Plasma Protein Therapeutics Association

PlasmaVigilance

Source Plasma Donor Hemovigilance Activities and Results

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AABB Annual Meeting
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Learning Objectives

- Describe PPTA and the Source Plasma industry
- Describe the purposes and content of the PPTA Donor Adverse Events Recording Standard
- Identify the goals, outcomes, and key takeaways of the pilot data collection per the Standard

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What is PPTA?

A trade and standards-setting organization representing private sector plasma collectors and producers of plasma-based and recombinant biological therapeutics. PPTA members:

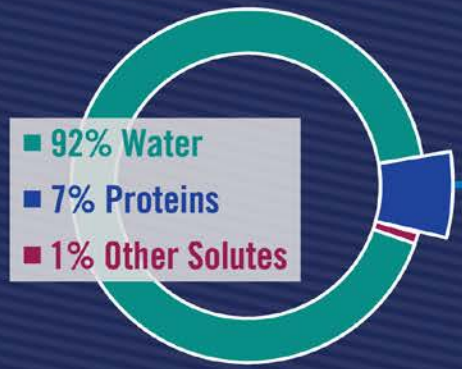
- **Provide more than 80% of the world's Source Plasma for fractionation**
- **Provide the majority of the world's life-saving plasma protein therapies**
- **PPTA and its members take an active role in the areas of pathogen safety, health policy, patient advocacy, awareness and standards setting**

What is in a Plasma Protein Therapy?

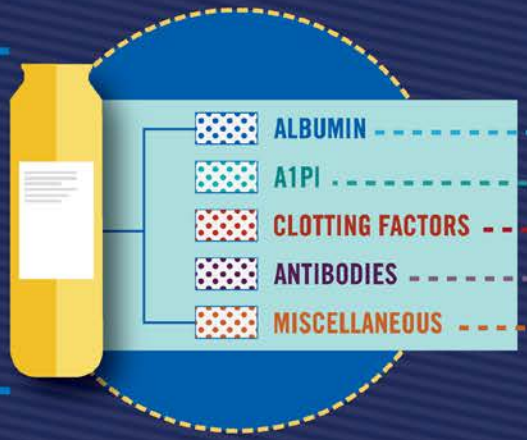
Your Blood is:

- 1% White Blood Cells & Platelets
- 44% Red Blood Cells
- 55% Plasma

Your Plasma is:



Proteins in Your Plasma:



Plasma Protein Therapies & the Diseases They Treat

Albumin
Shock, Burns, Adult Respiratory Distress Syndrome, Cardiopulmonary Bypass Surgery

Alpha-1 Antitrypsin
Alpha-1 Antitrypsin Deficiency (Genetic COPD)

Clotting Factors
Bleeding Disorders, FVII, FVIII, FIX, FXIII, ATIII, Protein C, Prothrombin Complex

Immunoglobulin
Hyperimmunes, Primary Immunodeficiency Diseases, Autoimmune Diseases, Chronic Inflammatory Demyelinating Polyneuropathy, Idiopathic Thrombocytopenic Purpura

Miscellaneous
C1 Esterase Inhibitor, Fibrin Glue, Factor Eight Inhibitor Bypass Activity (FEIBA), Fibrinogen

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Plasma Donations Needed

Donations Needed for One Patient for One Year*

Primary immunodeficiency disease	130
Alpha-1 antitrypsin deficiency	943
Hemophilia A	1,237

*Based on 150 lb. adult treated for one year.

