S(P)EAR

ANNUAL REPORT

2020

WMDA
matching donors • serving patients

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INTRODUCTION

In this 2020 S(P)EAR annual report, the World Marrow Donor Association (WMDA) presents an overview of all Serious (Product) Events and Adverse Reactions – S(P)EARs – in relation to blood stem cell donation by unrelated donors, blood stem cell collection/processing from unrelated donors, or in relation to other cellular donation from such a donor to the original recipient that have been reported in 2020.

Every year, close to 30 000 volunteer donors are asked to donate blood stem cells to a patient they do not know. To ensure the continued viability of the global system using volunteer donors, donor health and safety are of critical importance. The WMDA collects and analyses information on S(P)EARs that affect donors and/or products from all WMDA stem cell donor registries and cord blood banks. By doing so, the WMDA aims to gain insight in the occurrence of serious events and adverse effects in relation to blood stem cell donation by unrelated donors and blood stem cell collection/processing from unrelated donors. Reporting for related donors is highly encouraged as well, and the reporting tool fully supports this already.

In July 2019, the WMDA introduced a new online central global reporting system for WMDA member organisations to report Serious (Product) Events and Adverse Reactions. With this system, WMDA can systematically collect and analyse information on recipient and donor S(P)EARs. In 2020, a total of **474** S(P)EAR reports were accepted by the Committee.

A rapid alert system is used for rapid dissemination of information to members of the international community regarding critical cases. Two rapid alerts were sent out in 2020, both in reaction to concerning reports of products that will not be transfused due to processual issues with cryopreservation and the de-coupling of conditioning and donation procedure. In May 2020, the first rapid alert was addressing adequate communication, transportation, validated cell count tests, and feasibility of requested product specifications for cryopreservation. The second rapid alert was sent in July following a number of reports on recipients not sufficiently assessed at time of donation, including being not fully typed or no longer a fit candidate for transplantation. Both alerts encourage registries and donor centres to ensure all information is provided by the transplant centre before the donor starts the donation procedure.

2020 Key facts

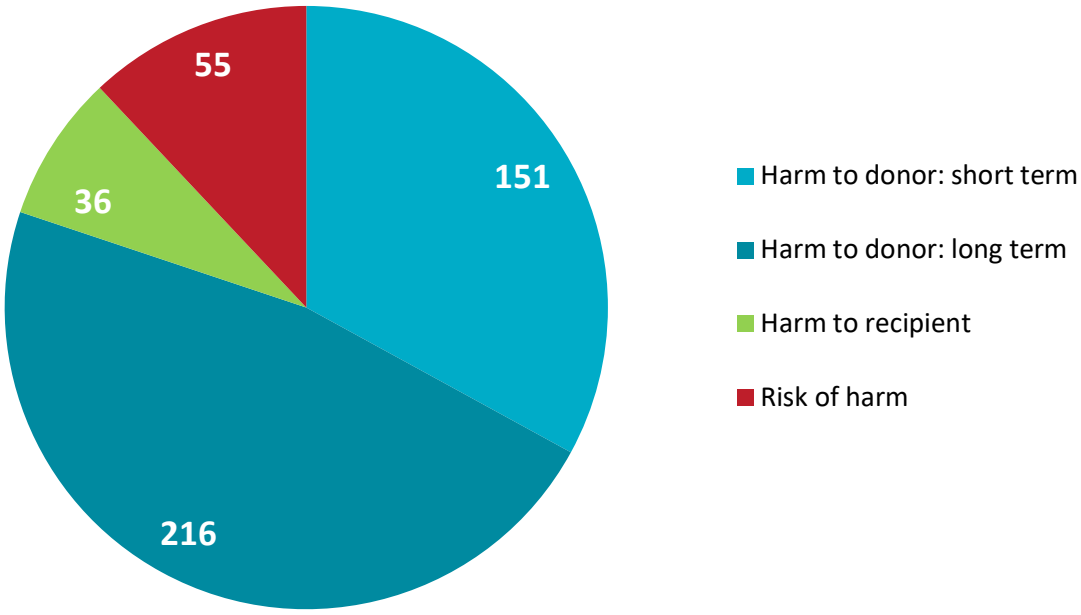
- The committee accepted **474** S(P)EAR incident reports in 2020, compared to 210 in 2019.
- The reports were received from **32** different organisations, compared to 27 reporters in 2019.
- 54 reports were classified as COVID-related.
- The online central S(P)EAR reporting system and data structure now allows for deeper analysis including benchmarking reporting behaviour.
- Two rapid alert notifications were sent in 2020 to all members of the international community.

