AABB DONOR IRON DEFICIENCY RISK-BASED DECISION-MAKING ASSESSMENT REPORT

Report of the Ad Hoc Iron-Deficiency Working Group

Recognizing the current concern around monitoring, limiting or preventing iron deficiency (ID) in blood donors to the US blood supply, the AABB Board of Directors tasked a specially formed working group (the Ad Hoc Iron-Deficiency Working Group) to conduct a thorough assessment of the breadth, risks and benefits of various options to respond to donor iron deficiency. The resulting recommendations will be used to inform the Board for policy development purposes.

1. Emerging Risk: Effect of Blood Donation on Donor Iron Stores [RBDM Stage 1]

The current AABB policy in this area consists of 1) AABB Standard 5.2.1, #5 (*Standards for Blood Banks and Transfusion Services*, 30th edition, effective April 1, 2016 – March 31, 2018),[1] which requires that, "Donors are given educational materials regarding the risks of postdonation iron deficiency" and 2) AABB Association Bulletin #17-02,[2] which contains information and recommendations on this topic.

The Ad Hoc Iron-Deficiency Working Group used the Alliance of Blood Operators' risk-based decision-making (RBDM) framework to undertake the assessment. The RBDM framework can be found at: https://allianceofbloodoperators.org/abo-resources/risk-based-decision-making/rbdm-framework.aspx. After reviewing the foundational principles of the framework and selecting the assessment principles that would guide its work, the group moved through each stage of the framework. The stages are identified in the table below.

Stage	Objective
Stage 1 Preparation	Review the risk management policy foundations that guide the decision-making process.
Stage 2 Problem formulation	Define and characterize the problem so the risk management options to consider, assess and evaluate can be identified.
Stage 3 Participation strategy	Identify the need for stakeholder involvement, identify the audiences and develop a participation plan.
Stage 4 Assessments	Accumulate the data necessary to effectively analyze the risk management options, by performing a series of assessments.
Stage 5 Evaluation	Use assessment results and stakeholder feedback to evaluate risk management options. Evaluate the risk tolerability of each option. Compare each risk management option.
Stage 6 Decision	Select the optimal risk management option and prepare recommendations.

2. Characterizing the Risk [RBDM Stage 2]

Evidence demonstrates that blood donors are at risk for iron depletion at a higher rate than the background rate in the general population. Certain donor subgroups are particularly at risk, including frequent donors, young donors and premenopausal women. As iron deficiency progresses, it eventually results in anemia. The potential for adverse health consequences definitely exists when anemia is present and may exist even before anemia occurs. Potential adverse effects from iron deficiency without anemia include fatigue, decreased exercise tolerance, cognitive dysfunction, pregnancy-related complications (e.g., perinatal mortality, preterm delivery, low birthweight, newborn neurodevelopmental abnormalities), pica, hearing loss and restless leg syndrome. Strong evidence exists only for pica.

Donors taking iron supplements to replace iron lost during donation recover lost iron stores much more rapidly than those not receiving supplements and generally do so within the currently allowable minimum interdonation intervals. However, there are concerns with supplementation. Some of these are well established, such as interference with absorption of some medications. Others are theoretical, such as obscuring the warning signs of gastrointestinal (GI) malignancy, over-replacement of iron in individuals with hereditary hemochromatosis and accidental overdose. Data to quantify these potential risks are not available. There are important social, ethical, legal, political, regulatory and jurisdictional dimensions when considering the potential harm of iron deficiency and its mitigation in blood donors.

3. Formulating the Problem and the Risk Management Options [RBDM Stage 2]

To precisely distinguish each decision point within a thorough RBDM analysis, one must first identify the pertinent decision drivers and questions to be answered. Given the complexity of this issue, it was critical to define the decision objectives detailed below, which then guided the selection and design of risk assessments.

At this stage in the RBDM process, a preliminary list of risk management options is also identified; the risk assessments will review each option vis-à-vis mitigation of the overall risk and any risk trade-offs that may be present.

Decision Drivers and Risk Assessment Question

Four decision drivers were identified as important to the RBDM analysis:

- Donor safety
- Social concern and public trust
- Availability of supply
- Economics and blood sector sustainability

The following assessment question was used to guide the evaluation:

> "Given the recognized concern about iron deficiency in blood donors, known available interventions, and taking an inclusive viewpoint of the range of issues that need to be addressed, what is the appropriate approach (or approaches) to adopt that will reduce the iron-deficiency risk to donors, while ensuring an adequate and sustainable supply of blood and blood products to meet patient need?"

Summary of Risk Management Options

Status Quo: Hemoglobin (Hb) testing and donor education on iron depletion (BB/TS Standard 5.2.1, #5).

In addition to the status quo, four risk management options were identified.

Option A: Facilitate access to supplemental iron for all donors or targeted subgroups of donors by offering vouchers or pills.

Option B: Lengthen the interdonation intervals for all donors or targeted subgroups of donors.

Option C: Implement ferritin testing as a basis for advising donors about body iron stores, taking iron supplements or extending donation intervals.

Option D: Limit donations from minor (16- and 17-year-old) donors to one donation per year, unless it can be demonstrated that they are iron replete, which would allow those individuals to donate sooner than the 12-month limit.

It was recognized that Option D – Limit donations from minor (16- and 17-year old) donors is a subset of Option B – Lengthen interdonation intervals. However, the working group believed it was important to specify an intervention that was specific to minor blood donors because this age group poses particular challenges around consent and/or the provision or recommendation of supplemental iron.

An underlying motivation for these options is an intent to maintain or restore iron levels in donors to the levels they had before donating, i.e., to replace the iron they lost in the donation. In contrast, the working group considers it outside the capability of blood centers to identify, diagnose and treat iron deficiency that exists independent of blood donation.

4. Communicating and Consulting on the Risk [RBDM Stage 3]

Risk communication and stakeholder participation are important elements of the RBDM process. At the outset of the RBDM process, stakeholders were identified for the purpose of consultation (online and face-to-face). The group then gathered stakeholder contact information from across the identified stakeholder groups, covering the broad geography of the US. The consultation question presented to stakeholders 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?”

Four face-to-face stakeholder engagement sessions and an online dialogue were conducted to obtain feedback on the recommended approaches. Over 300 stakeholders were invited to participate in the week-long online dialogue and 28% of invitees responded. There were 3,000 ratings (how participants felt about the input of others), and 1,000 unique comments. In total, participants spent 60 hours reading content, rating it and adding their opinions (see Supplemental Material). The face-to-face consultations were held in Boston and in Phoenix. Each of these consultations had two sessions: one for medical/technical participants and one for the public/lay stakeholders. Outputs from these consultations informed the assessments in the RBDM analysis, and are highlighted in the contextual assessments section.

5. Assessing the Risk and the Risk Management Options [RBDM Stage 4]

To help inform decisions on the risk management options, the following assessments were conducted by subgroups:

- Safety risk
- Budget impact
- Operational impact
- Contextual assessments
    - Ethical considerations
    - Legal and regulatory considerations
    - Social concerns (included in the stakeholder consultation)

A summary of the above-noted assessments follows. The detailed assessments can be found in Supplemental Material.

Safety Assessment

Iron deficiency exists along a continuum of severity. Because anemia is usually a later-stage manifestation, ID is divided into nonanemic iron deficiency (NAID): male Hb ≥13.5 g/dL, female Hb ≥12.0 g/dL) and iron deficiency anemia (IDA: Hb below these values with laboratory evidence of iron deficiency). The latter is associated with reasonably characterized adverse clinical outcomes. NAID can be further divided into two components: iron-deficient erythropoiesis (IDE) and absent iron stores (AIS). These were defined some years ago by REDS-II RISE[3] investigators, and similar definitions have been used in many other subsequently reported studies. This analysis adopts the terminology and definitions proposed and used by RISE:

- Iron deficient erythropoiesis (IDE) is defined as serum or plasma ferritin <26 ng/mL[4] (alternatively defined, <20 ng/mL in females and <30 ng/mL in males)
- AIS is defined as ferritin <12 ng/mL (alternatively, cutoffs of 9 or 15 ng/mL have been used in some other studies). This is a very specific finding, correlating in other studies with absent iron in the marrow and elevated soluble transferrin receptor levels.[3,5-8]

Anemia can occur in some persons with IDE but occurs more commonly with AIS.