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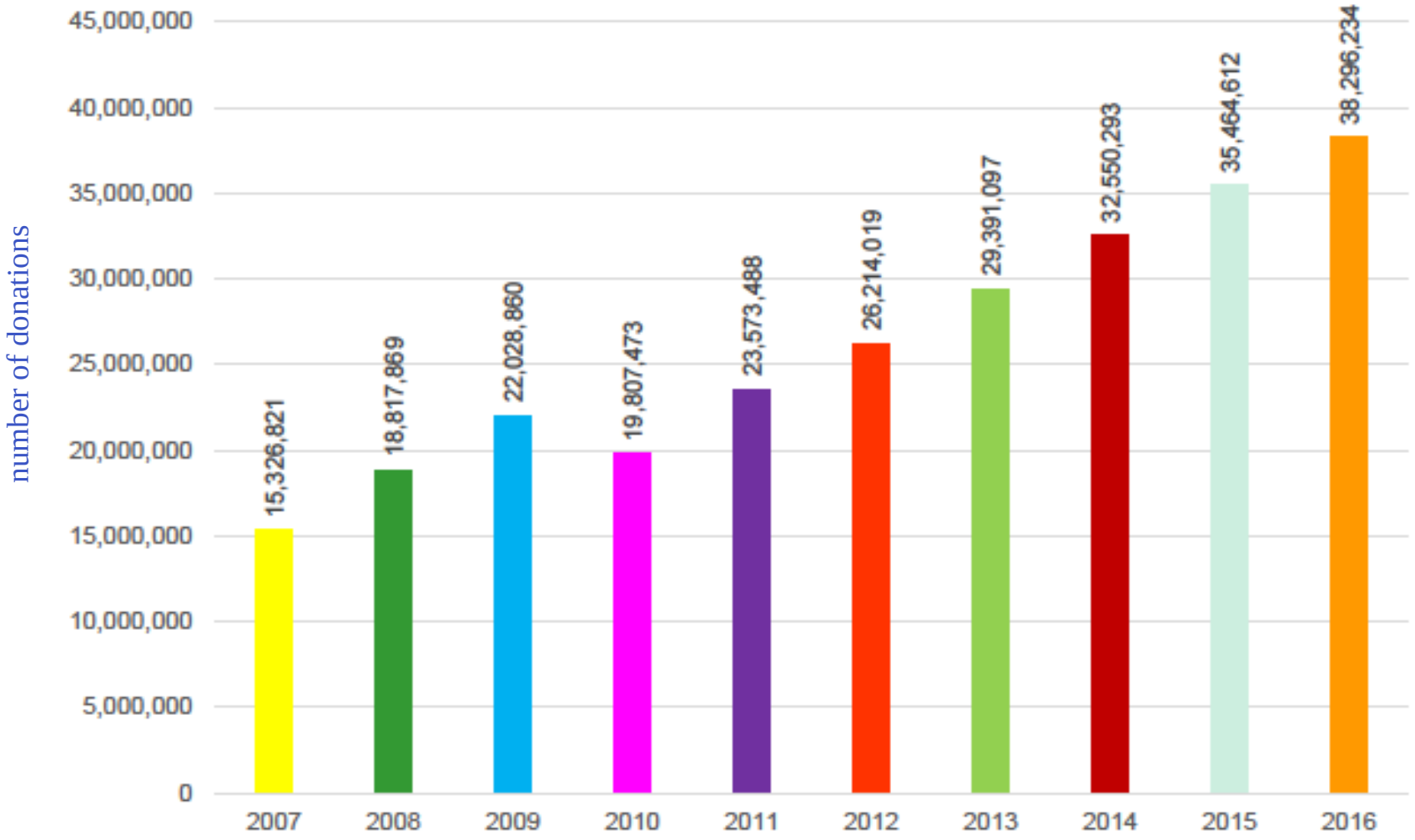
U.S. Total Plasma Collections



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647 U.S. Plasma Collection Centers

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Question 1

What is Source Plasma used to manufacture?

A Anti-hemophilic factor

B Immune globulin

C C1 esterase inhibitor

D Plasma televisions

E A, B, and C

A - E

Answer 1

The answer is E.

A. Anti-hemophilic factor

B. Immune globulin

C. C1 esterase inhibitor

D. Plasma televisions

E. **A, B, and C**

PPTA Donor Adverse Events Recording Standard

- Provides a common language to classify donor adverse events (DAE) within the industry
  - Each plasma organization has procedures in place to safeguard and monitor the health and safety of donors
  - The terminology between organizations was similar, but the definitions were not standardized.
  - Standardization was necessary for data aggregation and benchmarking.

PPTA Donor Adverse Events Recording Standard

- Detailed categories that are applicable to the plasma industry
- Easy to use with objective definitions based on simple and common signs and symptoms
- Strengthens the power of the data representing the entire plasma industry
- Standard implemented April 1, 2015
- Available on PPTA's website: http://www.pptaglobal.org/safety-quality/standards/iqpp

DAE Classifications

- The *Donor Adverse Event Classification Guide* provides the signs and symptoms that set the boundaries defining each category and sub-category.
- Eight (8) major categories were selected for recording of events.
- Most categories have sub-categories providing granularity to better reflect the severity spectrum within a category.

