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BLOOD DONORS AND BLOOD COLLECTION

TRANSFUSION

Plasmavigilance—Adverse events among US Source plasma donors

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Abstract

Background: Source plasma (SP) is the primary starting material for 87% of plasma-derived medicinal products globally. Plasmavigilance is a program designed to collect, analyze, and monitor donor adverse events (AEs) across the SP collection industry. Donor retention depends on donors having a safe and satisfactory experience. This study analyzes AE rates and SP donor characteristics that may be predictors of an AE.

Study Design and Methods: Donation data for 1.1 million donors making 12,183,182 SP donations over a 4-month period were analyzed. This represented approximately 72% of the donations collected by the U.S. plasma industry. The Standard for Recording Donor Adverse Events was used for AE definitions and classifications.

Results: The overall AE rate was $15.85/10^4$ donations. The two AEs with the highest rates were Hypotensive and Phlebotomy events (8.32 and $5.91/10^4$ donations, respectively). Females had higher overall AE rates than males (25.76 vs. $9.85/10^4$ donations), and first-time donors had higher overall AE rates than repeat donors (136.66 vs. $12.37/10^4$ donations). Weight, body mass index, age, and pre-donation estimated blood volume also were predictors of AE.

Discussion: SP donors have low AE rates with 90% being events classified as Hypotensive or Phlebotomy. Special attention and mitigation strategies should be directed to donors who are young, lightweight (between 100 and 124 pounds), female, or first-time donors to further reduce the incidence of AE, continue to ensure the donor has a safe experience, and facilitate donor retention.

KEYWORDS

adverse events, donation frequency, plasmavigilance, source plasma

Abbreviations: AE, adverse event; BMI, body mass index; DAE, donor adverse event; EBV, estimated blood volume; FDA, U.S. food and drug administration; IQPP, international quality plasma program; LOC, loss of consciousness; mL, milliliter; PPTA, plasma protein therapeutics association; RBC, red blood cells; SP, source plasma; TCV, total collection volume; US, United States.

1 | INTRODUCTION

Source plasma (SP) donation is essential for producing plasma-derived medicinal products that are life-saving medications for patients with several rare and genetic diseases. SP is collected from healthy donors through automated plasmapheresis. The Plasma Protein Therapeutics Association (PPTA) is the trade association whose members produce approximately 80% of the plasma protein therapies used in the United States.[1] PPTA staff and member companies are committed to providing essential data to its members, regulators, patients, and donors to monitor donor health.

SP donor recruitment and retention depend on a safe and positive donor experience. As Dr. Storch points out in her 2020 *Transfusion* editorial, "even minor adverse reactions are significantly correlated with decreased likelihood of subsequent donation, while major reactions lead to substantially lower rates of return."[2] The SP plasmavigilance program collects, analyzes, and monitors donor AEs across the SP industry to continuously improve processes that contribute to donor health and safety. The identification of donor characteristics associated with the increased odds of an AE is important so that plasma collectors can consider mitigation strategies to ensure donor safety and a favorable donor experience.

In 2019, donors gave 53.5 million SP donations (https://www.pptaglobal.org/plasma).[1] With 11.59 million units of whole blood and apheresis RBC collected[3] this is estimated to be over 80% of all blood and blood component donations in the United States. Donation of blood components by apheresis has been associated with low AE rates.[4–6] However, published literature on AE related specifically to SP collections is much smaller.[7] This analysis provides a tool to identify and study AEs associated with SP donation.

Automated plasmapheresis uses either centrifugation or filtration to remove blood from the donor, separate it into blood's four major components (red and white blood cells, platelets, and plasma), collect the plasma into a specialized container, and then return the other components to the donor.[8] This process requires several cycles to collect the required volume of plasma based on the donor's weight.[9] In the United States at the conclusion of the plasmapheresis, the donor receives up to 500 ml of a 0.9% IV sodium chloride solution or an oral electrolyte solution before leaving the center.[10]

Because of varying definitions and classification schemes for donor AEs by PPTA member companies, *the International Quality Plasma Program (IQPP) Standard for Recording Donor Adverse Events* was designed to provide a common language to classify SP AEs and to allow for aggregating and benchmarking data. The Standard requires the recording of donor AEs that occur during the time period from donor arrival at the collection center through 72 h post-donation. The current version of the Standard was implemented in April 2018 and was in effect during the study period.[11]

This report is a compilation of the AEs reported by three PPTA member companies that represent 72% of the SP donations made in the United States during the study period and provides the most comprehensive and current reporting of AE data from SP donation.

2 | MATERIALS AND METHODS

The *IQPP Standard for Recording Donor Adverse Events* was used to classify AEs into 10 detailed categories with applicable subcategories (Table 1). As described in the Standard, certain subcategories are not subject to tracking and trending and therefore are not captured in this analysis. The Donor Adverse Event Classification Guide, a supplement to the Standard, provides the signs and symptoms that set the boundaries defining each category and subcategory (Appendix A).[11] A donor AE is classified by a licensed physician or physician substitute using the available information and best medical judgment.

The Standard also requires that specific data elements be recorded for donations with an AE. In addition, information is collected for all donations made to calculate rates by various stratifications. This analysis includes age, gender, weight, height, donor status (first time or repeat), and timing when the reaction first began: pre-donation (prior to inserting the plasmapheresis needle), during donation, post-donation on-site (after collection is completed), or post-donation off-site.

Donation data were collected between May 1 and August 31, 2018, from three PPTA member companies: CSL Plasma, Grifols, and Takeda BioLife. Donations were made at 513 plasma centers in 41 states. Donation eligibility was determined by each individual company's standard operating procedures.

The data were reviewed for missing and incomplete information. Where possible, missing height, age, and weight were obtained from donations made prior to May 1, 2018. Donations with missing or erroneous values were excluded. These values were most likely due to technician input error since they would not have been allowed to donate based on procedural and/or regulatory requirements.

To calculate estimated blood volume (EBV), we used Nadler's formula, as it is generally accepted and used in literature to estimate blood volume, where H is the height in inches and W is the weight in pounds.[12]

$$\text{Male}: \left(0.006012 \times H^3\right) + (14.6 \times W) + 604$$

TABLE 1 Donor adverse event classifications

Category	Subcategory	Recording requirement (yes/no)
Hypotensive event (vasovagal/ hypovolemia)	Prefaint, no loss of consciousness (LOC) (minor)	No
	Prefaint (LOC) (moderate)	Yes
	LOC approximately ≤60 seconds	Yes
	LOC approximately >60 seconds	Yes
	Severe (with or without LOC)	Yes
	Injury	Yes
Major cardiovascular or respiratory event	—	Yes
Local injury related to phlebotomy event	Nerve irritation	Yes
	Hematoma/bruise (uncomplicated)	No
	Hematoma/bruise (complicated)	Yes
	Infection	Yes
	Arterial puncture	Yes
	Infiltration	No
	Major blood vessel injury	Yes
Citrate reaction event	Minor	No
	Moderate	Yes
	Severe	Yes
Hemolysis/hemoglobinuria event	Uncomplicated	Yes
	Complicated	Yes
Air embolus event	Uncomplicated	No
	Complicated	Yes
Allergic event	Local	Yes
	Generalized	Yes
	Anaphylaxis	Yes
Hyperventilation event	—	Yes
Immunization event	Local, mild	No
	Local, severe	Yes
	Systemic, mild	No
	Systemic, severe	Yes
	Hypotensive, no LOC	Yes
	Hypotensive, LOC	Yes
Other events	—	Yes

$$\text{Female}: \left(0.005835 \times H^3\right) + (15 \times W) + 183$$

2.1 | Statistical analysis

Logistic regression was conducted using statistical analysis software (SAS Enterprise Guide version 8.2.) to compare AE rates by weight in each target donation volume, by gender.