The primary focus of the Safety subgroup was on the clinical consequences of NAID because most donors with anemia would not be acceptable for donation based upon capillary hemoglobin. However, it was recognized that US males of European descent males with a hemoglobin between 13.0 and 13.5 g/dL are considered anemic[9], and the most likely contributing factor (or cause) in donors with these hemoglobin values is iron deficiency. Furthermore, a donor with NAID may become anemic following blood donation and remain anemic for a period in the absence of iron supplementation. Thus, while it would have been appropriate to consider the clinical consequences of IDA, such deliberation was considered outside the scope of this assessment. It is recommended, however, that this work should be undertaken by way of a future initiative.

Baseline Occurrence for IDE and AIS

Rates of IDE and AIS in categories of donors were taken from published studies as indicated below.

Donor Category	Data Source
Frequent adult donors	REDS-II RISE enrollment data[3]
Adolescent donors (ages 16-18)	REDS III CHILL data[10]
Premenopausal women	CHILL and Canadian Blood Services3[11-12]
Donors near Hb cutoff	Blood Systems Inc., 2014-2015[14,15]
Deferral due to low Hb	NBCUS 2013[16]
Donor return after Hb deferral	REDS II[17]

For each of the first four categories noted above, the data indicate that a substantial proportion of donors in each category has IDE and a smaller proportion has AIS. The detailed data are presented in Supplemental Material.

Estimating the Occurrence of IDA in Donors

A systematic estimate of IDA in a representative donor population has not been published. Although recent studies suggest that as many as 30% of donations may come from donors with ferritin levels <26 ng/mL,[10] the prevalence of IDA in donors is unknown, as is the proportion of IDA that is caused by donation itself. The Safety subgroup developed estimates that take donor presentations as the unit of analysis and partition presentations into deferrals due to IDA, donations made by a donor with IDA and donations made by a donor 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:

1. 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 beyond that observed in the nondonor population). Of all hemoglobin deferrals, the estimate is that 40% are due to excess IDA.
2. 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 and 13.5 g/dL).
3. Approximately 18% of donor visits leave a donor with postdonation lab values that are consistent with both iron deficiency and anemia. These occur in about a 3:1 female-to-male ratio.

In summary, these estimates suggest that an appreciable proportion of presenting blood donors have or develop IDA; approximately 1 in 20 presenting donors has "excess" IDA (sum of #1 and 2, above), and approximately 1 in every 5 to 6 donors develops lab values consistent with IDA. Although these abnormal lab values can persist for months in the absence of iron supplements, the clinical consequences are not well known. The healthy, mildly anemic blood donor population may not be equivalent to nonblood donors with severe IDA due to other causes, in whom clinical studies have been performed, and who will differ from otherwise well blood donors on a variety of demographic, socioeconomic and other characteristics.

Clinical Consequences

Clinical consequences of IDA were not extensively reviewed by the working group as it is unclear to what extent the consequences would apply to donors who are iron deficient before donation and then made anemic after blood donation. Some donors with lab values consistent with postdonation IDA, and a proportion of frequent donors without IDA, may have nonanemic low Hb values relative to their baseline Hb, were they not donating at all or not as frequently. The impact of such relative anemia has not been studied. However, it is recognized that some frequent donors deferred for low Hb after multiple successful donations are referred to their physician and undergo unneeded medical workups because their physician is unaware that frequent donation may have caused their anemia.

For NAID in blood donors, pica is the only well-documented clinical consequence. Subtle consequences such as decreased exercise tolerance and fatigue are difficult to assess in healthy donors. There are **theoretical** concerns about the following:

- Cognitive performance in adolescent (ages 16-18) donors.
- Ongoing brain development in adolescent and young (ages 16-25) donors.
- Adverse pregnancy outcomes.
- Fetal development, if the mother has prolonged ID.

Prioritization of Groups for Intervention

The Safety subgroup prioritized the donor groups for whom intervention should be considered. Due to lack of data on the long-term consequences of iron deficiency, this prioritization is based upon the precautionary principle and assumes the following:

- Because young persons (up to age 25) are still undergoing neurologic (i.e., brain) development and because iron is needed for this process, the assumption is made that ID might negatively affect this process.
- Because severe iron deficiency in pregnancy can affect fetal maturation and development, 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.

Based on these assumptions, the prioritization for intervention is:

Priority	Rationale
1. Adolescent donors (ages 16-18)	More extensive brain development is thought to occur at these ages. It is recognized that minor donors aged 16 and 17 are a vulnerable population and interventions may need to be adjusted accordingly. Donors aged 18 are also included because there are some data relevant to NAID in this group (e.g., the CHILL study)[11-13] 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.

Priority	Rationale
3. Premenopausal females [ages 26 to locally determined upper cutoff age (99.98% of 2015 US births occurred in women <50 years old and 99.78% to women <45 years old)].[18]	Ranked next due to fetal/newborn health concerns. NOTE: This report uses the term "premenopausal females" to refer to "females of childbearing potential."
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.

Quantitating the Effects of Interventions

The Safety subgroup arrived at the following conclusions based on a comprehensive review of the literature, review of factors affecting Hb deferral, estimates of the occurrence of IDA in donors, consideration of clinical consequences and calculation of safety risks and benefits of each of the risk management options under consideration.

Intervention	Conclusion
Iron supplementation	• Will decrease the proportion of donors with IDE/AIS. • Will decrease amount of time these donors remain iron deficient. – Is more effective than lengthening the interdonation interval (shown by HEIRS data).[19] • Will decrease donor deferrals for low Hb. – Estimated decrease of 25-50%. – Will likely increase number of units collected. • Side effects are indistinguishable between placebo and daily low-dose (18-38 mg) supplementation. • Repletion to baseline mostly occurs within 8 weeks with the largest effect in the first 4 weeks. • Assumed to be close to 100% effective if donors are compliant/adherent. • Adherence estimated at 50-75%.
Lengthened interdonation interval	• Replacement of the iron lost with a single whole blood donation requires an interdonation interval of ≥6 months for many donors. – In HEIRS, 67% had not recovered iron at 24 weeks.[19] – In CHILL,[11-13] donors who returned at 6-12 months had a two-fold higher odds ratio of having AIS and IDE than those who waited at least 12 months. – If the intent is to replace the iron lost by donation within current interdonation intervals, then iron supplementation is needed.
Ferritin testing and targeted strategy implementation	• Based on a low ferritin result, donors could be encouraged to take iron and/or to delay their next donation. • No uniform agreement as to: – Strength of the iron supplementation recommendation. – Length of any deferral.

Intervention	Conclusion
	– Whether the interdonation interval should be influenced by the donor's self-reported compliance with recommendations on iron supplementation. – Level of ferritin below which any given action was appropriate. • Good results in STRIDE,[20] but this was a select donor population (i.e., research volunteers).
Limit donations from minor (16- and 17-year-old) donors	• Any of the above risk management options could be applied, but giving iron directly to 16- or 17-year-old donors may not be feasible (e.g., need for parental consent, adherence to recommended action) • Blood Systems Inc. has implemented a ferritin testing strategy that results in a 6-month to 1-year deferral and a recommendation to take iron: – If donations are restricted to once every 6 or 12 months (or once per school year), it is estimated that 40% of donations from this group would be lost, which translates to loss of about 4-5% of all donations. – Acceptable ferritin results could be used to qualify adolescent donors for a shorter interdonation interval.