1. OVERVIEW

	HARM TO DONOR	HARM TO RECIPIENT	RISK OF HARM	TOTAL
TOTAL REPORTED	367	36	55	458[1]
- Short term harm (=<6 months)	151			151
- Long term harm (>6 months)	216			216
PHASE INCIDENT OCCURRED IN[2]				
- Mobilisation	28 / 4[3]	1	5	38
- Collection	19 / 6		14	39
- Distribution	-	1	1	2
- Processing	- / 4	6	6	16
- Transport	-	3	10	13
- Transplant	-		5	5
- =<30 days after collection	71			71
- >30 days after collection	35			35
- Donor aftercare	- / 9		2	11
- Donor assessment	- / 1	1	4	6
- Donor search and selection	- / 2	1		3
- Other/unsure	- / 5	2	8	15
- Unknown/not specified	(214[2])			(214[2])
TYPE OF (INTENDED) PRODUCT				
- HPC-apheresis	296	29	40	365
- HPC-marrow	68	7	10	85
- MNC-apheresis	3		2	5
- HPC-cord			3	3
PRODUCT CRYOPRESERVED				
- Yes		22	30	52
- No	2	8	17	27
- Unknown/not specified	365	6	8	379
DONOR DETAILS				
- Sex: male	214	2	32	248
- Sex: female	153	2	20	175
- Sex: not specified	-	32	3	35
- Average age [range] at donation	33.8 [18-67]	23.8 [19-30]	31.4 [1-80]	33.4 [1-80][4]

[1] 15 reports were *accepted*, but categorized as NOT A SEAR by the Committee, and are excluded from further analysis. The same applies to one duplicate report (see Chapter 5 for details)
[2] Only needed to specify for harm to a donor incidents =<6 months after donation
[3] Second figure describes contributing incident / Risk of harm
[4] 2 CB units and 12 related donors included

1.1 Chart: Type of report



2. HARM TO DONOR

A total of 367 harm to donor incidents were reported. Short term harm (less than or equal to six months after donation) was reported in 41.3% of the cases (n=151) and in 58.7% (n=216) of the reports harm to donor occurred more than six months after donation, which we classify as long term harm. This is a remarkable difference to 2019, when 56.6% of reports related to short term harm. In 295 harm to donor reports, the type of (intended) product was HPC-Apheresis (80.6%), 69 were HPC-marrow (18.9%), and 3 reports of MNC (intended) products (0.8%).

2.1 Type of harm to donor

	N
Acute systemic toxicity during mobilization or collection	**7**
Allergic reaction	**9**
Autoimmune disease	**113**
- Long term	85
- Short term	28
Haematological malignancy / neoplasia	**15**
- Long term	15
- Short term	-
Infection	**25**
Mechanical damage	**7**
Non-haematological malignancy / neoplasia	**102**
- Long term	99
- Short term	3
Thrombotic / embolic	**10**
Cardiovascular and cerebrovascular disease	**8**
Psychiatric / psychogenic disorder	**4**
Musculoskeletal / joint affection	**3**
Neurological disease	**11**
Unnecessary donor burden	**21**
Other[1]	**25**
TOTAL	**367**

[1] Other: e.g. COVID, lasting pain, anaemia

2.1.1 Malignancies

	N	TIME AFTER DONATION, YEARS [MEDIAN]	AGE[1] AT DIAGNOSIS, YEARS [MEDIAN]
Haematological malignancy	**15**	**4.5**	**42.8**
Breast cancer	17	3.5	44
Testicular cancer	15	2.5	33
Melanoma	10	5	39
Prostate cancer	10	5.5	55.5
Colorectal cancer	8	5.5	37
Thyroid cancer	7	4	47
Lung cancer	5	5	52
Cervix, uterus and ovarian cancer	5	6.5	53
Renal cancer	5	2	47
Oral cavity and oesophageal cancer	4	7.5	49
Intracranial neoplasia	4	5.5	36.5
Bile duct and pancreatic cancer	3	3	54.75
Connective tissue (liposarcoma)	3	7	36
Other[2]	6	3	51.5
TOTAL	**117**		