3 | RESULTS

A total of 12,330,000 donations collected from 1,076,469 unique plasma donors who made at least one donation during the data collection period were analyzed. The donor population was approximately 62% male and 38% female with an average donor age of 35.6 years. Nearly 93% of the donations were from repeat donors. The average age for first-time and repeat donors was 30 and

TABLE 2 Donor adverse event rates (per 10^4 donations) by timing of when the adverse event (AE) began

	AE rates								
	Hypotensive			Phlebotomy			All events		
Timing of AE	All donors	Female	Male	All donors	Female	Male	All donors	Female	Male
Pre-donation	0.08	0.07	0.08	0.06	0.07	0.05	0.20	0.23	0.18
During Donation	7.24	14.20	3.02	0.73	0.95	0.59	8.97	16.69	4.30
Post-donation on-site	0.63	1.16	0.31	0.32	0.38	0.28	1.17	1.84	0.76
Post-donation off-site	0.37	0.75	0.14	4.81	5.68	4.28	5.51	7.00	4.61

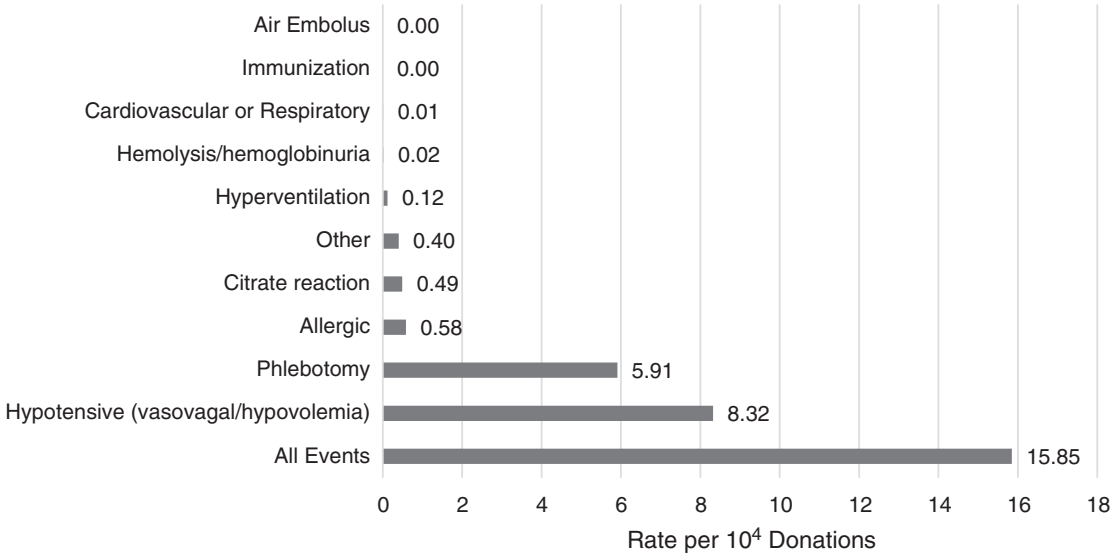

FIGURE 1 Donor adverse event rates (per 10^4 donations) by event category

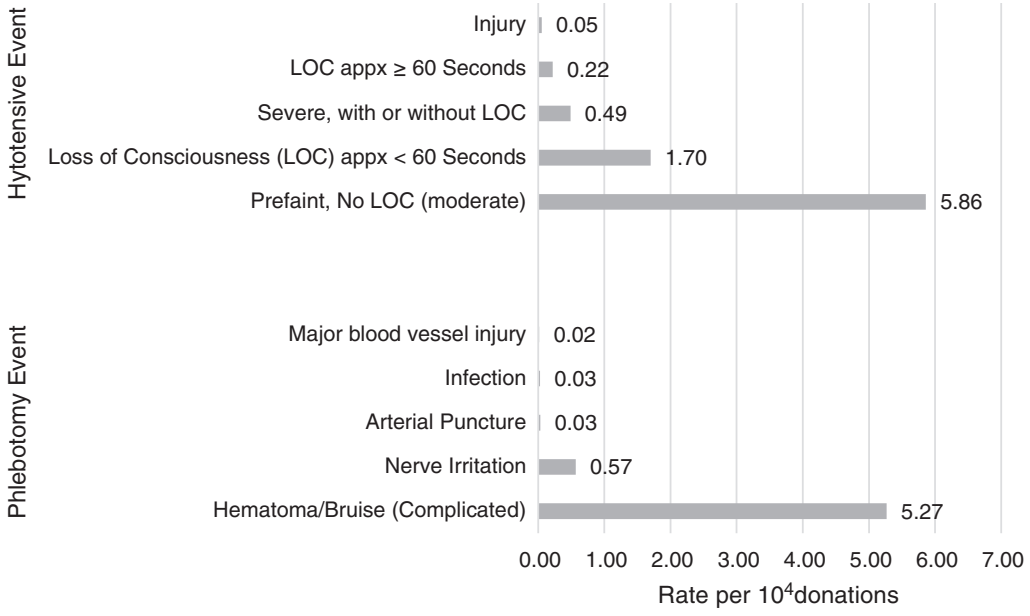

FIGURE 2 Hypotensive and phlebotomy subcategory adverse event rates (per 10^4 donations)

TABLE 3 Adverse event rates (per 10^4 donations) by gender, donor status, age, weight, and body mass index (BMI)