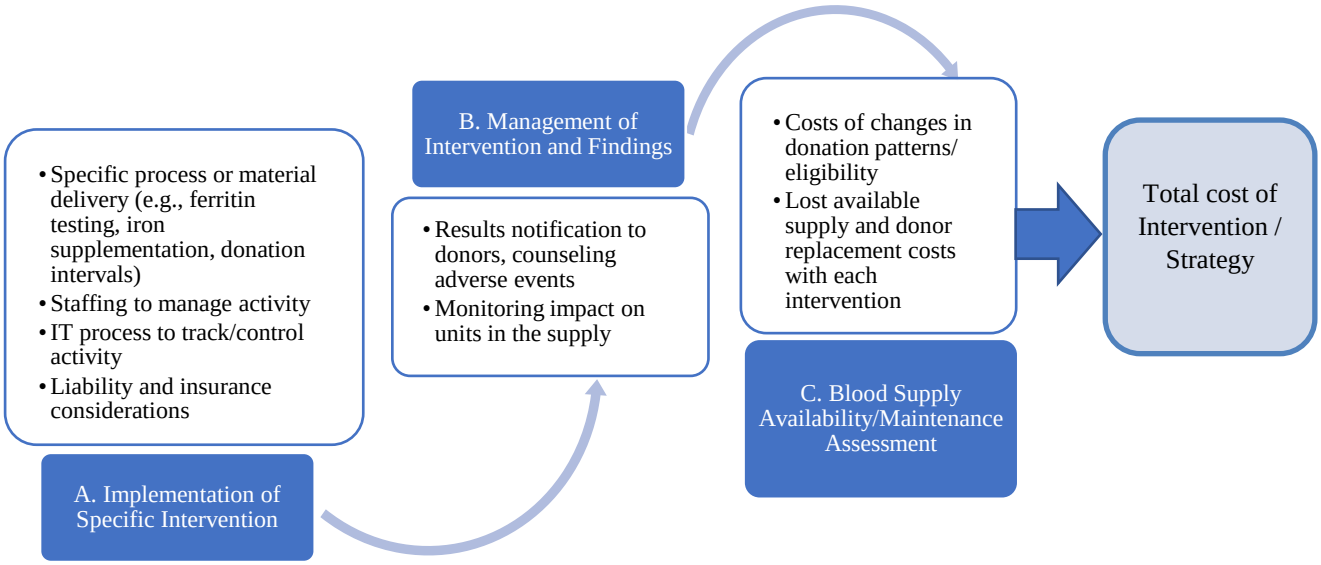
Health Economics: Budget Impact Assessment

Cost Model Strategy and Hierarchy

A budget impact analysis was conducted for each risk management option focused on the first year of implementation. Costs for each strategy were estimated from a health-care system perspective, meaning those costs to blood centers that accrue as part of implementing a strategy and the costs of interventions and adverse events. The preferred approach from a societal perspective, accounting for all costs and consequences that accrue to all members of society, was determined to be beyond the scope of this assessment.

The general structure for assessment of costs is provided in the accompanying figure as a hierarchical model. The stepwise hierarchy is not intended to suggest lower or higher priority costs; rather, the purpose is to define costs at the process or activity level. First is the baseline cost to implement a strategy *de novo* followed by a second level of costs to manage a strategy once implemented. Costs at the third level are wider ranging and assess the cost implications in terms of blood supply availability assuming the current number of units in the national supply will be maintained, i.e., 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.

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



Primary sources of cost and prevalence estimates, and preferred hierarchy, were obtained from: data from finance groups within blood centers where available; data from operations groups within blood centers to define the frequency of some events and proportions of donors and donations affected; estimated costs (to scale) from interventions that could be implemented such as ferritin testing; literature reviews for adverse event costs; and expert opinion and assumptions.

Each of the interventions was assessed for:

1. Cost of implementation (personnel, pills, equipment, logistics, IT system changes, education, insurance, liability).
2. Cost to manage the intervention (personnel, donor consultation, program effectiveness assessment).
3. Cost to maintain the blood supply at current level (percent of supply lost, donor replacement costs).

Following a literature review of available publications, it was decided not to include adverse events costs in the analysis because frequencies and associated costs of these events are not well understood in donor populations. However, adverse events are not expected to be cost drivers at this level of analysis.

Note: Assumptions and estimates of costs and number of donors or donations used in the economic assessment can be found in the Health Economics Budget Impact Analysis in the Supplemental Material.

Estimation and Analysis

The budget impact analysis focuses on a short-term horizon, providing gross overall estimates of each intervention's cost for the first year of implementation. To assess how costs of interventions might accrue to an individual organization and to the overall supply, two scenarios were developed. One estimated the

cost of each risk management option for a blood center collecting 2 million units per year and the other was scaled to the 11 million units in the overall national supply. The base case results for the two scenarios are provided in the table below.

Base Case Results for Two Scenarios

2,000,000 Units Collected	**16- to 18-Year Olds**	**19- to 49-Year-Old Females**	**Both Groups**	**Frequent Donor Program**
Base Case Results				
Active iron supplementation (18 mg)	$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	Not assessed
Donation intervals	$7,488,400	$17,269,350	$24,757,750	Not assessed
11,000,000 Units Collected	**16- to 18-Year Olds**	**19- to 49-Year-Old Females**	**Both Groups**	**Frequent Donor Program**
Base Case Results				
Active iron supplementation (18 mg)	$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	Not assessed
Donation intervals	$41,162,800	$94,981,425	$136,144,225	Not assessed

Ferritin testing and interdonation intervals interventions were not evaluated with respect to budget impact for all frequent donors (defined as female donors with 2 or more donations and male donors with 3 more donations per year) because of insufficient information. It was straightforward to estimate the number of donors who fall into those categories, thus permitting an estimate of iron supplementation program costs. However, it is not straightforward to model the expected consequences with ferritin testing or interval adjustment given the structure of the budget impact model. This is particularly important because separate submodels for 16- to 18-, 19- to 49-, and ≥50-year-old females, and 16- to 18- and ≥19-year-old males would have to be developed, and such submodels were considered beyond the scope of the current analysis.

For all interventions, donor replacement is the primary cost driver. Some donors may no longer be eligible to donate, and it must also be assumed that even with counseling or provision of supplements, some donors will not adhere to the recommended action, will be deferred and will need to be replaced. Based on personal communication with blood center recruiters for the baseline analysis, the Health Economics subgroup assumed the unit cost of replacing lost supply increases according to the percentage of the supply lost. It is estimated that if less than 2% of the blood supply is lost, the average cost to replace those donors is $55.00 per new donor. The cost continues to escalate incrementally to the point where a loss of supply greater than 15% would cost $135.00 per new donor. Sensitivity analysis was conducted assuming a flat donor recruitment replacement cost of $45.00, with the following results.

Sensitivity Analysis, Donor Recruitement Replacement Cost $45				
2,000,000 Units Collected	**16- to 18-Year Olds**	**19- to 49-Year-Old Females**	**Both Groups**	**Frequent Donors Program**
Active iron supplementation (18 mg)	$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	Not assessed
Donation intervals	$5,125,200	$9,431,100	$14,556,300	Not assessed
11,000,000 Units Collected	**16- to 18-Year Olds**	**19- to 49-Year-Old Females**	**Both Groups**	**Frequent Donor Program**
Active iron supplementation (18 mg)	$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	Not assessed
Donation intervals	$28,165,200	$51,871,050	$80,036,250	Not assessed

Additional sensitivity analyses were conducted assuming a higher cost per ferritin test of $8.00 per donation and a lower cost for iron supplementation cost of $3.00 per donor. The higher cost for ferritin testing is intended to reflect expected costs if a blood center must contract with an outside commercial laboratory for ferritin testing. The lower cost of iron supplementation is included to show how a supplementation program could become more affordable if supplementation costs were reduced, such as might be achieved under a voucher program.

