



**AABB DONOR IRON DEFICIENCY
RISK-BASED DECISION-MAKING
ASSESSMENT REPORT
SUPPLEMENTAL MATERIAL**

Prepared by the Ad Hoc Iron-Deficiency Working Group

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Iron-Deficiency RBDM Assessment—Supplemental Material

SAFETY ASSESSMENT

Safety Subgroup: Revised Summary

Iron deficiency (ID) exists along a continuum of severity. Because anemia is usually a later-stage manifestation, ID is divided into nonanemic iron deficiency (NAID) and iron-deficiency anemia (IDA)—the latter of which has been associated more frequently with adverse clinical outcomes. NAID can be further divided into two components. This was done some years ago by REDS-II RISE investigators¹ and a similar partitioning has occurred in many other subsequently reported studies.

This risk-based decision-making (RBDM) analysis adopts the terminology and definitions used by RISE. The two levels of NAID severity are:

1. Iron-deficient erythropoiesis (IDE). This is the less severe stage in which storage iron is depleted and red cell/tissue iron is compromised. In this stage, red cell production is impaired and some persons may have already developed anemia. Because erythropoiesis is partially compromised, transferrin receptor (TFR) is shed from red cells, resulting in an elevated soluble TFR (sTFR) level. RISE investigators formulated a definition of the point at which IDE manifests by determining the distribution of a derived measurement—the ratio $\log(\text{sTFR}/\text{plasma ferritin level})$ in first-time male donors—and selecting a cutoff value for IDE (ratio ≥ 2.07) corresponding to the highest 2.5% of the distribution. Subsequently, it was found that this was highly correlated with a ferritin level of <26 ng/mL.
2. Absent iron stores (AIS). On the basis of studies that have obtained marrow aspirates and biopsies, this stage describes a condition in which storage iron is fully depleted and the marrow lacks the iron needed to produce new erythrocytes. A donor is classified as having AIS if the ferritin level is <12 ng/mL. Anemia will be present in a greater percentage of donors with AIS than in those with IDE.

In RISE, donors with ferritin levels <26 ng/mL were designated to have IDE and those with ferritin levels <12 ng/mL were designated to have AIS. The data presentation was such that the percentage of donors in the IDE category also included donors with AIS. Some other studies (eg, CHILL²) have presented data in this same fashion (see Tables 1-3) whereas other studies [Canadian Blood Services (CBS) and Blood Systems, Inc, (BSI)]^{3,4} have separated the two categories such that the IDE classification does not include donors with AIS (see Tables 4 and 5). In addition, for purposes of this RBDM analysis, it is recognized that some studies have used slightly different ferritin values to establish these two NAID categories and the Safety subgroup has not altered such classifications. Thus, an IDE classification may deviate from the RISE definition by using ferritin values of <30 ng/mL in males and <20 ng/mL in females and the AIS classification may use values as low as <9 ng/mL or as high as <15 ng/mL for both male and female donors.

Similarly, the definition for anemia may vary across studies. The definition for anemia used in most blood donor studies cited in this RBDM analysis is actually a surrogate definition. It is the hemoglobin (Hb) value used to determine blood donor eligibility in the country in which the study was performed. In North America (US and Canada), this is a capillary hemoglobin value of 12.5 g/dL (125 g/L) in females and either 12.5 or 13.0 g/dL (125 or 130 g/L) in males, depending upon whether the study was conducted before or after May 2016, the month in which the Food and Drug Administration (FDA) changed the male donor eligibility criteria from a hemoglobin level of 12.5 to 13.0 g/dL. It should be noted that this surrogate definition does not fully correlate with the formal definitions of anemia used in epidemiologic and clinical

assessments in that those definitions are based upon a venous hemoglobin measurement and use hemoglobin values (usually 12 g/dL in females and 13.5 g/dL in males) that differ from the donor eligibility criteria values.

The primary focus of the Safety subgroup was on the clinical consequences of NAID because most donors with anemia would not be accepted to give a blood donation (ie, they would be ineligible based on the surrogate measure of capillary hemoglobin screening). However, in some analyses conducted by the Safety subgroup, it has been recognized that males with a hemoglobin <13.5 g/dL should be considered to be anemic and that the most likely contributing factor (or cause) is iron deficiency. Furthermore, a donor with NAID may become anemic following the donation of a unit of blood and may remain anemic for a protracted period in the absence of iron supplementation. Thus, it also may be appropriate to consider the clinical consequences of IDA.

Baseline Rates

- AIS and IDE
 - Frequent donors (adult first-time and repeat donors). See Table 1 taken from RISE enrollment data. The subgroup believes this is the best estimate to use as it was obtained in a controlled setting in the US. Results from other studies corroborate this estimate.

Table 1. AIS and IDE (also includes AIS) at Enrollment in RISE¹

Gender	Donor Status	AIS % ferritin <12 µg/L	IDE % Log (sTfR/F) ≥ 2.07
Females	FT/RA (n= 481)	6.5	24.6
	Fqnt (n= 769)	27.0	66.1
Males	FT/RA (n= 407)	0	2.5
	Fqnt (n= 768)	16.4	48.7

AIS = absent iron stores; IDE = iron deficient erythropoiesis; sTfR = soluble transferrin receptor; F = ferritin; FT = first time; RA = reactivated; Fqnt = frequent

- Teenage donors (ages 16-18). See Table 2 taken from REDS-III CHILL data, showing high values and expected variation with females > males and repeat donors > first-time donors. Also, recent data from BSI indicate an IDE rate of 18.8% in male donors (ferritin level <30 ng/mL) and 39.4% in female donors (<20 ng/mL).
- Premenopausal females. See Table 3, in which data were sourced from control donors enrolled in CHILL, and Table 4, in which data were sourced from CBS.

Table 2. Ferritin <12 ng/mL (AIS) and <26 ng/mL (IDE and AIS both included) in CHILL Teens at Enrollment²

Ferritin (ng/mL)	Donor	16-F	17-F	18-F	16-M	17-M	18-M	16-18 F	16-18 M
N	FTD							1237	1363
% <12	FTD	17.2%	18.5%	15.4%	3.0%	1.1%	0.8%	18.0%	1.4%
% <26	FTD	52.9%	52.3%	49.2%	12.1%	8.65%	8.1%	52.3%	9.2%
N	RPT							546	568
% <12	RPT	28.7%	33.2%	31.8%	6.8%	9.4%	7.9%	32.3%	8.8%
% <26	RPT	73.6%	71.1%	61.2%	22.7%	31.7%	30.3%	69.9%	30.6%

FTD = first-time donor; RPT = repeat donor

Table 3. Ferritin <12 ng/mL (AIS) and <26 ng/mL (IDE and AIS both included) in CHILL Female Control Donors at Enrollment²

Ferritin Value (ng/mL)	FTD vs RPT	% of Age 19-49 Female Donors*
n	FTD	109
% <12	FTD	7.3%
% <26	FTD	27.5%
n	RPT	183
% <12	RPT	24.0%
% <26	RPT	48.6%

*all assumed to be premenopausal

FTD = first-time donor; RPT = repeat donor

Table 4. Ferritin <12 ng/mL (AIS) and 12-24 ng/mL (IDE, but not including AIS) in Canadian First-Time Female Donors*

Ferritin Value (ng/mL)	Donor Group†	% of Donors
% <12	Age 17-24, first-time donor	12.5%
% <12	Age 25-45, first-time donor	7.9%
% 12-24	Age 17-24, first-time donor	32.9%
% 12-24	Age 25-45, first-time donor	24.9%

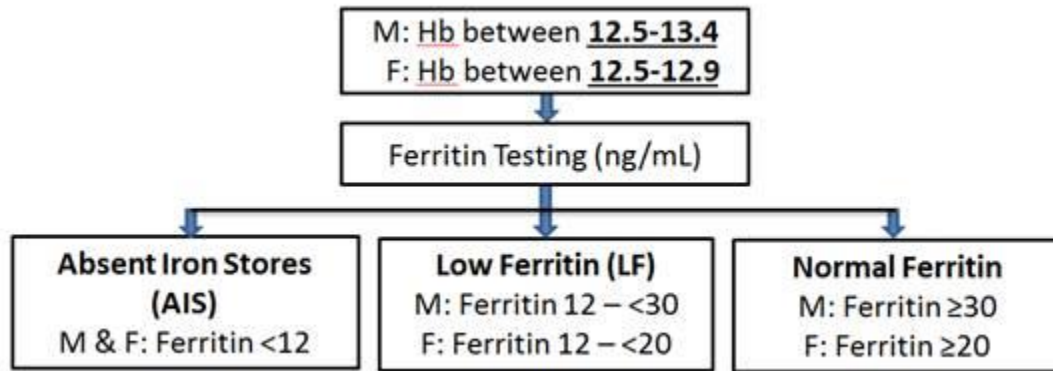
*ages 17-24 and 25-45 and assumed to be premenopausal.

†In this study by Goldman et al,³ data from repeat donors are divided into several categories based on the number of donations in prior 12 months and are not summarized here.

- Donors near the Hb cutoff (12.5-13.5 g/dL for males; 12.5-12.9 g/dL for females). See Table 5, in which data were sourced from BSI from 2014-2015.
- Deferral due to low Hb
 - 7.5%; data sourced from the National Blood Collection and Utilization Survey (NBCUS) 2013.⁵ This is also consistent with data from the NBCUS 2015.⁶

- Donor return after Hb deferral – data from REDS-II.
 - Repeat donors return at an 80% rate and successfully donate half of the time (ie, 40% of those deferred make a subsequent successful donation) over a several-year follow-up interval.
 - First-time donors return at a 40% rate and successfully donate 25% of the time (ie, 10% of those deferred make a subsequent successful donation).

Table 5. AIS and IDE (but not including AIS) in Successful Donations by Donors Near the Hemoglobin Cutoff⁴



UBS Data: 25 months 11/26/12 – 12/31/14

<u>Any Type of Donation</u>	<u>Male</u>	<u>Female</u>	<u>Total</u>
Donations tested for ferritin	706,416	631,193	1,337,609
Absent Iron Stores (AIS)	39,184 (6%)	98,493 (16%)	137,677 (10%)
Low Ferritin (LF)	8,490 (22%)	28,684 (29%)	37,174 (27%)
	11,011 (28%)	20,609 (21%)	31,620 (23%)
 <u>Whole Blood Donations</u>	 <u>Male</u>	 <u>Female</u>	 <u>Total</u>
<u>Donations</u> tested for ferritin	398,018	541,801	939,819
Absent Iron Stores (AIS)	26,805 (7%)	90,185 (17%)	116,990 (12%)
Low Ferritin (LF)	5,315 (20%)	26,156 (29%)	31,471 (27%)
	6,928 (26%)	18,590 (21%)	25,518 (22%)
 <u>Donors</u> tested for ferritin	 14,256 (18%)	 65,967 (82%)	 80,223
Mean # donations in study period	1.9	1.4	1.5

Estimating the Rate of IDA in Donors

- A systematic estimate of IDA in a representative donor population has not been previously produced. Although recent studies² suggest that as much as 30% of donations may come from donors with ferritin levels <26 ng/mL, the prevalence of IDA in donors is unknown, as is the proportion of IDA that is caused by donation itself. Sufficient data exist that these figures should be reasonable estimates. The subgroup developed estimates that take donor presentations as the unit of analysis and partition presentations into 1) deferrals due to IDA, 2) donations made by donors with IDA, and 3) donations made by donors without IDA but whose postdonation lab values are compatible with IDA due to loss of hemoglobin and iron in the donation.
- The Safety subgroup made the following estimates:
 - Based on a 13.0 g/dL male hemoglobin cutoff, approximately 3% of donor visits lead to hemoglobin deferral that is associated with IDA caused by donation (termed “excess” IDA). Of all hemoglobin deferrals, the estimate is that 40% are due to excess IDA.
 - Based on the same cutoff, approximately 2% of donor visits lead to a donation made by a donor with IDA (all are male donors; these are donors with hemoglobin levels between 13.0 and 13.5 g/dL).
 - Approximately 18% of donor visits lead to a donation made by a donor whose postdonation lab values are consistent with cutoffs used to define both iron deficiency and anemia. These occur in about a 3:1 female-to-male ratio.

Clinical Consequences of Iron Deficiency without Anemia

- Methodology note. Donors (or other study subjects) with NAID as described in some published studies may be a composite of donors with IDE and AIS per the REDS-III definitions. This makes it difficult to compare studies with regard to frequency of clinical occurrences and response to interventions because data from donors with differing degrees of ID may be lumped together.
- Results summary. No quantitative data for effects of NAID except for pica.
- Specific conditions
 - Fatigue and quality of life (QoL). Limited available evidence in blood donors with NAID is interpreted as not demonstrating this adverse outcome.
 - Exercise endurance. Demonstrated to occur in the nondonor setting, mostly in high-performance athletes. Not clear how often this occurs in blood donors but some evidence exists that the donors who have NAID with “relative anemia” experience improvement with iron therapy. In the blood donor setting, postdonation impairment of exercise endurance has another possible explanation, which is loss of a Red Blood Cell (RBC) unit during the donation.
 - Perinatal outcomes. No clear data in females with NAID. A Quebec study⁷ using a surrogate marker that correlates with NAID (number of donations in the 2 years before delivery) showed no association with low birthweight, preterm delivery, or stillbirth.
 - Neonatal brain development during infancy. From a review article,⁸ “In pregnant women with NAID, lower serum ferritin concentrations are seen in neonates, placing them at risk for earlier onset of postnatal ID that can affect brain development.” There are no data to confirm that this risk leads to adverse outcomes.
 - Cognition. The majority of measures of cognition were not impaired in young females with NAID in nondonor settings. Some impairment was shown in a few studies. Available data do not allow for quantitating this in blood donors.
 - Ongoing brain development. Despite the inconclusive results for the effects of NAID on adolescent cognition, it is well established that in the adolescent years (and up to age 23-25), there is still

significant brain development involving the myelination of important cortical association areas. One possible viewpoint is that concern around such impairment, even small difficult-to-measure changes, suggests that steps should be taken to prevent iron depletion in persons whose brains are continuing to undergo detectable remodeling and growth.

- Pica. In one study, pica was reported in 11% of donors with iron depletion (NAID) or iron deficiency vs 4% of iron-replete donors; excess risk was 7%. Pica was responsive to oral iron therapy. In a second study, pica occurred in 13% of female donors with AIS (ferritin <12 ng/mL) vs 2% in iron-replete females; excess risk was 11%.
- Restless leg syndrome (RLS). No conclusive data that NAID is associated with this clinical condition.
- Hearing loss. No data that NAID is associated with this clinical condition.

Clinical Consequences of Iron Deficiency with Anemia

- These data have not been summarized by the Safety subgroup. It is unclear to what extent they would apply to donors who are iron deficient before donation and then are made anemic by their blood donation.
 - In addition to some donors developing lab values consistent with IDA following donation (as described above), a proportion of frequent donors who do not develop IDA may have anemia relative to their baseline Hb, were they not donating as frequently. The impact of such relative anemia has not been studied.

Quantitating the Effects of Interventions

- Iron supplementation
 - Summary
 - Studies of iron supplementation in blood donors have compared different iron preparations, doses, duration, and methods of administration. The studies suggest that iron gluconate is tolerated better than iron sulfate.⁹ A daily dose of 19-38 mg of elemental iron is as effective as larger doses (eg, 60-105 mg) in maintaining or increasing ferritin.¹⁰⁻¹² The typical duration of iron supplementation is 60 days, during which the great majority of the benefit of oral iron is achieved. Furthermore, it appears that most of this benefit occurs in the first 4 weeks.¹¹
 - Quantifying the effect on iron status in terms of % of donors with AIS or IDE who were returned to predonation ferritin status or to iron sufficiency.
 - In STRIDE, iron supplementation given for each donation made during the 2-year follow-up interval resulted in a 70% decrease in AIS and a 50% decrease in IDE at the final visit.
→Providing either 19 or 38 mg of daily iron for 60 days or an iron status information letter with ferritin test results were all equally effective in mitigating postdonation iron deficiency.
 - Effect on number of units collected from donors with AIS or IDE.
 - Deferral rates dropped by 67-75% over a 2- to 12-month study period when donors (including premenopausal females and frequent donors) were given high-dose iron supplementation.¹³
 - Expected compliance and adherence
 - Estimated to be as high as 75% if iron pills are supplied^{14,15} and as low as 20% if only educational material is supplied.¹⁶
 - Iron gluconate pills containing 19-38 mg of elemental iron are generally well tolerated, although mild constipation and gastrointestinal (GI) symptoms occur in some donors. Dropout rates with these doses range from 5-10%; in STRIDE,¹⁰ this was not different from the group receiving placebo. Although higher doses for shorter periods also have been shown to be effective, they

are associated with higher rates of side effects and a 33% dropout rate. Compliance with iron replacement appears to be better when iron pills are provided directly (68-88%) vs providing instructions to obtain iron pills from a pharmacy (44%).

- Ferritin testing with subsequent mitigation options presented to the donor
 - Studies in the US, Canada, and Switzerland have produced consistent results indicating that the outcome of decreasing the number of ID donors is achieved with measurement of serum/plasma ferritin in 1) all donors (Canada, Switzerland) or 2) selected subgroups of donors (frequent donors in the US; premenopausal females in Switzerland) coupled with generalized counseling measures that inform donors of various options to mitigate iron deficiency.
 - In STRIDE,¹⁰ 50% of donors with IDE no longer had IDE when their ferritin was measured at study end. In a Canadian study³ there was a 47% decrease, although the measurement interval was not as uniform.
 - In STRIDE,¹⁰ AIS decreased by 70%.
 - Mean ferritin levels in donors with low ferritin increased by 10-17 ng/mL across both studies.
 - Total number of donations decreased (18% decrease in donor return rate and in those that did return, decrease of one annual donation per donor per year in Canadian study³).
 - In another study, deferral rate decreased by 37%.
 - Expected compliance and adherence
 - From CBS (164 donors)³ and STRIDE (80 donors)¹⁰ data, it is estimated that 50% of donors informed of their ferritin results made the decision to take iron supplements. The data from STRIDE also indicate that ~25% delayed their next donation. (It was recommended that the delay be 6 months.)
- Lengthening of the interdonation interval
 - If a change in the interdonation interval is the only strategy used to mitigate ID, it appears that the interval will need to be extended to at least 6 months to achieve iron repletion in some (but not all) ID donors. CHILL² data indicate that for some donors an interdonation interval up to 12 months may be needed to avoid ID.
 - In HEIRS,¹¹ 67% of participants not taking iron had not recovered their ferritin by 168 days. For these subjects, a 6-month deferral would not be adequate.
 - In CHILL, the risk for low ferritin extended up to 12 months for ferritin <12 or <26 ng/mL, with those donating at intervals of 24 to 52 weeks having an odds ratio approximately twice that of individuals donating at intervals longer than a full year.

Prioritization of Groups for Iron Intervention

The Safety subgroup was asked to prioritize the donor groups most in need of iron intervention. Due to lack of data on the long-term consequences of ID, this prioritization is based upon the precautionary principle and assumes the following:

- Because young persons (up to age 25) are still undergoing brain development and because iron is needed for this process, the assumption is made that ID could potentially affect this process.
- Severe iron deficiency in pregnancy can affect fetal maturation and development. Thus, it is assumed that ID that is worsened by blood donation in a female of childbearing potential could have some consequences for her newborn child.

