EFFICIENCY OF A PROPOSED BLOOD DONOR SCREENING STRATEGY

A MODEL STUDY

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BACKGROUND – Currently, pre-donation, capillary hemoglobin screening is the only measure of blood donor iron status in the Dutch blood donation practice. Ferritin measurements and targeted hemoglobin screening have been previously proposed as potential screening strategy advancements. Based on these advancements, a comprehensive new screening strategy was proposed. This study aimed to assess differences in efficiency between this new screening strategy, and the current, Dutch screening strategy standard.

METHODS – Differences in efficiency were assessed determining the incremental cost-effectiveness ratio of the proposed strategy over the current Dutch strategy. Donors approved for donation were considered screening strategy benefits. Screening strategy costs and benefits were evaluated fitting the screening strategies to a Markov model. Parameter values were based on a 2012 to 2014 dataset of Dutch blood donations, and relevant literature. A donation facility perspective was adopted.

RESULTS – At a five-year time-horizon, compared to the current strategy, the proposed screening strategy resulted in 33% higher female screening costs, and a 9% decrease in the number of female donors approved for donation. At the same time-horizon, among male donors, the proposed strategy resulted in a 21% decrease of screening costs, and an amount of approved donors equal to the current strategy.

CONCLUSION – Compared to the current Dutch screening strategy, the screening strategy as proposed would result in increased screening costs and decreased screening benefits among female donors, and decreased screening costs and increased screening benefits among male donors. The current Dutch donor population gender composition would result in female proposed strategy disadvantages outweighing male proposed strategy advantages. Future research might complement results derived by this study with quantified proposed strategy effects on donor health.

CONTENTS

1. INTRODUCTION

1.1 BLOOD DONOR SCREENING

Worldwide, blood banks screen blood donor hemoglobin levels in order to safeguard donors from donation induced anemia and secure sufficient quality of the donation produce collected. An insufficient hemoglobin level of potential blood donors is the main reason for donation deferral (Goldman, 2005; O'Meara et al., 2011; Sawant, Bharucha, & Rajadhyaksha, 2007). Donation deferral due to below cutoff hemoglobin levels subsequently has been reported to result in lower donor return rates, compared with those who successfully donated (Boulton, 2008; Newman, Newman, Ahmad, & Roth, 2006). Two main potential advancements in blood donor screening strategy recently presented in relevant literature. These two advancements are discussed below.

1.2 HEMOGLOBIN SCREENING

Screening of hemoglobin levels commonly occurs pre-donation, on capillary blood obtained with a finger prick (Gomez-Simon et al., 2007; Lotfi, Wernet, Starke, Northoff, & Cassens, 2005). However, this technique has been reported to be unreliable and unpractical (Boulton, 2008; Goldman, 2005; Lotfi et al., 2005), e.g. considered as highly operator-dependent and time consuming (Goldman, 2005; Lotfi et al., 2005). Additionally, in a 2005 Canadian survey, a mere 57% of the interviewed blood donors reported to be satisfied with finger prick sampling of capillary hemoglobin level screening blood (Goldman, 2005). As blood donor return rates are negatively influenced by negative donation experiences (Gillespie & Hillyer, 2002; Thomson et al., 1998), hemoglobin screening methods not requiring a finger prick should be preferred.

Aiming to avoid the limitations associated with blood donor hemoglobin level screening on capillary blood, an improved hemoglobin level screening strategy was developed (Lotfi et al., 2005; Ziemann et al., 2006). According to this strategy, blood donor suitability is determined based on the hemoglobin levels measured at their previous donation. Only for first-time donors and for donors who showed below cutoff hemoglobin levels at their previous donation, pre-donation capillary hemoglobin level measurement is required. Among all other donors, hemoglobin levels are measured on venous blood, avoiding capillary measurements.

1.3 PREVENTION OF IRON RESERVE DEPLETION

Blood donation may result in depletion of bodily iron reserves (Milman & Kirchhoff, 1991; O'Meara et al., 2011). Iron reserve depletion may ultimately result in iron deficiency anemia, which is associated with symptoms such as fatigue, and reduced physical and mental resilience. As anemia is defined by insufficient hemoglobin synthesis (Rubin & Strayer, 2012), iron reserve depletion may result in blood donor deferral due to below cutoff hemoglobin levels.

Low hemoglobin levels are a late manifestation of bodily iron store depletion (Bryant et al., 2012) Iron stores may be depleted among donors presenting with normal hemoglobin levels. Blood bank screening of donor hemoglobin therefore may prevent donation-induced anemia and donation by anemic donors, it however cannot completely prevent donation-induced depletion of donor iron stores, nor donation by iron store depleted donors (Alvarez-Ossorio, Kirchner, Kluter, & Schlenke, 2000; Eder, 2010; Kiss et al., 2013).

Timely diagnosis and treatment of iron reserve depletion in blood donors may avoid anemia and subsequent deferral of donation attempts (O'Meara et al., 2011). This may subsequently result in increased retention of successful blood donors, as donation deferral is associated with decreased donor return (Boulton, 2008; Newman et al., 2006). Measurement of donor ferritin levels has been proposed as donor iron store marker (Alvarez-Ossorio et al., 2000; Milman & Kirchhoff, 1991; O'Meara et al., 2011; Stern, O'Meara, Infanti, Sigle, & Buser, 2012). Two main treatment-approaches of donor iron store depletion have been discussed by previous literature: provision of iron supplementation, and tailoring donation intervals to donor iron status.

1.4 STUDY AIM

This study aimed to assess differences in efficiency between the current Dutch screening strategy standard, and a newly proposed approach, currently under consideration by Sanquin Blood Supply, the Dutch national blood bank. Differences in efficiency were identified by compared screening costs and benefits, associated with both strategies.

2 SCREENING STRATEGIES

According to the current Dutch screening strategy, only one type of donor hemoglobin screening is performed: A capillary hemoglobin measurement for every presenting donor. According to the newly proposed screening strategy, three types of hemoglobin screening are possible: A pre-donation, capillary hemoglobin measurement for donors at high risk of too low hemoglobin levels (1), and a post-donation, venous hemoglobin measurement (2), or exemption from any hemoglobin measurement (3) for donors at low risk of too low hemoglobin levels. Additionally, whereas donor iron stores are not under direct surveillance by the current screening strategy, according to the proposed strategy, donor iron stores are monitored by regular ferritin measurements.

The newly proposed screening strategy is graphically presented in appendix 1. The current Dutch screening strategy standard is depicted in appendix 2. This section presents the proposed screening strategy in more detail, discusses where it differs from the current Dutch strategy, and reviews the evidence it was is based on.