Sensitivity Analysis, Ferritin Testing Cost $8.00 per Donation				
2,000,000 Units Collected	**16- to 18-Year Olds**	**19- to 49-Year-Old Females**	**Both Groups**	**Frequent Donor Program**
Active iron supplementation (18 mg)	$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	Not assessed
Donation intervals	$7,488,400	$17,269,350	$24,757,750	Not assessed
11,000,000 Units Collected	**16- to 18-Year Olds**	**19- to 49-Year Old Females**	**Both Groups**	**Frequent Donor Programs**
Active iron supplementation (18 mg)	$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	$214,881,975
Donation intervals	$41,162,800	$94,981,425	$136,144,225	Not assessed

Sensitivity Analysis, Active iron supplementation cost $3.00				
2,000,000 Units Collected	**16- to 18-Year Olds**	**19- to 49-Year-Old Females**	**Both Groups**	**Frequent Donor Program**
Active iron supplementation (18 mg)	$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	Not assessed
Donation intervals	$7,488,400	$17,269,350	$24,757,750	Not assessed
11,000,000 Units Collected	**16- to 18-Year Olds**	**19- to 49-Year-Old Females**	**Both Groups**	**Frequent Donor Program**
Active iron supplementation (18 mg)	$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	Not assessed
Donation intervals	$41,162,800	$94,981,425	$136,144,225	Not assessed

It is important to note that donor iron-deficiency mitigation costs in years following the implementation year are expected to decrease year-over-year until a new steady state is achieved because fewer donors with low body iron stores or risk of iron deficiency will be deferred after adoption of an intervention. Once the system absorbs the initial impact in terms of cost of the adopted intervention and replacing lost donors/donations, greater clarity on the number of donors who will be deferred for low hemoglobin in the future will become evident. This assessment did not model that scenario because of a lack of real data. However, it is recommended that a future effort to do so would yield valuable information. For example, an expected benefit is a reduction in the number of deferrals for low hemoglobin levels over time with the implementation of any of the risk management options beyond the status quo. However, no data are available to include this cost offset in the current analysis, and the costs and consequences that will then accrue are specific to the selected risk management option.

Several potential future costs or savings cannot be captured with available data. Most of these potential costs or savings are focused on different aspects of donor health and behavior following the implementation of a risk mitigation strategy. Chief among these are 1) donors who are no longer deferred for low hemoglobin levels and/or iron stores and 2) new donors who first donate after the risk management option has been implemented and may never progress to low body iron stores. The long-term benefit to donors, the availability of the supply and cost savings with reduced recruitment/ replacement are unknown with current information. In addition, reduction in the number of deferrals may be nonlinear year-over-year and may not be the same for all donor groups given biological differences in body iron status. The diversity of the blood center's donor base by age, sex, race/ethnicity, and repeat donor frequency, as well as observed adherence to the intervention in each of those groups, will influence realized savings or additional costs accrued when seeking to maintain the supply at the same level. Finally, longer-term trends in blood utilization and the required total supply of blood will influence costs. Because data are not available, modeling the cost implications would require development of "what if" scenarios. The 1-year analysis horizon coupled with insufficient data make it inadvisable to venture into these types of speculative analyses, which are prone to bias. These potential negative and positive impacts need further consideration, but are outside of the 1-year analysis horizon.

In the economic assessment, on average approximately 8% of the blood supply is estimated to be affected, but this percentage varies substantially based on the targeted groups for each intervention. This could suggest that a phased approach or an iterative implementation process is more appropriate to mitigate the risk of significant supply disruption and to reduce the overall cost of recruiting new donors.

It is also recommended that additional sensitivity analyses be conducted on important cost drivers to further understand the implications of each intervention and the costs that will have the largest budget impact.

Operational Risk Assessment

The operational risk assessment was conducted to better understand the operational impact of Options A through D. The Operational subgroup provided background details for the operational risks that could arise from implementation of Options A through D, and identified current controls that are already in place and available to manage the risks. The subgroup also assessed both the likelihood and impact of each risk occurring. Finally, the subgroup identified potential mitigations. A complete list of operational risks and a "heat map" can be found in the Supplemental Material.

Outside of status quo, all options had high financial and operational risks.

Option A – Iron supplementation carried some legal risk due to variability in state "practice of medicine" requirements as well as complex logistical issues.

Option B – Lengthen interdonation intervals and Option D – Limit donations from minor (16- and 17-year-old) donors to once per year had high risk in hospital customer satisfaction due to the potential decline in availability of blood products for patients.

Option C – Ferritin testing indicated a high risk for adverse donor experience due to potential dissatisfaction with deferral because of test results and complexity of messaging around test results. This option could also trigger potential practice of medicine requirements in some states because medical results are being provided to donors.

Because all options have a high financial impact**, from an operational perspective,** Option D – Limit donations from minor (16- and 17-year-old) donors to once a year was seen as the most straightforward option to implement. The Operational subgroup noted that this option has a significantly lower impact on overall blood supply availability than Option B. Although Options A and C would require significant and complex operational implementation activities, they could feasibly be implemented. Option A most directly addresses donation-induced iron depletion and, unlike Options B and D, more effectively replaces lost iron. Option C may motivate donors with demonstrated IDE/AIS to take iron or delay donation. However, for those states where iron supplementation or ferritin testing are considered the practice of medicine, legal advice would be required in the development of operational procedures for implementation.

Contextual Assessments

Legal Assessment

It is not possible to avoid legal risk completely when collecting blood or formulating options to improve donor and patient safety. Blood collection and transfusion medicine professionals attempting to balance the needs of donors, patients and their own tolerance for risk may find themselves in "Catch-22" situations. Assessing the legal risks to blood collectors of implementing any of the Ad Hoc Iron-

Deficiency Working Group's risk management options to mitigate donor iron depletion exemplifies this challenge.

From a legal standpoint, maintaining the "status quo" presents risks that donors suffering from conditions associated with low iron will take legal action against blood collectors. Affected donors could claim negligent failure to take action (other than providing education[*]) to mitigate the donor's iron depletion despite recent studies evidencing the risks of blood donation. To the extent studies show that certain donor groups may benefit from lengthened donation intervals (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.

One concern with providing iron supplements to donors is that doing so may be considered the practice of medicine as a matter of state law. For purposes of this assessment, California, Florida, Indiana, New York, and Texas state statutes were reviewed. These statutes generally 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). In states where this is considered the practice of medicine, to comply with medical board requirements, the provision of supplements and/or ferritin testing 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.

A factor that may influence how a court or regulatory body views iron replacement is how the issue is framed. If an iron supplementation program is offered as part of a donor wellness initiative, along the lines of adequate hydration, nutrition and rest, it 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. This RBDM analysis focused on maintaining or restoring iron levels to those at presentation (iron replacement vs. treatment).

Although not a certainty, providing vouchers to donors for iron supplements may carry less risk for blood collectors for several reasons: 1) it may be less likely to be considered the practice of medicine because blood collectors would not directly provide supplements (i.e., not prescribing supplements); 2) it is consistent with an iron replacement program, rather than a low-iron treatment program; 3) instructions for donors could be included to seek advice from their medical professional before obtaining and taking the supplement; and 4) disclaimers also could be included on the voucher.

Although the level of risk is likely low, 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 exacerbation of pre-existing iron overload. Blood centers providing iron supplements could be held liable for these negative outcomes. This risk may be mitigated by understanding that iron supplementation is provided to replace that which was removed by donation, leaving the donor at his/her predonation iron status. Another point of view is that blood centers' responsible physicians already counsel blood donors requiring medical care after blood donation; this is not a new concept (e.g., syncope, accidental arterial venipuncture). Indeed, AABB *Standards for Blood Banks and Transfusion*

[*] Currently Standard 5.2.1 Donor Education, in AABB *Standards for Blood Banks and Transfusion Services, 30th edition* requires: "The blood bank shall have procedures to ensure that the following requirements are met for all prospective donors: . . . 5) Donors are given educational materials regarding the risks of postdonation iron deficiency."