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DAE Classifications

Category	Recording Requirement (* = record)	Sub-Category
Hypotensive Event (vasovagal/Hypovolemia)		
		Prefaint, No LOC (Minor)
	*	Prefaint, No LOC (Moderate)
	*	LOC approximately less than 60 Seconds
	*	LOC approximately 60 Seconds or longer
	*	Severe (With or Without LOC)
	*	Injury

DAE Classifications

Category	Recording Requirement (* = record)	Sub-Category
Major Cardiovascular or Respiratory Event	*	
Local Injury Related to Phlebotomy Event		
	*	Nerve Irritation
		Hematoma/Bruise (Uncomplicated)
	*	Hematoma/Bruise (Complicated)
	*	Infection
	*	Arterial Puncture
		Infiltration
	*	Major Blood Vessel Injury
Citrate Reaction Event		
		Minor
	*	Moderate
	*	Severe

DAE Classifications

Category	Recording Requirement (* = record)	Sub-Category
Hemolysis/Hemoglobinuria Event		
	*	Uncomplicated
	*	Complicated
Air Embolus Event		
		Uncomplicated
	*	Complicated
Allergic Event		
	*	Local
	*	Generalized
	*	Anaphylaxis
Hyperventilation Event	*	
Other Event	*	

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Question 2

Per the DAE recording standard, the following type of DAE shall be captured:

A Prefaint, No Loss of Consciousness

B Prefaint, No Loss of Consciousness (Moderate)

C Hematoma/Bruise (Uncomplicated)

D Infiltration

E Minor Citrate Reaction Event

A - E

Answer 2

The answer is B.

A. Prefaint, No Loss of Consciousness (Minor)

B. Prefaint, No Loss of Consciousness (Moderate)

C. Hematoma/Bruise (Uncomplicated)

D. Infiltration

E. Minor Citrate Reaction Event

For the other DAE, each company shall determine if the DAE is to be included in its recording system and the level of detail required.

Pilot data collection per Standard

- Identify problems and assess performance of the Standard by reviewing operational data
- Obtain a snapshot of events recorded over a 3-month period post-implementation
  - March 1 – May 31, 2016
- Demonstrate ability of companies to respond to ad hoc data requests by PPTA

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Company Participants

- 6 companies participated in the pilot study providing DAE data
- Nearly 7.6 million donations were collected by these 6 companies during the study period; ~79% of industry
- Only DAE that occurred during or post donation were evaluated

Data Analyses

- 15,300+ DAE were recorded over the 3-month pilot period and the data analyzed
- Adverse events were rare: 20.93 per 10,000 donations
  - Frequency of hypotensive adverse events: 14.77/10,000 donations, the majority of which was Prefaint (11.98/10,000 donations)
  - Frequency of phlebotomy adverse events: 4.56/10,000 donations