On the basis of these assumptions, the subgroup judged the prioritization for intervention to be:

1. Teenage donors (ages 16-18). More extensive brain development is thought to occur at these ages. It is recognized that donors aged 16 and 17 are minors and interventions may need to be adjusted accordingly. Donors aged 18 are also included because some data are relevant to ID in this group (eg, CHILL study²) and operationally many of these donors will present to donate at high school blood drives.
2. Other young donors (ages 19-25). Ranked next due to ongoing brain development.
3. Premenopausal females [ages 26 to risk-determined upper cutoff age (99.98% of 2015 US births occurred in females <50 years old and 99.79% to females <45 years old)]; ranked next due to fetal/newborn health concerns.
4. Frequent donors (males, 3 or more donations in a 12-month interval; females, 2 or more) and donors near the Hb cutoff (13.0-13.5 g/dL for males; 12.5-12.9 g/dL for females). These two groups were assigned equal priority.

Ferritin Measurement as a Means to Target Further Intervention

1. Goldman,³ Transfusion 2017
 - 18-month study of CBS donors in which representative samples from 12,595 donors (2.3% of donor base) were tested for ferritin.
 - If ferritin levels were <25 ng/mL (eg, very similar to the RISE definition of IDE), donors received a letter within 2 weeks giving them their results and advising them to 1) see their physician for further investigation and possible iron supplementation, 2) stop donating for 6 months, and 3) return to donating if their ferritin levels returned to normal.
 - Return rate was measured from index study donation (which occurred from July 2014 to December 2015) to end of study (July 2016); however, deferral rate on return was not reported.
 - Ferritin was measured on return donation, but measurement timing was dependent on return date.
 - Results:
 - 76% return rate in donors with normal ferritin (hence, no notification and usual recruitment) vs 58% in low-ferritin donors; absolute decrease of 18% and 1 fewer donation per donor over a mean follow-up period of 1 year in low-ferritin group.
 - Ferritin levels improved in low-ferritin females (from 13.6 to 25.7 ng/mL; increase of 12 ng/mL) and males (14.8 to 31.1 ng/mL; increase of 16 ng/mL) but decreased in donors who began with normal ferritin (decreased by 17 ng/mL in both genders). Expressed in another way, 53% of donors with low ferritin on index still had low ferritin on return and 32% of donors with normal ferritin had low ferritin on return.
 - This intervention worked to increase ferritin levels and to mitigate IDE (ie, 47% of donors with IDE no longer had IDE when their ferritin was measured subsequently).
 - Study was not controlled and there was uneven timing of return visits, uneven number of donations between tests, and no deferral information provided. There was no reporting of whether donors received iron supplementation after a visit to their health-care provider. Nevertheless, the conclusion that the intervention mitigated IDE in approximately half of the donors appears valid.
2. Goldman,¹⁷ Transfusion 2016
 - A small prospective observational study conducted in 2012 of 550 successful donations and 50 deferrals in Ottawa.
 - Ferritin measured; intervention similar to that in 2017 study in low-ferritin donors with the additional research procedures of distributing a questionnaire at 2 months and interviewing a small number of

individuals at 2 years after the index donation. Donors with normal ferritin levels also were informed of their results.

- Tracked donation frequency for 2 years before and 2 years after index donation.
- Return rate was not statistically different in donors with normal vs low ferritin (83% vs 78%) but was statistically different in repeat donors in each category (93% vs 85%; p= 0.018).
 - However, in contrast to the text in the results section and in Table 1, the discussion section states that 28% of iron-deficient repeat donors did not return to donate in the next 2 years vs 12% no-returns of donors with normal iron stores.
- Before the index donation, the low-ferritin group donated more often than the normal ferritin group in the 2 years prior to the index donations (6 vs 3 donations). After the index donation, the results were reversed (4 donations in low-ferritin group vs 5 in normal ferritin group).
- 164 donors completed a survey; 98 (60%) saw a physician and half of these took iron supplements.
- 21 donors were interviewed; however, as this number is small, the results probably cannot be generalized.

3. Gorlin,¹⁵ Vox Sang 2016

- 197 donors at 2 US sites; 170 had low ferritin (males ≤ 30 ng/mL; females ≤ 20 ng/mL; similar to RISE definition of IDE). These donors were deferred for 112 days, sent iron tablets by mail and advised to take 2 tablets per day for 100 days for a daily dose of 76 mg elemental iron (total dose of 7600 mg). Compared to other US studies, this is a higher dose and a longer duration of iron supplementation.
- Majority of donors had a successful return donation (117 of 133 return visits) during the study period (the length of which was unspecified). There were 16 deferrals, 10 of which were for low Hb. In the low-ferritin group given iron supplementation, this Hb deferral rate was 5% (6 of 116 return visits) vs 24% in the normal ferritin group (4 of 17).
- Because of the small number of donors, no quantitative conclusions could be reached.

4. O’Meara,¹⁸ Transfusion 2011

- Retrospective analysis of data from a single Swiss blood center from 1996 through 2009, involving periods before and after implementation of routine ferritin testing of donors.
- Eligibility criteria of capillary Hb of 12.3 g/dL for females and 13.3 g/dL for males. If deferred, donors received medical counseling, which consisted of 1) extending their interdonation interval, 2) taking iron supplementation, 3) making a dietary adjustment, or 4) a combination of these. No data were collected on which option a donor chose.
- As of 2004, ferritin was measured at donation or at Hb deferral. If levels were < 10 ng/mL (similar to RISE definition of AIS), donors received similar medical counseling as those who were deferred for low Hb.
- 160,612 visits by 23,557 donors (whole blood and double RBC donations).
- Results for females of childbearing potential (18-45 years of age) are shown in the following table.

Table 6. Study Results in Females

Parameter	Pre-2004	Post-2004	Difference
Mean Hb (g/dL)	13.42	13.70	+0.28 (95% CI: 0.26 to 0.30)
Anemia (< 12 g/dL)	4.9%	3.1%	-1.8% (95% CI: -1.4 to -2.4%)
Hb deferral	7.6%	4.8%	-2.8% (95% CI: -2.2 to -3.4%)

- Results for all donors:
 - Overall, of those donors rejected for low Hb, return rates at 2 or 4 years decreased by ~11% for donors after 2004 (72-75% returned before 2004 but 60-64% returned after 2004).
 - Similarly, return rates for nondeferred donors also decreased.
 - However, the mean time to return for both groups of donors was shorter after 2004.
- Authors could not separate out the effect of the different intervention options because these were not standardized. Most notably, rates of deferral for low Hb decreased substantially (eg, by 2.8%). This was attributed to ferritin testing screening out those donors who would likely have failed a Hb test on subsequent donation, although this was not proven.

5. Mast,¹⁹ Transfusion 2016 (STRIDE)

Frequent blood donors from three US blood centers were randomly assigned to one of five study arms. Donors in two intervention arms received either 19 mg or 38 mg of elemental iron as ferrous gluconate for 60 days after each donation. The third intervention arm was informational; in this arm (designated as the “Iron Status Information” arm), donors received letters informing them of their ferritin levels. The letter recommended continued frequent donation for donors with ferritin levels ≥ 26 ng/mL, while donors with ferritin levels < 26 ng/mL were advised to take self-purchased iron pills and/or delay donation for 6 months. The 2 control arms consisted of a placebo pill or a non-informational letter simply encouraging donation.

Ferritin level and hemoglobin concentration at the end of the 2-year study were statistically equivalent among donors randomly assigned to the 19- and 38-mg iron groups and the Iron Status Information arm. In the latter arm, when ferritin was measured at study end, 50% of donors with IDE no longer had IDE and 70% with AIS no longer had AIS. Of 80 donors with low ferritin who were sent the information letter, it was estimated that 50% of donors made the decision to take iron and ~25% delayed their next donation (it was recommended that the delay be 6 months).

6. Vassallo,²⁰ Transfusion (abstract) 2017

Blood Systems Research Institute implemented a ferritin testing program for donors aged 16-18. Upon successful donation, a tube is sent for ferritin determination. Deferral cutoffs are < 20 ng/mL in males and < 30 ng/mL in females. All deferred donors are advised to take iron for 60 days. Male donors below the male cutoff are deferred for 6 months, whereas females are deferred for 1 year. Overall, the iron-related deferral rate in these donors has been 28.6%; it differs twofold by gender—18.8% in males and 39.4% in females. Thus far, there are no follow-up data with regard to ferritin recovery, compliance with the recommendation to take iron supplements, or subsequent hemoglobin deferral.

7. Overall summary and assessment of the ferritin intervention

Studies have produced consistent results indicating that measurement of serum/plasma ferritin in all donors or in selected subgroups of donors—coupled with generalized counseling measures that inform donors of various options to mitigate iron deficiency—decreases the number of donors with iron deficiency (as evidenced by increased mean ferritin levels measured in donors undergoing follow-up or at a cross-sectional population level). In addition, donor deferrals and the average number of donations per donor decreased. It remains an open question as to whether robust quantitative data that would be generalizable to all US blood donors can be extracted from these studies.

Lengthening Interdonation Intervals as a Mitigation Strategy

1. Schotten,²¹ Blood 2016

This study investigated iron kinetics in 24 new donors (donation history of 1-2 previous lifetime donations) and 25 frequent donors (donation history of >10 previous donations) at a single center in the Netherlands. Many iron-related analytes were measured at 2, 4, 8, 15, 29, 57, 85, and 180 days. Even at 180 days, not all donors were back to their baseline ferritin levels. Recovery of ferritin was slower for new donors than repeat donors. The authors concluded that a 56-day donation interval in the absence of iron supplementation is not sufficient and that 180 days would be needed if the aim is to ensure that all donors recover their storage iron.

2. Kiss,¹¹ JAMA (HEIRS)

Also establishes that a 6-month deferral period is the minimum required for ferritin recovery in the absence of iron supplementation.

- Two-thirds of donors receiving no iron supplementation had not recovered lost iron by 24 weeks after donation, which was the last measurement recorded in the follow-up study.
- In enrolled donors with low ferritin who were not taking iron, the median time to postdonation recovery of hemoglobin (ie, recovery of 80% of the hemoglobin lost during donation) was 23 weeks.

3. Di Angelantonio,²² Lancet 2017 (Interval)

The Interval study is a recently completed, parallel group, pragmatic, randomized trial in which ~45,000 UK blood donors were enrolled and asked to donate at currently allowed intervals (12 weeks for males and 16 weeks for females) or at shorter intervals (10 and 8 weeks for males and 14 and 12 weeks for females). Hb and ferritin were measured and a questionnaire was administered. Over 2 years, more frequent donation resulted in lower mean Hb and ferritin concentrations and more deferrals for low Hb ($p < 0.0001$ for each) than those observed in the standard donation frequency groups. At study completion, the AIS rate for males in the 12-week group was 12% (compared to 24% in the 8-week group) and the rate for females in the 16-week group was 22% (compared to 27% in the 12-week group).

IDE rates were not reported; however, mean ferritin concentration in males declined from 45 $\mu\text{g/L}$ at study enrollment to 36 $\mu\text{g/L}$ in the 12-week group, whereas mean ferritin in females in the 16-week group did not change over the course of the study (24.4 vs 26.0 $\mu\text{g/L}$). There were no significant differences observed in QoL, physical activity or cognitive function across randomized groups. However, in the group with the shortest donation interval, more donation-related symptoms (eg, tiredness, breathlessness, feeling faint, dizziness, palpitations, and restless legs) were observed, especially among males.

Similar to the Interval AIS findings, it has been well established from other studies that a donation interval of 12 weeks in males and 16 weeks in females is not sufficient to substantially ameliorate high rates of IDE or AIS. Thus, the Interval study design and results (despite its size and success at randomization) do not provide useful data for US policy development with regard to whether (and, if so, how much) the interval needs to be lengthened in to allow recovery of iron stores in the absence of iron supplementation.

4. Spencer,¹⁶ Transfusion (abstract) 2017 (CHILL)

CHILL is a recently completed study at two US blood centers, enrolling 4265 donors (ages 16-49 years) at high school drives and following subsequent donations for an academic school year. Primary objectives were to

determine the prevalence of low ferritin (<12 and <26 ng/mL) in high-school-age donors and to assess the laboratory impact of donation. In longitudinal logistic regression models, investigators found that, compared to 19- to 49-year-old control donors, younger donors (16-18 years old) had a risk for ferritin levels <12 or <26 ng/mL that was more than two- or threefold greater, respectively. Findings also indicated that the risk for low ferritin (either <12 or <26 ng/mL) extended up to 12 months. Those donating at intervals of 24 to 52 weeks had an odds ratio approximately twice that of those donating at intervals longer than a full year. Assessment of an interaction term found that the rate of recovery (level of risk for low ferritin at different donation intervals) did not differ in 16- to 18-year-old and 19- to 49-year-old individuals. Although this is the first study to evaluate ferritin recovery for donation intervals up to a year in length, these findings are consistent with another study that showed that recovery of hemoglobin could take more than a year.²¹

5. Overall summary

If a change in the interdonation interval is the only strategy used to mitigate ID, it appears that the interval will need to be extended to at least 6 months to achieve iron repletion in some (but not all) ID donors. CHILL data indicate that for some donors an interval of up to 12 months may be needed to avoid ID.

Factors Effecting Hemoglobin Deferral

Donor Demographics and Behavior

Based on REDS-II analyses and data from NBCUS 2015,⁶ about 13-15% of blood donor visits are associated with deferral from donation, and half of these are due to low hemoglobin. Hence, as of 2015, roughly 7% of donation visits resulted in low hemoglobin deferral. Implementation of the FDA Final Rule in May 2016, which raised the minimum male hemoglobin concentration to 13.0 g/dL, has resulted in an absolute increase of about 1.3% in the hemoglobin deferral rate in male donors, such that the overall rate across all donor visits should now be about 7.5%.

The association of hemoglobin deferral with demographic factors is clear: females have a deferral rate about 10 times that of males (1.5% vs 15%), with different age patterns (deferral increases steadily with age in males and is flat in females until menopause, at which point it drops by 25-30%). African-Americans have a risk approximately double that of donors of European ethnicity. Donors in the lowest weight group (and lowest blood volume) also have risk that is two- and fourfold greater in females and males, respectively. These data were collected when the hemoglobin cutoff was 12.5 g/dL in both sexes, so they may differ somewhat now.

The association between donation frequency and hemoglobin deferral is complex. A REDS-II study by Custer et al²³ indicates a deferral rate in first-time donors (765 per 10,000 donor visits) virtually identical to that in repeat donors (775 per 10,000 visits). Several studies using multivariable regression^{1,16,24-26} found no association between donation frequency and risk for hemoglobin deferral, or alternately a counterintuitive result of lower risk with higher trailing donation counts. These findings most likely mask the opposing direction and magnitude of multiple effects. Unquestionably, blood donation contributes to deferral risk—the donation removes a substantial amount of both iron and hemoglobin and recovery of lost hemoglobin takes 6 months or longer in most donors not taking supplemental iron.^{11,23}

On the other hand, temporary deferral from donation has a disincentivizing impact on blood donors, such that the return donor pool becomes enriched for repeat donors who have not been deferred. These donors may be more robust in maintaining their iron and hemoglobin levels than donors who were deferred, which would bias the association toward

the null. An additional potential factor is a learning effect such that donors might identify a donation interval suitable for them that allows them to donate regularly without being deferred. The practice of self-initiated iron supplementation, more common in repeat donors, also facilitates recovery of hemoglobin and thus affects risk for deferral. The degree to which iron supplementation allows for the emergence of a greater number of long-term repeat donors or is increasingly adopted by new donors as they return for multiple visits, has not been studied. The complexity of these factors makes it challenging to estimate the attributable risk or excess risk of anemia in donors that is due to donation itself.

These donor behavior factors are compounded further by several factors extrinsic to donor health that affect hemoglobin fluctuations and/or hemoglobin deferrals. These include seasonality (more deferrals in warmer months), time of day, order of intake (health history screen vs hemoglobin/hematocrit determination performed first), sample source (venous vs capillary blood), lancet type, level of hydration, etc. Thus, when using gender-specific cutoffs based on population reference values or hemoglobin deferrals as a proxy for anemia, one should be mindful of these limitations.

Iron Supplementation

The net effect of wider initiation of iron supplementation in blood donors, or just in blood donors who are deferred for Hb, might be a gain of donated units in the range of 2-4% of all donor visits. This assumes that not all donors will be capable of or interested in (due to side effects or other reasons) taking supplemental iron on a consistent basis; a reasonable assumption is that 50-70% would do so. The benefit in terms of donor Hb recovery, would accrue to the 40% of Hb deferral visits that are estimated to be “excess” as caused by blood-donation-induced IDA (3% of donor visits out of 7.5% donor visits with Hb deferral). The same benefit may also accrue to many of the donors whose Hb deferral results from IDA caused by other than blood-donation-induced iron depletion (4.5% of the 7.5% of donor visits with Hb deferral). Assuming that those with Hb deferral due to excess IDA are more likely to take iron (high commitment level), the following estimates can be made:

- 60% iron supplementation (average of 50-70% range above) applied to 3% of donor visits and a 100% response rate = 1.8% donor visit recovery.
- 40% iron supplementation (just an estimate, could well be lower) applied to 4.5% of donor visits and a 100% response rate = 1.8% donor visit recovery.

However, the second group might be disincentivized from returning due to concern about (or lack of interest in) taking iron to support blood donation. Thus, the total estimate of 3.6% donor “recovery” from giving Hb deferred donors iron would be reduced if donors return less frequently or not at all. It would also decline if responsiveness in Hb kinetics subsequent to iron supplementation fell short of 100%.

Iron Status and Adverse Consequences in Blood Donors

Introduction

Functional iron is present in oxygen-transporting red cell hemoglobin and muscle myoglobin as well as cellular redox and respiratory enzymes. Iron-containing enzymes are essential for cell proliferation and growth, cellular energy maintenance, neurotransmitter metabolism, and neuronal myelination, hepatic synthesis of steroid hormones, proteins and bile acids, drug/toxin metabolism and immune system function. Surplus iron is stored in the form of ferritin and hemosiderin. When these stores are exhausted, functional Hb and tissue iron both decline, the former proportionately more in children and adults, while Hb is defended in the fetus and neonate.²⁷

Iron deficiency has been *associated* with several adverse effects (AEs), including fatigue, cognitive dysfunction, adverse pregnancy outcomes (perinatal mortality, preterm delivery, low birthweight, newborn cognitive abnormalities), impaired physical endurance/aerobic capacity, pica, RLS, and hearing loss.

Associational studies can be confounded by the effects of socioeconomic status and innate cognitive nature-/nurture-determined abilities, or even by health status (which secondarily affects dietary iron and other mineral absorption). Although the evidence for causality is present in most human studies of ID, a causal connection for some of these consequences, particularly in NAID, has not been irrefutably established. Blood donors most often have NAID, not IDA, the latter of which is more clearly and consistently associated with adverse outcomes and accounts for a high proportion of deferrals. Some donors are considered to have NAID based on low ferritin levels and do not meet the World Health Organization (WHO) definition of anemia. However, they have low tissue iron and “relative” anemia (ie, their current hemoglobin is lower than it would be if their iron stores were in the normal range) indicated by elevated sTFR levels. Such individuals are more likely to respond to iron therapy. Some individuals at the lowest acceptable Hb values for blood donation fall into this category and may develop frank postdonation IDA in the absence of a change in iron availability or absorption.