Services[i] requires all blood banks to have a medical director, in part because medical decisions are made on a daily basis regarding donors and the blood they donate.

As with iron replacement, ferritin testing may be considered the practice of medicine in some states, and it likely will depend on how the program is structured (e.g., whether all donors are tested or just those at high risk; who administers the program and advises donors; and the nature and extent of follow-up with low-ferritin level donors). 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 their advice, then it may be more difficult to argue that the blood collector was responsible for consequences related to low iron levels.

The table below sets out the legal risks relevant to the risk management options under consideration.

Potential Legal Risks to Blood Collectors							
	Status Quo	Option A: Iron Supplementation			Option B: Lengthen Inter-donation Intervals	Option C: Ferritin Testing	Option D: One Donation Annually from 16- and 17-Year-Old Donors
		Provide Pills to At-Risk Donors	Provide Pills to All Donors	Provide Vouchers			
Risk of claim of negligent failure to act	✓				✓		
Risk especially high for "at-risk" donors	✓						
New studies increase risk of viable negligence claim	✓	✓	✓				
Potential practice of medicine in some states		✓	✓	✓		✓	
Liability for adverse reactions to iron		✓	✓				
Liability for masking occult blood loss/GI malignancy		✓	✓				
Risk of parental complaints (e.g., lack of consent for adolescent donation)		✓	✓	✓			
Liability for lower adherence, especially youth				✓			
Large follow-up program for ferritin testing may increase risk of violating practice of medicine requirements						✓	
Improper testing/reporting/inaccurate test results; negligent donor counseling/staff training						✓	

Note: Strategies for mitigating the identified risks are enumerated in the Supplemental Material.

† 1.1.1 Medical Director Qualifications and Responsibilities
"The BB/TS shall have a medical director who is a licensed physician and qualified by education, training, and/or experience. The medical director shall have responsibility and authority for all medical and technical policies, processes, and procedures—including those that pertain to laboratory personnel and test performance—and for the consultative and support services that relate to the care and safety of donors and/or transfusion recipients. The medical director may delegate these responsibilities to another qualified physician; however, the medical director shall retain ultimate responsibility for medical director duties."[1]

Regulatory Assessment

The Food and Drug Administration (FDA) has wide-ranging jurisdiction with respect to the regulation of food, drugs, medical devices, vaccines, blood components and other products, but it does not directly license the individuals working in blood centers.

The FDA Centers for Biologics Evaluation and Research (CBER) provided the following response to the Working Group's questions:

1. 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 (i.e., 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. FDA would not take action against blood centers that routinely provide short-course, low-dose iron supplementation to blood donors over the age of 18 years to reduce the risk of nutritional iron deficiency through replacement of the approximate amount of iron lost in blood donation.
3. FDA remains concerned about the need to protect the health of teenage blood donors (16- to 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 (e.g., blood centers might limit donation to once per year unless normal iron status is documented).
4. FDA recognizes the effectiveness of programs that utilize ferritin measurement as reported in recent randomized controlled 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.

In conclusion, there is no mitigation approach to the donor iron deficiency issue that is free of all risks; 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 at least one risk management option, consistent with state law, that minimizes the potential harm to donors caused by donation-related iron depletion and work to have laws clarified or changed where appropriate.

Ethics Considerations

Relevant ethics 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 off from donating blood. Transient harm, such as pain from insertion of a needle, can be acceptable if there are countervailing reasons for donation (e.g., the needs of recipients) and 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 (e.g., 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 practice.

Background

Possible harms associated with collecting blood. Some teenagers and menstruating females have iron deficiency, which can be exacerbated by donating blood. Frequent blood donation can also cause iron deficiency (see Safety assessment). 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 randomized controlled studies in humans showing that iron supplementation of iron-deficient females improves cognitive function[21-22] and decreases fatigue.[23] Hence, evidence suggests but does not prove that blood donation could have deleterious effects including fatigue and decreased cognitive function. Although established iron-deficiency anemia has been associated with adverse outcomes in pregnancy, few data have been published addressing the impact of milder, nonanemic iron deficiency in otherwise healthy gravidae. A single retrospective study on blood donors who became pregnant found no association between frequency of blood donation and pregnancy outcome.[24]

Limited information on harm. The limited data on the risks of iron deficiency secondary to blood donation render analyses inexact and dependent 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, it is important to know whether there are deleterious effects on blood donors and, if so, to characterize the magnitude and reversibility of those effects. 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 among adolescents and other at-risk groups.

Donors with limited agency – adolescents (ages 16 and 17 years old). 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.[10] By accepting donors as young as 16 years, blood collectors may be increasing the prevalence of iron deficiency. The influence of iron lack on brain development is also a concern.[25,26]

- ***Adolescents do not have full agency.*** Cognitive and emotional immaturity can limit agency in regard to sound 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 a 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 those members of this group whose iron stores are already suboptimal. Given this, these regulations and practices should be modified to reduce the potential for harm to adolescents and data should be gathered regarding any untoward effects.

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 18-25) because of ongoing brain development that requires iron.
- Premenopausal females because menstruating females have lower average iron stores, females who become pregnant require iron for fetal and maternal health and 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 are not replete before the next donation.
- Donors near the Hb cutoff (13.0 -13.5 g/dL for males; 12.5-12.9 g/dL for females).

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 the groups noted above, 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.

Stakeholder Feedback and Social Concern

A broad cross-section of stakeholders was provided with an overview of the issue and reading material before the sessions. They were also presented with the risk management options under consideration. In general, stakeholders believed there must be a balance between a "theoretical risk" and a "sufficient blood supply." Although they thought the duty to address the issue at hand should be a collaborative effort among policy makers, donor centers and organizations respected by the scientific and medical community, they concluded it is each blood operator's duty to ensure blood donation is safe. Blood operators have a duty to minimize harm, protect donors and be clear about any known or potential risks.

The following is a summary of the common themes, suggestions and opinions obtained from the in-person and online stakeholder consultations. The detailed recording of the consultation sessions can be found in Supplemental Material.

Stakeholder feedback on status quo. The current donor educational efforts were seen as inadequate. It was felt that there is a need to raise awareness in the medical community of the effect of blood donation on donor iron. One stakeholder summed this up by saying, *"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."*

Stakeholder feedback on Option A – Iron supplementation. Many stakeholders believed that replacing only the amount of iron lost in a blood donation is a practical approach, but concern was expressed about individuals who should not take iron. Consultation with a health-care professional was deemed desirable, but it was felt to be mandatory to determine the cause of ID before definitive treatment. However, they did not think donors should have to pay for iron pills to replace the iron lost through blood donation. Medical/technical stakeholders were concerned that if the donor center provided iron supplements it could be considered the practice of medicine in certain states. Several suggested a testing-based approach should be taken to recommend supplements by measuring donor ferritin values.

There was special concern for young donors and it was suggested that parents and/or guardians should be made aware of any plan to provide iron supplements and that parents and/or guardians should provide written consent.

There was also consensus that if informed, healthy donors refuse to take supplements, but are otherwise willing and eligible to donate, the blood center should permit the donation. It was agreed more research needs to be done to understand the impact.

Stakeholder feedback on Option B – Lengthen interdonation intervals. Although stakeholders understood the benefit of lengthening donation intervals due to concern for young donors and premenopausal females, they also expressed concern about the negative effect this would have on the blood supply. They suggested that supplementation or ferritin testing and subsequent action based on the test results would generate more benefit to donors and to the blood supply.

Stakeholder feedback on Option C – Ferritin testing. Stakeholders supported ferritin testing and feedback for donors. They saw it as the most scientifically sound approach for guidance. There was disagreement as to appropriate cutoffs for low ferritin levels (the Centers for Disease Control and Prevention use a cutoff for children of less than 12 ng/mL and a cutoff for adults of less than 15 ng/mL). As with supplementation, there was general agreement that a discussion should be encouraged between

donors and their health-care providers, but it was concluded that ferritin testing should be the responsibility of the blood center.

