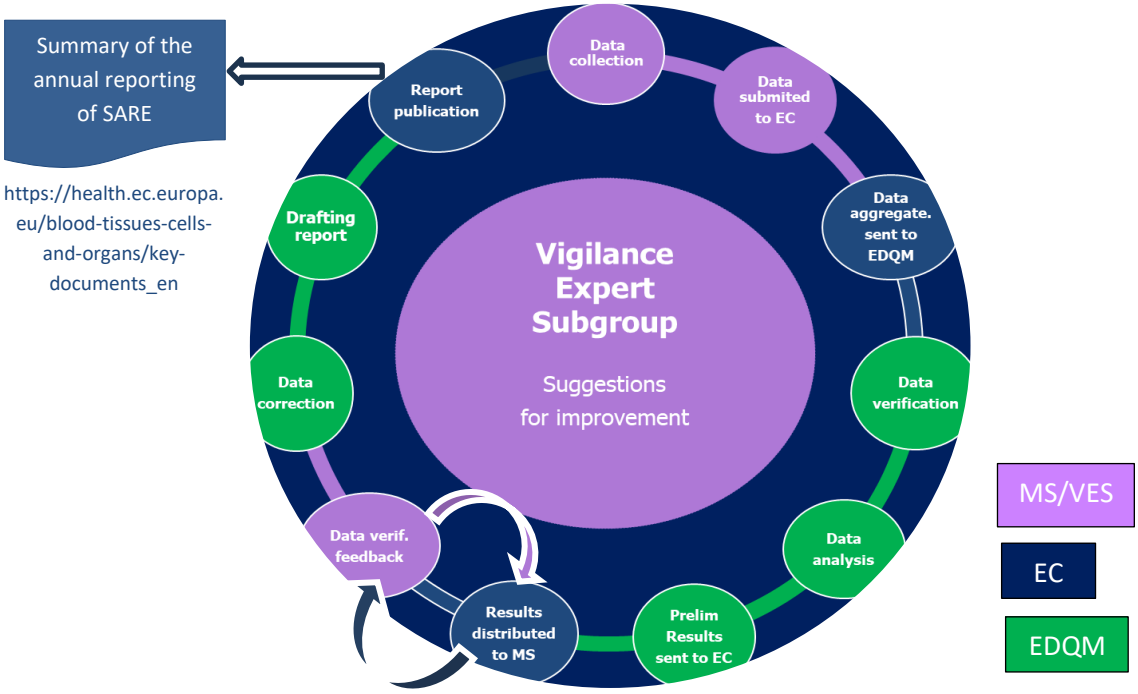
Data collection and analysis

This report provides a summary of the national data submitted to the EC by all EU MS and four non-EU countries (Iceland, Liechtenstein, Norway and UK (Northern Ireland)) pertaining to the reporting period from 1 January to 31 December 2023.

In 2023, the EC provided NCAs with improved tools to facilitate a standardised online data reporting approach:

1) ***An electronic reporting form (version 2024)***
2) ***The Common Approach, version 2024***, which complements the electronic reporting form and provides updated user instructions for data compilation.

The reporting countries and the Vigilance Expert Subgroup (VES) verified the preliminary results of the EDQM's analysis and interpretation of SARE data for 2023.
The process for issuing SARE reports (sequence of steps and involved parties) is presented in the image below.



Denominator data

- The total number of **recipients who had at least one unit of tissues or cells applied during the year concerned** was used as the denominator to calculate SAR incidence per 10,000 recipients.
  - 87% (27 of 31) countries reported this denominator in Replacement T&C
  - 87% (27 of 31) countries reported this denominator in HSC
  - 64% (20 of 31) countries reported this denominator in Reproductive T&C
- The total number of **T&C units processed** annually was used as the denominator to calculate SAE incidence per 10,000 units processed.
  - 87% (27 of 31) countries reported this denominator in Non-Reproductive T&C
  - 68% (21 of 31) countries reported this denominator in Reproductive T&C.

Limitations

- **Data variability**: incomplete reporting and inherent variations in reporting accuracy and quality must be considered during the interpretation of the results of SARE analysis.
- **Data coverage**: variations in the number of reporting countries year-on-year may influence total counts and calculated metrics. Whenever possible, data were normalised to account for these differences and, for transparency, the number of countries reporting each year was included alongside key metrics.

Key raw data for each MS are listed in the Annexes.

Updates and improvements

This year's SARE report incorporates several methodological improvements to enhance the accuracy, clarity and interpretability of T&C transplantation data.

Key updates include:

- International benchmarking and more detailed trend analysis across multiple years (2019–2023) with clearer breakdowns by category of T&C, type of reaction, etc., focusing on year-on-year changes while accounting for variations in the number of reporting countries.
- Refined statistical analysis, presenting total SAR and SAE incidence across Europe as well as the median SAR and SAE incidence per country to improve comparability across different reporting countries.
- Geographical distribution maps to enhanced data visualisation.
- Introduction of percentage change calculations, for larger baseline values, for understanding relative variations between 2022 and 2023. For small baseline values, absolute change calculations are used instead.

RESULTS

The outcomes of the data analysis are quantitative and qualitative indicators intended to provide information necessary for interpretation and conclusions regarding the safety of tissue and cell transplantation within the European space.

The SARE results are presented in four sections, each including the overall results, and separate results for each category of T&C, i.e. Replacement T&C, HSC and Reproductive T&C:

1. Activity Dataset
    a. Yearly trends in distribution and clinical application of Non-Reproductive T&C and Reproductive T&C (2019–2023)
    b. Geographic distribution of units distributed and number of recipients by category of T&C
    c. Overview of volume of activity by category of T&C; comparative analysis with 2022
    d. Country-specific trends (2022 vs. 2023) in distribution and clinical application by category of T&C
    e. Overview of volume of activity by category of T&C and by type of tissue/cell; comparative analysis with 2022
2. SAR in Recipients
    a. Yearly trends in SAR in Non-Reproductive T&C and Reproductive T&C (2019–2023)
    b. Geographic distribution of SAR by category of T&C
    c. Overview of SAR by category of T&C and by type of tissue/cell; comparative analysis with 2022
    d. Yearly trends in SAR by type of reaction in Non-Reproductive T&C and Reproductive T&C (2019–2023)
    e. SAR incidence by category of T&C and by type of reaction
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    h. Fatalities in recipients or offspring
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    b. Geographic distribution of SAE by category of T&C
    c. Overview of SAE by category of T&C and by activity step
    d. Yearly trends in SAE by specification in Non-Reproductive T&C and Reproductive T&C (2019–2023)
    e. Overview of SAE by category of T&C and by specification
    f. International benchmarking
4. SAR in Donors
    a. Overview of SAR by category of T&C and by type of reaction; comparative analysis with 2022

1 Activity Dataset

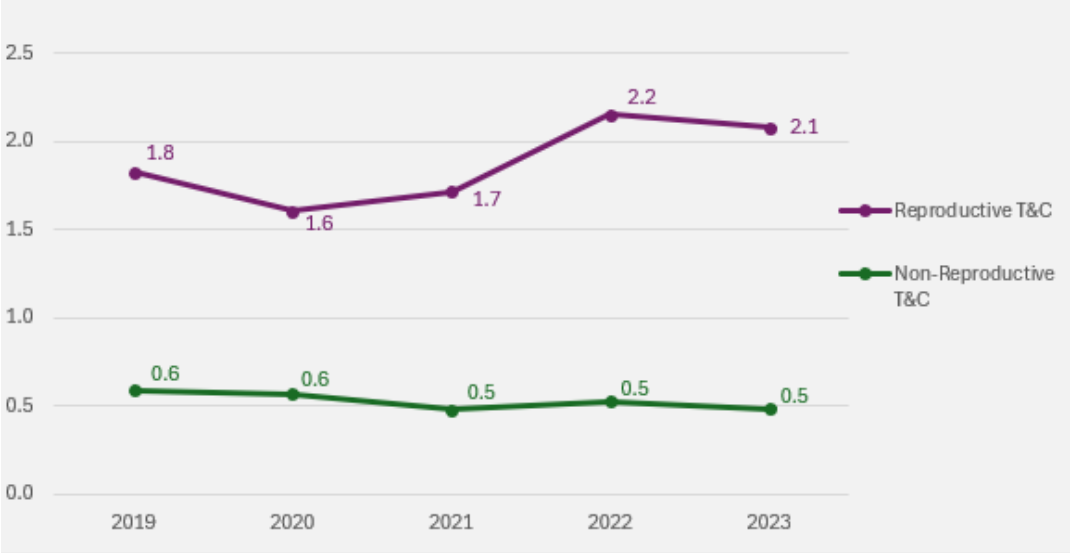
Key findings

- From 2019 to 2023, a general upward trend in distribution and clinical application rates can be observed for Reproductive T&C, while these remained stable for Non-Reproductive T&C.
- In 2023, 166 recipients pmp (median) were treated with Replacement T&C, 69 recipients pmp (median) with HSC and 1,380 recipients pmp (median) with Reproductive T&C, comparable with 2022 rates.
- There was a moderate increase in the number of units distributed and recipients of skeletal tissues and ocular tissues, in comparison with the previous year, as well as embryo (IVF) particularly associated with donor sperm and oocyte.

1.1 Yearly trends (2019–2023)

1.1.1. Distribution of T&C

Considering the demographic data[3] of reporting countries, Figure 1 presents the **Reproductive** and **Non-Reproductive T&C** (Replacement T&C and HSC) distribution rates (median) per 1,000 population across all reporting countries for each year from 2019 to 2023.



n (i)	19	22	21	22	23
n (ii)	27	26	27	29	30

Figure 1. Reproductive and Non-Reproductive T&C distribution rates (median) per 1,000 population; 2019–2023

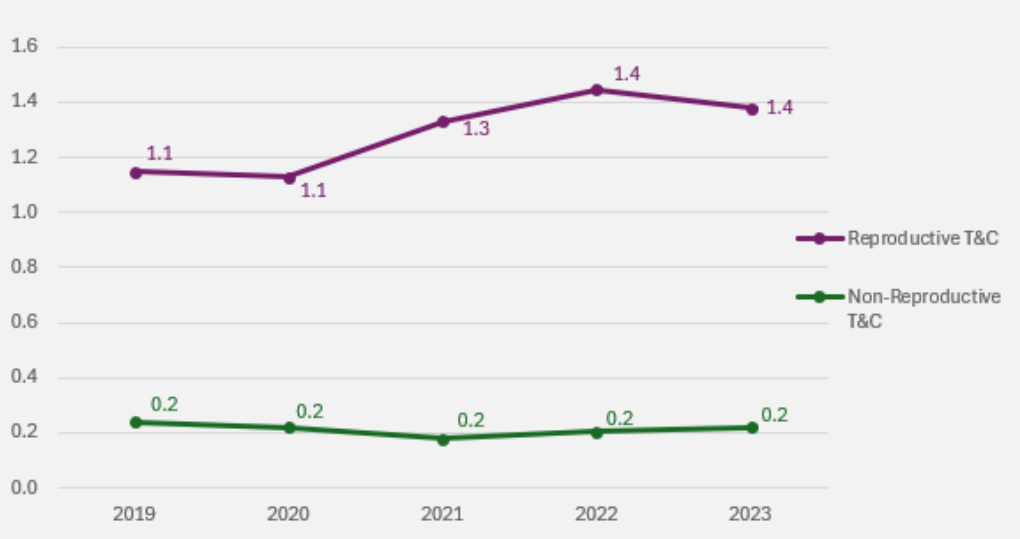
Note: i) Reproductive T&C ii) Non-Reproductive T&C.

Overall, Reproductive T&C distribution rates showed an upward trend over the 2019–2023 period, reaching a high in 2022. In contrast, Non-Reproductive T&C rates remained relatively stable at around 0.5–0.6 per 1,000 population. Notably, the number of countries contributing data has grown from 19 to 23 for Reproductive T&C and from 27 to 30 for Non-Reproductive T&C.

[3] https://ec.europa.eu/eurostat/ (Population on 1 January – total; following Brexit, UK = Northern Ireland only)

1.1.2. Clinical Application of T&C

Figure 2 shows the **Reproductive and Non-Reproductive T&C** (Replacement T&C and HSC) application rates (median) per 1,000 population across all reporting countries for each year from 2019 to 2023.



n (i)	16	15	16	20	20
n (ii)	21	19	23	25	27

Figure 2. Reproductive and Non-Reproductive T&C application rates (median) per 1,000 population; 2019–2023

Note: i) Reproductive T&C ii) Non-Reproductive T&C.

Similar to the distribution rate trends, between 2019 and 2023 clinical application rates for Reproductive T&C showed an upward trend, rising from about 1.1 to 1.4 per 1,000 population, while Non-Reproductive T&C rates remained fairly stable at around 0.2 throughout the five-year span. The number of reporting countries increased for both categories, more substantially for Non-Reproductive T&C (from 21 to 27).

1.2. Geographic distribution (units distributed) by category of T&C

1.2.1. Replacement T&C

Twenty-nine countries (AT, BE, BG, HR, CY, CZ, DK, EE, FI, FR, DE, EL, HU, IE, IT, LV, LT, LU, MT, NL, NO, PL, PT, RO, SK, SI, ES, SE and UK(NI)) reported a total of 449,719 units distributed in 2023. This was an 11% increase in comparison with the previous year, when 405,055 units were reported by 28 countries.

Considering the demographic data[4] of the reporting countries in 2023, the distribution rates of Replacement T&C per million population (pmp) are shown in Figure 3.

[4] https://ec.europa.eu/eurostat/ (Population on 1 January – total; following Brexit, UK = Northern Ireland only)

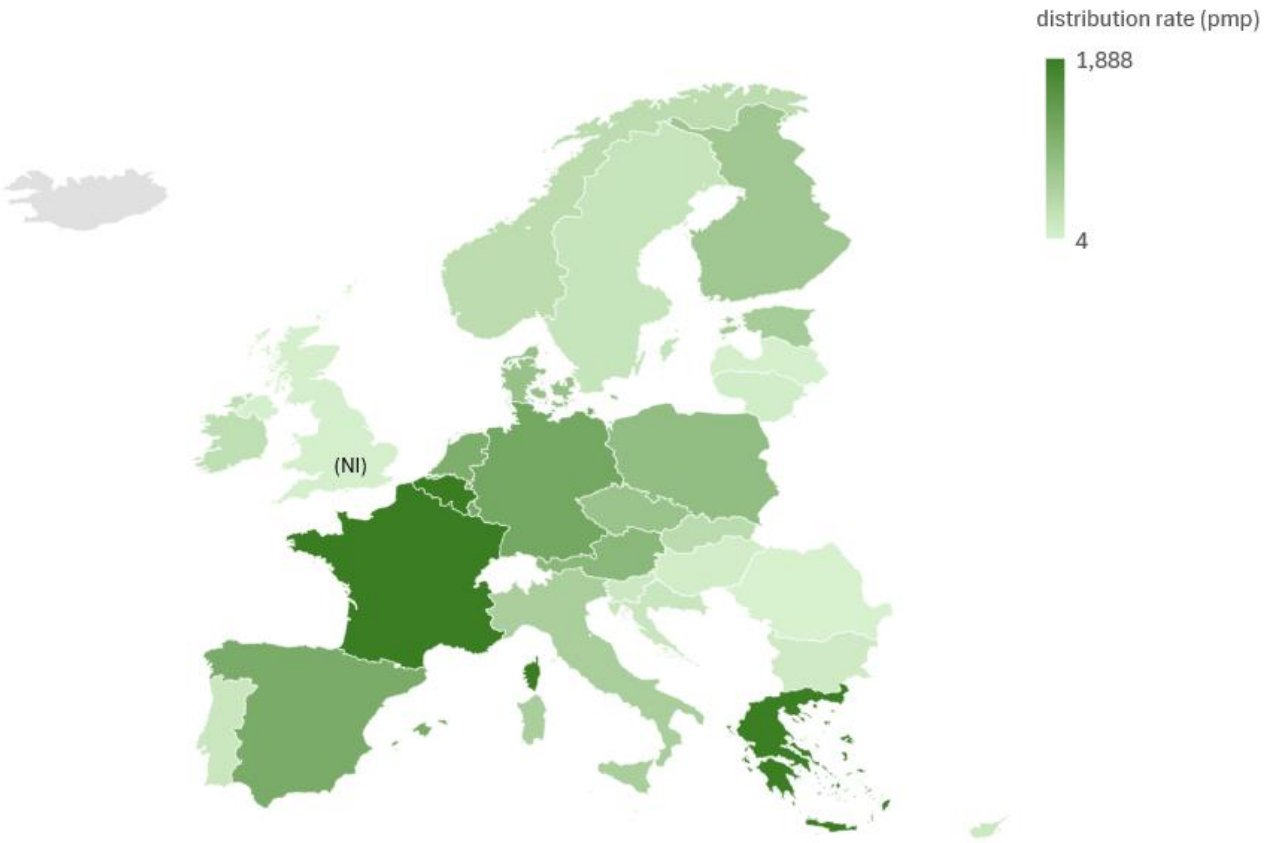


Figure 3. Distribution rates of Replacement T&C in Europe pmp in 2023

The distribution rate of Replacement T&C (median) was 365 units pmp [range 4(MT) – 1,888(BE)], 21% lower than in 2022 (461).

1.2.2. HSC

Twenty-five countries (AT, BE, BG, HR, CY, CZ, DK, EE, FI, DE, EL, HU, IS, IE, IT, LT, LU, NL, NO, PL, PT, SK, SI, ES and SE) reported a total of 43,943 units distributed in 2023. This was an 18% increase in comparison with the previous year, when 37,091 units were reported by 23 countries.

The distribution rates of HSC pmp are shown in Figure 4.

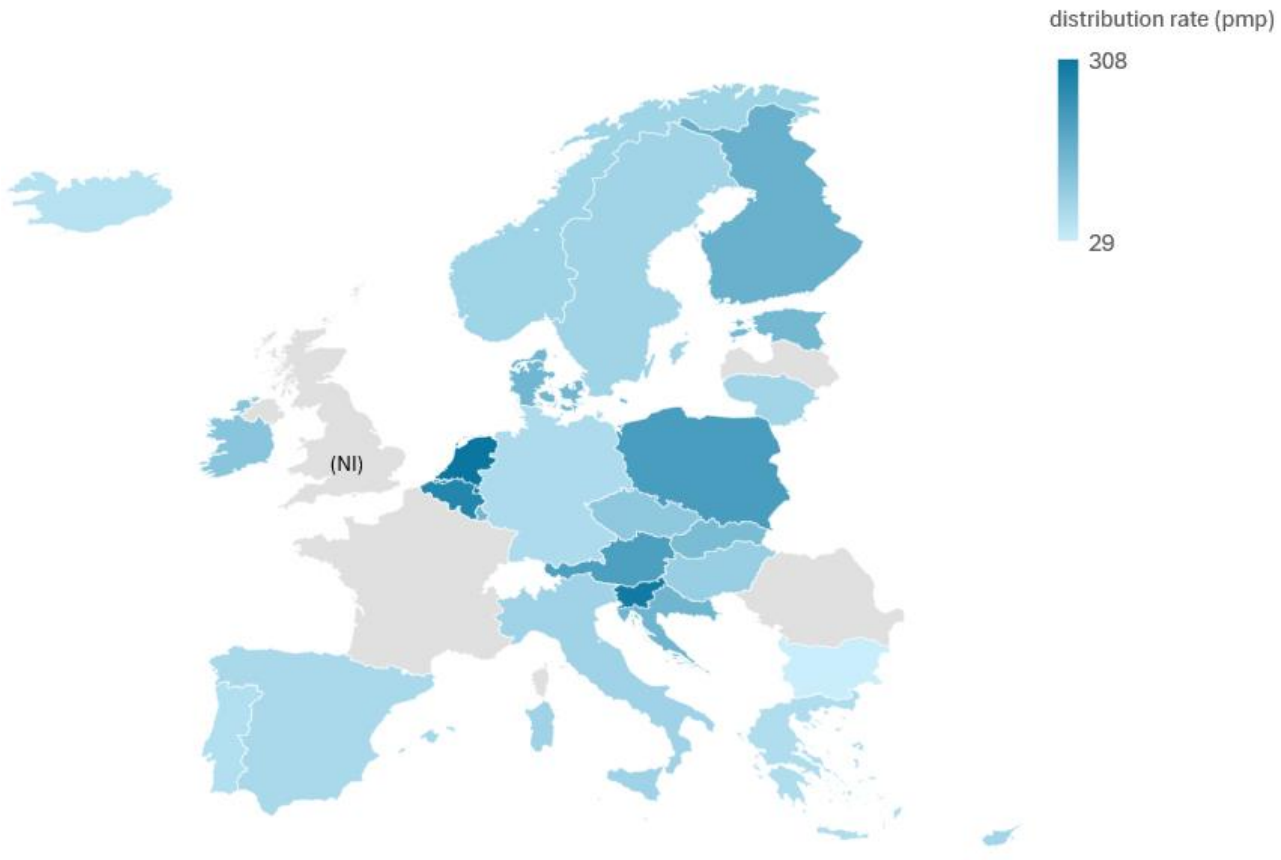


Figure 4. Distribution rates of HSC in Europe pmp in 2023

The distribution rate of HSC (median) was 107 units pmp [range 29(BG) – 308(NL)], marginally lower than in 2022 (108).

1.2.3. Reproductive T&C

Twenty-three countries (AT, BG, HR, CY, CZ, DK, FI, DE, HU, IS, IE, LV, LI, LT, LU, MT, NL, NO, RO, SK, SI, SE and UK(NI)) reported a total of 533,967 units distributed in 2023. This was a 5% increase in comparison with the previous year, when 506,429 units were reported by 22 countries.

The distribution rates of Reproductive T&C pmp are shown in Figure 5.

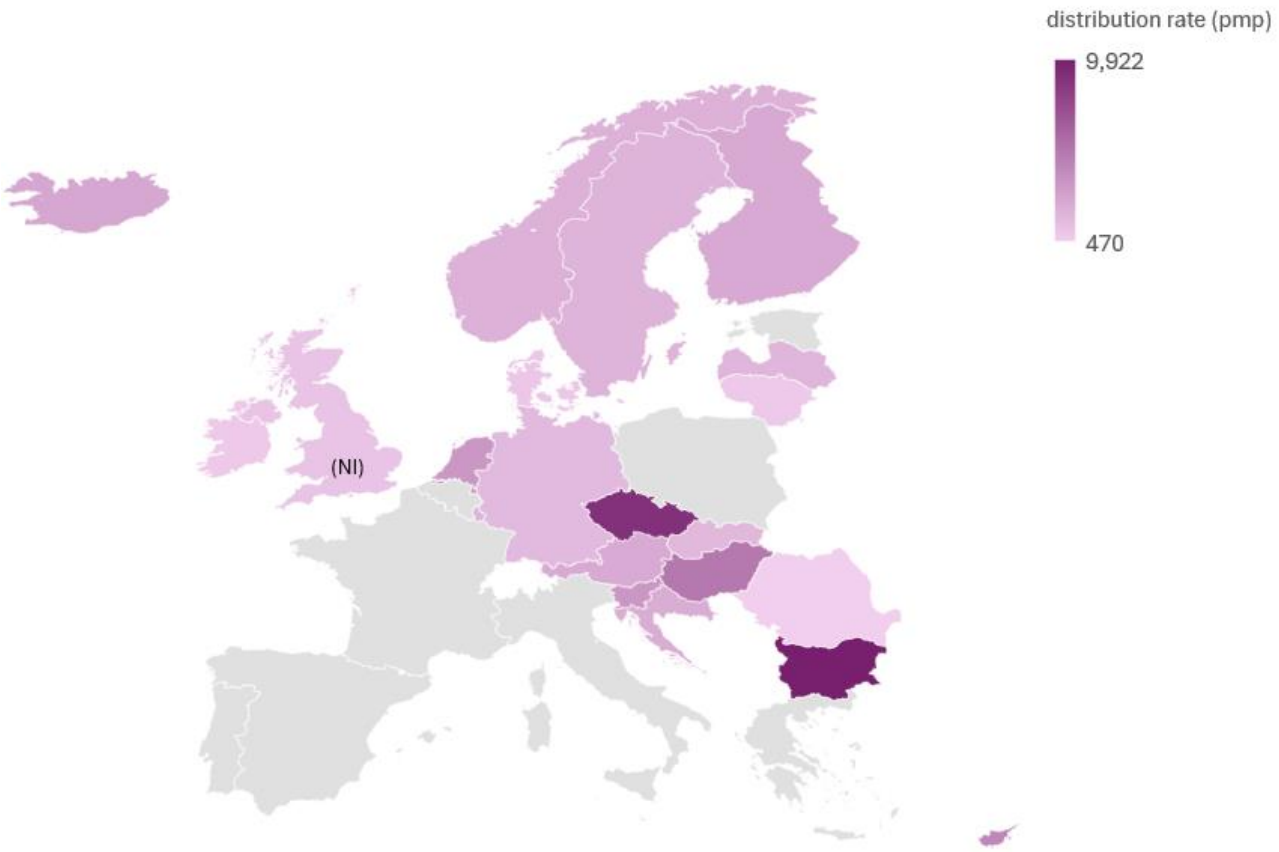


Figure 5. Distribution rates of Reproductive T&C in Europe pmp in 2023

The distribution rate of Reproductive T&C (median) was 1,925 units pmp [range 470(RO) – 9,922(BG)], 11% lower than in 2022 (2,152).

1.3. Geographic distribution (number of recipients) by category of T&C

1.3.1. Replacement T&C

Twenty-four countries (AT, BG, HR, CY, CZ, DK, EE, FI, FR, EL, HU, IE, LT, LU, MT, NL, NO, PT, RO, SK, SI, ES, SE and UK(NI)) reported a total of 177,327 recipients who received Replacement T&C in 2023. This was an 18% increase in comparison with the previous year, when 149,823 recipients were reported by 22 countries.

Rates of recipients who received Replacement T&C pmp in Europe are displayed in Figure 6 [range 4(MT) – 1,546(EL)].

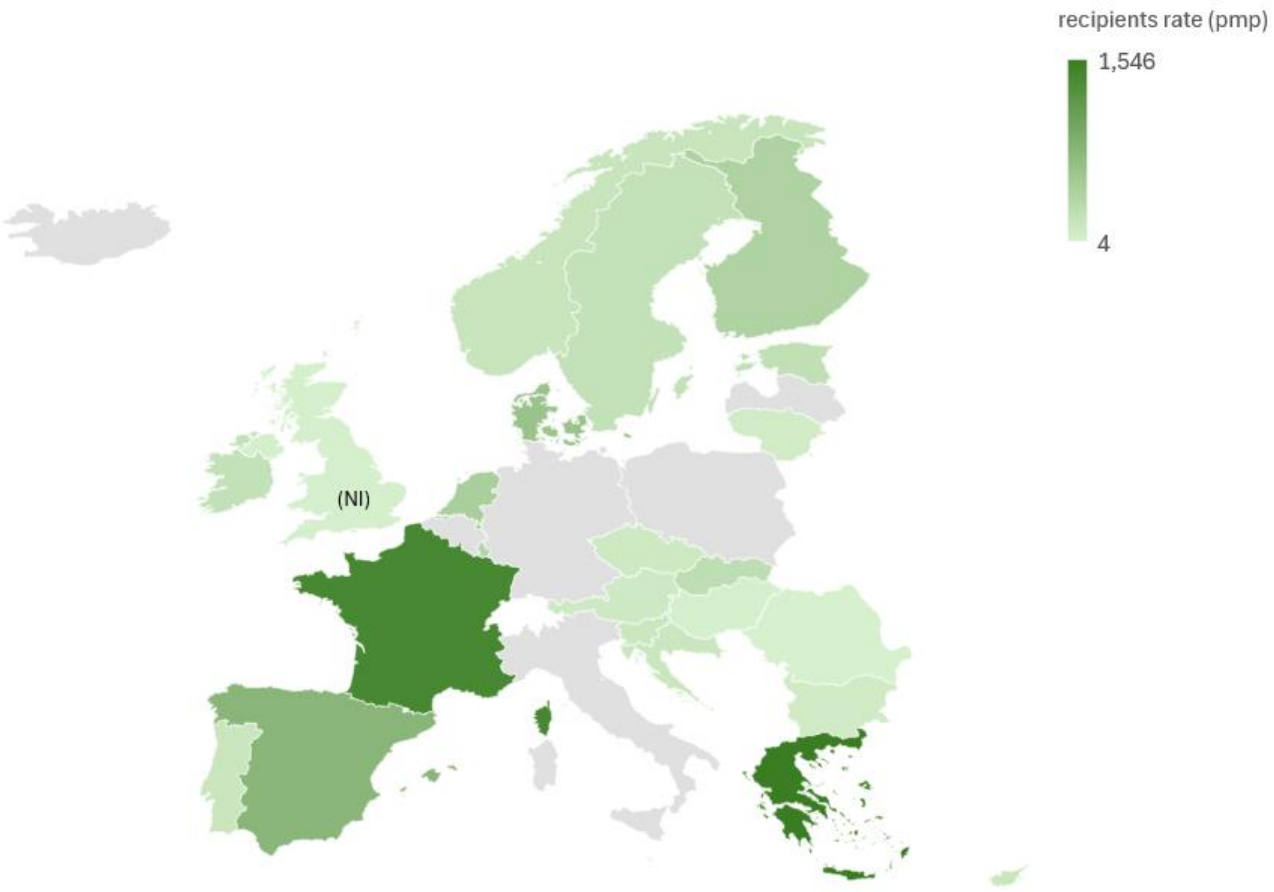


Figure 6. Application rates of Replacement T&C in Europe pmp in 2023

The European rate (median) in 2023 was determined to be 166 recipients treated with Replacement T&C pmp, slightly lower than in 2022 (177).

1.3.2. HSC

Twenty-four countries (AT, BE, BG, HR, CY, CZ, DK, EE, FI, DE, EL, HU, IS, IE, LT, LU, NL, NO, PL, PT, SK, SI, ES and SE) reported a total of 33,383 recipients who received HSC in 2023. This was a 15% increase in comparison with the previous year, when 29,155 recipients were reported by 22 countries.

Rates of recipients who received HSC pmp in Europe are displayed in Figure 7 [range 3(NO) – 202(SI)].