		Hypotensive			Phlebotomy			All events		
Category		**All donors**	**Female**	**Male**	**All donors**	**Female**	**Male**	**All donors**	**Female**	**Male**
Gender										
		8.32	16.18	3.56	5.91	7.09	5.20	15.85	25.76	9.85
Donor status										
First-time		87.48	140.62	37.25	40.47	37.84	42.96	136.66	191.37	84.95
Repeat		6.04	11.53	2.76	4.92	5.94	4.31	12.37	19.56	8.07
Age (years)										
≤20		23.24	46.07	8.54	9.80	11.56	8.66	35.81	61.74	19.13
21–24		13.39	27.15	5.68	6.38	7.13	5.96	22.00	37.59	13.27
25–44		6.71	12.71	3.15	5.32	6.39	4.69	13.55	21.42	8.86
45–64		5.65	11.11	2.13	5.91	7.37	4.96	12.78	20.53	7.78
≥65		6.8	12.33	2.69	12.97	12.33	13.45	21.62	26.83	17.76
Donor status by age (years)										
First-time	≤20	133.92	218.65	54.55	31.53	31.50	31.57	177.86	267.73	93.67
	21–24	115.13	183.52	52.83	33.06	29.59	36.22	157.73	226.87	94.76
	25–44	67.56	106.53	30.65	40.92	37.71	43.96	116.59	156.18	79.09
	45–64	60.92	105.78	16.05	58.65	55.57	61.74	124.71	170.82	78.61
	≥65	125.00	208.33	36.76	160.71	138.89	183.82	303.57	381.94	220.59
Repeat	≤20	13.76	27.44	5.24	7.93	9.41	7.02	23.65	39.50	13.78
	21–24	8.44	16.61	3.97	5.19	5.78	4.86	15.53	25.05	10.32
	25–44	5.09	9.47	2.52	4.35	5.25	3.82	10.75	16.66	7.28
	45–64	4.74	9.12	1.94	5.04	6.36	4.20	10.94	17.37	6.82
	≥65	5.76	10.26	2.44	11.68	10.99	12.20	19.16	23.08	16.26
Weight (pounds)										
110–124		25.98	33.85	7.53	8.21	8.94	6.51	38.05	47.70	15.45
125–149		11.16	17.13	4.88	6.79	7.96	5.55	19.94	27.54	11.93
150–174		11.37	22.44	4.67	5.94	7.77	4.83	19.21	33.03	10.84
≥175		6.35	12.74	3.02	5.67	6.51	5.24	13.41	21.48	9.21
BMI										
<18		10.14	23.79	8.44	6.76	13.60	5.91	18.40	37.39	16.05
18–24		8.53	19.06	4.54	5.76	8.15	4.85	16.18	30.11	10.90
25–29		8.41	19.09	3.66	5.75	7.49	4.97	15.74	29.45	9.63
30–34		9.27	19.67	3.12	6.00	7.91	5.30	16.86	29.47	9.41
≥35		7.27	11.13	2.61	5.94	6.18	5.64	14.72	19.39	9.06

36 years, respectively. Approximately 155,000 donations (1.2%) were not analyzed due to missing or erroneous data. Therefore, the results are based on 12,183,183 donations. There were 19,305 AEs resulting in an overall rate of 15.85 AE per 10,000 donations (0.16%); 18,700 unique plasma donors (1.74% of all donors) experienced at least one AE, and 570 donors (0.05% of all donors) experienced more than one. Females experienced most of the AEs: 45% of the 7049 Phlebotomy events and over 70% for all other categories, mostly Hypotensive events. AEs prior to the start of the donation were rare, accounting for just 1.27% of the total. Most AEs (56.59%) occurred during the donation process. Post-donation events onsite accounted for 7.38% of AEs, whereas post-donation events occurring or reported offsite, especially Phlebotomy AEs, accounted for 34.76%. Table 2 shows the AE rates by timing of when the AE began or was reported, with the highest rates occurring during donation. AE rates for donors who completed

TABLE 4 Donor adverse event (AE) rates (per 10^4 donations) by nomogram volume, weight, and gender

		Female			Male		
Nomogram volume	Weight (pounds)	AE rate	% of all AE	AE rate/(%)	AE rate	% of all AE	AE rate/(%)
690 ml	110–119.9	53.32	3.10	31.54/(16.90)	19.67	0.39	12.28/(5.57)
	120–129.9	38.48	4.26		13.89	0.92	
	130–139.9	27.81	4.58		11.82	1.69	
	140–144.9	26.45	2.59		11.53	1.16	
	145–149.9	22.71*	2.38		11.37*	1.40	
825 ml	150–154.9	40.21	3.95	33.03/(17.15)	12.59	1.86	10.84/(9.28)
	155–159.9	34.46	3.57		10.04	1.62	
	160–164.9	31.66	3.33		10.22	1.76	
	165–169.9	31.35	3.32		11.17	2.03	
	170–174.9	28.01*	2.98		10.41*	2.01	
880 ml	175–179.9	34.77	3.50	21.48/(29.10)	10.49	2.01	9.21/(22.00)
	180–189.9	29.51	5.92		9.85	3.87	
	190–199.9	26.69	5.07		9.82	3.73	
	200–224.9	22.25	9.19		9.33	7.59	
	225–249.9	17.99	5.41		8.53	4.81	
	250–274.9	14.59	2.78		8.62	2.95	
	275–299.9	13.96	1.50		8.75	1.70	
	300–349.9	11.07	0.94		8.27	1.36	
	350–399.9	11.80*	0.22		9.38	0.44	
	≥400	10.07[a]	0.01		9.61	0.02	

[a]Only 993 donations in the 880 ml, ≥400 pounds group with one AE.
*$p < .001$.

their donation ($9.40/10^4$ donations) were much lower than the overall AE rate. Among donors that had a partial donation (<90% of the target donation volume), the AE rate was significantly higher ($218.40/10^4$ donations).

As shown in Figure 1, the two classification categories with the highest rates were the Hypotensive event at $8.32/10^4$ donations and the Phlebotomy Event at $5.91/10^4$ donations. The rest of the AEs had rates ranging from 0.00 to $0.58/10^4$ donations. AEs classified as Other occurred in $0.40/10^4$ donations. There were no air embolus AEs.

Figure 2 shows the two most common AEs, Hypotensive (vasovagal/hypovolemia) and Phlebotomy, by subcategory. The most frequent Hypotensive subcategory was Prefaint with no loss of consciousness (LOC) (moderate), which accounted for 70.4% of the Hypotensive events. Hypotensive events associated with an injury were rare, $0.05/10^4$ donations (0.0005%). Hematoma/Bruise (complicated) had a rate of $5.27/10^4$ donations and accounted for 89.2% of all Phlebotomy events.

Table 3 shows the AE rates for Hypotensive, Phlebotomy, and All events by gender, donor status, age, age by donor status, weight, and body mass index (BMI). Females were 2.6 times more likely to experience an AE than males for All Events (25.76 vs. 9.85 per 10^4 donations) and 4.5 times more likely to have a Hypotensive event. Females were 1.4 times more likely to have Phlebotomy-related events.

The factor associated with the highest AE rate is donor status. First-time donors (e.g., never donated plasma or had not donated plasma in the past 6 months) had 11.0 times higher AE rates than repeat donors for any AE (136.66 vs. 12.37 per 10^4 donations). In addition, first-time donors were 14.5 times more likely to experience a Hypotensive AE and 8.2 times more likely to have a Phlebotomy AE. Female first-time donors were 9.8 times more likely to experience an AE than repeat female donors and were 3.8 times more likely to have a Hypotensive event than first-time male donors. The first-time male donors were 10.5 times more likely to have an AE than repeat male donors. Repeat female donors were 4.2 times as likely to have a Hypotensive event than repeat male donors.