Stakeholder feedback on Option D – Limit donations from minor (16- and 17-year-old) donors to once a year. Stakeholders supported the intention to protect young donors but were also concerned about the impact of an increased donation interval on the blood supply. They preferred iron supplementation or ferritin testing and subsequent action based on the test results. There were also many quite thoughtful ideas about awareness messaging and donor education, which can be found in the stakeholder consultation report in Supplemental Material

6. Managing the Risk: Risk Management Options Evaluation [RBDM Stage 5]

Informed by all the completed risk assessments, the risk management options were evaluated for strengths and weaknesses, risk tolerability, and the level of residual risk across the dimensions of safety/efficacy, financial/operational adequacy, legal/regulatory concerns and social concerns such as ethics, trust and societal tolerability. The assessment of risk tolerability[iii] considered stakeholder input, the contextual assessments and implementation factors.

Status Quo

The status quo involves donor education (BB/TS Standard 5.2.1, #5) on iron depletion and Hb testing to prevent frankly anemic donation. Educational materials recommending that donors should take iron are not necessarily read or followed, according to a study by Spencer[27] demonstrating that approximately 20% of a representative blood center population reported use of iron supplementation. The status quo is considered intolerable given existing and new data from large studies such as RISE,[3] HEIRS,[19] STRIDE,[20] CHILL[11-13] and others investigating donor iron depletion. The data raise particular concern for young donors, premenopausal females, frequent donors and donors near the Hb cutoff. Blood donation can cause or contribute to ID (and anemia) because some donors have ID the first time they present to donate. Even though there are gaps in data about the risk of harm to blood donors, the consensus was that the status quo is not a viable option.

The ethical principles of nonmaleficence and beneficence demand action given the information now available about potential harm to donors. The principle of transparency requires blood operators to raise awareness assertively with donors and other stakeholders about this issue and to ensure that it is incorporated into recruitment and consent processes for donation. Finally, given knowledge gaps about the clinical consequences of iron deficiency and clear concerns about potential harms, it is appropriate to follow the precautionary principle.

Option A – Iron Supplementation (Preferred)

Option A is one of two preferred options. Risks associated with this option are considered tolerable if this option is strongly managed. As it is apparent that not all blood donors are at risk of iron deficiency from blood donation, it is recommended that iron supplementation, via pills or vouchers, is provided first to targeted subgroups in the priority order noted in the Safety subgroup section, and then expanded more broadly.

Iron supplementation will significantly shorten prolonged periods of postdonation iron deficiency and prevent progressive iron loss in donors. Iron repletion occurs within 8 weeks with the largest effect in the first 4 weeks, so it will allow a 56-day interval for whole blood donation, thereby preserving the adequacy

of the blood supply. It is estimated that supplementation will decrease donor deferrals for low Hb by 25-50%, and possibly increase the number of Red Blood Cell units collected. It is assumed to be close to 100% effective if donors are compliant with taking the iron; however, not all donors will do so. It is estimated [ii]that adherence will be in the 50-75% range with provision of iron pills. Iron voucher provision may be expected to result in somewhat lower adherence due to the additional effort involved in voucher redemption. In general, side effects are indistinguishable between placebo and daily low-dose supplementation (18-38 mg).

Ethically, the principle of justice calls for fair treatment of all blood donors; it may be unfair to expect blood donors to pay for iron supplementation themselves because the donation process can contribute to iron deficiency in some donors. This sentiment was echoed by the stakeholders, who also believed that donors should not have to pay for iron supplements. This option does satisfy the ethical principles of nonmaleficence, beneficence and precaution. The principle of transparency requires ensuring awareness and education of all donors and, in the case of minor donors, their parents and guardians. In addition, as stakeholder feedback emphasized, the medical community also needs to be made aware of this issue.

Blood collectors will need to assess with counsel whether the provision of iron is considered the practice of medicine, or corporate practice of medicine, in their state(s). Although additional costs for supplements/vouchers and program oversight could be considerable, particularly for large, multi-state blood operators, some of the cost would be offset by reduced need to recruit replacement donors. The working group also believes it would be appropriate to solicit support from the Centers for Medicare and Medicaid Services/Department of Health and Human Services (CMS/HHS) to help the blood sector promote blood donation and to defray costs related to this and other risk management options.

Option B – Lengthen Interdonation Intervals for Targeted Subgroups

Option B is an acceptable option only if the associated risks are strongly managed. However, this option has the greatest potential negative impact on blood supply adequacy and increases the risk of blood shortages. Rebuilding iron stores in donors will take at least 6 months after a blood donation without iron replacement. As noted by the Safety subgroup, the HEIRS[19] study showed that 67% of donors had not increased their iron stores at 24 weeks and the CHILL[11-13] study indicated that some donors may need to wait 12 months. These results point to a sharp increase in donor deferrals and an accompanying decrease in the donor base should the interval be set at a length within which most donors would recover iron stores, with significant effort and cost to replace donors.

[ii] Risk tolerability is a judgment that a risk is reasonable given the expected benefits of an activity and required resources to manage the risk. Some risks are low enough that they require no management and are considered acceptable risks. By contrast, a risk is considered tolerable if it is justified by the benefits gained, managed at a level proportional to the rosks and benefits, fairly distributed to the extent possible and, undertaken with full knowledge. Factors that can make a risk less tolerable include activities without evident benefits, risk imposed without adequate consultations or consent, risks expected to be managed by an institution, risks resulting from incompetence or negligence, risks that apply to vulnerable individuals or groups and unequal distribution of risks and benefits in society. Additional information about risk tolerability can be found in Appendix I.

This option meets the identified ethical principles for blood donors, but there is the potential to harm patients if sufficient blood components are not available when needed. This raises the risk of increased social concern and potential loss of trust in the blood sector.

It is anticipated that implementing this option would incur considerable cost. Given the risk of blood shortages if replacement donors cannot be recruited quickly enough, it is recommended that CMS/HHS be called upon to promote blood donation and support the blood sector in defraying costs related to this risk management option.

Option C – Ferritin Testing (Preferred)

Option C is the second preferred option. It is not a stand-alone option but rather a data-driven approach by which blood operators may target iron-deficient donors for follow-up actions such as iron supplementation or lengthening the interdonation interval. Ferritin testing informs and empowers donors and enables donors to decide how they will schedule future donations. Ferritin values reflect the individual's iron stores, but do not guarantee that an informed donor will choose to take iron or even delay subsequent donation. Informed donors may even choose to stop donating altogether. This option supports the ethical principle of agency as it provides young donors with information that may deflect peer pressure to donate when it is not appropriate to do so.

This option also reassures those with ferritin values >50 ng/mL that they will not become iron deficient as a result of that donation. In addition, testing may identify pre-existing sources of blood loss or malabsorption. Providing test results to those with low values may significantly shorten periods of postdonation iron deficiency and prevent progressive iron loss if donors take iron. It may also prevent worsening depletion if donors choose to delay future donations.

This option meets the identified ethical principles for blood donors as long as accompanying action to mitigate iron deficiency is taken, i.e., iron supplementation or lengthened interdonation intervals. On the other hand, this option may raise practice of medicine concerns in some states.

Although the cost estimates of implementing ferritin testing are lower than the other options, it must be kept in mind that this is the only tool to help determine future action that will result in additional cost. Nevertheless, this risk is considered tolerable if well-managed.

Option D – Limit Donations from Minor (16- and 17-Year-Old) Donors to Once a Year

Option D is acceptable to reduce the risk for one donor group; however, it is inadequate on its own because it addresses risk only to minors. As noted by the Safety subgroup, there are several additional donor groups at risk for iron deficiency. Thus, the ethical principles of justice, nonmaleficence and beneficence for all are not addressed by this option and it does not address stakeholder concerns about premenopausal females, frequent donors and donors near the Hb cutoff level. As part of a phased approach to a donor iron risk management program, it would be reasonable to begin with the group considered to be at higher risk; however, it would be necessary to determine reasonable timelines within which the other groups would be included.