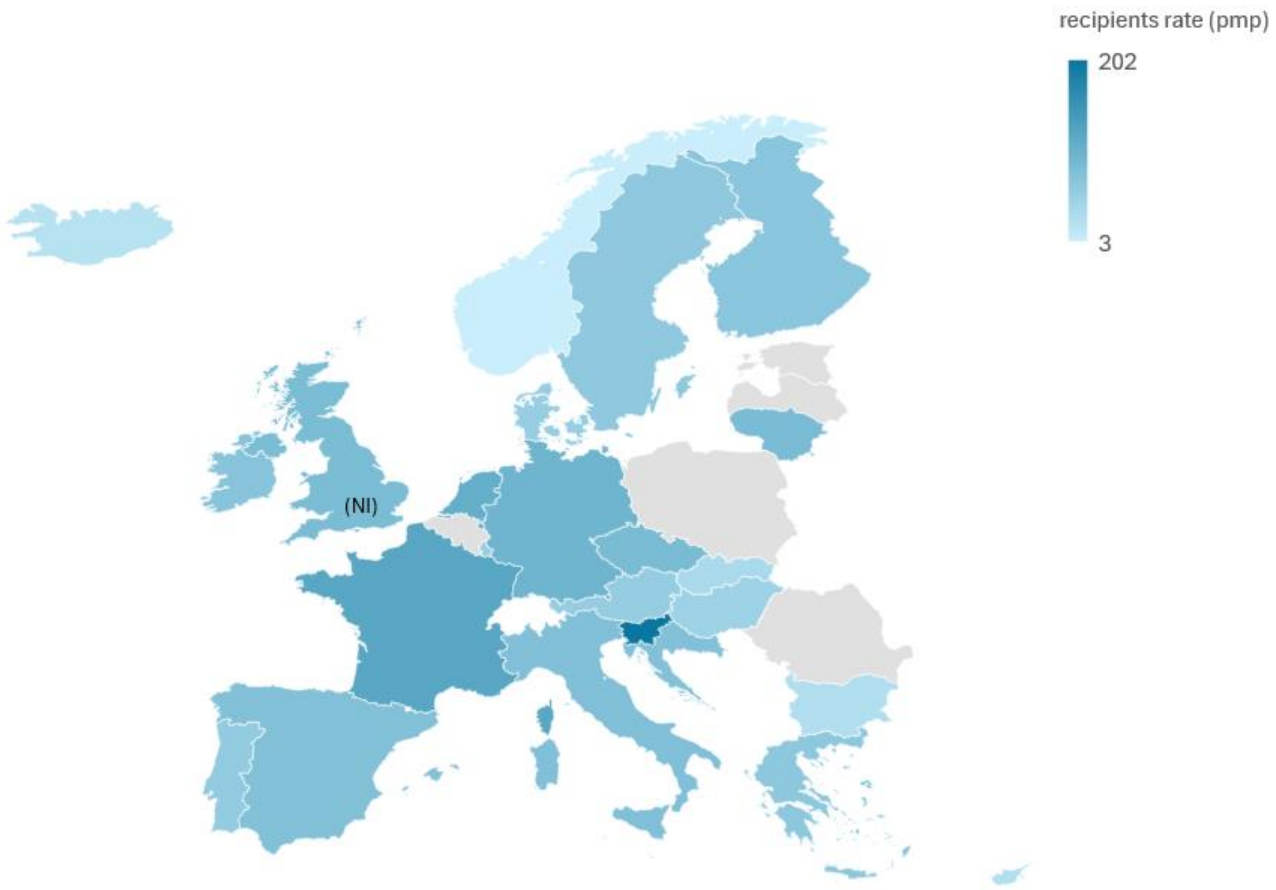


Figure 7. Application rates of Replacement T&C in Europe pmp in 2023

The European rate (median) in 2023 was determined to be 69 recipients treated with HSC pmp, similar to 2022.

1.3.3. Reproductive T&C

Twenty countries (AT, BG, HR, CY, CZ, DK, FI, HU, IS, IE, LI, LT, LU, MT, NL, NO, PT, SK, SI and SE) reported a total of 175,290 recipients who had at least one unit of tissues or cells applied in 2023. In the context of medically assisted reproduction (MAR), this means the number of patients who were inseminated with sperm (IUI) only or had an embryo transfer. This was a 15% increase in comparison with the previous year, when 156,651 recipients were reported by 20 countries.

Rates of Reproductive T&C recipients pmp in Europe are displayed in Figure 8 [range 38(NO) – 3,662(CZ)].

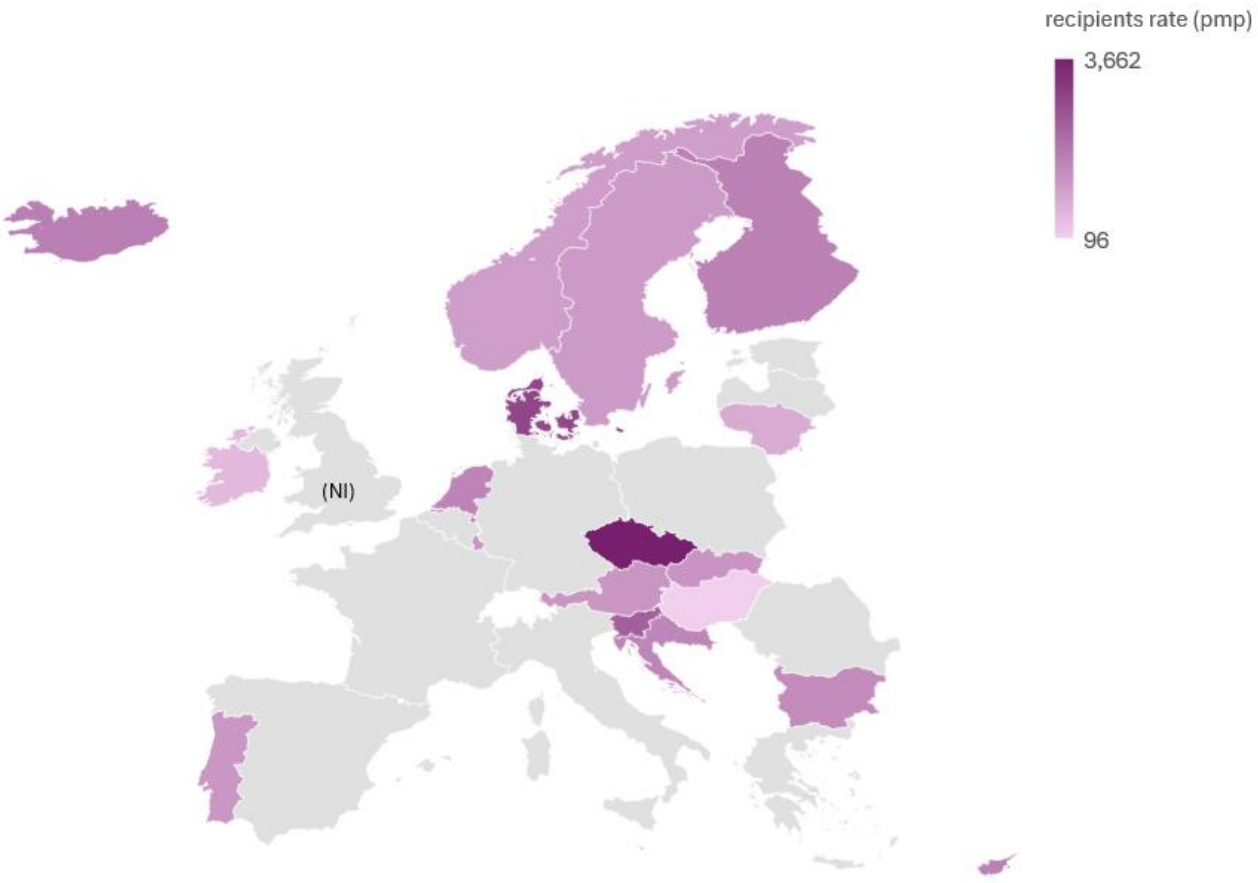


Figure 8. Application rates of Reproductive T&C in Europe pmp in 2023

The European rate (median) in 2023 was determined to be 1,380 Reproductive T&C recipients pmp, slightly lower than in 2022 (1,445).

1.4. Overview of volume of activity by category of T&C

1.4.1. Distribution of number of units processed, units distributed and recipients

Overall data collected in 2023 for number of units processed, units distributed and recipients by category of T&C are shown in Figure 9.

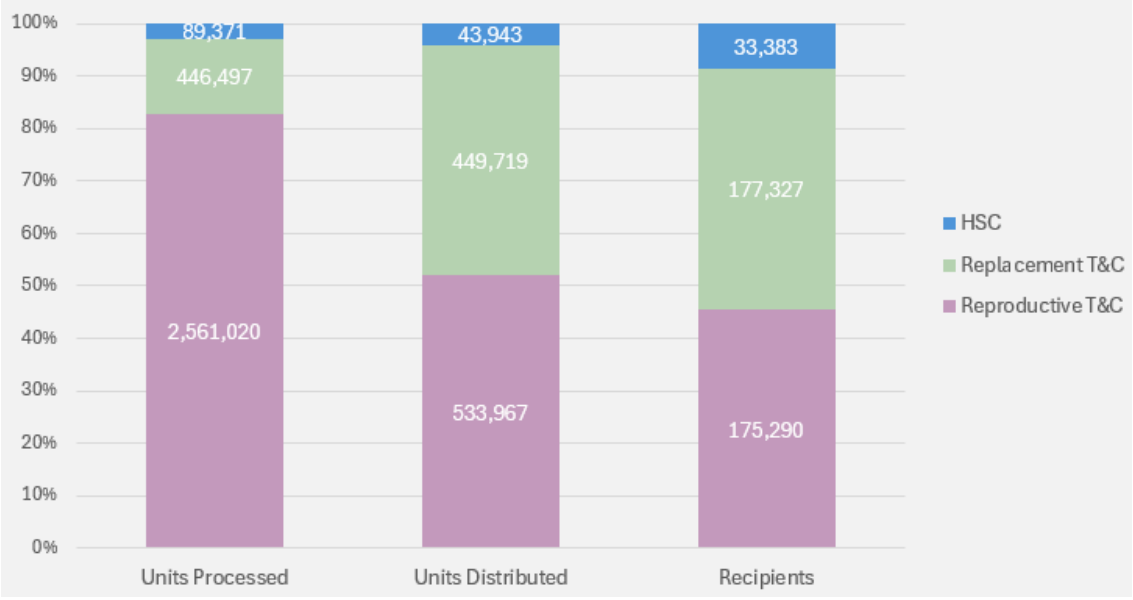


Figure 9. Percentage distribution of total number of units processed, units distributed and recipients by category of T&C in 2023

1.4.2. Comparative data

As shown in Table 1, Reproductive T&C continued to be the most processed and distributed category of T&C, while Replacement T&C was the category with the most recipients. In comparison with 2022, there was a notable increase across categories of T&C in terms of number of units distributed and number of recipients.

	Units Processed		% Change	Units Distributed		% Change	Recipients		% Change
T&C Category	2023	2022		2023	2022		2023	2022	
Replacement T&C	446,497	456,953	-2	449,719	405,055	+11	177,327	149,823	+18
HSC	89,371	98,407	-9	43,943	37,091	+18	33,383	29,155	+15
Reproductive T&C	2,561,020	2,359,270	+9	533,967	506,429	+5	175,290	156,651	+12
Total	3,096,888	2,914,630	+6	1,027,629	948,575	+8	386,000	335,629	+15
n (Replacement T&C)	26	23		29	28		24	22	
n (HSC)	23	20		25	23		24	22	
n (Reproductive T&C)	21	18		23	22		20	20	

Table 1. Summary of total number of units processed, units distributed and recipients by category of T&C; 2023 vs. 2022

1.5. Country-specific trends (2022 vs. 2023) in distribution by category of T&C

Considering the demographic data[5] of the reporting countries in 2022 and 2023, the distribution rate per million population (pmp) was calculated for each reporting country and for each category of T&C.

[5] https://ec.europa.eu/eurostat/ (Population on 1 January – total; following Brexit, UK = Northern Ireland only)

1.5.1. Replacement T&C

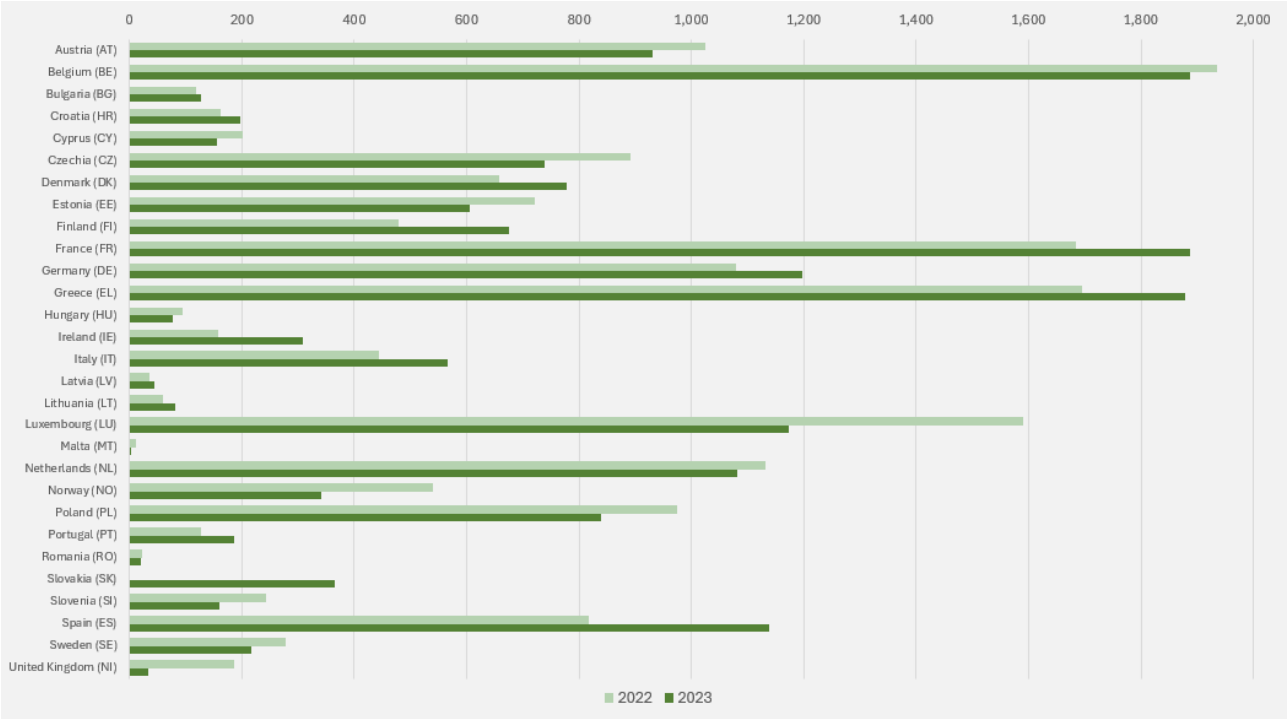


Figure 10. Distribution rates of Replacement T&C pmp per country; 2022 vs. 2023

1.5.2. HSC

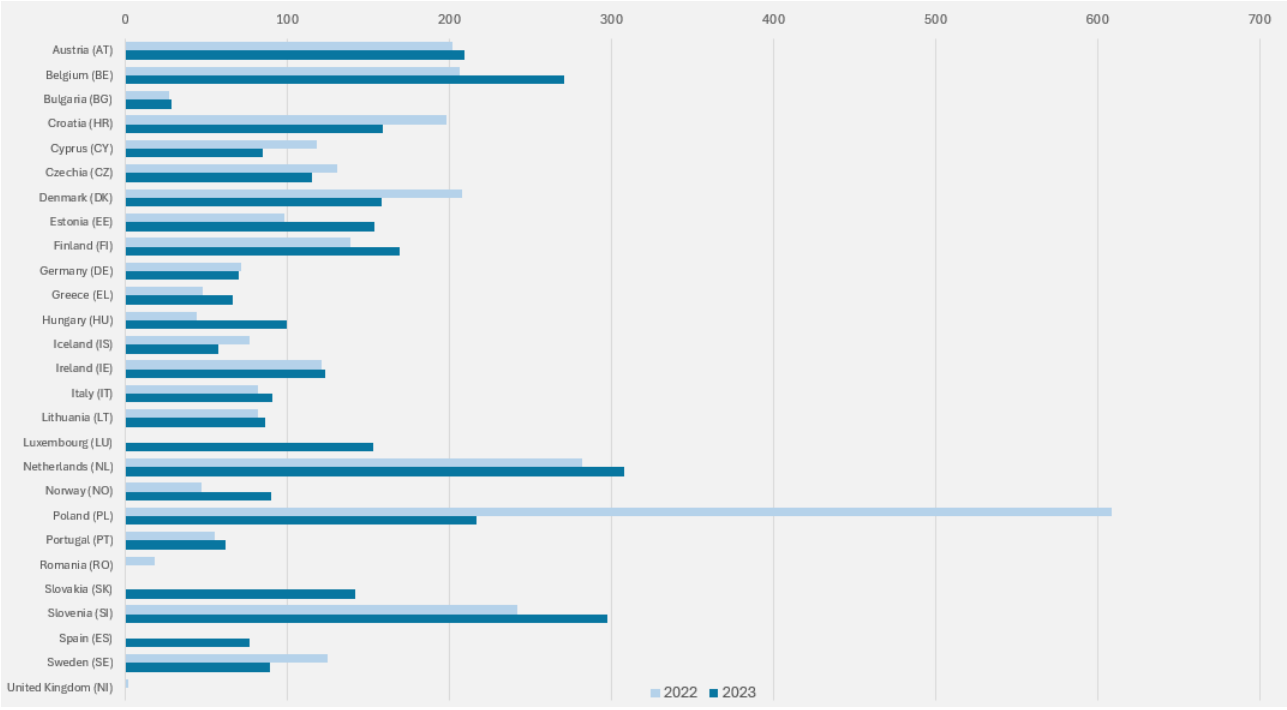


Figure 11. Distribution rates of HSC pmp per country; 2022 vs. 2023

1.5.3. Reproductive T&C

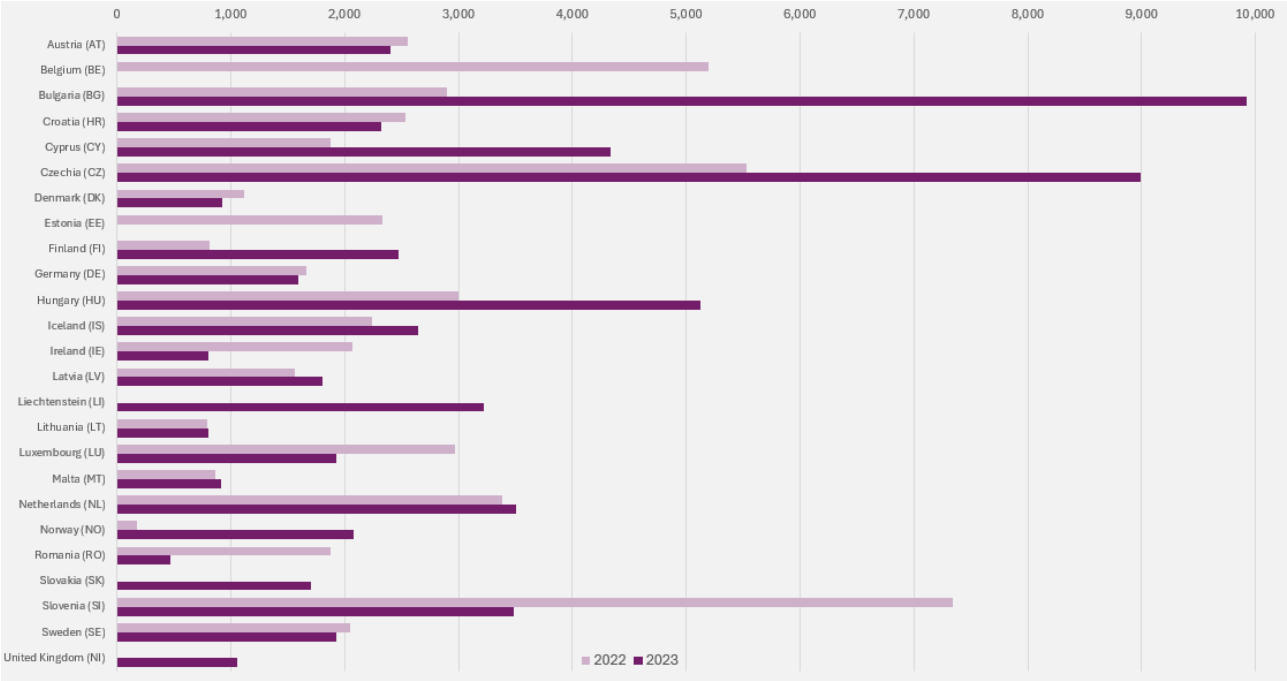


Figure 12. Distribution rates of Reproductive T&C pmp per country; 2022 vs. 2023

1.6. Country-specific trends (2022 vs. 2023) in clinical application by category of T&C

Considering the demographic data[6] of the reporting countries in 2022 and 2023, the application rate per million population (pmp) was calculated for each reporting country and for each category of T&C.

[6] https://ec.europa.eu/eurostat/ (Population on 1 January – total; following Brexit, UK = Northern Ireland only)

1.6.1. Replacement T&C

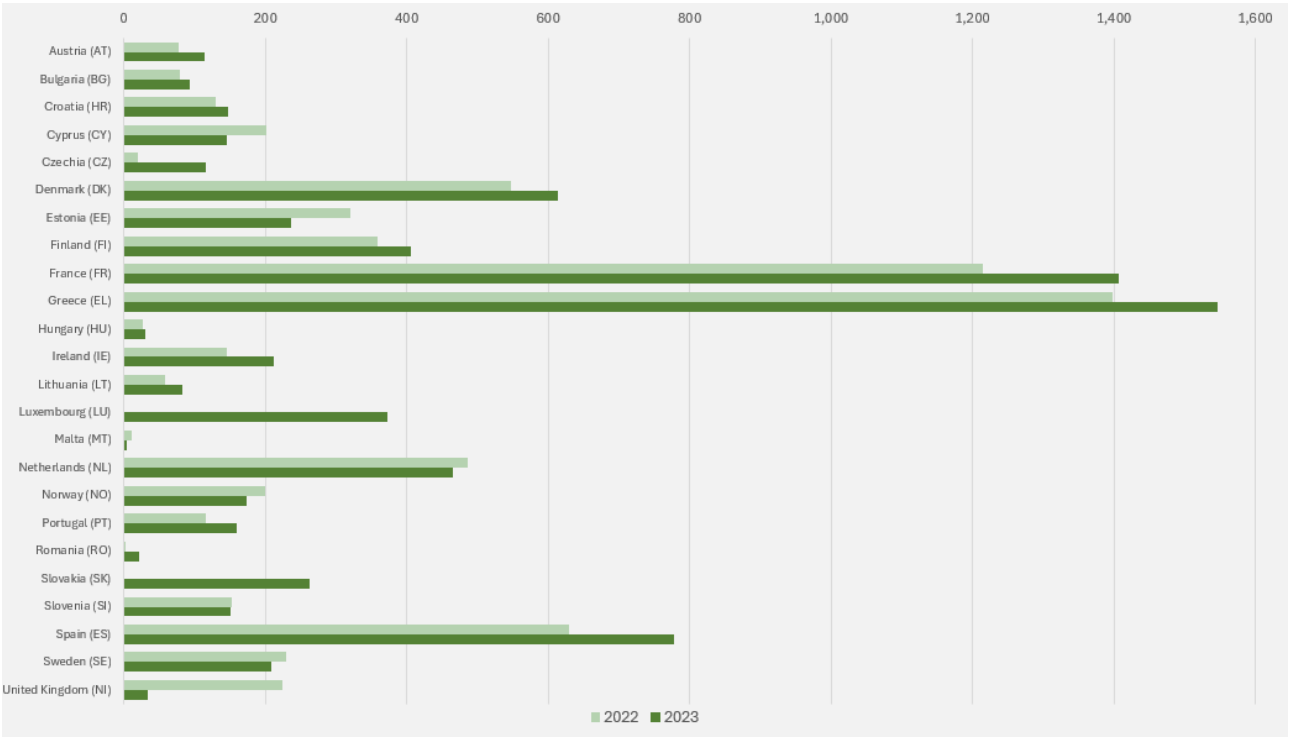


Figure 13. Application rates of Replacement T&C pmp per country; 2022 vs. 2023

1.6.2. HSC

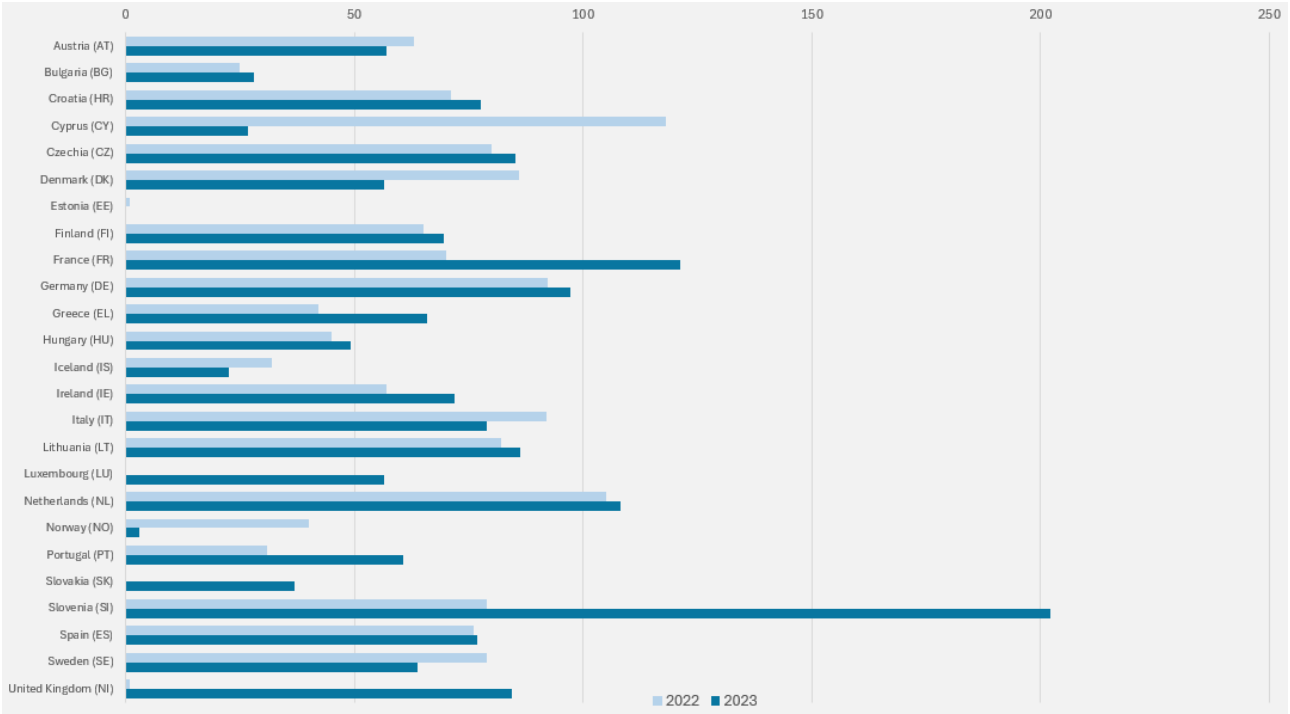


Figure 14. Application rates of HSC pmp per country; 2022 vs. 2023

1.6.3. Reproductive T&C

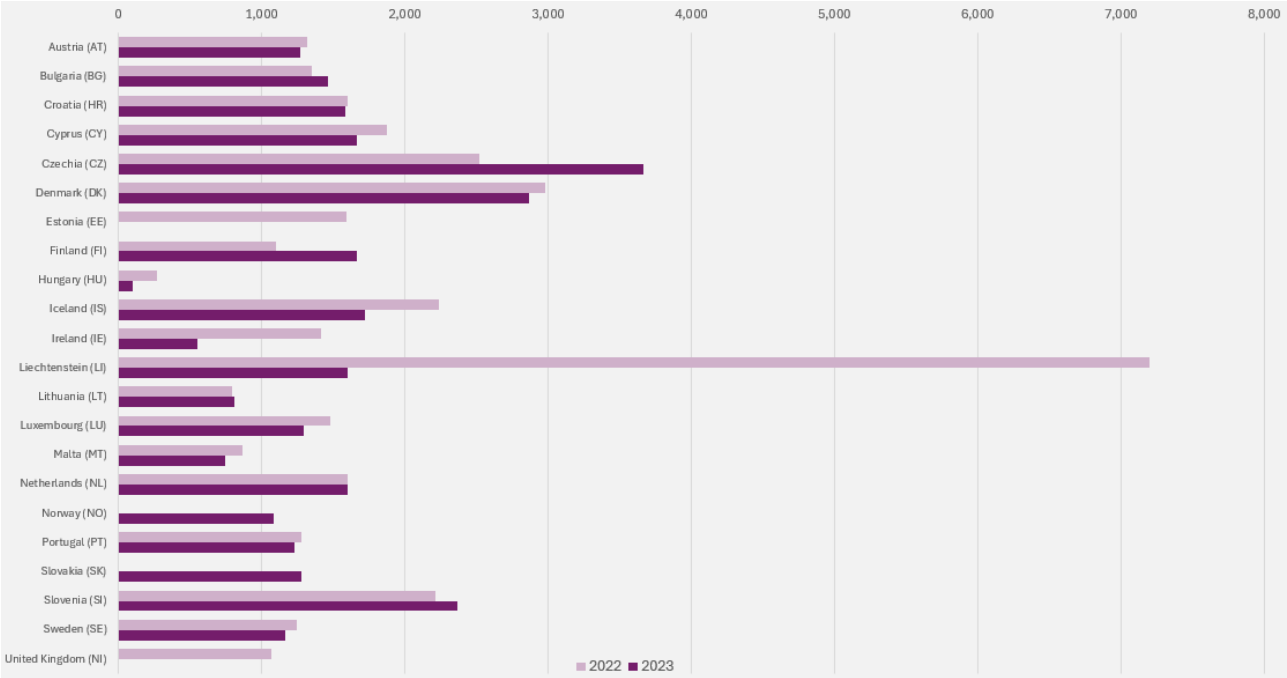


Figure 15. Application rates of Reproductive T&C pmp per country; 2022 vs. 2023

1.7. Overview of volume of activity by category of T&C and by type of tissue/cell

1.7.1. Distribution of number of units distributed and recipients – Replacement T&C

As shown in Figure 16, skeletal tissues was the main type of Replacement T&C distributed and applied (78%) in 2023 followed by ocular tissues, while other tissues or cells represented 8%.

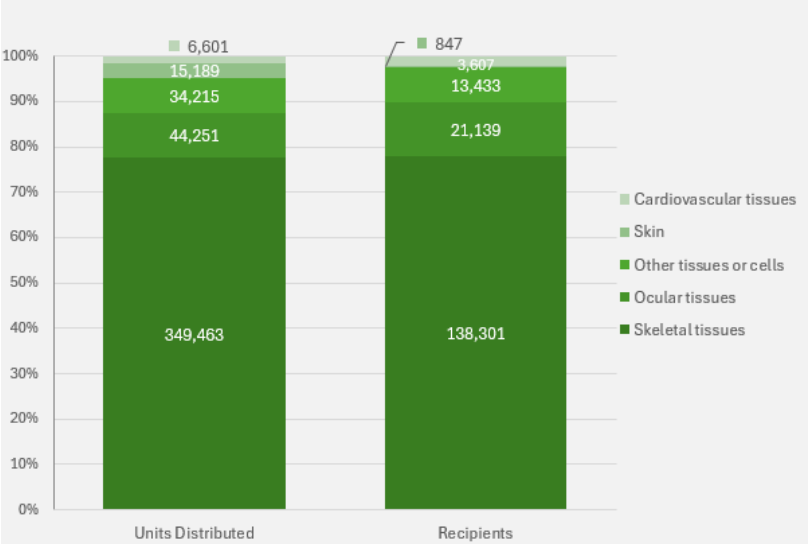


Figure 16. Percentage distribution of number of units distributed and recipients by type of Replacement T&C in 2023

1.7.2. Comparative data – Replacement T&C

As shown in Table 2, there was a moderate increase in number of units distributed and recipients of skeletal tissues and ocular tissues in comparison with 2022. In addition, a significant rise was observed for patients who received a skin transplant (225%).