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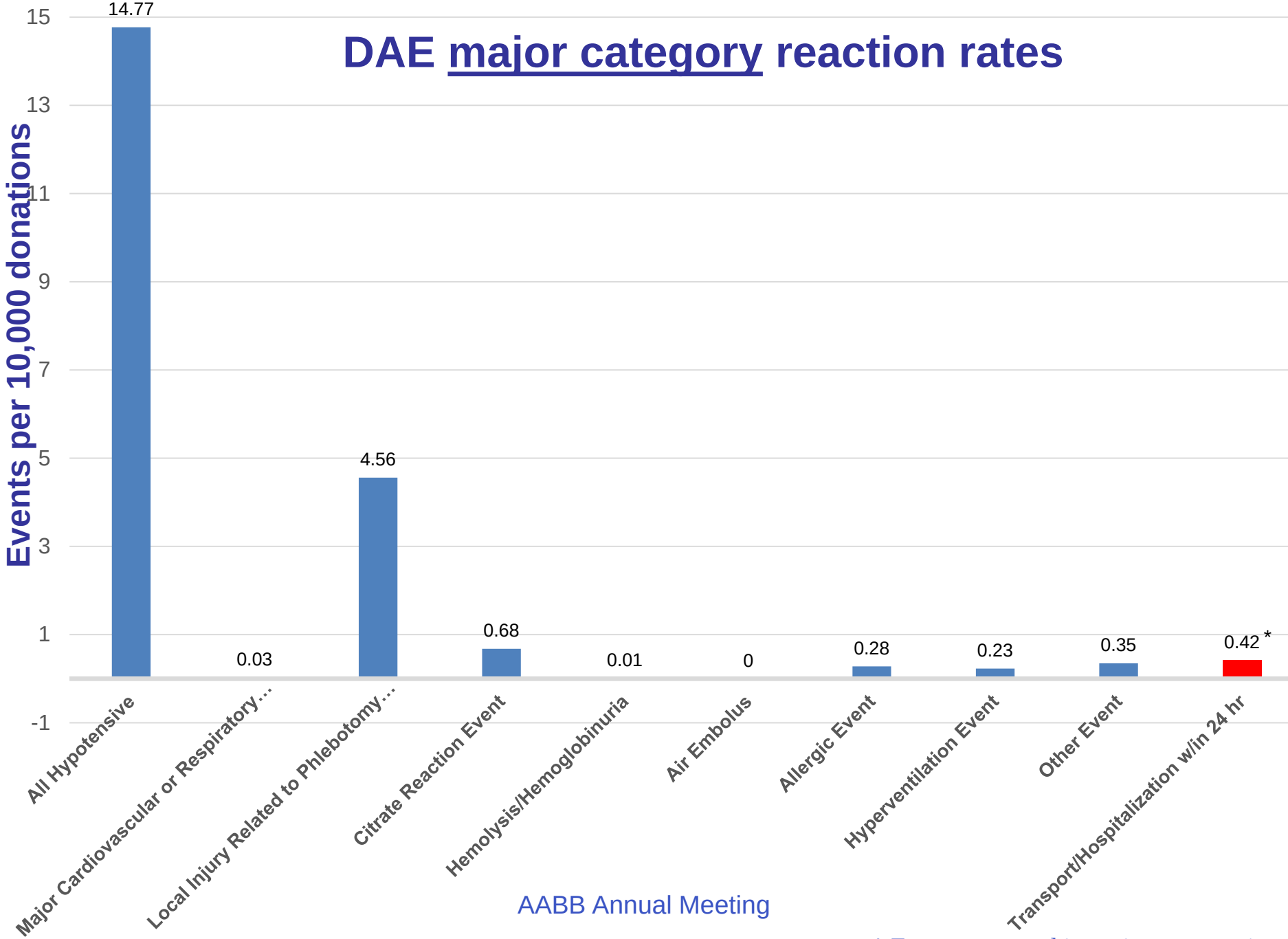
Top 6 DAE

Rank	Classification	% of DAE	Rate per 10,000 donations
1	Hypotensive: Prefaint, No LOC (Moderate)	57.3%	11.98
2	Local Injury Related to Phlebotomy: Hematoma/Bruise (Complicated)	18.2%	3.81
3	Hypotensive: LOC (brief)	9.0%	1.88
4	Hypotensive: Severe (with or without LOC)	3.2%	0.66
5	Local Injury Related to Phlebotomy: Nerve Irritation	3.2%	0.66
6	Citrate Reaction: Moderate	3.1%	0.65
All others		4.3%	1.29
	TOTAL	100%	20.93
	TOTAL DAE: 15,300+		

