14th International Donor Registry Conference & WMDA Meetings
25 – 29 June, 2024 – Cape Town, South Africa
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Biovigilance: Lessons Learnt from WMDA's SPEAR Reports

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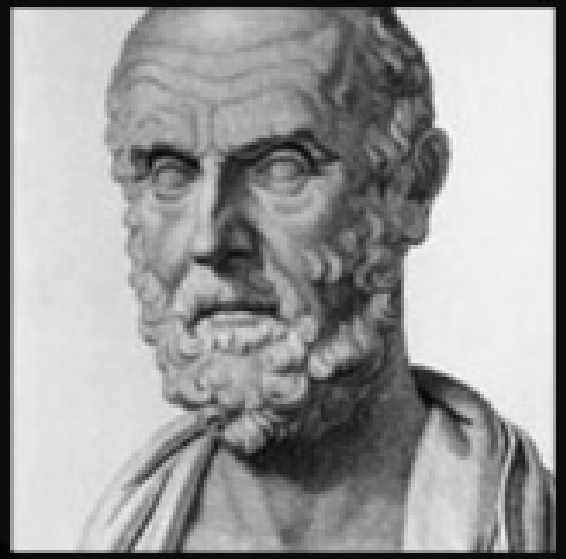
Serious Product Events and Adverse Reactions: Lessons Learnt

- Background – how, what and why?
- Lessons – who?