2.1 PRE-DONATION HEMOGLOBIN SCREENING FOR HIGH-RISK DONORS ONLY

The proposed screening strategy suggests pre-donation hemoglobin measurement to be limited to to those donors who are at high risk of having too low hemoglobin levels. In the current standard screening strategy pre-donation hemoglobin level measurement is mandatory for all who present to donate. High-risk donors were defined as blood donors who showed hemoglobin levels below a gender specific cutoff value (129 g/L and 139 g/L for female and male blood donors respectively) at their previous hemoglobin measurement. According to the proposed strategy, low-risk donors, with their previous donation hemoglobin level above the cutoff value, are allowed to donate without pre-donation capillary hemoglobin screening. Subsequently, low-risk donor hemoglobin levels are set to be measured post-donation from part of the donation produce itself. As pre-donation hemoglobin levels are measured among high-risk donors only, according to the proposed strategy, only high-risk donors can be deferred from donation based on too low hemoglobin levels. Deferred high-risk donors maintain their high-risk status during their subsequent presentation. appendix 3 discusses the establishment of the cutoff value granting donors to be low or high-risk donors.

2.1.1 EXEMPTION FROM ANY HEMOGLOBIN SCREENING FOR PERSISTENT LOW-RISK DONORS

The proposed screening strategy exempts persistent low-risk donors from any hemoglobin measurement at every second low-risk donation. This allows better exploitation of the principle of stable high hemoglobin levels used by Lotfi et al. (2005) and Ziemann et al. (2006), and previously reported by Baart et al., 2014.

2.2 FERRITIN SCREENING FOR SPECIFIC DONOR SUBGROUPS

Commonly, bodily iron stores are considered to be depleted at serum ferritin levels < 15 µg/L (WHO, 2011; Alvarez-Ossorio et al. (2000); Cable et al. (2011); Finch, Cook, Labbe, and Culala (1977); Kiss et al. (2013); Milman and Kirchhoff (1991); Simon, Garry, and Hooper (1981)). Prevalence of depleted iron stores has been reported to be absent among male first-time blood donors, but substantial among female first-time blood donors (Alvarez-Ossorio et al. (2000); Cable et al. (2011); Finch et al. (1977); Kiss et al. (2013); Milman and Kirchhoff (1991); Simon et al. (1981)). Increased yearly donation frequency and a higher absolute number of donations in a blood donor's history, have been reported to cause increased depletion of donor iron stores (Alvarez-Ossorio et al., 2000; Cable et al., 2011; Finch et al., 1977; Simon et al., 1981). Additionally, first-time blood donor ferritin levels have been reported to plateau following an initial decrease associated with the new donor's first few donations (Alvarez-Ossorio et al., 2000; Garry, Koehler, & Simon, 1995; Pedersen & Morling, 1978).

Given the absence of depleted iron stores among first-time male donors, the proposed strategy was set to measure ferritin levels among female first-time donors only. Subsequently, it was

argued a blood donor ferritin measurement at the fifth donation for both male and female new donors, provides an early identification of those donors who, due to their donation of blood, develop iron store depletion. As blood donor ferritin levels are reported to plateau, it was subsequently argued iron stores of those donors who are not iron store depleted after their first five donations, can thereafter be sufficiently monitored by conducting ferritin measurements at a lower frequency. Based on previous literature, this lower frequency was set at every 10^{th} donation. An in-depth review of the ferritin measurement subgroup selection conducted in this section is provided in appendix 4.

2.2.1 LOW FERRITIN LEVELS RESULT IN EXCLUSION FROM FURTHER FUTURE DONATIONS

As discussed in section 1, provision of iron supplementation or long-term postponement of the next donation of the applicable blood donors, are two main possible responses to below threshold donor ferritin levels. Aiming to contribute to the strand of literature advocating tailor-made donation intervals for individual donors, the screening strategy proposed by this study was set to exclude low-ferritin donors from any further future whole-blood donations.

3 METHODS

3.1 MARKOV MODEL

Screening strategy costs and benefits were evaluated fitting the respective screening strategies into a Markov model as defined by Drummond, Sculpher, Torrance, O'Brien, and Stoddart (2005). As male and female blood donors differ in various donation characteristics, as e.g. the minimum interval between subsequent donations, Markov models developed in this study were analyzed for a male, and a female donor population separately.

3.1.1 MODEL CYCLES

In a Markov model, time passes in explicit time cycles, based on the intervention analyzed. During these time cycles, each member of the model population occupies a specific model state (Drummond et al., 2005). Hence, in each model cycle a donor is allowed to make one donation attempt. Model cycles were set in order to accurately reflect the real-life, Dutch donation practice, at 2.5 months for male donors, and 4 months for female donors.

In the Netherlands, for both male and female donors, a minimum of 56 days between consecutive donations is required. Additionally, male blood donors are allowed to donate up to a maximum of 5 times per year, and female blood donors are allowed to donate up to a maximum of 3 times per year (Council of Europe, 2009). Due to these maximum donations per year, a model cycle of 56 days would result in an overestimation of the proportion of temporarily inactive donors. Therefore, cycle length was set based on the number of maximum yearly donations.

3.2 OUTCOMES AND PERSPECTIVE

Screening strategy efficiency differences were assessed determining the incremental cost-effectiveness ratio of the proposed strategy compared to the current strategy. Only screening strategy costs and benefits as incurred by the Dutch national blood bank were considered. Screening strategy blood donors approved for donation were appointed as screening strategy benefits.

3.3 MODEL STRUCTURE

Separate, screening strategy specific Markov models were developed for the current Dutch screening strategy standard (Figure 1), and the proposed screening strategy (Figure 2), respectively. These Markov models were based on screening strategy characteristics.

Most Markov states include several sub states. These sub states represent all chains of events possibly occurring in the applicable Markov main state. Sub states ultimately derive from the screening strategy decision trees depicted in appendix 1 and appendix 2. Throughout this text, Markov main states are denoted with capital letters. A brief description per Markov main state is provided in this section. Current strategy Markov states are discussed first. Graphic representations of sub states within Markov main states are provided in appendix 5.