DAE major category reaction rates



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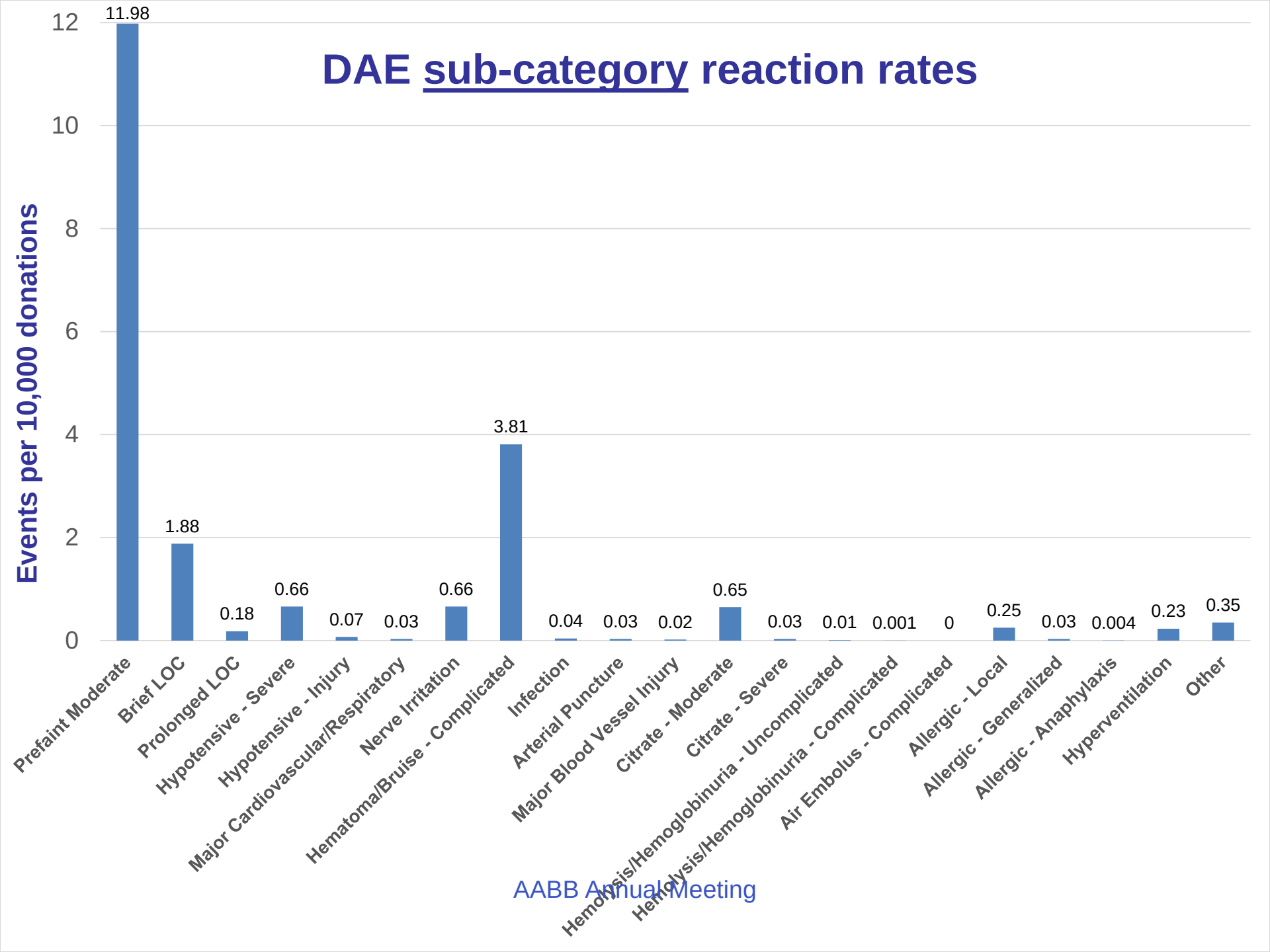
* Events occurred in various categories


DAE sub-category reaction rates
Events per 10,000 donations
12
10
8
6
4
2
0
11.98
1.88
0.18
0.66
0.07
0.03
0.66
3.81
0.04
0.03
0.02
0.65
0.03
0.01
0.001
0
0.25
0.03
0.004
0.23
0.35
Prefaint Moderate
Brief LOC
Prolonged LOC
Hypotensive - Severe
Hypotensive - Injury
Major Cardiovascular/Respiratory
Nerve Irritation
Hematoma/Bruise - Complicated
Infection
Arterial Puncture
Major Blood Vessel Injury
Citrate - Moderate
Citrate - Severe
Hemolysis/Hemoglobinuria - Uncomplicated
Hemolysis/Hemoglobinuria - Complicated
Air Embolus - Complicated
Allergic - Local
Allergic - Generalized
Allergic - Anaphylaxis
Hyperventilation
Other
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Findings

- Hypotensive – Prefaint no LOC (moderate) was most prevalent reaction (11.98/10,000 donations)

  This reaction:
  a. requires medical staff (physician substitute) intervention, OR
  b. involves signs/symptoms that did not resolve quickly (e.g. within approximately 10 minutes), OR
  c. additional signs/symptoms may be present.

