Topic II: Blood Collection and Adverse Events in Teenage (16-18 years) Blood Donors

Issue

FDA seeks advice from the Committee as to whether:

1. Adequate mechanisms exist to prevent adverse reactions and injuries following blood donation from teenage donors.
2. Teenage blood donors are more susceptible to developing iron deficiency and the resulting short or long term effects.

Background

Teenage blood donors (16-18 years) comprise a large and disproportionate population of blood donors in the United States. Although blood donation is generally a safe procedure, adverse reactions and injuries have been reported. A disproportionate number of severe reactions and injuries occur among teenage whole blood donors compared to adult donors across all age groups. The significance of the issue is augmented by the increasing recruitment of teenage blood donors through high school blood drives. In addition to the acute donation-related adverse reactions and injury, blood donation in teenage donors introduces other unanswered questions, such as both the short and long term effects of iron deficiency. Given that evidence show significant and lasting iron depletion in adult donors, [1, 2, 3, 4] the effect likely extends to teenage blood donors. Long term studies of iron deficiency related to blood donation in teenagers however, have not been performed.

Trends in teenage blood donation

In the last ten years, donations from teenage donors increased markedly, as demonstrated by a longitudinal study from 2005-2009 conducted by the American Red Cross. In 2005, whole blood collections from 16- to 18-year-old donors comprised

660,232/4,685,697 (14%) of total whole blood donations collected across eight ARC regional blood centers; by 2009, the number of blood collections from 16- to 18-year-olds increased to 710,922/4,451,925 (16%) collected across 30 ARC regional blood centers. [5,6] Teenagers continue to supply a disproportionate number of blood donations; 16- to 18-year-olds comprise approximately 3% of the U.S. population, [7] but contribute an estimated 10% of the U.S. blood supply. Data from the National Blood Collection and Utilization Survey (NBCUS) demonstrated that in 2011, 10.5% of collections were from 16- to 18-year olds.[8] Among teenage blood donors, 16- to 17-year-olds supply a greater proportion of collections than 18- to 19-year olds. [9] For example, in a 2007 study of 17- to 22-year-old donors, 17-year-olds donated 34% of collections compared to 23.3% by 18-year-olds and 13.5% by 19-year-olds. [10]

A parallel phenomenon is an overall and continuing decrease in U.S. blood collections since the mid-1990s.[11-13] In 2013, the National Blood Collection and Utilization Survey documented a 9.4% decrease in whole blood and apheresis red blood cell units collected in the United States compared to 2011 (14,237,000, 95% CI, 13,639,000-14,835,000 vs. 15,721,000, 95% CI, 15,521,000-15,921,000). [12] Concordantly, data from the 2013 AABB Blood Collection, Utilization, and Patient Blood Management Survey demonstrate an overall declining trend in allogeneic whole blood collections over 1989 to 2013. In 2011 the rate of collection was 76.2 units per 1000 persons, decreasing to 65.5 units per 1000 persons in 2013. [13] Despite a decrease in blood collections overall, the proportion of donors between the age of 16-18 has remained relatively constant and teenage donors continue to be overrepresented as a proportion of eligible donors.

Blood donation age requirements and parental consent

U.S. blood donors

FDA has not established age limits for blood donation. General donor eligibility requirements are set forth under 21 CFR 630.10 and 21 CFR 630.15. Minimum age of

blood donation currently falls under the purview of State regulation. Currently, many states have established a minimum age limit of 16 years for blood donation. Certain states for example Connecticut, Delaware, Florida, and New Mexico require a minimum donation age of 17 years. [14] In contrast, California allows 15-year-olds to donate, if there is documented parental consent and written authorization of a physician and surgeon. [15] In addition to establishing age limits for blood donation, many states require parental consent for donors 16 years and under. Currently, 37 states and the District of Columbia allow 16-year-olds to donate blood with parental consent, but five states don't require parental consent for 16-year-olds. Informed consent documents however, are developed by individual blood centers. A study of consent material provided to U.S. whole blood donors (informed consent and parental consent forms) showed that the content of these forms varied and did not always contain uniform and essential information.[16] Consequently the extent and quality of information conveyed to parents/guardians varies from state to state and even from blood center to blood center within a state.