[1] Calculated from age at donation and reported interval to diagnosis

[2] Other: 2x non-melanoma skin cancer, 2x ocular cancer, 1x laryngeal cancer, 1x unspecified

2.1.2 Haematological malignancy / neoplasia

	TYPE OF PRODUCT	**TIME AFTER DONATION, YEARS** (UNLESS STATED)	**AGE[1] AT DIAGNOSIS, YEARS**
Lymphoma, NOS (cervical and mandibular lymphadenopathy)	PBSC	10 months	42
B-CLL	BM	1	37
Diffuse large B-cell lymphoma	PBSC	1	39
Essential thrombocythemia	PBSC	2	38
Myeloproliferative Disease	PBSC	4	67
Hodgkin lymphoma	PBSC	4	62
Acute lymphatic leukaemia (ALL)	PBSC	4	24
CD30+ Lymphoma	PBSC	5	48
Indolent systemic mastocytosis	BM	5	36
Mycosis fungoides	BM	6	41
Gastric MALT lymphoma	PBSC	7	59
Chronic myeloid leukaemia (CML)	PBSC	7	36
Hodgkin lymphoma	PBSC	8	56
Non-Hodgkin lymphoma	PBSC	8	53
Diffuse large B-cell lymphoma	PBSC	9	47
TOTAL	15		

[1] Calculated from age at donation and reported interval to diagnosis

2.1.3 Autoimmune disorders

	N	TIME AFTER DONATION, YEARS [MEDIAN]	AGE[1] AT DIAGNOSIS, YEARS [MEDIAN]
IBD	21	2	27
Multiple sclerosis &transverse myelitis	15	4	33
Rheumatoid arthritis	12	2	47.5
Hypo- and hyperthyroidism	10	2	29.5
Connective tissue disease, granulomatosis, Raynauds	10	3.5	27.5
Ankylosing spondylitis	7	1	30.4
Sarcoidosis	5	1	33
Atopic dermatitis	5	7 days	27
Psoriasis	5	1 month	24.1
Purpura	3	1	27.3
Iritis, uveitis	3	1	25
Alopecia areata, vitiligo	3	7 days	23
Glomerulonephritis	3	28 days	36
Other[2]	10	-	-
TOTAL	**112**		

[1] Calculated from age at donation and reported interval to diagnosis

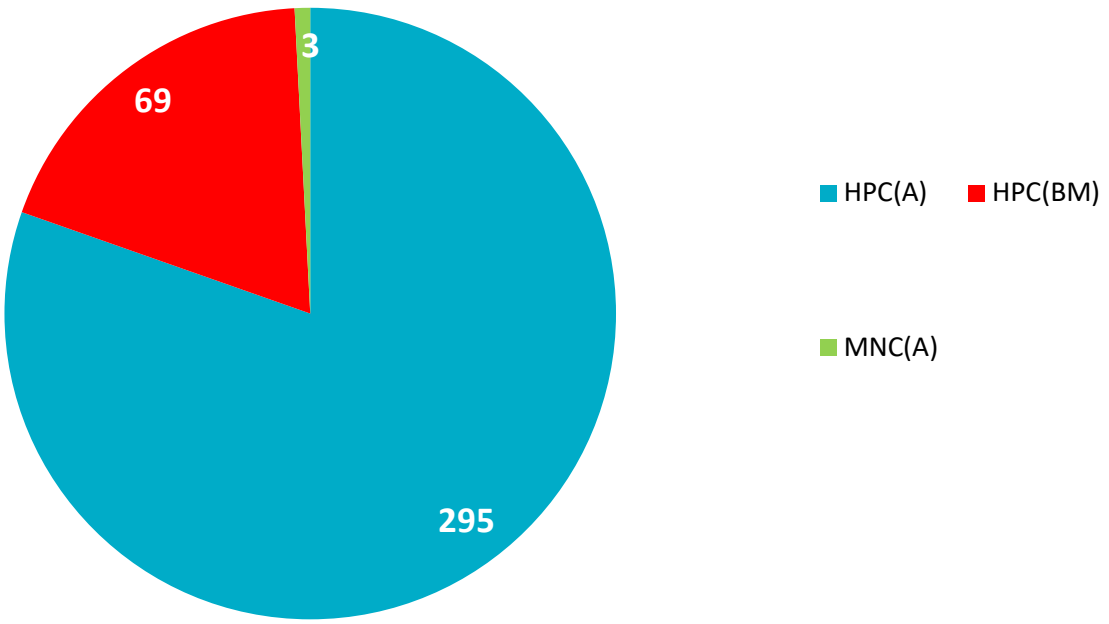
[2] Other: diabetes, lichen planus, eosinophile oesophagitis, autoimmune hepatitis, Pemphigus vulgaris, Erythema nodosum, suspected SLE, autoimmune pancreatitis