TABLE 5 Donor adverse event (AE) rates (per 10^4 donations) by pre-donation estimated blood volume (EBV) by applicable nomogram volume

		AE rates								
		Phlebotomy events only			All events except phlebotomy			All events		
Nomogram volume	EBV	All donors	Female	Male	All donors	Female	Male	All donors	Female	Male
690 ml	<3500	9.30	9.26	43.10	41.79	41.84	0.00	51.08	51.09	43.10
	3500–3999	7.78	7.71	9.07	19.84	20.42	9.07	27.62	28.13	18.14
	4000–4499	6.74	8.49	6.05	7.93	10.29	7.00	14.67	18.78	13.05
	4500–4999	4.94	7.70	4.93	6.38	0.00	6.40	11.32	7.70	11.33
	5000–5499	5.57	0.00	5.58	5.57	0.00	5.58	11.15	0.00	11.17
	≥5500	14.27	0.00	14.27	14.27	0.00	14.27	28.53	0.00	28.53
825 ml	<3500	0.00	0.00	0.00[c]	12.41	12.80	0.00[c]	12.41	12.80	0.00[c]
	3500–3999	7.74	7.75	0.00	42.50	42.56	0.00	50.24	50.31	0.00
	4000–4499	7.33	7.72	4.74	20.46	21.30	9.04	27.80	28.82	13.78
	4500–4999	5.27	8.30	4.92	6.97	13.03	6.28	12.25	21.33	11.20
	5000–5499	4.66	14.99	4.65	5.59	0.00	5.60	10.26	14.99	10.25
	5500–5999	4.46	0.00[c]	4.47	5.58	0.00[c]	5.85	10.31	0.00[c]	10.32
	≥6000	0.00	0.00[c]	0.00	14.04	1666.67[c]	7.05	14.04	1666.67[c]	7.05
880 ml	<3500	0.00[c]	0.00[c]	—	0.00[c]	0.00[c]	—	0.00[c]	0.00[c]	—
	3500–3999	0.00	0.00	0.00[c]	67.89	62.79	2500.00[c]	67.89	62.79	2500.00[c]
	4000–4499	6.80	6.81	0.00	30.79	30.78	32.95	37.58	37.59	32.95
	4500–4999	7.17	7.32	6.14	16.25	17.89	4.64	23.42	25.21	10.78
	5000–5499	5.63	6.05	5.35	7.84	12.12	5.09	13.47	18.18	10.44
	5500–5999	5.14	5.64	5.01	5.38	9.17	4.38	10.52	14.81	9.39
	6000–6499	5.20	6.29	5.00	3.97	6.61	3.48	9.17	12.90	8.47
	6500–6999	4.97	4.06	5.11	3.39	5.49	3.08	8.36	9.55	8.19
	7000–7499	5.82	7.26	5.65	2.94	4.26	2.78	8.75	11.52	8.42
	≥7500	5.74	8.94	5.52	2.70	4.17	2.60	8.44	13.11	8.12

Note: Rates marked with a "c" have less than 50 donations per group. There were no AEs with any of the donations noted with a "0.00," and there were no donations in the categories noted with a "-."

Age is another important factor related to AEs. Donors aged 20 and younger had higher AE rates compared with donors in all other age groups. For donors aged 20 and younger, females were 3.7 times more likely and male donors were 3.2 times more likely to experience a Hypotensive event than donors aged 65 years and older. However, both male and female donors aged 65 years and older had the highest Phlebotomy AE rates. When first-time and repeat donor Hypotensive rates by age were compared, AE rates for first-time donors were 9.7–22.7 times higher.

Weight is also an important factor related to AEs. Donors weighing 110–124 pounds had the highest total AE rates, as well as for Hypotensive and Phlebotomy events. For All events, donors weighing ≥175 pounds had lower AE rates. Donors weighing 110–124 pounds were 4.1 times more likely than donors weighing ≥175 pounds to have a Hypotensive event and 2.8 times as likely to have any AE. Both females and males weighing ≥175 pounds had lower Phlebotomy AE rates than donors weighing 110–124 pounds.

BMI, an estimate of body adiposity, is calculated by dividing weight in kilograms by height in meters squared. Individuals with higher BMI values generally have a larger EBV compared with individuals with lower BMI values. However, the relationship is not clear-cut since the EBV may be overestimated for individuals with high BMIs given that the adipose tissue is less vascular than the lean tissue.[13] Donors with a low BMI (<18) had higher AE rates for All, Hypotensive, and Phlebotomy events. In contrast, both female and male donors with BMI ≥35 had the lowest rates for All AE and Hypotensive events, except for males with a slightly higher AE rates

for Phlebotomy events. In all BMI classifications, females had considerably higher AE rates than males and the highest rates for all categories were for donors with the smallest BMI.

For SP collected in the United States, U.S. Food and Drug Administration (FDA) has approved three total collection volumes (TCVs)—690, 825, and 880 ml—or nomograms, determined by the donor's weight—110–149, 150–174, and ≥ 175 pounds, respectively (Appendix B).[9] The TCV includes the volume of plasma collected plus the volume of anticoagulant; approximately 9% of the TCV.

AE rates by nomogram, weight, and gender are shown in Table 4. Although females made 38% of the total donations, they accounted for 63.15% of the AEs and had higher AE rates at each weight in the nomogram. Females had 2.6, 3.0, and 2.3 times higher AE rates for the 690-, 825-, and 880-ml nomogram, respectively. Within each nomogram for both genders, the AE rate decreased as the weight increased. The least variation was seen in the male 880-ml nomogram. Within each gender and nomogram, logistic regression was used to compare the AE rate of the lowest weight with the highest weight. Except in the 880-ml nomogram, the differences in AE rates were statistically significant ($p < .001$) for both genders. Although the AE rate for females ≥400 pounds had the lowest rate, it was not significant. This was due to the small size for this comparison, since only one AE occurred in this group. However, the rate for those weighing 350–399.9 pounds was statistically less ($p < .001$) than for the lowest weight. Females in the transition from the highest weight grouping in a nomogram to the lowest weight grouping in the next nomogram showed a marked increase in the AE rate. We speculate that the increase may be attributable specifically to Hypotensive AEs. When a donor moves from the highest weight grouping in a nomogram to the lowest weight grouping in the next nomogram, the %EBV collected immediately increases before gradually dropping as the donor's weight increases.

Table 5 shows AE rates by EBV and nomogram. Since Phlebotomy AEs were not expected to be associated with a donor's EBV, AEs were separated into two groups: Phlebotomy and All events except Phlebotomy. Although females had generally higher Phlebotomy AE rates than males for most EBVs in each nomogram, they only accounted for 45% of all Phlebotomy AEs. However, females accounted for 61.4% of all the AEs by EBV.

When Phlebotomy events were excluded, females had over 70% of the remaining AEs. Females had higher AE rates than males in the 690 and 825 ml groups for the smaller EBVs. No AEs were seen in females with EBV > 4500 ml in the 690-ml group and for those with EBVs between 4500- and 5999-ml and in the 825-ml nomogram. The extremely high AE rate seen in the 6000–6999 EBV group is due to the small number of female donors with large EBV and for males in the 880-ml nomogram due to the small number of males with small EBV. In the 880-ml nomogram at all EBVs >4500 ml, females had higher AE rates. Overall, the data indicated that donors with higher EBVs are less likely to experience AEs.