Type of Tissue/Cell	Units Distributed 2023	Units Distributed 2022	% Change	Recipients 2023	Recipients 2022	% Change
Skeletal tissues	349,463	302,904	+15	138,301	117,064	+18
Ocular tissues	44,251	40,327	+10	21,139	19,180	+10
Other tissues or cells	34,215	40,643	-16	13,433	10,043	+34
Skin	15,189	14,531	+5	847	261	+225
Cardiovascular tissues	6,601	6,650	-1	3,607	3,275	+10
Total	**449,719**	**405,055**	+11	**177,327**	**149,823**	+18
n (skeletal tissues)	28	27		21	17	
n (ocular tissues)	28	28		23	21	
n (other tissues or cells)	24	20		21	16	
n (skin)	16	12		14	9	
n (cardiovascular tissues)	23	21		17	16	

Table 2. Summary of number of units distributed and recipients by type of Replacement T&C; 2023 vs. 2022

Regarding subtype of Replacement T&C (Table 3), it is worth noting the significant growth in units distributed of cornea (66%), sclera (44%) and other ocular (102%) tissues in comparison with 2022.

Subtype	Skeletal tissues 2023	Skeletal tissues 2022	% Change
Bone	264,933	236,038	+12
Tendons/ligaments	8,171	7,418	+10
Fascia	5,575	5,793	-4
Cartilage	3,658	3,423	+7
Other	4,993	3,815	+31
General	62,133	46,417	+34
Total	**349,463**	**302,904**	+15
n (bone)	18	19	
n (tendons/ligaments)	19	18	
n (fascia)	10	7	
n (cartilage)	8	9	
n (other)	13	12	
n (general)	8	8	

Subtype	Ocular tissues 2023	Ocular tissues 2022	% Change
Cornea	31,114	18,791	+66
Sclera	3,973	2,753	+44
Other ocular	545	270	+102
General	8,619	18,513	-53
Total	**44,251**	**40,327**	+10
n (cornea)	21	21	
n (sclera)	11	13	
n (other ocular)	3	4	
n (general)	6	7	

Subtype	Cardiovascular tissues 2023	Cardiovascular tissues 2022	% Change
Heart valve	1,769	1,638	+8
Vessel	4,323	4,432	-2
Other cardiovascular	387	417	-7
General	122	163	-25
Total	**6,601**	**6,650**	-1
n (heart valve)	18	17	
n (vessel)	19	17	
n (other cardiovascular)	9	7	
n (general)	1	1	

Table 3. Summary of number of units distributed by type of Replacement T&C and by subtype; 2023 vs. 2022
Note: the 'general' subtype is used by MS when only aggregated data for the type of tissue are available; the subtype 'other' in skeletal tissues includes meniscus and auditory ossicles, for example, while the subtype 'other' in other tissues or cells includes adipose tissue, tympanic membrane, etc.

Regarding skin, Table 4 shows the data for countries that reported units distributed in cm^2 (not included in Table 2).

Country	Skin (cm^2)		% Change
	2023	2022	
Belgium	215,412	209,197	+3
France	330,000	420,000	-21
Germany	243,430	202,646	+20
Spain	288,170	341,778	-16

Table 4. Summary data of countries reporting skin units in cm^2; 2023 vs. 2022

1.7.3. Distribution of number of units distributed and recipients – HSC

In 2023, peripheral blood stem cells (PBSC) represented 76% of all units of HSC distributed, followed by general haematopoietic progenitor cells (HPC) (13%) and bone marrow (5%).

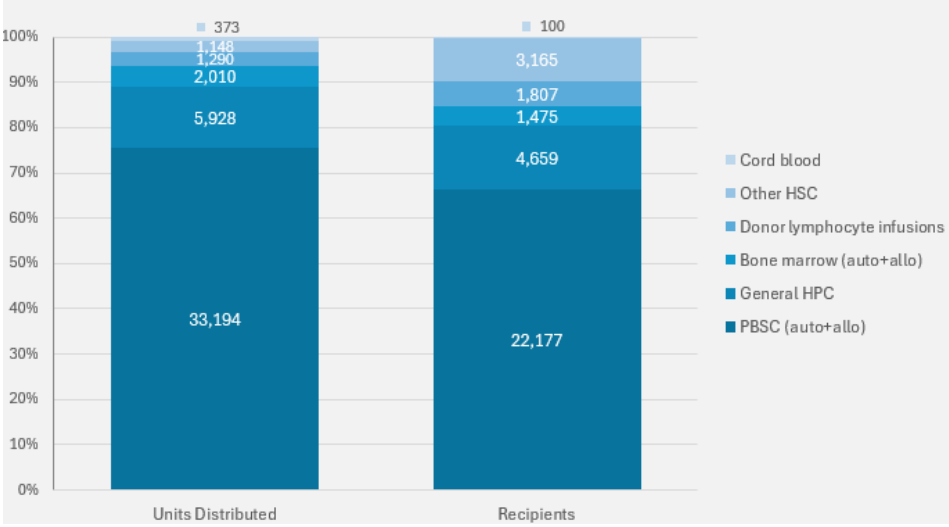


Figure 17. Percentage distribution of number of units distributed and recipients by type of HSC in 2023

1.7.4. Comparative data – HSC

As shown in Table 5, there was a significant increase in the number of units distributed of general HPC, as well as in the number of recipients of other HSC compared to 2022.

Type of Tissue/Cell	Units Distributed 2023	Units Distributed 2022	% Change	Recipients 2023	Recipients 2022	% Change
PBSC (auto+allo)	33,194	31,913	+4	22,177	21,703	+2
General HPC	5,928	655	+805	4,659	4,293	+9
Bone marrow (auto+allo)	2,010	2,192	-8	1,475	1,600	-8
Donor lymphocyte infusions	1,290	1,330	-3	1,807	1,355	+33
Other HSC	1,148	675	+70	3,165	50	+6230
Cord blood	373	326	+14	100	154	-35
Total	**43,396**	**37,091**	+18	**33,383**	**29,155**	+15

n (PBSC)	19	19	18	16
n (general HPC)	5	2	4	2
n (bone marrow)	18	18	15	17
n (donor lymphocyte infusions)	13	13	14	10
n (other HSC)	5	2	4	1
n (cord blood)	10	4	9	6

Table 5. Summary of number of units distributed and recipients by type of HSC; 2023 vs. 2022
Note: the 'general HPC' type is used by MS when only aggregated data for the type of tissue are available.

Regarding subtype of HSC (Table 6), it is worth noting that the number of units distributed of allogenic related bone marrow decreased by 45% in comparison with 2022.

Subtype	PBSC 2023	PBSC 2022	% Change	Bone marrow 2023	Bone marrow 2022	% Change	Donor lymphocyte infusions 2023	Donor lymphocyte infusions 2022	% Change
Allogenic related	2,511	2,349	+7	349	629	-45	232	273	-15
Allogenic unrelated	4,973	5,493	-10	526	577	-9	565	494	+14
Autologous	17,623	15,640	+9	27	47	-43	-	-	
General	8,087	8,431	-4	1,108	939	+18	493	563	-12
Total	**33,194**	**31,913**	+4	**2,010**	**2,192**	-8	**1,290**	**1,330**	-3

n (allogenic related)	12	12	10	10	8	8	
n (allogenic unrelated)	12	13	12	11	8	9	
n (autologous)	15	14	5	8	-	-	
n (general)	4	6	6	6	5	5	

Subtype	Cord blood 2023	Cord blood 2022	% Change	Other HSC 2023	Other HSC 2022	% Change
Allogenic related	2	3	-33	N/A	N/A	no change
Allogenic unrelated	43	210	-80	2	N/A	
Autologous	N/A	112		826	624	+32
General	328	1	*	320	51	+527
Total	**373**	**326**	+14	**1,148**	**675**	+70

*increase in 2023

n (allogenic related)	1	3	1	2
n (allogenic unrelated)	5	9	1	-
n (autologous)	-	1	1	1
n (general)	4	1	3	1

Table 6. Summary of number of units distributed by type of HSC and by subtype; 2023 vs. 2022

1.7.5. Distribution of number of units distributed and recipients – Reproductive T&C

Of the 533,967 units of Reproductive T&C distributed, 56% were related to embryo (IVF), 38% were associated with sperm (IUI) and 6% with other Reproductive T&C (Figure 18).

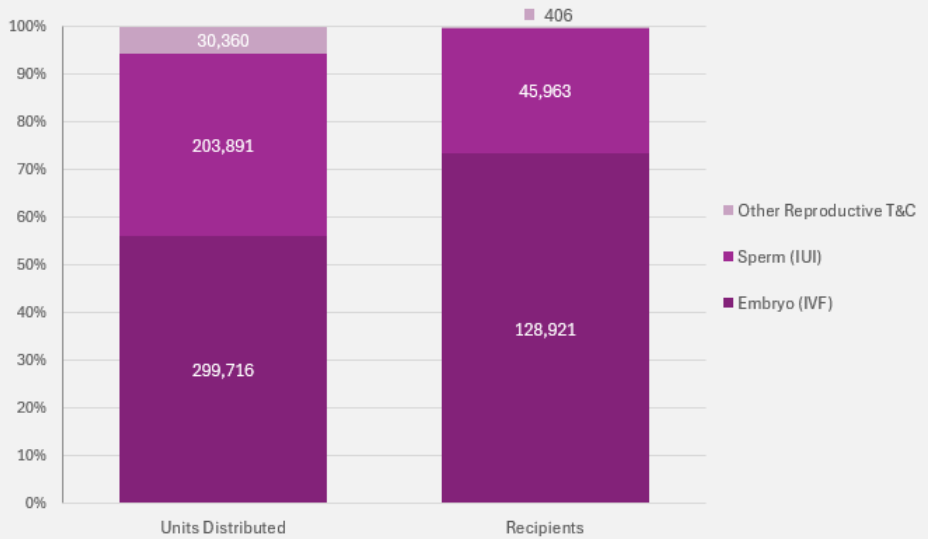


Figure 18. Percentage distribution of number of units distributed and recipients by type of Reproductive T&C in 2023

1.7.6. Comparative data – Reproductive T&C

As shown in Table 7, there was a 76% increase in the number of other Reproductive T&C distributed compared to 2022. Notably, there was a moderate rise in the number of units distributed and recipients of embryo (IVF) compared to the previous year, particularly associated with donor sperm and oocyte (Table 8).

Type of Tissue/Cell	Units Distributed		% Change	Recipients		% Change
	2023	2022		2023	2022	
Embryo (IVF)	299,716	246,743	+21	128,921	111,479	+16
Sperm (IUI)	203,891	242,409	-16	45,963	44,438	+3
Other Reproductive T&C	30,360	17,277	+76	406	734	-45
Total	533,967	506,429	+5	175,290	156,651	+8
n (embryo)	20	19		19	19	
n (sperm)	22	19		18	18	
n (other reproductive T&C)	11	12		8	9	

Table 7. Summary of number of units distributed and recipients by type of Reproductive T&C; 2023 vs. 2022
Note: the type 'other' includes ovarian and testicular tissue, for example.

Subtype	Embryo (IVF) 2023	2022	% Change
Donor oocyte, partner sperm	11,124	8,785	+27
Donor sperm and oocyte	2,180	583	+274
Donor sperm, partner oocyte	10,592	9,596	+10
Partner gametes	134,696	182,605	-26
General	141,124	45,174	+212
Total	**299,716**	**246,743**	**+21**
n (donor oocyte, partner sperm0	11	7	
n (donor sperm and oocyte)	11	6	
n (donor sperm, partner oocyte)	13	8	
n (partner gametes)	14	11	
n (general)	6	7	

Subtype	Sperm (IUI) 2023	2022	% Change
Non-partner donation	22,195	30,358	-27
Partner donation	38,745	60,604	-36
General	142,951	151,447	-6
Total	**203,891**	**242,409**	**-16**
n (non-partner donation)	14	13	
n (partner donation)	15	12	
n (general)	6	6	

Subtype	Other Reproductive T&C 2023	2022	% Change
Testicular tissue	1,722	2,901	-41
Ovarian tissue	132	14,376	-99
Other	28,506	N/A	
Total	**30,360**	**17,277**	**+76**
n (testicular tissue)	8	8	
n (ovarian tissue)	5	9	
n (other)	2	-	

Table 8. Summary of number of units distributed by type of Reproductive T&C and by subtype; 2023 vs. 2022

2 Serious Adverse Reactions in Recipients

Key findings

- As seen in previous years, the majority of SAR were associated with Reproductive T&C therapies, followed by HSC and Replacement T&C.
- Assigning and reporting imputability was done in 51% of cases (vs. 38% in 2022).

Non-Reproductive T&C:

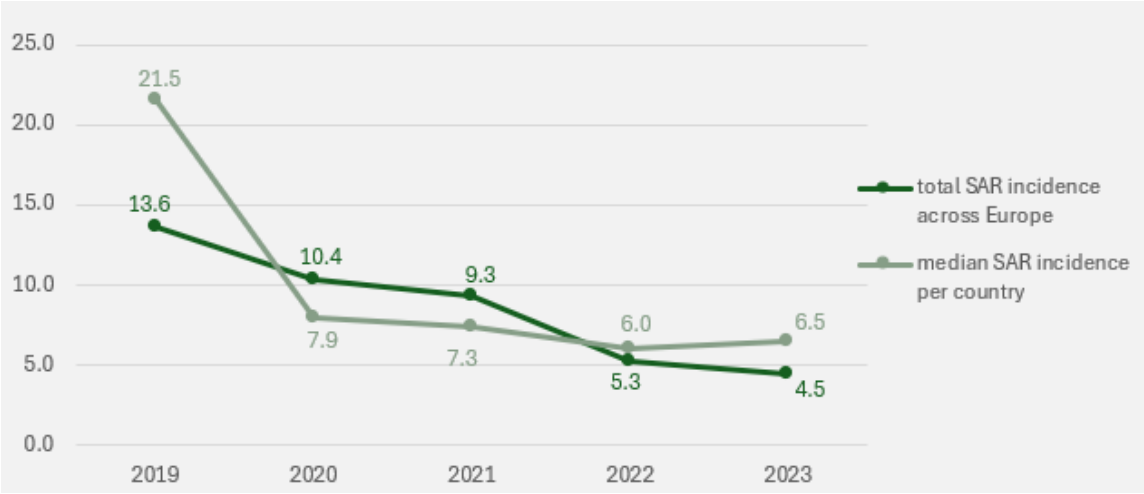
- Total SAR incidence has been trending downward in the last 5 years, reaching 4.5/10,000 recipients in 2023.
- While 'Other SAR' remains the dominant reaction type, there is a noticeable shift towards a slightly higher proportion of transmitted infection (TI)-related SAR in the most recent data.
- Graft failure/delayed engraftment continues to be the most common reaction subtype, mainly associated with skeletal tissues (in Replacement T&C), and PBSC and bone marrow transplantation (in HSC).

Reproductive T&C:

- Total SAR incidence has shown large year-to-year fluctuations (notably high in 2020 and 2022).
- Transmitted genetic conditions (TGC) and 'Other SAR' (specifically ectopic pregnancy) remain the most frequent reaction types.

2.1 Yearly trends (2019–2023)

Figure 19 presents the yearly trends in SAR (including cases of imputability of possible, probable, certain or unknown) incidence in Non-Reproductive T&C (Replacement T&C and HSC) from 2019 to 2023, using two complementary metrics: (1) total SAR incidence per 10,000 Non-Reproductive T&C recipients and (2) the median SAR incidence across all reporting countries. The first measures the overall frequency of adverse reactions at the European level, providing a comprehensive view of patient risk, while the second represents the typical national-level risk, highlighting the variability of safety outcomes among individual countries, unaffected by extremes.



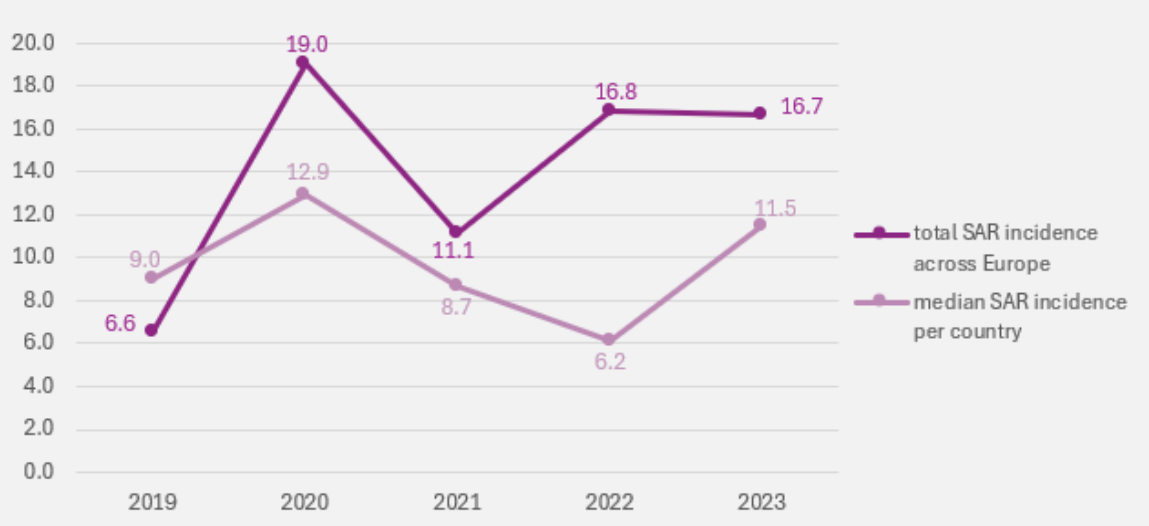
n	10	11	10	10	11

Figure 19. Yearly trends in SAR incidence in Non-Reproductive T&C: total SAR incidence/10,000 recipients and median SAR incidence per country; 2019–2023

Note: only countries that reported at least one SAR case and the number of recipients were included in the median SAR incidence calculations; for total SAR incidence refer to Annex 1.

Between 2019 and 2022, both total SAR incidence across Europe and the median SAR incidence per country showed a clear downward trend, with total incidence declining from roughly 14 to about 5 per 10,000 recipients, and the median from around 22 to 6. Notably, median SAR incidence increased slightly in 2023, while the total continued to fall. This increase in 2023 could stem from one or more countries with higher incidence joining the dataset.

Figure 20 presents the yearly trends in SAR (including cases of imputability of possible, probable, certain or unknown) incidence in Reproductive T&C from 2019 to 2023, using two complementary metrics: (1) total SAR incidence per 10,000 Reproductive T&C recipients and (2) the median SAR incidence across all reporting countries.



n	7	9	7	7	11

Figure 20. Yearly trends in SAR incidence in Reproductive T&C: total SAR incidence/10,000 recipients and median SAR incidence per country; 2019–2023

Note: only countries that reported at least one SAR case and the number of recipients were included in the median SAR incidence calculations; for total SAR incidence refer to Annex 1.

For Reproductive T&C, there were some significant year-to-year fluctuations in SAR incidence. On one hand, total SAR incidence increased sharply in 2020 and then fell in 2021, before rising again in 2022 and stabilising in 2023 at around 17 per 10,000 recipients. On the other hand, the median SAR incidence per country showed a similar spike in 2020 and drop in 2021, but in 2022 it reached its lowest point (6.2) before moving upward in 2023 to 11.5.
A key factor to consider is the relatively small group of countries reporting each year, meaning a single country's high or low numbers can significantly impact both the total and median.

2.2 Geographic distribution by category of T&C

2.2.1 Replacement T&C

Figure 21 shows the SAR (IL 1-3 or IL unknown) incidence rates per 10,000 Replacement T&C recipients across all reporting countries.

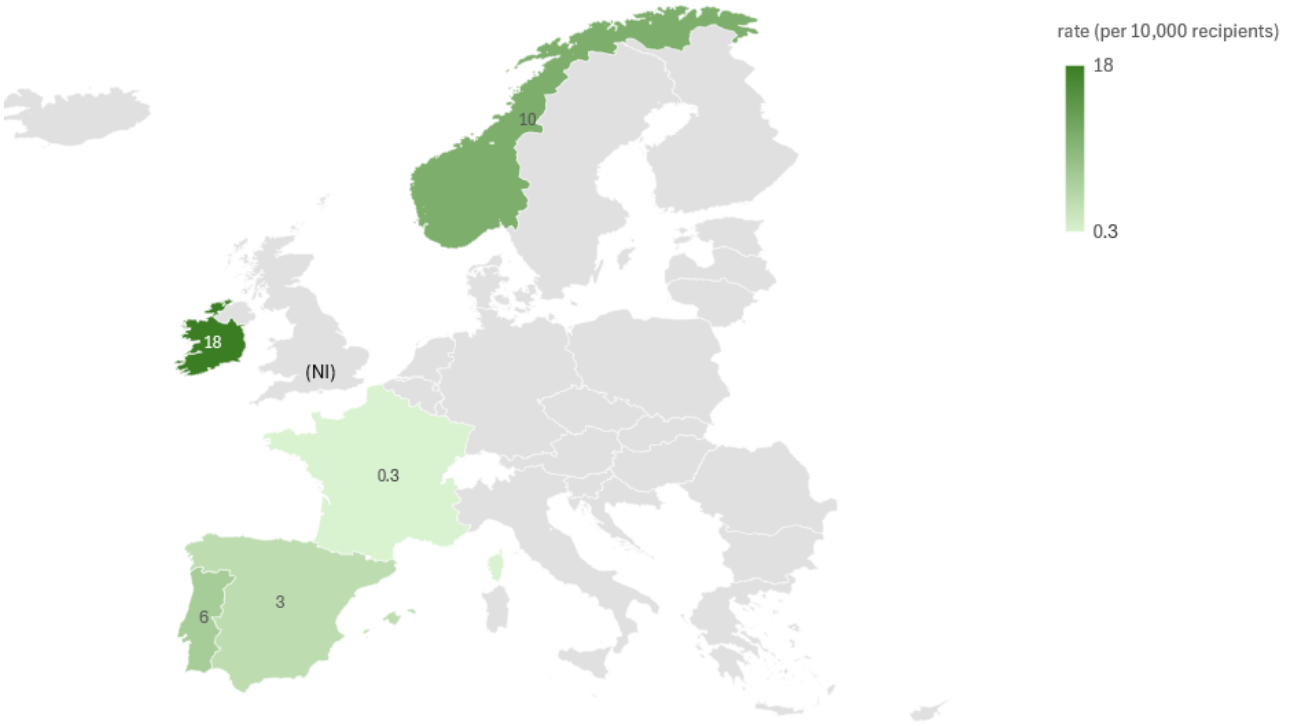


Figure 21. SAR incidence rates per 10,000 Replacement T&C recipients in Europe in 2023

Note: countries (DE and IT) that reported SAR cases but did not report the number of recipients (so incidence could not be calculated), countries reporting zero SAR (AT, BE, BG, HR, CY, CZ, DK, EE, FI, EL, HU, LV, LT, LU, MT, NL, PL, RO, SK, SI, SE and UK (NI)) as well as countries with no activity reported (IS and LI) are shown in grey.

2.2.2 HSC

Figure 22 shows the SAR (IL 1-3 or IL unknown) incidence rates per 10,000 HSC recipients across all reporting countries.

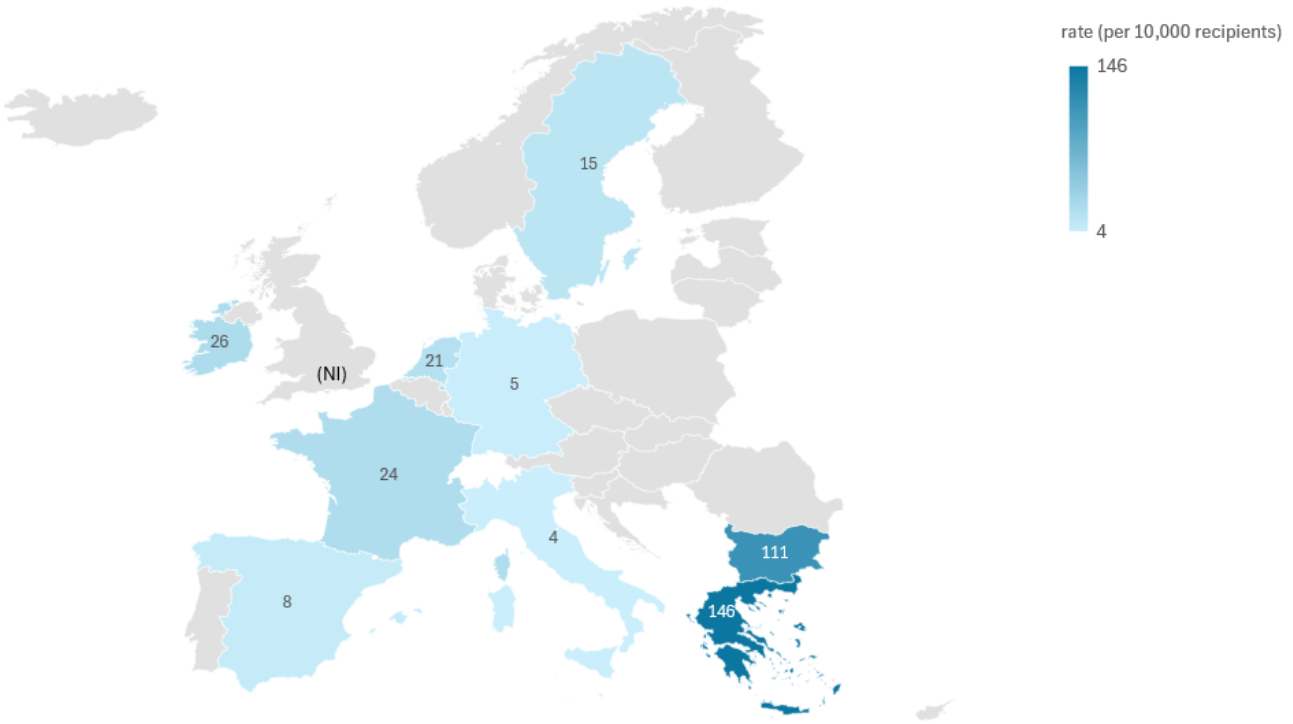


Figure 22. SAR incidence rates per 10,000 HSC recipients in Europe in 2023
Note: countries (BE and PL) that reported SAR cases but did not report the number of recipients (so incidence could not be calculated), countries reporting zero SAR (AT, HR, CY, CZ, DK, EE, FI, HU, IS, LT, LU, NO, PT, SK, SI and UK (NI)) as well as countries with no activity reported (LV, LI, MT and RO) are shown in grey.

2.2.3 Reproductive T&C

Figure 23 shows the SAR (IL 1-3 or IL unknown) incidence rates per 10,000 Reproductive T&C recipients across all reporting countries.

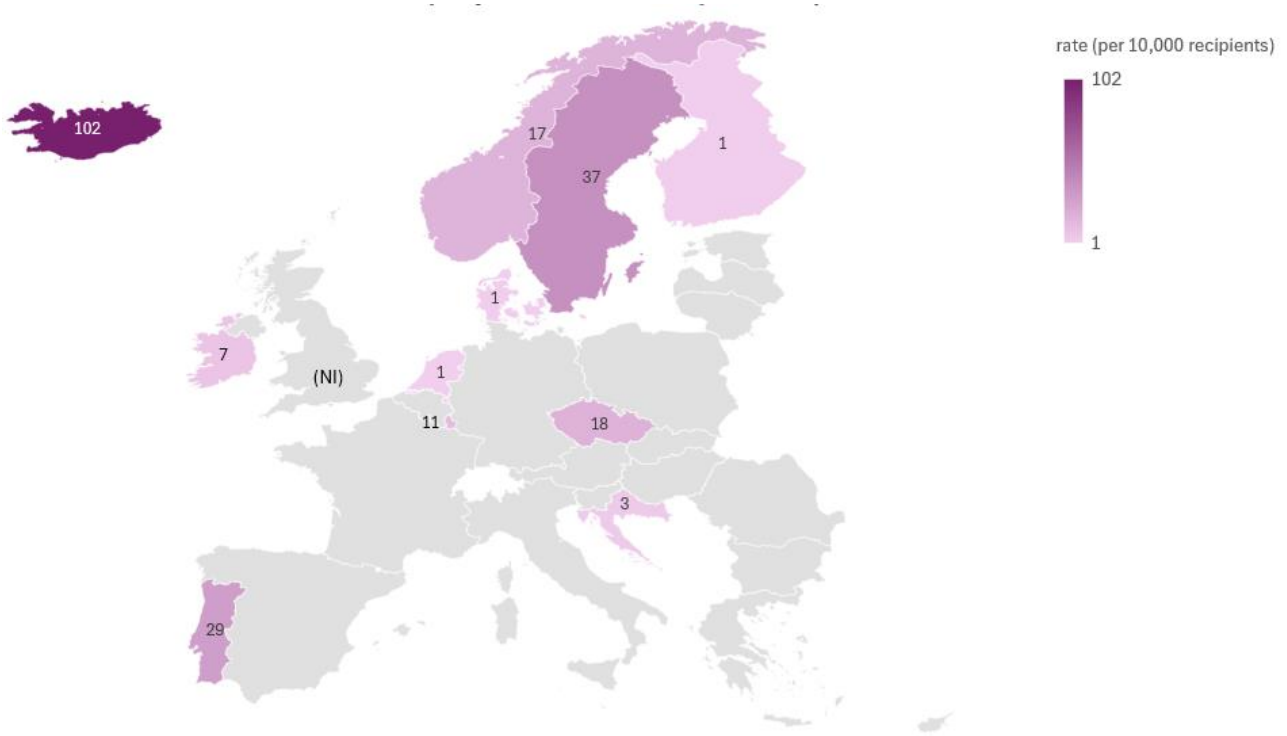


Figure 23. SAR incidence rates per 10,000 Reproductive T&C recipients in Europe in 2023

Note: countries (BE, FR, DE, IT and ES) that reported SAR cases but did not report the number of recipients (so incidence could not be calculated), countries reporting zero SAR (AT, BG, CY, EE, HU, LV, LI, LT, MT, PL, RO, SK, SI and UK (NI)) as well as countries with no activity reported (EL) are shown in grey.

