



Published in final edited form as:

*Transplant Cell Ther.* 2021 April ; 27(4): 352.e1–352.e5. doi:10.1016/j.jtct.2021.01.009.

## Serious Adverse Events in Related Donors: A Report from the Related Donor Safe Study

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**CONFLICTS OF INTEREST:**

The authors declare no competing financial interests in relation to this study.

## Abstract

The incidence and risk factors for severe adverse events (SAEs) in related donors (RD) of hematopoietic cell transplants is unknown. The Related Donor Safe (RDSafe) study is a prospective observational cohort of 1680 RDs, and represents an opportunity to examine characteristics of SAEs in RDs. In this cohort, we found that SAEs were reported in a total 12 (0.71%) RDs. Of these, five SAEs occurred in bone marrow donors (5/404, 1.24%), and seven (7/1276, 0.55%) were in donors of peripheral blood stem cells (PBSC). All of the SAEs were considered to be related (definite, probable, or possible) to the donation process. There were no donor fatalities. Of the 12 RDs who experienced an SAE, 10 were either overweight or obese. Five of the 12 RDs had pre-donation medical conditions that would have resulted in either possible or definite ineligibility for donation were they being assessed as unrelated donors. These SAE data will be useful in the counselling of prospective RDs prior to planned donation, and may be helpful in identifying donors who should be considered medically unsuitable for donation.

## Keywords

Allogeneic Hematopoietic Cell Transplantation; Related Donors; Adverse Events

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## INTRODUCTION:

The ethical and safe care of hematopoietic cell donors is of primary importance in the practice of allogeneic hematopoietic cell transplantation (HCT). In contrast to volunteer unrelated donors (URDs), there is heterogeneity in donor center processes and external oversight for related donors (RDs), and the experience and outcomes of RDs are not well known<sup>1,2</sup>. Catalyzed by these concerns, the Related Donor Safe (RDSafe) study was conceived in order to prospectively measure how RDs are selected, assessed, undergo hematopoietic cell collection, and followed-up.

The RDSafe study recruited RDs of any age between January 2010 and July 2014 from 53 HCT centers in the United States. The primary analysis of the RDSafe study focused on the nature, severity and duration of donation-related toxicities in RDs as compared to URDs<sup>3</sup>. The purpose of the current analysis is to describe the characteristics and determinants of serious adverse events (SAEs) that were reported in the RDSafe study.

## PATIENTS AND METHODS:

The patients and methods of the RDSafe study have been previously described<sup>3</sup>. In brief, 1680 related donors who were locally approved for donation were recruited to this institutional review board approved observational study, after obtaining informed consent. Donor symptoms were recorded at pre-donation, peri-donation [day +5 from start of granulocyte-colony stimulating factor (GCSF) for PBSCs and 1-2 days after bone marrow collection], and at 1, 6 and 12 months after donation. SAEs occurring peri-donation and thereafter were prospectively reported to the Medical Monitor of the RDSafe study. The definition of SAE aligned with the National Cancer Institute's reporting requirements for investigators<sup>4</sup>. Specifically, an SAE was defined as an event experienced by the donor that

resulted in one of the following outcomes: Death; a life-threatening adverse experience; in-patient hospitalization or prolongation of existing hospitalization (for more than 24 hours); a persistent or significant impairment in the ability to carry out normal activities; a congenital anomaly. Important Medical Events that were not lethal, not life-threatening, nor required hospitalization were still considered an SAE when the donor required medical or surgical intervention to prevent one of the aforementioned outcomes.

Relatedness of the SAE was classified as: Definite, Probable, Possible, Unlikely, or Unrelated. The presence and relatedness of the SAE, as well as whether the SAE represented an expected or unexpected event was adjudged independently by three of the RDSafe investigators (MS, MP, BS). If a disagreement occurred amongst these three investigators, the event was reviewed and discussed until consensus was achieved. Criteria for medical suitability in URDs, as recommended by the National Marrow Donor Program (NMDP), was applied to the related donors in the current analysis<sup>5</sup>. Descriptive statistics were used. Between group differences for categorical variables in those who did versus did not experience an SAE were compared by the Chi Square test.