TABLE 6 Donor adverse event rates (per 10^4 donations) by percentage (%) of estimated blood volume (EBV) Drawn[a] by nomogram volume

		AE rates		
Nomogram volume	**% EBV**	**All donors**	**Female**	**Male**
690 ml	<16%	35.91	412.70	15.92
	16%–19%	16.01	20.11	6.89
	20%–24%	23.18	23.19	19.69
	25%–29%	126.18	126.18	0.00
825 ml	<16%	64.13	343.03	37.18
	16%–19%	11.61	31.79	5.91
	20%–24%	20.57	20.69	0.00
	25%–29%	0.00	0.00	0.00
880 ml	<16%	15.07	36.03	10.98
	16%–19%	10.92	16.34	5.70
	20%–24%	18.51[b]	18.51	—[c]
	25%–29%	0.00	0.00	0.00

[a]The %EBV drawn includes the volume of plasma drawn plus the volume of anticoagulant, which overestimates the donor's %EBV by approximately 9%.

[b]n = 638 donations with AE; 637 females; 1 male.

[c]Rate is 14.79 but is based on 1 AE out of 676 donations.

TABLE 7 Donor adverse event rates (per 10^4 donations) by percentage (%) of estimated blood volume (EBV) Drawn[a] for full donations (≥90% of target nomogram volume)

		AE rates								
		Hypotensive			Phlebotomy			All events		
Donation	% EBV	All donors	Female	Male	All donors	Female	Male	All donors	Female	Male
Full donation	<16%	2.04	5.64	1.32	3.71	4.08	3.63	6.41	10.90	5.51
	16%–19%	8.82	10.73	1.54	4.88	5.06	4.10	15.05	17.38	6.16
	20%–24%	19.70	19.62	—[b]	6.53	6.65	0.00	28.33	28.26	—[b]
	25%–29%	0.00[c]	0.00[c]	—	0.00[c]	0.00[c]	—	0.00[c]	0.00[c]	—

[a]The %EBV drawn includes the volume of plasma drawn plus the volume of anticoagulant, which overestimates the donor's %EBV by approximately 9%.
[b]Only 131 males donated 20%–24%EBV with 1 Hypotensive AE.
[c]Only 12 females donated 25%–29%EBV.

AE rates by %EBV drawn by nomogram are shown in Table 6. Donations were grouped by their applicable nomogram and sorted by their %EBV drawn. Overall, donors in the 880-ml nomogram had lower AE rates by % EBV drawn compared with the same %EBV drawn in the other nomograms. Females had higher AE rates in each of the %EBV drawn groups compared to males, regardless of their nomogram. In all nomograms, donations of <16% of the donor's EBV had higher AE rates than those with larger donations. Of note, there were just four AEs in the 317 total donations in the female 690-ml nomogram group with a %EBV of 25%–29%, which may explain the unusually high AE rate.

The major contributor to the higher AE rate in donations of <16% EBV appears to be AEs that result in the early termination of the procedure, resulting in a partial donation. Of all donations <16%, 3.5% did not make a full donation. Among partial donations with <16% EBV, there were 7574 AEs out of 283,315 donations (2.67%) compared with 5035 AEs out of 7,856,996 for full donations (0.064%). Therefore, it is not surprising that the AE rates are higher for those with small %EBV donations. Most partial donations may be due to an AE resulting in the early termination of the procedure or non-AE situations, such as loss of venous access.

Looking at the AE rates by %EBV drawn for full donations, Table 7 shows a different picture. Males and females donating <16% EBV had the lowest rates for Hypotensive, Phlebotomy, and All Events. Among female donors completing a full donation, Hypotensive AE increased with increasing %EBV donated. This pattern was not seen in male donors, and few male donors donated ≥20% of their EBV; 52% of all AEs for females donating <16% EBV were Hypotensive compared to 24% for males. For females donating 16%–19% EBV, 62% of AEs were Hypotensive compared with 25% for males. Females donating 20%–24% EBV had 70% of AEs as Hypotensive.

4 | DISCUSSION

This AE analysis for 12,183,183 donations made by SP donors at 513 PPTA US member plasma collection centers in 41 states constitutes the most comprehensive review to date. The overall AE rate of 15.85 per 10^4 donations shows that very few donations (0.16%) result in an AE. Few (1.79%) of the 1,076,469 unique donors experienced an AE during the study period, and only 0.05% experienced more than one AE. The Hypotensive and Phlebotomy events rates were 8.32 and $5.91/10^4$ donations, respectively, and accounted for 90% of all the AEs recorded. Most Hypotensive events met the classification of "Pre-faint, no loss of consciousness (moderate)," which are events that can be managed with supportive care at the donation center and do not involve any injury. Most Phlebotomy events were related to bruising. Other AEs, including potentially serious AEs such as Major Cardiovascular or Respiratory events, were very rare.

Over 56% of the AEs occurred during the donation process, while post-donation events occurring after the donor left the donor center accounted for 34.78%. However, it is important to note that post-donation events included Phlebotomy-related events, such as bruises that were reported to center staff after a donation or upon presenting for the next donation. In fact, most post-donation AEs were due to Phlebotomy (61%), with the remaining 39% classified as Hypotensive.

Pre-donation AE accounted for 1.25% of all the AEs reported and an additional 1.82% occurred after the initial venipuncture, but prior to any plasma being collected. Based on this analysis, approximately 2600 donations would have been lost due to these early reactions. While the numbers appear low, it could lead to donors not returning for future donations. To ameliorate donor concerns and fears, centers monitor reactions and provide donor counseling and staff training to encourage

donors to try again. Future analyses could examine the effectiveness of interventions for these early AEs.[14–16]

SP donor characteristics associated with higher AE rates were first-time donor status, female gender, younger age, and lower pre-donation EBV. These characteristics have all been described as significant factors for AEs for whole blood donation as well.[17–19]

When considering the total AE rate for all classifications, first-time donors were 11 times more likely to experience an AE than repeat donors. This was most apparent for Hypotensive AE, where first-time donors were 14.5 times more likely than repeat donors to experience an event. Although this study was not designed specifically to distinguish between Hypotensive events due to changes in EBV versus those due to vasovagal reactions, it is known that there is an association between anxiety and the vagal response.[20] However, donors presenting for their first SP donation may experience anxiety associated with the procedure or with other potential stressors, such as the sight of blood or plasma. Therefore, first-time donors could be targeted for further research on prevention strategies.