2.3 Overview of SAR by category of T&C

2.3.1 Distribution of total number of SAR by country

Of the 31 reporting countries, 19 (BE, BG, HR, CZ, DK, FI, FR, DE, EL, IS, IE, IT, LU, NL, NO, PL, PT, ES and SE) reported 387 SAR associated with the clinical application of tissues or cells. Twelve countries (AT, CY, EE, HU, LV, LI, LT, MT, RO, SK, SI and UK(NI)) reported no SAR in recipients in 2023. The distribution of the number of SAR in recipients by country in 2023 is shown in Figure 24.

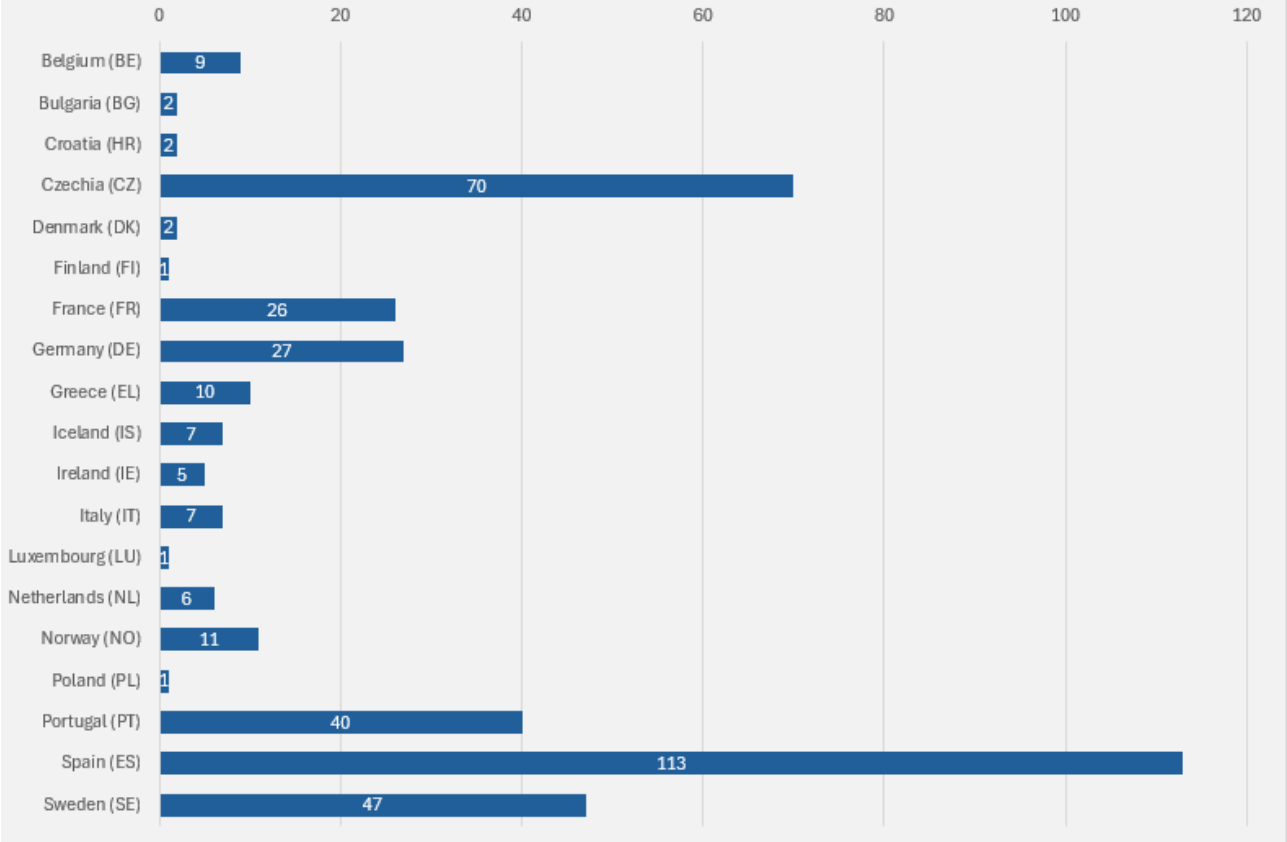


Figure 24. Distribution of total number of SAR in recipients by country in 2023

2.3.2 Distribution of total number of SAR by category of T&C

Overall data collected in 2023 for number of SAR by category of T&C are shown in Figure 25. Notably, Reproductive T&C accounted for the largest share of reported SAR in Europe. In 2023, 76% of all SAR were linked to the application of Reproductive T&C, followed by HSC (13%) and Replacement T&C (11%), a similar distribution to 2022.

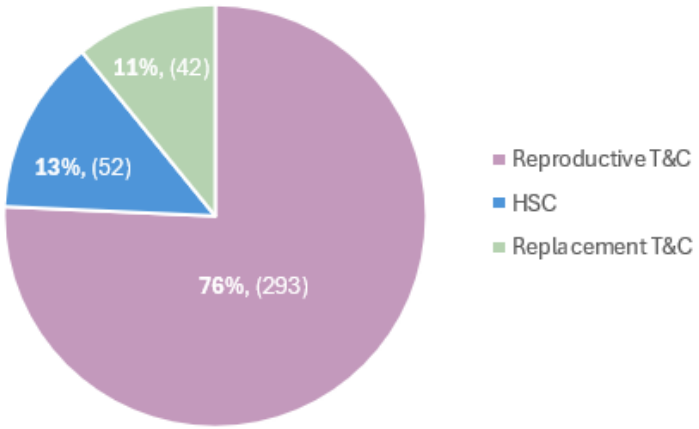


Figure 25. Percentage distribution of total number of SAR by category of T&C in 2023

The distribution of SAR by category of T&C and by country is presented in Figure 26.

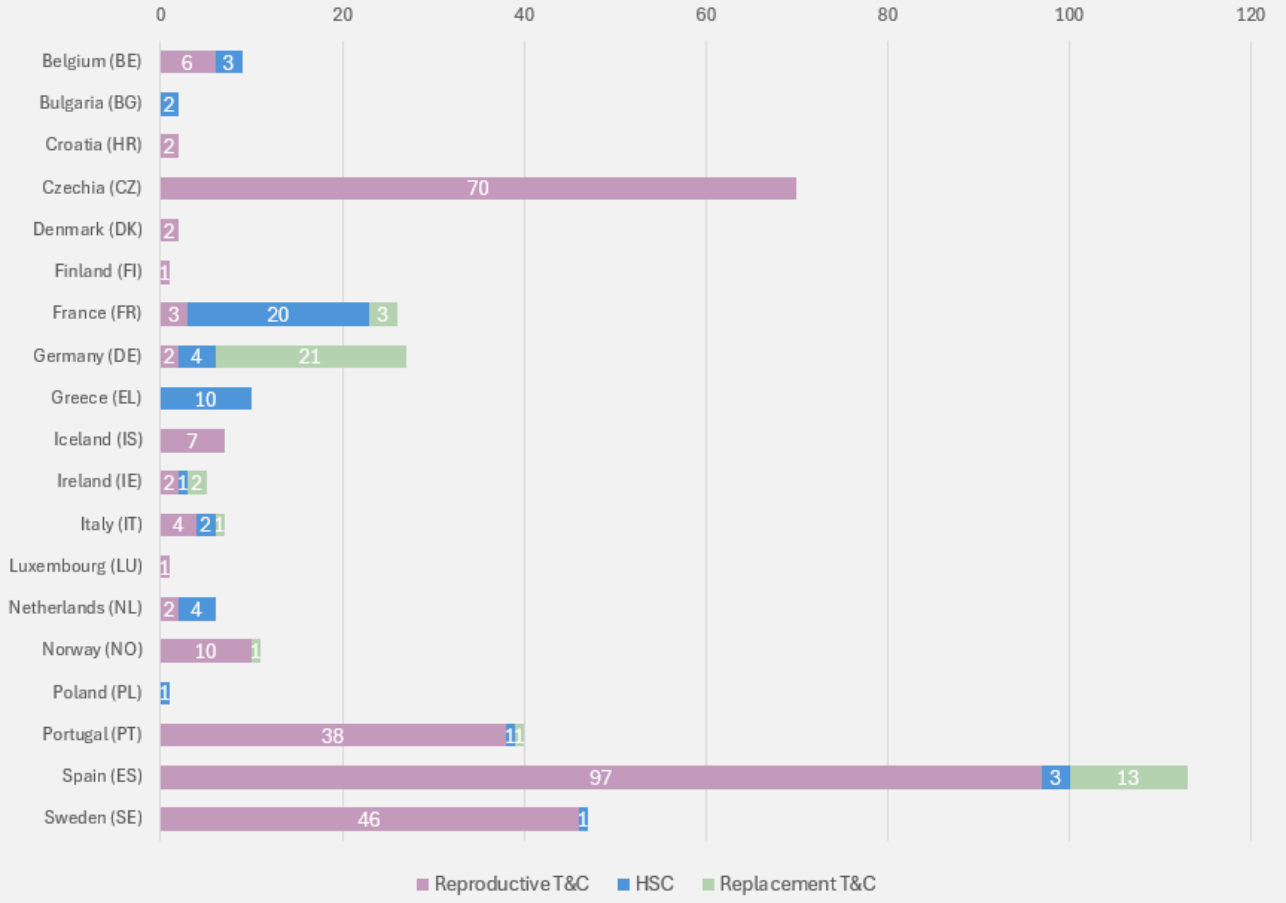


Figure 26. *Distribution of total number of SAR by category of T&C and by country in 2023*

2.3.3 Comparative data

As shown in Table 9, in 2023, there were 40 more SAR reported in the clinical application of Reproductive T&C than in 2022. For Replacement T&C and HSC, the number of SAR reported were similar to 2022.

T&C Category	Total number of SAR 2022	Total number of SAR 2023	Absolute Change
Replacement T&C	34	42	+8
HSC	60	52	-8
Reproductive T&C	253	293	+40
Total	**347**	**387**	**+40**
n (Replacement T&C)	7	7	
n (HSC)	10	12	
n (Reproductive T&C)	14	16	

Table 9. Summary of total number of SAR by category of T&C; 2023 vs. 2022

2.4 Overview of SAR by category of T&C and by type of tissue/cell

2.4.1 Replacement T&C

In 2023, the most frequent SAR were associated with the application of skeletal tissues (the most widely distributed tissue) and ocular tissues, representing 43% each. The number of SAR associated with cardiovascular tissues represented 14% of the total SAR in Replacement T&C (Figure 27).

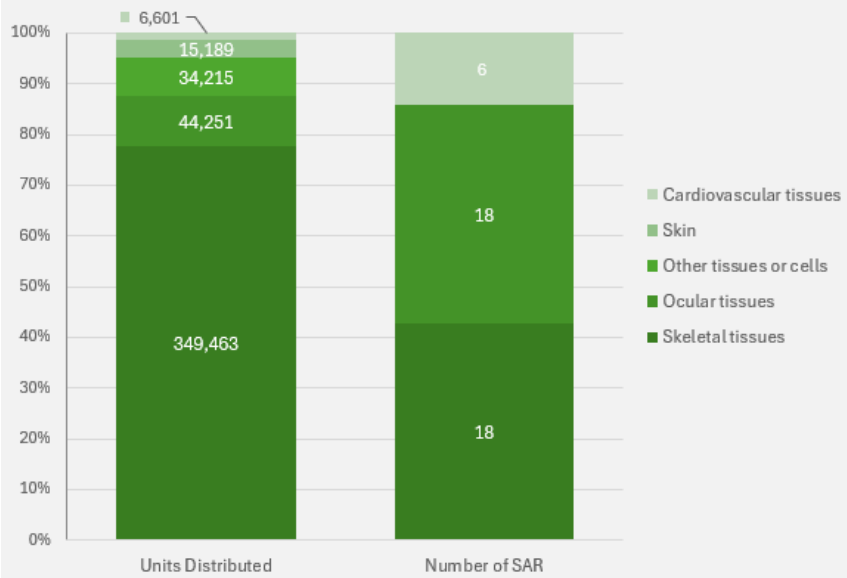


Figure 27. Percentage distribution of units distributed and number of SAR by type of Replacement T&C in 2023

2.4.2 Comparative data – Replacement T&C

The Replacement T&C subtype most frequently associated with SAR was cornea (16), which increased in comparison with 2022, followed by bone (14) and heart valve (5). Details are presented in Table 10.

Type of Tissue/Cell	Subtype *(Specification)*	2022	2023	Absolute Change
Skeletal tissues	Bone	11	14	
	Tendons/ligaments	1	0	
	Cartilage	0	2	
	General	3	2	
	Other (e.g. meniscus, auditory ossicles)	1	0	
	Total	**16**	**18**	**+2**
Ocular tissues	Cornea	2	16	
	General	7	2	
	Other	3	0	
	Total	**12**	**18**	**+6**
Cardiovascular tissues	Heart valve	5	5	
	Vessel	0	1	
	Total	**5**	**6**	**+1**
Other tissues or cells	Other (e.g. adipose tissue, tympanic membrane)	**1**	**0**	**-1**
	Total	**34**	**42**	**+8**

n (skeletal tissues)	3	3
n (ocular tissues)	5	6
n (cardiovascular tissues)	2	3
n (other tissues or cells)	1	0

Table 10. Summary of number of SAR by type of Replacement T&C and subtype; 2023 vs. 2022

2.4.3 HSC

In 2023, the most frequent SAR were associated with the application of PBSC (auto+allo), representing 56%, followed by bone marrow (19%) and cord blood (13%) (Figure 28).

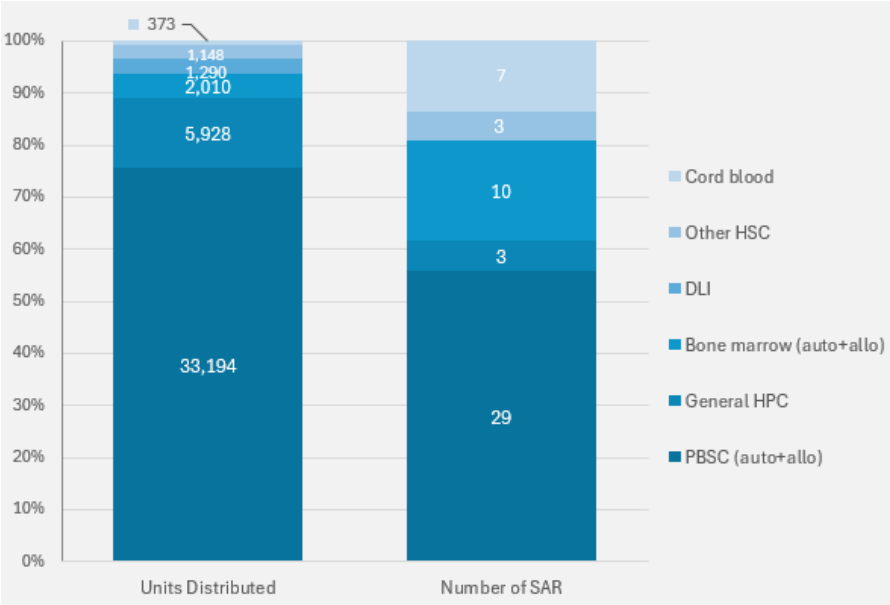


Figure 28. Percentage distribution of units distributed and number of SAR by type of HSC in 2023

2.4.4 Comparative data – HSC

The HSC subtype most frequently associated with SAR was autologous PBSC (13) followed by allogenic unrelated PBSC (10), which decreased in comparison with 2022. Details are presented in Table 11.

Type of Tissue/Cell	Subtype *(Specification)*	2022	2023	Absolute Change
PBSC	Allogenic related	9	5	
	Allogenic unrelated	19	10	
	Autologous	10	13	
	General	6	1	
	Total	**44**	**29**	**-15**
Bone marrow	Allogenic related	4	4	
	Allogenic unrelated	6	3	
	General	1	3	
	Total	**11**	**10**	**-1**
Cord blood	Allogenic unrelated	2	7	
	Total	**2**	**7**	**+5**
General HPC	General	**2**	**3**	**+1**
Other HSC	Autologous	1	2	
	General	0	1	
	Total	**1**	**3**	**+2**
	Total	**60**	**52**	**-8**

n (PBSC)	10	9
n (bone marrow)	6	4
n (cord blood)	2	2
n (general HPC)	1	1
n (other HSC)	1	2

Table 11. Summary of number of SAR by type of HSC and subtype; 2023 vs. 2022

2.4.5 Reproductive T&C

MAR procedures involving embryos were responsible for 91% of SAR in 2023 (vs 77% in 2022), followed by sperm insemination (8%, vs 17% in 2022) and other reproductive T&C (1%, vs 6% in 2022) as shown in Figure 29.

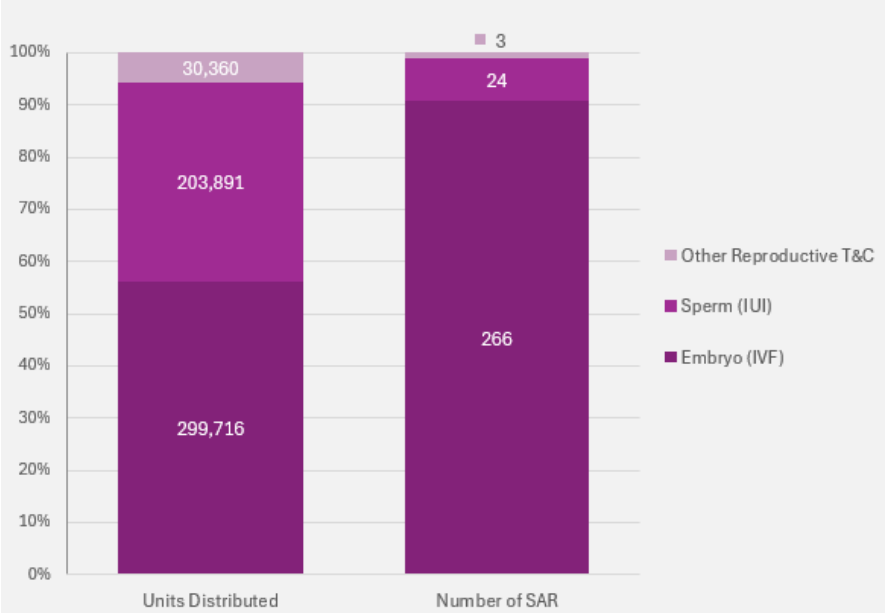


Figure 29. Percentage distribution of units distributed and number of SAR by type of Reproductive T&C in 2023

2.4.6 Comparative data – Reproductive T&C

SAR for both sperm used in IUI procedures and embryos after classical IVF or intracytoplasmic sperm injection (ICSI) were reported; the number for each subtype involved is presented in Table 12. The subtype general embryo (IVF) was the most frequently associated with SAR, a significant increase in comparison with the previous year.

Type of Tissue/Cell	Subtype *(Specification)*	2022	2023	Absolute Change
Embryo (IVF)	Donor oocyte, partner sperm	83	41	
	Donor sperm and oocyte	21	18	
	Donor sperm, partner oocyte	19	30	
	Partner gametes	55	56	
	General	17	121	
	Total	195	**266**	**+71**
Sperm (IUI)	Non-partner donation	31	16	
	Partner donation	7	7	
	General	4	1	
	Total	42	**24**	**-18**
Other Reproductive T&C	Other	16	2	
	Ovarian tissue	0	1	
	Total	16	**3**	**-13**
	Total	253	**293**	**+40**

n (embryo)	12	13
n (sperm)	7	10
n (other)	1	1

Table 12. Summary of number of SAR by type of Reproductive T&C and subtype; 2023 vs. 2022

2.5 Yearly trends (2019–2023) by type of reaction

According to the ***Common Approach***, 2024 edition, reactions are classified into major types and subtypes depending on the category of T&C (Table 13).

Replacement T&C and HSC	Reproductive T&C

• **Transmitted Infections (TI)**
  ○ bacterial
  ○ viral (*HBV, HCV, HIV, other*)
  ○ parasitical (*malaria, other*)
  ○ fungal
  ○ prion
  ○ other
• **Transmitted Malignant Diseases (TMD)**
• **Other Disease Transmissions (ODT)**
  ○ immunological disease
  ○ genetic disease
  ○ other donor derived disease
• **Other SAR**
  ○ cardiovascular reactions
  ○ pulmonary reactions
  ○ renal complications
  ○ neurological reactions
  ○ toxicity
  ○ immunological reactions
  ○ graft failure/delayed engraftment
  ○ undue exposure risk intervention
  ○ infusion related non-specific symptoms
  ○ others
	• **Transmitted Infections (TI)**
	  ○ bacterial
	  ○ viral (*HBV, HCV, HIV, other*)
	  ○ parasitical (*malaria, other*)
	  ○ fungal
	  ○ prion
	  ○ other
	• **Transmitted Malignant Diseases (TMD)**
	• **Transmitted Genetic Conditions (TGC)**
	• **Other SAR**
	  ○ anaphylactic reaction *(only for sperm (IUI))*
	  ○ rejection *(only for other reproductive T&C)*
	  ○ ectopic pregnancy *(only for embryo (IVF))*
	  ○ molar pregnancy *(only for embryo (IVF))*
	  ○ others

Table 13. Types and subtypes of reportable reactions in Replacement T&C, HSC and Reproductive T&C

Table 14 shows the percentages of total SAR by type of reaction, and Figure 30 and Figure 31 show the trend in reporting from 2019 to 2023 in Non-Reproductive and Reproductive T&C, respectively.

Type of Reaction	2019	2020	2021	2022	2023
Non-Reproductive T&C					
Other SAR	85	95	91	90	79
TI	15	4	8	10	18
TMD	1	1	0	0	1
ODT	0	0	1	0	2
Reproductive T&C					
TGC	67	52	59	49	46
Other SAR	29	47	34	49	50
TI	3	1	0	2	4
TMD	1	0	0	0	0

Table 14. Percentages of total SAR in Non-Reproductive and Reproductive T&C by type of reaction; 2019–2023

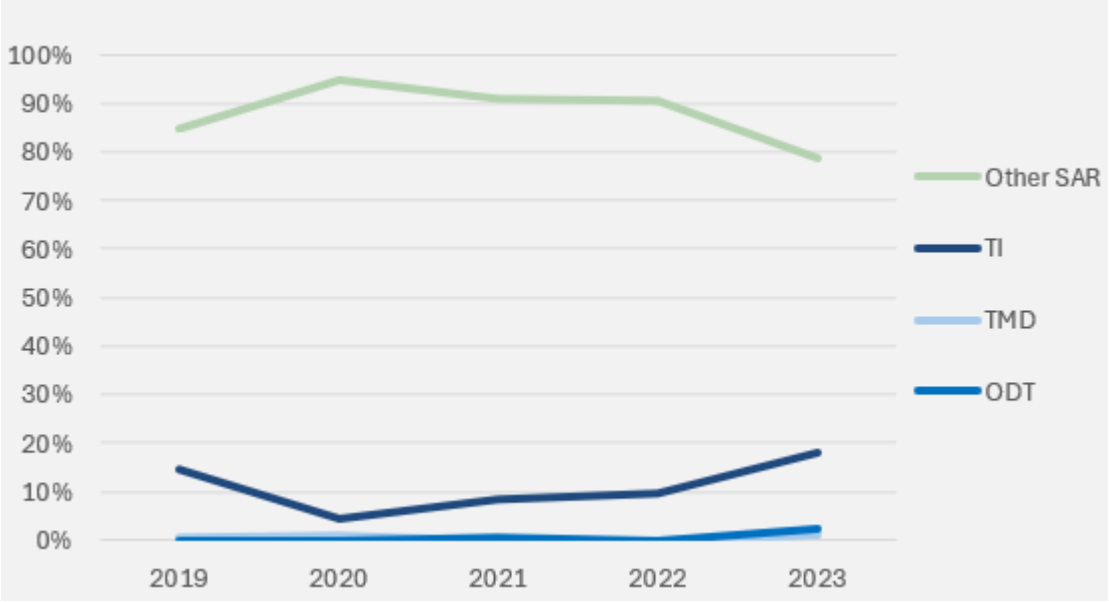


Figure 30. Yearly trends in percentage of total SAR by type of reaction in Non-Reproductive T&C; 2019–2023

Between 2019 and 2023, 'Other SAR' consistently represented the largest portion of reported cases for Non-Reproductive T&C across the five-year span, although it showed a modest decline after peaking in 2020. TI generally followed a reverse trend, taking a smaller share early on but gradually increasing in recent years. TMD and ODT remained very low throughout the entire period.

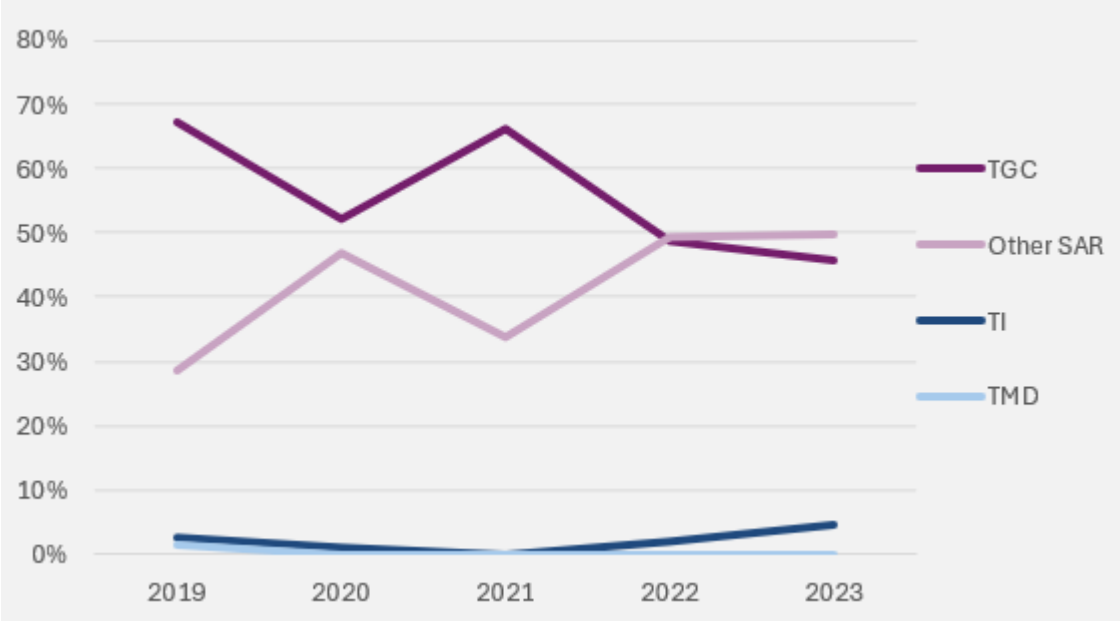


Figure 31. Yearly trends in percentage of total SAR by type of reaction in Reproductive T&C; 2019–2023

Despite some year-to-year variation, TGC and 'Other SAR' continued to be the dominant reaction types in Reproductive T&C. TGC represented the largest share, although the proportion varied from around 70% in 2019 to roughly 50% more recently. 'Other SAR' fluctuated between approximately 30% and 50%. TI remained relatively low but increased slightly in 2023. TMD continued to have a minimal or zero percentage.

2.6 SAR incidence by category of T&C and by type of reaction

In particular, the SAR incidence per 10,000 recipients by type of reaction for each reporting country is shown in Table 15.

	Replacement T&C		HSC			Reproductive T&C		
Country	**TI**	**Other SAR**	**TI**	**ODT**	**Other SAR**	**TI**	**TGC**	**Other SAR**
Bulgaria (BG)					111			3
Croatia (HR)								2
Czechia (CZ)							16	
Denmark (DK)							1	
Finland (FI)							1	
France (FR)		0.3	2	2	19			
Germany (DE)					5			
Greece (EL)					146			
Iceland (IS)							87	15
Ireland (IE)	9	9			26		7	
Italy (IT)					4			
Luxembourg (LU)						11		
Netherlands (NL)					21		1	
Norway (NO)	10				8	5		12
Portugal (PT)		6						29
Spain (ES)	2	1						
Sweden (SE)					15	7		30

Table 15. Summary of SAR incidence rates per 10,000 recipients by category of T&C, type of reaction and country in 2023

Note 1: Regarding Replacement T&C, the following countries' data are not captured above because they did not provide number of recipients so incidence could not be calculated (DE reported 4 TI and 17 Other SAR; IT reported 1 TI).
Note 2: Regarding HSC, the following countries' data are not captured above because they did not provide number of recipients so incidence could not be calculated (BE reported 1 TMD and 2 Other SAR; PL reported 1 Other SAR).
Note 3: Regarding Reproductive T&C, the following countries' data are not captured above because they did not provide number of recipients so incidence could not be calculated (BE reported 5 TGC and 1 Other SAR; FR reported 3 TGC; IT reported 4 TGC; ES reported 45 TGC and 52 Other SAR).

2.7 Overview of SAR by category of T&C and subtype of reaction

2.7.1 Replacement T&C

As shown in Figure 32, in 2023, graft failure/delayed engraftment was the most common reaction subtype (representing 52% of the 42 SAR reported), mainly associated with skeletal tissue transplantation. No cases of TMD or ODT were identified. TI were reported in 15 patients, representing 36% of the total SAR reported in Replacement T&C. More details on TI are provided in section 2.7.4.

In comparison with 2022, there were nine more SAR cases of TI, while the number of Other SAR cases remained fairly similar (Table 16).