Studies reporting the association of ID with adverse outcomes are more numerous in nondonors than in blood donors. Many outcomes have not been studied much in blood donors (eg, effects on cognition, pregnancy, or hearing loss), while others (eg, pica and RLS) have been assessed in randomized controlled trials (RCTs) of blood donors. Further, several recent RCTs in blood donors help to address the need for iron status assessment or repletion in the setting of blood donation. Based on extrapolation of studies in patients, otherwise healthy nondonors, and direct evidence from studies in blood donors, the balance of evidence indicates that ID likely causes or contributes to most of the negative outcomes. NAID is admittedly less well studied and can be linked most confidently with pica. Each of the outcomes is summarized below with regards to the strength of evidence linking it to ID and/or NAID.

Exercise Endurance

Anemia reduces the oxygen-carrying capacity of blood, eventually requiring increased cardiac output (which has finite limits) to meet total body oxygen demand with exercise or even at rest. IDA significantly impairs oxygen delivery and thus, maximal exercise capacity with even mild-to-moderate exercise. NAID does not limit oxygen delivery during the activities of daily living, and only minimally changes maximal exercise capacity at Hb concentrations within the normal range. Exercise impairment in NAID would be expected primarily in high-performance athletes, as occurs on occasion with the transient decrease in Hb following RBC donation.

Endurance, the maximum length of time an individual can sustain a given workload, depends not only on oxygen delivery, but also on the efficient use of oxygen by working muscle. Energetic efficiency is the amount of energy required to perform a given amount of external work. A reduction in tissue oxidative capacity during ID can impair exercise endurance by affecting efficiency.²⁸

Several studies²⁹⁻³⁵ have demonstrated decreased endurance and energetic efficiency in individuals (not blood donors) with NAID. This may be important to high-performance/endurance athletes, but NAID likely results in less noticeable changes in exercise endurance in others. The studies by Brownlie^{31,33} and Hinton^{30,34} suggest that women with NAID (indicated by low ferritin) who also have low tissue iron (indicated by elevated sTFR levels) have improved physical endurance/aerobic performance with iron therapy. Such individuals are thought to have “relative” anemia. IDA should clearly be avoided or corrected.

A recent meta-analysis by Van Remoortel et al³⁶ found that a standard blood donation was associated with a small but measurable reduction in exercise performance in the first 2 days after donation. The recovery period appears to be as long as 14 days (Zeigler³⁷). However, this performance alteration may be due to depletion of red cell mass rather than to iron deficiency.

Fatigue and Quality of Life

IDA has been associated with fatigue in multiple studies.^{35,38} In 1000 whole-blood donors interviewed after donation, the fatigue rate related to blood donation was 7.8%, 2.8 times higher in women (11.1%) than in men (4.0%; $p < 0.001$). The higher fatigue rate in women was suggested to be related to greater iron deficiency, the greater proportion of Hb removed, or a combination of these factors. Fatigue was reported to be associated with a 20% reduction in blood donor return rates at 1 year.

Several studies³⁹⁻⁴¹ of iron repletion (oral and intravenous) have shown that *patients* with NAID complaining of chronic fatigue experience benefit from iron repletion. Krayenbeuhl³⁹ found that individuals with the lowest ferritin levels (≤ 15 ng/mL) have the greatest improvement in fatigue symptoms, suggesting that those with absent or nearly absent tissue iron are the subset of NAID patients who are most likely to improve with iron therapy. However, these are individuals presenting to their physician with health complaints, not healthy donors.

A study in 154 Swiss Red Cross female blood donors with NAID provided with 80 mg of elemental iron daily for 4 weeks vs placebo measured fatigue on two scales, along with depression and QoL scores, and performed an exercise step test.⁴² Although the iron treatment group experienced an increase in ferritin from 15 to 28 ng/mL after adjustment for baseline differences, there was no clinical benefit of iron supplementation in the setting of a single blood donation except for two QoL improvements: less interference of pain with normal work and less limitation in work or other activities as a result of physical health. The authors were unable to explain these dimensions of improvement (particularly pain) and considered them “spurious.” The lack of other significant measured benefits of iron supplementation in a blood donor population is an important finding.

In a larger cross-sectional study⁴³ of 8692 male and 7683 female donors (the Danish Blood Donor Study), lower iron status was not accompanied by lower self-reported QoL. Self-reported physical scores (physical functioning, physical roles, bodily pain, general health) and mental scores (vitality, social functioning, emotional roles, mental health) were used to explore the association between iron stores and wellbeing. The analysis was based on the median scores as well as the odds of scoring in the bottom 10th percentile in these measures. Either as continuous or discrete variables, NAID ferritin values were not associated with lower well-being scores. It is important to note that QoL and fatigue scores are subject to accommodation, meaning that donors may adjust their QoL activities as they become progressively iron depleted and may not notice the accommodation until after iron supplementation (which was not part of this study).

Adverse Pregnancy Outcomes

The American College of Obstetricians and Gynecologists (ACOG) has stated⁴⁴ that IDA during pregnancy has been associated with an increased risk of low birthweight, preterm delivery, and perinatal mortality. However, they stated that it is unclear whether iron supplementation in well-nourished pregnant females without anemia affects perinatal outcomes. They do not advocate routine screening for ID, but do recommend anemia screening.

Among the 18.0% of ID pregnant females evaluated in the NHANES study (<0 mg/kg total body iron calculated from serum ferritin and sTFR), 16.2% were anemic (2.9% overall).⁴⁵ The US Preventive Services Task Force (USPSTF) has concluded that current evidence is insufficient to assess the balance of benefits and harms of screening for IDA in pregnant females to prevent adverse maternal health and birth outcomes (qualified as those without symptoms of IDA or those suffering from malnourishment, hematologic, or nutritional conditions that increase the need for iron).^{46,47} The task force stated: “Although treatment and supplementation with oral iron can improve maternal hematologic indexes, subsequent improvement in maternal and infant outcomes has not been well-demonstrated.”

On the contrary, a seminal review⁴⁸ of ID during fetal and neonatal development states: “The brain is at its most vulnerable during critical periods of development, including the last trimester of fetal life and the first 2 years of childhood—a period of rapid brain growth termed the ‘brain growth spurt.’ In most cases, performance deficits in children with IDA >2 years of age are ameliorated by iron treatment. In contrast, performance deficits were generally more difficult to reverse in children <2 years of age. Although direct evidence demonstrating an effect of NAID on brain functions is not conclusive, until shown otherwise, it seems prudent to assume that a gradation of effects of ID occurs in the brain, with milder anemia and NAID resulting in perhaps more subtle, but still potentially adverse, brain effects, particularly if they occur during sensitive periods of development.” In pregnant females with NAID, lower serum ferritin concentrations are seen in neonates, placing them at risk for earlier onset of postnatal ID that can affect brain development. Fetal/neonatal ID may also contribute to long-term developmental abnormalities seen in infants with growth retardation and those born of diabetic pregnancies.

Prenatal anemia screening protects against the established adverse outcomes of IDA. The effect of NAID on late fetal and early childhood brain development is not fully known. Definitive data regarding other perinatal outcomes are also lacking; however, there is some reassuring evidence that comes from a recent retrospective cohort series of 18,483 Quebecois blood donors with one or more births recorded in the provincial birth registry.⁴⁹ There was no association between the frequency of blood donation in the 2 years preceding delivery and low birthweight, preterm delivery, or stillbirth, despite robust stratified and logistic regression analysis to minimize bias. The study did not measure iron status, but was conducted in the population of interest, female blood donors.

Cognition

Cognition can be defined as the activities of thinking, understanding, learning, and remembering. Cognition is important for quality of life, such that impaired cognitive function is correlated with poorer quality of life. Brain iron is required for myelination, neurotransmitter function (serotonin, dopamine, and norepinephrine metabolism), and hippocampal development. Brain iron accumulates from birth through early adulthood. Perhaps for this reason, brain iron levels are more sensitive to iron deficiency in the young than in adults. This is particularly so *in utero* and for the first 2 years of life during the most intense period of brain formation, but possibly throughout brain growth into early adulthood.

Magnetic resonance imaging (MRI) of the brain has revealed changes through adolescence and young adulthood that begin to resemble the adult brain only by the early 20s. This correlates with the acquisition of cognitive and behavioral skills that mark the adolescent transition from childhood to adulthood.

The MRI-measured volume of gray matter, where thought and memory are based, peaks in early adolescence and then begins to decline. This decline appears to be part of maturation, thought to be due to an increase in cortical myelination during the development of associational hubs, but later in adult life due to pathologic neuronal loss. Another feature of brain maturation involves changes in the number of synapses, the connections between brain neurons. Synapses multiply

in the first 2 years of life, during the most rapid period of brain growth, to significantly exceed adult connectivity. As maturation proceeds, however, there is a loss of synapses, thought to be indicative of improved brain efficiency. The integrity of neuronal connectivity through appropriate synapses and myelination determines the efficiency of collaboration of various brain structures and likely determines the growth of intellect.

Fourteen RCTs of children, adolescents, and women were identified in a 2010 systematic review⁵⁰; no RCTs were conducted in men or older individuals. In anemic groups, supplementation improved attention, concentration, and intelligence, but had minimal effect on nonanemic participants and no effect on memory, psychomotor skills, or scholastic achievement in either group. The limited number of identified RCTs were generally small (only 3 exceeded 200 total subjects, 7 studies were in developing countries) and methodologically weak, prompting a call for additional study.

In a widely quoted interventional RCT of attention by Murray-Kolb et al,⁵¹ memory, learning, and reaction time among 152 women aged 18-35 who were iron replete, had NAID, or had IDA, the effect of 16 weeks of daily iron sulfate (60 mg elemental iron) or placebo was reported. Those with NAID scored lower, but not statistically differently from iron-replete women, while both did better than women with IDA in nearly all dimensions. Analyzed continuously, anemia affected reaction time but not performance, while low iron status affected performance but not reaction time in the lowest vs highest quintiles. Women with any significant rise in ferritin had improved scores that bore no relation to the magnitude of their ferritin change. Unfortunately, the impact of ferritin changes was not reported in the 3 subgroups separately, so improvement could have occurred primarily in the IDA group. Another widely quoted study⁵² followed 78 girls with NAID treated with 130 mg elemental iron or placebo twice daily for 8 weeks. Girls who received iron performed minimally better on a test of verbal learning and memory than girls in the control group. Of reported change, 93% was related to baseline scores and only 7% due to the iron supplementation. No differences were seen in attention or self-reported energy, mood, concentration, or memory.

A limitation of this study and others in NAID is that the individuals were not stratified by sTFR and, thus, data may have obscured whether tissue iron depletion is related to cognition effects.

Blood collectors recruit and draw blood from adolescents, many of whom have NAID. In nondonors, measures of educational attainment in NAID relative to iron-replete individuals for both language and mathematics skills have not been shown to be statistically significantly different.⁵³ In infants, neither mental development index nor psychomotor development demonstrated statistically significant impairment by NAID compared with development in normal infants.

Despite the inconclusive results for the effects of NAID on adolescent cognition, this is a period of significant brain development involving the myelination of important cortical association areas. Concern around impairment, even small difficult-to-measure changes, suggests that steps should be taken to prevent iron depletion in persons whose brains are continuing to undergo detectable remodeling and growth.

Pica

Pica is the continual craving and consumption of nonnutritional substances such as ice, dirt, clay, chalk, starch, coal, or paper. The most common manifestation (and the symptom most closely linked with iron deficiency) is pagophagia, the pathologic consumption of ice. Two recent clinical trials have studied pica in blood donors. Bryant et al⁵⁴ studied 1236 blood donors deferred for anemia and 400 nondeferred control donors at the National Institutes of Health (NIH). All donors underwent iron testing, received 60 days of oral iron supplements, and underwent questioning for symptoms of

pica. Pica was reported in 11% of donors with iron depletion or iron deficiency vs 4% of iron-replete donors ($p < 0.0001$). Donors with pica experienced complete resolution of the behavior after 14 days of iron supplementation. Spencer et al⁵⁵ reported their experience with 1334 RISE blood donors who underwent iron testing and completed a questionnaire on symptoms of pica. Pica was reported by 5.5% of blood donors and the prevalence increased with the degree of iron depletion in women (13% ferritin < 12 ng/mL vs 2% in iron-replete women). Neither study showed a significant association between iron status and the incidence of pica in men.

These studies suggest that pica—in particular, pagophagia—is common in female blood donors who are iron deficient. In those females with NAID (ferritin $< 9-12$ ng/mL) the incidence of pica was 13.3-21%. The data from Bryant et al⁵⁴ strongly suggest that pica symptoms in blood donors are reversible with oral iron therapy.

Restless Leg Syndrome

RLS is a common condition reported in 5-15% of the general population and is characterized by an uncomfortable movement disorder of the lower extremities that worsens at rest and interferes with sleep. Primary RLS is a disorder of the central nervous system, while secondary RLS is associated with, or worsened by, iron deficiency. Iron deficiency, however, is neither required for, nor sufficient to cause, RLS.

Several studies have reported on the prevalence and potential association of RLS with blood donation and iron deficiency. Bryant et al⁵⁴ studied 1236 donors deferred for low hemoglobin and 400 nondeferred donors. They found that symptoms of RLS were reported in 16% of subjects with iron depletion or deficiency vs 11% in those who were iron replete ($p = 0.012$). This finding was limited to men with low hemoglobin and no association with RLS was found in men with NAID or with women with low hemoglobin or low ferritin. In the RISE study, Spencer et al⁵⁵ enrolled 1166 donors who completed RLS questionnaires. They reported 9% of donors with probable RLS and 20% with possible/probable RLS. It is important that RLS was not correlated with donation intensity or iron depletion in men or women. Pedrazzini et al⁵⁶ of the Swiss Red Cross studied 291 women 1 week after donation and reported a prevalence of 6.9%. There was no association of RLS with number of previous donations, hemoglobin concentration, or ferritin level.

These studies suggest that RLS is weakly, if at all, correlated with NAID. RLS may be more prevalent in male donors who are anemic and iron deficient; however, even among these donors iron repletion will have variable efficacy in resolving symptoms.

Hearing Loss

Iron deficiency has been associated with sudden sensorineural hearing loss (SNHL) characterized by a rapid loss of hearing function over a 72-hour period (OR, 1.34; 95% CI, 1.11-1.61; $p < 0.01$).⁵⁷ The mechanism is unknown. A rat model of IDA and sudden SNHL identified a number of cochlear defects induced by iron deficiency potentially as a result of ischemic damage exacerbated by IDA.

Schieffer et al⁵⁸ performed a retrospective cohort study of IDA and SNHL, conductive hearing loss, and combined hearing loss in 305,339 adult *patients* seen at Hershey Medical Center from 2011 to 2015. The prevalence of IDA was 0.7% ($n = 2274$). Both SNHL and combined hearing loss were significantly associated with IDA. Conductive hearing loss was not significantly associated with IDA. In a logistic regression analysis the adjusted OR for SNHL was 1.82 (95% CI, 1.18-2.66) and combined hearing loss 2.4 (95% CI, 1.90-3.01.) The study did not look at patients who were iron deficient without anemia. The same group at Hershey Medical Center published a similar study⁵⁹ in 20,113 pediatric

patients 4-21 years old. ID (ferritin <15 ng/mL) and anemia were present in 2.3% of patients. Pediatric patients with IDA demonstrated increased odds of SNHL (OR, 3.67; 95% CI, 1.60-7.30), but not conductive hearing loss (OR, 1.74; 95% CI, 0.60-3.94).

These data suggest that adult and pediatric *patients* with IDA may have an increased risk of hearing loss. These data do not inform whether NAID is associated with hearing loss, nor whether the findings in patients would also be true in healthy blood donors. The data do strengthen the case that IDA should be avoided.

Table 7. Safety of Iron Supplementation

Study	Population and Intervention(s)	Outcome Measures	Outcome/ Conclusion	Adherence	Safety	Exclusions
20 mg Fe RCT reg. blood donors (Radke et al ⁶⁰)	526 qualified, regular donors randomly assigned to take vitamins with 40, 20, or 0 mg/day elemental Fe for 6 mos. and continuing to donate (males x 3, females x 2). Male Hb \geq 13.5 g/dL, female Hb \geq 12.5 g/dL	Hb, ferritin, soluble transferrin receptor at each donation. Log (sTFR/ferritin).	Ferritin and iron stores fell in placebo arm. Ferritin and iron stores maintained in 20- and 40-mg arms. Hb deferrals = 1.7%, higher in placebo (small numbers). Modest repletion in females, stability in males.	Assessed by counting pills at visits, but undefined: “Poor in roughly 1/3 of the male participants” and in “roughly 1/4 of females.”	Equivalent in all three groups. Dropouts 49%, slightly higher in placebo.	None described.
NIH Fe supplement deferred and depleted donors (Bryant et al ⁹)	1236 Hb-deferred (<12.5 g/dL), 400 nondeferred unmatched “controls.” 65 mg elemental Fe (SO ₄). 38 mg gluconate for history of SO ₄ intolerance. Taken for 60 days with each presentation. Controls= no Fe at subsequent visit unless Fe depletion/deficiency. Fe depleted = 9-19 females, 18-29 males Fe deferred = <9 females and <18 males	Safety of giving Fe. Improvement of symptoms, normalization of lab values. Rate of Hb deferral.	Routine Fe is safe and prevents Fe depletion and deferral in donors. Hb rose with Fe, as did ferritin. MCV rose and RDW fell. Hb rose but ferritin remained stable in those without Fe depletion/deferral.	68% of doses taken. 5% discontinued Fe.	Intolerance in 29.5%. “Our donor evaluation process easily allowed us to identify subjects requiring referral to personal physicians for more comprehensive workup. Rather than posing a risk of harm to the donor, it is more likely that early attention to iron depletion and deficiency would lead to earlier detection of occult malignancy and a higher chance of cure.”	<18 years of age, diagnosis of hereditary hemochromatosis (HH), control donors already taking Fe.
HEIRS Fe vs placebo Hb and Fe recovery (Kiss et al ¹¹)	215 qualified (not deferred) >18-year-old donors RCT (unblinded, no placebo) stratified by ferritin, gender, age with no WB/RBC donation x 4 mo. 38 mg elemental vs no iron x 24 weeks.	Time to recovery of 80% of postdonation Hb drop and to baseline ferritin.	Hb and ferritin recovery faster w/ Fe and majority w/o Fe did not recover either by 24 weeks. True in both lower and higher ferritin strata. See also Cable, below. ⁶⁰	92.% with pill counts.	Minimal AEs attributed to Fe. Dropout rate 9% with Fe and 1% without.	Ferritin >300 ng/mL.