Blood donors in other countries

In Europe, the minimum age of donation is 18 years although some countries have established legislation to allow collections from 17 year-olds. The National Blood Service in the United Kingdom allows donations from 17-year-old donors, but has additional donor safety selection criteria for females under 20 years, such as requiring a minimum estimated blood volume (EBV) of 3500 mL for whole blood and platelet donations. [17] Australia allows 16-year-old donors with a parental consent requirement in some states/territories, but restricts donation frequency of 16- and 17-year-old donors to once per year. [18]

Donor Safety

Blood donation, although largely safe, carries attendant risk (Table 1). Most donation reactions occur during phlebotomy or shortly thereafter. Approximately 2-6% of

donors experience a complication after donation, most of which are classified as minor hematomas or mild vasovagal reactions. [19-21, 22] Severe reactions, involving syncope and injury occur in 0.1 to 0.3% of donors, [23] although higher rates, e.g. 0.8% have been documented among 16- to 19-year old donors. [6] A significant and disproportionate amount of select reactions and injuries occur in teenage blood donors. Donation reactions span various categories, which have been described in the literature as mild, moderate and severe, or local and systemic. Recently, blood centers collaborated on common definitions, with joint authorship and ownership of the International Society of Blood Transfusion (ISBT), the International Hemovigilance Network (IHN), the AABB, and with formal endorsement by the European Blood Alliance (EBA) and Alliance of Blood Operators (ABO), published online December, 2014. Reaction types are broadly categorized as:

A. Local symptoms
B. Generalized symptoms
C. Related to apheresis
D. Allergic reactions
E. Other serious complications.

The reaction categories are further defined as follows:

Table 1: Definitions of donor complications, optional categories in *italics*

Reaction Category	**Reaction Type**	**Etiology**
A. Local symptoms	1. Blood outside vessel	Hematoma, arterial puncture
	2. Arm pain	Nerve injury/irritation
	3. Localized infection/inflammation	• *Thrombophlebitis* • *Cellulitis*

Reaction Category	Reaction Type	Etiology
	4. Other major blood vessel injury	• Deep venous thrombosis • Arteriovenous fistula • Compartment syndrome • Brachial artery • pseudoaneurysm
B. Generalized symptoms - discomfort and weakness with anxiety, dizziness and nausea	1. Vasovagal reactions	• No loss of consciousness • Loss of consciousness • *>60 sec, +/- complications* • *<60 sec, without complications* • *With or without injury* • *On or off collection site*
C. Related to apheresis	• Citrate reactions • Hemolysis • Air embolism • *Infiltration*	
D. Allergic reactions	• Local • Generalized (anaphylactic)	
E. Other serious complications	e.g. major cardiovascular event, transient ischemic attack death within 24 hrs of donation	

Adapted from Vox Sanguinis 2016; 110:185-188

Risk factors for adverse reactions

Multiple studies have demonstrated that risk factors for donation reactions include

young age, female gender, first time donation, and low estimated blood volume [9, 24, 25, 26-28]. Further, the risk of these factors is additive. [9,26] In the 2008 study by Eder et al evaluating adverse reactions and injury, stepwise logistic regression analysis demonstrated young age to have the strongest association with an adverse reaction (odds ratio [OR] 3.05; 95% confidence interval [CI], 2.52- 3.69; P<.001), followed by first-time donation status (OR 2.63; 95% CI, 2.24-3.09; P<.001), and female sex (OR of 1.87; 95% CI, 1.62-2.16, P<.001). [9] Others have shown similar findings, identifying first time donation, female gender and younger age as risk factors for vasovagal reactions and related complications including injuries. [6]

Adverse reactions to Whole Blood donation by teenage donors

Teenage donors are at heightened risk of reaction, both severe and mild. [5, 25, 26] Presyncopal symptoms, such as dizziness, lightheadedness, and pallor occur in 5% to 10% of donors younger than 19 years of age compared to 2% to 5% of all presenting donors. [5, 22, 28] Major systemic reactions with syncope are reported to occur in about 0.5% of 16- and 17-year-olds compared to approximately 0.08% to 0.41% of all presenting donors. [9, 29, 23] A 2008 study conducted across nine American Red Cross blood centers evaluated adverse reactions following allogeneic whole blood collection from 16- and 17-year-olds, compared to 18- and 19-year-olds, and to donors 20 years of age and older . Sixteen- and 17-year-olds experienced moderate or major systemic syncopal reactions at rates significantly greater than 18- and 19-year-old donors (53.1/10,000 vs 33.4/10,000; OR 1.59; 95% CI, 1.41-1.80) and even more so compared to donors 20 years of age and older (8.0/10,000; OR, 6.65; 95% CI, 6.08-7.28).