## RESULTS:

A total of 12 SAEs were confirmed in 12 (0.71%) of the 1680 donors. Of these, five SAEs occurred in bone marrow donors (5/404, 1.24%), and seven (7/1276, 0.55%) occurred in donors of peripheral blood stem cells (PBSC). Tables 1 and 2 summarize donor and event characteristics for each SAE. The SAEs were cardiac or respiratory in eight donors, gastrointestinal/hepatic in two donors, hematological in one donor, and musculoskeletal in one donor. There were no donor fatalities reported. All of the SAEs were considered to be related (definite, probable, or possible) to the donation process.

Amongst the seven PBSC donors who experienced an SAE, all but one was either overweight or obese. Similarly, in the bone marrow harvest SAE donors, four of the five were either overweight or obese. Within the PBSC group, doses of GCSF surpassed 10micrograms/kg/day in 4 of the 7 (57%) donors. Two PBSC donors had pre-donation comorbid conditions that would have rendered them ineligible for donation according to NMDP URD criteria, while an additional three donors (2 PBSC, 1 bone marrow) had comorbid conditions that would have possibly been grounds for URD exclusion, albeit with the need for more clinical information from the donor center in order to clarify their medical suitability. Given the relatively small number of observed SAE events, there were no statistically significant differences in age group, BMI, comorbid conditions, and type of cell source when comparing the 1668 donors who did not experience and the 12 who did experience an SAE (data not shown).

## DISCUSSION:

SAEs are a key indicator of the risks inherent in any medical intervention, including HCT donation. We have demonstrated in a large prospective cohort study that SAEs, some of which are potentially life-threatening, occur in a small but measurable proportion of RDs, regardless of whether bone marrow or PBSCs are collected, with SAE rates of 1.24% and

0.55%, respectively. By comparison, SAE rates in URDs are reported to be 0.99% for BM and 0.31% for PBSC<sup>6</sup>. These SAE data will be useful in the counselling and consenting process of all donor prior to their planned donation.

SAEs are especially relevant in donors at extremes of age or with comorbid medical conditions, situations more likely to be observed in RDs rather than URDs. Our data are striking in that most of the SAE episodes, and all of the probable and definite SAEs attributed to donation, were in overweight or obese donors.

Although there was no statistical difference in the proportion of overweight (BMI 25-29.9) or obesity (BMI 30+) amongst the 1668 donors without SAE compared to the 12 who did experience an SAE, this comparison is limited by statistical power. Of the total 1680 donor cohort in the RD Safe study, 72.4% of PB donors, and 64.2% of BM donors were overweight or obese, respectively<sup>3</sup>. In contrast, within the SAE cohort, 85% of PB donors, and 80% of BM donors were overweight or obese, respectively. Donors with high BMI require heightened vigilance as a risk factor for SAEs, as prior data support that higher weight also increases AE risks in unrelated donors<sup>7,8</sup>. There are data to suggest that overweight and obese donors are able to mobilize peripheral blood stem cells of greater quantity compared to donors of lesser weight<sup>9</sup>. Obese or overweight donors may thus be able to receive lower doses of GCSF in order to reduce collection related toxicities while still maintaining stem cell harvest efficiency, an hypothesis which requires further study.

Ideally, a quantifiable risk estimate for developing SAEs in RDs based on pre-donation clinical characteristics and co-morbidities would aid in the counseling and selection process of RDs, especially when alternative related or volunteer donors exist. In the RDSafe Trial we collected extensive data describing organ dysfunction-based comorbidities. We showed a direct correlation with grade 2-4 pain at collection and non-recovery from toxicities at one year after collection<sup>3</sup>. Because the numbers of SAEs were low and the SAEs were varied, we were not able to establish associations with specific comorbidities. Associations with specific comorbidities or a development of a risk score would require a much larger study due to the rarity of SAE events.

Also notable in our results is that RDs may be allowed to proceed to donation with pre-existing conditions that would definitively or possibly render them unsuitable for donation were they being assessed by URD registry<sup>3,5,10</sup>. Although it is reassuring that there were no fatal events amongst these RDs, the gravity of many of the observed SAEs raises concern that RDs may be still be considered eligible for donation at some centers despite the existence of pre-donation risk factors for adverse outcomes<sup>5</sup>. Although recent steps in RD management and oversight may have helped to highlight the vulnerability of RDs and their needs, further work is needed in order to ensure that RDs enjoy the same quality of care experienced by URDs<sup>10,11</sup>. The number of RDs is steadily increasing, in large part because of the increasing popularity of haplo-identical transplantation<sup>12</sup>. This further reinforces the need for enhanced attention at international, national, and hospital levels in order to ensure the health and safety of RDs<sup>13</sup>.