FIGURE 1
Markov model current screening strategy

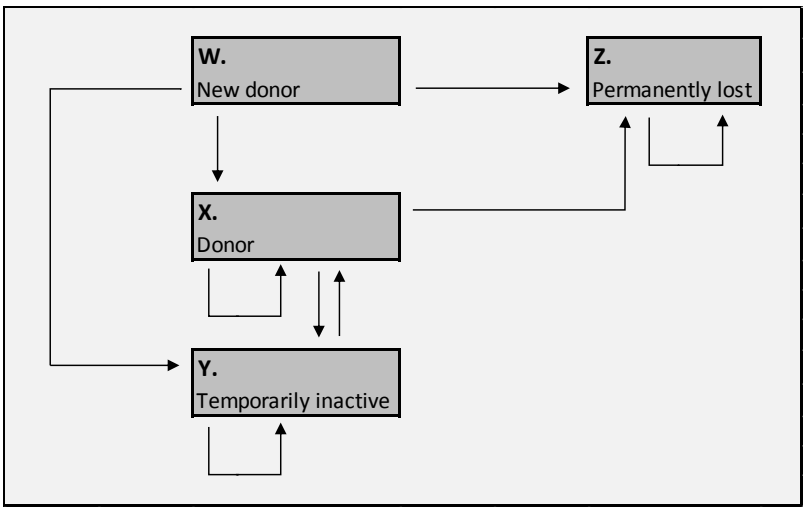
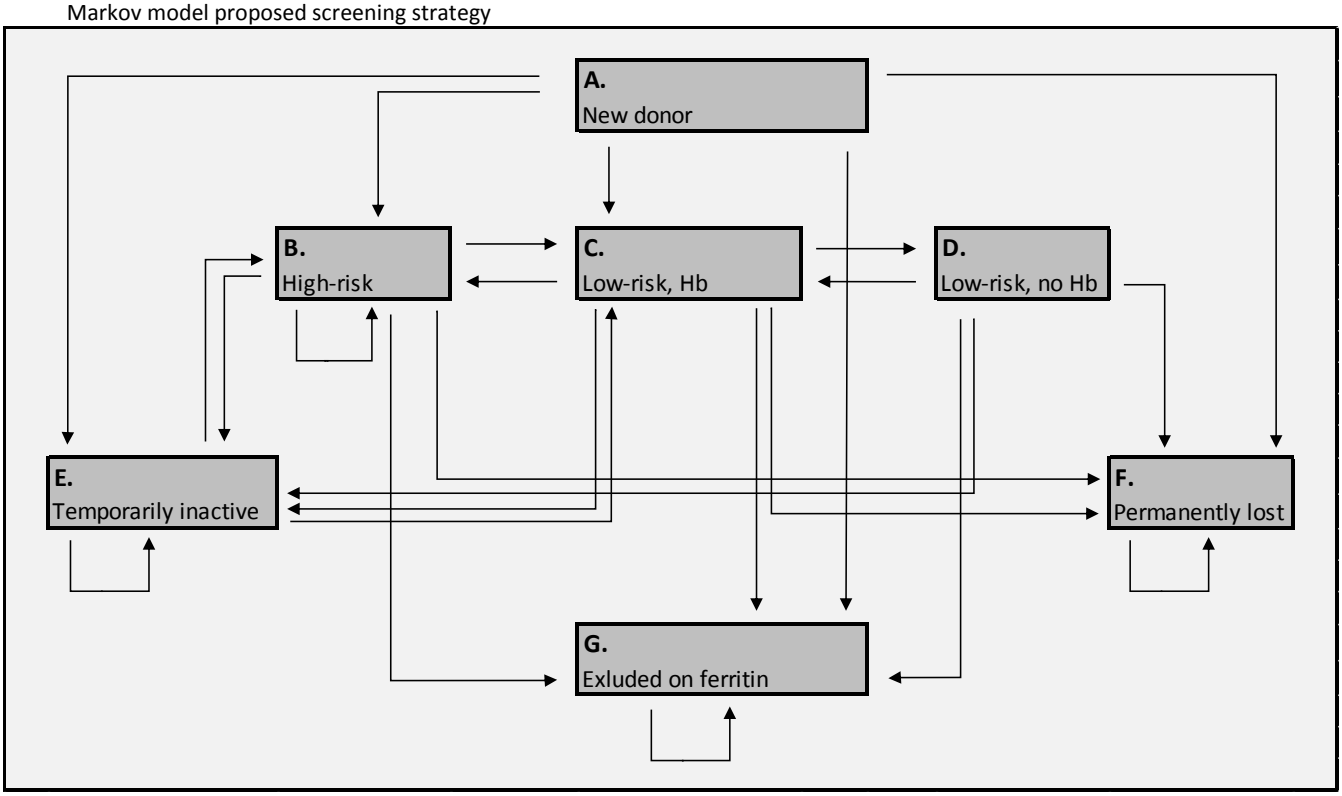


FIGURE 2
Markov model proposed screening strategy



3.3.1 CURRENT SCREENING STRATEGY

State W: *New donor*

New donors are donors who present to a donation facility without having made a blood donation in the previous two years. New donors are subjected to a comprehensive set of screening tests, including a capillary hemoglobin measurement, but are not allowed to actually donate blood. Donors can be new donors during one model cycle. New donors can transfer to all other model states.

State X: *Donor*

Except for new donors, all potential donors who present to a donation facility with the intention to donate are included in model state *Donor*. All potential donors are subjected to a pre-donation capillary hemoglobin measurement. Based on their revealed hemoglobin level, potential donors are allowed to donate blood, or are deferred from donation. Donors included in model state *Donor* can transfer to model state *Donor*, *Temporarily inactive* or *Permanently lost* at the end of the respective model cycle.

State Y: *Temporarily inactive* & State Z: *Permanently lost*

Donors who occupied Markov state *New donor* or *Donor* in a previous model cycle, but do not donate during a present model cycle, are considered to be inactive donors. After two years of inactivity, former donors are treated as new donors in case they again present to a donation facility (de Kort, 2010). Hence, if a donor after occupying model state *New donor* or *Donor* does not present to donate for at least two years, that donor transfers to model state *Permanently lost.* Once occupying model state *Permanently lost*, a donor can no longer transfer to any other model state.

3.3.2 PROPOSED SCREENING STRATEGY

State A: *New donor*

New donors are donors who present to a donation facility without having made a blood donation in the previous two years. New donors are subjected to a comprehensive set of screening tests, including a venous hemoglobin measurement, but are not allowed to actually donate blood. Female new donors are additionally subjected to a ferritin measurement. Only female new donors can transfer to model state *Excluded on ferritin*. All new donors can transfer to all remaining model states, except model state D: *Low-risk, no Hb*. Donors can be new donors during one model cycle only.