Study	Population and Intervention(s)	Outcome Measures	Outcome/ Conclusion	Adherence	Safety	Exclusions
Observational Fe replacement in Denmark (Magnussen et al ⁶¹)	Operational eval of donors presenting under Hb and ferritin-based algorithm to provide varying length of iron (Fe 100 mg elemental or 25 mg with intol). No. of initial pills varied with ferritin but was 20/donor after 1st course until next ferritin. GP referral restricted to “suspect history” (poorly defined) and low Hb with ferritin ≥40 ng/mL or not done. Minimum ID interval 90 days. Ferritin testing increased mid-course due to inability to maintain Hb.	Donor Hb at every donation, ferritin at index and every 10th thereafter.	8,555/96,336 male and 19,144/85,142 female donations qualified for iron. Donor Hb levels increased and low Hb presentations decreased (male <13.5 g/dL or female <12.5 g/dL). % of donations with Rx required fell steeply.	No formal assessment reported.	No formal assessment reported.	“Suspect history,” or Hb deferral and ferritin ≥40 ng/mL or not done.
STRIDE RCT education vs Fe supplementation (Mast et al ¹⁹)	5-arm RCT. Otherwise qualified male ≥3 donations x 12 mo., females ≥2. ≥18 years old. Keep giving vs iron status letters, 19 mg, 38 mg elemental Fe vs 0 mg.	Prevalence of ferritin <12 or <26 ng/mL. Hb increase.	692 enrollees, 393 completed. Among completers, prevalence of low ferritin fell >50% and not different in the 3 “active interventions” (19 mg, 38 mg, and iron status letter). Fe status worsened without intervention.	Pill groups de-enrolled 39% vs 7 with letters. No difference among the three pill groups.	No major safety issue and the nearly equivalent rates of AE/withdrawal in 0 mg, 19 mg, and 38 mg groups.	HH, those taking iron and lifetime deferrals were excluded before randomization (n=12/704).
HEIRS Fe effect on total body iron and stores (Cable et al ⁶²)	215 qualified (not deferred) >18-year-old donors RCT (unblinded, no placebo) stratified by ferritin, gender, age with no WB/RBC donation x 4 mo. 38 mg elemental vs no iron x 24 weeks.	Estimated total body iron by adding red cell and storage compartments.	Daily iron at this dose allows RECOVERY of iron lost BY DONATION. Degree of iron repletion inversely proportional to baseline ferritin level	92.% with pill counts.	Minimal AEs attributed to Fe. Dropout rate 9% with Fe and 1% without.	Ferritin >300 ng/mL.

Study	Population and Intervention(s)	Outcome Measures	Outcome/ Conclusion	Adherence	Safety	Exclusions
STRIDE 19 mg and 38 mg are equivalent (Bialowski et al ⁶³)	5-arm RCT. Otherwise qualified male ≥ 3 donations x 12 months, females ≥ 2 . ≥ 18 years old. Keep giving vs iron status letters, 19 mg, 38 mg elemental Fe vs 0 mg.	Estimated total body iron by adding red cell and storage compartments.	Total body iron decreased in placebo and “no pill” groups in complete dataset (no change in those with completed initial and final visits). With 19 and 38 mg, identical increases after first 60-day course and maintained subsequently. Antacids reduced storage iron.	Pill groups de-enrolled 39% vs 7 with letters. No difference among the three pill groups.	No major safety issue and the nearly equivalent rates of AE/withdrawal in 0 mg, 19 mg, and 38 mg groups	HH, those taking iron and lifetime deferrals were excluded before randomization (n=12/704).
Prospective feasibility of READ vs DIRECT (Pasricha et al ¹⁴)	Female 18-45 years, ≥ 1 WB donation x 12 months. READ=message to get Fe. DIRECT=provision of Fe (67.5 mg elemental) x 20 days (60 pills). Not an RCT, and undertaken in different centers. Follow-up after enrollment available in 45% of READ and 60% of DIRECT.	Donor uptake of intervention, AEs, maintenance of Fe stores (ferritin).	44% and 88% (READ vs DIRECT) took Fe. READ did not maintain Fe and DIRECT did. READ effective for stores if $>75\%$ “adherence.”	Self-reported via questionnaire.	“Mild” but slightly more common with Fe. 33% who took Fe stopped iron for AE.	Personal or family history of HH, personal history of red cell disorders. In READ asked to consult physician before taking Fe. DIRECT excluded irritable bowel disease, polyps, and cancer.

RCT = randomized controlled trial; Hb = hemoglobin; NIH = National Institutes of Health; MCV = mean corpuscular volume; RDW = red cell distribution width; GP = general practitioner; AE = adverse effects; HH = hereditary hemochromatosis

HEALTH ECONOMICS ASSESSMENT

Cost Model Strategy and Hierarchy

A budget impact analysis assessment was conducted for each strategy. The costing of each strategy was taken from the health-care system perspective—those costs that accrue to the blood centers as part of implementing a strategy and medical care costs of interventions and adverse events. The preferred approach of the societal perspective, accounting for all costs and consequences that accrue to all members of society, is beyond the scope of the current assessment.

The generalized structure for assessment of costs is provided in Figure 1 as a hierarchical model. The hierarchy is not intended to suggest lower or higher priority costs. Rather, the purpose is to define costs at the process level. First is the baseline cost to implement a strategy *de novo* followed by a second level of costs to run/manage a strategy once implemented. The third level of costs are wider ranging and relate to the cost implications in terms of blood supply availability, assuming the current overall number of units in the national supply is maintained. In other words, any units that are lost because donors are ineligible or do not adhere to the intervention strategy will be made up by recruiting additional donors to restore the lost units in the supply.

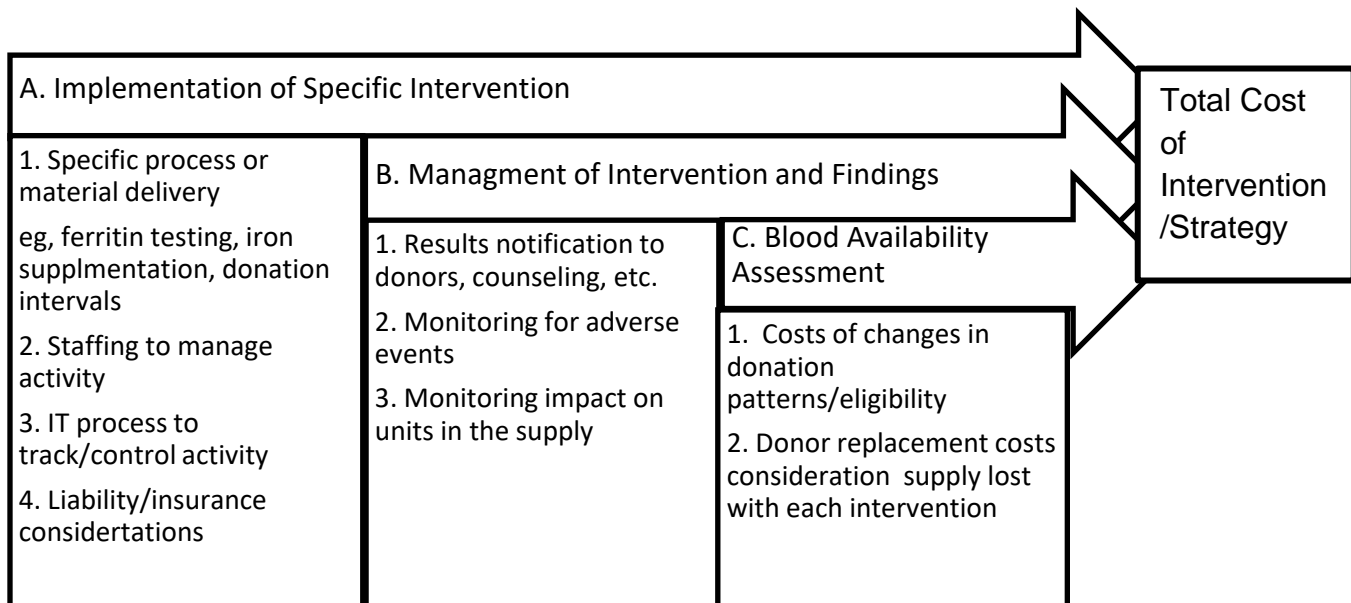


Figure 1. General structure used to estimate the cost of each intervention option.

Primary Sources of Cost and Prevalence Estimates and Preferred Hierarchy

1. Data from Finance groups within blood collection organizations (BCOs) where available.
2. Data from Operations groups within BCOs to define the frequency of some events and proportions of donors and donations affected.
3. Estimated costs (to scale) from interventions that could be implemented (eg, ferritin testing).
4. Literature reviews for adverse event costs.
5. Expert opinion and assumptions.

Work Plan/Approach

1. Use ARC and BSI as the centers for estimating the number of donors/donations and costs of each strategy. Consult with America's Blood Centers (ABC) to obtain estimates for smaller BCOs, if available.
2. Combine these sources to develop an estimated national impact for implementation of each strategy.

Interventions

OPTION A: Iron Supplementation

For this intervention the analysis used a blood-center-based supplementation program, because the cost of such a program would be expected to be highest. A voucher program is estimated by subtracting the cost of supplementation from an active supplementation program.

A. Costs of Intervention Implementation

- Full-time equivalents (FTEs) to establish program (How many FTEs would be needed?).
 - Most interventions at the majority of organizations would not require new hires, but might require shifting the work tasks of existing employees to cover the additional responsibilities.
 - The analysis did not separately include specific costs of FTEs which were included in start-up costs.
- Pill cost (voucher program would have a different cost stream).
 - Although the analysis evaluated no specific dose, the cost of providing 18-mg iron supplements available at wholesale cost seems most appropriate for the approximation.
 - The cost for a 30-day supply or was estimated at \$8.50, inclusive of pills, warehousing, transportation, and dispensing.
- Logistics (kitting, fixed and mobile drive provision, communications, pharmaceutical licensing, if required).
 - These costs are assumed to be included in the provision of pills based on the work of White et al.⁶⁴ New costing studies for these activities were considered beyond the scope of this analysis.
- IT system changes to document provision of voucher or supplements and to track AEs
 - Assessment of whether any current donor management systems can be programmed compared to developing a novel system for this purpose.
 - Broad estimates from ARC were provided as well as more detailed time and effort estimates for BSI. Broader estimates were selected for this analysis because of lack of information on whether the detailed BSI time and effort estimates would be applicable to other blood centers.
 - A summary cost of IT system modification of \$400,000 was assumed. This value is not scaled to account for individual costs to blood collection organizations.
- Cost of educational program to explain iron supplementation.
 - These data are not available; however, a \$1000 cost to develop this information was included in the analysis.

- Cost of educational program specific to schools and parents if a young-donor supplementation program is adopted.
 - These data are not available and were not included in the analysis.
- Establishment of blood-center-based “anemia clinics.”
 - These data are not available and were not included in the analysis.
- Insurance rider to cover program.
 - The analysis includes cost estimates of \$300,000 to resolve up to three lawsuits/settlements for potential harm in an organization collecting 1,000,000 donations per year. The insurance cost is adjusted to the total number of donations collected, so that the total cost for an 11,000,000-unit supply would be \$3,300,000.
- Legal review of program risks/liability.
 - Legal review was included as a single review regardless of the number of units collected and was assumed to be \$20,000.

B. Cost of Management of Intervention and Findings

- FTEs to manage program
 - Assumed to be covered as part of start-up costs.
- Staff time to respond to donor questions about results and recommended actions, including recommendations for iron supplementation.
 - Assumed that BCOs would have donor counselors with physician oversight and referral for serious events.
 - AEs that could incur follow-up medical care costs are listed below.
 - Potential for poisoning.
 - Inadvertent treatment/masking of GI inflammation and malignancy, malabsorption, and gynecologic-disease-related ID with consequent delayed diagnosis and treatment.
 - Interference with medication absorption [tetracyclines, fluoroquinolones, levodopa, thyroxine, angiotensin-converting enzyme (ACE) inhibitors].
 - Negation of benefit and likely over-replacement in hemochromatosis.
 - Data on rate of occurrence/frequency of these AEs are not available, making cost estimates very difficult to project. Thus, they were not included in this analysis.
- Assessment of program effectiveness.
 - Rates of supplementation recommendation and donor refusal.
 - Rates of voucher redemption/provision of iron.
 - Impact on donor hemoglobin/eligibility to donate at next donation attempt.
 - Rates of AEs.

- No data are available on effectiveness of large-scale programs. The analysis used a nominal program review cost of \$100 per year as a placeholder. This was included as a flat cost regardless of the size of the organization.

C. Cost to Maintain Blood Supply at Current Level

- Assessment of percent of current supply lost following implementation (estimated and actual observed). Note that the quality of available data is weak, affecting the ability to generate solid cost estimates; accurate data are not available.
- Cost to recruit donors to replace lost supply.
 - The cost of recruiting new donors was scaled to the percentage of the donor population and donations collected according to the schedule in Table 8.
 - Within each defined donor group, the recruitment of new donors to replace those who are not able to donate as frequently (or at all) would be from within the same demographic group. This was done because of the complexity introduced in trying to model shifting the target recruitment population to different demographic groups. Modeling how different organizations may approach replacement of lost donations is beyond the scope of this analysis.

Table 8. Schedule of Replacement Cost According to the Percent of the Supply Lost

Percent Loss of Total Collections	Cost of Recruiting Each New Donor
<2%	\$55.00
2 to 5%	\$70.00
5 to 7%	\$85.00
7 to 10%	\$100.00
10 to 15%	\$120.00
>15%	\$135.00

- In the sensitivity analysis, the cost of recruiting new donors was assumed to be a flat \$45 per donor, regardless of the percentage loss of the supply. This assumption was made to assess the lowest possible replacement cost estimated by the working group.

OPTIONS B and D: Donor-Specific Interdonation Intervals by Demographic Group

A. Costs of Intervention Implementation

- FTEs to establish program.
 - None.
- Cost to define group-specific intervals.
 - No assumed costs.

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- IT system changes to document and manage different donation intervals—assumed to be at the group level rather than the individual level.
 - Assessment of whether any current donor management systems can be programmed compared to development of a novel system for this purpose.
 - Assumed to be \$80,000 per 1,000,000 donations to implement necessary controls on donation for affected donor groups. A proportional cost was assumed when implemented across multiple BCOs.
- Cost of educational program to explain donor-specific intervals.
 - Assumed to be \$5000.
- Insurance rider to cover program.
 - Assumed to be negligible (\$100).
- Legal review of program risks/liability.
 - Assumed to be negligible (\$100).

B. Cost of Management of Intervention and Findings

- FTEs to manage program.
- Staff time to respond to donor questions about the program.
 - Assumed to be donor counselors.
- Assessment of program effectiveness.
 - Rates of adherence to intervals.
 - Impact on donor hemoglobin/eligibility to donate at next donation attempt.
 - All of these costs were assumed to be negligible and were not included in the analysis.

C. Cost to Maintain Blood Supply at Current Level

- Assessment of percent of current supply lost following implementation (estimated and actual observed).
- Cost to recruit donors to replace lost supply.
 - Based on the estimated number of donations obtained from different donor groups using information from two large blood collectors. These data were then used to project replacement costs on a per donor basis. The subsequent donation career was not modeled. Detailed information is provided in Tables 9 and 10.

OPTION C: Postdonation Ferritin Testing

A. Costs of Intervention Implementation

- FTEs to establish program.

- The analysis does not include a separate start-up cost for staff time for ferritin testing. This is included as part of an overall per donation testing cost.
- Ferritin testing cost (supplies, reagents, instruments, etc).
 - Highly dependent on whether current BCO testing laboratory has established this capacity already or, if not, is willing to begin such testing. If not, additional sample tube collection at the time of donation and services of an outside laboratory vendor to conduct testing will be necessary. The cost structure of these different types of ferritin testing programs may be very different. Information from a large blood testing laboratory was used to help inform the cost structure for a lab that has already established testing capacity.
- Laboratory logistics.
 - The cost estimate for ferritin is for a high-throughput lab already conducting this testing. The estimated cost is per test and includes all aspects of sample acquisition, reagents, instruments, and logistics.
 - Base case cost of \$4.75 per donation tested was assumed and includes labor.
 - In sensitivity analysis, this was increased to \$8.00 per test to reflect smaller-volume labs or in-house testing.
- IT system changes to document testing results.
 - Assumed to be \$100,000 per million donations. A proportional cost was assumed when implemented across multiple BCOs.
- Cost of educational program to explain ferritin testing.
 - Assumed to be \$1,000.
- Insurance rider to cover program.
 - Assumed to be \$50,000 for a 1,000,000-unit supplier and scaled for an 11,000,000-unit supply (\$550,000 supply), reflecting one settlement per 1,000,000 donations per year.
- Legal review of program risks/liability.
 - Assumed to be a flat \$20,000.

B. Cost of Management of Intervention and Findings

- FTEs to manage program and staff time to respond to donor questions about the range of possible adverse events.
 - The BCO is assumed to have donor counselors with instructions to refer serious events to physicians.
 - Impact of notification of IDE and/or AIS and costs of medical follow-up for AEs.
 - Include supplementation costs for donors who need iron supplementation?
 - If this is a blood-center-managed activity, the BCO would incur cost items described in subsection B of Option A, Iron Supplementation above.
 - Implementation of staff and other resources to support monitoring and support work tasks for donor notification. Assumed to be a cost of \$82,000 per 1,000,000 donations collected.

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- Assessment of program effectiveness.
 - Monitoring ferritin results by donor group.
 - Donor follow-up with regard to recommended iron replacement strategies.
 - Impact on donor hemoglobin/eligibility to donate at next donation attempt.
 - Rates of AEs.
 - Actual notification of AIS by staff. Assumed to be a flat cost of \$200,000.

C. Cost to Maintain Blood Supply at Current Level

- Assessment of percent of current supply lost following implementation (estimated and actual observed).
- Cost to recruit donors to replace lost supply.
 - Based on the estimate number of donations obtained from different donor groups using information from two large blood collectors. These data were then used to project replacement costs on a per donor basis. The subsequent donation career was not modeled. Detailed numerical information is provided in Tables 9 and 10.

Estimated Adverse Event Costs from Existing Studies

Literature reviews focused on “burden of illness” studies for adverse event costs, with emphasis on categories of adverse events for populations similar to donors. A brief summary of findings follows:

Quality of life – Nothing available in the population subgroups for which the donor iron interventions are likely to be applied. No studies of 16- to 20-year-olds. No studies of pregnant women that aren’t also focused on other serious comorbidities.

Fatigue – Nothing available in the population subgroups for which the donor iron interventions are likely to be applied. No studies of 16- to 20-year-olds. No studies of pregnant women that aren’t also focused on other serious comorbidities. Patient studies are available, but costs are not considered transferable to blood donors.

Diminished exercise capacity – Nothing available.

Pica – Relevant information not available.

RLS – Clearly established link to donor iron status has not been demonstrated. Patient populations with “burden of illness” studies likely not representative of young blood donors.

None of the frequencies of these events and the associated costs are well understood in donor populations. As a result, no AE costs were included in this analysis.

