# SPEAR ANNUAL REPORT 2022


matching donors • serving patients

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# CONTENTS

# 1. INTRODUCTION

*In this annual report the World Marrow Donor Association presents the analysis of the in 2022 reported reactions in donors and patients and the adverse events related to stem cell donation and transplantation. With this report and with the system we maintain, we aim to provide insight into the frequency of complications and, if possible, the opportunities to prevent them.*

**The reporting system**

The World Marrow Donor Association (WMDA) hosts an online reporting tool for reporting of adverse events and reactions related to stem cell donation by unrelated and related donors or affecting product quality. Reporting of such Serious Product Events and Adverse Reactions (SPEARs) is a requirement of donor registries and cord blood banks seeking WMDA certification and a reporting system has been operational since 2003. Organisations in full compliance with WMDA Standards are required to report:

- Any adverse event or reaction in connection with a donation affecting the donor, recipient, or product quality. (Well-known side effects and quality deviations do not have to be reported if mild and no serious consequences).
- Any malignancy, severe autoimmune disease, or donor death (unless definitely not related) within 10 years of stem cell donation.

Reporters are asked to categorise reports as:

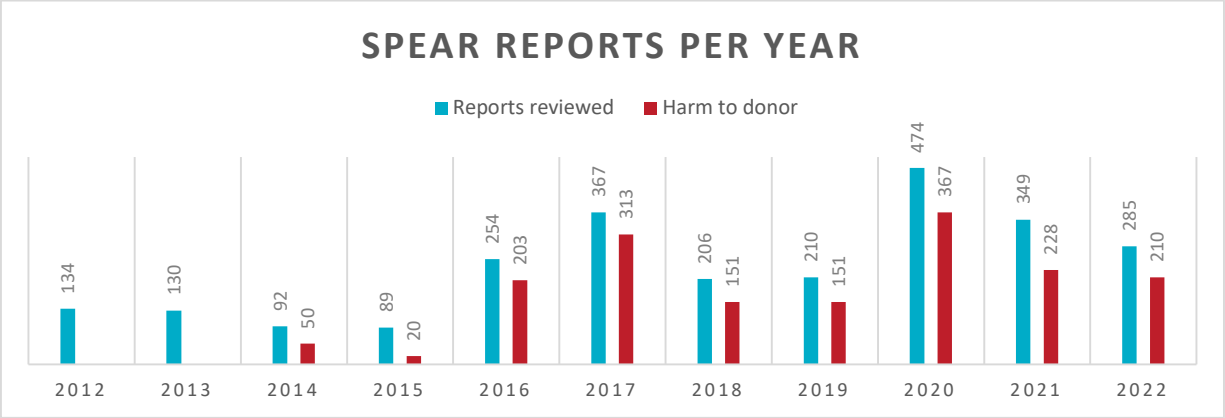
- **Harm to donor:** an adverse reaction in a donor during or after a donation procedure, including unnecessary procedures.
- **Harm to recipient:** an adverse reaction in a recipient during or after the infusion of a cell therapy product including any harm as a consequence of product quality issues, delay in delivery etc.
- **Risk of harm (an adverse event):** any problem or incident that could have had (but did not have) negative consequences for the donor or recipient or the system as a whole.

A committee of registry and cord blood bank experts assess the reports and evaluate imputability and impact. A rapid alert system is used for rapid dissemination of information to members of the international stem cell donor community in cases of critical importance. Annual reviews are prepared to share awareness of adverse events and reactions related to donation and this is the aim of this current report.

This report summarises the reports received in 2022 (shown in Table 1) and aims to give an overview of the type of events and reactions occurring in association with stem cell donation. Some cases that are interesting and educational are also discussed. Some cases appear in more than one category. For example, donors testing positive for SARS-CoV-2 are reported as harm to donor (Chapter 1) and as SARS-CoV-2-related SPEARs (Chapter 4).

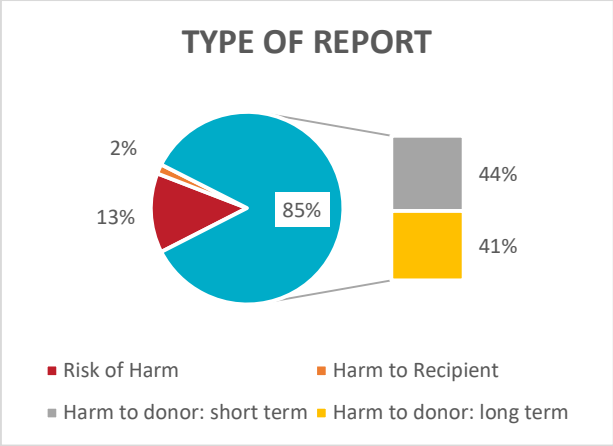
## 2022 KEY FACTS

- 285 SPEAR incident reports were reviewed by the committee in 2022.
- 282 reports were accepted, compared to 349 in 2021 and 474[1] in 2020.
- Reports were received from 35 different organisations, equal to 35 organisations in 2021.
- 35 reports were accepted but deemed not to fulfil the criteria for classification as SPEARs.[2]
- 11 reports (3,9%) concerned related donors, compared to 18 (5,2%) in 2021.
- No rapid alert notifications were sent in 2022.
- There were no reports of any deaths related to stem cell donation.




### *Historic overview of reports*

The graph above provides details on the number of reports reviewed (in blue) and the number of harm to donor reports per year (in red, when available) for the period 2012-2022. The percentage of harm to donor reports versus other reports has fluctuated between 23% and 85% of the total over the years, with an average of 71.8% of reports classified as 'harm to donor' in the last five years.