State B: *High-risk*, State C: *Low-risk, Hb* and State D: *Low-risk, no Hb*

Except for new donors, all donors who present with the intention to donate during a certain model cycle, are included in model state B, C, or D, during that cycle. Whether a donor is included in a high-risk or in a low-risk state depends on the hemoglobin level as measured at that donor's previous donation, or new-donor-screening. Pre-donation hemoglobin measurement is conducted among high-risk donors only. Hence, only high-risk donors can be deferred from donation due to too low hemoglobin levels. Among low-risk donors, hemoglobin levels are measured post-donation from the donation produce. However, for every second consecutive low-risk donation, donors are exempted from any hemoglobin measurement. These hemoglobin measurement exempted donors in model state *Low-risk, no Hb* automatically transfer to model state *Low-risk, Hb* during their possible subsequent donation.

Ferritin measurements are performed at the same interval for all donors, low and high-risk. Ferritin measurements are performed on blood taken from the donation produce. Hence, high-risk donors deferred from donation based on too low pre-donation hemoglobin levels do not receive a ferritin measurement.

State E: *Temporarily inactive* & State F: *Permanently lost*

Donors who previously occupied Markov state *New donor* or one of the donation states (*High-risk*; *Low-risk, Hb*; *Low-risk, no Hb*), but do not donate during a present model cycle, are considered to be inactive donors. After two years of inactivity, former donors are treated as new donors in case they again present to a donation facility (de Kort, 2010). Hence, if a donor, after occupying model state *New donor* or one of the donation states, does not present to donate for at least two years, that donor transfers to model state *Permanently lost.* Once occupying model state *Permanently lost*, a donor can no longer transfer to any other model state.

State G: *Excluded on ferritin*

Model state *Excluded on ferritin* contains those donors who were excluded from further future donations based on revealed too low ferritin levels. Once transferred to model state *Excluded on ferritin*, the transferred donor remains in that model state infinitely.

3.4 TRANSITION PROBABILITIES

At the end of a model cycle, donors transfer to the Markov state they will occupy during the next model cycle. Probabilities donors transition between Markov states are discussed in this section. Current strategy transition probabilities are discussed first. Where relevant, branch probabilities incorporated within Markov sub states are discussed in appendix 6 (current strategy) and appendix 7 (proposed strategy).

3.4.1 CURRENT SCREENING STRATEGY

All current strategy transition probabilities were calculated applying the applicable definitions of Markov states and model cycles to a three-year dataset of Dutch blood donations available to this study. This dataset contains information on all blood donations and deferred donation attempts, made in the Netherlands in 2012, 2013, and 2014. For each donation (attempt), information on general donor characteristics, donor hemoglobin level at presentation, and donated blood volume is included. Individual donors are included in the dataset with a unique donor ID-number. As this ID-number did not change over time, proportions of donors transitioning between states at the end of a model cycle could be determined. Last, for each donor, the date of the donor's first presentation to a donation facility is included in the dataset. Hence, first-time donors were easily identified.

During the period covered by the dataset, 193,260 unique females presented with the intention to donate blood. Of those females, 94,422 presented as first-time donor. For males, 145,799 unique donors presented with the intention to donate blood, of whom 42,201 presented as first-time donor.

Current strategy transition probabilities are stated in Table 1. Calculation of the Table 1 transition probabilities is discussed in more detail in appendix 6.

TABLE 1
Current strategy Markov model transition probabilities. Standard errors are stated in parentheses.

	Transition to			
Transition from	**New donor**	**Donor**	**Temporarily inactive**	**Permanently lost**
Female donors				
New donor	0	0.3856 (0.0046)	0.1573 (0.0034)	0.4571 (0.0047)
Donor	0	0.5599 (0.0018)	0.3295 (0.0017)	0.1106 (0.0011)
Temporarily inactive	0	0.4482 (0.0020)	0.5518 (0.0020)	0
Permanently lost	0	0	0	1
Male donors				
New donor	0	0.3953 (0.0089)	0.2245 (0.0076)	0.3802 (0.0088)
Donor	0	0.5397 (0.0022)	0.3951 (0.0021)	0.0652 (0.0010)
Temporarily inactive	0	0.3841 (0.0020)	0.6159 (0.0020)	0
Permanently lost	0	0	0	1

3.4.2 PROPOSED SCREENING STRATEGY

At the time the present study was conducted, the proposed screening strategy was not active in practice. Specific screening elements had been evaluated in previous literature. Therefore, proposed strategy transition probabilities were based on the current strategy transition probabilities, adjusted based on relevant literature where appropriate. Final proposed screening strategy transition probabilities are stated in Table 2. appendix 7 describes the establishment of the Table 2 transition probabilities in more detail.

TABLE 2
Proposed strategy Markov model transition probabilities. Standard errors are stated in parentheses. Ranges are stated between brackets.

	Transition to						
Transition from	**New donor**	**High risk**	**Low risk, Hb**	**Low risk, no Hb**	**Temporarily inactive**	**Permanently lost**	**Excluded on ferritin**
Female donors							
New donor	0	0.0208	0.3262	0	0.1416 (0.0034)	0.4114 (0.0047)	0.1000 [0.05 - 0.15]
High-risk	0	0.2354 (0.0038)	0.3421 (0.0042)	0	0.3153 (0.0044)	0.0959 (0.0028)	0.0113 [0.01 - 0.01]
Low risk, Hb	0	0.0895 (0.0013)	0	0.4941 (0.0023)	0.3270 (0.0023)	0.0781 (0.0013)	0.0113 [0.01 - 0.01]
Low risk, no Hb	0	0	0.5836 (0.0023)	0	0.3270 (0.0023)	0.0781 (0.0013)	0.0113 [0.01 - 0.01]
Temporarily inactive	0	0.0874 (0.0025)	0.18035 (0.0025)	0.18035 (0.0025)	0.5519 (0.0020)	0	0
Permanently lost	0	0	0	0	0	1	0
Excluded on ferritin	0	0	0	0	0	0	1
Male donors							
New donor	0	0.0000	0.3953	0	0.2245 (0.0076)	0.3802 (0.0088)	0
High risk	0	0.1771 (0.0051)	0.3884 (0.0065)	0	0.3809 (0.0065)	0.0489 (0.0029)	0.0047 [0.00 - 0.01]
Low risk, Hb	0	0.0517 (0.0011)	0	0.5144 (0.0025)	0.3834 (0.0025)	0.0458 (0.0011)	0.0047 [0.00 - 0.01]
Low risk, no Hb	0	0	0.5661 (0.0025)	0	0.3834 (0.0025)	0.0458 (0.0011)	0.0047 [0.00 - 0.01]
Temporarily inactive	0	0.0512 (0.0022)	0.16645 (0.0022)	0.16645 (0.0022)	0.6159 (0.0020)	0	0
Permanently lost	0	0	0	0	0	1	0
Excluded on ferritin	0	0	0	0	0	0	1

3.5 COSTS AND BENEFITS MARKOV STATES

All Markov states are associated with state specific costs and benefits. These costs and benefits are discussed in this section. Current strategy Markov states are discussed first. Costs per screening test are derived in appendix 8.