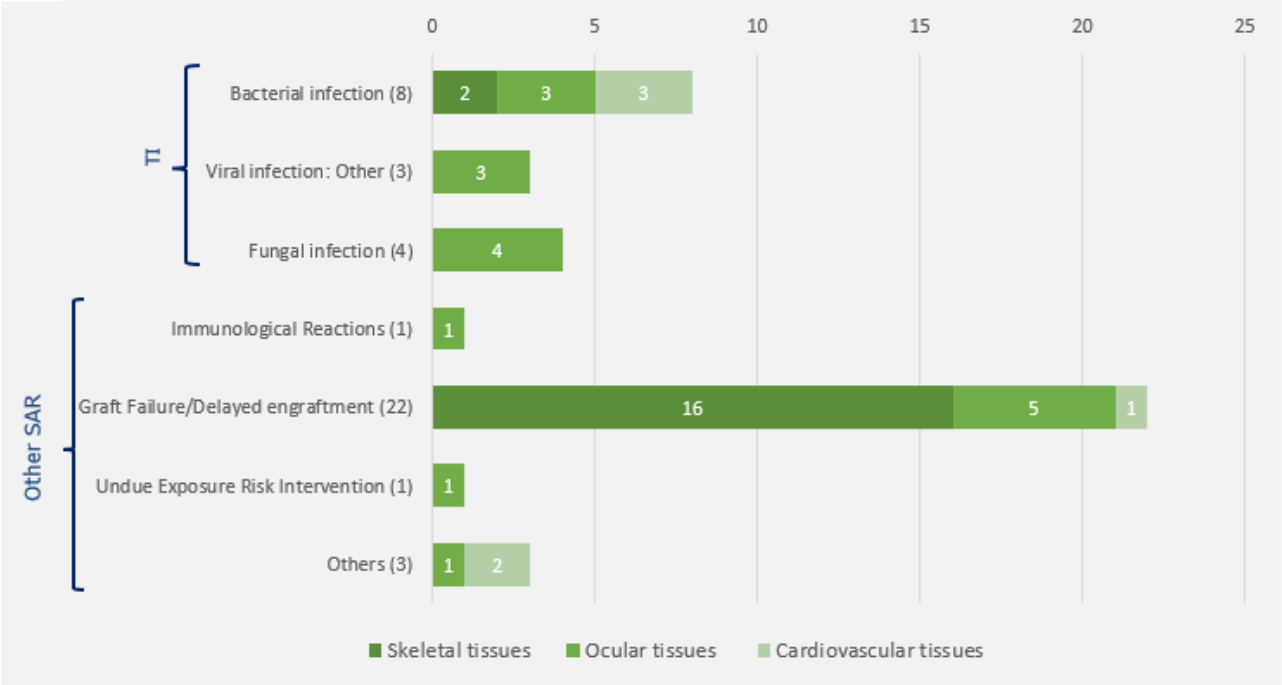


Figure 32. Distribution of SAR by subtype of reaction and type of Replacement T&C in 2023

Subtype of Reaction	2022	2023	Absolute Change
Bacterial infection	3	8	+5
Viral infection: Other	0	3	+3
Fungal infection	3	4	+1
Immunological Reactions	0	1	+1
Graft Failure/Delayed engraftment	23	22	-1
Undue Exposure Risk Intervention	3	1	-2
Others	2	3	+1

Table 16. Summary of number of SAR by subtype of reaction in Replacement T&C; 2023 vs. 2022

Of the SAR reported as 'Others':

- (1) vessel: haemorrhagic shock following graft ligature rupture;
- (1) heart valve: crossing between pulmonary/aortic valves. It was decided to implant an aortic valve in the pulmonary position;
- (1) cornea: crystalline keratopathy.

2.7.2 HSC

As shown in Figure 33, similar to Replacement T&C, the most prevalent reaction subtype in 2023 was graft failure/delayed engraftment following transplantation of PBSC and bone marrow. One case of TMD (an acute myeloid leukaemia) and two cases of bacterial infection were reported. More details on TI are provided in section 2.7.4.

In comparison with 2022, there were three new ODT cases, eight fewer cases of immunological reactions and seven fewer 'others' cases (Table 17).

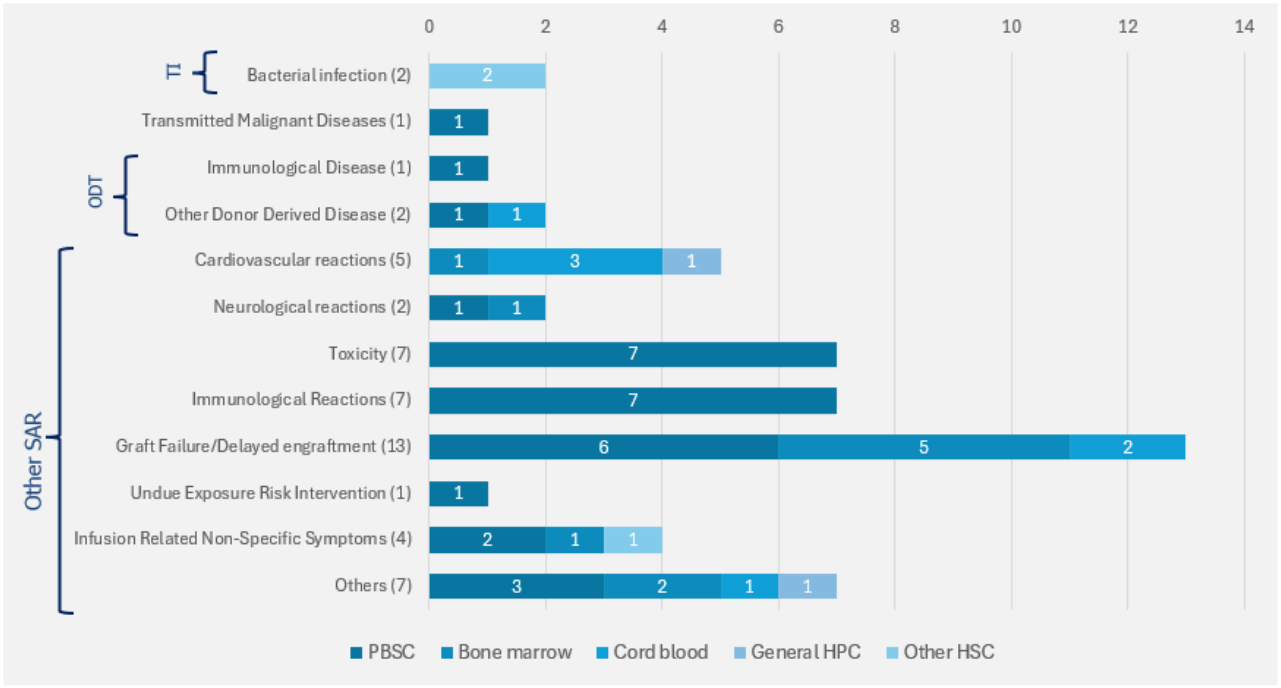


Figure 33. Distribution of SAR by subtype of reaction and type of HSC in 2023

Subtype of Reaction	2022	2023	Absolute Change
Bacterial infection	2	2	**0**
Transmitted Malignant Diseases	0	1	**+1**
Immunological Disease	0	1	**+1**
Other Donor Derived Disease	0	2	**+2**
Cardiovascular reactions	1	5	**+4**
Neurological reactions	2	2	**0**
Toxicity	6	7	**+1**
Immunological Reactions	15	7	**-8**
Graft Failure/Delayed engraftment	7	13	**+6**
Undue Exposure Risk Intervention	1	1	**0**
Infusion Related Non-Specific Symptoms	4	4	**0**
Others	14	7	**-7**

Table 17. Summary of number of SAR by subtype of reaction in HSC; 2023 vs. 2022
Note: in 2022, one viral infection: other, three pulmonary reactions and four renal complications were also reported (not shown above).

Of the SAR reported as 'Others':

- (1) bone marrow allogenic related veno-occlusive disease;
- (1) bone marrow allogenic related thrombotic microangiopathy;
- (1) cord blood allogenic unrelated juvenile chronic myelomonocytic leukaemia;

- (1) PBSC allogenic unrelated veno-occlusive disease;
- (1) PBSC general hypoxia, asystole, reanimation;
- (1) PBSC autologous septic shock (*Klebsiella pneumoniae* and *Candida krusei*);
- (1) general HPC patient with multiple myeloma undergoing autologous transplant of HPC by apheresis, cryopreserved at -150°C the next day in five bags. During infusion of the first bag, there were symptoms of lack of air and desaturation was observed.

2.7.3 Reproductive T&C

Among the 293 SAR associated with the application of Reproductive T&C, 42% were classified as TGC, followed by ectopic pregnancy (35%) and 'others' (15%), predominantly observed in embryo (IVF) (Figure 34).

There were 31 more cases of ectopic pregnancy, 14 more cases of TGC and 8 more bacterial infections observed in 2023 compared to 2022 (Table 18). More details on TI are provided in section 2.7.4.

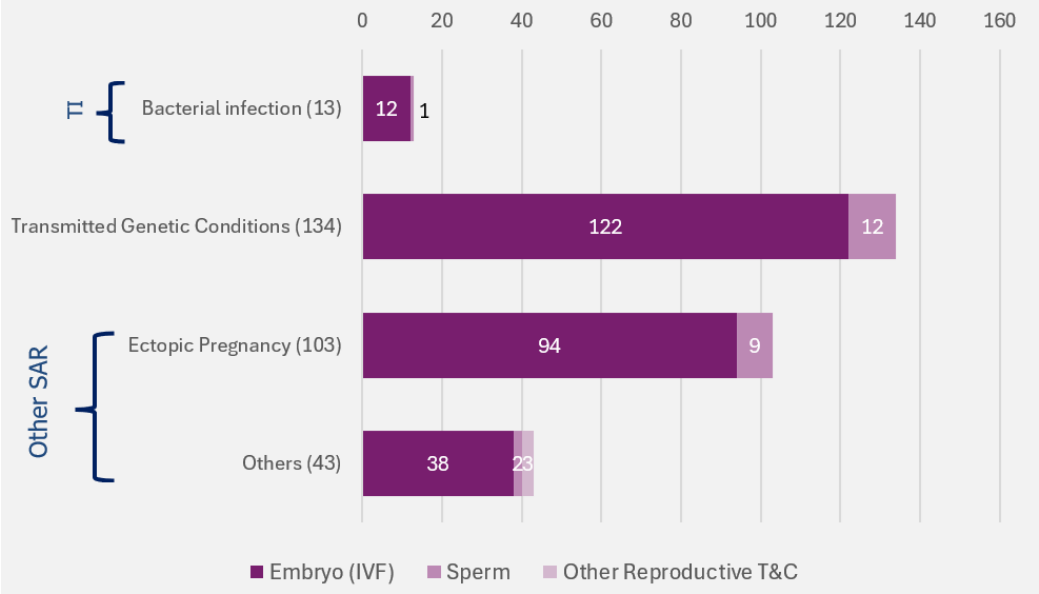


Figure 34. Distribution of SAR by subtype of reaction and type of Reproductive T&C in 2023

Subtype of Reaction	2022	2023	Absolute Change
Bacterial infection	5	13	**+8**
TGC	123	134	**+11**
Ectopic Pregnancy	72	103	**+31**
Others	50	43	**-7**

Table 18. Summary of number of SAR by subtype of reaction in Reproductive T&C; 2023 vs. 2022
Note: in 2022, 3 molar pregnancies were also reported (not shown above).

Of the SAR reported as 'Others' the details are captured below.

#SAR	Type of Tissue/Cell (and Subtype)	Description/Comments provided
1	Embryo (IVF) (general)	Mix-up of embryo during transfer One embryo was transferred to the wrong woman. Contraceptive measures were taken and successful. No pregnancy.
3	Embryo (IVF) (donor sperm, partner oocyte)	Detected pathological development
3	Embryo (IVF) (donor sperm, partner oocyte)	Haematoma around the ovary and abdomen
30	Embryo (IVF) (general)	OHSS (after embryo transfer) with hospitalisation total number: 30, of which required ascites drainage 17, ascites and pleural drainage 3. Pulmonary embolism 1. Hospitalisation for observation, pharmacological treatment, etc. but no drainage: 9.
3		Torsion of ovaries, surgical intervention
1	Sperm (IUI) (non-partner donation)	Recipient developed endometritis, required hospitalisation
1	Sperm (IUI) (non-partner donation)	Donor with germline mutation – disease transmissions
1	Other Reproductive T&C (ovarian tissue)	Cyst ruptured right ovary compatible with endometrioma, signs of abdominal infection
1	Other Reproductive T&C (other)	Pelvic inflammatory disease
1		Ectopic pregnancy after oocyte donation

Table 19. Summary of description/comments provided of SAR reported as 'Others' in Reproductive T&C

2.7.4 Transmitted Infections

Table 20, Table 21 and Table 22 present in more detail the SAR cases of TI reported in Replacement T&C, HSC and Reproductive T&C, respectively.

Subtype of Reaction	(#SAR) and IL	Type of Tissue/Cell (and Subtype)	Infectious Pathogen	Other information provided
Bacterial infection	(3) IL1	Cardiovascular tissues (heart valve)	1x *Staphylococcus* spp. 1x *Staphylococcus aureus* 1x *E. coli*	1x endocarditis 1x suspected endocarditis, stenosis 1x precordial wound infection
	(1) IL1	Skeletal tissues (General)	*Staphylococcus aureus*	after operculum replacement
	(1) IL1	Skeletal tissues (General)	*Pseudomonas aeruginosa*	-
	(3) IL2	Ocular tissues (cornea)	*Pseudomonas aeruginosa/ E. coli/ Mycobacterium abscessus*	-
Viral infection	(1) IL2 (2) IL3	Ocular tissues (cornea)	Other: Herpes simplex virus 1 (HSV-1)	two recipients previously negative from the same donor developed HSV infection. One case of evisceration due to infectious keratitis/endophthalmitis with negative cultures
Fungal infection	(1) IL1	Ocular tissues (cornea)	*Microascus* spp.	endophthalmitis
	(1) IL1	Ocular tissues (cornea)	*Candida* spp.	detected in the recipient. Patient was regrafted. The source of the contamination was not identified.
	(1) ?	Ocular tissues (cornea)	?	contamination
	(1) IL1	Ocular tissues (cornea)	?	pre-implant scleral ring with fungus in the implant centre (right and left DSAEK). A satisfactory cornea evolution and another re-implantation

Table 20. Summary data of TI by subtype of reaction, by IL and by type/subtype of Replacement T&C in 2023

Subtype of Reaction	(#SAR) and IL	Type of Tissue/Cell (and Subtype)	Infectious Pathogen	Other information provided
Bacterial infection	(2) IL3	Other HSC (autologous)	?	septic shock

Table 21. Summary data of TI by subtype of reaction, by IL and by type/subtype of HSC in 2023

Subtype of Reaction	(#SAR) and IL	Type of Tissue/Cell (and Subtype)	Infectious Pathogen	Other information provided
Bacterial infection	(1) ?	Sperm (IUI) (partner donation)	?	tube-ovarian abscess as a possible consequence of IUI
	(3) ?	Embryo (IVF) (donor sperm, partner oocyte)	?	contamination
	(9) ?	Embryo (IVF) (general)	?	gynaecological infection after embryo transfer, requiring hospitalisation

Table 22. Summary data of TI by subtype of reaction and by type/subtype of Reproductive T&C in 2023

2.8 Imputability reporting by category of T&C

The distribution of SAR by category of T&C and by imputability level (IL) 1, 2, 3 or unknown is displayed in Figure 35.

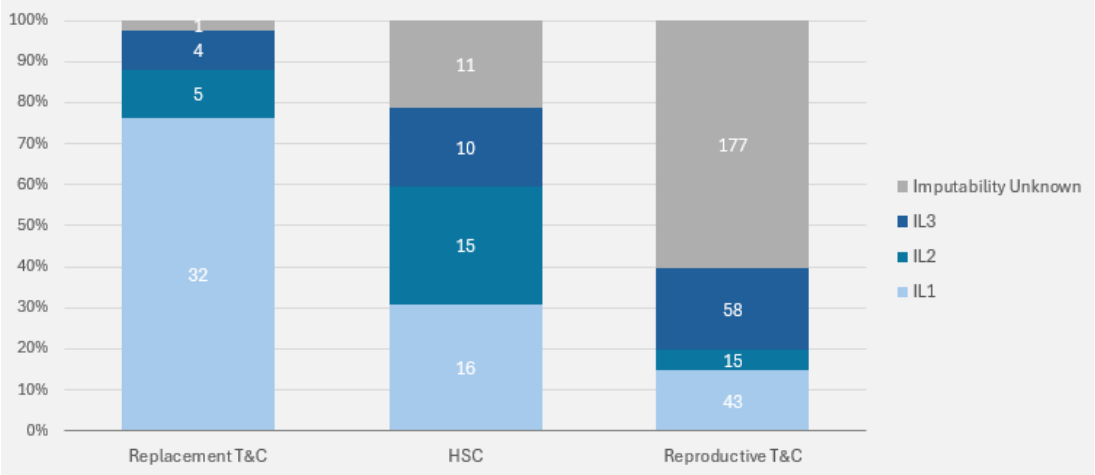


Figure 35. Distribution of total number of SAR by category of T&C and by IL in 2023

2.8.1 Comparative data

As shown in Table 23, 51% of SAR reported were assigned an IL, which is a significant improvement in comparison with 2022 (38%). Nevertheless, imputability assignment for SAR related to Reproductive T&C remains at the lowest level among the three categories of T&C.

The distribution of the number of SAR by IL and by category of T&C is presented in Table 24.

T&C Category	SAR with IL reported		Absolute Change	% SAR with IL reported	
	2022	2023		2022	2023
Replacement T&C	29	41	+12	85	98
HSC	45	41	-4	75	79
Reproductive T&C	59	116	+57	23	40
Total	133	198	+65	38	51
n (Replacement T&C)	5	6			
n (HSC)	6	10			
n (Reproductive T&C)	5	7			

Table 23. Summary of total number of SAR with IL reported by category of T&C; 2023 vs. 2022

T&C Category	Imputability Unknown		IL1		IL2		IL3	
	2022	2023	2022	2023	2022	2023	2022	2023
Replacement T&C	5	1	18	32	2	5	9	4
HSC	15	11	23	16	16	15	6	10
Reproductive T&C	194	177	29	43	10	15	20	58
Total	214	189	70	91	28	35	35	72
n (Replacement T&C)	2	1	3	6	1	2	3	1
n (HSC)	4	2	3	4	4	5	4	6
n (Reproductive T&C)	10	9	4	4	4	4	4	5

Table 24. Summary of total number of SAR by IL and by category of T&C; 2023 vs. 2022

2.9 Fatalities in recipients or offspring

2.9.1 Yearly trends (2019–2023)

Regarding fatal outcomes, as can be seen in Table 25, they are rare but have occurred, mostly following the application of HSC or Reproductive T&C. Fatalities are usually reported by the same countries.

T&C Category	2019	2020	2021	2022	2023
Replacement T&C	0	1	0	1	0
HSC	0	7	16	5	5
Reproductive T&C	0	6	4	6	12
n (Replacement T&C)	-	1	-	1	-
n (HSC)	-	4	4	1	2
n (Reproductive T&C)	-	3	2	1	4

Table 25. Summary of total number of fatalities by category of T&C; 2019–2023

As vigilance systems are in place to protect recipients and offspring, the EC and MS deemed it appropriate to regularly collect, on a voluntary basis, information on reported deaths. The ***Common***

Approach, 2024 edition, states: "Additional information should always be provided giving relevant details such as:

• **a brief description of patient initial illness details**
• a brief description of the occurrences that led to the fatality **and the level of imputability**
• list of the tissue or cell products applied and any relevant information regarding the preparation of the implicated product(s)
• the conclusions and follow-up actions (corrective and preventive), if appropriate."

Out of hundreds of thousands of transplants performed in 2023, only 17 recipient or offspring deaths were attributed to tissue/cell therapy: five to HSC application and 12 to Reproductive T&C application.

2.9.2 Fatalities following the application of HSC

Information on the five reported HSC fatalities is provided below:

- **one death after other HSC** application (autologous, IL3) involved extracorporeal photochemotherapy. Septic shock resulted in the death of the recipient. The patient was treated for Sézary syndrome. The graft showed contamination after harvesting from an infected catheter. The results of the bacterial investigation were delayed, which led to a delay in antibiotic treatment.
- **one death after PBSC** transplantation (allogenic related, IL1) in a recipient with acute myeloid leukaemia with poor prognosis, at three months post-transplant in the context of multiple infectious complications. The cellular quantity of the graft was not as expected without evident explanation (2.75×10^6/kg instead of 4×10^6/kg). A second salvage allogeneic transplant (from a different donor) was performed but did not allow recovery.
- **one death after PBSC** transplantation (autologous, IL1) in a patient with multiple myeloma and end-stage renal disease, whose death occurred within 30 days of transplantation. Tissue establishment cultures were negative with no abnormalities, and the source of infection could not be identified. Corrective and preventive action (CAPA): perform blood cultures before auto transplantation even in the absence of signs of infection.
- **two deaths after cord blood** transplantation (allogenic unrelated, IL1). Both patients benefited from a second transplant with a haploidentical donor, but this did not allow recovery.

2.9.3 Fatalities following the application of Reproductive T&C

Information on the 12 reported **MAR-related fatalities** is provided below:

- three cases of voluntary termination of pregnancy due to foetal malformations;
- two cases of legal termination of pregnancy due to foetal malformations;
- seven offspring deaths (IVF) due to TGC.

3 Serious Adverse Events

Key findings

Non-Reproductive T&C:

- From 2019 to 2023, total SAE incidence/10,000 units processed fluctuated significantly (peaks in 2020 and 2022), before dropping in 2023. A different trend was observed for median SAE incidence.
- In the Replacement T&C category, the top three activities where SAE occurred or were identified were 'other', processing and testing, mainly related to ocular tissues; while in HSC, procurement, processing and testing were the most frequent activity steps reported, the majority associated with PBSC.
- From 2019 to 2023, tissue or cell defect peaked in some years, then decreased substantially; human error and system failure showed moderate increases in 2022-2023.

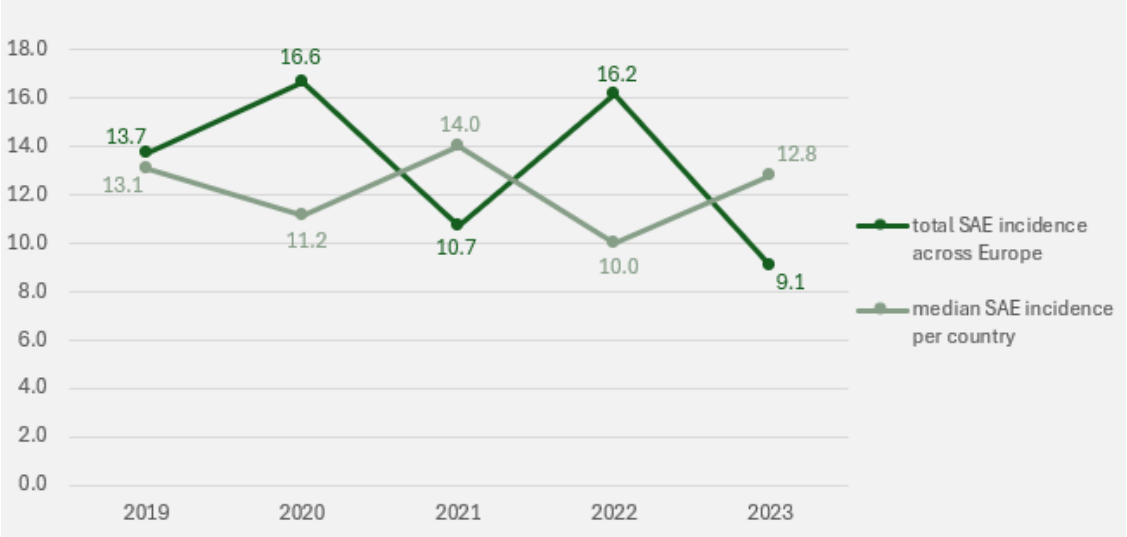
Reproductive T&C:

- TGC and 'Other SAR' remain the most frequent reaction types.
- Most of the SAE reported in relation to MAR procedures occurred or were identified during processing, donor selection, 'other' and procurement, mainly affecting oocytes.
- Human error, the leading cause in 2021-2022, declined slightly in 2023. Tissue or cell defect, which had dropped considerably in 2021, partially rebounded.

3.1 Yearly trends (2019–2023)

SAE occur at all stages of the transplantation chain, from donation to clinical application, but the only available denominator is number of units of T&C processed, which is not optimal. Due to the lack of appropriate data, SAE incidence rates were calculated in relation to numbers of T&C processed, irrespective of where the events occurred.

Figure 36 presents the yearly trends in SAE incidence in **Non-Reproductive T&C** (Replacement T&C and HSC) from 2019 to 2023, using two complementary metrics: (1) total SAE incidence per 10,000 Non-Reproductive T&C units processed and (2) the median SAE incidence across all reporting countries. The first measure reflects the overall frequency of errors or quality issues within the tissue and cell processing chain, providing insight into the general reliability and operational safety across Europe, while the second highlights the typical country-level operational safety, showing how consistently safety standards and practices are implemented across different national systems, minimising the effect of outlier countries.



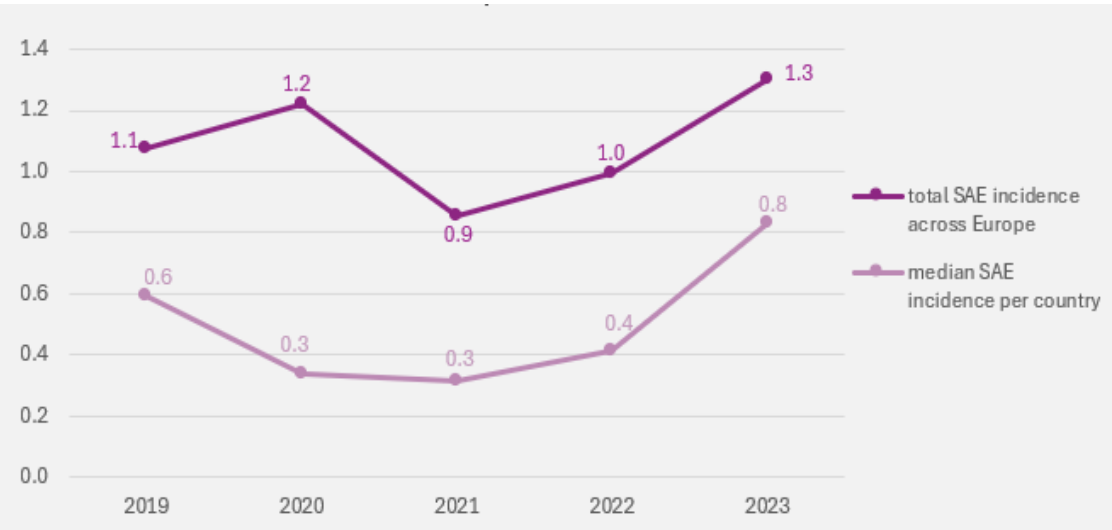
n	15	15	17	17	18

Figure 36. Yearly trends in SAE incidence in Non-Reproductive T&C: total SAE incidence/10,000 units processed and median SAE incidence per country; 2019–2023

Note: only countries that reported at least one SAE case and the number of units processed were included in the median SAE incidence calculations.

From 2019 to 2022, total SAE incidence for Non-Reproductive T&C showed pronounced variations, rising sharply in some years (e.g. 2020 and 2022) and dropping in others, before substantially declining in 2023 to 9 events per 10 000 units processed. By contrast, the median SAE incidence per country declined from 2019 to 2022, with a spike in 2021, and then rose again in 2023. This divergence suggests that while a few high-volume or high-incidence countries can significantly shift the overall total (for instance, the dip in 2021, partly attributed to the UK's departure from the EU, as the UK had been a major contributor to the vigilance data), the "typical" country may follow a different trend.

Figure 37 presents the yearly trends in SAE incidence in **Reproductive T&C** from 2019 to 2023, using two complementary metrics: (1) total SAE incidence per 10,000 Reproductive T&C units processed and (2) the median SAE incidence across all reporting countries.



n	12	13	11	10	10

Figure 37. Yearly trends in SAE incidence in Reproductive T&C: total SAE incidence/10,000 units processed and median SAE incidence per country; 2019–2023

Note: only countries that reported at least one SAE case and the number of units processed were included in the median SAE incidence calculations.

Over the 2019–2023 period, the total SAE incidence for Reproductive T&C generally followed a U-shaped pattern, declining from about 1.2 (in 2020) to 0.9 (in 2021) and then climbing back up to 1.3 in 2023. The median incidence per country mirrored this trend in a more pronounced way, dropping from 0.6 in 2019 to 0.3 in 2020-2021, then rising steadily to 0.8 by 2023.

3.2 Geographic distribution by category of T&C

3.2.1 Replacement T&C

Figure 38 shows the SAE incidence rates per 10,000 Replacement T&C units processed across all reporting countries.

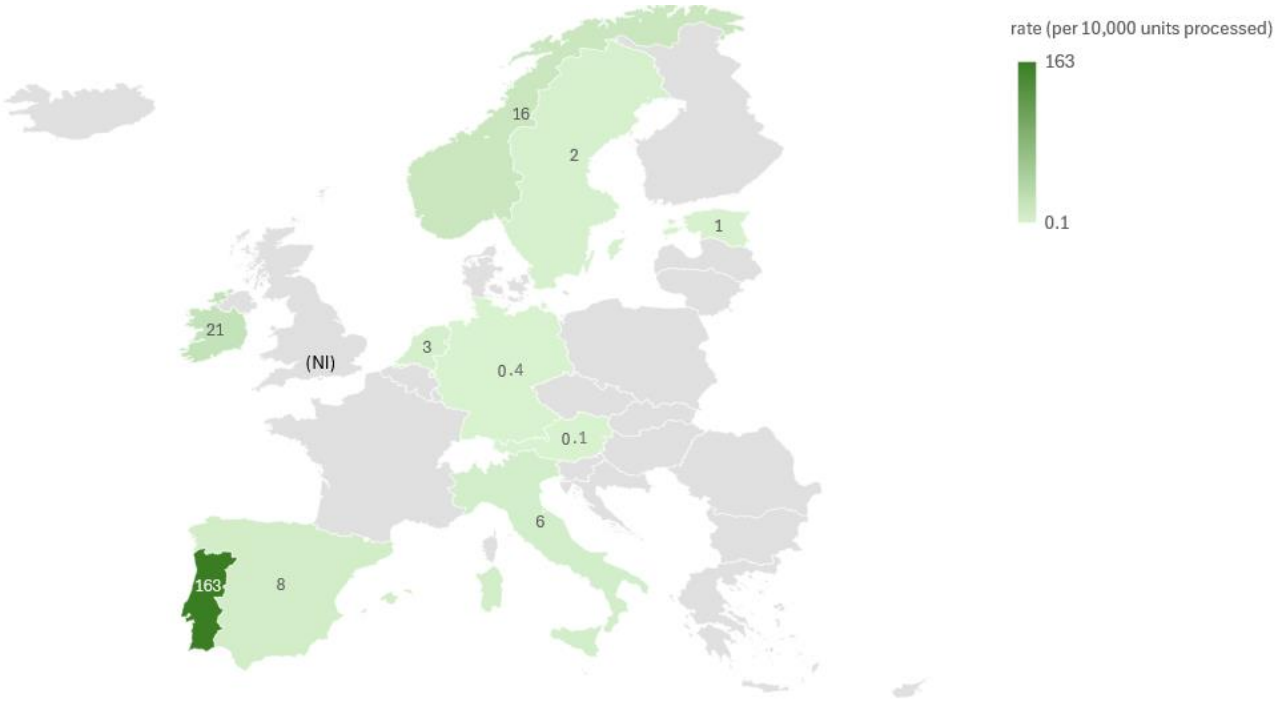


Figure 38. SAE incidence rates per 10,000 Replacement T&C units processed in Europe in 2023
Note 1: countries (BE and FR) that reported SAE cases but did not report the number of units processed (so incidence could not be calculated), countries reporting zero SAE (BG, HR, CY, CZ, DK, FI, LV, LU, MT, PL, RO, SK, SI and UK(NI)) as well as countries with no activity reported (IS, LI and LT) are shown in grey.
Note 2: outliers EL (10,000) and HU (879) are not shown above.