Budget Impact Analysis

Table 9. Base Case Results

2,000,000 Units Collected				
<u>Strategy</u>	<u>16- to 18-Year-Old Donors</u>	<u>19- to 49-Year-Old Females</u>	<u>Both Groups</u>	<u>Frequent Donor Programs</u>
Active iron supplementation	\$10,696,300	\$16,200,000	\$26,896,300	\$39,069,450
Voucher iron supplementation	\$7,550,300	\$12,800,000	\$20,350,300	\$27,303,750
Ferritin testing	\$3,778,006	\$4,936,539	\$8,714,545	
Donation intervals	\$7,488,400	\$17,269,350	\$24,757,750	

11,000,000 Units Collected				
<u>Strategy</u>	<u>16- to 18-Year-Old Donors</u>	<u>19- to 49-Year-Old Females</u>	<u>Both Groups</u>	<u>Frequent Donor Programs</u>
Active iron supplementation	\$56,933,800	\$89,100,000	\$146,033,800	\$214,881,975
Voucher iron supplementation	\$41,525,300	\$70,400,000	\$111,925,300	\$150,170,625
Ferritin testing	\$19,584,722	\$27,033,002	\$46,617,724	
Donation intervals	\$41,162,800	\$94,981,425	\$136,144,225	

Table 10. Sensitivity Analysis

Flat donor recruitment replacement cost (\$45)

2,000,000 Units Collected				
<u>Strategy</u>	<u>16- to 18-Year-Old Donors</u>	<u>19- to 49-Year-Old Females</u>	<u>Both Groups</u>	<u>Frequent Donor Programs</u>
Active iron supplementation	\$8,771,300	\$12,400,000	\$21,171,300	\$27,355,950
Voucher iron supplementation	\$5,625,300	\$9,000,000	\$14,625,300	\$15,590,250
Ferritin testing	\$3,410,532	\$3,561,648	\$6,972,180	
Donation intervals	\$5,125,200	\$9,431,100	\$14,556,300	

Table 10. Sensitivity Analysis (continued)
Flat donor recruitment replacement cost (\$45)

Strategy	11,000,000 Units Collected			
	<u>16- to 18-Year-Old Donors</u>	<u>19- to 49-Year-Old Females</u>	<u>Both Groups</u>	<u>Frequent Donor Programs</u>
Active iron supplementation	\$46,346,300	\$68,200,000	\$114,546,300	\$150,457,725
Voucher iron supplementation	\$30,937,800	\$49,500,000	\$80,437,800	\$85,746,375
Ferritin testing	\$17,563,619	\$19,471,101	\$37,034,720	
Donation intervals	\$28,165,200	\$51,871,050	\$80,036,250	

Ferritin testing cost \$8.00 per donation

Strategy	2,000,000 Units Collected			
	<u>16- to 18-Year-Old Donors</u>	<u>19- to 49-Year-Old Females</u>	<u>Both Groups</u>	<u>Frequent Donor Programs</u>
Active iron supplementation	\$10,696,300	\$16,200,000	\$26,896,300	\$39,069,450
Voucher iron supplementation	\$7,550,300	\$12,800,000	\$20,350,300	\$27,303,750
Ferritin testing	\$4,590,506	\$4,936,539	\$9,527,045	
Donation intervals	\$7,488,400	\$17,269,350	\$24,757,750	

Table 10. Sensitivity Analysis (continued)

Ferritin testing cost \$8.00 per donation

Strategy	11,000,000 Units Collected			
	<u>16- to 18-Year-Old Donors</u>	<u>19- to 49-Year-Old Females</u>	<u>Both Groups</u>	<u>Frequent Donor Programs</u>
Active iron supplementation	\$56,933,800	\$89,100,000	\$146,033,800	\$214,881,975
Voucher iron supplementation	\$41,525,300	\$70,400,000	\$111,925,300	\$150,170,625
Ferritin testing	\$24,053,472	\$27,033,002	\$51,086,474	
Donation intervals	\$41,162,800	\$94,981,425	\$136,144,225	

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Active iron supplementation cost \$3.00

2,000,000 Units Collected				
<u>Strategy</u>	<u>16- to 18-Year-Old Donors</u>	<u>19- to 49-Year-Old Females</u>	<u>Both Groups</u>	<u>Frequent Donor Programs</u>
Active iron supplementation	\$9,321,300	\$14,000,000	\$23,321,300	\$31,456,350
Voucher iron supplementation	\$7,550,300	\$12,800,000	\$20,350,300	\$27,303,750
Ferritin testing	\$3,778,006	\$4,936,539	\$8,714,545	
Donation intervals	\$7,488,400	\$17,269,350	\$24,757,750	

Active iron supplementation cost \$3.00

11,000,000 Units Collected				
<u>Strategy</u>	<u>16- to 18-Year-Old Donors</u>	<u>19- to 49-Year-Old Females</u>	<u>Both Groups</u>	<u>Frequent Donor Programs</u>
Active iron supplementation	\$49,371,300	\$77,000,000	\$126,371,300	\$173,009,925
Voucher iron supplementation	\$41,525,300	\$70,400,000	\$111,925,300	\$150,170,625
Ferritin testing	\$19,584,722	\$27,033,002	\$46,617,724	
Donation intervals	\$41,162,800	\$94,981,425	\$136,144,225	

OPERATIONAL RISK ASSESSMENT

Identifying the Risks

Risk: “Effect of uncertainty on objectives.” Simply put for these purposes, “risk” is a potential, future event that may negatively affect blood center operations and that may be introduced through implementation of any of these options. **What risks to blood center operations are introduced by implementing Option “X”?**

Tools to help in this analysis include the following:

- **Risk universe** to prompt ideas on risks—used in the risk identification activity.
- **Risk exposure plot**—used as a guide to assess level of impact by providing examples and thresholds; includes likelihood definitions.

Risk Universe and Management Options

Table 11. Risk Universe

Risk Management Option: Status Quo: Conduct hemoglobin test; provide enhanced educational materials to donors							
Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
Financial resources	<ul style="list-style-type: none"> • A percentage of donors will continue to be deferred by the hemoglobin test and will need to be replaced 	<ul style="list-style-type: none"> • Unchanged present cost of recruiting replacement donors 	Current deferral percentage built into donor recruitment costs	1	1	Low	
Donor experience	<ul style="list-style-type: none"> • A significant proportion of donors may be made iron deficient by blood donation 	<ul style="list-style-type: none"> • Donors may experience reversible health problems; low likelihood of irreversible cognitive effects 	Hb test avoids anemia in most donors; donor education	3	3	Medium	

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
			materials are available				
Operational effectiveness	<ul style="list-style-type: none"> No significant operational impact 	<ul style="list-style-type: none"> Unchanged operations other than responding to public perception 	None; not implemented	1	1	Low	
Reputation	<ul style="list-style-type: none"> Public perception of “doing nothing” 	<ul style="list-style-type: none"> Donors may elect not to continue donating and require replacement; adverse media coverage 	Donor education materials available	5	4	High	Develop PR materials
Laws and regulations	<ul style="list-style-type: none"> Regulators may not allow status quo inactivity 	<ul style="list-style-type: none"> Interventions are currently voluntary, but may be mandatory for accreditation or regulatory compliance Dependent upon evolving information on harms of ID in blood donors 	None	4	5	High	

Table 11. Risk Universe (continued)

Risk Management Option: Option A: Blood collectors provide access to supplemental iron for all donors or targeted subgroups of donors

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
Financial resources	<ul style="list-style-type: none"> Additional logistical demands will increase operational costs Providing vouchers will require new partnerships with coupon providers 	<ul style="list-style-type: none"> Additional cost for supplements/ vouchers provided to donors Logistical considerations include warehousing, drive provision, mailing, pharmaceutical licensing, effectiveness monitoring New processes and manufacturer partnerships will need to be developed Ongoing cost of program oversight 	None; not implemented	5	3	High	
Donor experience	<ul style="list-style-type: none"> Iron supplementation may have negative impacts on donors, including: <ul style="list-style-type: none"> Side effects of iron 	<ul style="list-style-type: none"> Donors may self-exclude if they experience negative impacts such as: abdominal pain, N/V/D, constipation at doses >45 mg; exacerbation of UC/Crohn’s; stool discoloration; dysgeusia; tooth discoloration with liquid iron 	None; not implemented	3	4	Medium	

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
	<ul style="list-style-type: none"> Potential for poisoning Delayed diagnosis of underlying disease, inadequate therapy or loss of disease control Donors may continue to be iron deficient even with supplementation Negation of benefit and likely over-replacement in hemochromatosis 	<ul style="list-style-type: none"> Sixty 18-mg pills can result in severe toxicity to a 45-lb child or significant symptoms in a 150-lb teen Inadvertent partial treatment of GI inflammation/malignancy, mal-absorption and gynecologic-disease-related ID with consequent delayed diagnosis and treatment; interference with antibiotics or control of Parkinson’s, hypothyroidism, hypertension and osteoporosis 60-day supplementation may not fully address significant previous loss-related tissue iron depletion Donor harm from iron overload 					
Donor compliance	<ul style="list-style-type: none"> Donors may not take the iron supplements 	<ul style="list-style-type: none"> Donors will continue to be iron deficient Donors will continue to be deferred Requires some monitoring of effectiveness on donors’ iron status 	None; not implemented.	3	2	Medium	

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
Operational effectiveness	<ul style="list-style-type: none"> Donors most at-risk for iron deficiency must be identified, addressed and monitored 	<ul style="list-style-type: none"> Complicated algorithms for identifying donors may confuse staff; additional staff may be required to oversee program IT systems (at blood drives and in the facility) will be required to help identify at-risk donors 	None; not implemented	5	4	High	
Reputation	<ul style="list-style-type: none"> Public perception of potential harm involved with donation unless they medicate 	<ul style="list-style-type: none"> Donors may elect not to continue donating and require replacement; adverse media coverage 	None; not implemented	2	3	Medium	
Laws and regulations	<ul style="list-style-type: none"> Laws in some states may consider iron supplementation the practice of medicine, which will affect blood center operations 	<ul style="list-style-type: none"> Providing iron may require dispensing licensure Malpractice liability for medical directors (claims of harm or abandonment) Additional legal considerations: <ul style="list-style-type: none"> Triggering of HIPAA covered-entity status Possible need for donor charting and ongoing review Physician dispensing compliance responsibilities (dispensing licenses, licensure in every state where iron is dispensed) 	None; not implemented	5	4	High	

Table 11. Risk Universe (continued)

Risk Management Option: Option B: Curtail donations or lengthen interdonation interval for all donors or targeted subgroups of donors

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
Financial resources	<ul style="list-style-type: none"> Additional costs will be incurred for backfilling a thousand to several hundred thousand donations by blood operator recruitment staff 	<ul style="list-style-type: none"> Significant new recruitment costs incurred 	Budgeting process	4	4	High	
Donor experience	<ul style="list-style-type: none"> At-risk donors will continue to be negatively affected by blood donation (for up to 75% of donors, as a stand-alone mitigation, longer interdonation intervals do not prevent prolonged periods of tissue iron depletion); a significant proportion of donors will continue to be iron deficient from prior blood donation Some donors will not be allowed to donate at their usual interval, others not at all, which some could find distressing 	<ul style="list-style-type: none"> Donors may experience reversible health problems from ongoing ID; very low likelihood of irreversible cognitive effects Donor dissatisfaction may result in disengagement or cessation of donation 	A percentage of new donor recruitment is currently factored into recruitment plans and budget; however, it will need to be significantly expanded with this option	4	3	Medium	
Customer experience	<ul style="list-style-type: none"> Insufficient product available in inventories to meet customer needs 	<ul style="list-style-type: none"> Limiting WB donations to 1x or 2x a year will significantly affect 	Demand and supply planning	5	5	High	

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
	<ul style="list-style-type: none"> Operators may not be able to recruit new donors fast enough to replace current donors who are restricted from donating too frequently 	<p>collections/inventory for most (5% to 25% for at-risk donors)</p> <ul style="list-style-type: none"> Donations may be insufficient to meet hospital demand Customer service issue as availability of product to hospitals may be affected Major effort required to backfill lost donors 	systems are in place within blood centers				
Operational effectiveness	<ul style="list-style-type: none"> Donation losses must be backfilled at significant expense Operational complexity introduced to handle varying interdonation intervals 	<ul style="list-style-type: none"> Significant additional cost and effort required to avoid shortages IT systems will need to be reconfigured to accommodate complex donation intervals for identified at risk donors 	Demand and supply planning systems Donor recruitment programs Donor messaging IT reconfiguration processes	5	5	High	
Reputation	<ul style="list-style-type: none"> Public perception of potential harm involved with donation if only limited exposure is allowed 	<ul style="list-style-type: none"> Donors may elect not to continue donating and require replacement; public trust could be negatively affected 	Messaging to donors about iron depletion and educational material distributed on how to avoid iron depletion	3	3	Medium	

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
Laws and regulations	<ul style="list-style-type: none"> Satisfies accreditation and regulatory body desire for ID mitigation activities 	<ul style="list-style-type: none"> Significant regulatory exposure may occur if supply constraints lead to potential for patient harm 	None	1	5	Medium	

Table 11. Risk Universe (continued)

Risk Management Option: Option C: Implement ferritin testing as a basis for advising donors about taking iron supplements or lengthening interdonation intervals for targeted subgroups of donors (teens, frequent donors, premenopausal females, donors with borderline Hb)

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
Financial resources	<ul style="list-style-type: none"> Significant additional costs will be incurred for test implementation and ongoing program support 	<ul style="list-style-type: none"> Testing, IT changes, infrastructure for donor notification and counseling 	Budgeting process	5	4	High	
Donor experience	<ul style="list-style-type: none"> Donors will be asked to choose a preferred intervention that puts them at previously described risks with status-quo inactivity, iron supplementation or interdonation interval adjustment 	<ul style="list-style-type: none"> Some donors may experience side effects of iron, have delayed diagnosis/loss of disease control and incur risk of poisoning with iron therapy Some donors may experience reversible health problems from 	Hemoglobin test	4	3	High	First-time donors present for sample testing only at first visit to blood center

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
	<ul style="list-style-type: none"> Donors may do nothing or self-defer due to confusion from test result communications 	<ul style="list-style-type: none"> ongoing ID; very low likelihood of irreversible cognitive effects Complex messaging about various ferritin levels and varying responses to values >50 ng/mL, lower-normal values, IDE and AIS levels can be confusing to donors Donor dissatisfaction may result in disengagement or cessation of donation 					
Operational effectiveness	<ul style="list-style-type: none"> Significant process changes affect multiple areas within blood operations and require time, money and effort to implement Some donation loss inherent with donor concern triggered by diagnosis of ID and with choice of extended interdonation intervals as a response 	<ul style="list-style-type: none"> Requires new testing platform, sample logistics, staff training, process development, IT programming Effectiveness check is inherent in serial ferritin measurements, which requires additional infrastructure to analyze and take appropriate action(s) 	Blood centers have the infrastructure in place to accommodate this kind operational change	4	4	High	
Reputation	<ul style="list-style-type: none"> Public perception of potential harm involved with donation if safety monitoring is required Dissatisfaction regarding donor funding of iron supplements 	<ul style="list-style-type: none"> Donors may elect not to continue donating and require replacement; public trust could be negatively impacted 	Messaging to donors about iron depletion and educational material distributed on	3	2	Medium	

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
			how to avoid iron depletion				
Laws and regulations	<ul style="list-style-type: none"> “Practice of medicine” concerns may apply depending upon the message Blood center may be responsible for taking action to medically treat donors with declining ferritin values 	<ul style="list-style-type: none"> Extension of malpractice liability and HIPAA covered-entity status possible Complexities of tracking serial values and potential for responsibility for action with declining values 	None	2	4	Medium	

Table 11. Risk Universe (continued)

Risk Management Option: Option D: Limit donations from 16- and 17-year-old donors to one donation per year, unless it can be demonstrated they are iron replete, which would make them eligible to donate sooner than the 12-month limit.

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
Financial resources	<ul style="list-style-type: none"> Additional costs will be incurred for backfilling thousands to several hundred thousands of donations by blood operator recruitment staff 	<ul style="list-style-type: none"> Significant new recruitment costs incurred 	Budgeting process	4	4	High	

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
Donor experience	<ul style="list-style-type: none"> Some donors will continue to be negatively affected by blood donation (for up to 75% of donors, as a stand-alone mitigation, longer interdonation intervals don't prevent prolonged periods of tissue iron depletion); a significant proportion of donors will continue to be iron deficient from prior blood donation Some donors will not be allowed to donate at their usual interval, which some could find distressing 	<ul style="list-style-type: none"> Donors may experience reversible health problems from ongoing ID; unknown likelihood of nonreversible cognitive effects Donor dissatisfaction may result in disengagement or cessation of donation 	A percentage of new donor recruitment is currently factored into recruitment plans and budget; however, it will need to be significantly expanded with this option	4	3	Medium	
Customer experience Customer experience (continued)	<ul style="list-style-type: none"> Insufficient product available in inventories to meet customer needs Operators may not be able to recruit new donors fast enough to replace current donors who are restricted from donating too frequently 	<ul style="list-style-type: none"> Limiting WB donations to 1x a year will significantly affect collections/inventory for most operators (~4% for these donors) There may be insufficient donations to meet hospital demand Customer service issue as availability of product to hospitals may be affected Significant effort required to backfill lost donors 	Demand and supply planning systems are in place within blood centers	5	5	High	

Risk Identification			Risk Assessment				Risk Treatment
Category	Risk Description	Impact Details	Current Controls	Likelihood	Impact/Exposure	Overall Risk Rating	Additional Mitigations
Operational effectiveness	<ul style="list-style-type: none"> Donation losses must be backfilled at significant expense Operational complexity introduced to handle age-unique interdonation intervals 	<ul style="list-style-type: none"> Significant additional cost and effort required to avoid shortages IT systems will need to be reconfigured to accommodate complex donation intervals for identified at-risk donors 	Demand and supply planning systems; Donor recruitment programs; Donor messaging; IT reconfiguration processes	5	5	High	
Reputation	<ul style="list-style-type: none"> Public perception of potential harm involved with donation if only limited exposure is allowed 	<ul style="list-style-type: none"> Donors may elect not to continue donating and require replacement; public trust could be negatively affected 	Messaging to donors re: iron depletion and educational material on how to avoid iron depletion	3	3	Medium	
Laws and regulations	<ul style="list-style-type: none"> Satisfies accreditation and regulatory body desire for ID mitigation activities 	<ul style="list-style-type: none"> Significant regulatory exposure may occur if supply constraints lead to potential for patient harm 	None	1	5	Medium	

Risk Exposure Plot

Table 13. Sample Risk Exposure Plot		Likelihood of risk occurring.....				
Purpose: To assess the likelihood of a risk materializing and the level of impact a risk may have on the organization if it materializes, and to confirm whether the impact of the risk is “above” or “within” the organization’s risk appetite.		Almost Certain	Likely	Possible	Unlikely	Rare
		> 70%	41%-70%	16%-40%	5%-15%	< 5% chance
Examples of impact if risk occurs		5	4	3	2	1