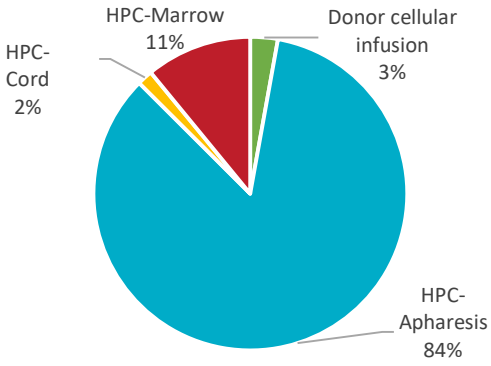

### *Distribution of report types*

In 2022, harm to donor reports accounted for 85% of reports, with an almost even division between cases of long-term harm and short-term harm (41 versus 44 percent). Risk of harm: 13% of reports, and 2% harm to recipient reports.

[1] In 2020, a notable increase in reports within the long-term donor harm category was recorded, resulting in a higher overall number of reports for the year. However, the involved reporting organisation declared to have submitted more reports due to backlog processing efforts.
[2] Details on reports classified as “Not a SPEAR” can be found in Chapter 4.

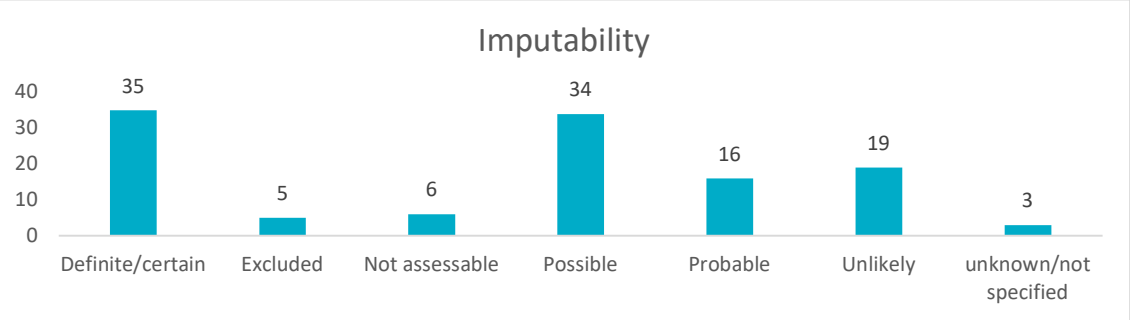
### *Type of products*

The annually published WMDA Global Trends report[7] indicates that in 2022, 79% of shipments (19,108 out of 24,217) comprised products collected through HPC-Apheresis. This figure aligns closely with the percentage of reports received on HPC-A, which stands at 84% (209 out of 247 reports). Reports involving bone marrow collection (HPC-Marrow) accounted for 11%, while donor cellular infusion and cord blood products made up 3% and 2% respectively.

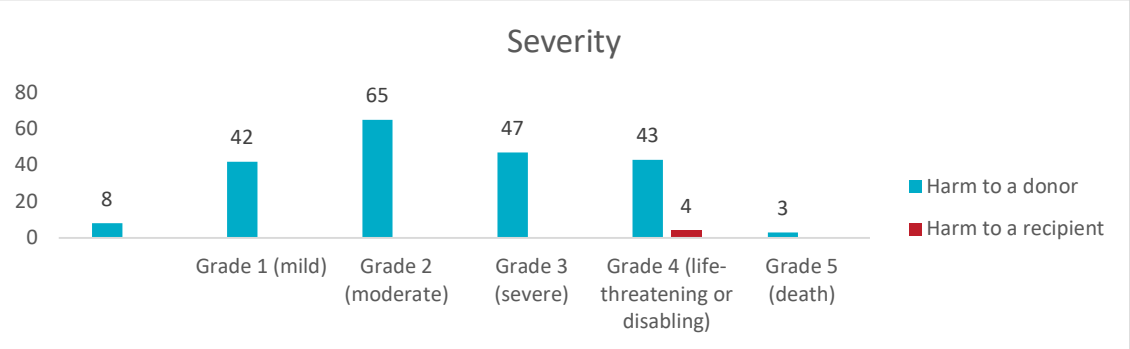



### *Imputability and severity of the reaction*

The reporting registry assesses the causation (imputability) for each harm to donor incident that occurs within 6 months and for harm to recipient reports. Imputability refers to the probability that an adverse reaction is linked to the donation or transplantation process. The graphs below demonstrate the distribution of the assessed imputability and the severity of the reaction.




Severity of the reaction is also requested for certain report types. The WMDA follows the Common Terminology Criteria for Adverse Events (CTCAE) guidance for severity assessment, where grading varies from grade 1 (mild) to 5 (death). Please note that the 3 cases of a grade 5 severity (death) occurred in donors 4, 5 and 8 years after donation, all due to a non-haematological malignancy.



| Table 1: *Overview Of 2022 SPEAR Reports* | HARM TO DONOR | HARM TO RECIPIENT | RISK OF HARM | TOTAL |
|---|---|---|---|---|
| **Total reported** | 210 | 4 | 33 | 247[3] |
| • Short term harm (=<6mths) | 109 | - | - | - |
| • Long term harm (>6mths) | 101 | - | - | - |
| **Donor complication occurred[4]** | | | | - |
| • During mobilisation | 28 | - | - | - |
| • During collection procedure | 18 | - | - | - |
| • =<30 days after collection | 8 | - | - | - |
| • >30 days after collection | 53 | - | - | - |
| **Phase incident occurred in[5]** | | | | |
| • Collection | 7 | 1 | 8 | 16 |
| • Distribution | 0 | 0 | 0 | 0 |
| • Donor aftercare | 8 | 0 | 0 | 8 |
| • Donor assessment | 1 | 0 | 1 | 2 |
| • Donor search and selection | 0 | 0 | 1 | 1 |
| • Mobilisation | 3 | 0 | 4 | 7 |
| • Processing | 1 | 1 | 3 | 5 |
| • Transplant | 0 | 0 | 1 | 1 |
| • Transport | 1 | 0 | 6 | 7 |
| • Other/unsure | 3 | 0 | 6 | 9 |
| • Unknown/not specified | 85 | 2 | 3 | 90 |
| **Type of (intended) product** | | | | |
| • Donor cellular infusion | 7 | 0 | 0 | 7 |
| • HPC-apheresis | 181 | 4 | 24 | 209 |
| • HPC-cord | 0 | 0 | 4 | 4 |
| • HPC-marrow | 22 | 0 | 5 | 27 |
| **Product cryopreserved** | | | | |
| • Yes | 2 | 2 | 19 | 23 |
| • No | 2 | 2 | 9 | 13 |
| • Unknown/not specified | 208 | 0 | 5 | 213 |
| **Donor details** | | | | |
| • Sex: male | 116 | 2 | 23 | 141 |
| • Sex: female | 94 | 2 | 8 | 104 |
| • Sex: not specified | 0 | 0 | 2 | 2 |
| • Average age [range] at donation | 33.8 [18-68] | - | 33.7 [22-57] | 34 18-68] |