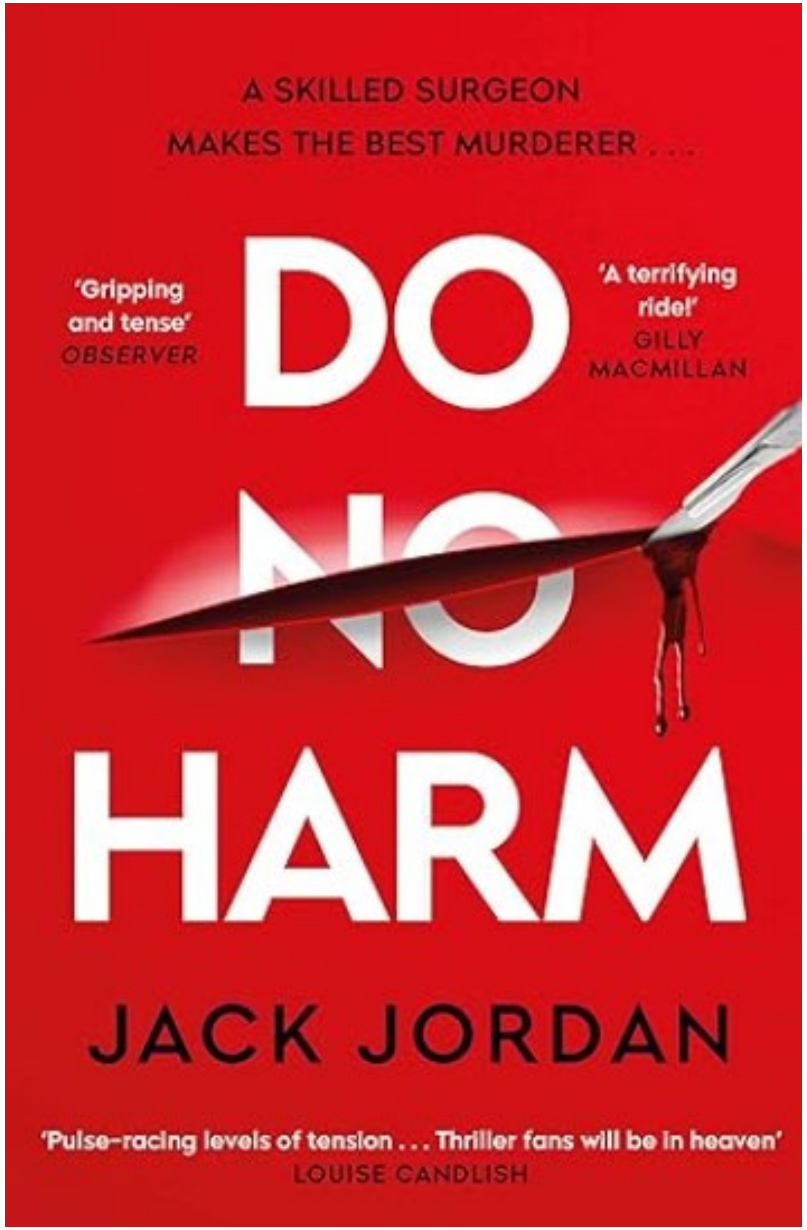
Do No Harm

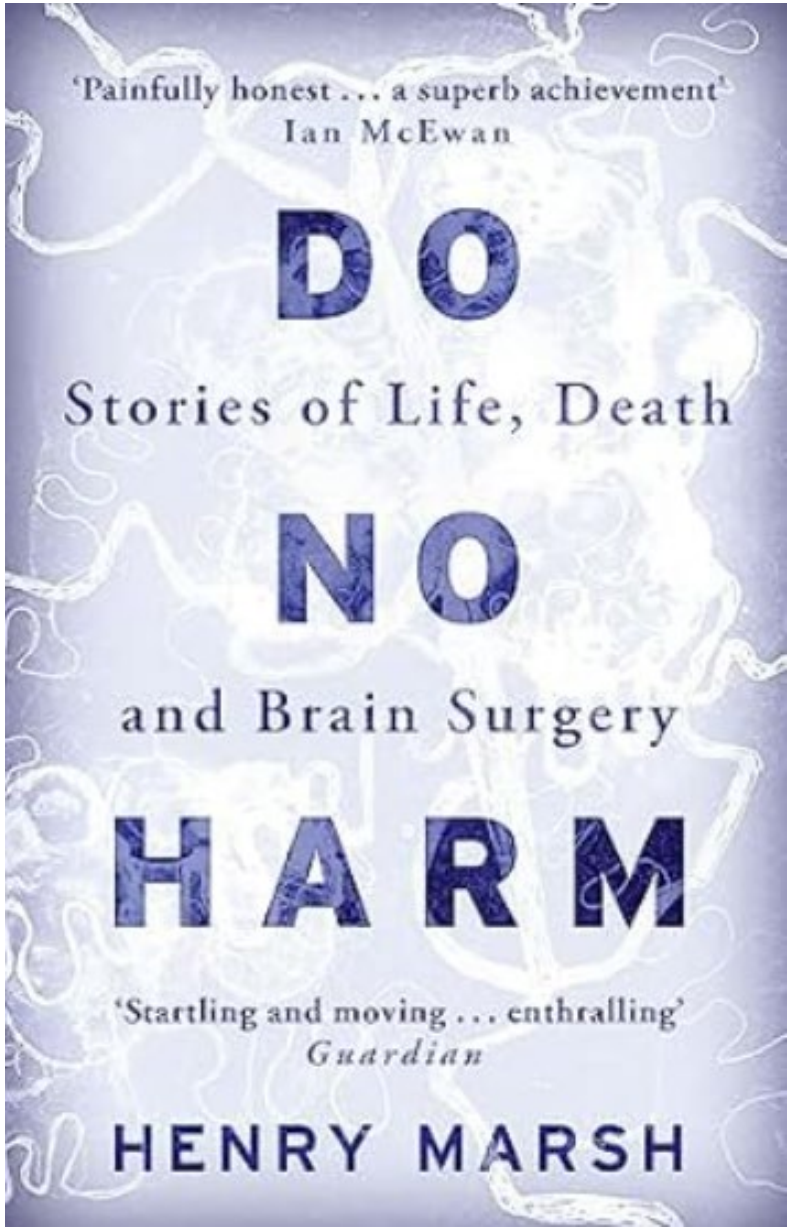
Hippocrates



Declare the past, diagnose the present, foretell the future; practice these acts. As to diseases, make a habit of two things--to help, or at least to do no harm.

Of the Epidemics, c 400 BC



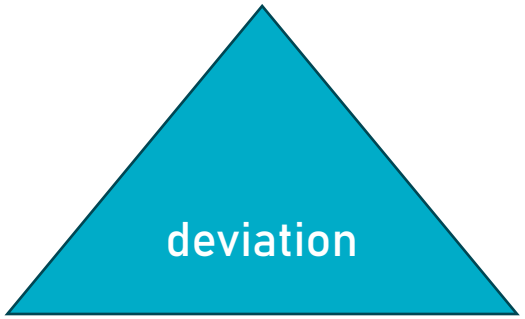


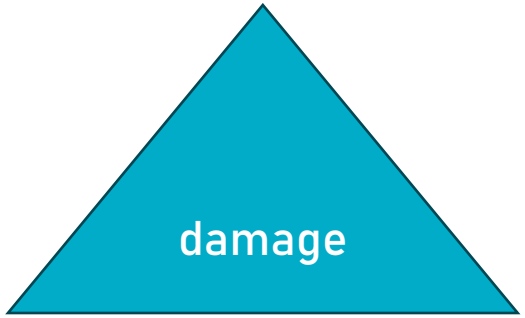
WMDA Serious Product Events and Adverse Reactions (SPEAR)