- Hematoma/bruise (complicated) had second highest rate (3.81/10,000 donations)

  A hematoma/bruise that is approximately >2” x 2.”

Additional Findings – Hypotensive

- Brief LOC (<60 sec) occurred in 1.88/10,000 donations
- Prolonged LOC (≥60 sec) was rarely observed: 0.18/10,000 donations
- Severe hypotensive events (with or without LOC) occurred in 0.66/10,000 donations
- Hypotensive injury occurred in 0.07/10,000 donations

Illustrative Results: Rate per 10,000 donations and number of events (N)*

	ALL reactions	Hypotensive	Phlebotomy
Gender			
Female	38.31 (N=9427)	30.48 (N=7501)	5.38 (N=1325)
Male	11.45 (N=5882)	6.46 (N=3319)	3.89 (N=1997)
No events with unknown gender			
Donor status			
First time	85.65 (N=4607)	68.45 (N=3682)	12.21 (N=657)
Repeat	15.16 (N=10,702)	10.11 (N=7138)	3.77 (N=2665)
Events with unknown donor status were distributed using the ratio of first time to repeat events			
Age [years]			
18-20	57.00 (N=2900)	45.79 (N=2328)	8.52 (N=433)
21-24	27.55 (N=3317)	21.65 (N=2487)	5.13 (N=589)
25-44	16.00 (N=6372)	11.00 (N=4376)	3.67 (N=1461)
45-64	13.70 (N=2634)	8.27 (N=1590)	4.15 (N=798)
65+	21.00 (N=86)	9.51 (N=39)	10.00 (N=41)
Events with unknown age were distributed using the ratio of events by age group			

* Data limited to centers that could provide detailed variable distributions

Findings

- Females are 3.3 times more likely than males to have a DAE
  - Hypotensive reactions are 4.7 times more likely to occur in females than in males
  - Females are 1.4 times more likely to experience phlebotomy reactions than males

Hypotensive DAE / 10^4 donations, by donation type and age

	Female	Male
Donor status		
First time	130.2 (N=2784)	30.61 (N=992)
Repeat	20.98 (N=4716)	4.80 (N=2327)
Events with unknown donor status were distributed using the ratio of first time to repeat events		
Age [years]		
18-20	101.30 (N=1695)	18.59 (N=634)
21-24	48.63 (N=1704)	9.81 (N=783)
25-44	22.57 (N=2893)	5.50 (N=1483)
45-64	18.22 (N=1179)	3.22 (N=411)
65+	20.84 (N=31)	3.06 (N=8)
Events with unknown age were distributed using the ratio of events by age group		

Hypotensive DAE / 10^4 donations by weight

	Female	Male
Weight [pounds]		
110-124	58.68 (N=623)	44.96 (N=66)
125-149	34.53 (N=1469)	8.94 (N=402)
150-174	39.48 (N=2000)	8.10 (N=844)
175+	23.97 (N=3409)	5.58 (N=2008)
Events with unknown weight were distributed using the ratio of events by weight group		

Findings

- For hypotensive reactions:
  - First-time female donors had rates 6.2 times higher than repeat donors; similar to males, where the rate was 6.4 times higher
  - For first-time donors, female rate is 4.3 times that of males
  - For repeat donors, female rate is 4.4 times that of males
  - For both genders, younger and lighter donors have higher rates