[3] This number excludes reports that were rejected or classified as Not a SPEAR by the committee.
[4] Only for short term donor harm (<6 months after collection)
[5] Only appliable for short term donor harm (<6 months after collection), risk of harm and harm to recipient

# 1. HARM TO DONOR

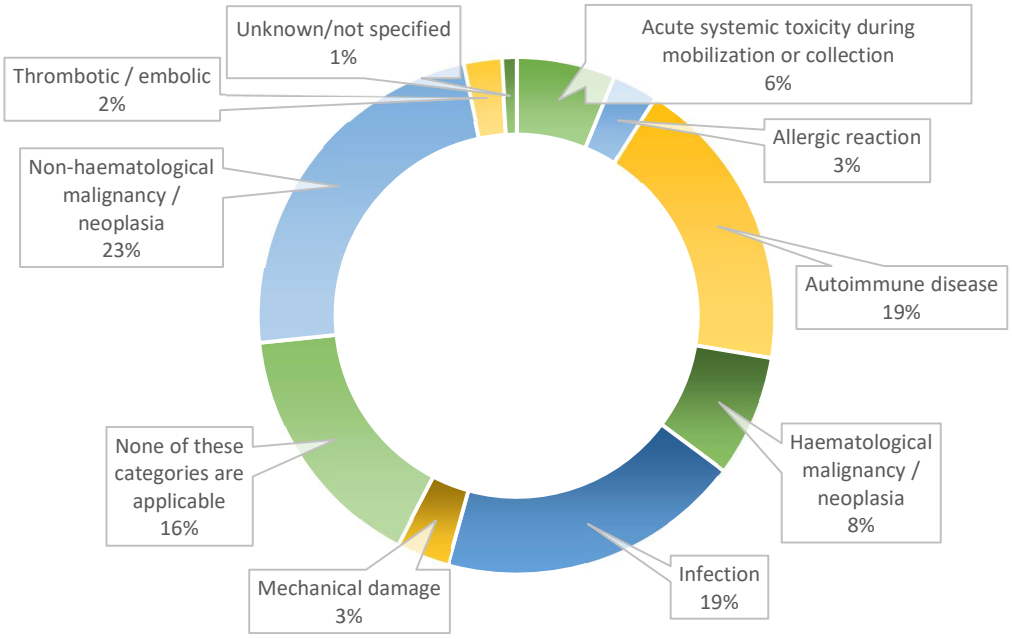
## 1.1 Description of Harm to Donor Reports

A total of 210 harm to donor (HtD) incidents were reported, comprising 181 HPC-A donations, 22 HPC-M, and 7 MNC-A donations. Of these, 109 incidents (52%) were categorised as short-term harm, occurring within six months after donation, and 101 incidents (48%) were classified as long-term harm, occurring more than six months after donation (see Table 2). Conditions developing more than 6 months after donation are thought highly unlikely to be related to donation and an assessment of imputability is not requested from the reporter or the SPEAR committee.

Table 2: *Timing Of And Type Of Donor In Harm To Donor Reports*

| | **TOTAL** |
|---|---|
| **HARM TO DONOR LESS THAN SIX MONTHS OR SIX MONTHS AFTER DONATION** | 109 |
| • Allogeneic related | 5 |
| • Allogeneic unrelated | 109 |
| **HARM TO DONOR MORE THAN SIX MONTHS AFTER DONATION** | 103 |
| • Allogeneic related | 6 |
| • Allogeneic unrelated | 101 |
| **TOTAL** | **210** |

Reporters are required to select a type of harm when submitting a harm to donor report, for both short-term harm and long-term harm. As shown in Graph 1 and Table 3, non-haematological malignancies/neoplasias (23%), autoimmune diseases (19%), and infection (19%) account for more than half of the reported cases. The percentages for non-haematological malignancies and autoimmune diseases are consistent with those of previous years, but there is a higher percentage of reports detailing infections due to SARS-CoV-2 infections. In fact, 73% of reports on infection in donors could be attributed to the COVID-19 pandemic.



| Table 3: *Type of Harm to Donor* | SHORT TERM HARM | LONG TERM HARM | TOTAL |
|---|---|---|---|
| Acute systemic toxicity during mobilization or collection | 13 | 0 | 13 |
| Allergic reaction | 6 | 0 | 6 |
| Autoimmune disease | 2 | 37 | 39 |
| Haematological malignancy / neoplasia | 1 | 15 | 16 |
| Infection | 40 | 0 | 40[1] |
| Mechanical damage | 7 | 0 | 7 |
| None of these categories are applicable: | 32 | 1 | 33 |
| - *Cardiovascular and cerebrovascular disease* | 2 | 0 | 2 |
| - *Musculoskeletal / joint affection* | 6 | 0 | 6 |
| - *Neurological disease* | 2 | 0 | 2 |
| - *Respiratory disorder* | 3 | 0 | 3 |
| - *Unnecessary donor burden* | 11 | 0 | 11 |
| - *Other*[2] | 8 | 1 | 9 |
| Non-haematological malignancy / neoplasia | 1 | 48 | 49 |
| Thrombotic / embolic | 5 | 0 | 5 |
| Unknown/not specified | 2 | 0 | 2 |
| **T0TAL** | **109** | **101** | **210** |

1 Of 40 reports where infection is the type of harm, 29 were considered "COVID-related".

2 'Other' included: duodenal ulcer disease with acute bleeding (1), intraperitoneal cyst (1), respiratory and cardiovascular symptoms (3), retinal vascular disease (1), other (3).