- "Evaluate the risk of harm with any healing event"
- Reporting of serious events and adverse reactions related to stem cell donation or affecting product quality (SPEAR)
- Unrelated and related donors
- Reporting of SPEAR is a requirement for WMDA accreditation
- Online tool

WMDA applies the EU definitions for serious adverse event or reaction

EU definition of a serious adverse event DIRECTIVE 2004/23/EC, article 3 (m)	**EU definition of a serious adverse reaction** DIRECTIVE 2004/23/EC, article 3 (n)
'serious adverse event' means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.	*'serious adverse reaction' means an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.*
WMDA classification: *Risk of Harm*	*WMDA classification:* Harm to a Donor / Recipient





Types of SPEAR Report

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.

- Well-known side effects and quality deviations do not have to be reported if mild and no serious consequences

How the SPEAR Reports are Handled

- Reporting organisations can be **self-reporting or report via a parent organisation**.
- If latter, parent must first view the report and then submits it to WMDA

- The WMDA **medical advisor is the first to review all reports** on accuracy and completeness.
- Questions can be sent back to the reporter if details are missing.
- Some common reports are handled directly by the medical advisor.

- When complete, notable reports are assigned by the medical advisor to a committee member for review; committee members review based on their area of expertise and are excluded from reviewing reports of their own or affiliated organisations.

- Member reviews and checks imputability, severity, ICD coding

Committee Outputs

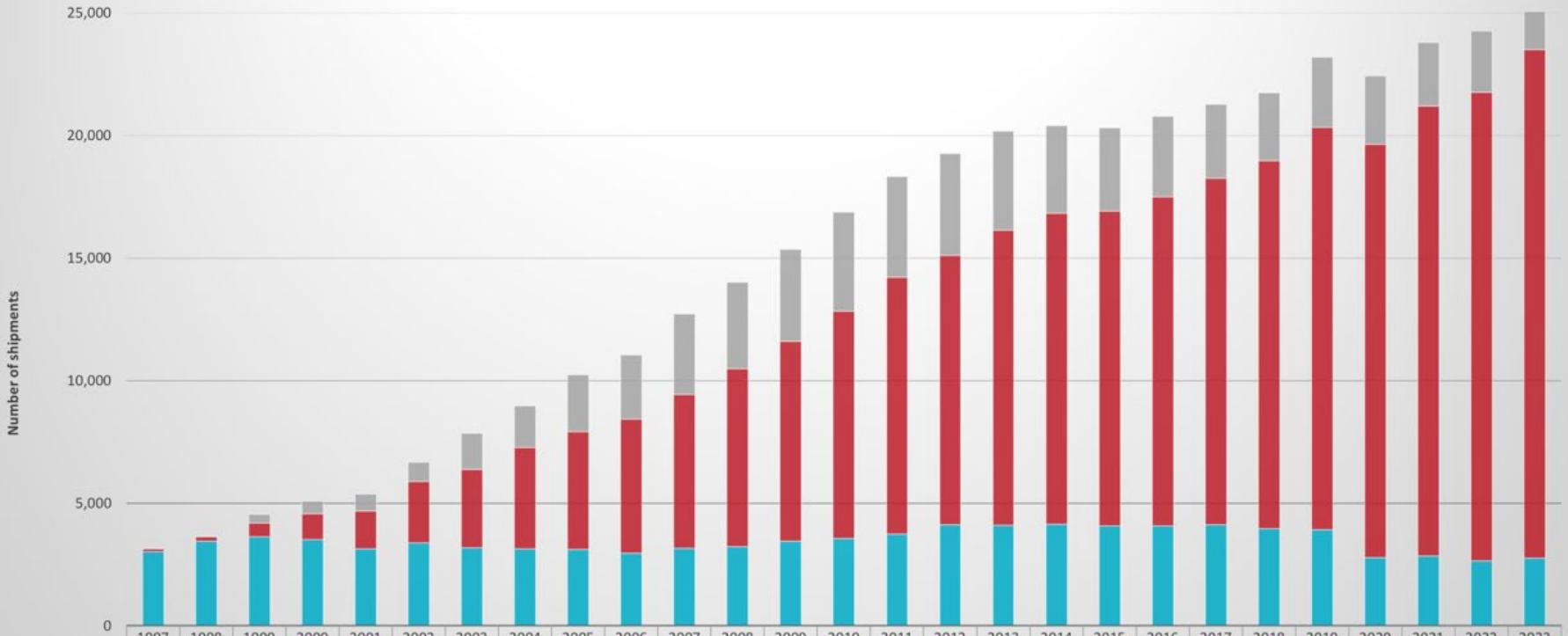
- Educational communication on topics related to ensuring donor well-being is safeguarded
- Trends/similar cases
- Annual report
- https://share.wmda.info/display/PromotingDonorCare/SPEAR+Annual+reports
- Rapid alerts
- Input for WMDA Standards and certification
- Publications, e.g. on COVID-related incidents https://doi.org/10.1016/j.jtct.2023.05.020

Lessons Learnt?