This option also carries risks outlined in Option B – Lengthen interdonation intervals of potential supply shortages and significant donor replacement costs. The Safety subgroup estimated that restricting donations to once a year from this group would cause a loss of 40% of donations from 16- and 17-year-olds, which translates to a loss of 4-5% of all blood donations nationally. Therefore, blood operators may consider modifying the deferral period in the event donors can be qualified to shorten the interval, e.g.,

through ferritin testing and/or provision of supplements. Parental awareness and consent would be an important component of such an approach.

For the reasons outlined above, Option A – Iron supplementation and Option C – Ferritin testing were ranked equally as the best options. Option D – Limit donations from minor (16- and 17-year-old) donors to once a year was ranked next because of the urgency to address risk to the most vulnerable donors, but the impact on adequacy of the blood supply was a concern. Option B – Lengthen interdonation intervals, while a tolerable option, carries significant risks to blood component availability and was seen as a less-desirable option. Status Quo was rejected because it is considered to have intolerable risk status.

Risk Scale Low-1; Medium-2; High-3	**Risk Management Option**				
Risks	**Status Quo**	**Option A**	**Option B**	**Option C**	**Option D**
Safety/Efficacy		1	2	1.5	2.5
Financial/Operational (adequacy)		2	3	2	1.5
Social/Contextual (ethics, trust, stakeholder tolerability)		2	2	1.5	2
Total		**5**	**7**	**5**	**6**
Risk tolerability (tolerable, tolerable if managed, intolerable)	**INTOLERABLE**	**TOLERABLE IF MANAGED**	**TOLERABLE IF MANAGED**	**TOLERABLE IF MANAGED**	**TOLERABLE IF MANAGED**
Rank	**Eliminated due to intolerable risk status**	**1**	**3**	**1**	**2**

7. Conclusion: Recommendations [RBDM Stage 6]

The aim of these recommendations is to prevent iron depletion caused by blood donation and minimize postdonation anemia, while maintaining the adequacy of the blood supply. It is recognized that mitigation of donor iron deficiency is a precautionary intervention. Although there is suggestive evidence of adverse effects on quality of life from iron deficiency, there is not unequivocal evidence of a more serious clinical impact of donor iron depletion. However, based on the findings of the RBDM assessment, it is the determination of the Ad Hoc Iron-Deficiency Working Group that the status quo of donor education and Hb testing is no longer an adequate risk management option given recently accrued data.

It is recognized that decisions must reflect the balance of donor safety and adequacy of the blood supply; with any option, a level of iron depletion consistent with that in the nondonor population will still exist, and some donor loss will occur. The magnitude of donor loss is difficult to estimate, but will be offset somewhat by an expected reduction in Hb deferrals in donors who take iron supplements.

It is also recognized that there can be different interpretations of state laws regarding practice of medicine, and blood centers will need to design individual programs that avoid physician or corporate state practice of medicine conflicts. Consequently, there is no single optimal risk management option for

all facilities, donor groups or individual donors. All of the options that follow should be considered within the context of each blood center's state law and legal requirements.

It is recommended that:

1. The preferred risk management options are either iron supplementation or ferritin testing to inform appropriate follow-up action.
2. Iron supplementation and ferritin testing with follow-up actions may trigger state-specific physician or corporate "practice of medicine" rules. Blood centers should make reasonable attempts to design iron supplementation or ferritin testing programs in such a way that avoids physician or corporate state practice of medicine conflicts.
3. Increased interdonation intervals may be selected under some circumstances but it should be noted that they have the greatest potential impact on blood supply adequacy. Under any circumstances, extensions to 12- or 16-week deferrals are not adequate as stand-alone steps. Repletion of lost iron in the absence of oral iron replacement is incomplete for at least 6 months and, for the preponderance of donors, even longer.
4. Limiting donations from minor (16- and 17-year-old) donors to once a year represents an acceptable first step for lengthening the interdonation interval for blood collectors unable to implement iron replacement or ferritin testing. This is not in and of itself a final, stand-alone iron depletion risk management option.
5. Blood collectors should require parental consent for all minors due to concern for potential risk associated with blood donation that could result in iron depletion of undetermined long-term clinical significance.
6. Implementation of any of the above options including iron supplementation, ferritin testing with follow-up action and/or increased interdonation intervals should recognize the need to prioritize attention to the following identified at-risk groups in the priority order below:
    a. 16- and 17-year-old donors.
    b. 18-year-old donors.
    c. Young donors 19 to 25 years of age.
    d. Premenopausal females (i.e., females who are of childbearing potential) who are potential donors.
    e. Frequent donors.
    f. Donors near the Hb cutoff level.
7. Application of the risk management options should be viewed as progressive steps that are expected to be extended over time to all prioritized risk groups as experience with the strategies and data regarding the significance of donor iron depletion accumulate.
8. The blood community should engage CMS/HHS regarding:
    a. Defraying the costs related to the risk management interventions and, most importantly, to donor loss and replacement as a result of these interventions.
    b. Assistance, to the extent possible, to minimize the extent to which provision of low-dose replacement iron and appropriate response to ferritin levels may be considered the "practice of medicine" by state medical boards or the "corporate practice of medicine" according to state law.
    c. Ongoing public support for the continued importance of blood donation and the need for donors, despite the risk of iron depletion.
9. All blood centers should collect adequate data to understand the impact of the recommendations set forth by this group.

a. Donor/donation losses by ABO type.
b. Costs.
c. Impact on ferritin levels in donors from supplementation or lengthened interdonation intervals should be compared to the nondonor/general population.

Doing the Right Thing ultimately involves facilitating access to replacement iron for all donors who can safely take iron.

REFERENCES

1. Ooley P, ed. Standards for blood banks and transfusion services, 30th edition. Bethesda, MD: AABB, 2016.
2. AABB. Updated strategies to limit or prevent iron deficiency in blood donors. AABB Association Bulletin #17-02. Bethesda, MD: AABB, 2017.
3. Cable RG, Glynn SA, Kiss JE, et al, for the NREDS, II. Iron deficiency in blood donors: The REDS-II Donor Iron Status Evaluation (RISE) study. Transfusion 2012;52:702-11. [Available at: http://dx.doi.org/10.1111/j.1537-2995.2011.03401.x.]
4. Kiss JE, Steele WR, Wright DJ, et al for the NHLBI Retrovirus Epidemiology Donor Study I. Laboratory variables for assessing iron deficiency in REDS-II Iron Status Evaluation (RISE) blood donors. Transfusion 2013;53:2766-75. [Available at: http://dx.doi.org/10.1111/trf.12209.]
5. Punnonen K, Rajamaki A. Evaluation of iron status of Finnish blood donors using serum transferrin receptor. Transfus Med 1999;9:131-4.
6. Punnonen K, Irjala K, Rajamaki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. Blood 1997;89:1052-7.
7. Radtke H, Meyer T, Kalus U, Rocker L, Salama A, Kiesewetter H, Latza R. Rapid identification of iron deficiency in blood donors with red cell indexes provided by Advia 120. Transfusion 2005;45:5-10.
8. Ali MA, Luxton AW, Walker WH. Serum ferritin concentration and bone marrow iron stores: A prospective study. Can Med Assoc J 1978;118:945-6.
9. Beutler E, Waalen J. The definition of anemia: What is the lower limit of normal of the blood hemoglobin concentration? *Blood* 2006; 107: 1747-50.
10. Spencer B. Comparison of the history of donation and iron levels in teen blood donors — CHILL. Presented at the 114th Meeting of the FDA Blood Products Advisory Committee. Silver Spring, MD, November 17, 2016.
11. Goldman M, Uzicanin S, Scalia V, O'Brien SF. Iron deficiency in Canadian blood donors. Transfusion 2014;54:775-9. [Available at: http://dx.doi.org/10.1111/trf.12380.]
12. Goldman M. Iron depletion and routine ferritin measurement in blood donors. ISBT Science Series 2015;10:124-8. [Available at: http://dx.doi.org/10.1111/voxs.12117.]
13. Goldman M, Uzicanin S, Osmond L, et al. A large national study of ferritin testing in Canadian blood donors. Transfusion 2017;57:564-70. [Available at: http://dx.doi.org/10.1111/trf.13956.]
14. Custer B, Bravo M, Tomasulo P, et al. Factors associated with absent iron stores (AIS) in male and female donors tested for ferritin (abstract). Transfusion 2013;53(Suppl):34A. [Available at: http://dx.doi.org/10.1111/trf.12401.]
15. Bravo M, Custer B, Tomasulo P, Kamel H. Age and gender relationships observed in routine ferritin testing (abstract). Transfusion 2014;54(Suppl): 116-7A. [Available at: http://dx.doi.org/10.1111/trf.12845.]
16. Sapiano MRP, Savinkina AA, Ellingson KD, et al. Supplemental findings from the National Blood Collection and Utilization Surveys, 2013 and 2015. Transfusion 2017;57:1599-624. [Available at: http://dx.doi.org/10.1111/trf.14168.]
17. Custer B, Schlumpf KS, Wright D, et al. Donor return after temporary deferral. Transfusion 2011;51:1188-96.
18. Martin J, Hamilton B, Osterman M, et al. Births: Final data for 2015. *National vital statistics report*; 66: Hyattsville, MD: National Center for Health Statistics. 2017. [Available at: https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_01.pdf.]
19. Kiss JE, Brambilla D, Glynn SA, et al. Oral iron supplementation after blood donation: A randomized clinical trial. JAMA 2015;313:575-83.