2.2 Assessment of imputability

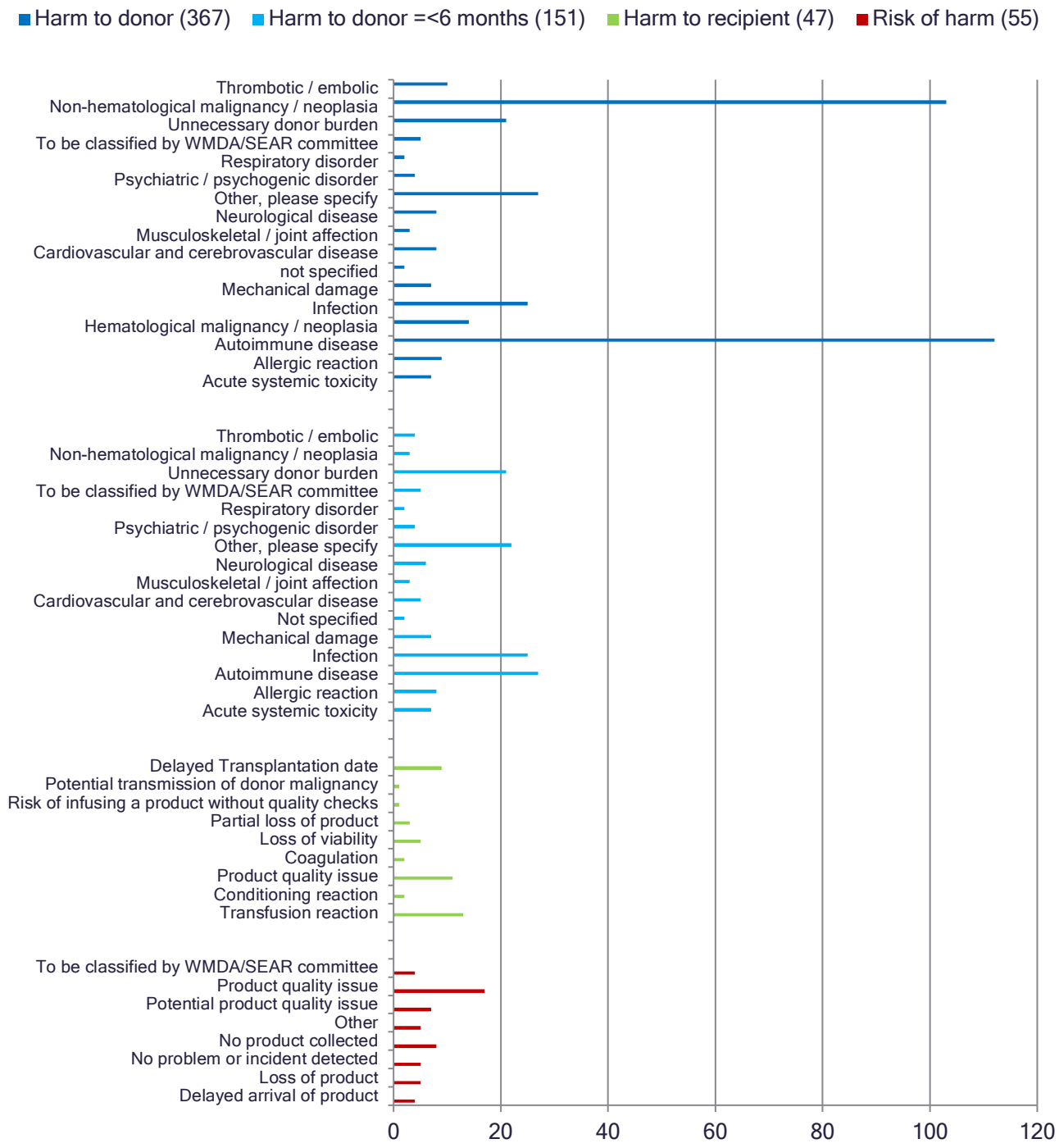
The reporting registry makes an assessment of the causation for each harm to donor incident that occurs within 6 months. The committee then reviews the imputability and proposes changes where necessary. Below, the final imputability scores for short term harm to donor reports are displayed (for long term harm imputability does not have to be reported).