Lesson 1
Stem Cell Donation is Safe

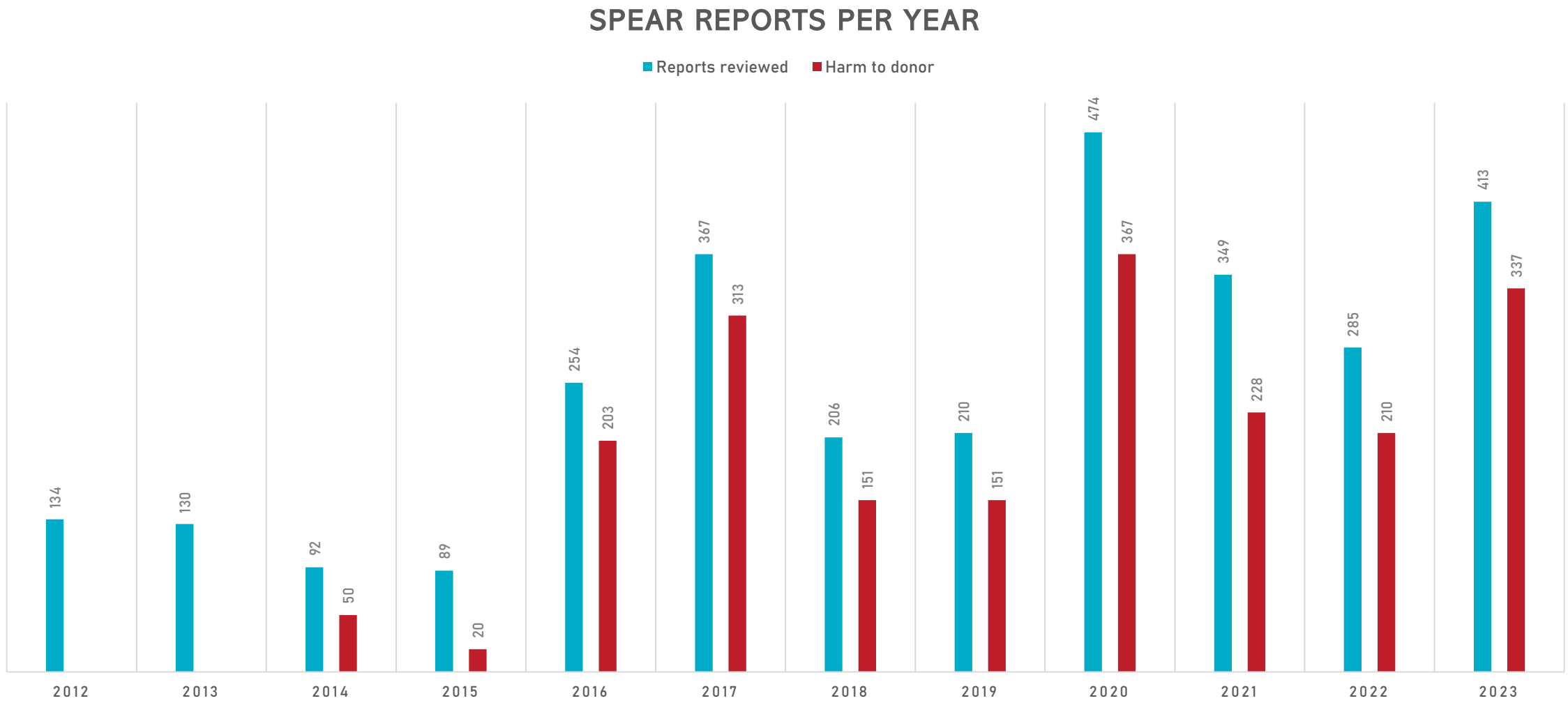
Unrelated HPC marrow, HPC apheresis and HPC cords shipped worldwide 1997–2023