3.5.1 CURRENT SCREENING STRATEGY

Table 3 lists all relevant costs and benefits associated with the current donor screening strategy. Table 3 costs and benefits were derived from the current Dutch donation practice, and are discussed in more detail in appendix 9.

TABLE 3
Current strategy costs and benefits

Markov state	Potential tests conducted	Probability test is conducted†	Cost of test	Expected costs Markov state	Potential benefits	Benefit probability†
Female donors						
New donor	Capillary hemoglobin	100%	EUR 1.00	EUR 1.00	None	-
Donor	Capillary hemoglobin	100%	EUR 1.00	EUR 1.00	Approved donor	93.9
Temporarily inactive	None	-	-	-	None	-
Permanently lost	None	-	-	-	None	-
Male donors						
New donor	Capillary hemoglobin	100%	EUR 1.00	EUR 1.00	None	-
Donor	Capillary hemoglobin	100%	EUR 1.00	EUR 1.00	Approved donor	97.2
Temporarily inactive	None	-	-	-	None	-
Permanently lost	None	-	-	-	None	-

† Derived from appendix 7 branch probabilities

3.5.2 PROPOSED SCREENING STRATEGY

Table 4 lists all relevant costs and benefits associated with the proposed screening strategy. Table 4 costs and benefits were based on the current strategy costs and benefits stated in Table 3, adjusted according to evidence presented by previous literature where appropriate. The proposed strategy costs and benefits are discussed in more detail in appendix 10.

TABLE 4
Proposed strategy costs and benefits

Markov state	Potential tests conducted	Probability test is conducted†	Cost of test	Total expected costs Markov state	Potential benefits	Benefit probability†
Female donors						
New donor	Venous hemoglobin	100%	EUR 1.10*	EUR 3.10	None	-
	Ferritin measurement	100%	EUR 2.00**			
High-risk	Capillary hemoglobin	100%	EUR 1.00***	EUR 1.1372	Approved donor	85.3%
	Ferritin measurement	6.86%	EUR 2.00**			
Low-risk, Hb	Venous hemoglobin	100%	EUR 1.10*	EUR 1.2372	Approved donor	100%
	Ferritin measurement	6.86%	EUR 2.00**			
Low-risk, no Hb	Ferritin measurement	6.86%	EUR 2.00**	EUR 0.1372	Approved donor	100%
Temporarily inactive	None	-	-	-	None	-
Permanently lost	None	-	-	-	None	-
Excluded on ferritin	None	-	-	-	None	-
Male donors						
New donor	Venous hemoglobin	100%	EUR 1.10*	EUR 1.10	None	-
High-risk	Capillary hemoglobin	100%	EUR 1.00***	EUR 1.1054	Approved donor	91.9%
	Ferritin measurement	5.27%	EUR 2.00**			
Low-risk, Hb	Venous hemoglobin	100%	EUR 1.10*	EUR 1.2054	Approved donor	100%
	Ferritin measurement	5.27%	EUR 2.00**			
Low-risk, no Hb	Ferritin measurement	5.27%	EUR 2.00**	EUR 0.1054	Approved donor	100%
Temporarily inactive	None	-	-	-	None	-
Permanently lost	None	-	-	-	None	-
Excluded on ferritin	None	-	-	-	None	-

* Based on expert opinion
** Based on Bravo et al. (unpublished), Magnussen et al. (2015) and O'Meara et al. (2011)
*** Based on current Dutch donation practice
† Derived from appendix 8 branch probabilities

3.5 LOST DONORS

Estimated current and proposed strategy totals of lost donors were compared in an additional analysis. Here, lost donors were defined as donors who presented to a donation facility with the intention to donate at a certain point in time, and subsequently did not present for at least two years, regardless of the reason for this non-presentation. According to the current strategy, donors can terminate their donor career, and hence become lost donors, by their own decision only. According to the proposed strategy, donors can additionally be forced to terminate their donor career, and hence be forced to become lost donors, by the donation facility in case a too low ferritin level is measured. Lost donors could be argued to be associated with recruitment costs of replacement donors. These recruitment costs were not included in the main screening strategy costs.

3.6 TIME HORIZON AND MODEL POPULATION

Markov models were analyzed on a one-year, a five-year, and a ten-year time-horizon, providing a notion of time-dependency of derived results. All analyses were conducted populating the Markov models with 1000 new donors in the first model cycle.

3.7 RESULTS DUTCH DONOR POPULATION

Ultimately, female and male donor results were synthesized as to reflect the effect of the proposed screening strategy on the Dutch donation practice. Influence of female and male results on this final synthesis was made proportionally to their respective presence in the Dutch donor population.

3.8 SENSITIVITY ANALYSES

Three parameters were identified during strategy construction to be subject to substantial uncertainty: Costs per ferritin measurement, low-risk donor transition probabilities towards *Permanently lost*, and prevalence of depleted iron stores. Therefore, in order to grasp insight into the influence of this parameter uncertainty on strategy efficiency, these parameters were included in a sensitivity analysis. Separate, univariate sensitivity analyses were conducted for each parameter. In addition, multivariate analyses incorporating multiple parameters were conducted. Finally, proportions of female and male donors in the Dutch donor population were varied, in order to assess the influence of donor population composition on synthesized results.

Sensitivity analyses were performed in two stages. First, univariate sensitivity analyses were conducted. Parameters were varied over a wide, 50% to 150%, range of their deterministic value, in order to thoroughly evaluate the influence of potential parameter uncertainty on final results. Where applicable, parameter values were increased or decreased in order to find a turning-point, reaching costs and benefits results opposing those found in deterministic analyses. Second, parameters

identified as potentially most influential on final results, were simultaneously varied in a multivariate sensitivity analysis, constructing better and worse case scenarios. All sensitivity analyses were conducted at a five-year time-horizon.

4 RESULTS

4.1 DETERMINISTIC RESULTS

Table 5 reports final model results regarding screening strategy costs, screening strategy benefits, and the number of screening strategy associated lost donors, for a one-year, a five-year and a ten-year model time-horizon. Screening costs included in table 5 are total screening costs per screening strategy. A breakdown of total screening costs per screening technique is provided in appendix 11 for both screening strategies. The number of lost donors per screening strategy is divided between *excluded*; those donors who were forced to terminate their donor career due to too low ferritin levels, and *permanently lost*; those donors whose donor career was terminated due to any other reason. All results as included in table 5, and as discussed further in this section, were derived assuming 1000 participants entering at the start of the model as new donors.