Donor reaction injuries

While the majority of donor reactions are mild, they can include syncope and be associated with severe injury. [28, 19, 30] Syncope-related injuries can include head

trauma, lacerations, and dental injury. [31] A study evaluating 194,000 blood donations among donors of all age groups found an incidence of syncopal reactions of 0.09% (178), of which 14% (25) resulted in traumatic injury. Eleven of these donors required a visit to the Emergency Room.[24] The likelihood of injury is also higher in younger donors; in the American Red Cross study evaluating adverse reactions and injuries in blood donors, 16- and 17-year-old donors were 2.5 times more likely to experience syncope-related injuries than 18- and 19-year-olds, and 14.5 times more likely than donors 20 years or older. [9] Young donors (16- and 17-year olds) have the highest rate of complications and account for half of all injuries at drives but less than 10% of donations. [9, 21]

Effect of adverse reactions on donor return

In order to maintain an adequate blood supply it is essential that donors return for future donations. In a survey of U.S. whole blood and red blood cell collections in 2013, about 70% of successful donors were repeat donors. [13] Adverse reactions, even when mild, have a negative effect on the individual donor's donation experience. Further, donors who experience reactions are less likely to return. [31-35] Custer et al studied blood donors in six US blood centers to determine if adverse reactions or other factors impacted future donations. Their study revealed that minor and major reactions negatively impacted donor return. However, they determined that the risk factors for adverse reactions to donation (e.g. gender, age) did not significantly impact donor return. [32] Notari and colleagues also found similar findings among first time donors. Donation reactions decreased donor return rates. Interestingly, young donors had a high return rate within 13 months despite being at risk for adverse reactions. [36] However, the observed return rates dropped to the lowest among the age groups from 18-24 years and then gradually rose with age. In a study of 69,289 allogeneic whole blood donors, Eder et al showed that 27% of donors who had any type of reaction returned to donate compared to 35% of those with no reaction. Only 18% of donors who experienced syncope made a repeat donation. Further the study examined 16- to

18-year-old donors as a distinct demographic group. As seen in Table 2, 30% of 16- to 18-year-olds with a reaction at first donation returned to donate versus 37% of those with no reaction at first donation. [31]

Table 2: Effect of adverse reaction after 1st donation on return donation in 16- 18-yr-olds*

Study group: reaction at first donation			Control group: no reaction at first donation		
Donor age (yrs)	# of donors	Repeat donation	# of donors	Repeat donation	Study vs control
16-18	34,495	10,343 (30%)	382,317	141,317 (37%)	$p < 0.0001$

Eder et al, Transfusion. 2012 Dec;52(12):2570-6

Studies of mitigation measures

Various mechanisms have been employed to mitigate adverse donation reactions specifically in teenage donors. In 2008, AABB released Association Bulletin #08-04 on strategies to mitigate the risk of injuries and adverse reactions in donors under 20 years of age. The Bulletin addressed the blood drive environment and specific blood center interventions. The recommendations to improve blood drive environments and structure include site supervision, site selection, controlled donor flow and adequate staff, donor escorts directly following donation, donor observation for at least 15 min following donation, pre-donation and post-donation areas for hydration and refreshment, and staff trained to respond to donation reactions. Recommended interventions include distraction techniques, e.g. audiovisual devices or social media, encouraging donors to drink around 500 ml of water prior to donation, applied muscle tension (AMT) or leg lifting exercises, postreaction instructions, and donor selection criteria. Several blood centers in the U.S. have instituted or studied processes to reduce the risk of adverse reactions and injuries in teenage blood donors.