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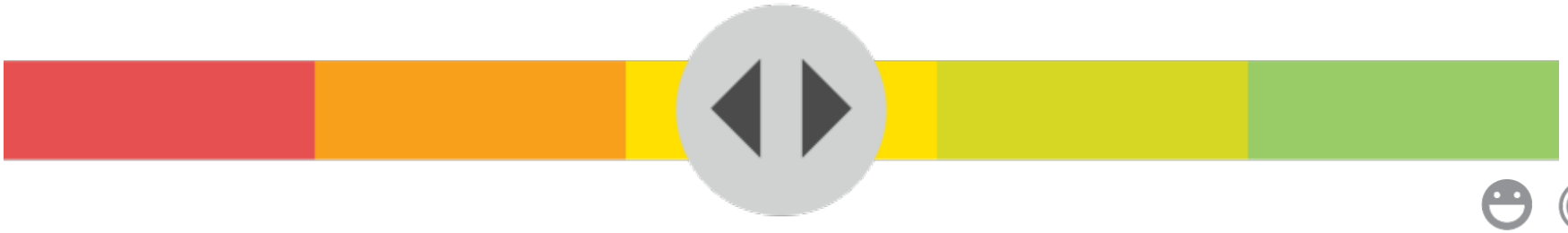
Question 3

In light of current literature reporting the most frequent donor reaction in blood centers, the Source Plasma industry's profile is similar.

Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree



Agree

Answer 3

Strongly agree:

- **young,**
- **lower-weight,**
- **female, and**
- **first-time donors**

have the most hypotensive reactions.

Results of Standard Evaluation

- The pilot data collection and analyses identified areas for interpretation/revision
- Interpretation of “nausea” sign/symptom not uniform
- Categories of “uncomplicated” and “complicated” hematoma/bruise needed clarification
- “Anxiety” as a sign/symptom not understood
- Considerable unknown/other data in DAE records

Key Takeaways

- Pilot data collection identified areas requiring clarification for standardization of recording
- Companies successful in providing the data within the timetable requested
- Companies were able to populate most of the fields but unknown/other data was common
- Most of the categories in the Standard were clear, but a learning time is necessary to familiarize center staff with requirements for data recording

Conclusion

- Source Plasma donation is safe
- With 38,000,000 annual plasma donations, recording of donor adverse events affords an opportunity to examine adverse events on a large number of donations and donors
- Event rates can be monitored, and when issues are identified be quickly investigated, thus offering another level of assurance to Source Plasma donors

Acknowledgments

- Industry members contributed their time to develop the DAE recording standard
- The PPTA Medical Policy Committee evaluated the performance of the Standard's implementation
- PPTA and its member companies are dedicated to guaranteeing the health of their donors
- The recording standard is a very valuable tool for monitoring adverse events

Back up

Classifications (Attachment A: Classification Guide)

DAE Classification	Description	Signs/Symptoms/Findings
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 minutes)	May include one or more of the following: a.Cold Extremities, Chills/Shivering; b.Feeling of Warmth; c.Hypotension; d.Lightheaded/Dizziness; e.Pallor, Pale Skin or Lips; f.Sweating; g.Visual Disturbance; or h.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 minutes), OR c.additional signs/symptoms may be present.	May include any in 1.1 AND any of the following: a.Nausea; or b.Vomiting.

Classifications (Attachment A: Classification Guide)

DAE Classification	Description	Signs/Symptoms/Findings
1.3 Hypotensive: LOC (brief)	In this reaction, LOC lasts approximately less than one minute.	May include any in 1.1 or 1.2.
1.4 Hypotensive: LOC (prolonged)	In this reaction, LOC lasts approximately one minute 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.Carpopedal Spasms; b.Chest Pain; c.Convulsions/Seizures d.Loss of Bladder/Bowel Control; or e.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); or f.Other	May include any of 1.1 – 1.5 as well as any signs/symptoms related to the injury itself.

Classifications (Attachment A: Classification Guide)

DAE Classification	Description	Signs/Symptoms/Findings
2.0 Major Cardiovascular or Respiratory Event	Major cardiovascular or respiratory event that occurs within 24 hours 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; or f.Respiratory Arrest
3.1 Local Injury Related to phlebotomy: Nerve Irritation		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; or d.Weakness of Arm.

Classifications (Attachment A: Classification Guide)

DAE Classification	Description	Signs/Symptoms/Findings
3.2 Local Injury Related to phlebotomy: Hematoma/Bruise (uncomplicated)	A hematoma/bruise that is approximately ≤ 2" x 2."	May include any of the below: a.Mild Pain; b.No Restriction of Movement; c.Skin Discoloration; or d.Swelling.
3.3 Local Injury Related to phlebotomy: Hematoma/Bruise (complicated)	A hematoma/bruise that is approximately >2" x 2."	May include any of the below: a.Significant Pain; b.Paresthesias, Numbness/Tingling of Fingers, Hand, or Arm; c.Pressure; d.Redness; e.Restricted Movement; f.Shooting Pain Down Arm; g.Swelling; h.Tenderness; i.Warmth; or j.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; or f.Warmth.