Very High	Business risks	<ul style="list-style-type: none"> • Financial - Material deviation from approved budget: ± 5-10%. • Reputation - National or sustained negative media exposure; extreme degradation of relationship with governments and/or stakeholders lasting several months. • Customer (Patients/Hospitals/Physicians) Expectations - Unexpected/unanticipated adverse events (significant number of patients); extreme degradation of relationship with customers lasting several months; and/or material deviation in meeting demand. • Operational Effectiveness - Material increase in supply chain labor hours per unit; material decrease in blood inventory levels and/or donor base; and/or severe and sustained negative impact on employees. 	5	High (25)	High (20)	High (15)	Medium (10)	Medium (5)
High	Business risks	<ul style="list-style-type: none"> • Financial - Significant deviation from approved budget: ± 3.5-4.5%. • Reputation - Consistent negative media exposure (local, smaller media outlets); major degradation of relationship with governments and/or stakeholders lasting several months; and/or repeated major audit observations. • Customer (Patients/Hospitals/Physicians) Expectations - Unexpected/unanticipated adverse event(s); major degradation of relationship with customers lasting several months; and/or significant deviation in meeting demand. • Operational Effectiveness - Significant increase in supply chain labor hours per unit; significant decrease in blood inventory and/or donor base; and/or substantial and prolonged negative impact on employees. 	4	High (20)	High (16)	Medium (12)	Medium (8)	Medium (4)
Moderate	Business	<ul style="list-style-type: none"> • Financial - Moderate deviation from approved budget: ± 2.5-3%. • Reputation - Limited negative media exposure; moderate degradation of relationship with governments and/or stakeholders lasting several weeks; and/or major audit observations. • Customer (Patients/Hospitals/Physicians) Expectations - Expected/anticipated adverse events; moderate degradation of relationship with customers lasting several weeks; and/or moderate deviation in meeting demand. • Operational Effectiveness - Moderate increase in supply chain labor hours per unit; Moderate decrease blood inventory and/or donor base; substantial but limited negative impact on employees. 	3	High (15)	Medium (12)	Medium (9)	Medium (6)	Low (3)
Minor	Business	<ul style="list-style-type: none"> • Financial - Minimal deviation from approved budget: ± 1.5-2%. • Reputation - Minimal negative media exposure; minor degradation of relationship with governments and/or stakeholders; and/or minor but frequent audit observations. • Customer (Patients/Hospitals/Physicians) Expectations - Expected/anticipated adverse events; minor degradation of relationship with customers; and/or minor deviation in meeting demand. • Operational Effectiveness - Limited increase in supply chain labor hours per unit; limited decrease in blood inventory and/or donor base; and/or some negative impact on employees. 	2	Medium (10)	Medium (8)	Medium (6)	Low (4)	Low (2)
Not significant	Business	<ul style="list-style-type: none"> • Financial - Slight deviation from approved budget: ± 1%. • Reputation - Negligible negative media exposure; no degradation of relationship with governments and/or stakeholders; and/or minor audit observations • Customer (Patients/Hospitals/Physicians) Expectations - Expected/anticipated adverse events; no degradation of relationship with customers; and/or negligible deviation in meeting demand. • Operational Effectiveness - Negligible increase in supply chain labor hours per unit; no decrease in blood inventory and/or donor base; and/or Negligible negative impact on employees. 	1	Medium (5)	Medium (4)	Low (3)	Low (2)	Low (1)

Intervention Benefits/Barriers

OPTION A: Facilitating Iron Access

- Benefits
 - ≥ 18 mg iron as supplement or multivitamin daily for 60 days definitively replaces the iron in the donation of a single unit of blood (37.5 mg resulted in slight over-replacement in ID donors in the HEIRS study)
 - Significantly shortens long periods of postdonation ID
 - Prevents progressive iron loss and may decrease donor loss due to low Hb levels
 - May permit a 56-day WB donation interval (21-day ferritin recovery of iron in low-ferritin group)
 - Can be targeted or universally implemented
 - Can be positively messaged
- Barriers
 - Pill cost/complex logistics (warehousing, drive provision, mailing, possible pharmaceutical licensing)
 - Complexities of partnership negotiations with coupon providers
 - Donor acceptability and side-effect experience
 - Abdominal pain, nausea, vomiting, diarrhea or constipation at doses >45 mg; exacerbation of ulcerative colitis/Crohn's disease; stool discoloration; dysgeusia; tooth discoloration with liquid iron
 - Donor compliance and ethical duty to donors who choose not to take iron, but want to continue donating
 - Public perception of harm/"pharming" with resultant decline in donations
 - Potential for poisoning (symptoms at 10-20 mg/kg, severe toxicity at 50 mg/kg)
 - Sixty 18-mg pills can result in severe toxicity to a 45-lb child or significant symptoms in a 150-lb teen
 - Inadvertent treatment of iron deficiency from GI inflammation and malignancy, malabsorption and gynecologic-disease-related ID with consequent delayed diagnosis and treatment
 - Interference with medication absorption (tetracyclines, fluoroquinolones, levodopa, thyroxine, ACE inhibitors, osteoporosis medications)
 - Negation of benefit of blood donation and likely over-replacement of iron in hemochromatosis
 - 60-day supplementation may not fully address significant previous loss-related tissue iron depletion
 - State practice-of-medicine rules may trigger HIPAA covered-entity status, pharmaceutical dispensing requirements, increased medicolegal risk from physician-patient relationship
 - Complexities of parental consent and potential requirement for predonation ferritin assessment in minors (16- to 17-year-olds)
 - Potential need to document lack of contraindications (\pm release form) or robust donor communication re: who should NOT take iron
- Required Changes for Facilitating Iron Access
 - Determination of target subgroup
 - Assessment of geographic coverage and retailer contracting for vouchers
 - Negotiation with manufacturers for iron pills
 - Potential licensing for dispensing iron
 - Legal opinion: minor consent, state practice-of-medicine law review and lobbying for carve-out, iron release forms
 - Iron logistics (pill distribution vs store redemption and billing, kitting/reconciliation of bottles and expiry monitoring)
 - Development and dissemination of new educational and public relations materials via documents and websites

- Messaging re: risks of iron and development of forms/IT documentation of donor notification and acknowledgment
- Donor replacement costs for donors unwilling or unable to take iron
- Possible IT changes for documentation of minor consent and predonation ferritin
- Monitoring changes (ferritin statistical sampling/trending, compliance questionnaires)

OPTIONS B and D: Prolonged Interdonation Interval

- Benefits
 - Minimal cost and effort for testing or iron supplementation
- Barriers
 - Futility as sole intervention (in light of HEIRS data) without significant loss of donations and inadequacy of the blood supply
 - Public perception of harm or “pharming” with resultant decline in donations
 - Alone, does not prevent prolonged periods of tissue iron depletion
- Required Changes for Prolonged Intervals
 - Determination of target subgroup
 - Development and dissemination of new educational and public relations materials via documents and websites
 - IT changes for new interval periods
 - Donor replacement plan and costs
 - Loss of double RBC donations from donors limited to once annually (eg, minors)

OPTION C: Ferritin Testing

- Benefits
 - Informs and empowers donors; principle of self-determination
 - Reassures donors with ferritin values >50 ng/mL (which may be used as a prequalification for subsequent donations from minors)
 - May identify pre-existing sources of blood loss or malabsorption in first-time donors
 - May significantly shorten periods of postdonation iron deficiency and prevent progressive iron loss if donor takes iron
 - Can be targeted or universally implemented
 - Can be positively messaged
- Barriers
 - Cost (testing, infrastructure for donor notification and counseling)
 - Regulatory risk of deviation from standard operating procedures
 - Public perception of harm/“pharming” with resultant decline in donations
 - Adverse impact on the blood supply due to reliance upon donor choice of mitigation strategy, which includes decreased donation frequency and self-exclusion from the donor pool or inaction (with documentation of declining values)
 - Dissatisfaction of donors asked to self-fund iron repletion
 - Issues with test timing relative to iron loss (dual presentations for predonation testing vs postdonation perception of donation exacerbating pre-existing deficiency)
 - Complexities of tracking serial values and potential for responsibility for action with declining values

- Complex messaging of reassurance with ferritin >50 ng/mL, compared with donors at risk for a period of IDE after donation but with ferritin 26-50 ng/mL before donation (ie, those who did not yet have IDE)
- Potential for standard-setting regarding various ferritin action values; dissonance with public health messaging about what is a “concerning” low value
- Required Changes for Ferritin Testing
 - Determination of target subgroup
 - New educational and public relations materials (including use of documents and websites)
 - IT changes for new deferrals
 - Low/high action levels and letters
 - Chagas model vs every donation
 - Automatic vs manual monitoring of serial values
 - Cost of ferritin test and logistics of getting tubes to test site (particularly an additional tube to an alternate test site)/result return
 - Assessment of geographic coverage/contracting for mailed pills or vouchers
 - Cost of iron (store redemption and billing vs mailed pills)
 - Development of new donor contact letters and staff training
 - Cost of additional mailing materials and Donor Health FTEs
 - Monitoring program impact and costs
 - Donor replacement plan and costs

Additional Considerations

- What about double RBC and apheresis donations?
 - WB donation equivalency and alterations to risk mitigation strategies (longer supplementation for double RBCs, timing of iron for apheresis donors – ie, daily course after 4 donations or continuous iron daily or every 3 days for frequent donors)
- Donor loss mitigation
 - Consider recapturing healthy, euferremic female donors with Hb values 12.0-12.4 g/dL
- Postimplimentation monitoring strongly encouraged
 - Mechanism for monitoring of compliance with iron and/or serial ferritin values
- Does childbearing potential end at age 45 or 50?

Quantifiable Data Provided

- Percentages of at-risk donors with ferritin <26 ng/mL
- Current percentages of donors/donations in various risk categories
 - Projected RBC losses with interdonation interval changes in various subgroups
- New procedural steps (and estimated cost) for each of the three interventions
 - Cost of new donor recruitment
 - Additional FTEs for donor notification and counseling staff
 - Cost of obtaining/mailling iron pills
 - Ferritin testing costs

LEGAL/REGULATORY ASSESSMENT

Legal Issues Overview

It is not possible to avoid legal risk completely when collecting blood from volunteer donors or formulating strategies to improve donor and patient safety. Blood collection and transfusion medicine professionals attempting to balance the needs of donors, patients, and their own risk management profiles may find themselves in “Catch-22” type of situations. Assessing the legal risks to blood collectors of implementing any of the RBDM Working Group’s strategies to mitigate donor iron depletion exemplifies this challenge.

The goal of this assessment is to identify the significant legal issues related to each of the strategies under consideration and provide an analysis of the general factors that blood collectors should consider in making decisions about how best to mitigate these risks. It is important to note that AABB is not able to provide legal advice to third parties, including blood collectors. Blood collectors should seek the advice of legal counsel familiar with each collection facility’s unique circumstances, as well as state and local laws and regulations.

A key concept in analyzing legal issues affecting blood banking and transfusion medicine professionals is the concept of negligence, ie, the legal duty to adhere to the appropriate standard of care in collecting, processing, testing, and administering blood and blood components. Although their interpretation varies according to state law, the four elements of a negligence claim are: 1) the defendant owed a duty of care to the plaintiff; 2) the defendant breached the duty; 3) the plaintiff’s injury was directly or proximately caused by the breach; and 4) the plaintiff suffered damages as a result. In short, the theory of negligence holds that, as a general proposition, blood collectors and medical service providers are responsible for offering safe products and services that will not harm donors or patients.

Blood collection facilities are familiar with donor injury claims and typically have policies and procedures in place to minimize the risk of both donor injury and litigation resulting from injury. Donors are most likely to be injured by the phlebotomy itself or, after the donation, because of a fall or loss of consciousness. These risks can be mitigated if the facility continually updates information in its consent for donation, is prepared for adverse reactions at the donation site, and educates donors about postdonation care.

Appendix A sets forth the intervention strategies under consideration by the Working Group, as well as the relevant legal risks and countervailing strategies identified to date.

Regulatory Framework and FDA Communication

Regulatory Framework

The FDA has wide-ranging jurisdiction with respect to the regulation of food, drugs, medical devices, vaccines, blood components, and other products. It is important to note that the FDA promulgates and enforces regulations for blood collection and for the manufacturing of blood products. The FDA does not, however, directly license the individuals working in blood centers. This is relevant because consideration needs to be given to the laws and regulations that apply to the individuals who interact directly with blood donors and who may make recommendations regarding donation-related iron deficiency.

The FDA does not license or regulate individuals such as physicians, nurses, or phlebotomists. Rather, medical professionals are governed by applicable state agencies; for example, physicians must be licensed by the medical board in the state in which they practice. Each state has specific requirements for licensure, and licenses do not transfer from one state to another. Each state also has laws and regulations defining “the practice of medicine,” and most states make it a crime to practice medicine without a license.

FDA Communication Regarding Donor Iron Deficiency

The FDA Center for Biologics Evaluation and Research provided the following responses to the Working Group's questions:

1. *Will FDA object if blood centers give donors iron tablets or vouchers and coupons for iron?*

FDA does not object to the routine use of iron supplementation by provision of iron tablets, coupons or vouchers to reduce the risk of nutritional iron deficiency due to blood donation, provided the iron tablets are meant to replace the approximate amount of iron lost with a blood donation using an appropriate regimen (ie, short-course, low-dose) of oral iron. Donors should be counseled about iron loss from blood donation and the benefits and risks of iron supplementation.

2. *Is it likely that FDA would take regulatory action against blood centers that implement an iron replacement program?*

FDA would not take action against blood centers that routinely provide short-course, low-dose iron supplementation to blood donors over age 18 years to reduce the risk of nutritional iron deficiency through replacement of the approximate amount of iron lost in blood donation.

FDA remains concerned about the need to protect the health of teenage donors (16-18 years old). Based on the November 2016 Blood Products Advisory Committee recommendations, FDA considers this an area for policy development on effective strategies to mitigate iron deficiency in adolescent blood donors (eg, blood centers might limit donation to once per year unless normal iron status is documented).

FDA recognizes the effectiveness of programs that utilize ferritin measurement as reported in recent randomized control trials and ongoing studies, especially for targeted subgroups of blood donors at particular risk for iron deficiency. However, FDA regards the use of ferritin testing to guide iron supplementation as a matter of Medical Director discretion that may be subject to oversight through state laws.

Interventions

Status Quo

One of the assumptions agreed upon by the Working Group is that, “Education alone is not a feasible mitigation option, although the enhanced education recommended in Association Bulletin #17-02 should be provided as a supplementary activity to other options.” From a legal standpoint, maintaining the “status quo” presents risks that donors suffering from conditions associated with low iron levels will file suit against blood collectors. Such suits likely would claim negligent

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failure to take action (other than providing education⁶⁵) to mitigate the donor's iron depletion despite recent studies evidencing the risks of blood donation.

Negligent failure to act played a central role in the 1990s, and for roughly a decade thereafter, when the blood community was faced with negligence claims brought by transfusion recipients who were identified as being HIV-positive. Claimants alleged the blood community did not act quickly enough to require surrogate testing that may have prevented transmission. Those cases resulted in a New Jersey court decision holding that AABB, in addition to blood collectors, was negligent in failing to act sooner to help safeguard the blood supply.⁶⁶

Iron Intervention

Framing the Issue. A factor that may influence how a court or regulatory body views iron supplementation is how the issue is framed. An iron supplementation program that is offered as part of a donor wellness initiative—along the lines of adequate hydration, nutrition, and rest—may be less likely to be viewed as the practice of medicine. On the other hand, if the program is offered to prevent and treat iron deficiency, a finding of the practice of medicine may be a more likely outcome. For example, different legal interpretations might depend on the aim and circumstances of the program for iron replacement and ferritin testing as follows:

1. *Iron replacement*

- * The aim of providing iron tablets to donors is to replace the iron removed with a whole blood donation (not to treat or prevent a disease⁶⁷).
- * The aim of providing iron tablets (to some or at-risk donors) is to prevent iron deficiency or treat possible pre-existing iron deficiency.

2. *Ferritin testing*

- * The aim of using ferritin as a screening test is to provide donors with information that might be important to their health.
- * The intent of using ferritin testing is to prevent or treat iron deficiency among blood donors and provide medical advice to individual blood donors.

State Medical Boards. One concern with providing iron supplements to donors is that doing so may be considered the practice of medicine by the state. In states where this is considered the practice of medicine, to comply with medical board[§] requirements, the provision of supplements would need to be overseen by a licensed physician. This could present logistical difficulties for blood collectors. For example, for mobile blood drives, there may not be a physician present.

For purposes of this assessment, the statutes of the states of California, Florida, Indiana, New York and Texas were reviewed. These states, except for Indiana, collect a significant percentage of blood in the US. Indiana has been included because Indiana Blood Center currently manages an iron replacement program that targets at-risk female donors. It was impractical to conduct a 50-state survey on the definition of practice of medicine's definition.

[§]In general, state medical boards are responsible for regulating physicians, surgeons, and other allied health professionals. Typically, the boards' responsibilities include issuing licenses and certificates, administering enforcement and disciplinary actions, suspending or revoking licenses after disciplinary hearings, and reviewing the quality of the medical practice carried out under the boards' jurisdiction.

Practice of Medicine. Appendix B provides a summary of the definition of “practice of medicine” under the relevant state statutes. These statutes, for the most part, are quite broad and encompass the prevention, diagnosis, or treatment of a physical or mental condition (although, arguably, providing iron to replace what was removed is not prevention, diagnosis, or treatment). Therefore, the provision of iron supplements, in some states, may be considered the practice of medicine or the corporate practice of medicine (defined below).

Even if a licensed physician oversees the provision of iron supplements, state laws and regulations govern how physicians and other licensed health professionals may delegate certain medical acts to licensed and/or unlicensed individuals. States may permit the delegation of certain medical acts through “standing orders.” However, any licensing or certification requirements of the individual to which the acts have been delegated would also require further analysis and review. The individual’s license or certification may prohibit them from performing certain delegated medical acts, as it would not fall under their scope of practice. Further, the standing orders, state law, and facility policies or guidelines may also require that the individual have a specific level of supervision when performing such medical acts. Therefore, because of the variation and specificity of each state’s law, it is difficult to determine whether certain individuals, or groups of individuals, would be permitted to provide iron supplements even if overseen by a licensed physician. The analysis is fact-intensive (eg, how the state’s laws are written, the qualifications and training of the person tasked with handing out the supplement, whether a voucher or the actual supplement is provided to the donor) and requires a detailed legal analysis beyond the scope of this assessment.

Corporate Practice of Medicine Doctrine. This state law doctrine prohibits corporations from practicing medicine or employing a physician to provide medical services, with general exceptions made for hospitals and professional corporations providing health-care services. The doctrine, first championed by the American Medical Association in the 1930s, is rooted in public policy concerns regarding the, “perceived evils that corporations and laypeople motivated by profit will exert control over physicians, tainting the fiduciary role of the physician vis-a-vis patient and compromising the medical judgments of physicians.”⁶⁸

From the perspective of blood collection facilities, providing iron supplements or monitoring ferritin levels could trigger corporate practice of medicine considerations and raise legal concerns.

Vouchers. Although not at all a certainty, providing vouchers to donors for iron supplements may carry less risk for blood collectors for several reasons:

1. Arguably, distributing vouchers is less likely to be considered the practice of medicine or to run afoul of the corporate practice of medicine doctrine because blood collectors would not be directly providing supplements; donors would have to take the extra step of redeeming the vouchers.
2. A voucher for a generic multivitamin is consistent with an iron replacement program, rather than a low-iron treatment program.
3. The vouchers could include instructions for donors to seek advice from their medical professional before obtaining and taking the supplement.
4. Disclaimers also could be included on the voucher, although the validity of any disclaimer would need to be determined by each blood collector’s legal counsel.

Other Considerations. Although the level of risk is unclear, there is some concern that iron supplementation could result in complications for a relatively small percentage of donors such as treatment toxicity, masked GI malignancies or

exacerbated hemochromatosis sequelae. Blood centers providing the iron supplements could be held liable for these negative outcomes.

