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The strategies to reduce iron deficiency in blood donors randomized trial: design, enrolment and early retention

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Abstract

Background and Objectives—Repeated blood donation produces iron deficiency. Changes in dietary iron intake do not prevent donation-induced iron deficiency. Prolonging the interdonation interval or using oral iron supplements can mitigate donation-induced iron deficiency. The most effective operational methods for reducing iron deficiency in donors are unknown.

Materials and Methods—‘Strategies To Reduce Iron Deficiency’ (STRIDE) was a two-year, randomized, placebo-controlled study in blood donors. 692 donors were randomized into one of two educational groups or one of three interventional groups. Donors randomized to educational groups either received letters thanking them for donating, or, suggesting iron supplements or delayed donation if they had low ferritin. Donors randomized to interventional groups either received placebo, 19-mg or 38-mg iron pills.

Results—Iron deficient erythropoiesis was present in 52.7% of males and 74.6% of females at enrolment. Adverse events within 60 days of enrolment were primarily mild gastrointestinal symptoms (64%). The incidence of de-enrolment within 60 days was more common in the interventional groups than in the educational groups ($P = 0.002$), but not more common in those receiving iron than placebo ($P = 0.68$).

Conclusion—The prevalence of iron deficient erythropoiesis in donors enrolled in the STRIDE study is comparable to previously described cohorts of regular blood donors. De-enrolment within

60 days was higher for donors receiving tablets, although no more common in donors receiving iron than placebo.

Keywords

anaemia; blood donation; ferritin; iron deficiency

Introduction

Blood donors are a special community resource and fill a vital role in the medical care delivery system. In the United States, they are allowed to donate 500 ml of whole blood every 56 days. The erythrocytes removed from the donor in each unit contain approximately 230 mg of iron, and, consequently, whole blood donation frequently produces iron deficiency [1, 2]. The prevalence of iron deficiency in frequent whole blood donors was recently assessed in the REDS-II Iron Status Evaluation (RISE) study, which enrolled 1537 frequent donors, finding that nearly one-half of male donors donating at least three times in the previous 12 months and over two-thirds of female donors donating at least two times in the past 12 months had iron deficient erythropoiesis (IDE) [3]. As erythrocytes also are removed during apheresis, frequent platelet apheresis donors also can become iron deficient [4].

The high prevalence of iron deficiency in blood donors is neither evaluated nor prevented by the donor screening process. In the United States, both male and female donors are required to have a predonation fingerstick haemoglobin equal to or above 12.5 g/dl. This eligibility criterion prevents donation by those with significant anaemia, but does not prevent donation by those with iron deficiency in the absence of anaemia. The recognition and prevention of iron deficiency in donors are important, because even in the absence of significant anaemia, it is associated with fatigue, [5, 6] decreased exercise capacity, [7] pica, [8, 9] and restless legs syndrome [8, 9]. In addition, studies performed in young women have shown that iron deficiency is associated with decreased cognitive performance over a broad range of cognitive tasks, [10] and longitudinal studies of teenagers have shown that iron status during adolescence is associated with micro- and macro-neuroanatomical variations in early adulthood [11]. Thus, blood donation-induced iron deficiency is of particular concern for high school-aged blood donors who are providing an increasing proportion of the United States blood supply.

In response to the recent data about the prevalence of iron deficiency in blood donors, AABB issued a Bulletin #12-03 on 21 September 2012 recommending that blood collecting organizations educate donors about the risks of postdonation iron deficiency, and further, to take actions that monitor, limit, or prevent iron deficiency in blood donors [www.aabb.org/programs/publications/bulletins/Pages/ab12-03.aspx]. Potential actions include instructing donors to take oral iron supplements, providing donors with iron supplements, or prolonging the interdonation interval beyond 56 days. Also of interest is a recent study by O'Meara and colleagues, who found that simply providing donors with information about their iron status obtained by measurement of plasma ferritin, and then allowing the donor to decide to use

iron supplements, prolong their donation interval, and/or alter their diet effectively reduced the prevalence of anaemia and iron deficiency in blood donors [12].