While multiple studies have evaluated the effect of interventions such as drinking water

prior to donation and AMT, results have proved inconclusive. Some studies have shown moderate decreases in perceived presyncopal symptoms, pre-donation anxiety and fear, and reporting of vasovagal symptoms and reactions; [37, 38] none have demonstrated a decrease in syncopal reactions or injury. [10, 39]

Pre-donation education

Fear and anxiety are factors known to predict the risk of vasovagal reactions in young blood donors. [40] Several psychological interventions to reduce donor anxiety prior to donation and improve the donation experience have been studied. These have included direct interactions with the donor, questions about fear in the donor questionnaire, educational material about the donation process, and audiovisual materials. [41, 42] Some of these interventions improve the donors experience and may enhance donor return. [42] The impact of these interventions alone on the rate of vasovagal reactions, syncope and injuries is inconclusive.

Drinking water before phlebotomy and applied muscle tension

Drinking water pre-donation is thought to reduce the rate of vasovagal reactions by either causing gastric distention, which leads to sympathetic discharge or vasoconstriction, stimulation of the osmoreceptors, or plasma expansion. AMT exercises decrease vasovagal reaction rates by increasing stroke volume and cardiac output. France et al performed a randomized controlled study on 414 blood donors (mean age- 20 years) to examine the effects of pre-donation water and AMT. The authors reported fewer donor reports of presyncopal reactions in the pre-donation water and AMT group compared to placebo and standard donations. [38] Conversely, Van den berg et al studied the impact of preloading South African adolescent blood donors (16-20 years) with 500mL of water. They did not observe any difference in the rate of pre-syncope and syncope in in this group. They however noted that other variables could have impacted the results of this study, (i.e. donor race) and generally lower incidence of vasovagal reactions compared to U.S. donors. [43]

Donor selection based on estimated total blood volume

Limiting donations from the most vulnerable population of teenage donors however, has shown benefit. Eder et al [5] performed a study of young donors (ages 16-20 years) evaluating the impact of donor specific selection criteria based on self-reported height (m), weight (kg) and gender. The algorithm required donors to have an estimated blood volume (EBV) of at least 3.5L as determined by the following formulas:

Male donors: Blood volume (L) = $(0.3669)(\text{Height})^3 + (0.03219)(\text{Weight}) + 0.6041$
Female donors: Blood volume (L) = $(00.3561)(\text{Height})^3 + (0.03308)(\text{Weight}) + 0.1833$

Following implementation of the criteria, the authors found a significant decrease in the rate of all presyncopal and syncopal complications among 16- to 18-year-old donors. The rates of presyncopal reactions, which comprised the majority of the complications, were reduced by 33, 25, and 18% for 16-, 17- and 18-year-old donors respectively ($p < 0.0001$). The magnitude of the decrease inversely correlated with donor age, demonstrating the most pronounced benefit in the youngest age group. No significant reduction in loss of consciousness (LOC) or injury was demonstrated overall. Conversely, significant although not consistent increases in LOC and injury were observed in 19-year-old donors and 18-year-old donors respectively.

Similarly, in a study evaluating mitigation measures, Tomasulo et al observed the highest impact in young female donors with low EBV. The authors compared the likelihood of adverse reactions in 17- to 22-year-old donors over a 12-month period before (Jan ’07 - Dec ’07) and a 12-month period after (Aug ’08 - Jul’09) implementation of three specific interventions. The interventions included restricting donations to <15% EBV for donors < 22-year-old, recommending applied muscle tensing exercises, and offering 16 fl oz (473-500 mL) of water within 30 min prior to phlebotomy. Overall reactions decreased from 32.7 per 1000 donations pre-intervention to 24.8 per 1000 post-intervention, a 24% reduction. Rates of LOC

decreased from 7.4 per 1000 to 5.8 per 1000, a 22% reduction. Reduction in the rate of falls was not demonstrated, and importantly showed a not statistically significant increase in female donors, as well as off-site LOC reactions in male donors with EBV over 3500 mL. While rates of reactions demonstrated an improvement, primarily of mild and moderate severity, the worrisome reactions of off-site LOC and fall (which could lead to injury) demonstrated inconsistent results. [10]