As shown in Figure 38, SAE incidence rates in Replacement T&C appeared to be relatively low across Europe, with the lowest being 0.1 (AT) and the highest reaching 163 (PT). The median was 4.5 SAE/10,000 units processed, which was 49% lower than the previous year (8.7).

3.2.2 HSC

Figure 39 shows the SAE incidence rates per 10,000 HSC units processed across all reporting countries.

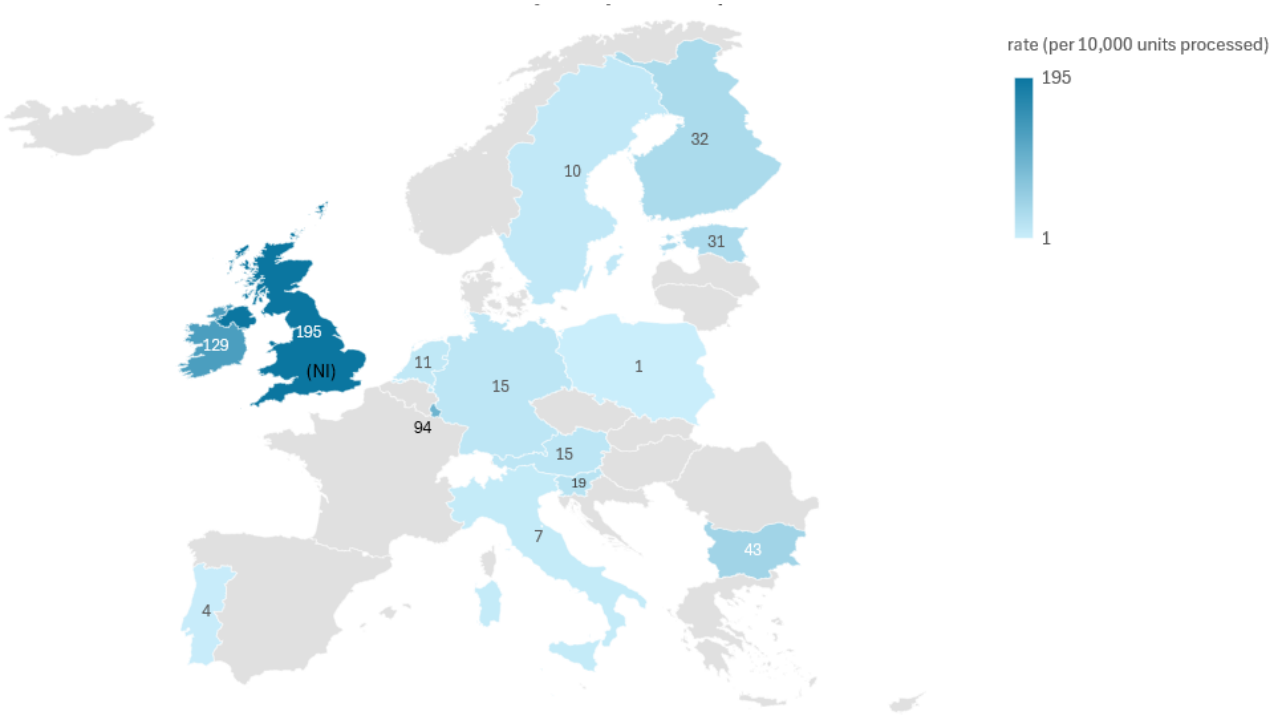


Figure 39. SAE incidence rates per 10,000 HSC units processed in Europe in 2023
Note 1: countries (BE, FR, NO and ES) that reported SAE cases but did not report the number of units processed (so incidence could not be calculated), countries reporting zero SAE (HR, CY, CZ, DK, HU, IS, LV and SK) as well as countries with no activity reported (LI, LT, MT and RO) are shown in grey.
Note 2: outlier EL (10,000) is not shown above.

SAE incidence rates in HSC show a wide range with the lowest being 1 (PL) and the highest reaching 195 (UK(NI)). The median was 16.9 SAE/10,000 units processed, which was 26% higher than the previous year (13.4).

3.2.3 Reproductive T&C

The SAE incidence rates per 10,000 Reproductive T&C units processed across all reporting countries are displayed in Figure 40.

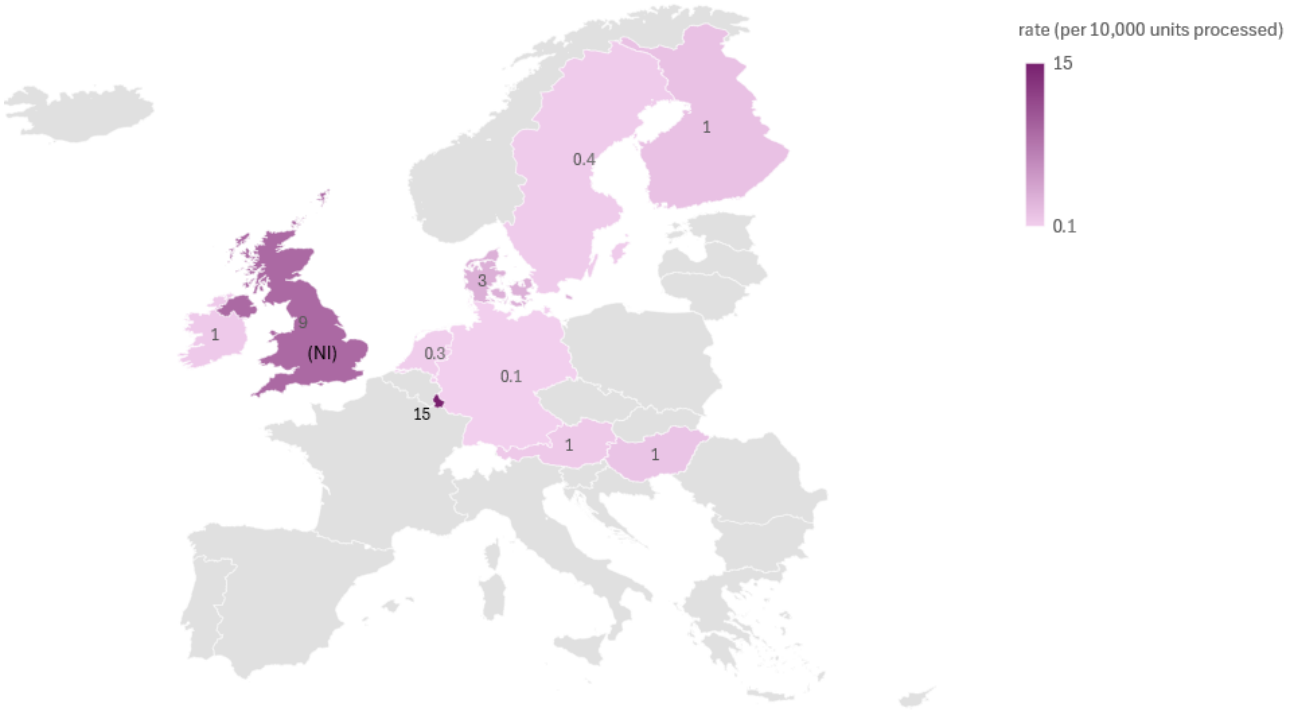


Figure 40. SAE incidence rates per 10,000 Reproductive T&C units processed in Europe in 2023
Note: countries (BE, EE, FR, IT, NO, PT and ES) that reported SAE cases but did not report the number of units processed (so incidence could not be calculated), countries reporting zero SAE (BG, HR, CY, CZ, EL, IS, LV, LI, LT, MT, PL, RO, SK and SI) as well as countries with no activity reported (EL, LT and PL) are shown in grey.

As shown in Figure 40, SAE incidence rates in Reproductive T&C appeared to be relatively low across Europe, with the lowest being 0.1 (DE) and the highest reaching 15 (LU). The median was 0.8 SAE/10,000 units processed, lower than the previous year (0.4).

3.3 Overview of SAE by category of T&C

3.3.1 Distribution of total number of SAE by country

Twenty-one countries (AT, BE, BG, DK, EE, FI, FR, DE, EL, HU, IE, IT, LU, NL, NO, PL, PT, SI, ES, SE and UK(NI)) reported a total of 819 SAE. Nine countries (HR, CY, CZ, IS, LV, LI, MT, RO and SK) reported no SAE in 2023 while LT reported no activity. The distribution of the number of SAE by country in 2023 is shown in Figure 41.

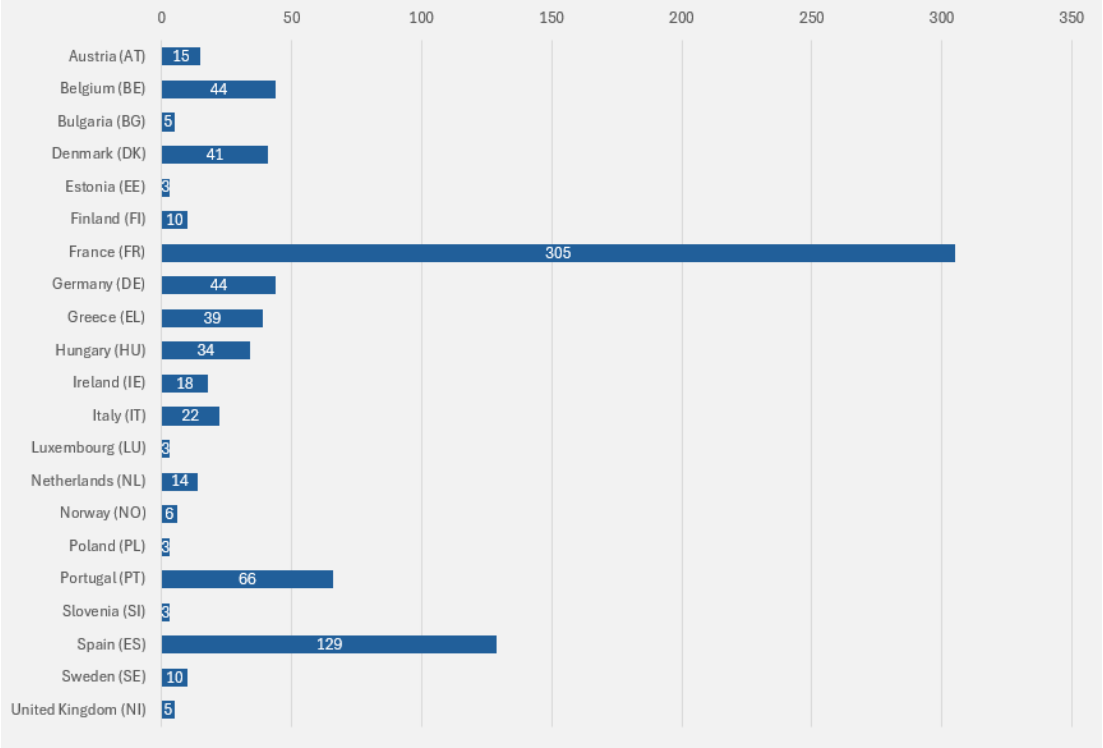


Figure 41. Distribution of total number of SAE by country in 2023

3.3.2 Distribution of total number of SAE by category of T&C

Of the 819 SAE reported in 2023, 41% were related to Reproductive T&C, 36% to HSC and 23% to Replacement T&C (Figure 42), a different distribution from the previous year (21%, 61% and 18%, respectively).

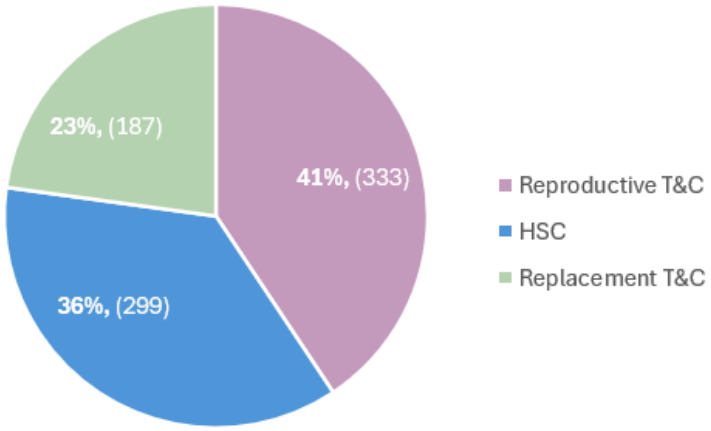


Figure 42. Percentage distribution of total number of SAR by category of T&C in 2023

The distribution of SAE by category of T&C and by country is presented in Figure 43.

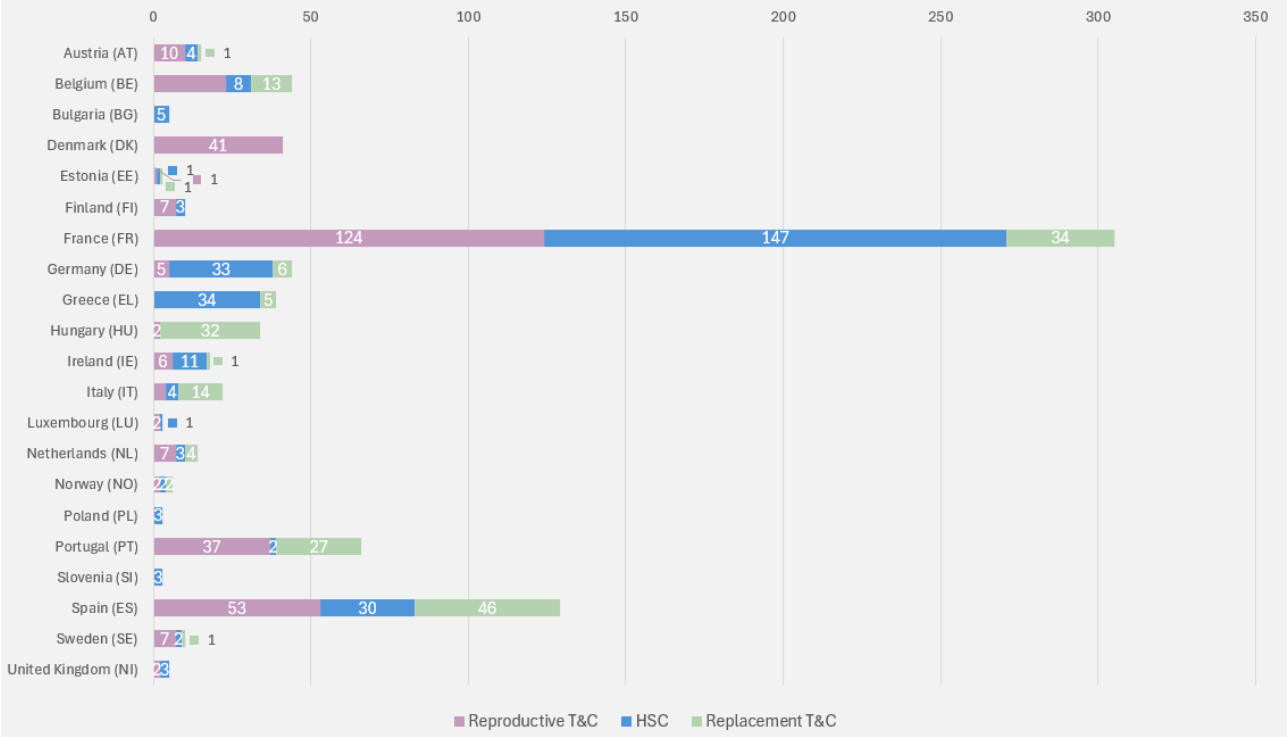


Figure 43. Distribution of total number of SAE by category of T&C and by country in 2023

3.3.3 Comparative data

As shown in Table 26, in 2023, the total number of SAE reported decreased 28% compared to 2022, mostly due to a reduction in SAE related to HSC.

T&C Category	2023	2022	% Change
Replacement T&C	187	209	**-11**
HSC	299	689	**-57**
Reproductive T&C	333	235	**+42**
Total	**819**	**1,133**	**-28**

n (Replacement T&C)	14	14
n (HSC)	19	17
n (Reproductive T&C)	17	17

Table 26. Summary of total number of SAE by category of T&C; 2023 vs. 2022

3.4 Overview of SAE by activity step

According to the ***Common Approach***, 2024 edition, the activity steps, i.e. where/when a SAE could occur or be identified, include transport, donor selection, procurement, testing, processing, storage, product selection, issue, distribution and other.

In 2023, regardless of category of T&C, processing was the most frequent step (36%), followed by procurement (22%) and other (12%) (Figure 44).

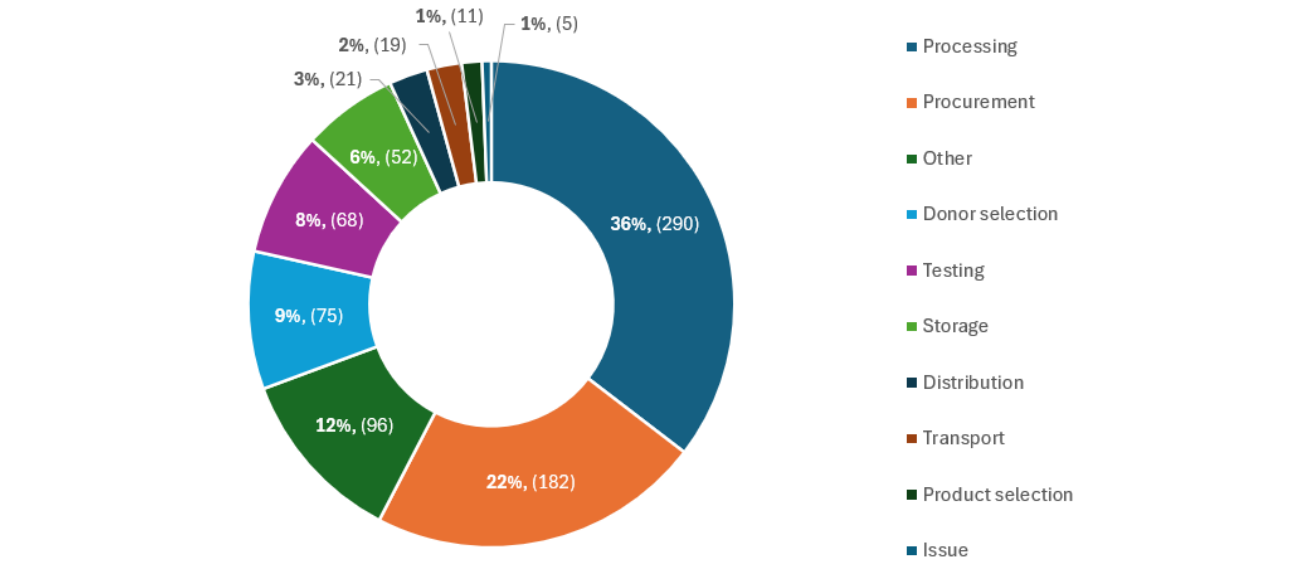


Figure 44. Percentage distribution of SAE by activity step regardless of category of T&C (and absolute numbers) in 2023

An overview of the SAE reported by activity step and by category of T&C is presented in Figure 45.

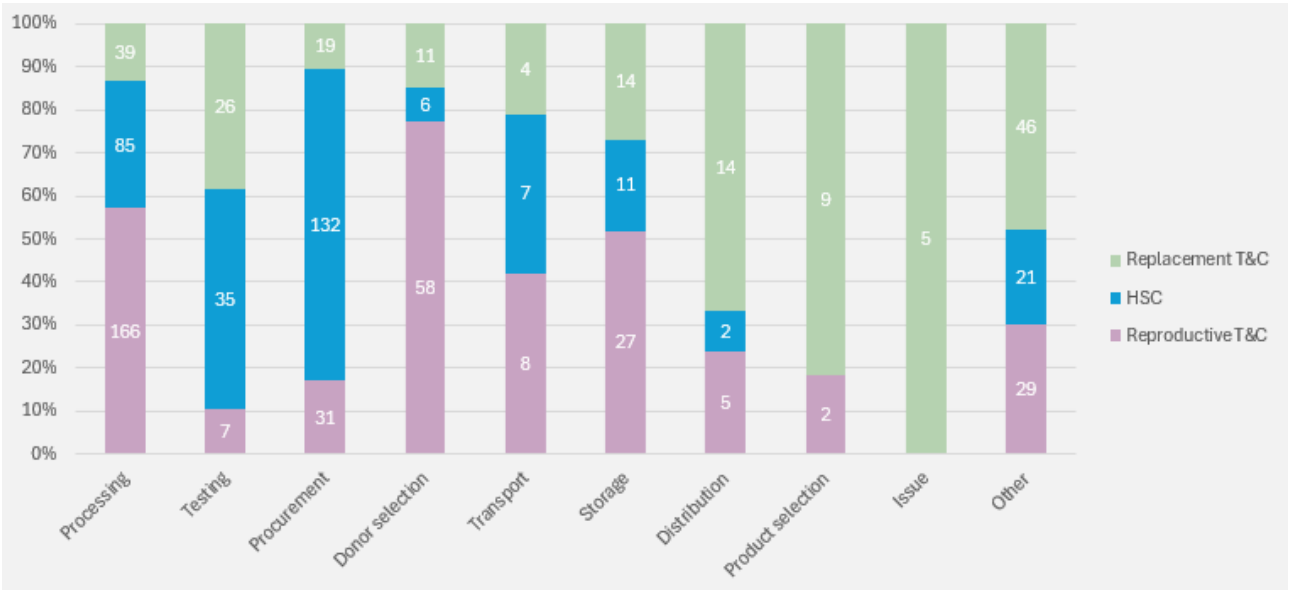


Figure 45. Percentage distribution of SAE by activity step and by category of T&C (and absolute numbers) in 2023

In the Replacement T&C category, the top three activities where SAE occurred or were identified were 'other' (25%), processing (21%) and testing (14%), mainly related to ocular tissues, a change from the previous year when processing was the activity associated with the highest number of SAE (63).

Regarding HSC, procurement (44%), processing (28%) and testing (12%) were the most frequent activity steps reported, the majority associated with PBSC. In comparison with 2022, there was a significant decrease in the number of SAE associated with processing (85 vs. 225) as well as testing (35 vs. 160) and donor selection (6 vs. 108).

Similar to the previous year, most of the SAE reported in relation to MAR procedures occurred or were identified during processing (50%), donor selection (17%), 'other' (9%) and procurement (9%), mainly affecting oocytes.

3.5 Yearly trends by specification (2019–2023)

According to the ***Common Approach***, 2024 edition, the specifications (i.e. causes) which can be associated with a specific event include tissue or cell defect, system failure, equipment failure, materials, human error and other. Figure 46 and Figure 47 show the yearly trends in percentage of total SAE by type of specification in **Non-Reproductive T&C** and **Reproductive T&C** from 2019 to 2023, respectively.

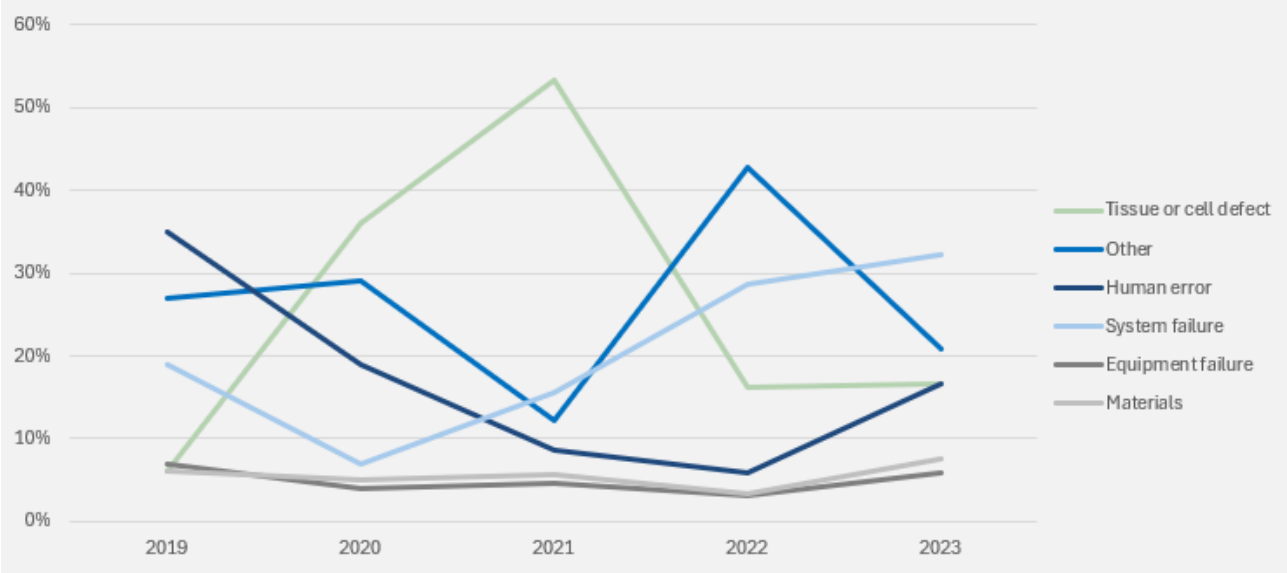


Figure 46. Yearly trends in percentage of total SAE by specification in Non-Reproductive T&C; 2019–2023

From 2019 to 2023, the most notable pattern is the considerable fluctuation in tissue or cell defect. After a substantial increase between 2019 and 2021, numbers decreased substantially in the subsequent years. 'Other' also showed significant variations over time, peaking around 2020 and 2022 and then declining thereafter.

Notably, human error showed an overall downward trend. While it started out relatively high in 2019 and 2020, the proportion decreased across subsequent years, indicating a potential improvement in procedural adherence or staff training.

In contrast to human error, system failure has been gradually increasing over time, although the proportion varied from year to year. Equipment failure and materials consistently represented a smaller percentage of SAE compared to the other causes.

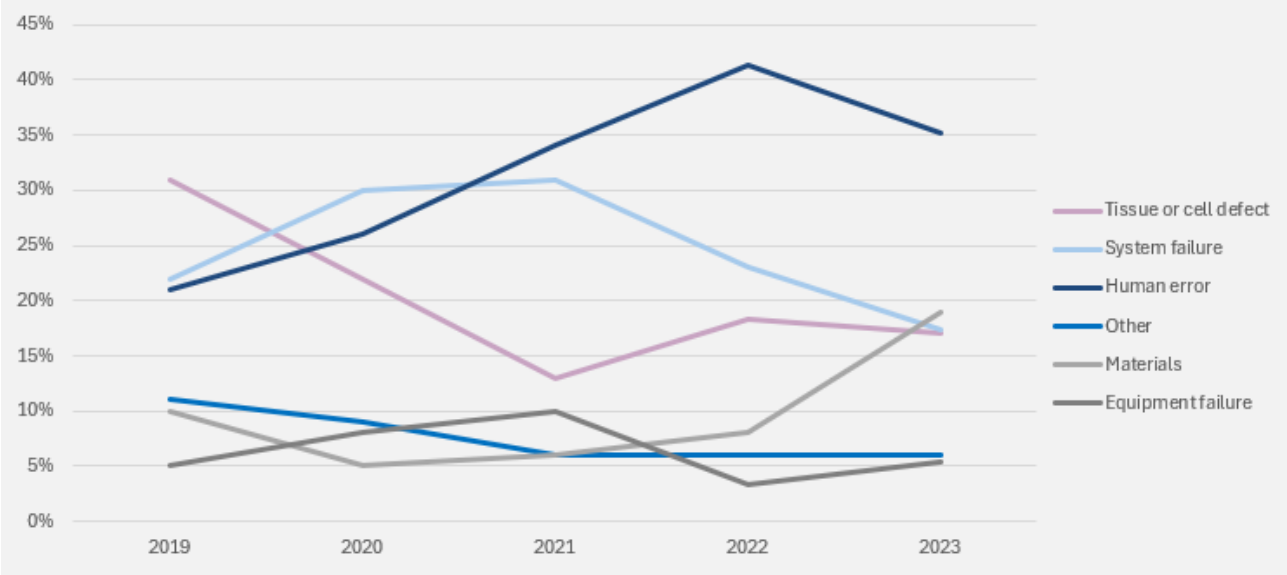


Figure 47. Yearly trends in percentage of total SAE by specification in Reproductive T&C; 2019–2023

Overall, human error stands out as the dominant cause of SAE in Reproductive T&C from about 2021 onward, peaking at around 40% in 2022 before decreasing slightly in 2023. Tissue or cell defect started out high (around 30% in 2019), decreased over 2020-2021 and then levelled off in later years. System failure showed moderate variability, while materials and equipment failure consistently remained among the least frequently reported causes, even though materials showed a modest increase in 2023.

3.6 Overview of SAE by specification

The most commonly reported SAE in 2023 were related to system failure (26%) and human error (24%) (Figure 48), a change from the previous year when 'other' represented 35% of the total SAE reported.

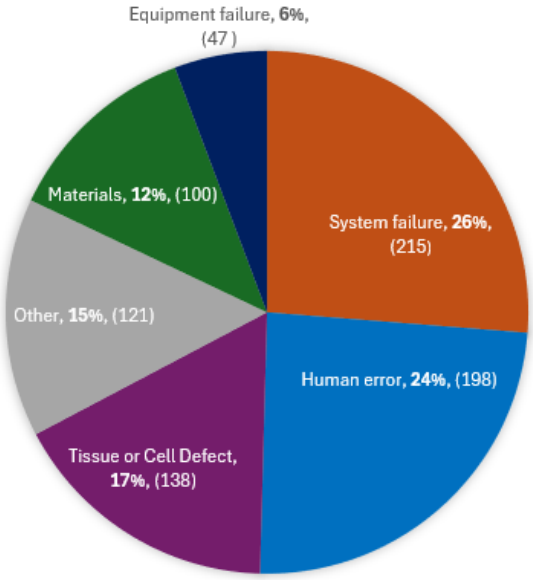


Figure 48. Percentage distribution of SAE by specification regardless of category of T&C (and absolute numbers) in 2023

The percentage distribution of SAE by specification regardless of category of T&C for each reporting country is displayed in Figure 49.