WMDA
matching donors · serving patients



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Cords	14	49	366	508	691	796	1,466	1,703	2,336	2,622	3,276	3,523	3,760	4,047	4,110	4,150	4,040	3,579	3,413	3,274	3,001	2,783	2,865	2,783	2,584	2,492	2,330
Apheresis	113	170	549	1,049	1,549	2,485	3,198	4,133	4,798	5,479	6,284	7,259	8,161	9,259	10,468	10,986	12,047	12,666	12,831	13,432	14,129	14,998	16,408	16,855	18,349	19,108	20,759
Marrow	3,033	3,461	3,638	3,514	3,136	3,392	3,187	3,132	3,111	2,952	3,155	3,221	3,441	3,574	3,744	4,126	4,091	4,150	4,073	4,068	4,128	3,964	3,926	2,788	2,857	2,659	2,750

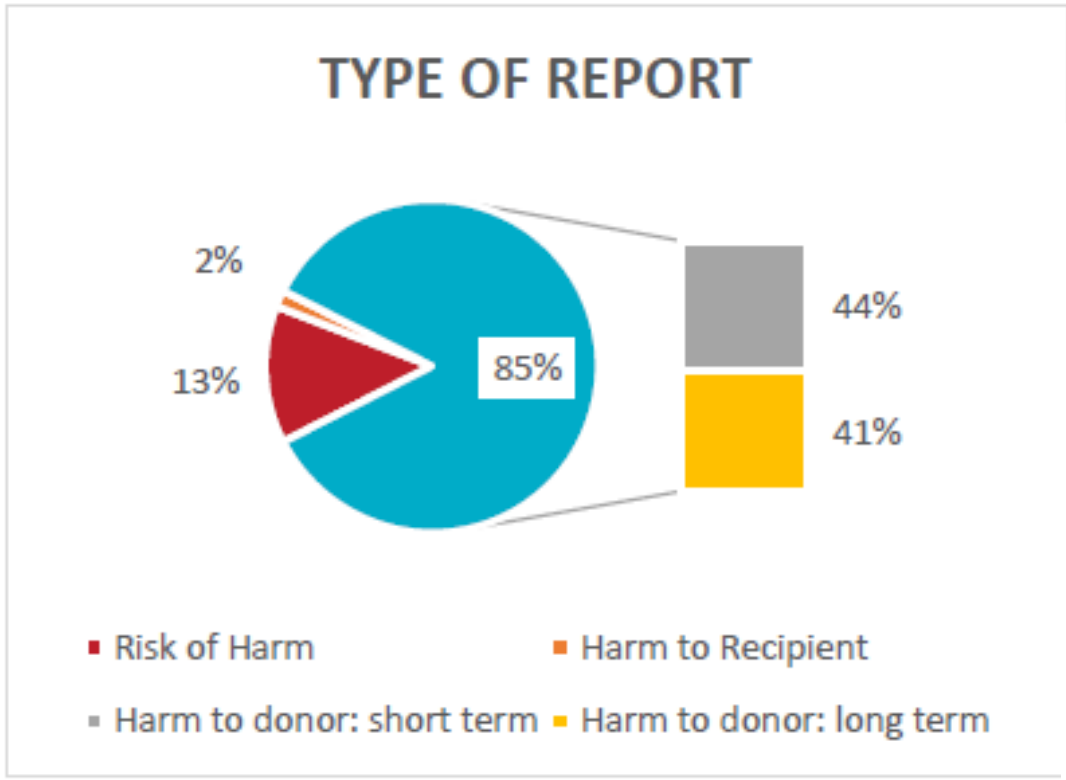
SPEAR reports per year (2012-2023)