Iron Balance

Blood donation has both immediate and long term effects on iron balance in donors. A whole blood collection of 525 mL removes approximately 200-250 mg of iron. While iron stores in men average around 1000 mg, iron stores in women average around 300 mg rendering women more susceptible to iron deficiency following blood donation.[44]

The iron status of teenage blood donors has not been well characterized; however teens, like all donors, are at presumed risk of iron deficiency due to blood donation. Extrapolations from studies of adult donors showing prolonged and progressive iron depletion with successive donations [45-49, 50] suggest a similar phenomenon in teens should be expected. Teenage donors have additional unique risk factors for iron deficiency, including ongoing growth coupled with poor nutrition, as well as new onset of menses in teenage girls. Consequently up to 11% of teenage girls are iron deficient. [51, 52]

While screening for blood donation assesses for adequate hemoglobin levels (≥12.5 g/dl in females and ≥13 g/dl in males), it does not assess iron status. Hemoglobin testing is not an accurate measure of iron stores and does not accurately predict iron deficiency. Data from the National Health and Nutrition Examination Survey (NHANES) III showed a prevalence of 11% iron deficiency in 16- to 19-year-old females, but only 3% had iron deficiency with anemia. [53, 54]

In contrast, iron deficiency occurs in only <1% of teenage boys.[55] Full discussion of iron deficiency in donors and related studies is addressed in the *Considerations for Iron Management for Blood Donors* Issue Summary.

Consequences of iron deficiency

Consequences of iron deficiency include signs and symptoms such as fatigue, poor concentration, pica, restless leg syndrome, and decreased exercise capacity. In pregnancy, iron deficiency imparts an increased risk of pre-term delivery and low birth weight. [51, 52, 56]

Over both the short and long term, iron deficiency can have adverse effects on cognition. As such, adequate iron status has been linked to school performance in teenagers. [57, 54, 56] A study of 5398 children aged six to sixteen showed that iron deficiency imparted an odds ratio of 2.3 (95% CI: 1.1-4.4) of scoring below average in math. Among the subgroup of 12- to 16-year-old girls, differences in math scores were statistically significant; iron-deficient girls scored 85.1 compared to 93.5 for girls with normal iron status ($p = 0.003$).[54] Further, as adequate iron is needed for myelination, iron deficiency could potentially adversely affect teenagers' ultimate mental and physical development. [51, 57]

Management of iron deficiency

Interventions are also being considered to mitigate iron deficiency in blood donors. Potential interventions include providing iron supplements, distributing educational materials conveying the impact of blood donation on iron stores, modifying donation frequency or the type of blood component to be donated based on an individual's iron status, and iron status testing (e.g. ferritin, soluble transferrin receptor). Multiple studies are underway or recently completed to inform the most effective approach. There are no completed studies evaluating iron replacement and blood donation-induced iron deficiency in teenagers. However, an NHLBI sponsored study entitled

"Comparison of the History of Donation and Iron Levels in Teen Blood Donors" (CHILL Study) is currently underway. The study will assess iron status primarily in blood donors 16- to 18-years old, measuring ferritin and other markers of iron deficiency. Preliminary results will be presented at this meeting.

Summary

Blood donation by teenage blood donors carries similar risks when compared to older donors, but is associated with higher rates of various complications and injuries per donation. The number of donations by teenage donors has risen in recent years and the proportion of blood donations by teenagers continues to increase. High school blood drives provide an ample source of motivated donors who are readily recruited and are likely to continue to donate blood. While the FDA has not established age limits for blood donation, states have adopted minimum age limits for blood donation. These age limits together with the requirement of informed consent vary by state. Parental consent forms are established by individual blood centers, hence also vary in the degree and the quality of information conveyed to parents. Mechanisms to protect donor safety by mitigating adverse donation reactions have shown limited success in preventing presyncopal reactions and have not consistently reduced severe syncopal reactions or injuries. Iron deficiency is another complication that could have short or long term implications in these donors. Further studies addressing iron status of teenage donors may provide a direction forward.

An NHLBI 2016 Scientific Priorities in Pediatric Transfusion Medicine conference held April 5, 2016 to April 6, 2016, addressed the issue of teenage blood donation. The following questions were posed:

1. Does the age at first blood donation correlate with behaviors likely to result in future donation and long-term donation behavior in adulthood?
2. What are the long- term effects of blood donation-induced iron deficiency including neurocognition in teenagers?