## ACKNOWLEDGEMENTS:

Staff of the CIBMTR and NMDP provided administrative personnel, statistical analyses, and software support for this study. Final analysis and interpretation of the data, as well as manuscript completion, were the responsibility of the primary investigator and co-authors. Stephanie Bo-Subait assisted with manuscript preparation.

### FUNDING:

The study was funded by R01 HL085707 through the NHLBI. Funding for this study was provided the Center for International Blood and Marrow Transplantation (CIBMTR) and National Marrow Donor Program (NMDP). The CIBMTR is supported primarily by Public Health Service U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); U24HL138660 from NHLBI and NCI; R21HL140314 and U01HL128568 from the NHLBI; HHS250201700006C, SC1MC31881-01-00 and HHS250201700007C from the Health Resources and Services Administration (HRSA); and N00014-18-1-2850, N00014-18-1-2888, and N00014-20-1-2705 from the Office of Naval Research; Additional federal support is provided by P01CA111412, R01CA152108, R01CA215134, R01CA218285, R01CA231141, R01HL126589, R01AI128775, R01HL129472, R01HL130388, R01HL131731, U01AI069197, U01AI126612, and BARDA. Support is also provided by Be the Match Foundation, Boston Children's Hospital, Dana Farber, Japan Hematopoietic Cell Transplantation Data Center, St. Baldrick's Foundation, the National Marrow Donor Program, the Medical College of Wisconsin and from the following commercial entities: AbbVie; Actinium Pharmaceuticals, Inc.; Adaptive Biotechnologies; Adienne SA; Allovir, Inc.; Amgen, Inc.; Anthem, Inc.; Astellas Pharma US; AstraZeneca; Atara Biotherapeutics, Inc.; bluebird bio, Inc.; Bristol Myers Squibb Co.; Celgene Corp.; Chimerix, Inc.; CSL Behring; CytoSen Therapeutics, Inc.; Daiichi Sankyo Co., Ltd.; Gamida-Cell, Ltd.; Genzyme; GlaxoSmithKline (GSK); HistoGenetics, Inc.; Incyte Corporation; Janssen Biotech, Inc.; Janssen Pharmaceuticals, Inc.; Janssen/Johnson & Johnson; Jazz Pharmaceuticals, Inc.; Kiadis Pharma; Kite Pharma; Kyowa Kirin; Legend Biotech; Magenta Therapeutics; Mallinckrodt LLC; Medac GmbH; Merck & Company, Inc.; Merck Sharp & Dohme Corp.; Mesoblast; Millennium, the Takeda Oncology Co.; Miltenyi Biotec, Inc.; Novartis Oncology; Novartis Pharmaceuticals Corporation; Omeros Corporation; Oncoimmune, Inc.; Orca Biosystems, Inc.; Pfizer, Inc.; Phamacyclics, LLC; Regeneron Pharmaceuticals, Inc.; REGIMMUNE Corp.; Sanofi Genzyme; Seattle Genetics; Sobi, Inc.; Takeda Oncology; Takeda Pharma; Terumo BCT; Viracor Eurofins and Xenikos BV. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration (HRSA) or any other agency of the U.S. Government.

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**Highlights:**

- Severe Adverse Events (SAEs) occur in 1.24% of related bone marrow donors, and 0.55% of related peripheral blood stem cell donors
- Related Donors (RDs) who are overweight or obese may be at heightened risk of SAEs
- We recommend careful attention is paid to RD co-morbid conditions