20. Mast AE, Bialkowski W, Bryant BJ, et al. A randomized, blinded, placebo-controlled trial of education and iron supplementation for mitigation of iron deficiency in regular blood donors. Transfusion 2016;56:1588-97.
21. Bruner AB, Joffe A, Duggan AK, et al. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. Lancet 1996;348:992-6. [Available at: http://www.ncbi.nlm.nih.gov/pubmed/8855856.]
22. Murray-Kolb LE, Beard JL. Iron treatment normalizes cognitive functioning in young women. Am J Clin Nutr 2007;85:778-87. [Avaiable at: http://www.ncbi.nlm.nih.gov/pubmed/17344500.]
23. Krayenbuehl PA, Battegay E, Breymann C, et al. Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration. Blood 2011;118:3222-7. [Available at: http://www.ncbi.nlm.nih.gov/pubmed/21705493.]
24. Germain M, Delage G, Robillard P, et al. The association between frequency of blood donation and the occurrence of low birthweight, preterm delivery, and stillbirth: A retrospective cohort study. Transfusion 2016;56:2760-7.
25. Pratt JJ, Khan KS. Non-anaemic iron deficiency - a disease looking for recognition of diagnosis: A systematic review. Eur J Haematol 2016;96:618-28. [Available at: http://www.ncbi.nlm.nih.gov/pubmed/26256281.]
26. Sowell ER, Thompson PM, Holmes CJ, et al. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nat Neurosci 1999;2:859-61. [Available at: http://www.ncbi.nlm.nih.gov/pubmed/10491602.]
27. Spencer B, Cable R, Papallo C, et al. Male plateletpheresis donors are an unrecognized group with risk for iron depletion (abstract). Transfusion 2016;56(Suppl):4A. [Available at: http://dx.doi.org/10.1111/trf.13807.]

ADDITIONAL REFERENCES

1. AABB. Strategies to monitor, limit, or prevent iron deficiency in blood donors. AABB Association Bulletin #12-03. Bethesda, MD: AABB, 2012.
2. Zuck TF, Thomson RA, Schreiber GB, et al for the REDS group. The Retrovirus Epidemiology Donor Study (REDS): Rationale and methods. Transfusion 1995;35:944-51. [Available at: http://dx.doi.org/10.1046/j.1537-2995.1995.351196110900.x.]

Ad Hoc Donor Iron-Deficiency Working Group

The group assembled for this RBDM analysis included various types of relevant subject-matter expertise.

Member	Title
Ralph R. Vassallo, MD (Chair)	Executive VP / Chief Medical and Scientific Officer, Blood Systems, Inc.
James J. Berger, MS, MT(ASCP)SBB	Senior Advisor for Blood and Tissue Policy, Blood Safety and Availability, HHS
Christopher Bocquet	Director, Standards Development, AABB
Brian Boyle	Donor-advocate representative
Brian Custer, PhD, MPH	Director, Epidemiology and Health Policy Science, VP Research and Scientific Programs, Blood Systems Research Institute
Dana V. Devine, PhD	Chief Medical and Scientific Officer, Canadian Blood Services
Anne F. Eder, MD, PhD	Associate Deputy Director for Medical Issues and Policy Development, CBER, FDA
Dale Hammerschmidt, MD	Professor Emeritus of Medicine (Hematology), University of Minnesota
Louis M. Katz, MD	Chief Medical Officer, Acting CEO, America's Blood Centers
Diane Killion, JD	General Counsel, AABB
Steven Kleinman, MD	Clinical Professor of Pathology, University of British Columbia
Sarah Madden, MA	Patient-advocate representative
E. Mary O'Neill, MD	Interim Chief Medical Officer, American Red Cross
Jacquelyn M. Powers, MD, MS	Assistant Professor of Pediatrics, Section of Hematology/ Oncology, Baylor College of Medicine
Rita Reik, MD, FCAP	Chief Medical Officer, OneBlood
Merlyn H. Sayers, MBBCh, PhD	President and CEO, Carter BloodCare
Bryan Spencer, PhD	Research Scientist, American Red Cross
Steven R. Sloan, MD, PhD	Medical Director, Boston Children's Hospital
Jeremy Sugarman, MD, MPH, MA	Harvey M. Meyeroff Professor of Bioethics & Medicine, Berman Institute of Bioethics and Department of Medicine, Johns Hopkins University
Darrell J. Triulzi, MD	University of Pittsburgh and Institute for Transfusion Medicine
Sheila Ward, BA	Associate Director, International Collaboration, Canadian Blood Services
Jessica Yozwiak, MS	Specialist, Cellular Therapy, Regulatory and Public Policy, AABB

APPENDIX I


Risk Tolerability Evaluation Tree
Estimated Risk Level
Risk Tolerability Guidelines
Intolerable Risk
· high health risk
· uncertainty
· emerging risk
· high social concern
Risk unlikely to be tolerable
· tolerable for high-need patients with clinical protocols
· consult emergency plan for adjustment to standard procedures
Tolerable Risk
· above acceptable threshold
· justified by benefits received
· managed to be as low as possible with existing economical methods
· no available means of further reduction
· base risk at high end of tolerable range
· uncertainty
· potential for higher risk
· no clear benefits to justify risk
Risk tolerable only in exceptional circumstances
· blood supply emergency
· tolerable with actions
· stakeholder consultation
· intensive risk reduction
· risk created by organisation
· risk socially intolerable
· risk management incomplete
· high profile/legacy issue
Tolerable range
· greater tolerability with adequate communication
· greater tolerability with managed measurements
· existing risk justified by supply or demand emergency
Acceptable Risk
· low enough to be of minimal concern
· justified by benefits received
· does not warrant costs of further reduction
· socially sensitive issue
· vulnerable risk bearers
· means available to reduce risk
· adverse impact on donors
Risk Tolerable if Qualified
· risk reduction measures in place
· compliance with regulations
· added voluntary risk reduction actions
· consultation with affected groups
· no serious concerns
Acceptable Risk
· No further reduction necessary
· document decision