For female donors, the proposed screening strategy was found to result in higher costs and lower benefits compared to the current screening strategy, at all time-horizons. At a one-year time-horizon the incremental costs of the proposed screening strategy over the current screening strategy were found to amount to EUR 1969 (a 117% increase of the current screening strategy costs). At a five-year and at a ten-year time-horizon these incremental costs were found to amount to EUR 1289 and EUR 843, respectively (a 33% and a 16% increase of the current strategy screening costs, respectively).

For female donors, at a one-year time-horizon, the incremental benefits of the proposed screening strategy over the current screening strategy were found to amount to -37 approved donors (a 6% decrease of the current screening strategy benefits). At a five-year and at a ten-year time-horizon these incremental benefits were found to amount to -249 and -437 approved donors, respectively (a 9% and a 11% decrease of the current strategy screening benefits, respectively).

For male donors, at a one-year time-horizon, the proposed strategy was found to dominate the current strategy, generating more benefits, at lower total costs. After five, and after ten years, the proposed strategy was found to result in lower total costs, but at a small loss of benefits. At a one-year time-horizon, the proposed screening strategy was found to result in EUR -137 incremental costs over the current screening strategy (a 6% decrease), and to generate 23 incremental approved donors over the current strategy (a 2% increase). At time-horizons of five and ten years, the proposed screening strategy was found to result in incremental male screening costs of EUR -1259

and EUR -2042, respectively (a 21% and a 24% decrease, respectively). At the same time-horizons, the proposed screening strategy was found to generate incremental male benefits of -6 and -129 approved donors, respectively (a 0% and a 2% decrease, respectively).

For both male and female donors, the proposed screening strategy was found to result in increased total numbers of lost donors, at all time-horizons. At a one-year, five-year, and ten-year time horizon, the proposed strategy was found to result in an additional total loss of 53, 39 and 22 female donors, respectively (a 1%, a 5% and a 2% increase, respectively), and an additional total loss of 5, 15 and 13 male donors, respectively (a 1%, a 2%, and a 2% increase, respectively).

Based on the three-year Dutch donation dataset, 69.1% (30.9%) of all new donors were found to be female (male) donors. These proportions were used to calculate the weighted average of female and male donor results, hence reflecting results applying the proposed strategy to the Dutch donor population. At all time-horizons, compared to the current strategy, the proposed strategy was found to result in higher costs and lower benefits for the Dutch donation practice.

TABLE 5
Results. For every time-horizon, results were based on 1000 donors entering at the start of the model at model state *New donor*. Costs were rounded to the nearest Euro. Numbers of approved and lost donors were rounded to the nearest integer. Lost donors are divided between those who are forced to terminate their donor career due to too low ferritin levels measured (included in *Excluded*), and those who become lost due to other reasons (included in *Permanently*).

		COSTS	BENEFITS		LOST DONORS		
		EUR	Approved donors	ICER	Permanently	Excluded	Total
Female donors							
1-year time horizon	Current	1672	631	**current dominates proposed**	500	0	500
	Proposed	3641	593		449	104	553
	Increment	**1969**	**-38**				**53**
5-year time horizon	Current	3890	2714	**current dominates proposed**	763	0	763
	Proposed	5179	2465		675	127	802
	Increment	**1289**	**-249**				**39**
10-year time horizon	Current	5109	3858	**current dominates proposed**	906	0	906
	Proposed	5951	3421		790	138	928
	Increment	**843**	**-437**				**22**
Male donors							
1-year time horizon	Current	2233	1199	**proposed dominates current**	443	0	443
	Proposed	2096	1222		443	5	448
	Increment	**-137**	**23**				**5**
5-year time horizon	Current	6079	4937	**220.46**	702	0	702
	Proposed	4820	4931		694	23	717
	Increment	**-1259**	**-6**				**15**
10-year time horizon	Current	8480	7271	**15.81**	864	0	864
	Proposed	6438	7141		843	34	877
	Increment	**-2042**	**-129**				**13**
Donor population (weighted average female and male donors)							
1-year time horizon	Current	1845	806	**current dominates proposed**	482	0	482
	Proposed	3163	787		447	73	520
	Increment	**1318**	**-19**				**38**
5-year time horizon	Current	4566	3401	**current dominates proposed**	744	0	744
	Proposed	5068	3227		681	94	775
	Increment	**502**	**-174**				**31**
10-year time horizon	Current	5109	4912	**current dominates proposed**	893	0.00	893
	Proposed	5951	4571		806	106	912
	Increment	**-49**	**-342**				**19**

4.2 SENSITIVITY ANALYSES

Sensitivity analyses are discussed in the subsections below. First, potential influence of parameter uncertainty on final results is presented. Where applicable, turning-points reversing final results as derived by deterministic analysis are discussed. Second, a multivariate sensitivity analysis is

performed and better and worse case scenarios are constructed. Last, influence of the ratio between female and male donors on donor population wide results is evaluated.

4.2.1 INFLUENCE OF POTENTIAL PARAMETER UNCERTAINTY ON FINAL RESULTS

A graphic overview of the influence of potential uncertainty in main parameters on final costs and benefits results is provided in figures 3, 4, 5 and 6. Final costs and benefits results are the incremental costs and benefits of the proposed screening strategy over the current screening strategy, assuming a five-year time-horizon, and 1000 first-time donors at the start of the model. Influence of potential parameter uncertainty on final results was assessed by granting the deterministic parameter value to be the 100% index value, and subsequently varying this index value between 50% and 150%. Hence, figures 3, 4, 5 and 6 present an overview of parameter influence on final results, rather than an overview of parameter uncertainty itself. Influence of potential parameter uncertainty on final results is presented for final costs results and final benefits results separately, and for male and female donors separately. A legend applicable to figures 3, 4, 5 and 6 is provided in figure 7.

Figure 3: influence of potential parameter uncertainty on final **incremental costs** of the proposed screening strategy over the current screening strategy**,** for **female donors**. For all included model parameters, the deterministically derived parameter value is the 100% index value.