Being female was also a predictor for AEs. Females experienced AEs at a rate 2.61 times higher than males. This was most notable for Hypotensive events where females had rates 4.54 times higher. The physiological reasons for this are of interest and are likely multifactorial. Orthostatic hypotension and syncope occur more in females because the vasoconstrictor reserve can be overwhelmed by reduced stroke volume and impaired cardiac filling during hypovolemia.[21] The current nomograms in the United States are not gender specific and therefore do not account for the gender differences in EBV for individuals of the same height and weight. At each of the three nomograms, females were more likely than males to experience an AE. Females transitioning from the highest weight grouping in a nomogram to the lowest weight grouping in the next nomogram showed a sharp increase in the overall AE rate, probably due to the increased percentage of EBV collected when moving from one nomogram to the next.[22,23]

Age was also a predictor for AE. Donors ≤ 20 years old had overall AE rates that were 1.74 times higher than donors aged 45–64. However, younger donors are also more likely to be first-time donors, so it is not entirely clear if age is an independent predictor or simply associated with first-time donors. Donors ≥ 65 years had the highest rates of Phlebotomy events. It is possible this is explained by structural changes to veins with age or the accumulated effect of repeat venipunctures over time. When examining the influence of age separately for first-time and repeat donors, first-time donors of all ages have AE rates significantly higher than repeat donors. Interestingly, the phlebotomy rates are higher for both first-time and repeat donors > 65 years, especially for first-time donors, suggesting that special attention should be given to these donors.

Weight, BMI, and pre-donation EBV were the predictors of AE. This was particularly apparent for Hypotensive AE where rates decreased as weight and BMI increased and pre-donation EBV decreased.

The %EBV collected provides a measure of the role of volume on reported events. For females in each of the nomograms, the highest AE rates were seen in those who donated <16% of their pre-donation EBV. However, most Hypotensive AEs result in the discontinuation of the plasmapheresis process prior to the target collection volume being reached. For males, the picture was not as clear as only in the 825-ml group was the <16% group higher. Therefore, the %EBV collected may not be the best predictor of risk for a Hypotensive AE. Rather, it is important to look at the AE rates for those making full donations to evaluate the importance of %EBV donated as a risk factor, particularly for females. Gender differences may contribute to the physiological response to intravascular blood volume shifts that occur during the automated plasmapheresis. In addition, the nomogram is not gender specific, so for males and females at the same weight females may have lower pre-donation EBVs than males, thereby increasing the %EBV collected. Analyzing AE for full donations removes donors from the analysis whose low-volume donations were due to having an early reaction.

Our analysis has several limitations. While we were able to analyze data from many donors and donations, the donations were made over only a 4-month period. Therefore, it may not be fully representative since there are seasonal variations in donor demographics. A planned future AE analysis will cover a 12-month period to ensure any seasonal variations are described. We attempted to provide fine breakdowns of the variables to examine whether there were relationships and trends. However, even with the large number of donations, at the extremes of the distributions frequently the number of AEs were small, as were the number of donations, yielding unstable estimates of the event rates. As noted, some of the factors analyzed were interrelated. We did not conduct multifactorial analyses to discern the contribution of each factor to the possibility of having an AE. We feel the more detailed analysis would be best conducted on a larger dataset. Since AE risk factors appear to be like those for blood collections, we feel it is important to share the findings of this analysis with others.

The *IQPP Standard for Recording Donor Adverse Events* was designed to capture donor AEs related to SP collection in a standardized manner across the plasma industry. While the blood collection industry has developed a similar donor hemovigilance program to standardize the AE classification, the classification categories and definitions are in some cases different from the PPTA Standard.[24] Since our analysis did not include the minor subcategories, as they are excluded from the Standard, our data are not directly

comparable to other hemovigilance programs. We recognize that by excluding these categories, we have not captured all of AEs that occur. However, in most cases, these events are minor and resolve without further donor complications. Thus, caution must be exercised when trying to compare blood and plasma donor reaction rates.

As we have shown, SP donation in the United States, using the current nomogram and donation frequency is a safe process. A robust plasma vigilance program is essential to continue monitoring the safety of the process, evaluate reactions from donating plasma, and improve donor satisfaction. It will also establish a benchmark that will allow a more vigorous assessment of the impact of any future changes related to donor selection or the donation process.

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CONFLICT OF INTEREST

GBS and MF are the employees of the Plasma Protein Therapeutics Association. MB is an employee of Biomat USA, Inc. JH and JL are the employees of Takeda/BioLife Plasma Services LP. GS is an employee of FEI Systems. And TS is an employee of CSL Plasma.

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REFERENCES

1. Plasma Protein Therapeutics Association (2020). Current members. Plasma Protein Therapeutics Association. Available from: https://www.pptaglobal.org/about-us/current-members. Accessed Jul 13, 2020.
2. Storch EK. Donor hemovigilance: a call to arms. Transfusion. 2020;60:1115–7.
3. Jones J, Sapiano M, Mowia S, et al. Has the trend of declining blood transfusions in the United States ended? Findings of the 2019 National Blood Collection and Utilization Survey. Transfusion. 2021. https://doi.org/10.1111/trf.16449.
4. Wiltbank T, Giordano G. The safety profile of automated collections: an analysis of more than one million collections. Transfusion. 2007;47:1002–5.
5. Winters J. Complications of donor apheresis. J Clin Apheresis. 2006;21:132–47.
6. McLeod B, Price T, Owen H, Ciavarella D, Sniecinski I, Randels MJ, et al. Frequency of immediate adverse events associated with apheresis donations. Transfusion. 1998;38:938–43.
7. Schulzki K, Seidel H, Storch H, Karges H, Kiessig S, Schneider S, et al. A prospective multicentre study on the safety of long-term intensive plasmapheresis in donors (SIPLA). Vox Sanguinis. 2006;91:162–73.
8. Nguyen TC, Kiss JE, Goldman JR, Carcillo JA. The role of plasmapheresis in critical illness. Crit Care Clin. 2012;28:453–68.
9. Food and Drug Administration. Volume Limits—Automated Collection of Source Plasma. 1992. Available from: https://www.fda.gov/media/70951/download. Accessed Jul 10, 2020.
10. Plasma Protein Therapeutics Association. IQPP Donor Fluid Administration Standard. Plasma Protein Therapeutics Association. 2014. Available from: www.pptaglobal.org. Accessed Dec 4, 2019.
11. Plasma Protein Therapeutics Association. IQPP Standard for Recording Donor Adverse Events. Plasma Protein Therapeutics Association. 2018. Available from: https://www.pptaglobal.org/images/IQPP/Standards_Revisions/2018/IQPP_DAERS_V2.pdf. Accessed Dec 4, 2019.
12. Nadler SB, Hidalgo JU, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962;51:224–32.
13. Holme S, Elfath MD, Heaton A, Whitley P, McNeil D. Prediction of red cell and blood volumes distribution by various nomograms: do current nomograms overestimate? Transfusion. 2008;48:910–6.
14. Custer B, Rios J, Schlumpf K, Kakaiya RM, Gottschall JL, Wright DJ, et al. Adverse reactions and other factors that impact subsequent blood donation visits. Transfusion. 2012;52:118–26.
15. Wiltbank TB, Giordano GF, Kamel H, Tomasulo P, Custer B. Faint and prefaint reactions in whole-blood donors: an analysis of predonation measurements and their predictive value. Transfusion. 2008;48:1799–808.
16. Yuan S, Gornbein J, Smeltzer B, Ziman AF, Lu Q, Goldfinger D. Risk factors for acute, moderate to severe donor reactions associated with multicomponent apheresis collections. Transfusion. 2008;48:1213–9.
17. Eder A, Kiss J. Adverse reactions and iron deficiency after blood donation. In: Simon T, McCullough J, Snyder E, Solheim B, Strauss R, editors. Rossi's principles of transfusion medicine. 5th ed. West Sussex, UK: John Wiley and Sons; 2016.
18. Trouern-Trend JJ, Cable RG, Badon SJ, Newman BH, Popovsky MA. A case-controlled multicenter study of vasovagal reactions in blood donors: influence of sex, age, donation status, weight, blood pressure, and pulse. Transfusion. 1999;39:316–20.
19. Goldman M, Osmond L, Yi Q-L, Cameron-Choi K, O'Brien SF. Frequency and risk factors for donor reactions in an anonymous blood donor survey. Transfusion. 2013;53:1979–84.
20. Seheult JN, Lund ME, Yazer MH, Titlestad K. Factors associated with vasovagal reactions in apheresis plasma and whole blood donors: a statistical-epidemiological study in a European donor cohort. Blood Res. 2016;51:293–6.