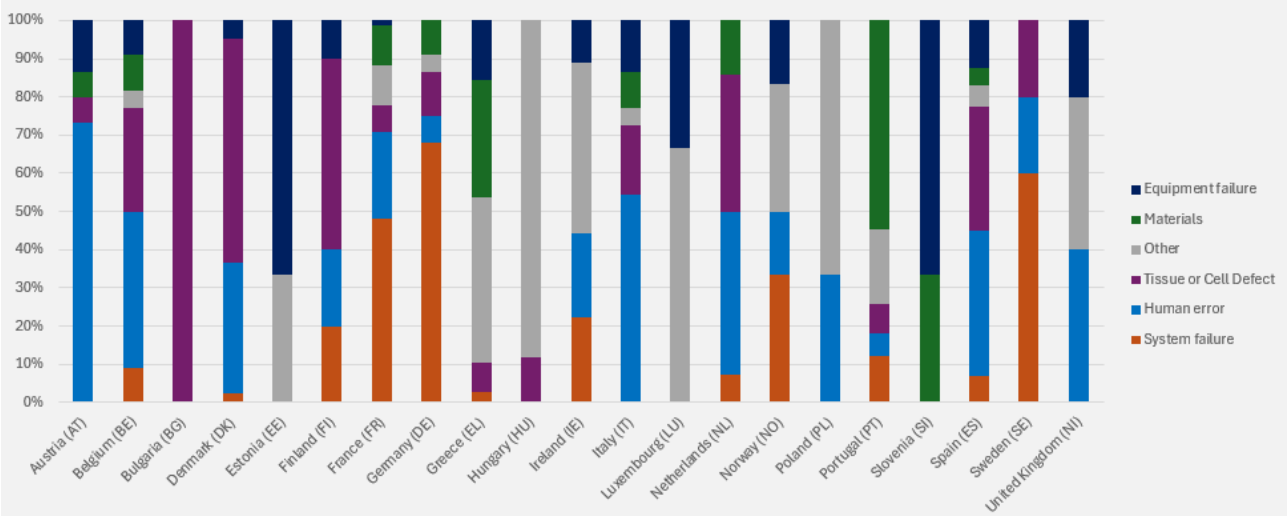


Figure 49. Percentage distribution of SAE by specification regardless of category of T&C per country in 2023

Regarding events assigned with the causes system failure or human error, the specific type of error/failure was also reported (Figure 50). Regarding system failure, 51% of events reported were related to inadequate process, procedure or documentation and 44% were related to other failure of the quality management system, a similar distribution to 2022. In terms of human error, the majority of the events reported were associated with incorrect decision or omission following the correct procedure.

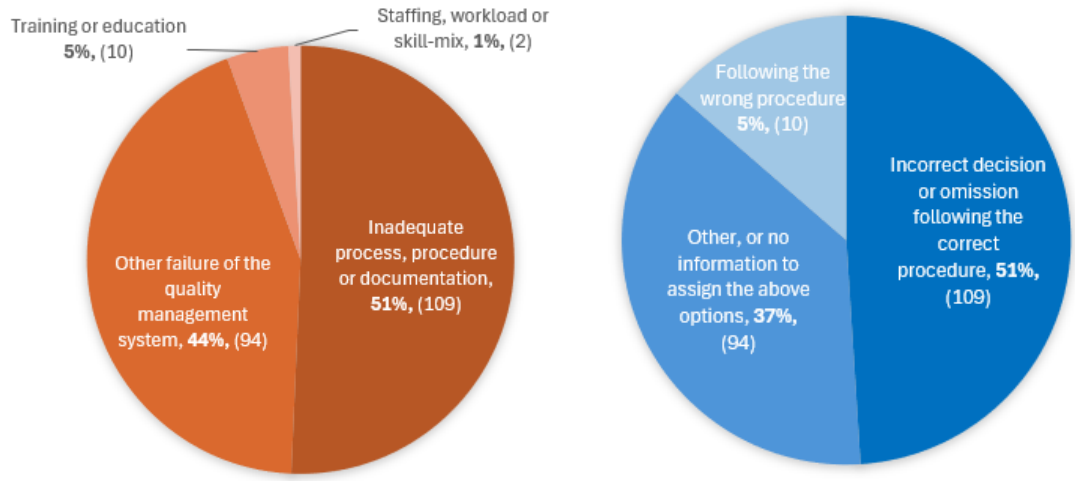


Figure 50. Percentage distribution of SAE classified as system failure (in orange) or human error (in blue) by type of error regardless of category of T&C (and absolute numbers) in 2023

An overview of the SAE reported by specification and by category of T&C is presented in Figure 51.

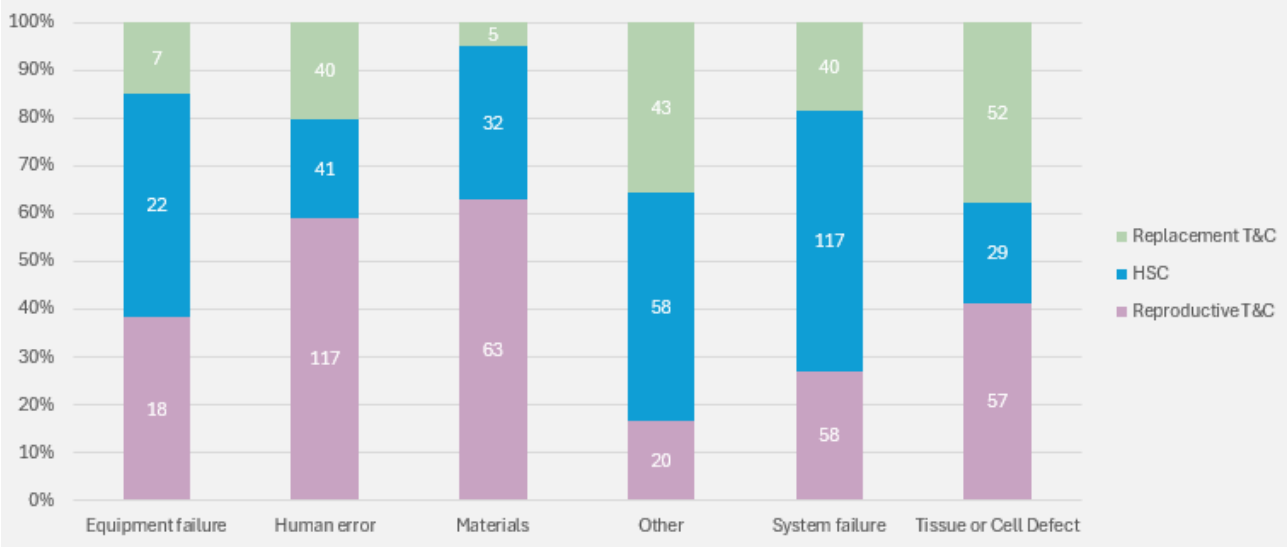


Figure 51. Percentage distribution of SAE by specification and by category of T&C (and absolute numbers) in 2023

Regarding Replacement T&C, 28% of the SAE were attributed to tissue or cell defect, 23% to 'other', 21% to system failure and 21% to human error, a similar distribution to 2022. For more details, refer to Annex 8. Examples of SAE and assigned specification for Replacement T&C.

In the HSC category, system failure represented 39% of the SAE reported, followed by 'other' (19%) and human error (14%). In comparison with the previous year, there was a major decrease in events classified as 'other'.
For more details, refer to Annex 9. Examples of SAE and assigned specification for HSC.

In Reproductive T&C, as seen in the previous year, human error was the most frequent SAE reported, representing 35% (vs. 41% in 2022). Materials was the second most frequent cause (19% vs. 8% in 2022), followed by system failure (17%) and tissue or cell defect (17%). For more details, refer to Annex 10. Examples of SAE and assigned specification for Reproductive T&C.

Note that the information provided in these Annexes is intended as an illustration of SAE for the main specifications reported, not an exhaustive list. A recurring concern is that the SAE descriptions were not always clear or complete. Across all categories of T&C, cases of ambiguous language or missing information could lead to misclassification.

3.7 International benchmarking

Globally, the pattern of SARE in tissue and cell therapy is broadly similar to that in Europe, primarily within the **Non-Reproductive T&C**, although reporting systems vary by region.

In **North America**, particularly in the United States, tissue and cell therapies are applied in high volumes annually. Historical estimates indicate approximately 1.5 million tissue allografts (bone, skin, valves, etc.) are implanted each year [1], although exact recent annual figures may vary slightly.

The US Food & Drug Administration (FDA) requires any SAR involving communicable disease transmission from tissues to be reported (via its MedWatch system). Available data indicate that SAR are exceedingly rare relative to this volume. For example, an FDA review found only 83 infection

cases reported over a four-year span (2001–2004) among tissue transplant recipients. Most of those involved bacterial or fungal infections in grafts like heart valves and tendons, and a small number (11) of fatalities were recorded (nearly all in heart valve recipients, which underscores the higher risk with cardiac tissue implants). In the years since, US tissue banks have further tightened protocols and publications suggest the incidence of transmitted infection or disease has remained extremely low – on par with European rates. The types of adverse reactions mirror those seen in Europe: sporadic bacterial infections, rare donor-derived disease (for instance, a few cases of tuberculosis transmission via tissue graft were historically reported in North America) and graft failures [1].

In **Asia**, formal biovigilance programmes are still emerging in many countries, but transplant activity is high. Countries like Japan and South Korea have large bone marrow transplant and IVF programmes. Japan's national transplant registry reports adverse outcomes in HSC transplants consistent with European and North American observations, and efforts are underway to implement a global reporting system for stem cell transplant complications. Some Asian nations have reported isolated incidents that confirm global concerns, for instance, a few infection outbreaks traced to tissue grafts or cases of donor sperm transmitting genetic disease, but comprehensive data are less accessible. [2]

The **World Health Organization (WHO)** has been actively encouraging and assisting development of vigilance systems in these regions. According to a 2022 WHO report, there is asymmetrical development of transplant oversight globally. Through the WHO's Global Observatory on Donation and Transplantation and regional initiatives, more data are now being gathered in Asia and Latin America. The trends observed align with the low adverse event frequencies seen in Europe/North America, with infections and human error being the primary reported issues when they occur. Notably, no region has reported a completely new type of adverse reaction beyond what is known, indicating that the same safety challenges (infection, rejection, genetic issues) are universal. [3, 4]

Global organisations have launched platforms to improve data sharing. The **WHO's Notify Library**, a collaboration with the Italian National Transplant Centre, has compiled over 1,700 case reports of adverse events/reactions worldwide in cells, tissues, and organs. This includes contributions from Asia and the Americas and focuses on lessons from each case (especially with emerging pathogens). Such global databases allow regions with newer programmes to learn from others' past incidents. [3, 4]

In summary, when comparing Europe to North America and Asia, the incidence and types of SARE are broadly comparable, mainly in Non-Reproductive T&C, with any differences largely due to how systematically incidents are captured. All regions strive for the same goal: near-zero transmission of diseases and highest possible graft success, and international cooperation is essential to advancing worldwide safety standards further.

4 Severe Adverse Reactions in Donors

Key findings

- Overall, SAR in donors decreased slightly (6%) in comparison with 2022.
- No SAR were reported in the category Replacement T&C.
- 'Other' continues to be the most common type of reaction in HSC donors.
- There was a 28% increase in the number of surgical complications in oocyte donors in comparison with 2022.

As per the ***Common Approach***, 2024 edition, reporting SAR in donors is mandatory when they affect the safety or quality of donated tissues or cells, but optional for reactions with no such impact. Many EU MS track donor reactions that do not compromise tissue or cell safety. Some reactions, such as ovarian hyper-stimulation syndrome (OHSS) from ovulation medications or granulocyte colony-stimulating factor (GCSF) reactions after stem cell collection are reported through other vigilance systems like pharmacovigilance or medical device monitoring. Recognising the value of these data, the EC continues to encourage EU MS to submit them on a voluntary basis.

4.1 Overview of SAR in donors by category of T&C

4.1.1 Distribution of total number of SAR in donors by category of T&C

Nineteen countries (AT, BE, BG, HR, CZ, EE, FI, FR, DE, EL, IE, IT, NL, NO, PL, PT, SI, ES and SE) reported a total of 727 SAR in donors in 2023, of which 93% were associated with Reproductive T&C while 7% were related to HSC donations.

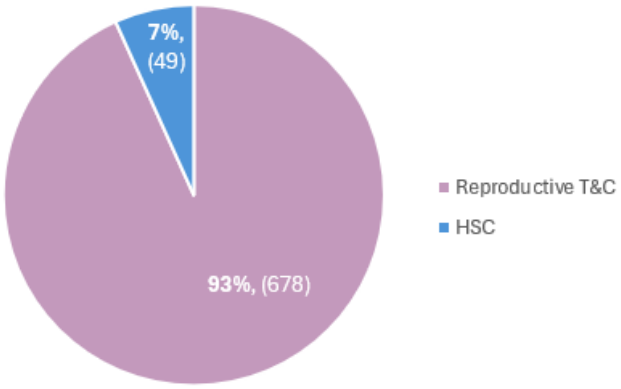


Figure 52. Percentage distribution of total number of SAR in donors by category of T&C in 2023

The distribution of SAR in donors by category of T&C and by country is presented in Figure 53.

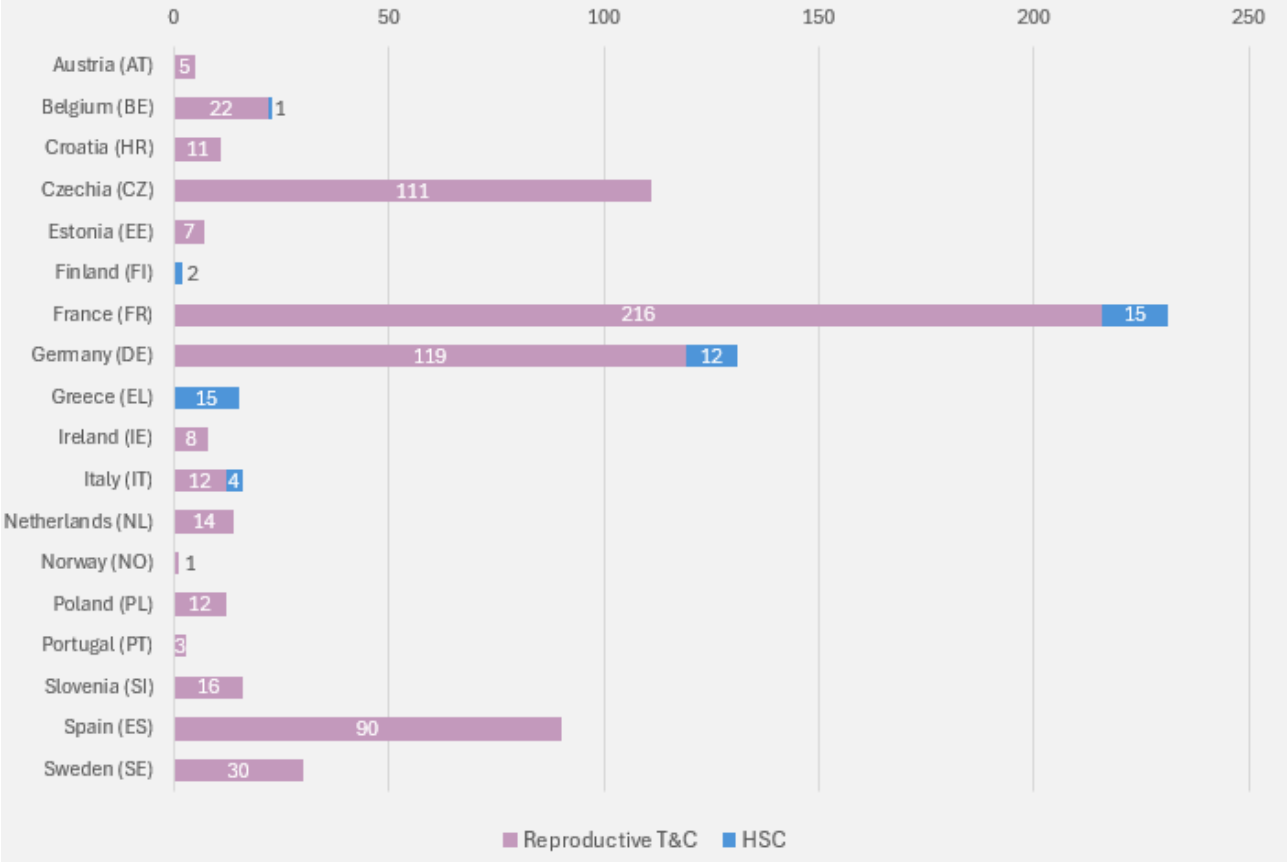


Figure 53. Distribution of total number of SAR in donors by category of T&C and by country in 2023

4.1.2 Comparative data

As shown in Table 27, in 2023, the total number of SAR in donors reported decreased slightly compared to 2022, mostly due to a reduction in SAR related to HSC.

T&C Category	2023	2022	% Change
Replacement T&C	0	2	*
HSC	49	79	-38
Reproductive T&C	678	693	-2
Total	**727**	**774**	**-6**

* no data reported in 2023

n (Replacement T&C)	0	2
n (HSC)	6	11
n (Reproductive T&C)	17	17

Table 27. Summary of total number of SAR in donors by category of T&C; 2023 vs. 2022

4.2 Overview of SAR by category of T&C and by type of reaction

4.2.1 HSC

As shown in Figure 54, 'other' was the most common type of reaction, representing 63% of the 49 SAR reported. Additional information on the SAR reported is provided in Annex 11. Additional information on SAR in HSC donors.

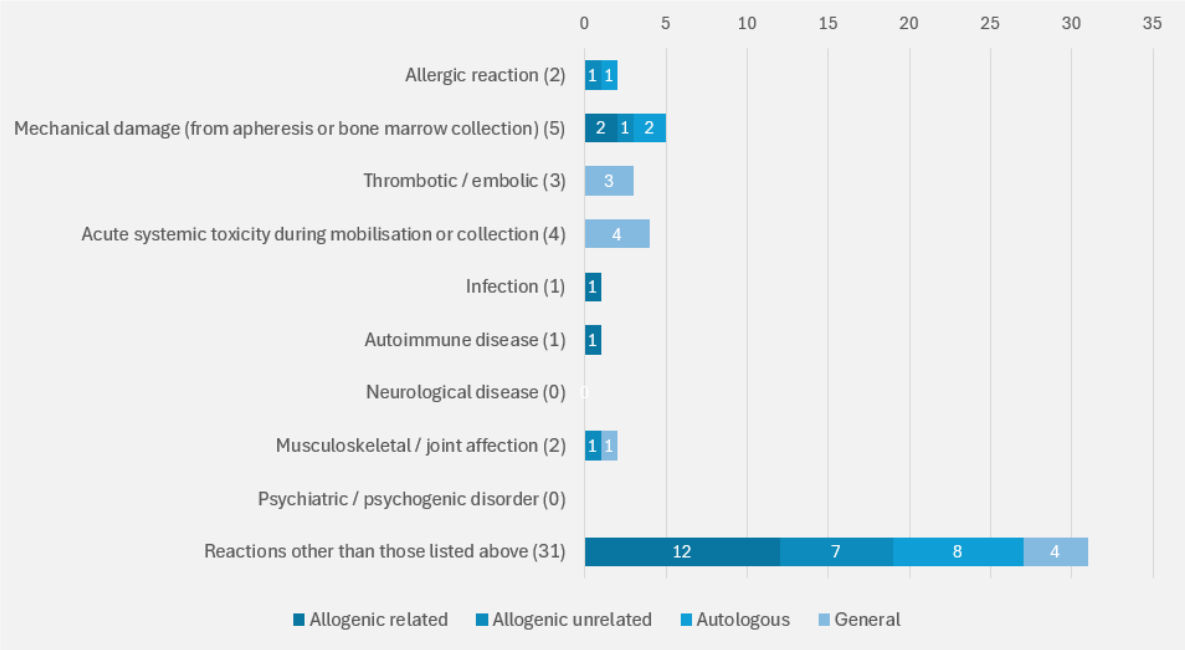


Figure 54. Distribution of SAR in donors by type of reaction and subtype of HSC in 2023

In comparison with 2022, there were eight fewer cases of acute systemic toxicity, six fewer cases of infection and six fewer cases of autoimmune disease (Table 28).

Type of Reaction	2022	2023	Absolute Change
Allergic reaction	2	2	**0**
Mechanical damage (from apheresis or bone marrow collection)	5	5	**0**
Thrombotic / embolic	4	3	**-1**
Acute systemic toxicity during mobilisation or collection	12	4	**-8**
Infection	7	1	**-6**
Autoimmune disease	7	1	**-6**
Neurological disease	3	0	**-3**
Musculoskeletal / joint affection	1	2	**+1**
Psychiatric / psychogenic disorder	0	0	**0**
Reactions other than those listed above	38	31	**-7**

Table 28. SAR in HSC donors by type of reaction; 2023 vs. 2022

4.2.2 Reproductive T&C

Of the 678 SAR related to Reproductive T&C, 675 occurred following donation of oocytes. Most of the SAR in oocyte donors were OHSS (49%) and surgical complications (34%); the remaining cases included 'other' reactions, infection and torsion of the ovary, as shown in Figure 55. Examples of SAR for the most frequent types of reactions (except OHSS and torsion of the ovary) are presented in Annex 12. Additional information on SAR in Reproductive T&C donors.

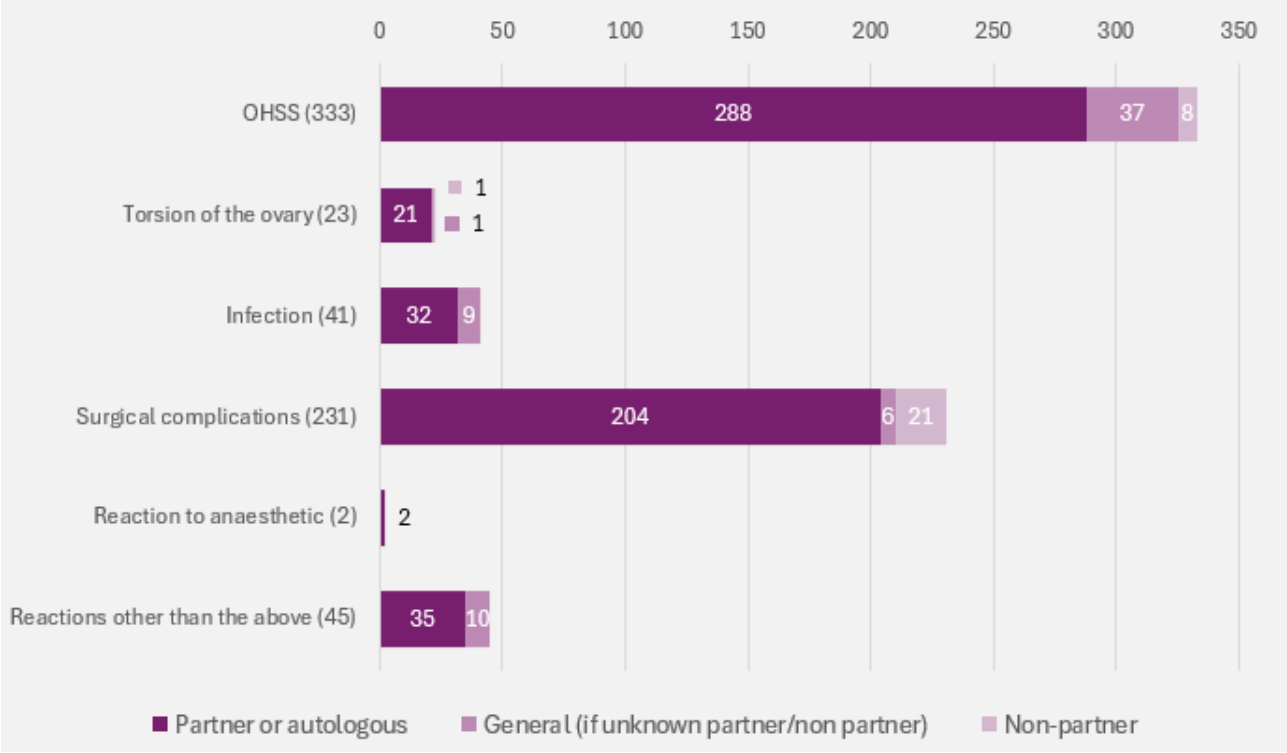


Figure 55. Distribution of SAR in oocyte donors by type of reaction and subtype in 2023

In comparison with 2022, there was an increase in the number of surgical complications and a reduction in OHSS (Table 29).

Type of Reaction	2022	2023	Absolute Change
OHSS	355	333	-22
Torsion of the ovary	24	23	-1
Infection	44	41	-3
Surgical complications	180	231	+51
Reaction to anaesthetic	0	2	+2
Reactions other than the above	40	45	+5

Table 29. SAR in oocyte donors by type of reaction; 2023 vs. 2022

Regarding donors of sperm or other reproductive tissues, it is worth nothing the significant reduction in the number of cases reported in other reproductive tissues (Table 30). Additional information on the SAR reported is provided in Annex 12. Additional information on SAR in Reproductive T&C donors.

Type of Reaction	Sperm (including MESA, PESA and TESE)			Other reproductive tissues (e.g. ovarian tissue)		
	2022	2023	Absolute Change	2022	2023	Absolute Change
Infection	0	1	+1	4	1	-3
Surgical complications	0	0	0	28	0	-28
Reaction to anaesthetic	1	0	-1	0	0	0
Reactions other than the above	2	1	-1	15	0	-15

Table 30. SAR in sperm and other reproductive tissues donors by type of reaction; 2023 vs. 2022
Note 1: for sperm, in 2023 the infection case occurred in general (if unknown partner/non-partner) while the 'other' reaction occurred in partner or autologous.
Note 2: for other reproductive tissues, in 2023, the infection case occurred in partner or autologous (fertility preservation).

4.3 Fatalities in donors

No fatalities in donors were reported in 2023 in any of the categories of T&C.

CONCLUSIONS

This year's report reflects significant improvements in the analysis and presentation of T&C transplantation data, enabling more precise tracking of SARE. By refining the methodology and introducing more detailed benchmarking, the report provides a clearer, more actionable assessment of transplantation safety trends across Europe.

The Annual SARE Report 2024 continues to recognise the commitment of MS to this initiative, with 31 European countries submitting their reports.

Interpretation of the analysis and results provided in this report should consider the limitations of the reporting exercise, notably the completeness and quality of the data reported.

1. Summary of Key Findings

- Overall, T&C transplantation trends from 2019 to 2023 point to modest but steady increases in distribution and clinical application rates in Reproductive T&C, while Non-Reproductive T&C shows more stable figures.
- SAR remain infrequent across Europe, with total incidence consistently low reflecting robust European biovigilance frameworks and high regulatory compliance. Over the past five years, the trend has been downward in Non-Reproductive T&C with approximately 5 SAR per 10,000 recipients *(or 2 SAR per 10,000 units distributed)* in 2023, while in Reproductive T&C, the overall incidence has varied significantly, with approximately 17 SAR per 10,000 recipients *(or 6 SAR per 10,000 units distributed*) in 2023.
- Safety risks vary significantly between different T&C categories:
    - Replacement T&C: TI, the primary safety concern, remains rare, although there were nine more cases than in 2022;
    - HSC: high inherent treatment risk persists (graft failure, immunological reactions);
    - Reproductive T&C: genetic transmission to offspring remains predominant.
- Imputability reporting continues to improve, reaching 51% overall. Nevertheless, imputability assignment for SAR related to Reproductive T&C remains at the lowest level among the three categories of T&C. This suggests MAR clinics may need guidance.
- Seventeen recipient or offspring deaths were attributed to tissue/cell therapy: five to HSC application and 12 to Reproductive T&C application.
- SAE primarily originated from system failure (26%) and human error (24%), namely related to inadequate process, procedure or documentation, and incorrect decision or omission following the correct procedure, respectively. This highlights ongoing opportunities to improve training, protocol standardisation and traceability systems.
- Overall, international benchmarking underscores that Europe maintains a strong position regarding T&C therapy safety, with SAR rates comparable or favourable to other leading global regions. Continuous global cooperation and data sharing remain essential to advancing worldwide safety standards further.
- SAR in donors decreased slightly (6%) in comparison with 2022, mainly driven by a SAR reduction in HSC. OHSS and surgical retrieval complications continue to be the most frequent issues in oocyte donors. No fatalities were reported this year.

2. Challenges and Areas for Improvement

- The description provided on cause of events continues to be unclear and incomplete, preventing a determination of the effectiveness of the management of events at individual country level and EU level. Additionally, the SAE specification assigned was not always accurate.

3. Future Recommendations

- Strengthening genetic screening protocols of donors in reproductive medicine.
- Reinforce the importance and value of providing descriptive data to improve quality of TI investigations (e.g. moment of symptom onset, exact pathogen responsible for infection, treatment, at home or in hospital, and patient outcome).
- Maintain focus on human error reduction through continuous efforts in training, procedural verification and digital traceability tools.
- SAR incidence rates in donors require reliable data on the number of non-reproductive and reproductive donors per country. Future reporting should include standardised donor denominator data to enable cross-country comparisons.
- Implementing a harmonised reporting dataset.

In conclusion, transplantation of human T&C in Europe continues to demonstrate consistently high safety standards, supported by robust regulatory oversight and proactive international cooperation. Nevertheless, the findings captured in this report reinforce the importance of consistent reporting, continued vigilance and targeted improvement efforts across all T&C categories to maintain and advance patient safety.