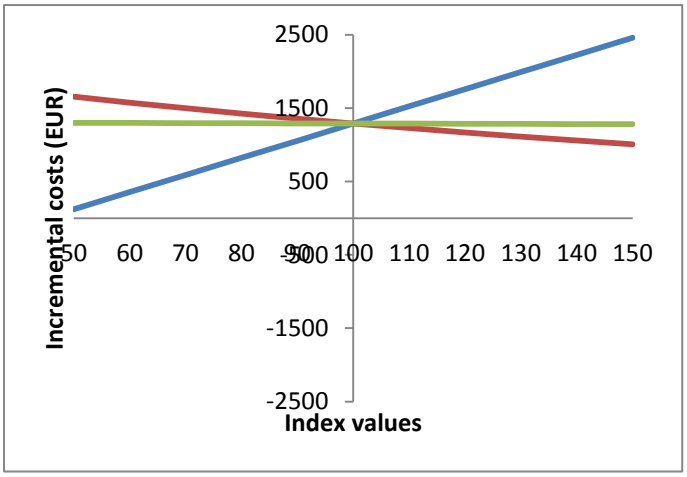


Figure 4: influence of potential parameter uncertainty on final **incremental costs** of the proposed screening strategy**,** for **male donors**. For all included model parameters, the deterministically derived parameter value is the 100% index value.

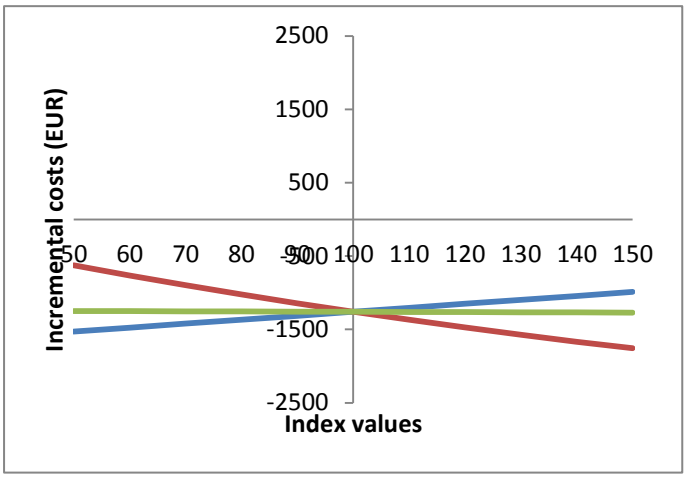


Figure 5: influence of potential parameter uncertainty on final **incremental benefits** of the proposed screening strategy over the current screening strategy**,** for **female donors**. For all included model parameters, the deterministically derived parameter value is the 100% index value.

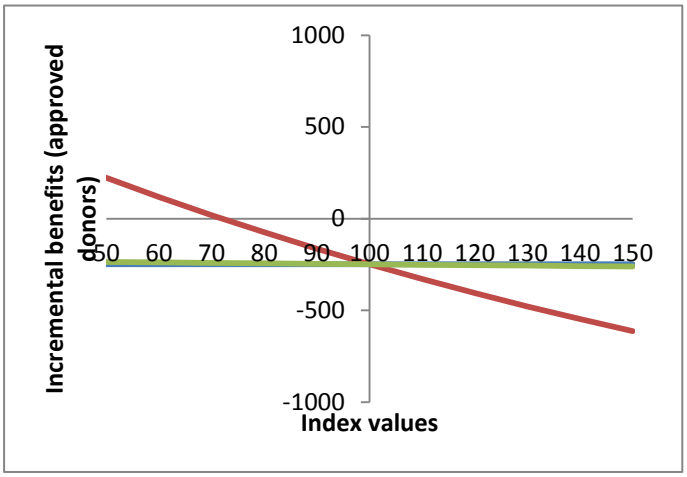


Figure 6: influence of potential parameter uncertainty on final **incremental benefits** of the proposed screening strategy over the current screening strategy**,** for **male donors**. For all included model parameters, the deterministically derived parameter value is the 100% index value.

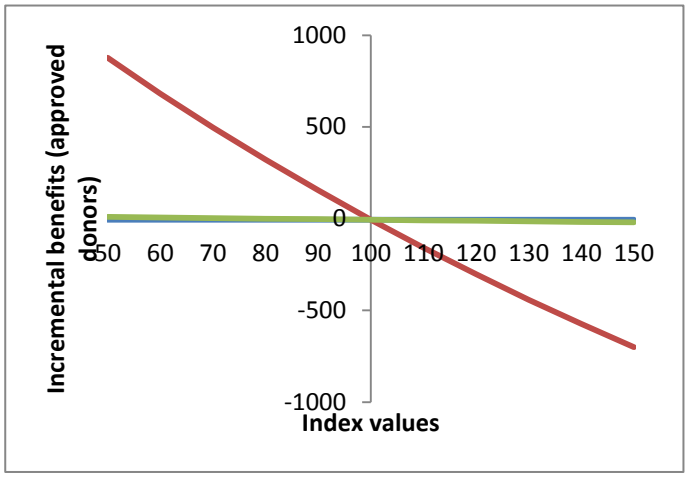
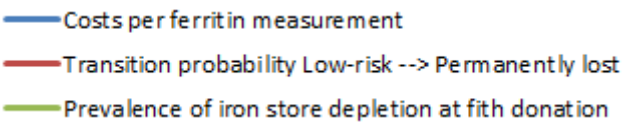


Figure 7: Legend applicable to figures 3, 4, 5 and 6



<u>Influence of potential parameter uncertainty on incremental *costs*</u>

<u>Parameter: *Costs per ferritin measurement*</u>

Female donors (figure 3)

All else equal, for female donors, costs per ferritin measurement were found not to alter the deterministic result of the proposed screening strategy being cost-increasing compared to the current screening strategy. In order to reach parity between proposed and current strategy costs, cost per ferritin measurement had to be decreased to EUR 0.90 (or the 45% index value), in additional univariate sensitivity analyses.

Male donors (figure 4)

All else equal, for male donors, costs per ferritin measurement were found not to alter the deterministic result of the proposed screening strategy being cost-decreasing compared to the current screening strategy. In order to reach parity between proposed and current strategy costs, cost per ferritin measurement had to be increased to EUR 6.67 (or the 334% index value), in additional univariate sensitivity analyses.

Parameter: *Low-risk donor transition probability towards* Permanently lost

Female donors (figure 3)

All else equal, for female donors, low-risk donor transition probabilities towards *Permanently lost* were found not to alter the deterministic result of the proposed screening strategy being cost-increasing compared to the current screening strategy.

Male donors (figure 4)

All else equal, for male donors, low-risk donor transition probabilities towards *Permanently lost* were found not to alter the deterministic result of the proposed screening strategy being cost-decreasing compared to the current screening strategy.