21. Fu Q, Levine BD. Why do young women (donors) faint? Transfusion. 2010;50:522–5.
22. Karger R, Slonka J, Junck H, Kretschmer V. Extracorporeal blood volume of donors during automated intermittent-flow plasmapheresis and its relevance to the prevention of circulatory reactions. Transfusion. 2003;43:1096–106.
23. Karger R, Halbe M, Dinges G, Wulf H, Kretschmer V. Blood volume regulation in donors undergoing intermittent-flow plasmapheresis involving a high extracorporeal blood volume. Transfusion. 2006;46:1609–15.
24. AABB. Standard for Surveillance of Complications Related to Blood Donation. 2014. Available from: https://www.aabb.org/docs/default-source/default-document-library/resources/donor-standard-definitions.pdf?sfvrsn=21834fa4_0. Accessed Feb 20, 2020.

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APPENDIX A: DONOR ADVERSE EVENT CLASSIFICATION GUIDE

Donor Adverse Event (DAE) classification	Description	Signs/symptoms/findings
1. Hypotensive (Vasovagal/Hypovolemia)		
Hypotensive reaction (vasovagal/hypovolemia) that falls into any of the following categories.		
NOTE: For the purposes of this IQPP Standard, "medical staff intervention" means the use of expertise from the physician or physician substitute to make decisions regarding management of the DAE.		
1.1 Hypotensive: Prefaint, no LOC (minor)	This reaction a. Must resolve without medical staff (e.g., physician substitute) intervention, AND b. Involves signs and symptoms that resolved quickly (e.g., within approximately 10 min).	May include one or more of the following: a. Abdominal cramps; b. Auditory disturbance (e.g., sounds coming from a distance or "buzzing" in the ears); c. Chills or Shivering; d. Clammy; e. Cold extremities; f. Dizziness; g. Epigastric discomfort; h. Facial pallor (e.g., pale skin or lips); i. Feeling of warmth; j. Headache or neck ache; k. Hypotension; l. Lightheadedness; m. Nausea; n. Palpitations; o. Sweating; p. Visual disturbance (e.g. blurred or faded vision) q. Weakness.
1.2 Hypotensive: Prefaint, no LOC (moderate):	This reaction a. Requires medical staff (physician substitute) intervention, OR b. Involves signs/symptoms that did not resolve quickly (e.g., within approximately 10 min), OR c. Additional signs/symptoms may be present.	May include any in 1.1 AND a. Vomiting.
1.3 Hypotensive: LOC (brief)	In this reaction, LOC lasts approximately less than 60 s.	May include any in 1.1 or 1.2.

Donor Adverse Event (DAE) classification	Description	Signs/symptoms/findings
1.4 Hypotensive: LOC (prolonged)	In this reaction, LOC lasts approximately 60 s or longer.	May include any in 1.1 or 1.2.
1.5 Hypotensive; severe (with or without LOC):	This reaction may or may not include LOC.	May include any in 1.1 through 1.4 and any of the following: a. Chest pain b. Convulsions/Seizures c. Loss of bladder/bowel control d. Prolonged signs or symptoms that do not resolve.
1.6 Hypotensive; injury	A hypotensive event that results in ANY type of injury such as a. Closed head injury; b. Dental injury; c. Fracture; d. Laceration; e. Soft tissue injury (not phlebotomy-related); f. Other.	May include any of 1.1–1.5 as well as any signs/symptoms related to the injury itself.
NOTE: If the donor exhibits the symptoms of a hypotensive event (1.1 through 1.6), in addition to "anxiety," then the event should be classified according to "1.1–1.6 Hypotensive."		
2. Major cardiovascular or respiratory event Major cardiovascular or respiratory event that occurs within 24 h of the completion of donation and which falls into the following:		
2.1 Major cardiovascular or respiratory event	Major cardiovascular or respiratory event that occurs within 24 h of the completion of donation.	May include any of the below: a. Angina pectoris; b. Cardiac arrest; c. Cerebrovascular accident; d. Myocardial infarction; e. Transient ischemic attack f. Respiratory arrest.
3. Local injury related to phlebotomy Local injury related to phlebotomy that falls into one of the following categories:		
3.1 Local injury related to phlebotomy: nerve irritation	Persistent signs, symptoms, or findings in a peripheral nerve distribution associated with the venipuncture area, which began at venipuncture or later (in the absence of a visible hematoma).	May include any of the below: a. Immediate intense pain at site; b. Paresthesias, numbness/tingling of fingers, hand, or arm; c. Shooting pain down arm; d. Weakness of arm.
3.2 Local injury related to phlebotomy: hematoma/bruise (uncomplicated)	A hematoma/bruise that is approximately $\leq 2'' \times 2''$. **"$\leq 2'' \times 2''$"** means that both dimensions are **$\leq 2''$**. For example, a hematoma/bruise, that is, $2'' \times 2''$, in the absence of signs/symptoms/findings for "complicated," would be classified as "uncomplicated." However, a hematoma/bruise, that is, $3'' \times 1''$, would be classified as "complicated." If following initial classification and prior to resolution, the hematoma/bruise is found to meet the classification requirements for "complicated," then it shall be reclassified as "complicated" and/or recorded appropriately in the facility's DAE documentation system.	May include any of the below: a. Mild pain; b. No restriction of movement; c. Skin discoloration; d. Swelling.