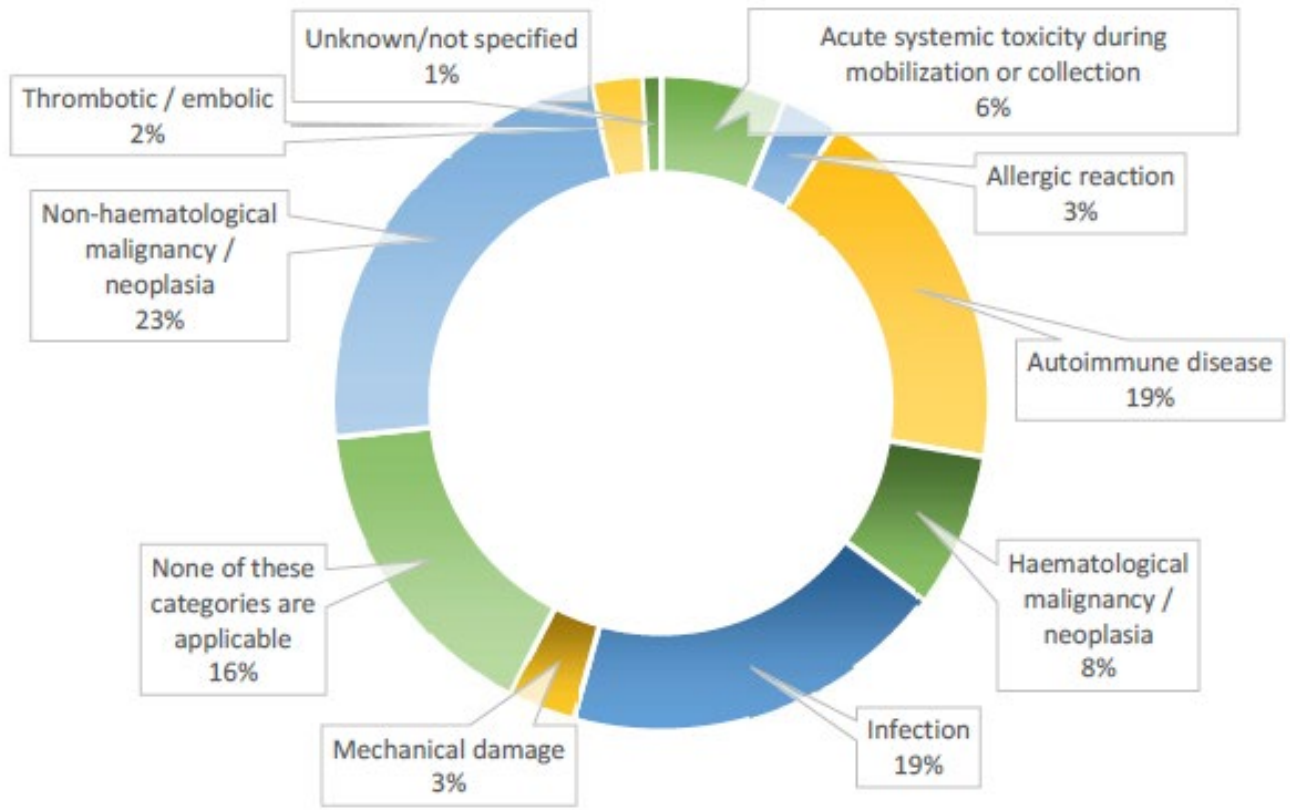


Stem Cell Donation is Safe…..

- 24,217 shipments of donor products in 2022
- 56% of these involved WMDA-accredited registries
- = 13,561 shipments from registries that should be reporting adverse events into the SPEAR database
- 282 SPEAR reports accepted in 2022

SPEARs Reported in 2022





Most reports classed as severe (CTCAE grade 3 or above) were malignancies > 6mths

Serious Adverse Events are RARE

2020:

- S(P)EAR Rapid Alert: July 2020 - Timely Patient Verification and Extended Typing
- S(P)EAR alert: May 2020 - Cryopreservation during COVID-19 pandemic (update 11 June 2020 in red)

2019:

- S(P)EAR Rapid Alert: Dec 2019 - Lost Product
- S(P)EAR Rapid Alert: April 2019 - A fatal event in an unrelated Bone Marrow donor

2013:

- S(P)EAR Rapid Alert: Nov 2013 - Wrong Donor Cells Transplanted
- S(P)EAR Rapid Alert: May 2013 - Cardiac arrest following double CBU infusion

2011:

- S(P)EAR Rapid Alert: Dec 2011 - Donor death haemo/pneumothorax following CVC

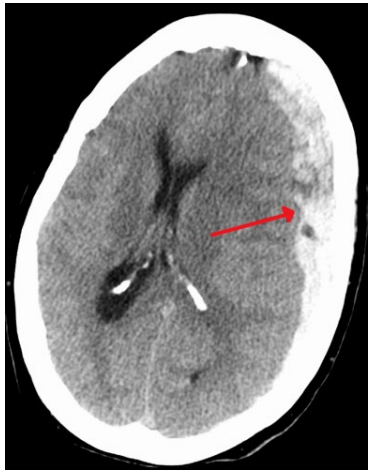
Lesson 2
Assessing Imputability Can be Difficult

WMDA	SPEAR Communication: Subdural Hemorrhage			
	Document type	Communication	Approved by	SPEAR chair
	Document reference	PCD_1304_COMM	Approval date	8/24/2023
	Version	1.1	Approval status	approved
	Pillar / Scope	P3 / SPEAR	Status	Public

SUBDURAL HAEMORRHAGE AFTER PBSC DONATION

The WMDA SPEAR Committee has received three reports of subdural haemorrhage (SDH) in unrelated PBSC donors since the beginning of 2021. The cause of this condition in these donors and the relation to donation is not clear, however we feel it is good to share a summary of these events and some of the things that are worth considering regarding donor care.