**Table 1:**

SAEs in Bone Marrow Harvest Donors

Age (years)	Gender	Race	BMI (Category)	NMDP URD Comorbid Condition Group: Accept/Defer	Donation #	Anesthesia	Harvest volume/recipient weight (ml/kg)	OR duration (minutes)	Timing Of SAE (days)*	Expected?	Related?	SAE Description and CTCAE grade
5	M	U	25.1 (Overweight)	None: Accept	1st	GA	11.9	109	0	No	Definite	Aspiration pneumonitis. Post-GA vomiting. Admitted to hospital. Recovered. CTCAE 3.
25	M	W	23.2 (Normal)	None: Accept	1st	GA	18	138	22	No	Possible	Staphylococcal pneumonia. Hospitalized. Recovered. CTCAE 3
49	F	W	38.7 (Obese)	None: Accept	1st	GA	14.7	136	0	Yes <sup>#</sup>	Probable	Myocardial Infarct (confirmed by cardiac enzymes and EKG) presenting as intra-operative hypotension. Severe LV dysfunction on echocardiogram. Hospitalized but non-fatal. CTCAE 4
60	F	W	31.7 (Obese)	CV: CNS/ Psych: Accept/Defer unknown <sup>a</sup>	1st	GA	17.9	142	-1	Yes	Definite	Severe back pain after marrow harvest. Hospitalized. Recovered. CTCAE 3
44	F	W	25.8 (Overweight)	None: Accept	1st	GA	3.8	94	0	Yes	Probable	Hypotension (SBP <60mmHg) near conclusion of marrow harvest. Vasovagal event suspected. Recovered. CTCAE 4

<sup>a</sup>Based on NMDP unrelated donor guidelines, more information would be needed to determine whether to accept or defer

SAE: Serious Adverse Event; Gender: M=Male, F=Female; Race: W=White, U=Unknown; BMI: Body Mass Index; URD: Unrelated Donor; CV: Cardiovascular; CNS: Central Nervous System; Psych: Psychiatric; Anesthesia type: GA=General Anesthesia; OR: Operating Room; CTCAE: Common Terminology Criteria for Adverse Events; LV: Left Ventricular;



\* : Days before or after initiation of hematopoietic cell collection;  
# : Hypotension and myocardial ischemia was considered an expected risk of general anesthesia

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Table 2

SAEs in Peripheral Blood Apheresis Donors

Age (yr)	Gender	Race	BMI (Category)	NMDP URD Comorbid Condition Group	Donation no.	Timing of SAE(d)*	GCSF dose/d ay ( $\mu$ g/kg)	GCSF (days)	Cumulative Apheresis Blood Volume (L)	Apheresis Duration (d)	CVAD	Expected?	Related?	SAE Description and CTCAE Grade
69	M	W	32.5 (Obese)	CV: Defer	1st	2	12.2	5	60	3	Yes	Yes	Definite	Thrombocytopenia. Hospitalized. Recovered. CTCAE 3
54	F	W	40.3 (Obese)	CV: Accept/Defer unknown <sup>†</sup>	1st	-1	7.1	3	30	1	No	No	Probable	Pneumonitis. Possibly due to GCSF. Recovered. CTCAE 3.
57	M	W	26.5 (Overweight)	CV: Accept	1st	0	10.5	5	23.1	2	No	Yes	Probable	Vasovagal syncope with hypotension and bradycardia. Recovered after IV fluids. CTCAE 4.
34	F	API	23.2 (Normal)	Hemorrhage requiring medical attention: GI: Accept	2nd	-3	10.72	6	24.5	2	Yes	No	Possible	Upper GI bleed. Gastric ulcer documented by EGD. History of prior GI bleed. Recovered. CTCAE 4
52	F	W	28.1 (Overweight)	CNS/Psych: Defer	1st	11	18.1	5	24	2	Yes	No	Probable	Hospitalized for observation of liver test abnormalities and elevated WBC. Recovered. CTCAE Unknown.
41	F	W	49.9 (Obese)	CV; Psych: Accept/Defer unknown <sup>†</sup>	1st	0	8.1	6	30	2	Yes	No	Probable	Supraventricular tachycardia during apheresis. Hospitalization for heart rate control. Prior history of tachycardia Recovered. CTCAE 4
63	M	W	32.3 (Obese)	None: Accept	1st	2	10	6	15	1	No	No	Possible	Orthopnea and hypoxemia 2 days after collection. CT chest. EKG without significant

Age (yr)	Gender	Race	BMI (Category)	NMDP URD Comorbid Condition Group.	Donation no.	Timing of SAE(d)*	G-CSF dose/day (μg/kg)	G-CSF (days)	Cumulative Apheresis Blood Volume (L)	Apheresis Duration (d)	CVAD	Expected?	Related?	SAE Description and CTCAE Grade
														findings. Orthopnea resolved on day 3 post collection. CTCAE 3

API indicates Asian/Pacific Islander; CVAD, central venous access device; WBC, white blood cell count; CT, computed tomography.

\* Days before or after initiation of hematopoietic cell collection.

† Based on NMDP unrelated donor guidelines, more information would be needed to determine whether to accept or defer.