REPORTED IMPUTABILITY	N
Definite/certain	44
Probable	24
Possible	47
Unlikely	23
Excluded	6
Not assessable	7
TOTAL	151

2.3 Chart: Type of product



2.4 Chart: Type of harm / problem



3. HARM TO RECIPIENT

A total of 36 harm to recipient incidents were reported. The majority of incidents occurred in the context of HPC-Apheresis (80.6% (n=29)), 7 after HPC-Marrow transplants (19.4% (n=7)). WMDA received no reports on harm to recipient related to HPC-Cord or MNC in 2020.

In 22 cases, the product was cryopreserved, 7 were not, 4 unknown, and in 3 reports there was no product collected. For only 2 out of the 22 cryopreservations, a causal connection can be ruled out. In 12 reports, processing or manipulation to the product may have contributed (including 8 cryopreservations).

3.1 Type of harm to recipient

	N	SUBCATEGORY / COMMENT	
Delayed Transplantation date	9	(loss of the intended product)	
Transfusion reaction	13	(1 fatal, 7 after cryo)	
Conditioning reaction	2	(to ATG)	
Product quality issue	11	Coagulation	2
		Partial loss of product	3
		Loss of viability	5
		Risk of transmission of other disease	1
Potential transmission of donor haematological malignancy	1		
TOTAL	36		

3.2 Transplantation performed

	N
Transplantation performed as planned	17
Transplantation performed on later date than planned	5[1]
Transplantation performed using different product	1
Transplantation not performed	9
Unknown	4
TOTAL	36

[1] Discrepancy to 3.1: not all reports confirm if transplant from a BU donor / alternative product was performed

3.3 Assessment of imputability

The reporting registry makes an assessment of the causation for each harm to recipient. The committee then reviews the imputability and makes changes where necessary. Below, the final imputability scores for harm to recipient reports are displayed.

REPORTED IMPUTABILITY	N
Definite	18
Probable	6
Possible	9
Unlikely	1
Excluded	-
Not assessable	2
TOTAL	36

4. RISK OF HARM

Fifty-five (55) risk of harm incidents were reported. Forty (40) incidents took place during or after HPC-Apheresis, 2 during MNC-Apheresis, 10 following HPC-Marrow and 3 following HPC-Cord. Risk of harm incidents occurred during various phases of the procedure, but mainly during collection (n=14) and transport (n=10). In 30 reports, the product was cryopreserved, in 17 it was not, and in 8 cases no matching product was collected.

Eighteen (18) transplantations were performed as planned, 24 transplantations were not performed, 7 were performed on a later date than planned, 4 transplants were performed using different product and for 2 incidents it was not specified or it was unknown. Of the 24 transplantations not performed, 17 relate to COVID, thereof 11 to cryopreservation and 6 to donors tested positive for SARS-CoV-2.