3. Can blood centers reduce the risk of syncope and injuries after blood donation on high school blood drives?
4. What are the short term effects of blood donation-induced iron deficiency in teenagers?

The consensus reached was that teenage blood donation poses a potential risk to the health of this population, and further studies could examine the effect of donation-induced iron deficiency on cognition and athletic performance. [58]

FDA is seeking advice from the committee on the elements of concern regarding blood donation in teenagers, the most appropriate adverse reaction mitigation measures, and the short-term and long-term concerns of blood donation-induced iron deficiency in teenagers and potential interventions.

Questions for the Committee:

1. Does the available scientific evidence confirm that adverse reactions and injuries after blood donation in teenage donors is a concern?
2. Considering possible mechanisms to reduce the risk of adverse reactions and injuries in teenage blood donors:
    a. Does the available evidence support applying donor-specific selection criteria (e.g. EBV >3500 ml) as a means to mitigate donor reactions?
    b. Do the available data indicate that specific measures (e.g. applied muscle tension) to mitigate reactions are effective?
    c. Should consent material contain adequate information to inform parents and donors of increased risk of adverse reactions and injuries?
3. Does the available scientific evidence suggest that teenage blood donors are susceptible to developing iron deficiency and related short or long term effects?
    a. If so, please comment on possible interventions including:
        i. Further studies evaluating the effect of iron deficiency in teenage blood donors
        ii. Donor education
        iii. Iron management by ferritin testing, iron supplementation or limiting donation frequency.
4. Please discuss whether there is enough associated risk in teenage donors to warrant restriction of the donor pool to individuals aged 18 years and over.

References

1. Cable RG, Glynn SA, Kiss JE, et al. Iron deficiency in blood donors: the REDS-II Donor Iron Status Evaluation (RISE) study. *Transfusion*. 2012; 52(4):702-711.
2. Cable RG, Glynn SA, Kiss JE, et al. Iron deficiency in blood donors: analysis of enrollment data from the REDS-II Donor Iron Status Evaluation (RISE) study. *Transfusion*. 2011; 51(3):511-522.
3. Mast AE, Foster TM, Pinder HL, et al. Behavioral, biochemical, and genetic analysis of iron metabolism in high-intensity blood donors. *Transfusion*. 2008; 48(10):2197-2204.
4. Simon TL, Garry PJ, Hooper EM. Iron stores in blood donors. *JAMA*. 1981; 245(20):2038-2043.
5. Eder AF, Dy BA, Kennedy JM, et al. Improved safety for young whole blood donors with new selection criteria for total estimated blood volume. *Transfusion*. 2011; 51(7):1522-1531.
6. Reiss RF, Harkin R, Lessig M, Mascari J. Rates of vaso-vagal reactions among first time teenaged whole blood, double red cell, and plateletpheresis donors. *Ann Clin Lab Sci*. 2009; 39(2):138-143.
7. Howden LM, JA. 2010 Census Briefs. 2011; United States Census Bureau(Age and Sex Composition: 2010).
8. The 2011 National Blood Collection and Utilization Survey report. Washington (DC): US Department of Health and Human Services.
9. Eder AF, Hillyer CD, Dy BA, Notari EPt, Benjamin RJ. Adverse reactions to allogeneic whole blood donation by 16- and 17-year-olds. *JAMA*. 2008; 299(19):2279-2286.
10. Tomasulo P, Kamel H, Bravo M, James RC, Custer B. Interventions to reduce the vasovagal reaction rate in young whole blood donors. *Transfusion*. 2011; 51(7):1511- 1521.
11. Zou S, Musavi F, Notari EPt, Fang CT, Group AR. Changing age distribution of the blood donor population in the United States. *Transfusion*. 2008; 48(2):251-257.