## Harm to donor: overview of malignancies

Table 4 offers detailed insights into malignancies, which primarily are reported as long-term harm to a donor; usually occurring years after donation. Both haematological malignancies and non-haematological malignancies, occurred in 97% of reports > 6 months after donation with an average time of 5,2 years after donation.

| Table 4: *Type Of Malignancies In Harm To Donor Reports* | ICD-10 (2016) CODE RANGE | N | MEAN TIME AFTER DONATION[1], MONTHS | MEAN AGE[2] AT DIAGNOSIS, YEARS |
|---|---|---|---|---|
| Genitourinary Malignancies | C61-C68 | 13 | 55 | 48 |
| Haematological malignancy | C81-C96 | 14 | 53 | 38.4 |
| Head & neck and oral cavity malignancies | C00-C14; C73-C75 | 3 | 83.5 | 49.3 |
| Malignant neoplasm of brain | C71-C71 | 4 | 55 | 39.1 |
| Malignant neoplasm of breast | C50-C50 | 14 | 60.6 | 48 |
| Malignant neoplasms of digestive organs | C15-C26 | 5 | 84 | 49.4 |
| Melanoma and other malignant neoplasms of skin | C43-C44 | 6 | 34 | 42 |
| Melanoma in situ | D03-D03 | 1 | 4 | NOT GIVEN[3] |
| Neoplasms of uncertain or unknown behaviour | D37-D48 | 1 | 73 | NOT GIVEN[3] |
| Non-epithelial malignancies | C45-C49; C51-C58; C30-C39 | 4 | 72 | 45.9 |
| **TOTAL** | | **65** | **62.4 [4-116]** | **45 [20-70]** |

1 Calculated as the average interval between reported (intended) date of collection and the date donor complication is detected.

2 Derived from donor age at (intended) donation and the calculated interval between the (intended) date of collection and detection of donor complication.

3. To protect the identity of the donor, (mean) age at diagnosis is not provided if only one case was reported.

## Harm to donor: haematological malignancies

Table 5 summarizes details of reports on haematological malignancies in donors post-donation, expanding on the details shown in Table 4. The mean time after donation for diagnosis varies, ranging from 4 months to 9 years after donation. By presenting age of the donor at diagnosis per age range, confidentiality is maintained while still providing essential information about the age distribution of donors diagnosed with haematological malignancies. This approach respects donor privacy and confidentiality while allowing for meaningful analysis of the data.

| Table 5: *haematological malignancies in harm to donor reports* | **ICD-10 (2016) CODE RANGE** | **N** | **TYPE OF PRODUCT** | **MEAN TIME AFTER DONATION[1], MONTHS [RANGE]** | **AGE RANGE[1,2] AT DIAGNOSIS** |
|---|---|---|---|---|---|
| Hodgkin lymphomas | C81-C81 | 2 | PBSC | 56.9 [4-110] | 2 |
| Follicular lymphoma | C82-C82 | 1 | PBSC | 102 | 5 |
| Non-follicular lymphomas | C83-C83 | 2 | PBSC | 62.4 [61-64] | 4 |
| Other and unspecified types of non-hodgkin lymphomas | C85-C85 | 2 | PBSC | 26 [23-29] | 2 |
| Multiple myelomas and malignant plasma cell neoplasms | C90-C90 | 2 | BM/PBSC | 82 [62-101] | 4 |
| Lymphoid leukaemias | C91-C91 | 2 | PBSC | 55 [24-85] | 3 |
| Myeloid leukemias | C92-C92 | 3 | PBSC | 26.3 [12-49] | 4 |
| **TOTAL** | | **14** | | **53 [4-110]** | **--** |

1 Calculated from reported age at donation and reported date donor complication is detected

2. Age ranges: 1: Children and teenagers (<21 years old); 2: Young adults (21-30 years old); 3: Adults (30-40 years old); 4: Middle-aged (40-50 years old); 5: Older middle-aged (50-60 years old); 6: Elderly (>60 years old)

## Harm to donor: autoimmune diseases

Autoimmune diseases accounted for 19% of reported harm to donors, totaling 39 reports. The time after donation varies from 3 to 109 months, with an average of 3.8 years post-donation observed. The (mean) age at diagnosis is not provided for cases with only 1 occurrence to protect donor privacy.