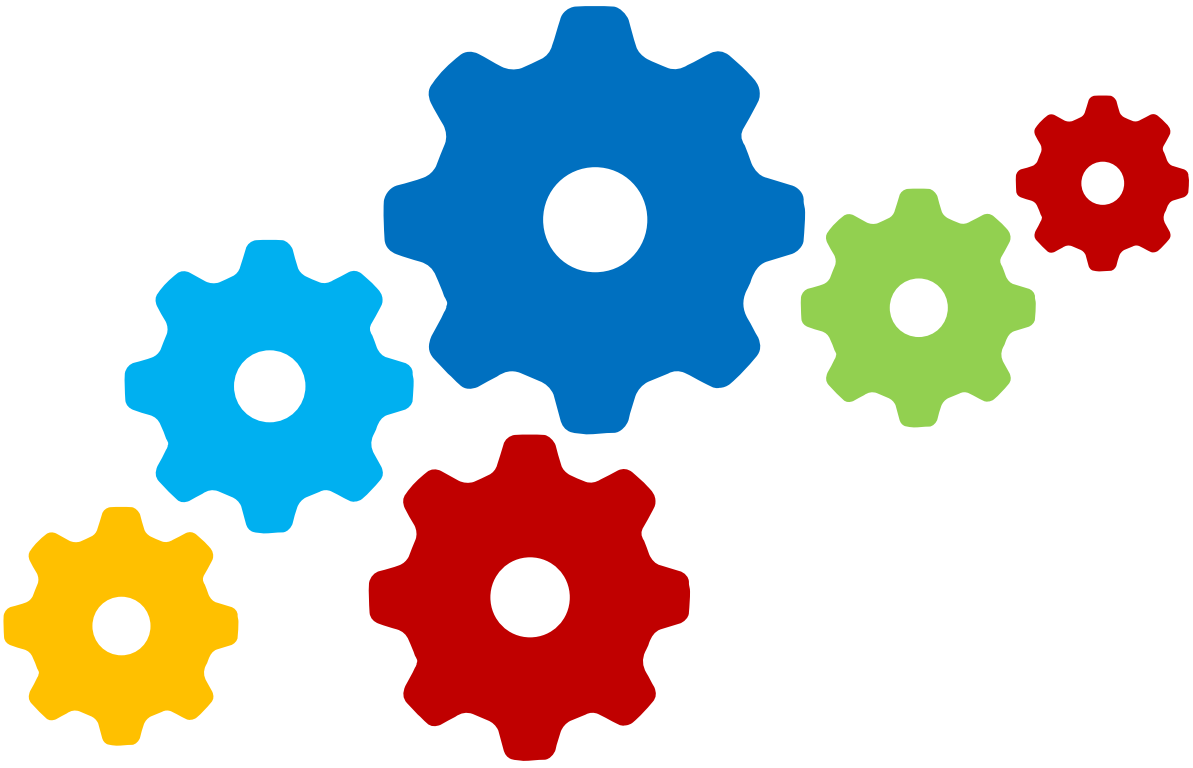
4.1 Type of risk of harm

	N	SUBCATEGORY	
Delayed arrival of product	4		
Loss of product	5		
No product collected	8		
Product quality issue	17	Bacterially contaminated product	2
		Incorrect label and/or samples	3
		Low viability	6
		Other	4
		Risk of transmission of other disease	1
		To be classified by WMDA/SEAR committee	1
Potential product quality issue[1]	5		
Other	5		
Risk of harm to donor	9	Incorrect donor health screening	3
		Potentially unnecessary donation procedure	6
TOTAL	**55**		

[1]. Potential product quality issues: e.g. positive donor testing, problem with storage temperature

4.2 Phase of procedure event occurred

	N
Collection	14
Distribution	1
Donor aftercare	2
Donor assessment (health screening)	4
Mobilisation	5
Processing	6
Transplant	5
Transport	10
Other or unsure	8
TOTAL	55



5. COVID-19 RELATED REPORTS

Fifty-four (54) reports were classified as COVID-related reports: an incident was either an effect of an infection (suspected / confirmed) with SARS-CoV-2, or directly caused by mitigation measures such as travel restrictions, quarantine, or cryopreservation of HSC products.

Due to the new and very specific situation especially at the beginning of the SARS-CoV-2 pandemic, consistent and unambiguous categorization of COVID-19 related incidents within the existing categories of the reporting tool was often not feasible. For example, a BM product not transfused due to loss of viability during cryopreservation after prolonged shipping time and expected low cell counts because of weight ratio can be classified as Risk of harm (recipient, best product not available), Risk of harm (transport), Risk of harm (product quality issue), or Harm to donor (unnecessary donor burden). An in-depth analysis of the COVID-19 related cases is outside the scope of this Annual Report, but is currently in preparation with the intention to publish together with the COVID survey results.