Another point of view is that the blood centers' responsible physicians already counsel blood donors requiring medical care after blood donation; this is not a new concept (eg, syncope, accidental arterial venipuncture). Indeed, AABB *Standards for Blood Banks and Transfusion Services*^{63(p1)} requires all blood banks to have a medical director, in part because medical decisions need to be made regarding donors and the blood they donate.

Pros and Cons of Collaboration with State Medical Boards. One strategy is to educate/inform state medical boards regarding the importance of iron replacement programs. The boards could be requested to issue rulings/FAQs/white papers clarifying that iron replacement programs are not considered the practice of medicine. There are several logistical and political obstacles to this approach, however:

1. There could be inconsistent, and possibly critical or negative, responses among the various agencies contacted, both intra- and interstate (note: some states have more than one agency that would need to be contacted).
2. Blood collectors likely would need to provide state agencies with descriptions of their proposed iron replacement programs because responses will be highly dependent on program specifics (eg, what donors are included; who dispenses the supplement; what, if any, follow-up is made with the donor).

Interdonation Interval/Annual Maximum Modification

To the extent studies show that certain donor groups may benefit from lengthened donation intervals or adjusted annual donation maximums (see Safety subgroup assessment), a decision not to make any changes could pose the risk of negligent failure-to-act claims being brought against blood collectors. Risk mitigation strategies include:

1. Adjust donation interval for young donors and premenopausal females.
2. Combine ferritin testing with the decision to adjust donation intervals.
3. Tailor deferral periods based on monitoring iron replacement and ferritin measurement for individual donors.
4. Modify recruitment strategies to prevent donors with low or borderline iron balance from donating too soon or too often each year.

Ferritin Testing

As with iron supplementation, ferritin testing may be considered the practice of medicine in some states and likely will depend on how the program is structured. For example:

1. Are all donors tested or just those at high risk?
2. What medical professionals administer the program and advise donors?
3. To what extent is specific medical advice provided?
4. What provisions are made to prevent a breach of medical consent obligations for minors who might be tested when donating?
5. Is postdonation ferritin testing offered?
6. How extensive is the follow-up with low-ferritin-level donors (treatment plan should be developed/maintained by donor's health-care provider)?

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On the other hand, ferritin testing programs, arguably, could be designed to inform and empower donors. This autonomy may help lower the risk of liability to blood collectors. For example, if donors are given test results to share with their health-care providers and directed to seek the advice of their primary care physician, then it may be more difficult to argue that the blood collector was responsible for consequences related to low iron levels.

Conclusion

There is no mitigation approach to the donor iron deficiency issue that is risk-free; all of the approaches discussed carry some degree of risk. From a legal perspective, the Working Group's recommendation should not put blood collectors in conflict with state law.[◇] Rather, they should adopt one or more strategies, consistent with state law, that minimizes the harm to donors caused by donation-related iron depletion.

[◇]Note that the Introduction to *AABB Standards* provides, "The requirements in this publication . . . do not preempt your federal, state, and/or local laws and regulations."⁶⁵(p ix)

ETHICAL ASSESSMENT

Conflicts of Interest

The Ethics subgroup explicitly recognizes that that nearly all of the members of the RBDM Working Group have some conflicts of interest that may inadvertently influence the work and recommendations of the group. This is because the livelihoods of many members of the RBDM Working Group are at least in part dependent on the blood collection industry and the report could affect that industry. These conflicts must be disclosed in any reports and recommendations to maximize transparency and attempt to minimize potential biases.

Ethical Principles

Relevant ethical considerations for policies regarding blood-donation-related iron deficiency include, in order of salience for this issue:

- **Nonmaleficence.** It is essential that individuals are not made substantially worse from donating blood. Transient harm, such as pain from insertion of a needle can be acceptable if there are countervailing reasons for donation (eg, the needs of recipients) and if such harms are transparent and acceptable to potential donors. However, longer-term, more serious harm, is not acceptable.
 - **Precautionary principle.** In the absence of clear data regarding potential harms of particular actions, it is appropriate to take a precautionary approach and revisit this decision as additional data become available.
- **Respect for Autonomy.** Donors (and parents/guardians of donors who have not reached the age of majority) must be positioned to make an informed and voluntary decision regarding whether to donate.
 - **Transparency.** The risks and potential risks of donation must be disclosed to potential and actual donors. This information should be provided in an understandable fashion, ideally both during recruitment and at the time of blood donation.
 - **Agency.** Individuals must have the capacity to act independently and make their own free and voluntary choices. Some donors, notably minors, are unlikely to have full agency (eg, as a result of their stage of development, peer pressure) and special considerations apply to such donors.
- **Beneficence.** Collecting blood is beneficent for recipients. However, blood centers also have obligations of beneficence to those who are harmed because of donation.
- **Justice.** All donors and potential donors need to be treated fairly and this needs to be thoroughly considered for all options. As an example, an option that requires people to pay for iron supplements may not be just to those of limited economic means.

Some actions are ethically required, and “must” be taken. However, this minimum ethical standard differs from ethical aspirations, which are desirable and arguably “should” be met whenever feasible and likely constitute ethically best practices.

Key Ethical Issues

Possible Harms Associated with Giving Blood

Some teenagers and menstruating females have iron deficiency, which can be exacerbated by donating blood. Frequent blood donation can also cause iron deficiency.

There is less evidence on the consequences of iron deficiency in blood donors because most studies have focused on people whose iron deficiency was not due to blood donation. It is difficult to determine whether clinical conditions in these individuals are directly caused by iron deficiency because they may have other contributing factors. Some of the strongest evidence for a significant risk associated with iron deficiency alone comes from nonhuman animal studies and RCTs in humans showing that iron supplementation of iron-deficient females improves cognitive function^{51,52} and decreases fatigue.³⁹ Hence, evidence suggests but does not prove that blood donation could have deleterious effects including fatigue and decreased cognitive function. Other weaker evidence suggests that iron deficiency may adversely affect pregnancies and brain development in adolescents and individuals in their early 20s.^{53,69-71}

Limited Information on Harm

The limited data on the risks of iron deficiency secondary to blood donation renders analyses inexact and based on expert opinion, extrapolating data from some patient populations to healthy blood donors. Because of this:

- If there is a reasonable potential of harm, even if it is unknown, it is reasonable to take a precautionary approach to minimize the possibility of harm, even though it might not actually exist.
- There is an ethical obligation to study this issue. Specifically, whether there are deleterious effects on blood donors needs to be known and, if so, the magnitude and reversibility of those effects need to be categorized. Although blood centers are the most logical agents to study this, their financial resources are limited and the obligation to help finance these studies extends to the larger health-care system.

Groups Meriting Special Attention

Despite limitations of the existing evidence base, there are special concerns about adolescents and other at-risk groups.

Donors with Limited Agency—Adolescents

Adolescents are of particular concern for several reasons:

- ***Collecting blood from adolescents is more likely to be harmful than collecting blood from many other groups.*** Adolescents typically undergo a growth spurt between the ages of 11 and 15; by the end of the growth spurt, iron deficiency—sufficient to decrease exercise stamina—is fairly common.² By accepting donors as young as 16 years of age, blood collectors may be increasing the prevalence of iron deficiency. The influence of iron lack on brain development is also a concern.^{53,71}
- ***Adolescents do not have full agency.*** Cognitive and emotional immaturity can limit agency in regard to decision-making among adolescents. In addition, youth are more often subject to peer pressure, especially in the context of blood drives conducted at schools and other youth-centered organizations.

For these reasons, there is an especially strong ethical obligation to follow the precautionary principle for adolescents and to minimize the chance that harm is being done to them (nonmaleficence). Current regulations in the US allow for frequent donation in nonanemic adolescents; this practice may be harming the members of this group whose iron stores are already suboptimal. Given this, there is a strong ethical argument to modify these regulations and practices to reduce the potential for harm to adolescents.

Additional Groups

Additional groups who are at potential risk for iron deficiency augmented by or caused by blood donation and to whom blood centers need to pay special attention include:

- Other young donors (ages 19-25) because of ongoing brain development that requires iron.
- Premenopausal females because menstruating females have lower average iron stores, those who become pregnant require iron for fetal and maternal health, and because iron depletion associated with pregnancy can take years to resolve.
- Frequent donors because there is the potential for donors to become anemic if their iron stores have not been restored before the next donation.

Summary

Careful analysis of existing data is required to determine the potential for harm associated with blood donation. Given the limitations of available data, it is appropriate to employ a precautionary approach to ensure nonmaleficence. Because of the decreased agency of adolescents and increased potential harm to adolescents and other groups, one could consider policies focused at specific groups.

Additionally, it is imperative to have transparency about this issue and to study it further. Transparency is essential to decision-making by all key stakeholders. In addition, relevant data will facilitate developing safe approaches to donation while ensuring an adequate blood supply for patients.

SOCIAL CONCERN/STAKEHOLDER CONSULTATION

Consultation Approach

At the RBDM Working Group meeting in May 2017, the options for engaging stakeholders on the topic of iron store depletion in donors were shared, stakeholders were mapped for the purpose of consultation (online and face-to-face) and the locations for the face-to-face meetings were discussed. Appendix C illustrates the stakeholder map.

Over the next 2 months, the Stakeholder subgroup gathered contact information from across the stakeholder groups identified, covering the broad geography of the US. The focus question, after much consultation with the full Working Group was stated as, “Given the issue of reduced iron in some donors, what should we consider that will reduce the risk to donors, maintain a sufficient supply for patients, and ensure physicians are supportive?”

Just over 500 points of contact were gathered, from which 309 stakeholders were invited to participate in the online dialogue. The dialogue ran from August 8 to August 16, with personal invitations from Dr. Vassallo and the Lighthouse system. Generally, response rates for an external survey are 10-15%. The online dialogue achieved a response rate of 28.2%, roughly double the norm. There were a total of 3000 ratings (how participants felt about the input of others) and 1000 unique comments. In total, participants spent 60 hours reading content, rating it, and adding their opinions (see Appendix D). This demonstrated a depth of engagement and commitment to providing ideas and opinions. The results of the online dialogue were organized by theme and tagged by the Stakeholder subgroup. The summary below provides a subjective overview of outputs.

In terms of face-to-face consultations, two locations were identified: Phoenix and Boston. It was decided to host two meetings at each location; one for medical/technical participants and another for public/lay stakeholders. The consultations were held in Boston on September 25, 2017, and in Phoenix on September 28, 2017. The participant lists for each consultation are found in Appendix E.

Executive Summary

Stakeholders who participated in the consultations, both online and face to face, expressed appreciation for the opportunity to learn and share their opinions. Below are common outputs from across all consultations per noted topics.

NOTE: *indicates the number of times a comment was repeated/Red Font indicates “key” input.

Education

The challenge is in “ensuring” that donors are healthy and that no harm is accidentally done to a subset of donors. Data indicate that education alone is inadequate to spur most donors to effective action.*** “I think that we should educate both the doctors and the donors; this needs to be a ‘check box’ on all doctor’s forms, and patients need to keep their doctors informed.” There was disagreement as to whether the topic should/would be considered a public health issue.

Duty

The “duty” or task should be a collaboration between policy makers, donor centers, and organizations respected by the scientific and medical community. It is the blood operator’s duty to ensure blood donation is safe.

Recruitment

There was overall agreement that it is more effective to maintain the existing donor base than to recruit new donors. New marketing approach: Educate at high school, collect at colleges/universities.

Research

“As a behavioral researcher, I can state that knowledge is only one small component of whether people actually choose to engage in a particular behavior. Testing and follow-up action plan are needed.” ***

Supplements

There was concern raised about the donor center providing supplements, which could be seen as the practice of medicine in certain states. “Information is good but treatment options should remain between the patient and health-care provider.” There was also consensus that if donors refuse to take supplements, and are otherwise eligible to donate, the blood center should collect the unit.

Ferritin Testing

Testing and feedback for high-risk donors is the most scientifically sound approach for guidance.*** There was disagreement at the Boston technical consultation, as to the correct cutoff for determining low ferritin levels. The CDC uses a cutoff for children of less than 12 ng/mL and for adults less than 15 ng/mL, whereas the medical community believes different values are more appropriate. There was general agreement that a discussion should be encouraged between donors and their health-care providers.*** Ferritin testing is the responsibility of the blood center.***

Hemoglobin Levels

Raise minimum screening hemoglobin levels by 1 g/dL.

Practice of Medicine

Blood centers cannot develop and maintain a treatment plan for these donors; this is for health-care providers.**

Risk

This has to be a balance between a “theoretical risk” and a “sufficient supply.”

Stakeholder Feedback

Insights from the stakeholder consultations are provided in Table 14.

Table 14. Feedback from Stakeholders by Topic, Location, and Stakeholder Group

Topic	Phoenix – Technical	Phoenix – Public	Boston – Technical	Boston – Public	Online
Overall Reaction	Donors will need to understand the correlation between ferritin levels and donation to take action (if the ferritin level is low = take action). Make sure those in high-risk groups understand the potential risk.	More research needs to be conducted to understand the impact. This is a larger public health issue. It is better to maintain the existing donor base than to recruit new donors.	Are there any studies on how to incentivize donors? This would help inform the strategy. Make sure to include plateletpheresis donors in the message/strategy. This is not a public health issue.	What problem are we solving? It’s a matter of informed consent. Public needs to understand the difference between hemoglobin and iron stores.	Treatment options for addressing iron depletion should be left to primary care physicians (PCPs).
Communication	Send electronic letter with ferritin values noted, and coupon for supplement purchase; suggest donors share letter and discuss with their health-care providers.** Partner with local pediatricians to ensure understanding of issue with youth. Partner with public health to raise awareness. Use a targeted approach in the messaging. Take steps to ensure PCPs are aware of issue in relation to blood donation. Partner with other organizations (such as public health agencies, AMA, etc). Put a link on the website for	Put all information on website with portal for donors and health-care providers. Note on website where to get ferritin testing. Train the coordinators to train those who run the blood drives. Use the blood drive advocates to share the information. Set up a hot-line to respond to donor questions. Develop a small postcard size communication piece and a video that could be played after donation. Use social media to get word out. Tap into the call	Blood donors have to be informed of the potential risk, and the need for supplements. Messages should be tailored to the type of donor, particularly frequent donors (make sure to clearly explain the need to take supplements).	Blood drive sponsors should be “educated” on how to inform donors on addressing ferritin levels. Donors need to understand the symptoms and potential harm of iron deficiency. Donors with low ferritin levels should be sent a letter/email advising them to share the information with their PCPs. For new donors, emphasis should be on saving lives with the benefit of insights into their overall health (cholesterol levels, iron stores, etc). Communications should be a partnership between public health agencies, CDC, AMA, ACP,	Ensure lay terms are used; messages are targeted to different audiences; could use a donor “card” that gives advice on maintaining iron stores; show video with information on ferritin levels in postdonation reception area. By monitoring certain aspects of donor health, blood operators are contributing to overall donor wellbeing. Following donation, use social media to thank donors and remind them to take iron over 8-week period.** Include messaging about what aids in iron absorption (such as vitamin C). Create a video

Topic	Phoenix – Technical	Phoenix – Public	Boston – Technical	Boston – Public	Online
Communication (continued)	<p>health-care providers to inform themselves. Use the words, “there is some evidence to suggest blood donation might lead to ...” The overarching message could be “we care about your health.” Frequent blood donation may deplete iron stores, which has possible consequences (list). “Taking supplements will increase iron stores and return you to the predonation level, which will allow you to continue donating. Your donation is critical to maintaining a sufficient supply of blood for patients.” Create an infographic specific to youth and frequent donors. Produce a “cheat sheet” for use on blood drives and for blood drive sponsors.</p>	<p>centers. Replace what was lost during donation; your ongoing health is yours and your health-care provider’s responsibility. Stop saying it’s easy to give blood; it’s not easy, but it means life or death for a patient. Physicians – info dissemination via the AABB Board, conduct educational session at seminars, partner with pharmacists; give info card to donors to share with their health-care providers; encourage donors to share their donation health history with their health-care providers. Youth – equip blood drive coordinators with information on iron depletion for youth. Even with a healthy diet, iron repletion will take longer without a supplement.</p>		<p>blood operators, physicians, donors/guardians, schools, sponsors, school nurses, school principals and health insurance companies. The sponsors of high school blood drives need to have clear messaging to inform schools and potential donors. For the public, communications should be responsive, rather than proactive. Top Message is: This is necessary to replace the iron lost through blood donation. Many donors will feel that they wouldn’t be allowed to donate if it wasn’t safe (it will take effective messaging to break through this belief). Message should also note the percentage of donations that come from each of the “at-risk” groups so they recognize how important their donations are to maintaining a sufficient supply.</p>	<p>tutorial that people must watch before or after donating blood. The video could display 1) the various people saved by blood donation, 2) personal considerations before donating, 3) blood tests to request during annual checkup, and 4) ways to maintain good health/blood count/iron level. Replacing what was removed is a good message.* Partnering with public health, although a good idea, would slow down educating donors; it is primarily a blood operator responsibility. ** Concern expressed around different strategies for different blood centers across the country, and the possibility of donor confusion.</p>
Medical Community			<p>Steps should be taken to inform physicians, health-care providers, nurse practitioners and</p>	<p>Raise awareness with the medical community so they are aware the blood system is not testing for iron stores.</p>	

Topic	Phoenix – Technical	Phoenix – Public	Boston – Technical	Boston – Public	Online
			assistants. It would be effective to target medical directors of the insurance companies. Insurance will not cover cost of ferritin testing unless Hb is low and donor/patient has symptoms of anemia.		
Intent to Donate				This will not adversely affect committed donors. New donors will need more information on the benefits of donation so they will take up the cause.	
Education				There should be commercials made that focus on maintaining your health as part of being a donor that could play on TV stations.	Educate physicians* (so they make the connection between donors and iron depletion), blood operator staff and donors. Education alone is not enough.*
Supplements Supplements (continued)	Send a postdonation reminder to high-risk groups (youth, frequent donors, premenopausal females) to take supplements. Give youth a bottle of supplements, and all others a coupon. To keep it simple, recommend supplements to all donors. Use caution in recommending vitamin intake as there is	It is better to supply the supplements in case some donors cannot afford to buy them (donors should not be “out of pocket” as a result of their donation).	It was noted that, even though there may be better compliance with handing out pills, this should be left to the PCPs as it could be the practice of medicine. Recommend an 8-week course of supplements to all	In terms of providing pills directly to donors, a preferred course of action would be to discuss with their PCP first. There is a belief that low ferritin is the responsibility of the medical community. A cautionary note was offered in terms of providing pills or coupons that are from a specific company/ supplier as	Donors should have a health evaluation with a PCP to reduce the risk of any underlying etiology.* Reality is that some blood operators will not be allowed to distribute supplements or suggest their use. Use an evidence-based approach to recommending supplements by first doing a ferritin test.**