| Table 6: Type of A*utoimmune Diseases in Harm To Donor Reports* | **ICD-10 CODE RANGE** | **N** | **MEAN TIME AFTER DONATION[1], MONTHS** | **MEAN AGE AT DIAGNOSIS[2,3], YEARS** |
|---|---|---|---|---|
| Vitamin b 12 deficiency anaemia | D51-D51 | 1 | 89 | NOT GIVEN[3] |
| Sarcoidosis | D86-D86 | 2 | 72 [60-84] | 45.5 |
| Disorders of thyroid gland | E00-E07 | 4 | 38 [15-49] | 42.4 |
| Diabetes mellitus | E10-E14 | 2 | 62.1 [31-93] | 31.2 |
| Multiple sclerosis | G35-G35 | 3 | 65.9 [35-97] | 30.5 |
| Iridocyclitis | H20-H20 | 1 | 13 | NOT GIVEN[3] |
| Asthma | J45-J45 | 1 | 3 | NOT GIVEN[3] |
| Oesophagitis | K20-K20 | 3 | 27.6 [11-47] | 31 |
| Noninfective enteritis and colitis | K50-K52 | 5 | 42.9 [8-85] | 31.8 |
| Chronic hepatitis, not elsewhere classified | K73-K73 | 1 | 100 | NOT GIVEN[3] |
| Psoriasis | L40-L40 | 2 | 33.8 [19-49] | 31.3 |
| Alopecia areata | L63-L63 | 2 | 11.4 [4-19] | 39.9 |
| Inflammatory polyarthropathies | M05-M14 | 4 | 43 [10-61] | 38.3 |
| Other systemic involvement of connective tissue | M35-M35 | 1 | 97 | NOT GIVEN[3] |
| Spondylopathies | M45-M49 | 7 | 38.2 [1-109] | 37.3 |
| **TOTAL** | | **39** | **45 [1-109]** | **35.2 [19.7-62.1]** |

1 Calculated as the average interval between reported (intended) date of collection and the date donor complication is detected.

2 Derived from donor age at (intended) donation and the calculated interval between the (intended) date of collection and detection of donor complication.

3. To protect the identity of the donor, (mean) age at diagnosis is not provided if only one case was reported.

## 1.2 Harm to Donor Less Than 6 Months After Donation – Interesting Cases

Cases occurring shortly after donation warrant closer examination, as the connection to stem cell donation may be more evident. Interesting cases of short-term donor harm are described below.

**Unnecessary donor burden (11 cases)**: Donor-related SPEARS were classified as “unnecessary donor burden” when the donor gave a product that remained unused and when this situation may have been prevented. In 2022, 11 cases were classified as "unnecessary donor burden", involving unused products and preventable situations. Nearly half of these cases were related to the patient's condition, including deterioration, relapse, or death, often due to communication errors or SARS-CoV-2.

- Almost half of the cases were related to the patient's condition: deterioration of the patient's condition, relapse, death.
- Several cases were caused by communication errors, others, related to SARS-CoV-2.
- Three cases related to a failure to cancel donations. For example, one donor was known to be a back-up donor, but their clearance was accepted by the transplant centre (TC) and their donation was not cancelled when the primary donor collected successfully. The SPEAR Committee has highlighted the issue of unnecessary collections in Stem Cell Matters and elsewhere,[1,2] strongly recommending improvements to the patient qualification system (including timing thereof) and minimizing communication errors to avoid unnecessary donations, which potentially carry the risk of adverse events in donors.

**SARS-CoV-2-Related reports (34 cases):** Of the 109 reports of HtD less than 6 months after donation, 34 were listed as SARS-CoV-2-related. Some of these cases resulted in aborted mobilisation. There were no reports of donors becoming severely unwell with COVID-19 or of transmission of infection to recipients. More details on SARS-CoV-2-related cases can be found in Chapter 4.

**HPC-M donations (5 cases):** the most frequent reports of harm to HPC-M donors were of back pain post-procedure, with three out of five cases starting within a day of donation. 3 donors had MRI scans which were helpful in management. No cases of osteomyelitis were reported, and no preventable causes were identified.

**Reactions of Grade 4 Severity (5 cases):** Among the 43 reports classified as life-threatening or disabling, five were flagged as special interest cases. The relationship of one case to the donation was deemed not assessable, involving an HPC-A donor who experienced a seizure the night after their donation. Three other cases involved young (<40) male donors without obvious risk factors and presented infarctions and thrombosis in various organs/locations in donors. All three donors have successfully recovered. An additional case, unlikely related to HPC-A donation, involved the development of Hodgkin's disease four months after donation.

**Continuation of mobilisation in donor with serious infections (2 cases):** two reports were received of donors who were continued on G-CSF despite severe and potentially fatal infections requiring hospitalisation and intravenous antibiotics. The SPEAR Committee considers continuing G-CSF in a donor with a serious infection poses a significant risk to the donor’s health and should not be done. There is also risk to the recipient by possible contamination of the stem cell product. Mobilisation should be stopped, and donation considered only after full recovery of the donor.

**Haemoptysis in HPC-A Donors (2 cases):**

Two reports of haemoptysis were received, both in HPC-A donors. Both were smokers, one was young. Haemoptysis developed during the donation procedure. In both cases the diagnosis was 'smoking-related lung disease.' It is conceivable that G-CSF could exacerbate pre-existing airway inflammation to precipitate haemoptysis. Thorough investigation to exclude other causes is obviously important**.**

# 2. HARM TO RECIPIENT

A total of 4 reports were accepted that identified recipient harm. Three of these 4 reports were from the same reporting registry, suggesting a strong potential for underreporting.

## 2.1 Harm to Recipient – Interesting Cases

Two cases of donor-derived malignancy in transplant recipients were reported. In one case of a patient with ALL, donor-derived AML was reported several years post-transplant. 100% donor chimerism was noted. The donor registry was notified but it is not clear if the donor was contacted or informed or whether any donor-specific testing or assessment occurred. In the second case, donor-derived multiple myeloma was reported some years post-transplant. Also in this case, the donor registry was notified, and it was reported that the registry determined that donor notification and assessment was not warranted. Specifics about patient treatment and outcome are not known. WMDA medical committee are publishing guidance for registries on handling of genetic abnormalities that are possibly donor derived.

There was one case of poor viability of a product post-cryopreservation with CD45 and CD34 viabilities of 24% and 5%, respectively. The patient experienced failed engraftment and a second donation of HPC-A was refused by the donor registry, offering instead HPC-M that was declined by the donor. A second 9/10 HLA-mismatched donor was secured for donation and was successfully transplanted with engraftment and full donor chimerism reported by the registry. The delay was deemed to have harmed the recipient.