(Continues)

Donor Adverse Event (DAE) classification	Description	Signs/symptoms/findings
3.3 Local injury related to phlebotomy: hematoma/bruise (complicated)	A hematoma/bruise that is approximately >2″ × 2″. **"**>2″ × 2″**"** means that at least one dimension is **>2**″. For example, a hematoma/bruise that is 3″ × 2″ would be classified as "complicated." However, a hematoma/bruise, that is, 2″ × 1,″ would be classified as "uncomplicated," unless also has signs/symptoms/findings for "complicated."	May include any of the below: a. Paresthesias, numbness/tingling of fingers, hand, or arm; b. Pressure; c. Redness; d. Restricted movement; e. Shooting pain down arm; f. Significant pain; g. Skin discoloration; h. Swelling; i. Tenderness; j. Warmth; k. Weakness of arm.
3.4 Local injury related to phlebotomy: infection		May include any of the below: a. Drainage; b. Pain; c. Redness; d. Swelling; e. Tenderness; f. Warmth.
3.5 Local injury related to phlebotomy: arterial puncture	An apparent arterial puncture	May include any of the below: a. Bright red blood; b. Pulse sensation in tubing; c. Pulsing blood flow.
3.6 Local injury related to phlebotomy: infiltration	An apparent infiltration in the absence of bruising or hematoma	May include any of the below: a. Pain; b. Swelling.
3.7 Local injury related to phlebotomy: major blood vessel injury		May include any of the below: a. Arteriovenous fistula; b. Brachial artery pseudoaneurysm; c. Compartment syndrome; d. Venous thrombosis; e. Phlebitis; f. Thrombophlebitis.
4. Citrate reaction Citrate reaction that falls into one of the following categories:		
4.1 Citrate reaction: minor	Resolves quickly with or without reducing flow rate or providing calcium.	May include any of the below: a. Metallic taste; b. Paresthesia (perioral—lips Tingling/numbness); c. Paresthesia (peripheral—hands/feet tingling/numbness).
4.2 Citrate reaction: Moderate		Any of 4.1 that progress to the rest of the body AND any of the below: a. Carpopedal spasms; b. Chest pressure; c. Cold extremities; d. Chills/shivering; e. Muscle tightness and/or cramping; f. Nausea; g. Pallor, pale skin, or lips; h. Shortness of breath; i. Sneezing/nasal congestion; j. Tetany (transient);

Donor Adverse Event (DAE) classification	Description	Signs/symptoms/findings
		k. Tremors (sensation of vibration); l. Twitching; m. Vomiting.
4.3 Citrate reaction: severe		Any of 4.1 or 4.2 that progress to the rest of the body AND any of the below: a. Bluish tint to skin (cyanosis); b. Chest pain; c. Heart arrhythmia; d. Hypotension (severe); e. Incontinence; f. Mental confusion; g. Tetany (severe).
5. Hemolysis/Hemoglobinuria Reaction that falls into one of the following categories:		
5.1 Hemolysis/Hemoglobinuria: uncomplicated		Red-/brown-colored urine as the only sign
5.2 Hemolysis/Hemoglobinuria: complicated		Red-/brown-colored urine and any of the below: a. Back/flank pain; b. Bluish tint to skin (cyanosis); c. Mental confusion; d. Pallor, pale skin or lips; e. shortness of breath.
6. Air embolus Air embolus that falls into one of the following categories.		
6.1 Air embolus: uncomplicated		None
6.2 Air embolus: complicated		May include any of the below: a. Back/flank pain; b. Bluish tint to skin (cyanosis); c. Chest pain; d. Mental confusion; e. Nausea; f. Shock; g. Shortness of breath; h. Vomiting.
7. Allergic Allergic reaction that falls into one of the following categories:		
7.1 Allergic: Local	In the antecubital area.	May include any of the below: a. Itching; b. Rash/Hives; c. Redness.
7.2 Allergic: generalized		May include any of 7.1 AND any of the below: a. Itching, generalized; b. Rash/hives, generalized; c. Sneezing/nasal congestion.
7.3 Allergic: anaphylaxis		May include any of 7.1 AND any of 7.2 AND any of the below: a. Anxiety; b. Arrhythmia; c. Bluish tint to skin (cyanosis); d. Gastrointestinal symptoms; e. Laryngeal edema with stridor;

(Continues)

Donor Adverse Event (DAE) classification	Description	Signs/symptoms/findings
		f. Restlessness g. Scratchy feeling in throat; h. Shortness of breath; i. Swollen tongue, throat, eyes, and face; j. Wheezing; k. Hypotension. *NOTE*: The term "anxiety" as used here, includes significant anxiety and is more than simply being "tense" or verbalizing nervous feelings a new donor may report, such as nervousness about: • Needles; • Blood; • Pain or discomfort; • Fainting; • Being deferred; • Medical environments.
8. Hyperventilation Hyperventilation that results in any of the following signs and symptoms.		
8.1 Hyperventilation	This reaction • Is more than simply being "tense" or verbalizing anxious feelings a donor may report, such as nervous about • Needles; • Blood; • Pain or discomfort; • Fainting; • Being deferred; • General environment. • Requires medical staff (physician substitute) intervention • Involves signs/symptoms that do not resolve quickly with supportive care and reassurance (e.g., within 10 min)	May include any of the below: a. Anxiousness/anxiety;[a] b. Carpopedal spasms; c. Chest tightness; d. Dry mouth; e. Paresthesia (Perioral—tingling/numbness); f. Paresthesia (Peripheral—hands/feet); g. Respiration, rapid; h. Restlessness; i. Shaking; j. Shortness of breath; k. Tetany.
9. Other Reaction that does not fall into any other category listed above or in Section 10.		
9.1 Other	A reaction that does not fall into any other category listed above	Any
10. Immunization Immunization reaction that falls into one of the following categories:		
10.1 Immunization: local, mild	Associated with the site of injection	May include any of the below: a. Induration (hardening); b. Itching; c. Nodule formation; d. Pain; e. Rash; f. Redness; g. Swelling; h. Tenderness; i. Urticaria.
10.2 Immunization: local, severe	Associated with the site of injection	May include any of 10.1 AND any of the below: a. Brachial neuritis; b. Infection; c. Necrosis

Donor Adverse Event (DAE) classification	Description	Signs/symptoms/findings
10.3 Immunization: systemic, mild		May include any of the below: a. Arthralgia; b. Diarrhea; c. Dizziness; d. Fatigue; e. Fever; f. Flu-like symptoms; g. Headache; h. Lymphadenopathy (enlarged, sometimes tender lymph glands); i. Malaise; j. Myalgia (muscular pain); k. Nausea; l. Rash, disseminated, diffuse; m. Vomiting
10.4 Immunization: systemic, severe	Includes specific reactions related to administration of the vaccine or antigen and the complications that may result as well as life-threatening reactions. Immediate medical care is necessary.	May include any of 10.3 AND any of the below: a. Anaphylaxis or anaphylactoid reactions; b. Hemolytic transfusion reaction (when human red blood cells are used as the antigen); c. Serum sickness See package insert for information on adverse reactions specific to vaccine administered.
10.5 Immunization: Hypotensive (no LOC)	Onset of symptoms considered to be related to an immunization	May include any of 1.1 and 1.2
10.6 Immunization: Hypotensive (LOC)	Onset of symptoms considered to be related to an immunization	May include any of 1.3 and 1.4

[a] If the donor exhibits significant anxiety only resulting from hyperventilation, then classify the event as "8.1 Hyperventilation." If the donor exhibits symptom(s) of "8.1 Hyperventilation" and another event (e.g., citrate), then classify the DAE as the other event.

APPENDIX B: PLASMA VOLUME AND TOTAL COLLECTED VOLUME,[a] BY DONOR'S WEIGHT

Donor's weight (pounds)	Plasma volume (ml)	Total collection volume (ml)
110–149	625	690
150–174	750	825
≥ 175	800	880

[a] Anticoagulant is approximately 9% of the total collection volume.