It is in this context that the Strategies To Reduce Iron Deficiency (STRIDE) study of blood donors has been conducted. STRIDE is a double-blinded, placebo-controlled, multicentre, two-year longitudinal randomized trial designed to evaluate two alternate programmes to replace iron lost during blood donation and effectively prevent the development of iron deficiency in frequent blood donors or improve the iron status of already iron deficient donors. A key component of the study design is using conditions as close as possible to normal operations at three geographically and operationally diverse blood centres with the goal that the results will be widely applicable to community blood centres. The two specific aims of the study are (1) to determine whether regular blood donors provided with accurate information about their iron status and written recommended courses of action will take steps to mitigate the iron lost from donation on their own; and (2) to determine if providing iron supplements (without providing information about iron status) to donors following each donation will effectively replace iron lost during donation. Here, we report the results of the baseline demographics and laboratory measures of 692 randomized donors along with analyses of the 62 donors who de-enrolled from the study within 60 days following their randomization.

Materials and methods

Participating blood centres, recruitment, and enrolment

Recruitment for STRIDE occurred between June 2011 and April 2012 at three blood centres: BloodCenter of Wisconsin in Milwaukee, WI, USA, The Institute for Transfusion Medicine in Pittsburgh, PA and American Red Cross Blood Services New England Region in Dedham, MA, USA for a two-year longitudinal study that closed in May 2014. Study management and data co-ordination were conducted by Westat Inc., Rockville, MD, USA. Eligible subjects were identified using local blood centre donation registries based on number of donations in the previous 12-month period. Recruitment letters mailed to home addresses were used to solicit interest among eligible donors. Supplementary recruitment methods included use of posters, emails and in-person recruitment at blood drives that were tailored for each blood centre based on local requirements. This study was approved by institutional review boards at all participating institutions and at the data co-ordinating centre.

Study participants

Frequent blood donors 18 years of age and older were enrolled after providing informed consent. Frequent male donors were defined as having three or more whole blood donations in the previous 12-month period. Frequent female donors were defined as having two or more whole blood donations in the previous 12-month period. Apheresis double red cell collections were treated as two standard whole blood donations because the iron lost is equivalent. Donors were advised about the potential for iron supplements to mask anaemia developing secondary to gastrointestinal blood loss, including colon cancer at the time of informed consent.

Enrolled donors were asked to make a minimum of two (female) or three (male) red cell donations per year during the study. Subjects having taken an oral iron supplement, or a multiple vitamin containing iron, within 30 days prior to enrolment were ineligible and enrolled donors agreed not to use self-administered iron supplements for the duration of the study. Pregnant females and females planning pregnancy during the follow-up period were excluded. Ferritin was measured in all donors enrolled in STRIDE. Donors with baseline ferritin >300 mg/l ($n = 0$) were not allowed to participate.

Laboratory testing and definitions of iron deficiency

Laboratory testing was performed on peripheral blood samples obtained at enrolment. Complete blood count was obtained using venous blood samples collected before blood donation (Sysmex XE2100D or Beckman Coulter LH 750s). Ferritin and soluble transferrin receptor (sTfR) were performed at ARUP Laboratories (Salt Lake City, Utah, USA). Ferritin was measured using the ADVIA Centaur (Siemens Healthcare Diagnostics, Deerfield, IL, USA). sTfR was measured using the Tina-quant sTfR assay (Roche Diagnostics, Indianapolis, IN, USA). Ferritin <12 mg/l was used to define absent iron stores (AIS), and $\log_{10}\text{sTfR/ferritin} - 2.07$ was used to define iron deficient erythropoiesis (IDE) [3].

Randomization and mailings

Donors were randomly allocated into educational or interventional arms (Fig. 1). In the educational arm, one group received a letter following each donation informing them of their plasma ferritin at the time of donation. If ferritin was <26 mg/l, the letter recommended taking iron supplements or delaying donation for 6 months; if ferritin was ≥ 26 mg/l, the letter recommended continuing donating twice (female) or three times (male) per year. A second group of donors in the educational arm served as a control. The control group received a letter thanking them for their donation and encouraging them to continue making donations twice (female) or three times (male) per year. The research staff at each blood centre was unaware of the group assignment.