Transplant centres and registries are encouraged to report recipient-related harms that are attributed to donor-related issues. Identifying a greater proportion of cases that may be occurring will enhance the ability to identify trends and introduce measures to limit the impact of donor-related harms on transplant recipients.

# 3. RISK OF HARM

A total of 33 risk of harm reports were identified, with 6 marked as SARS-CoV-2-related. As Table 7 illustrates, incidents occurred across various phases and predominantly during collection (n=8) and transport (n=6). The breakdown of events showed 24 during or after HPC-A, 5 following HPC-M donation, and 4 after HPC-CB. Outcomes varied: 11 transplants were executed as planned, 12 were not performed, 4 were delayed, and 4 utilized a different product. For 2 cases, outcomes remained unknown.

**Cancelled transplants:** among the 12 cancelled transplants, 5 events were related to transport problems, including 3 cryopreserved products arriving thawed at TC and 2 fresh products transported at extreme temperatures. Problems during cell processing and cryopreservation resulting in low cell dose and/or low cell viability caused the loss of 3 other products and in two cases there was partial loss of collected HSC products (one broken bag). These events suggest the need for improvements in cell processing and transport processes to assure the quality of HSC donation.

**Pre-collection events:** the pre-collection events included 3 aborted collections due to donors testing positive for SARS-CoV-2. Two mobilization failure events were associated with incorrect Filgrastim reconstitution and administration by donors emphasizing the importance of donor education.

Table 7: *Phase of Procedure When Risk of Harm Event Occurred*

| | **NUMBER OF REPORTS** |
|---|---|
| Collection | 8 |
| Donor assessment (health screening) | 1 |
| Donor search and selection | 1 |
| Mobilisation | 4 |
| Other | 6 |
| Processing | 3 |
| Transplant | 1 |
| Transport | 6 |
| Unknown/not specified | 3 |
| **TOTAL:** | **33** |

## 3.1 Risk of Harm – Interesting Cases

**Near-miss case of donor with HIV seroconversion:** a case which could have led to HIV transmission was reported. A donor who tested negative for HIV by nucleic acid testing and serology at their medical was found to be HIV-positive by both methodologies on the day of donation. The TC had requested their own sample for infectious disease marker (IDM) testing on collection day. Luckily, the donation had been cryopreserved and the result was received before the patient started conditioning.

Although the exact mode or timing of infection of the donor was not pinpointed the donor declared some high-risk behaviours between their medical and the day of donation. Additionally, the donor stopped the use of PrEP before contacting and without informing the registry. It is against the registry guidelines to stop PrEP use to proceed with any donation. Following this case, the registry has implemented various corrective actions and measures to prevent similar cases in the future, like the adaption of the Health History Questionnaire (HHQ) conducted at the pre-donation medical examination and the guidelines on additional HBV/HCV/HIV PCR testing for donors who are considered to be at higher risk based on their HHQ.

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### This case was highlighted in Stem Cell Matters e-mail communication in February 2023 with recommendations as follows: [3]

- Donors should be asked at the medical specifically about any high-risk behaviour in the window period of transfusion-transmissible infections such that repeat IDM testing can be arranged before clearance if necessary.
- Donors should be reminded to avoid behaviours or exposures that pose a high risk of transmissible infections from the time of their selection as final donors until after donation.
- They should be informed of the rationale and importance of this when selected as a final donor and again at their counselling and medical assessment.
- They should be asked to inform the donor registry immediately if they are exposed to any risk in this period.
- The registry can consider whether extra testing is needed or a deferral period.

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Individual registries may consider whether they wish to undertake day of donation infectious disease marker testing. This is not a mandatory test in most jurisdictions and, in the standard transplant scenario of fresh issue of cells, a result would usually only be available after the infusion of stem cells and the infusion of a marker-positive product could not be avoided. Registries that do undertake day of donation testing should ensure transplant centres are aware of this practice.

**Errors of labelling of recipient identifiers:** a case was reported of difficulty in confirming recipient identification as the recipient had a multi-part name. The name was in the format [C, A B] at the TC but was documented as [B C, A] on the product label. Multi-part names are common in certain areas of the world and care should be taken to clarify the correct identifier. The use of names as identifiers is generally discouraged.

**Low CD34 cell viability and discrepant reports post-cryopreservation:** An HPC-A collection with a CD34 viability of over 99% pre-cryopreservation went unused because viabilities on two cryovials were around 50% pre-transplant, on a segment attached to the bag 30% and less than 20% on a sample of the bag post-thaw. A haploidentical donor was used for the transplant instead. Subsequent testing of a third cryovial gave a better reading of 64% CD34 viability. This report highlights the lack of reproducibility in results obtained from different types of samples analysed (bags, cryovials and segments) and between different laboratories involved (collection centre and transplant centre laboratories).

Failure of vials and segments to represent the content of the graft to be infused has been recognised for cryopreserved cord blood units.[4] The authors of the article recommended the use of pre-cryopreservation data and this could be relevant for cryopreserved PBSCs, especially where processing has been undertaken in laboratories with appropriate certification by governmental authorities of the country or by FACT JACIE accreditation which will ensure the quality of processes for processing, storage and transport of cryopreserved products.

Another possible contributory factor to discrepant viability results between laboratories is the lack of harmonization in the technique of thawing the sample and flow cytometry analysis. An exercise carried out by several cord blood banks made it possible to identify the factors that could contribute to obtaining much better harmonized results for the number and viability of post-thawing CD34 cells.[5] A similar effort is currently ongoing for the harmonisation of the analysis of HPC-A and HPC-M.