12. Chung KW, Basavaraju SV, Mu Y, et al. Declining blood collection and utilization in the United States. *Transfusion*. 2016; 56(9):2184-2192.
13. Whitaker B, Rajbhandary S, Kleinman S, Harris A, Kamani N. Trends in United States blood collection and transfusion: results from the 2013 AABB Blood Collection, Utilization, and Patient Blood Management Survey. *Transfusion*. 2016; 56(9):2173-2183.
14. American Red Cross: Information for 16 year old Donors. Accessed Sept. 23, 2016, 11:45 am; http://www.redcrossblood.org/students/sixteen.
15. California Health and Safety Code: Section 1602.5-1608.1607.5(b): A person age 15 may consent to donate blood with the written consent of parents or guardian, and written authorization of a physician: http://www.leginfo.ca.gov/cgi-bin/displaycode?section=hsc&group=01001-02000&file=01602.01005-01608
16. Shaz BH, Demmons DG, Hillyer CD. Critical evaluation of informed consent forms for adult and minor aged whole blood donation used by United States blood centers. *Transfusion*. 2009; 49(6):1136-1145.
17. United Kingdom Blood Transfusion Services (UKBTS).Whole Blood and Component Donor Selection Guidelines (Edition 203 - Published 1 June 2007): Release 35 – Published 01 September 2016.
18. National Blood Authority Hemovigilance Advisory Committee of Australia: Australian Hemovigilance Report. 2011-2013; https://www.blood.gov.au/pubs/2015- haemovigilance/part-03-donor-vigilance/review-donor-adverse-events-2012-13.html.
19. Eder AF, Dy BA, Kennedy JM, et al. The American Red Cross donor hemovigilance program: complications of blood donation reported in 2006. *Transfusion*. 2008; 48(9):1809-1819.
20. Shehata N, Kusano R, Hannach B, Hume H. Reaction rates in allogeneic donors. *Transfus Med*. 2004; 14(5):327-333.
21. 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(9):1799-1808.
22. Eder AF. Improving safety for young blood donors. *Transfus Med Rev*. 2012;

26(1):14-26.

23. Newman BH. Donor reactions and injuries from whole blood donation. *Transfus Med Rev*. 1997; 11(1):64-75.
24. Newman BH, Graves S. A study of 178 consecutive vasovagal syncopal reactions from the perspective of safety. *Transfusion*. 2001; 41(12):1475-1479.
25. Newman BH. Vasovagal reactions in high school students: findings relative to race, risk factor synergism, female sex, and non-high school participants. *Transfusion*. 2002; 42(12):1557-1560.
26. Newman BH, Satz SL, Janowicz NM, Siegfried BA. Donor reactions in high-school donors: the effects of sex, weight, and collection volume. *Transfusion*. 2006; 46(2):284-288.
27. 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(3):316-320.
28. Popovsky MA, Whitaker B, Arnold NL. Severe outcomes of allogeneic and autologous blood donation: frequency and characterization. *Transfusion*. 1995; 35(9):734-737.
29. Kamel H, Tomasulo P, Bravo M, et al. Delayed adverse reactions to blood donation. *Transfusion*. 2010; 50(3):556-565.
30. Newman BH, Pichette S, Pichette D, Dzaka E. Adverse effects in blood donors after whole-blood donation: a study of 1000 blood donors interviewed 3 weeks after whole- blood donation. *Transfusion*. 2003; 43(5):598-603.
31. Eder AF, Notari EPt, Dodd RY. Do reactions after whole blood donation predict syncope on return donation? *Transfusion*. 2012; 52(12):2570-2576.
32. Custer B, Rios JA, Schlumpf K, et al. Adverse reactions and other factors that impact subsequent blood donation visits. *Transfusion*. 2012; 52(1):118-126.
33. Morand C, Coudurier N, Rolland C, et al. Prevention of syncopal-type reactions after whole blood donation: a cluster-randomized trial assessing hydration and muscle tension exercise. *Transfusion*. 2016.
34. France CR, Rader A, Carlson B. Donors who react may not come back: analysis

of repeat donation as a function of phlebotomist ratings of vasovagal reactions. *Transfus Apher Sci.* 2005; 33(2):99-106.