- **Case 1** was a female in her early thirties who had acute onset of a headache 4 days after donation having had a minor head injury the previous day (3 days after donation). SDH was diagnosed 9 days later. The relation between the head injury and the SDH remains unclear.
- **Case 2** was a male in his twenties who had an acute onset headache within 2 days of apheresis.
- **Case 3**, (the most recent) was of a male donor in his thirties with pre-existing hypertension well-controlled on single agent treatment. The donor had a headache at the end of apheresis and was markedly hypertensive. The donor was immediately transferred to an acute facility and was diagnosed with an SDH.
- All 3 donors underwent neurosurgery and made good recoveries.



- Further case of SDH reported in 2024
- No obvious predisposing factors or history of head injury
- Committee aware of 8 cases in unrelated donors (7 SDH, 1 SAH)
- 5/8 onset < 48 hours after PBSC donation
- Reports are over 16 years, estimate >80,000 PBSC donations

- Association does NOT mean causation
- No obvious causal link - ?how to handle?

Lesson 2.5 !
Making Recommendations Can be Difficult!

Important :

- Monitor donors/report symptoms post-donation
- Know how to access to emergency care
- Consider transfer to acute facility if severe headache
- Consider adding to donor information and/or consent
- Consider deferral of donors with a h/o brain injury ??

Lesson 3
Learning from Near-Misses

- Donor tested negative for HIV by NAT and serology at medical
- Found to be HIV positive on day of donation (both methodologies)
- Luckily….
- Planned cryopreservation – patient not conditioned
- TC had requested sample for DoD testing in own lab (lost prev.)

- Exact mode or timing of infection of donor not pinpointed
- Some high-risk behaviours between medical and donation

WMDA	SPEAR Communication: “Near-Miss” Donation From Donor With Hiv			
	Document type	Communication	Approved by	SPEAR chair
	Document reference	PCD_1302_COMM	Approval date	2/15/2023
	Version	1.0	Approval status	approved
	Pillar / Scope	P3 / SPEAR	Status	Public

“NEAR-MISS” DONATION FROM DONOR WITH HIV: IMPORTANCE OF COUNSELLING ABOUT HIGH-RISK BEHAVIOURS

- ask at medical specifically about any high-risk behaviour in the window period of TTIs - repeat IDM testing as needed
- remind to avoid behaviours or exposures that pose a high risk of TTIs from selection as FD until after donation
- inform of rationale and importance of this when selected as a FD and at medical
- ask to inform donor registry immediately if exposed to any risk in this period
- registry can consider whether extra testing is needed or a deferral period

Risk of Harm SPEAR

Lesson 4
Expect the Unexpected

Bild STARTSEITE NEWS POLITIK REGIO UNTERHALTUNG SPORT FUSSBALL LIFESTYLE RATGEBER GESUNDHEIT SEX & LIEBE AUTO SPIELE DEALS

BILD › Regional › Ruhrgebiet › Hauptbahnhof Duisburg: Dieb stiehlt lebensrettende Stammzellen