Topic	Phoenix – Technical	Phoenix – Public	Boston – Technical	Boston – Public	Online
	<p>contradictory literature on the benefits. Deal with youth via informed consent letters to parents/guardians.** Partner with a pharmacy chain to address the concern around ‘practice of medicine.’ If donors refuse to take supplements and otherwise are eligible, proceed with the donation. Give coupon out with messages.</p>		<p>adult donors with clear messages on the reasons.</p>	<p>this may be seen as an endorsement for financial gain. Group recommends a generic voucher. The voucher would give the message that “they care about my health.” It could also help as a retention tool. Youth should be flagged in the system so that a letter is sent to their guardian(s) noting the importance of taking a multivitamin containing iron to continue donating. Should they state they are taking the multivitamin at their donation, take them at their word, and take the donation.</p>	<p>Offer vouchers to donors who are iron depleted and suggest they consult with their PCP first.* Several blood operators (especially hospital-based) would not be allowed to provide supplements.*</p>
<p>Targeted Approach</p>	<p>For donors who donate only once per year, give them the information on potential risk, provide a coupon for supplements and survey them to see what works best for them. Premenopausal females are the second priority; advise of the increased potential for risk, particularly via pregnancy.</p>	<p>Youth – Letter to parents to take supplements and consult with health-care provider; give link to more information on website. Launch a “bring a buddy” approach and highlight peer recipients, to ensure sufficient supply. Premenopausal females – Should be made aware of potential for increased risk; use targeted messages; conduct periodic ferritin testing;</p>		<p>Focus on frequent donors</p>	<p>Develop “health packet” to inform young donors; raise minimum age to 17 years; Donors need to see a PCP before taking iron as there is a possibility it could cover up other health issues. Launch a pre-emptive strategy for school blood drives that gives young donors the information for informed consent before their donation appointment. This is the most vulnerable segment of the donor base, given the potential for cognitive implications.</p>

Topic	Phoenix – Technical	Phoenix – Public	Boston – Technical	Boston – Public	Online
<p>Targeted Approach (continued)</p>		<p>provide supplements at point of donation.</p>			<p>Therefore, testing and iron supplementation is critical. This latter point needs more research. Reduce reliance on high-school donors; focus on universities and colleges.* Increase age of donation for females. Hold information sessions at high schools and collect blood at universities and colleges.</p> <p>Education for all; testing for subgroups at risk (youth, premenopausal females, frequent donors, Hb near minimum) and share results with the donor to encourage action.*** Testing could be rotated for high-risk donors, every 5th or 6th donation for example.</p>
<p>Donation Interval</p>	<p>Youth should be deferred for 1 year unless they take supplements. It was noted that by increasing the interval for youth, the blood operator is missing an opportunity to secure life-long donors.</p>		<p>CDC noted that they believe the cutoff of 26 ng/mL is too high; for children it should be less than 12 ng/mL and for adults it should be less than 15 ng/mL. Consider conducting ferritin testing at the first donation, and at specific predetermined intervals (ie, every</p>	<p>It is the duty of the blood operator to limit the number of donations of youth to 1 per year, with detailed explanations and information for their guardians. All frequent donors (other than youth) should be subjected to ferritin testing as it demonstrates “care for their well-being.” If ferritin testing is not possible, then the donation interval should be set</p>	<p>Increase donation interval only for the donors who have low ferritin levels and not taking supplements. Increasing the donation interval seems to be of limited utility and will have a negative effect on supply. *****</p>

Topic	Phoenix – Technical	Phoenix – Public	Boston – Technical	Boston – Public	Online
			<p>third donation). It was suggested to use a mean corpuscular volume test to determine iron stores (2 weeks lag time). Premenopausal females should be limited to two donations per year (consider impact on supply), unless they agree to take supplements.</p>	<p>at twice per year with information on taking multivitamins with iron. It will be important to get health insurance companies on board to obtain a CMS code (to pay for ferritin testing). Note: There may be ferritin “test seekers” who donate to find out what their ferritin levels are.</p>	
Compliance				<p>If the blood operator chooses to do ferritin testing of the “at-risk” groups, then compliance is not an issue. For blood operators who do not do ferritin testing, there has to be an increase in inter-donation intervals.</p>	
Recruitment				<p>There should be a specific recruitment strategy developed to replace the donors who will be lost through low-ferritin deferrals.</p>	<p>Design campaign around recipients meeting donors with the message, “you have taken care of me, now I want to take care of you.” Focus recruitment on diverse populations.</p>
Duty	<p>The blood operator has a duty to do no harm. The blood operator has an ethical obligation to protect donors from harm. There is a duty to</p>	<p>There is a higher standard of care in terms of informing and addressing the impact on youth.</p>	<p>The blood operator has a duty in terms of youth/ parent/guardian and the potential cognitive impact. The</p>	<p>It is the duty of the blood operator to be clear about a risk, even if it is potential, so donors pay attention to it, and take action. Parents have a</p>	<p>To ensure health of lifelong donors blood operators have a duty to not do harm.** Donor health is a shared responsibility between the</p>

Topic	Phoenix – Technical	Phoenix – Public	Boston – Technical	Boston – Public	Online
	<p>inform donors of their ferritin test results and suggest they discuss with their health-care provider – nothing more. In terms of the precautionary principle, the blood system focuses on “do no harm”; this is not the case with other parts of medicine. The blood operator should bear the cost of iron supplements and ferritin testing.</p>		<p>blood operator is contributing to iron deficiency, so should be proactive in replacing it (eg, pay for ferritin testing). If adult donors refuse to take supplements, after having been informed of potential risk, the blood operator should take the donation. The blood operator has a duty to inform and prevent harm to donors.</p>	<p>right to know the potential risk their child might be facing.</p>	<p>donor and the donor center. It is important to consider an individual’s choice and autonomy; if a donor chooses not to take supplements, and they are otherwise eligible, then the blood operator should still take their blood.** On this latter point, the exception is with young donors. Maintaining donor health is an obligation the donor center takes on when collecting a unit of blood.** Blood centers cannot transfer the cost of testing/supplements to the health-care system.</p>
Ferritin Testing	<p>To notify donors of ferritin test results, use email with confirm receipt tag.</p>	<p>Set a specific threshold and don’t take donation if donor falls below it. Consider conducting periodic ferritin testing (ie, every third donation).</p>	<p>Ferritin cutoff levels are set too high.*</p>		<p>Ferritin testing first, followed by iron for donors whose levels are low.** Ferritin level cutoff for frequent donors should be higher than for other donors. * Blood centers should offer postdonation ferritin testing (at 18 years, and every 2 years after).*</p>
Other	<p>Add a question to the donor questionnaire as to whether the donor has taken their supplements and repeat the messages about the potential risk.*** Hire a dietician to do follow-ups via telephone with</p>	<p>Add a question to the donor questionnaire or the donation interview. Recommend undertaking some pre-emptive work with school principals so as not to have too many</p>			<p>Neither the donor, nor the health-care system should bear the cost of testing and supplementation; it should be the blood operator.* Need to consider that not all donors have PCPs nor the finances to</p>

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Topic	Phoenix – Technical	Phoenix – Public	Boston – Technical	Boston – Public	Online
	high-risk groups. Keep in mind the cost of the blood system for smaller hospitals.	cancellations of high school blood drives.			pay for testing or supplements. In addition, insurance plans may not cover the cost.

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Appendix A. Legal and Regulatory Assessment

	Status Quo-Education	Iron Intervention			Inter-donation Interval/ Annual Max. Modification	Ferritin Testing	Combination Strategies
		1. Provide pills to at-risk donors	2. Provide pills to all donors	3. Vouchers			
FDA Response on Iron Supplements and Ferritin Testing	N/A	FDA does not object to the routine use of iron supplementation by provision of iron tablets, coupons or vouchers to reduce the risk of nutritional iron deficiency due to blood donation, provided the iron tablets are meant to replace the approximate amount of iron lost with a blood donation using an appropriate regimen (ie, short-course, low-dose) of oral iron. Donors should be counseled about iron loss from blood donation and the benefits and risks of iron supplementation.			N/A	FDA recognizes the effectiveness of programs that utilize ferritin measurement as reported in recent RCTs and ongoing studies, especially for targeted subgroups of blood donors at particular risk from iron deficiency. However, FDA regards use of ferritin testing to guide iron supplementation as a matter of medical director discretion that may be subject to oversight through state laws.	N/A

	Status Quo-Education	Iron Intervention			Inter-donation Interval/ Annual Max. Modification	Ferritin Testing	Combination Strategies
		1. Provide pills to at-risk donors	2. Provide pills to all donors	3. Vouchers			
Legal Risk(s) to Blood Collector	<ul style="list-style-type: none"> • Risk of claim by donors suffering from low-iron-related conditions of negligent failure to act • Risk especially high for “at-risk” donors • Recent studies demonstrating the benefit of iron mitigation strategies increase risk of viable negligence claim 	<ul style="list-style-type: none"> • Might be considered practice of medicine or corporate practice of medicine in some states • Liability for adverse reactions to iron supplement including interference of medication absorption • Liability for possibly masking occult blood loss/ GI malignancy • Risk of parental complaints about minor donors given supplements 	<ul style="list-style-type: none"> • Might be considered practice of medicine or corporate practice of medicine in some states • Risk of parental complaints about minor donors given supplements • Liability for adverse reactions to iron supplements including interference of medication absorption • Liability for possibly masking occult blood loss/GI malignancy 	<ul style="list-style-type: none"> • Might be considered practice of medicine or corporate practice of medicine in some states • Liability risk for lower adherence/ compliance esp. among young donors 	<ul style="list-style-type: none"> • Risk of negligent failure to act if no change is made, or if a change that has been shown to be ineffective is made, especially regarding at-risk donors 	<ul style="list-style-type: none"> • Might be considered practice of medicine or corporate practice of medicine in some states • Extensive follow-up program may increase risk • Improper testing or reporting of inaccurate test results; negligent donor counseling/staff training could impose risk 	<ul style="list-style-type: none"> • Introduces increasing levels of complexity and risk exposure as multiple interventions are implemented

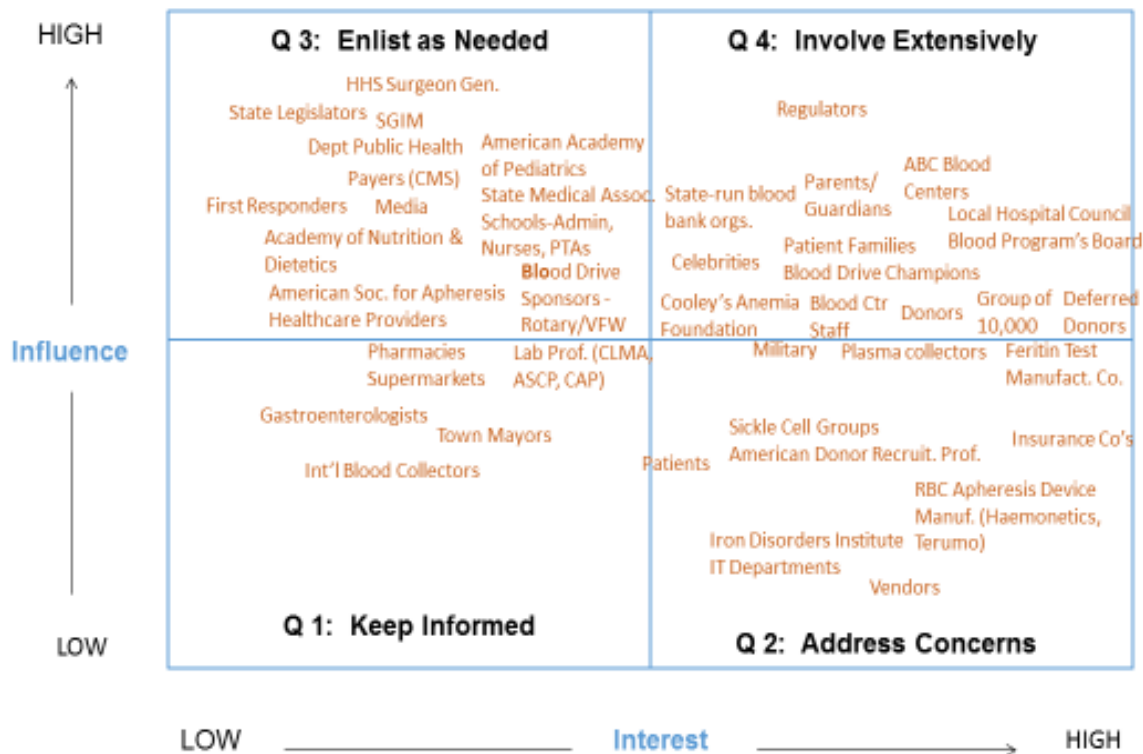
	Status Quo-Education	Iron Intervention			Inter-donation Interval/ Annual Max. Modification	Ferritin Testing	Combination Strategies
		1. Provide pills to at-risk donors	2. Provide pills to all donors	3. Vouchers			
Risk Mitigation Strategies and Counter-vailing Considerations	<ul style="list-style-type: none"> • Increase education efforts 	<ul style="list-style-type: none"> • Blood collectors already assume risk for donation-related injury • Licensed medical director to approve supplements • Advise donors to consult with PCP • Educate state medical boards, request issuance of FAQs or white papers. However, broaching subject with medical boards could have negative consequences and/or produce inconsistent results among state agencies • Focus on donor health rather than “treatment” • Risks of adverse effects/donor informed consent 	<ul style="list-style-type: none"> • Blood collectors already assume risk for donation-related injury • This option focuses on donor health rather than “treatment” • Iron supplement labels have disclaimer re: no evaluation by FDA; product not intended to treat or prevent conditions 	<ul style="list-style-type: none"> • Use 3rd party providers for voucher program and/or make voucher for generic multivitamins • Relies more strongly on donor choice • Include instructions for donor to seek advice from PCP and a disclaimer 	<ul style="list-style-type: none"> • No risk but possibly no benefit to adjust interval for at-risk donors as mitigation strategy • Combine ferritin testing with decision to adjust intervals for at-risk donors 	<ul style="list-style-type: none"> • This option might be considered a screening test, similar to testing already performed by blood collectors (HIV, HCV) • Informs and empowers donors, may identify pre-existing sources of blood loss: autonomy may help lower risk • Direct donors to consult with PCP 	<ul style="list-style-type: none"> • Direct donors to consult with PCP • Seek state-specific legal counsel

Appendix B. State Statutes: Defining Practice of Medicine

State	Statute Number	Definition
California	§ 2052	<p>(a) Any person who practices or attempts to practice, or who advertises or holds himself or herself out as practicing, any system or mode of treating the sick or afflicted in this state, or who diagnoses, treats, operates for, or prescribes for any ailment, blemish, deformity, disease, disfigurement, disorder, injury, or other physical or mental condition of any person, without having at the time of so doing a valid, unrevoked, or unsuspended certificate with some other provision of law is guilty of a public offense, punishable by a fine not exceeding ten thousand dollars (\$10,000), by imprisonment in a county jail not exceeding one year, or by both the fine and imprisonment.</p> <p>(b) Any person who conspires with or aids or abets another to commit any act described in subdivision (a) is guilty of a public offense, subject to the punishment described in that subdivision.</p>
Florida	§ 458.303	(3) “Practice of medicine” means the diagnosis, treatment, operation, or prescription for any human disease, pain, injury, deformity, or other physical or mental condition.

State	Statute Number	Definition
Indiana	§ 25-22.5-1-1.1	<p>Sec. 1.1. As used in this article:</p> <p>(a) “Practice of medicine or osteopathic medicine” means any one (1) or a combination of the following:</p> <p>(1) Holding oneself out to the public as being engaged in:</p> <p>(A) the diagnosis, treatment, correction, or prevention of any disease, ailment, defect, injury, infirmity, deformity, pain, or other condition of human beings;</p> <p>(B) the suggestion, recommendation, or prescription or administration of any form of treatment, without limitation...</p> <p style="text-align: center;">***</p> <p>(D) the prevention of any physical, mental, or functional ailment or defect of any person...</p> <p style="text-align: center;">***</p> <p>(4) Providing diagnostic or treatment services to a person in Indiana when the diagnostic or treatment services:</p> <p style="text-align: center;">***</p> <p>(d) “Drug or medicine” means any medicine, compound, or chemical or biological preparation intended for internal or external use of humans, and all substances intended to be used for the diagnosis, cure, mitigation, or prevention of diseases or abnormalities of humans, which are recognized in the latest editions published of the United States Pharmacopoeia or National Formulary, or otherwise established as a drug or medicine.</p>
New York	§ 6521	The practice of the profession of medicine is defined as diagnosing, treating, operating or prescribing for any human disease, pain, injury, deformity or physical condition.
Texas	§ 151.002	<p>(13) “Practicing medicine” means the diagnosis, treatment, or offer to treat a mental or physical disease or disorder or a physical deformity or injury by any system or method, or the attempt to effect cures of those conditions, by a person who:</p> <p>(A) publicly professes to be a physician or surgeon; or</p> <p>(B) directly or indirectly charges money or other compensation for those services.</p>

Appendix C. “Map” of Stakeholder Engagement



Appendix D. Summary of Activity from Stakeholder Consultations

SUMMARY OF ACTIVITY

	Total	Blood Operations	Core Team	Don/Pt/Vlntr	Gen Public	Medical/Scientific	Regulatory Bodies
Total Responses	74	12	15	32	0	14	1
Total Ratings	3002	463	252	1403	224	565	95
Total Comments	962	123	101	476	22	218	22
Number of Invitees	309	95	8	114	21	58	13
Unique Logins	107	23	8	41	9	24	2
Active Users	84	18	7	33	8	16	2
Active %	27.18%	18.95%	87.50%	28.95%	38.10%	27.59%	15.38%

- 84 active participants produced 74 responses, submitted 3000 ratings and almost 1000 comments in a combined effort of 59 hours
- Balanced contributions from blood operations and medical/scientific and
- Donors'/patients' voices weighed strongly

Appendix E. Participant List for Face-to-Face Consultations

Phoenix - Technical	Phoenix – Public	Boston – Technical	Boston - Public
MD, Pediatric Heme/Onc	Multi-gallon whole-blood donor	Blood center medical director	Sponsor HS blood drives
MD, County DPH	Frequent donor, coordinator and parent of cancer patient	Medical director, MABB	Regular blood donor
Nutritionist, County DPH	Freq. donor, coordinator (spouse of parent of cancer patient)	Medical representative, Mass. Medical Society	Multigallon whole-blood and regular apheresis platelet donor, unrelated kidney donor
Nutritionist, County DPH	Blood recipient, parent of donor, coordinator	Epidemiologist, CDC	Blood drive sponsor
BB Supervisor, Area Hospital	Freq. WBD / platelet donor	State Epidemiologist, Mass. DPH	Regular 24/year apheresis platelet donor
BB Supervisor, Area Hospital	Coordinator and donor	Representative, Mass. Sickle Cell Consortium	Patient advocate
BB Med. Dir., Area Hospital	Casual donor (spouse of coordinator and donor)	Transfusion medical director /director of hospital collection program	African-American deferred female donor, patient advocate
Quality Specialist, Area Hospital	Community leadership council member, sponsor	Transfusion medical director/ director of pediatric hospital collection program	Blood drive sponsor
Hospital Chief of Staff / Head of Pathology	Multi-gallon platelet donor	Transfusion medical director/director of hospital collection program	Blood donor
	Multi-gallon whole-blood donor / platelet donor	Hospital transfusion medical director	Blood donor and blood drive sponsor
	Coordinator, frequent donor, parent of donor	Transfusion service medical director,	