# 4. OTHER CATEGORIES

*This chapter delves into the intricacies of SPEARs, examining them through distinct lenses, namely: related donors, SARS-CoV-2-related reports, cord blood unit reports, and reports that were excluded or marked as "Not a SPEAR". Unlike preceding chapters, the content herein transcends the regular classifications of harm to donor, harm to recipient, or risk of harm.*

## 4.1 Related Donors

Eleven (11) reports of harm to related donors were received, six involving solid organ malignancies emerging 1 – 8 years after HPC-A or MNC donation. These donors were older than most unrelated donors, ranging from age 49 to 68 at the time of their donations. Additionally,5 cases of short-term harm were reported. Two cases were symptomatic donors who tested positive for SARS-CoV-2, on the first and respectively second day of HPC-A. Collection was completed in both cases and the cells were used without any reported adverse effect on the first recipient. For the second case, cells were cryopreserved, and no further information is available. One donor developed a post-traumatic radiculopathy due to the bone marrow donation with symptoms fluctuating and lasting at least a few months.

Table 8: *Number Of Related Donor Reports Per Organisation*

| | Short term harm | Long term harm | Total |
|---|---|---|---|
| Organisation A | 2 | 6 | 8 |
| Organisation B | 2 | 0 | 2 |
| Organisation C | 1 | 0 | 1 |
| **TOTAL** | **5** | **6** | **11** |

Although the reporting system is designed to accommodate and encourage future reporting on related donor outcomes, only three organisations (Table 8) have reported related donor harm. WMDA encourages reporting on all donors, related and unrelated to the recipient, and hopes to see more reports on related donors for an enhanced understanding of potential risks and safety measures.

## 4.2 SARS-CoV-2-related SPEARs

At the time of the data analysis, forty-one (41) reports were classified as SARS-CoV-2-related reports in 2022, details on report type and severity grade can be found in Table 9.

Prior to July 2022, SPEARs were recommended to be reported for any cases in which SARS-CoV-2 impacted donation, from the start of donor's mobilization for HSC donation until infusion of the product in recipient, in addition registries were asked to report donors who contracted SARS-CoV-2 infections up to 30 days after donation. As of July 2022, recommendations were changed asking registries to report any infection from start of donation (first day of G-CSF or admission for bone marrow harvest) until 7 days after collection.

Table 9*: Type Of Report And Severity Grade For SARS-CoV2-Related Reports*

| | Not provided | Grade 1 (mild) | Grade 2 (moderate) | Grade 3 (severe) | Grade 4 (life-threatening or disabling) | Total |
|---|---|---|---|---|---|---|
| **HARM TO A DONOR** | | **20** | **14** | | | **34** |
| **HARM TO A RECIPIENT** | | | | | **1** | **1** |
| *HPC - apheresis* | | | | | 1 | 1 |
| **RISK OF HARM** | **4** | **1** | | **1** | | **6** |
| *HPC - apheresis* | 2 | 1 | | 1 | | 4 |
| *HPC - marrow* | 2 | | | | | 2 |
| **TOTAL** | **4** | **21** | **14** | **1** | **1** | **41** |

The uniqueness of the SARS-CoV-2 pandemic impact on transplant made consistent and accurate categorization of SARS-CoV-2-related incidents difficult, both Harm to Donor and Risk of Harm being appropriate. WMDA conducted a focused review of 74 cases reported as SARS-CoV-2-related adverse events in 2020, revealing that, despite the pandemic, nearly all patients received cells successfully[2]. It also showed that mobilization did not appear to cause more severe illness in donors that tested positive in the peri-donation period, nor was there evidence of transmissibility of SARS-CoV-2 by transfusion of stem cells. However, an increase in unused products during the pandemic was noted, emphasizing the importance of registries implementing mitigation strategies. Also of note, of the 13 donors in the analysis who tested positive for SARS-CoV-2 during mobilization or at the time of donation, none had a severe illness, nor did any of the 6 donors who tested positive in the 30 days after donation.[2] These findings are similar to the 2023 cases outlined in Table 9, which details the severity across report types. Notably, only two cases of grade 3 or higher were reported.

The recommendations made in the publication of the analysis of SARS-CoV-2-related adverse events in 2020, remain applicable today: registries should recognize and address the increased risks faced by altruistic donors during pandemic lockdowns, including exposure to clinical settings, air travel, and lodging[2].

## 4.3 SPEAR Reports Related To Cord Blood

Five events associated with cord blood have been reported. They all posed a risk of harm to a recipient.

Two reports were associated with documentary errors: one a discrepancy in the anti-CMV result appearing on product reports sent to the transplant centre and the other, incorrect reporting of the sex of the cord blood donor revealed at post-transplant chimerism testing of the recipient. The segregation of a product and its accompanying documentation as well as processing of only one product at a time are effective ways to reduce the risk of similar errors.

The other three events related to the transport of cryopreserved cord blood units with problems with dry shippers resulting in one product arriving thawed. As a reminder, according to FACT standards, the cord blood bank is responsible for having validated procedures for transportation and shipping of cryopreserved CB units. This includes the presence of a temperature monitor configured to adequately record data covering the entire duration of transport.

## 4.4 Reports Not Included – Not A SPEAR

Reports are *accepted* and reviewed by the Committee as long as they contain relevant information and are not duplicate entries. In 2022, three (3) reports were rejected prior to Committee review. All three of these rejected reports were withdrawn by the reporters due to being entered in error or a draft report that was submitted inadvertently. Thirty-five (35) reports were accepted, but after committee review were categorized as NOT A SPEAR , since they did not fulfil the defined criteria for a SPEAR incident (see Table 10).