There were three groups of donors in the interventional arm. One group received 60 tablets with 38 mg elemental iron as ferrous gluconate following each donation. A second group received 60 tablets with 19 mg elemental iron as ferrous gluconate following each donation. A third group received 60 placebo tablets following each donation. Subjects randomized to receive tablets were provided a letter with instructions on how to take the pills (once daily with half a glass of water), a list of possible side-effects of taking the pills, a bottle of pills (two bottles for double red cell donations) and a postage-paid return envelope. Tablet bottles for the 38 mg, 19 mg and placebo pills were identical except for a colour coded band that allowed for blinding. Subjects were asked to return the previous tablet bottle. Staff at the central distribution centre counted remaining pills to assess compliance. The interventional arm was double-blinded, and donors were asked to make donations twice (female) or three times (male) per year.

BloodCenter of Wisconsin served as the central distributor of both tablets and letters for all sites based on blinded distribution lists generated at Westat. Entry of laboratory test results from samples obtained at the time of donation into the centralized data management system

triggered entry of the donor into the mailing queue. Weekly shipping events collated all completed visits for the previous week.

Iron supplements

Pill formulation, development, and, compounding were performed specifically for this study (CoreRX, Clearwater, FL, USA). All pills were comprised of two proprietary cellulose components and magnesium stearate (vegetable source) with or without ferrous gluconate. Specifications for iron-containing pills were ± 1.3 mg for 19 mg elemental iron and ± 2.7 mg for tablets containing 38 mg elemental iron. Final products were subject to internal quality assurance and received GMP certification statements from the manufacturer before release.

Adverse events and de-enrolment

Subjects receiving pills were provided a list of possible side-effects with each mailing and asked to report these or any other symptom that made them feel uncomfortable by calling their local research team. Reports of adverse events were recorded by research staff on a standard form and reviewed by an off-site physician to provide consistent follow-up to donors. The off-site physician was blinded to the pill group to which the donor was randomized. Subjects requesting de-enrolment from the study were asked to explain their reason for de-enrolment.

Statistical methods

All statistical analyses were performed using *SAS* V9.3 (SAS Institute, Inc., Cary, NC, USA). Frequency distributions of demographic characteristics and donation type by group assignment were produced to assess the randomization across groups. The arithmetic means, standard deviations and medians were calculated for haemoglobin, ferritin and soluble transferrin receptor by gender and group assignment. Statistical differences in continuous variables were calculated with *ANOVA*, using *SAS* procedure GLM. Statistical differences in categorical variables were calculated using Chi-square analysis.

Results

Donor enrolment

The STRIDE study enrolled and randomized 692 frequent blood donors. The demographic characteristics of each of the five randomized groups and the total cohort are presented in Table 1. Males and females are equally represented (50.6% and 49.4%, respectively). Older donors are well represented with 66.7% ≤ 50 years old and 32.7% >60 . Most participants are White (95.7%) with $<2\%$ representation by each non-White racial group (eight African American, six Asian, ten Hispanic and six identify with 'Other' race). Whole blood donors comprise 81% of the cohort, and double red cell donors are 19%. The five assignment groups are equally balanced in regards to these demographics. However, the enrolled donor cohort does not closely resemble the population of frequent donors at the three blood centres during the enrolment period (Table 1), due to varying consent rates among frequent donors (e.g. older donors were more likely to enrol) and due to varying eligibility rates among frequent donors (e.g. female donors excluded due to prior iron supplementation use).

Donor haemoglobin and iron status

Venous haemoglobin, ferritin, sTfR and $\log_{10}$ sTfR/ferritin for females, males and the entire cohort are presented in Table 2. The mean venous haemoglobin was 13.3 ± 1.0 g/dl for females and 14.7 ± 1.2 g/dl for males. Consistent with previous data, [3] AIS and IDE were common in this population of frequent donors. AIS was present in 32.0% of females and 17.2% of males with a mean ferritin of $19.7 + 17.4$ mg/l for females and $34.7 + 34.9$ mg/l for males (Table 2). IDE was present in 74.6% of females and 52.7% of males with a mean $\log_{10}$ sTfR/ferritin of $2-3 \pm 0.4$ for females and $2.1 + 0.4$ for males. Table 3 provides enrolment venous haemoglobin, ferritin and sTfR for all randomized subjects by group assignment. Analysis of variance indicated a lack of any significant variation between assignment groups: haemoglobin $P = 0.85$; ferritin $P = 0.22$; sTfR $P = 0.81$; $\log_{10}$ [sTfR/ferritin] $P = 0.33$.