5.1 Overview COVID-19 related incidents

(categorization subject to change)

	N
A1 - Donor, infection during collection	3
A2 - Unnecessary donor burden	18
A3 - Donor, product not infused after donor tests positive	5
A4 - Donor, other	2
B2 - Recipient, no product from original donor after start of conditioning	4
B3 - Recipient, relevant delay for start of conditioning	1
B4 - Recipient, other	4
C1 - Technical problem, low cell dose/viability	10
C2 - Technical problem, equipment, procedure or validation (Controlled rate freezer)	1
C2 - Technical problem, equipment, procedure or validation (dry shipper)	2
C3 - Technical problem, material, procedure or validation (bags)	2
C4 - Technical problem, lack of coordination	1
D2 - Transport issues, prolonged shipping	1
TOTAL	**54**

6. REPORTS NOT INCLUDED

Reports will be accepted as long as they contain relevant information. Nevertheless, 15 reports have been categorized as NOT A SEAR after review by the Committee, since they did not fulfil the defined criteria for a SEAR / SPEAR incident. In addition, for one event reports were submitted from both the receiving as well as the sending registry.

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

	N	REASON FOR EXCLUSION
Time incident occurred	3	Regular incident more than 10 years after donation
	2	Incident before start of donation / conditioning procedure
'Expected' non-critical events	5	ABO incompatibility, coagulation, X-ray, increased shipping temperature (all products could be transfused)
	1	Poor mobilization (scheduled cryopreservation)
Differing practice / standards for package or labelling between CC and TC	2	Product shipped w/o incident, and identifiable
Genetic findings in donor cells	2	
2 reports for 1 incident	1	
TOTAL	**16**	

The committee encourages all reporters to keep sending information on **all** incidents if the reporter is in doubt about what should be reported or not.

7. INDICATORS FOR PARTICIPATION

7.1 Indicator I: Total reports per shipments

Indicator I	
Count of reports per shipments:	**1.2 reports per 100 shipments**

Comparative figures for expected reporting frequency were calculated based on:

Count of reports 2020 on donor harm from start of procedure until 6 months after donation (N = 157), reported by 18 registries (out of 474 by 32 registries total)

- Reports categorized as NOT A SEAR by the Committee are *included*.
- Late harm to donor reports were not considered because long-term donor follow-up is dependent on local jurisdiction, is resource-intensive, and collection was usually well before 2020. Newer registries have fewer donors in long-term follow up. Also, early events are more often in causal connection, more informative, and more likely to result in a Rapid Alert.
- Risk of harm and harm to recipient were not included since responsibilities are not always clear, and the number of those reports does not have to correspond with registry size.

Number of HPC shipments in 2020 by the 18 reporting registries (N = 13 020), representing 69% of total shipments

- CB units were not included, since there is no known donor harm.

7.2 Indicator II: Median reports per shipments

Indicator II

Median count per shipments from the contributing registries: 1.9 reports per 100 shipments

Comparative figures for expected reporting frequency were calculated based on count of reports and shipments for all registries with reports on early harm to donor. For confidentiality reasons, WMDA does not disclose rates from single registries.

Principle:

REGISTRY	RATIO REPORTS PER SHIPMENTS	REPORTS	SHIPMENTS
A	1.42%	2	141
B	0.39%	1	254
C	1.96%	4	204
D	2.33%	1	43
E	1.05%	13	1 233
MEDIAN	**1.24%**		

- *Means* were not considered, since COVID affected some registries more than others. Also, if a small registry with <10 shipments has reported a single case, the ratio is very high, and the statistically expected circa 9 registries of comparable size with no incident will not be included in the denominator
- Relation to the *total* number of shipments by WMDA in 2020 is not informative, since the share of the reporting registries among the different product types is not proportional, with HPC-Marrow (national) underrepresented (only 42% of shipments by registries with reports included), thus reporting bias is not *random*.

Conclusion:

Including reports on late donor harm, risk of harm, and harm to recipient, a ratio of **1 – 2 reports per 100 adult collections** can be expected. As a reminder, S(P)EAR reporting is mandatory for accreditation, so all WMDA members should assess their respective ratio. The SEAR Committee is happy to provide assistance and expertise.

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