List of Abbreviations

CAPA	Corrective and Preventive Action
DLI	Donor Lymphocyte Infusions
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EU	European Union
FDA	US Food and Drug Administration
GCSF	Granulocyte Colony-Stimulating Factor
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPC	Haematopoietic Progenitor Cells
HSC	Haematopoietic Stem Cells
ICSI	Intracytoplasmic Sperm Injection
IL	Imputability Level
IUI	Intrauterine Insemination
IVF	In-Vitro Fertilisation
MAR	Medically Assisted Reproduction
MESA	Microsurgical Epididymal Sperm Aspiration
MS	Member States
NCA	National Competent Authorities
ODT	Other Disease Transmissions
OHSS	Ovarian Hyper-Stimulation Syndrome
PBSC	Peripheral Blood Stem Cells
PESE	Percutaneous Epididymal Sperm Aspiration
PMP	Per Million Population
SAE	Serious Adverse Events
SAR	Serious Adverse Reactions
SARE	Serious Adverse Reactions and Events
spp.	Species
T&C	Tissues and Cells
TESE	Testicular Sperm Extraction
TI	Transmitted Infections
TGC	Transmitted Genetic Conditions
TMD	Transmitted Malignant Diseases
VES	Vigilance Expert Subgroup

AT	Austria
BE	Belgium
BG	Bulgaria
HR	Croatia
CY	Cyprus
CZ	Czechia
DK	Denmark
EE	Estonia
FI	Finland
FR	France
DE	Germany
EL	Greece
HU	Hungary
IS	Iceland
IE	Ireland
IT	Italy
LV	Latvia
LI	Liechtenstein
LT	Lithuania
LU	Luxembourg
MT	Malta
NL	Netherlands
NO	Norway
PL	Poland
PT	Portugal
RO	Romania
SK	Slovakia
SI	Slovenia
ES	Spain
SE	Sweden
UK	United Kingdom
UK(NI)	Northern Ireland

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Annex 1. Executive summary (2019–2023)

Parameter	2020 (Data 2019)		2021 (Data 2020)		2022 (Data 2021)		2023 (Data 2022)		2024 (Data 2023)	
Non-Reproductive T&C										
	n	Number	n	Number	n	Number	n	Number	n	Number
Units processed	24	503,374	23	396,639	24	431,427	25	555,360	27	**535,868**
Units distributed	27	393,625	26	378,237	27	430,284	29	457,314	30	**493,662**
Number of recipients	21	114,425	19	134,242	23	155,599	25	178,978	27	**210,710**
SAR in recipients	12	156	16	139	12	145	11	94	13	**94**
Total SAR incidence per 10,000 recipients *(or per 10,000 units distributed)*		13.6 *(4.0)*		10.4 *(3.7)*		9.3 *(3.2)*		5.3 *(2.1)*		**4.5 *(1.9)***
Fatalities in recipients	-	0	4	8	4	16	2	6	2	**5**
SAE	17	689	19	660	20	461	19	898	20	**486**
Total SAE incidence per 10,000 units processed		13.7		16.6		10.7		16.2		**9.1**
SAR in donors	5	47	10	95	10	80	12	81	6	**49**
Fatalities in donors	-	0	-	0	-	0	2	2	-	**0**

Reproductive T&C										
	n	Number	n	Number	n	Number	n	Number	n	Number
Units processed	21	2,418,743	19	2,046,925	18	2,727,935	18	2,359,270	21	**2,561,020**
Units distributed	19	966,690	22	738,282	21	761,919	22	506,429	23	**533,967**
Number of recipients	16	228,771	15	110,816	16	162,868	20	156,651	20	**175,290**
SAR in recipients or offspring	12	150	18	211	13	181	14	253	16	**293**
Total SAR incidence per 10,000 recipients *(or per 10,000 units distributed)*		6.6 *(1.6)*		19.0 *(2.9)*		11.1 *(2.4)*		16.8 *(5.0)*		**16.7 *(5.5)***
Fatalities in recipients or offspring	-	0	3	6	2	4	1	6	4	**12**
SAE	17	260	20	250	16	233	17	235	17	**333**
Total SAE incidence per 10,000 units processed		1.1		1.2		0.9		1.0		**1.3**
SAR in donors	15	856	17	751	14	715	17	693	17	**678**
Fatalities in donors	-	0	-	0	-	0	2	2	-	**0**

Methodological details: *the total SAR incidence was calculated by dividing the number of reported SAR by the number of recipients (or by the number of units distributed) and then expressing the result per 10,000 recipients (or per 10,000 units distributed). It is important to note that fewer countries reported data on SAR cases in recipients than those reporting number of recipients (or units distributed). Although this results in a broader denominator(s), the consistency of the reporting gap over time allows for reliable analysis of overall trends. The total SAE incidence was calculated by dividing the number of SAE by the number of units processed, with the result expressed per 10,000 units processed. It is important to note that in this case, a slightly larger number of countries provided data on the number of units processed compared to those reporting SAE cases. Although this results in a broader denominator, the trend analysis remains robust as the reporting pattern is consistent over time. This disclosure allows for a better understanding of the potential limitations or biases in the incidence calculation.*

Annex 2. Data Supplement – Distribution rates of Non-Reproductive T&C and Reproductive T&C per 1,000 population in the last five years
(Refer to Figure 1)

Data Year	2019		2020		2021		2022		2023	
Country	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C
Austria (AT)	1.15	2.50	1.16	2.38	1.20	2.31	1.23	2.55	1.14	2.40
Belgium (BE)			1.80	17.74	2.07	24.06	2.14	5.19	2.16	
Bulgaria (BG)	0.13	0.87	0.14	3.66	0.14	9.56	0.14	2.90	0.16	9.92
Croatia (HR)	0.32	2.73	0.28	2.42	0.35	2.66	0.36	2.53	0.36	2.32
Cyprus (CY)							0.32	1.87	0.24	4.34
Czechia (CZ)	0.95	8.76	0.75	10.65	1.00	8.70	1.02	5.53	0.85	9.00
Denmark (DK)	1.24	12.10	0.94	11.85	0.78	1.13	0.87	1.11	0.94	0.92
Estonia (EE)	0.65	3.26	0.64	2.92	0.66		0.82	2.33	0.76	
Finland (FI)	0.37		0.68	0.20	0.75	0.16	0.62	0.81	0.84	2.48
France (FR)	0.24		1.26		1.53		1.68		1.89	
Germany (DE)	1.20	7.67	0.97	1.31	1.06	1.72	1.15	1.66	1.27	1.59
Greece (EL)	0.95		0.93		1.46		1.74		1.94	
Hungary (HU)	0.77	0.72	0.50	0.45	0.12	1.04	0.14	3.00	0.18	5.12
Iceland (IS)							0.08	2.24	0.06	2.65
Ireland (IE)	0.40	1.09	0.33	0.85	0.31	2.17	0.28	2.07	0.43	0.81
Italy (IT)	0.75		0.47		0.10		0.53		0.66	
Latvia (LV)	0.02	1.83	0.02	1.34	0.02	1.59	0.04	1.57	0.04	1.81
Liechtenstein (LI)						0.28				3.22
Lithuania (LT)	0.12	0.80	0.13	0.81	0.14	0.76	0.14	0.79	0.17	0.81
Luxembourg (LU)	0.21	2.76	0.93	2.55	6.09	3.10	1.59	2.97	1.33	1.93
Malta (MT)	0.02	0.67	0.01	0.84	0.01	0.59	0.01	0.86	0.00	0.91
Netherlands (NL)	1.27	3.87	1.10	3.55	4.38	3.86	1.42	3.39	1.39	3.51
Norway (NO)	0.03			0.00	0.21	1.68	0.59	0.18	0.43	2.08
Poland (PL)	1.26		0.87		0.89		1.58		1.06	
Portugal (PT)	0.17	1.16	0.12	0.98	0.17	0.52	0.18		0.25	
Romania (RO)	0.00	0.37	0.00	0.39	0.03	0.54	0.04	1.87	0.02	0.47
Slovakia (SK)	3.40	1.29							0.51	1.70
Slovenia (SI)	0.59	3.61	0.20	2.61	0.48	3.52	0.49	7.34	0.46	3.49
Spain (ES)	0.81		0.65		0.75		0.82		1.22	
Sweden (SE)	0.40	0.28	0.29	1.88	0.30	2.00	0.40	2.05	0.31	1.92
United Kingdom (I	0.71		0.42	0.93	0.03		0.19		0.03	1.05
Median	**0.6**	**1.8**	**0.6**	**1.6**	**0.5**	**1.7**	**0.5**	**2.2**	**0.5**	**2.1**

Note: following Brexit, UK = Northern Ireland only.

Annex 3. Data Supplement – Application rates of Non-Reproductive T&C and Reproductive T&C per 1,000 population in the last five years
(Refer to Figure 2)

Data Year	2019		2020		2021		2022		2023	
Country	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C
Austria (AT)	0.11	1.29	0.18	1.22	0.24	1.21	0.14	1.32	0.17	1.27
Belgium (BE)										
Bulgaria (BG)	0.11	1.97	0.12	1.87	0.11	1.41	0.11	1.35	0.12	1.47
Croatia (HR)	0.22	1.40	0.18	1.25	0.21	1.48	0.20	1.60	0.22	1.58
Cyprus (CY)							0.32	1.87	0.17	1.66
Czechia (CZ)	0.52	3.45	0.00		0.10	3.38	0.10	2.52	0.20	3.66
Denmark (DK)	0.91	3.02	0.74	2.35	0.50	3.05	0.63	2.98	0.67	2.87
Estonia (EE)	0.24	0.19	0.22	0.19	0.25		0.32	1.59	0.24	
Finland (FI)	0.07		0.41	1.01	0.41	1.25	0.42	1.10	0.48	1.66
France (FR)	0.25		0.99		1.21		1.28		1.53	
Germany (DE)							0.09		0.10	
Greece (EL)	0.78		0.76		0.90		1.44		1.61	
Hungary (HU)					0.14	0.09	0.07	0.27	0.08	0.10
Iceland (IS)							0.03	2.24	0.02	1.72
Ireland (IE)	0.18	0.73	0.25	0.55	0.29	1.44	0.20	1.41	0.28	0.55
Italy (IT)	0.37		0.33		0.08		0.09		0.08	
Latvia (LV)										
Liechtenstein (LI)								7.20		1.60
Lithuania (LT)	0.12		0.13		0.14	0.76	0.14	0.79	0.17	0.81
Luxembourg (LU)		1.57		1.29		1.57		1.48	0.43	1.29
Malta (MT)	0.02	0.43	0.01	0.41	0.01	0.59	0.01	0.86	0.00	0.74
Netherlands (NL)	0.68	1.67	0.59	1.50	0.53	1.78	0.59	1.60	0.57	1.60
Norway (NO)	0.17	1.09		0.00	0.17		0.24		0.18	1.09
Poland (PL)					0.06					
Portugal (PT)	0.19	1.11	0.16	0.97	0.18	0.65	0.15	1.27	0.22	1.23
Romania (RO)	0.00	0.37	0.00	0.39	0.02	0.54	0.00		0.02	
Slovakia (SK)	0.24	1.08							0.30	1.28
Slovenia (SI)	0.57		0.19	1.95	0.17	2.38	0.23	2.21	0.35	2.36
Spain (ES)	0.66		0.26		0.58		0.71		0.85	
Sweden (SE)	0.33	0.13	0.26	1.13	0.29	1.17	0.31	1.24	0.27	1.16
United Kingdom (		1.18			0.10		0.23	1.07	0.12	
Median	**0.2**	**1.1**	**0.2**	**1.1**	**0.2**	**1.3**	**0.2**	**1.4**	**0.2**	**1.4**

Note: following Brexit, UK = Northern Ireland only.

Annex 4. Data Supplement – Distribution rates and Clinical Application rates pmp in Replacement T&C, HSC and Reproductive T&C; 2022 vs. 2023

(Refer to Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8, Figure 10, Figure 11 and Figure 12)

	Distribution rates						Clinical Application rates					
Data Year	2022			2023			2022			2023		
Country	Replacement T&C	HSC	Reproductive T&C	Replacement T&C	HSC	Reproductive T&C	Replacement T&C	HSC	Reproductive T&C	Replacement T&C	HSC	Reproductive T&C
Austria (AT)	1,024	202	2,555	931	209	2,403	78	63	1,316	114	57	1,265
Belgium (BE)	1,935	206	5,192	1,888	271							
Bulgaria (BG)	118	27	2,900	127	29	9,922	80	25	1,351	94	28	1,465
Croatia (HR)	162	198	2,529	198	159	2,323	129	71	1,603	147	78	1,582
Cyprus (CY)	202	118	1,874	155	85	4,338	202	118	1,874	146	27	1,665
Czechia (CZ)	892	131	5,533	738	115	8,995	19	80	2,517	115	85	3,662
Denmark (DK)	657	208	1,115	778	158	925	547	86	2,976	613	56	2,868
Estonia (EE)	721	98	2,332	606	153		320	1	1,588	236		
Finland (FI)	478	139	814	675	170	2,476	358	65	1,099	406	69	1,665
France (FR)	1,684			1,887			1,214	70		1,407	121	
Germany (DE)	1,079	72	1,663	1,197	70	1,595		92			97	
Greece (EL)	1,694	48		1,878	67		1,398	42		1,546	66	
Hungary (HU)	94	44	2,999	78	100	5,121	26	45	269	30	49	96
Iceland (IS)		77	2,238		58	2,650		32	2,238		23	1,720
Ireland (IE)	157	121	2,067	308	124	807	146	57	1,414	212	72	549
Italy (IT)	444	82		567	91			92			79	
Latvia (LV)	35		1,565	44		1,806						
Liechtenstein (LI)						3,223			7,200			1,599
Lithuania (LT)	59	82	793	82	86	807	59	82	793	82	86	807
Luxembourg (LU)	1,590		2,969	1,174	153	1,925			1,475	373	57	1,295
Malta (MT)	12		864	4		912	11		864	4		742
Netherlands (NL)	1,132	282	3,389	1,082	308	3,506	487	105	1,601	465	108	1,600
Norway (NO)	541	47	180	341	90	2,077	200	40		174	3	1,086
Poland (PL)	974	609		839	217							
Portugal (PT)	127	55		186	62		116	31	1,273	159	61	1,226
Romania (RO)	23	18	1,874	20		470	2			22		
Slovakia (SK)				365	142	1,700				263	37	1,279
Slovenia (SI)	244	242	7,343	160	298	3,488	153	79	2,213	151	202	2,363
Spain (ES)	818			1,139	77		629	76		778	77	
Sweden (SE)	279	125	2,053	218	89	1,925	230	79	1,242	208	64	1,164
United Kingdom (I	186	2		34		1,053	225	1	1,066	33	84	
Median	**461**	**108**	**2,152**	**365**	**107**	**2,077**	**177**	**70**	**1,445**	**166**	**69**	**1,380**

Note: following Brexit, UK = Northern Ireland only.

Annex 5. Data Supplement - SAR incidence rates in Non-Reproductive T&C and Reproductive T&C in the last five years
(Refer to Figure 19 and Figure 20)

Data Year	2019				2020				2021				2022				2023			
	Non-Reproductive T&C		Reproductive T&C		Non-Reproductive T&C		Reproductive T&C		Non-Reproductive T&C		Reproductive T&C		Non-Reproductive T&C		Reproductive T&C		Non-Reproductive T&C		Reproductive T&C	
Country	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
Austria (AT)	21	2							14	3										
Belgium (BE)						1		0.2		3		0.3		1		1		1		
Bulgaria (BG)													69	51			25	20		
Croatia (HR)			9	5	43	27	4	2			9	5							3	2
Cyprus (CY)																				
Czechia (CZ)			13	5				4			15	6			31	14			18	7
Denmark (DK)			18	4	5	4	18	4	7	4	16	44	5	4	1	3			1	4
Estonia (EE)	63	23					163	10							5	3				
Finland (FI)	28	5			4	3	2	9			7	58							1	1
France (FR)	26	27			4	3			8	6			3	3			2	2		
Germany (DE)		3		0.03		3		0.3		3			29	2		0.4	31	2		0.2
Greece (EL)	25	21			44	36			18	11			7	5			6	5		
Hungary (HU)																				
Iceland (IS)																			102	66
Ireland (IE)	22	10			8	6	4	2	21	19	4	3					20	13	7	5
Italy (IT)	4	2			5	4			2	2			7	1			6	1		
Latvia (LV)																				
Liechtenstein (LI																				
Lithuania (LT)																				
Luxembourg (LU							37	19							11	5			11	8
Malta (MT)																				
Netherlands (NL)	10	5	3	1	8	4	5	2	2	0.3			4	2	1	1	4	2	1	0.3
Norway (NO)			14				10,000	10,000				26				185	10	4	17	9
Poland (PL)									33	2										
Portugal (PT)			3	2	25	31	13	13	5	6	9	11	13	11	29		9	8	29	
Romania (RO)																				
Slovakia (SK)																				
Slovenia (SI)																				
Spain (ES)	9	7			11	5			5	4			3	3			4	3		
Sweden (SE)	3	2			15	13	39	24			3	2	3	2	6	4	3	3	37	23
United Kingdom (		1	1			1		1												
Median	**21.5**	**5.2**	**9.0**	**3.5**	**7.9**	**3.9**	**12.9**	**3.5**	**7.3**	**3.6**	**8.7**	**5.8**	**6.0**	**2.6**	**6.2**	**3.2**	**6.5**	**2.7**	**11.5**	**4.6**

Note 1: (a) per 10,000 recipients; (b) per 10,000 units distributed.
Note 2: Since 2021, SAR data on Non-Reproductive T&C has been captured separately in Replacement T&C and HSC. SAR incidence in Non-Reproductive T&C for each country was calculated as the number of SAR reported for Replacement T&C + HSC divided by the number of recipients reported for Replacement T&C + HSC multiplied by 10,000. In 2021, IT provided SAR counts for both categories but reported number of recipients for only one; the same for DE and IT in 2022 and 2023. Likewise, In 2021, FR and DE provided SAR counts for both categories but reported units distributed for only one; same for FR and ES in 2022, and FR in 2023. In these cases, the available recipient/units distributed count was used as the denominator. Sensitivity analysis excluding these countries did not affect the year-to-year trend.
Note 3: outliers highlighted in red.
Note 4: following Brexit, UK = Northern Ireland only.

Annex 6. Data Supplement - SAR incidence rates in Replacement T&C, HSC and Reproductive T&C per 10,000 recipients in 2023

(Refer to Figure 21, Figure 22 and Figure 23)

Country	Replacement T&C	HSC	Reproductive T&C
Austria (AT)			
Belgium (BE)			
Bulgaria (BG)		111	
Croatia (HR)			3
Cyprus (CY)			
Czechia (CZ)			18
Denmark (DK)			1
Estonia (EE)			
Finland (FI)			1
France (FR)	0.3	24	
Germany (DE)		5	
Greece (EL)		146	
Hungary (HU)			
Iceland (IS)			102
Ireland (IE)	18	26	7
Italy (IT)		4	
Latvia (LV)			
Liechtenstein (LI)			
Lithuania (LT)			
Luxembourg (LU)			11
Malta (MT)			
Netherlands (NL)		21	1
Norway (NO)	10		17
Poland (PL)			
Portugal (PT)	6	16	29
Romania (RO)			
Slovakia (SK)			
Slovenia (SI)			
Spain (ES)	3	8	
Sweden (SE)		15	37
United Kingdom (NI)			
Median	**5.9**	**18.1**	**11.5**

Annex 7. Data Supplement – SAE incidence rates in Non-Reproductive T&C and Reproductive T&C per 10,000 units processed in the last five years

(Refer to Figure 36, Figure 37, Figure 38, Figure 39 and Figure 40)

Data Year	2019		2020		2021		2022		2023			
Country	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C	Non-Reproductive T&C	Reproductive T&C	Replacement T&C	HSC	Non-Reproductive T&C	Reproductive T&C
Austria (AT)	0.8		0.6	0.3	1.1		0.2	0.3	0.1	14.6	0.6	0.6
Belgium (BE)					19.1	0.7						
Bulgaria (BG)				0.1	20.8	0.1	15.4			42.7	21.5	
Croatia (HR)	6.2	0.3	4.3		11.3	0.4						
Cyprus (CY)												
Czechia (CZ)	13.1	1.2	0.9	0.5	1.5	0.2	3.0	0.1				
Denmark (DK)		1.4	4.4	4.9		4.8		0.9				2.8
Estonia (EE)				0.3					0.8	31.0	1.6	
Finland (FI)	24.6	7.3	28.8		12.9		5.1	1.6		32.1	4.0	1.3
France (FR)							31.8					
Germany (DE)	2.1	0.1	4.0	0.03	2.4	0.1	2.4	0.1	0.4	14.7	2.2	0.1
Greece (EL)	10,000.0		10,000.0		10,000.0		10,000.0		10,000.0	10,000.0	10,000.0	
Hungary (HU)	16.8		45.9	2.1	326.8		43.7	0.5	879.1		49.0	1.1
Iceland (IS)								10.9				
Ireland (IE)	169.1	0.6	84.1	0.3	88.6	0.3	57.0	1.0	21.1	129.4	90.6	0.6
Italy (IT)	2.9		13.2		14.0		10.1		6.0	6.6	6.1	
Latvia (LV)		0.3		0.3		0.3						
Liechtenstein (LI)												
Lithuania (LT)												
Luxembourg (LU)										94.3	22.0	15.4
Malta (MT)					1,666.7		1,666.7					
Netherlands (NL)	4.0	0.5	2.6	0.7	5.7	0.2	9.8	0.4	2.9	11.0	4.3	0.3
Norway (NO)	41.7	0.2							16.0		31.9	
Poland (PL)	1.4		1.3		0.8		0.6			1.0		
Portugal (PT)	87.8	0.8	154.3	0.2	478.2	7.5	377.7		163.4	3.5	39.6	
Romania (RO)		6.4										
Slovakia (SK)												
Slovenia (SI)							9.3			19.2	14.8	
Spain (ES)	10.4		11.2		11.3		10.8		7.8		12.8	
Sweden (SE)	27.6	0.6	16.0	0.4	26.6	0.6	8.0	0.2	2.1	10.4	4.5	0.4
United Kingdom (I	31.3		45.9	0.8	76.3					194.8	109.1	9.1
Median	**13.1**	**0.6**	**11.2**	**0.3**	**14.0**	**0.3**	**10.0**	**0.4**	**4.5**	**16.9**	**12.8**	**0.8**

Note 1: Since 2021, SAE data on Non-Reproductive T&C has been captured separately in Replacement T&C and HSC. SAE incidence in Non-Reproductive T&C for each country was calculated as the number of SAE reported for Replacement T&C + HSC divided by units processed reported for Replacement T&C + HSC multiplied by 10,000. In 2021, DE, PT, ES and UK(NI) provided SAE counts for both categories but reported units processed for only one; the same for FR and ES in 2022, and NO and ES in 2023. In these cases, the available units processed count was used as the denominator. Sensitivity analysis excluding these countries did not affect the year-to-year trend.

Note 2: outliers highlighted in red.

Note 3: following Brexit, UK = Northern Ireland only.

Annex 8. Examples of SAE and assigned specification for Replacement T&C

Specification	SAE Examples
Tissue or cell defect 28% (52 out of 187)	• Infections detected in the pre-implant microbiological control (15) • Observation of an abnormally high proportion of corneas entirely coloured by trypan blue • Malaria screening positive in organ and tissue donor. Recovered skin discarded before result of confirmatory test (negative) • In the intraoperative kidney biopsy of an organ and corneal donor, presence of germs compatible with active tuberculosis is detected/Donor serology positive for *Strongyloides* (IgG) • Corneal endothelium with poor appearance • Discovery of a notch on the graft (pre-cut cornea) which revealed a free lamella • Detachment of the endothelium, with the presence of atheromatous plaques requiring endarterectomy
Other 23% (43 out of 187)	• COVID-19 positivity (6); HBV positivity (6), stroma opacity (3); *Treponema* positivity (2); anti-HBc, anti-CMV IgG, anti-*Toxoplasma* IgG positivity (2) • The outer pocket of bag containing a heart valve was inflated when it came out of the storage tank. Damage to the external bag posed a risk of internal contamination, leading to tissue discard • Unexpected external contamination event during transport that did not result from internal procedural errors • Unforeseen packaging defect or environmental factor led to tissue damage, not clearly attributable to procedural mistakes or systemic issues • Regulatory or external communication issues led to the tissue being placed in quarantine and ultimately discarded • Inconclusive microbiological results: no application • Incomplete serology
System failure 21% (40 out of 187)	• Bacterial contamination of the graft (15) • Contamination of the wash solution after thawing (5) • Positive microbiology results found after transplant • Loss of a bone graft during its storage • Antibiotic transport solution for cardiovascular tissue carried out in an unsuitable safety cabinet • Cryogenic freezing was compromised due to an unreliable nitrogen level gauge • Discovery of a foreign body in a vial of spongy bone granules
Human error 21% (40 out of 187)	• Imported cornea with defect (white material, opacity, detected on the endothelium of the cornea) from foreign Tissue Establishment: no application (4) • Corneas with *Aspergillus niger* pre-implant culture on different days in the same implant centre (3) • The tissue was damaged during cornea preparation, before transplant surgery: no application (3) • Corneal graft with asymmetry in the cut • Cornea arrived in the transport refrigerator at room temperature • Logistical complications (e.g. courier delays or external mishandling) that resulted in tissue compromise • The corneas accidentally arrived frozen at the tissue bank. Frozen plate instead of a cooled plate used in transport device • *S. hominis/S. epidermidis* were found in microbiological control carried out in the operating room at the time of implantation • Autologous calvarium was placed in NaCl instead of being packaged natively • A complaint that no DMEK roll was found in the sent bottle with possibilities including the tissue being sucked in during sampling or lost in the operating room • An operator's omission (failing to verify the presence of tissue post-sampling) led to the distribution of an incomplete product

Annex 9. Examples of SAE and assigned specification for HSC

Specification	SAE examples
System failure 39% (117 out of 299)	• Bacterial contamination of the graft (60) • Detection of *Cutibacterium acnes*, *E. coli*, *Staphylococcus spp.*, *Bacillus cereus*, aerobic spore-forming bacteria (20) • After apheresis, a large difference in leucocyte concentration was noted; an error in the CD34 determination was identified due to the loss of a manual check when switching to an automatic system • Insufficient yield and low collection efficiencies after stem cell apheresis were traced to a misapplied dilution factor following the removal of a manual control • Event related to the graft procurement procedures, non-compliance with cell separator clamping precisions for NaCl • Procedural oversight in data transmission led to inaccurate cell counts • Loss of a graft during transport due to theft of the case • Inadequate documentation and training resulted in measurement discrepancies • Change in system protocols without proper staff retraining caused repeated errors
Other 19% (58 out of 299)	• One cord with positivity to HTLV, One cord to CMV IgG and IgM/HSC: five positive cultures in cell products (*B. fragilis, E. coli*, *Pseudomonas oryzihabitans* and two not specified) (7) • Post-donation information: leukemic stem cells identified during bone marrow procurement in a donor; discovery of metastatic lung cancer in the donor; discovery of a pericentric inversion of chromosome 3, etc. (5) • Poor mobilisation • Insufficient cell quantity • Contamination of the cryopreservation bags
Human error 14% (41 out of 299)	• Product release without or with low cell count/Product release without sterility results (10) • Distribution of microbiologically contaminated bone marrow • During lymphopheresis, the anaerobic sterility test revealed *Cutibacterium acnes*, indicating probable contamination attributable to handling issues • Circuit break or leak of a pocket • Event related to the graft preparation procedures, error at the prescription validation step • Incubation of samples for microbial testing accidentally lasted only five instead of seven days • An incorrect procedural step resulting in product mishandling • Manual input error led to incorrect data entry, affecting subsequent decisions

Annex 10. Examples of SAE and assigned specification for Reproductive T&C

Specification	SAE Examples
Human error 35% (117 out of 333)	• Handling incidents (excluding falls) (20) • Defect during the identification process (15) • Error(s) in hormone treatment - prescription/administration (5) • Material fall (4) • Seminogram results were entered into the file of a patient who did not match; one straw affected • Use of the wrong culture medium resulting in the loss of all of the patient's embryos; 19 embryos affected • Non-compliance with prescription instruction • Organisational failures of the MAR procedure • Incorrectly labelled sperm cryotube for sperm cryopreservation: cryotube destroyed • Testicular biopsy without prior serology. Failure to follow the SOP. One testicular biopsy affected • Two donor samples were exchanged between two patients coming for treatment on the same day; one straw affected • The semen sample was not frozen, and the ovarian puncture had to be performed a second time; one straw partner and one oocyte-partner affected
Materials 19% (63 out of 333)	• Toxicity in culture oil (34) • Incidents related to the use of defective equipment (excluding incubators and tanks) • Defects in the storage of straws (5) • The thawing solution of a batch of the devitrification kit was defective and resulted in a decrease in survival rate; one oocyte-partner and one oocyte-non-partner affected • Failure in a batch of mineral oil used for embryo culture with a high abortion rate
System failure 17% (58 out of 333)	• Culture contamination (10) • Environmental disturbance(s) (4) • Handling incidents (excluding falls) (4) • Defects in the storage of straws (3) • A posteriori discovery(s) of abnormal biological tests • Lack of agreement between the number of cryotop embryos recorded in the records in paper format with those recorded in the cryotops • Post-donation information • Inappropriate use of a product • Organisational failures of the MAR procedure • Defects in the management of the thawing planning
Tissue or cell defect 17% (57 out of 333)	• Donor tested positive for HAART after samples had been collected Straws were destroyed. Initial serology was negative. Donor tested positive on post-procurement serology; 14 samples affected • A subsequent sample was registered in the registry, and this prevented a previous sample from being registered; Two straws affected • Embryo contaminated with *Candida parapsilosis* • The sperm bank notified that a donor was a carrier of neurofibromatosis type 1. The recipient was not pregnant; one straw non-partner and one oocyte-partner affected • Donor fragile X syndrome (FMR1) carrier with mutation 47 & 39 CGG repeats (2); donor glucose-6-phosphate dehydrogenase deficiency carrier (2)

Annex 11. Additional information on SAR in HSC donors

Type of Reaction	Descriptions/Comments
Reactions other than those listed above (31)	• No description provided (13) • Atrial fibrillation (1); myopericarditis (1); citrate reaction (1); thrombocytopenia (1) • Spleen rupture (1); citrate reaction (3); hypovolaemic shock: the volume collected was considered higher than what was expected (1) • Acute colitis (1); fever, neutropenia, liver abscess, gram negative sepsis (1); suspected capillary leak syndrome, dyspnoea, hypoxia, haemoptysis (1); vasovagal reaction with syncope (1) • Donor was feeling very ill/unwell after donation, needed examination at the hospital (2) • Hospitalisation of PBSC unrelated donor after first GCSF dose administration for breathing difficulties and hypotension (1) • Severe hypocalcaemia from citrate (2)
Mechanical damage (from apheresis or bone marrow collection) (5)	• Haematoma (3) • Bleeding after removing the pressure bandage of the dialysis catheter (1) • No description provided (1)
Acute systemic toxicity during mobilisation or collection (4)	• Reaction to citrate (4)
Thrombotic/embolic (3)	• Subdural haematoma (1); blood clot formation due to inadequate inflow of anticoagulation solution (1); transient ischaemic attack (1)
Allergic reaction (2); Musculoskeletal/joint affection (2)	• Citrate reaction (1); Quincke's oedema (1) • Attack of gout (1); pain (1)
Infection (1); Autoimmune disease (1)	• Hospitalisation for 13 days after bone marrow donation in a subject with thalassaemia trait due to onset of fever with positive blood culture for oxacillin-resistant *Staphylococcus caprae* (1) • Multiple sclerosis (1)

Annex 12. Additional information on SAR in Reproductive T&C donors

Type of Reaction	SAR Examples - oocytes
Surgical complications (231)	• Haemoperitoneum (178) • No description provided (12) • Ovarian abscess (8) • Tubo-ovarian abscess (5) • Abdominal pain and bleeding after ovarian pick-up (4) • Bladder injury (4) • Pulmonary embolism (3) • Ureter lesion (2) • Pelvic abscess (2) • Bladder clot • Bladder puncture • Ovarian haematoma • Haemorrhagic ovarian cyst • Post-puncture haematoma • Bladder clot • Bladder puncture with presence of haematuria
Other reactions (45)	• One abdominal pain; one rapidly worsening cold symptoms, sweating, coma, reanimation, death; one sepsis, peritonitis and Douglas abscess; one colicky pain and collapsing; two pain; one Hb drop without bleeding and increase in transaminases; one collapse after follicle puncture; one pulmonary embolism; one thrombosis • Heavier venous bleeding (8) • Post-puncture vasovagal reaction • Acute myocarditis • Arm/leg deep vein thrombosis • Myocardial infection • Pyelocalic dilatation • Pelvic pain • Ischaemic stroke • Stress-induced cardiomyopathy
Infection (41)	• Pelvic inflammatory disease (10) • Hospitalisation because of bacterial infection after oocyte pick-up (9) • Pelvic peritonitis (4) • Urinary infection

Type of Reaction	Description/Comments
Infection (1 sperm; 1 other tissue)	• Pain and infection • Male with non-obstructive azoospermia for which testicular biopsy on 17/03/2023. Reported on 30/03/2023 with testicle pain and swelling. Investigation showed a late concomitant bacterial infection that damaged the testicular tissue to the point where orchiectomy was required. All preventive measures were taken during the operation. This was an isolated complication
Other reactions (1 sperm)	• Ischaemic stroke

Annex 13. References

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