Classifications (Attachment A: Classification Guide)

DAE Classification	Description	Signs/Symptoms/Findings
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; or 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; or 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.Deep Vein Thrombosis; e.Phlebitis; or f.Thrombophlebitis.

Classifications (Attachment A: Classification Guide)

DAE Classification	Description	Signs/Symptoms/Findings
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 (Peripheral – Lips Tingling/Numbness); or 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, Chills/Shivering; d.Muscle Tightness and/or Cramping; e.Nausea; f.Pallor, Pale Skin or Lips; g.Shortness of Breath; h.Sneezing/Nasal Congestion; i.Tetany (Transient); j.Tremors (Sensation of Vibration); k.Twitching; or l.Vomiting.
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; or e.Shortness of Breath.

Classifications (Attachment A: Classification Guide)

DAE Classification	Description	Signs/Symptoms/Findings
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; or h.Vomiting.

Classifications (Attachment A: Classification Guide)

DAE Classification	Description	Signs/Symptoms/Findings
7.1 Allergic: Local	In the antecubital area.	May include any of the below: a.Itching; b.Rash/Hives; or c.Redness.
7.2 Allergic: Generalized		May include any 7.1 AND any of the below: a.Itching, Generalized; b.Rash/Hives, Generalized; or 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, Restlessness; b.Arrhythmia; c.Bluish Tint to Skin (Cyanosis); d.Gastrointestinal Symptoms; e.Laryngeal Edema with Stridor; f.Scratchy Feeling in Throat; g.Shortness of Breath; h.Swollen Tongue, Throat, Eyes, and Face; i.Wheezing; or j.Hypotension.

Classifications (Attachment A: Classification Guide)

DAE Classification	Description	Signs/Symptoms/Findings
8.1 Hyperventilation		May include any of the below: a. Anxiety; b. Carpopedal Spasms; c. Chest Tightness; d. Circumoral Paresthesia; e. Dry Mouth; f. Paresthesia (Perioral - Tingling/Numbness); g. Paresthesia (Peripheral - Hands/Feet); h. Respiration, Rapid; i. Restlessness; j. Shaking; k. Shortness of Breath; or l. Tetany.

DAE Classification	Description	Signs/Symptoms/Findings
9.1 Other	A reaction that does not fall into any other category listed above	Any

Rationale behind PPTA definitions

- After evaluation, it was determined that other existing vigilance definitions had limitations when applied to characteristics that are unique to plasmapheresis
  - Since most of the adverse events in plasma donors are related to hypotensive events, more granularity was needed
  - Greater specificity on definitions is needed to avoid misrepresentation of the types of events occurring
  - Additional reaction types needed to segregate events unique to the plasmapheresis process
    - Long donation process, multiple cycles, removing and returning red cells
    - Fixed site
    - Product collected on two available machines with fundamental differences (filter vs. centrifuge technology)

Methodology – Data collected

- Donor ID (if SSN is used, then code last 5 digits)
- Bleed number (number)
-
- First time in center or repeat (F or R)
-
- Age (years)
- Gender (M or F)
- Weight (pounds)
- Height (inches)
-
- Date of donation (mm/dd/yyyy)
- Time of donation (military)
-
- Pre-donation SBP (mmHg)
- Pre-donation DBP (mmHg)
- Pre-donation pulse (bpm)
-
- Timing when DAE was first known to begin, either:
  - Pre-donation;
  - During donation;
  - Post-donation on-site (include immunization); or
  - Post-donation off-site
-
- Change in SBP (mmHg)
- Change in DBP (mmHg)
- Change in pulse (bpm)
-
- Collected volume at time of DAE (ml)
-
- Transport and/or hospitalization within 24 hours (Y or N)
- If yes, then follow up (free text or NA)
-
- DAE classification (number per Standard, Attachment A)
- If Other Event, then specify (free text or NA)