Donor adverse events

A total of 22 subjects (9 male, 13 female) reported adverse events within 60 days of enrolment (Table 4). Adverse events were only reported in subjects randomized to the interventional arm of the study. Donors reporting adverse events were encouraged to take pills every other day instead of daily and to remain enrolled in the study. Nevertheless, 17 of the 22 donors (77%) reporting adverse events de-enrolled from the study. Donors receiving 38-mg iron pills reported 12 adverse events (10 de-enrolled); subjects receiving 19-mg iron pills reported 6 (4 de-enrolled); and those receiving placebo pills reported 4 (3 de-enrolled). Adverse events reported were primarily gastrointestinal (14 cases with 12 being significant enough for de-enrolment), followed by rash/itching (3 reports; 2 de-enrolled), and leg cramps, frequent urination, head-ache, superficial thrombophlebitis and not otherwise specified (NOS) (1 case of each; 3 de-enrolled) (Table 4). Differences in adverse event incidence among the three pill groups were not statistically significant ($P = 0.11$).

Donor de-enrolment

A total of 62 (27 males and 35 females) of the 692 randomized donors de-enrolled within 60 days of their enrolment. The reasons for de-enrolments were classified into four categories: (1) Not eligible for the study (9 donors; 8 taking multivitamins with iron within 30 days prior to enrolment and 1 receiving a lifetime deferral from blood donation); (2) Refused to continue for a non-medical related reason (28 donors); (3) Adverse event related to pills (17 donors; 12 gastrointestinal symptoms, 4 non-gastrointestinal symptoms, 1 not otherwise specified); and 4) Medical reasons other than an adverse event (8 donors; 5 physician recommend withdrawal, 2 under-went surgery, 1 with a previous history of gastrointestinal disorder who de-enrolled before taking pills) (Table 5). Overall de-enrolment for all causes was higher in groups of donors who were in the interventional arm compared to donors in the educational arm ($P = 0.002$), but did not vary among participants randomized to receive the three types of pills ($P = 0.68$) (Table 5). Within the interventional arm, the most common reason for de-enrolment was simply that the donor refused to continue because they did not want to take pills. This included 10 donors randomized to receive placebo pills, 6 receiving 19-mg iron pills and 8 receiving 38-mg iron pills.

Discussion

Iron stores are often depleted in frequent donors. Once they are depleted, the donor must replace the iron lost from additional donations through absorption of dietary iron during the interdonation interval. The vast majority of blood collection agencies encourage donors, particularly those deferred for low haemoglobin, to eat an iron-rich diet to maintain iron stores [13]. However, several previous studies have demonstrated that eating iron-rich foods has little to no effect on donor iron stores [3, 14, 15]. Effective strategies to prevent iron deficiency in frequent donors include the use of oral iron supplements [16–18] or delaying the interdonation interval well beyond the 56 day minimum donation interval [19].

A major goal of STRIDE is to test the effectiveness of methods to replace the iron lost during blood donation that can be implemented in community blood centres under standard operational conditions. Frequent donors were enrolled and, as expected, [3] many of the male and female subjects had significant iron deficiency at baseline, making them a valuable and representative resource in evaluating the effectiveness of the two research arms. The disparity in gender balance between the STRIDE cohort and the population of frequent donors could be the result of frequent female donors taking an iron supplement more commonly than their male counterparts, making more females ineligible for the study. We can only speculate as to why older donors are over represented in the STRIDE cohort, although one possibility is that donors in this age group are more familiar or comfortable with taking pills as compared to younger donors.

Plasma ferritin <26 mg/l, [3] or the approximate equivalent serum ferritin 30 mg/l, [20] provides a specific and sensitive measure of iron stores, particularly in otherwise healthy individuals. As such, it is the best single test to use to determine iron status in blood donors and is the centrepiece of the letter arm of the study. Within a week following each donation, control subjects in the educational arm received a letter simply thanking them for donating and encouraging them to make additional donations. Test subjects in the educational arm, however, received a letter that described the ferritin test, how it is interpreted, and what their ferritin value was at the time of donation. Donors with ferritin <26 mg/l received further instructions suggesting the use of an oral iron supplement or a six month interval until their next blood donation. In this way donors were allowed to utilize information provided by the blood centre to make individual choices to prevent iron deficiency.