Am Hauptbahnhof Duisburg

Dieb stiehlt lebensrettende Stammzellen

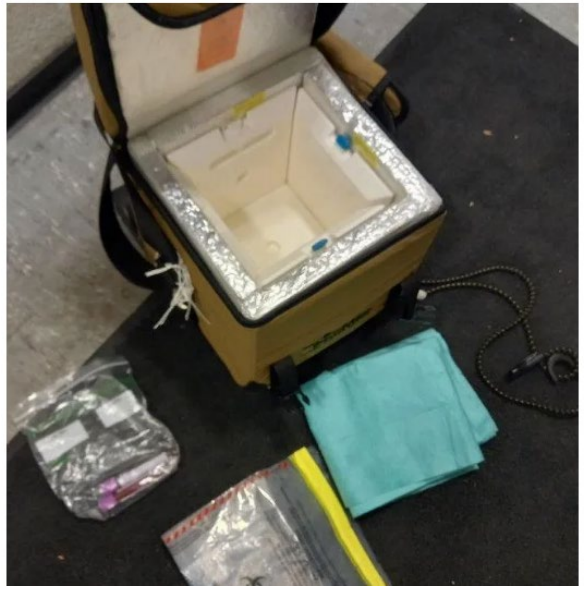
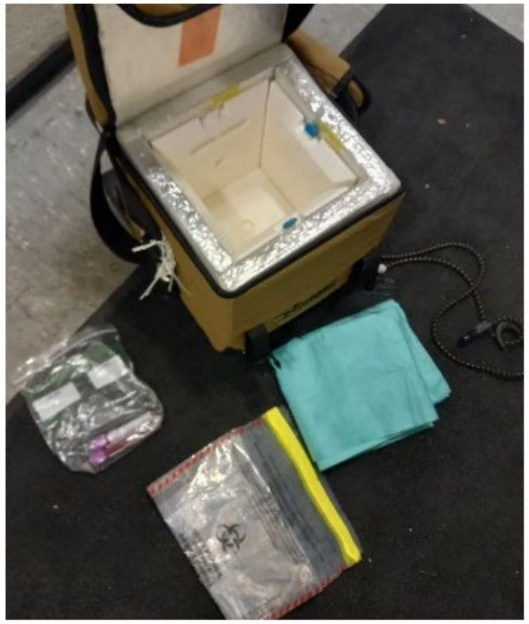


Bild HOME PAGE NEWS POLITICS REGIO ENTERTAINMENT SPORT FOOTBALL LIFESTYLE ADVISOR BLESS YOU SEX & LOVE CAR GAMES DEALS

IMAGE › Regional › Ruhr area › Duisburg Central Station: Thief steals life-saving stem cells

At Duisburg Central Station

Thief steals life-saving stem cells



In this refrigerated transport box, the stem cells were in a bag. Only two blood tubes are left
Photo: Federal Police Directorate Sankt Augustin

COMPANY-TODAY

HOME ENTERPRISE FINANCES POLITICS ENGINE TECHNOLOGY PAN

News

Stem cell donation stolen from express train in North Rhine-Westphalia

AFP In NEWS November 14, 2023, 11:30 a.m.

Great Train Robberies?

Duisburg 2023

- Bag containing the PBSC graft taken from courier just seconds before door closing and train departure
- Empty bag found outside station, product lost
- Donor could donate for 2nd day

Bonn 2015

- BM product was stolen during the transport in the train by "train thieves“.
- Police informed and announcements were made on radio and on TV
- The container with the graft was found in another train in another city.
- Temperature monitoring showed that the container had not been opened
- TC decided to infuse; successful engraftment

Lesson 4.5
Train(station)spotting

- NL, GB: ticket control to enter or leave station (mainlines, Underground)
- IT, ES, FR: ticket control to enter platforms for high-speed trains, airport connector
- ES, FR, BE: ticket with seat reservation required for high-speed trains (show when boarding)
- DE, AT, CH:no technical measures to limit access

Ensure (foreign) couriers are aware of the unresticted access to trains in Germany

Amsterdam Centraal

Paris, Gare de Lyon

Thanks to Thilo Mengling for slide!

1	WMDA SPEAR Alert: HPC Products Missing During Transport			
	Document type	Form-Rapid Alert	Approved by	Committee chair
	Document	PDC.1305.COMM.Transpor	Approval date	Approved
	Version	4.0	Pages	Page 1 of 2
	Pillar	Pillar 3-DC – Donor Care	Status	Public

To WMDA members and affiliated transplant & collection centres, professional societies and all whom this may concern.

SPEAR ALERT: HPC PRODUCTS THAT HAVE GONE MISSING DURING TRANSPORT

- Recommendations for couriers
- Courier training
- Manual control of product at all times important
- Courier fitness, preparedness, alertness

Last Lesson
Benchmarking –Expected Reporting Rates

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

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.

Summary / Revision!

- How SPEAR reporting works
- Stem cell donation is safe…
- Assessing imputability can be difficult
- (Making recommendations too..)
- Learn from near-misses (Risk of Harm)
- Expect the unexpected
- Expected reporting rates

SPEAR Committee Membership 2023

- Eefke van Eerden 
- David Allan 
- Chloe Anthias 
- Meghann Cody 
- Mirjam Fechter 
- Diane Fournier 
- Gabriela Marti 
- Danielli Cristina Muniz de Oliviera 
- Gayathri Nair 
- Grazia Nicoloso de Faveri 
- Jason Oakes 
- Thilo Mengling 
- Rachel Pawson 
- Jeff Szer 
- Tigran Torosian 
- Juliana Villa López 

Thank You

- Committee
- Tigran Torosian – chair elect
- Eefke van Eerden
- Thilo Mengling

Thank you.

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