35. France CR, France JL, Roussos M, Ditto B. Mild reactions to blood donation predict a decreased likelihood of donor return. *Transfus Apher Sci.* 2004; 30(1):17-22.
36. Notari EPt, Zou S, Fang CT, Eder AF, Benjamin RJ, Dodd RY. Age-related donor return patterns among first-time blood donors in the United States. *Transfusion*. 2009; 49(10):2229-2236.
37. Ditto B, France CR, Lavoie P, Roussos M, Adler PS. Reducing reactions to blood donation with applied muscle tension: a randomized controlled trial. *Transfusion*. 2003; 43(9):1269-1275.
38. France CR, Ditto B, Wissel ME, et al. Predonation hydration and applied muscle tension combine to reduce presyncopal reactions to blood donation. *Transfusion*. 2010;50(6):1257-1264.
39. Kamel H CB, Bravo M, Tomasulo P. Do multiple interventions to reduce adverse reactions in young female donors lower rates of reactions? A preliminary analysis. *Transfusion*. 2009; 49(Suppl):3A.
40. France CR, France JL, Kowalsky JM, et al. Assessment of donor fear enhances prediction of presyncopal symptoms among volunteer blood donors. *Transfusion*. 2012; 52(2):375-380.
41. France CR, France JL, Himawan LK, et al. How afraid are you of having blood drawn from your arm? A simple fear question predicts vasovagal reactions without causing them among high school donors. *Transfusion*. 2013; 53(2):315-321.
42. France CR, France JL, Kowalsky JM, Cornett TL. Education in donation coping strategies encourages individuals to give blood: further evaluation of a donor recruitment brochure. *Transfusion*. 2010; 50(1):85-91.
43. van den Berg K, Lam J, Bruhn R, Custer B, Murphy EL. Water administration and the risk of syncope and presyncope during blood donation: a randomized clinical trial. *Transfusion*. 2012; 52(12):2577-2584.
44. Summary of a report on assessment of the iron nutritional status of the United

States population. Expert Scientific Working Group. *Am J Clin Nutr*. 1985; 42(6):1318-1330.

45. Kiss JE, Brambilla D, Glynn SA, et al. Oral iron supplementation after blood donation: a randomized clinical trial. *JAMA*. 2015; 313(6):575-583.
46. Boulton F. Evidence-based criteria for the care and selection of blood donors, with some comments on the relationship to blood supply, and emphasis on the management of donation-induced iron depletion. *Transfus Med*. 2008; 18(1):13-27.
47. Finch CA, Hegsted M, Kinney TD, et al. Iron metabolism; the pathophysiology of iron storage. *Blood*. 1950; 5(11):983-1008.
48. Finch S, Haskins D, Finch CA. Iron metabolism; hematopoiesis following phlebotomy; iron as a limiting factor. *J Clin Invest*. 1950; 29(8):1078-1086.
49. Wiersum-Osselton JC, Marijt-van der Kreek T, de Kort WL. Donor vigilance: what are we doing about it? *Biologicals*. 2012; 40(3):176-179.
50. Radtke H, Meyer T, Kalus U, et al. Rapid identification of iron deficiency in blood donors with red cell indexes provided by Advia 120. *Transfusion*. 2005; 45(1):5-10.
51. Cogswell ME, Looker AC, Pfeiffer CM, et al. Assessment of iron deficiency in US preschool children and nonpregnant females of childbearing age: National Health and Nutrition Examination Survey 2003-2006. *Am J Clin Nutr*. 2009; 89(5):1334-1342.
52. Falkingham M, Abdelhamid A, Curtis P, Fairweather-Tait S, Dye L, Hooper L. The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. *Nutr J*. 2010; 9:4.
53. National Center for Health Statistics. *Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988-1994*. Hyattsville, MD: National Center for Health Statistics 1994.
54. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. *Pediatrics*. 2001; 107(6):1381-1386.
55. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of

iron deficiency in the United States. *JAMA*. 1997; 277(12):973-976.

56. Murray-Kolb LE, Beard JL. Iron treatment normalizes cognitive functioning in young women. *Am J Clin Nutr*. 2007; 85(3):778-787.

57. Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet*. 1996; 348(9033):992-996.

58. NHLBI. 2016 Scientific Priorities in Pediatric Transfusion Medicine. http://www.nhlbi.nih.gov/research/reports/2016-scientific-priorities-pediatric- transfusion-medicine.