In the interventional arm of the study, the amount of iron was selected to represent that found in commonly available ‘over-the-counter’ multiple vitamins, 19 mg, or iron tablets, 38 mg, that are relatively simple to recommend to donors. The maximum daily iron absorption in blood donors has been estimated in one report to be about 4 mg per day [15]. Assuming oral supplementation allows for maximal iron absorption, either amount of iron may be adequate to replace the iron lost during donation. Concerns about providing iron to donors include the possibility of worsening iron overload in patients with hemochromatosis or masking the symptoms of a clinically important gastrointestinal bleed or other underlying medical condition. Ferritin was measured at each donor visit for all enrolled STRIDE donors. The study protocol required exclusion of donors with ferritin >300 mg/l, however, none of the recruited donors met this exclusion criterion. Patients with hemochromatosis

typically have ferritin >1000 mg/l and screening using family history and/or ferritin should be considered before enrolling in an iron supplementation programme. Blood centres should also provide information to these donors about various gastrointestinal disorders that could be masked by iron supplementation. Such information ought to indicate that a family history of colon cancer should be discussed with personal physicians and people over 50 years of age should be screened for colon cancer [21]. This guidance was provided to STRIDE enrollees at the time of informed consent only.

Gastrointestinal symptoms accounted for 12 adverse events in the subjects receiving iron and two in the placebo group suggesting that gastrointestinal symptoms may be more common in those receiving iron. This disparity did not reach statistical significance, although the study was not originally powered on this outcome. Radtke and colleagues performed a placebo-controlled study of iron supplementation in blood donors that resulted in complaints of gastrointestinal upset no more frequent in iron treatment groups (40 mg and 20 mg) than placebo [17].

Donors asked to take tablets were more likely to withdraw from the two-year longitudinal study within the first 60 days of participation, whereas donors receiving a letter only (control or interventional) remained as active participants. De-enrolment within this time frame allowed for only one disbursement of letters or tablets from the research team. Although the randomization aspect of the STRIDE study was communicated to donors at the time of consent, this finding should be taken into consideration for blood centres comparing these two programmes for use in managing donor iron deficiency as it relates to donor compliance. Although designed to mimic programmes that can be readily implemented at community blood centres, a key limitation of STRIDE is that it is a randomized study and, thus, STRIDE donors may not behave identically to community donors not participating in a study. Donors in the interventional arm were randomized to pills of unknown iron content and some donors de-enrolled because they did not want to take iron. Others de-enrolled because they thought they were taking the placebo and wished to take iron. Several donors who de-enrolled were instructed to do so by their doctor, sometimes because the donor had iron deficiency anaemia diagnosed and were prescribed iron replacement and sometimes because the doctor did not want the donor to be taking an unknown pill. These donors may have remained as active participants if the content of iron supplements was known to the donor.

Regular blood donation produces iron deficiency and mitigating these effects is important to maintain donor safety and an adequate blood supply. Previous studies have shown that modifications to blood donor diets do not effectively replace the iron lost from donating blood regularly suggesting that oral iron supplementation may be necessary to maintain iron balance in regular blood donors. However, in this study, de-enrolment within 60 days was higher for the interventional arm, although no more common in donors receiving iron than placebo tablets indicating that some donors will be resistant to taking a pill regularly. Longitudinal analyses of the STRIDE cohort will compare iron balance between donors randomized to intervention and donors randomized to information. These analyses will determine if providing regular donors with information about their iron status is a more effective approach to replenishing the iron lost during regular blood donation.

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Fig. 1.
Recruitment, enrolment, randomization and follow-up schema for subjects enrolled in STRIDE.