Some reasons why a report might be categorized as NOT A SPEAR are:

- the event or adverse effect is a known and non-critical complication of donation (e.g., nausea related to GCSF, drop in haemoglobin level after bone marrow harvest)
- a not clinically relevant and previously known genetic findings in recipient believed to be of potential donor origin
- the incident occurred prior to donor mobilisation and patient conditioning and did not impact the transplant timeline or outcome.
- the incident occurred more than 10 years after donation.
- the event was “expected” or non-critical (e.g., ABO incompatibility, minimal product clumping, poor mobilization)
- the incident could not have been prevented or acted upon in a timelier manner and did not jeopardize the availability or safety of the product.

These reports are included in the submission statistics but excluded from data analysis.

Table 10: *Reports Classified As "Not A SPEAR"*

| | **TOTAL** |
|---|---|
| **HARM TO DONOR: SHORT TERM HARM** | **14** |
| ["Covid-related", "not a sear"] | 8 |
| ["Not a sear"] | 6 |
| **HARM TO DONOR: LONG TERM HARM** | **6** |
| ["Not a sear"; "possible change of standards or recommendation"] | 1 |
| ["Not a sear"] | 5 |
| **HARM TO DONOR: TIME SINCE DONATION NOT INDICATED[2]** | **3** |
| ["Covid-related", "not a sear"] | 2 |
| ["Not a sear"] | 1 |
| **HARM TO A RECIPIENT** | **2** |
| ["Not a sear"] | 2 |
| **RISK OF HARM** | **10** |
| ["Educational", "not a sear"][3] | 1 |
| ["Not a sear"] | 9 |
| **TOTAL** | **35** |

# 5. INDICATIONS OF PARTICIPATION/BENCHMARKING

This section aims to give reporters an indicator of the number of occurrences that would be expected to be reportable as SPEARs according to the activity level within their organisation. The calculation is based on the number of reports of donor harm from the start of procedure until 6 months after donation received over the last 3 years. This is divided by the number of HPC shipments over the same period by registries that are actively submitting SPEAR reports into the WMDA reporting tool (defined as registries who submit at least one report per year).

Between 2020 and 2022, 397 reports have been received from such registries with a total of 38,068 shipments. This equates to an expected level of reports of approximately 1 report per 100 shipments (calculations based on reports of short-term harm to donor reports and shipment data of the WMDA Global Trends Report (GTR))[7].

## Expected count of reports <6 months per shipments: 1 report per 100 shipments

*If including reports on late Donor Harm, Risk of Harm, and Harm to Recipient, a ratio of 1 – 2 reports per 100 adult collections is expected.*

## Of note:

- Reports not categorized as SPEARs are included in calculations.
- Late harm to donor reports were excluded due to jurisdictional, resource, and temporal constraints. Newer registries, with fewer long-term follow-ups, further limit their inclusion. Early events are more likely causally connected, informative, and prompt Rapid Alerts.
- Risk of harm and harm to recipient reports were omitted due to unclear responsibilities and the lack of correspondence with registry size.
- CB units were excluded as there is no documented donor harm associated.

**Also of note,** 56% of global shipments of HPCs in 2022 were made by registries who submitted any type of SPEAR reports.

Reporters of Harm to Donor < 6 months accounted for only 48% of all HPC-A and HPC-M shipments in 2022, compared to 67% in 2021. This is caused by a small group of larger registries with a strong domestic focus responsible for 30% of total shipments that did not submit any reports in 2022, not a general trend towards less participation.

Registries are reminded that SPEAR reporting is mandatory for WMDA certification (section 8.09, WMDA Standards).[6]

# 6. CLOSING REMARKS

We hope that the above report gives insight into the type of serious events and adverse effects associated with stem cell donation. Unfortunately, the data captured does not allow calculation of the prevalence of adverse events and reactions with stem cell donation.

Although reporting of SPEARs is a requirement of donor registries and cord blood banks seeking WMDA certification, it is not mandatory for others. This leads to the cases received are not a full representation of adverse events occurring worldwide.

In 2022, there were 24,217 shipments of donor products in, with 56% of these involving WMDA-accredited registries. Of the 13,561 shipments from registries expected to report adverse events, only 285 reports were received, providing a measure of reassurance regarding the safety of stem cell donation. There were also no reports of donor fatalities, suggesting that the reported events are likely skewed toward the more serious cases.

Despite these reassurances, the data highlighted several important considerations:

1. **Unnecessary Donor Burden**: the issue of "unnecessary donor burden" was highlighted, emphasizing the importance of improvements to the patient qualification system (including timing thereof), and minimizing communication errors to avoid unnecessary donations, which potentially carry the risk of adverse events in donors.

2. **G-CSF in Donors with serious infections**: the SPEAR Committee considers continuing G-CSF in a donor with a serious infection poses a significant risk to the donor's health and should not be done. Mobilisation should be stopped, and donation considered only after full recovery of the donor.

3. **Recipient-Related Harm**: 85% of the reports were categorized as harm to the donor. Transplant centres and registries are encouraged to report recipient-related harms that are attributed to donor-related issues. Identifying a greater proportion of cases that may be occurring will enhance the ability to identify trends and introduce measures to limit the impact of donor-related harms on transplant recipients.

4. **Donor Safety:** specific recommendations regarding information to the donor on high-risk behaviours, infectious exposures, and reporting were provided. Registries may consider day-of-donation infectious disease marker testing, with awareness and coordination with transplant centres.

5. **Expected Reporting Ratios:** Registries are reminded of the expected reporting ratios of 1-2 report per 100 shipments and that SPEAR reporting is mandatory for WMDA certification.

In conclusion, our findings highlight the need for continued vigilance, communication, and adherence to reporting standards to ensure the ongoing safety and success of stem cell donation practices worldwide. While participation in SPEAR reporting cannot replace or remove the need for organisations to comply with legal reporting requirements of their national/competent authorities or other regulatory bodies, existence of a worldwide database is an important framework for evaluation of locally reported rare incidents. We hope this report can be shared across these communities to inform and increase awareness of donor issues.

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