Table 1

Demographic characteristics by group assignment

	Group assignment [n (%)]					Frequent donor population N (%)
	Letter arm	Pill arm			Total n (%)	
Iron status information only	No information or treatment	38 mg Iron × 60 days	19 mg Iron × 60 days	Placebo × 60 days		
Total	137 (100.0)	139 (100.0)	139 (100.0)	138 (100.0)	692 (100)	75 547 (100)
Gender						
Female	68 (49.6)	69 (49.6)	68 (48.9)	68 (49.3)	342 (49.4)	45 628 (60.4)
Male	69 (50.4)	70 (50.4)	71 (51.1)	70 (50.7)	350 (50.6)	29 939 (39.6)
Race/Ethnicity						
White	128 (93.4)	134 (96.4)	132 (95.0)	135 (97.8)	662 (95.7)	69 581 (92.1)
Non-White	9 (6.6)	5 (3.6)	7 (5.0)	3 (2.2)	30 (4.3)	5986 (7.9)
Age (in years)						
<30	6 (4.4)	13 (9.4)	15 (10.8)	14 (10.1)	59 (8.5)	11 659 (15.4)
30–39	13 (9.5)	10 (7.2)	17 (12.2)	8 (5.8)	54 (7.8)	7953 (10.5)
40–49	29 (21.2)	26 (18.7)	14 (10.1)	26 (18.8)	117 (16.9)	14 189 (18.8)
50–59	46 (33.6)	46 (33.1)	52 (37.4)	43 (31.2)	236 (34.1)	22 105 (29.3)
60+	43 (31.4)	44 (31.7)	56 (40.3)	47 (34.1)	226 (32.7)	19 661 (26.0)
Donation Type						
Whole blood	107 (78.1)	117 (84.2)	113 (81.3)	115 (83.3)	561 (81.1)	61 110 (82.2)
Double RBC	30 (21.9)	22 (15.8)	26 (18.7)	23 (16.7)	131 (18.9)	13 457 (17.8)

Ten participants de-enrolled prior to assignment to a study group.

Table 2

Baseline summary lab measures by gender

	Female	Male	Overall
Haemoglobin (g/dl)			
Mean	13.3	14.7	14.0
Standard deviation	1.0	1.2	1.3
Median	13.2	14.7	13.9
Ferritin (mg/l)			
Mean	19.7	34.7	27.3
Standard deviation	17.4	34.9	28.6
Median	16.0	25.0	19.0
Geometric Mean	15.4	25.1	19.7
Per cent <26 mg/l	76.1	51.5	63.7
Per cent <12 mg/l (AIS)	32.0	17.2	24.5
sTfR (mg/l)			
Mean	3.6	3.6	3.6
Standard deviation	1.1	1.3	1.2
Median	3.3	3.2	3.3
log ₁₀ sTfR/Ferritin			
Mean	2.3	2.1	2.2
Standard deviation	0.4	0.4	0.4
Median	2.3	2.1	2.2
Per cent 2.07 (IDE)	74.6	52.7	63.5

Table 3

Baseline summary lab measures by group assignment

	Group Assignment			
	Iron status information only	No information or treatment	38 mg Iron × 60 days	19 mg Iron × 60 days
Haemoglobin (g/dl)				
Mean	14.0	13.9	14.0	13.9
Standard deviation	1.3	1.3	1.4	1.2
Median	13.2	14.0	13.9	13.7
Ferritin (mg/l)				
Mean	26.9	29.4	27.0	23.6
Standard deviation	18.7	28.2	29.2	25.9
Median	22.0	19.0	17.0	18.0
Geometric Mean	21.0	20.5	19.2	17.2
Per cent <26 mg/l	59.9	61.2	64.7	75.5
Per cent <12 mg/l (AIS)	20.4	21.6	27.3	29.5
sTfR (mg/l)				
Mean	3.5	3.6	3.7	3.6
Standard deviation	1.1	1.3	1.2	1.2
Median	3.2	3.2	3.6	3.3
log ₁₀ sTfR/Ferritin				
Per cent >2.07 (IDE)	59.9	59.7	66.9	73.4
				60.9

Testing the difference in proportion with ferritin <12 mg/l by gender, $P < 0.0001$.

Testing the difference in proportion with log₁₀ sTfR/Ferritin 2.07 by gender, $P < 0.0001$.

Table 4

Adverse events reported

	38 mg Iron × 60 days	19 mg Iron × 60 days	Placebo × 60 days
Gastrointestinal symptoms	8	5	1
Non-Gastrointestinal Symptoms	4	1	2
Not otherwise specified	0	0	1
No adverse events reported	127	133	134
Total	139	139	138

Table 5

De-enrolments by treatment group

	Iron status information only	No information or treatment	38 mg Iron × 60 days	19 mg Iron × 60 days	Placebo × 60 days
Not eligible	3	0	0	4	2
Refused to continue	2	2	8	6	10
Adverse event	-	-	10	4	3
Medical event	0	0	3	1	4
No de-enrolment	132	137	118	124	119
Total	137	139	139	139	138