Parameter: *Prevalence of iron store depletion*

Female donors (figure 3)

All else equal, for female donors, prevalence of iron depletion among first-time donors, at the fifth donation of new donors, and at every tenth donation of non-new donors, was found not to alter the deterministic result of the proposed screening strategy being cost-increasing compared to the current screening strategy.

Male donors (figure 4)

All else equal, for male donors, prevalence of iron depletion at the fifth donation of new donors, and at every tenth donation of non-new donors, was found not to alter the deterministic result of the proposed screening strategy being cost-decreasing compared to the current screening strategy.

Influence of potential parameter uncertainty on incremental *benefits*

Parameter: *Costs per ferritin measurement*

Female donors (figure 5)

All else equal, costs per ferritin measurement were found not to have any influence on female screening strategy benefits.

Male donors (figure 6)

All else equal, costs per ferritin measurement were found not to have any influence on male screening strategy benefits.

Parameter: *Low-risk donor transition probability towards* Permanently lost

Female donors (figure 5)

Parity between female proposed and current screening strategy incremental benefits was reached after a reduction of low-risk donor probabilities to transition towards *Permanently lost* with 3.10 percentage points to 7.96% (a relative reduction of 28.0%). This reduction hence resulted in breach of female current strategy dominance. At the point of benefit parity, proposed strategy screening costs were 38.1% higher than current strategy screening costs.

Male donors (figure 6)

All else equal, varying low-risk donor transition probabilities towards *Permanently lost* was found to have import impact on model results, as graphically presented in figure 6. The deterministic transition probability was found to result in (near) parity between current and proposed strategy benefits. Increasing and decreasing the transition probability was found to result in negative and positive incremental proposed screening strategy benefits, respectively.

Parameter: *Prevalence of iron store depletion*

Female donors (figure 5)

Parity between female proposed and current screening strategy incremental benefits was reached after a reduction of iron store depletion prevalence among **first-time donors** with 9.08 percentage points to 0.92% (a relative reduction of 90.8%). This reduction hence resulted in breach of female current strategy dominance. At the point of benefit parity, proposed strategy screening costs were 38.5% higher than current strategy screening costs.

All else equal, varying prevalence of iron depletion among **new donors at their fifth donation**, and among **non-new donors at their every tenth donation**, was found not to alter the deterministic result of the proposed screening strategy being benefit-decreasing compared to the current screening strategy. This deterministic result was uphold even when iron store depletion prevalence was assumed zero among new donors at their fifth donation, and zero among non-new donors at their tenth donation simultaneously.

Male donors (figure 6)

All else equal, varying male iron store depletion prevalence (among both new donors at their fifth donation, and non-new donors at their every tenth donation) was found to have negligible influence on male donor proposed screening strategy incremental benefits.

4.2.1.1 *Composition donor population*

Where the proposed strategy was found to result in higher costs and lower benefits for female donors, for male donors it was found to result in lower costs and higher benefits. Higher proportions of male donors in the donor population composition will hence result in more favorable donor population wide proposed screening strategy costs and benefits effects. At a five-year time-horizon, donor population proposed strategy costs were found to equal current strategy costs, when the donor population proportion of female donors was decreased to 49.4%. At this proportion, proposed strategy benefits were found to be 3.3% lower than current strategy benefits. At a five-year time-horizon, no donor population composition will result in higher than current strategy proposed strategy benefits, as at this time-horizon both female and male donor proposed strategy benefits were found to be lower than current strategy benefits.

4.2.2 MULTIVARIATE SENSITIVITY ANALYSES, BETTER AND WORSE CASE SCENARIOS

In this subsection it was sought to further test the robustness of the deterministic results by simultaneously varying multiple model parameters, and subsequently constructing better and worse case scenarios. As costs per ferritin measurement and the probability of a low-risk donor transitioning to model state *Permanently lost* were found to have the greatest potential influence on final results, these model parameters were selected for multivariate sensitivity analysis.

As can be derived from figures 4, 5, 6, and 7, for both female and male donors, incremental proposed screening strategy costs decrease with decreasing costs per ferritin measurement. Based on the same figures it becomes clear decreasing transition probabilities of low-risk donors towards *Permanently lost* result in increasing proposed screening strategy incremental benefits. Given these results, better and worse case scenarios were constructed in table 7, by simultaneously decreasing (better cases) and increasing (worse cases) costs per ferritin measurement, and the respective transition probabilities.

For female donors, it was found simultaneous reduction of costs per ferritin measurement and low-risk donor transition probabilities towards becoming permanently lost never (i.e. up to the maximally modeled 50% reduction of their deterministic values) results in proposed strategy cost savings. Female donor proposed strategy incremental benefits were found to be positive for the first time at a simultaneous reduction of the respective parameters to a 70% index value of their deterministic 100% index value.

For male donors, compared to the deterministically derived costs per ferritin measurement and low-risk donor transition probabilities towards *Permanently lost*, simultaneously reducing these parameter values resulted in increasing proposed strategy incremental benefits, and increasing proposed strategy incremental costs. These incremental costs, however, did always remain negative.

Simultaneously increasing the above male donor parameters resulted in further decreasing proposed strategy incremental costs, at the costs of increasingly negative proposed strategy incremental benefits.

TABLE 6: Better and worse case scenarios.

Index value		Incremental costs/benefits proposed strategy (% change compared to current strategy)			
		Female donors		Male donors	
Costs per ferritin measurement	Transition probability low-risk --> *Permanently lost*	Costs	Benefits	Costs	Benefits
50	50	12	8	-16	18
60	60	16	4	-17	14
70	70	20	1	-18	10
80	80	24	-3	-19	7
90	90	29	-6	-20	3
100	**100**	**33**	**-9**	**-21**	**0**
110	110	38	-12	-22	-3
120	120	42	-15	-23	-6
130	130	46	-18	-23	-9
140	140	51	-20	-24	-12
150	150	55	-23	-25	-14

5 DISCUSSION

This study aimed to assess the efficiency of a newly proposed blood donor screening strategy, developed in order to better prevent donation induced donor iron store depletion and anemia, and to better secure a high-quality donation product. Main new features of the proposed screening strategy included exemption of pre-donation capillary hemoglobin measurements based on donor's previous hemoglobin levels, and periodical donor iron store surveillance by ferritin measurements. Efficiency of the proposed screening strategy was compared to the current Dutch screening strategy standard, by means of calculating the proposed strategy's incremental cost-effectiveness ratio over the current Dutch strategy. Time-dependent screening strategy costs and benefits were derived by applying the proposed and current screening strategy to a Markov model. The perspective of the Dutch blood donation facilities was adopted for assessment of screening strategy costs and benefits. Screening-approved donors were considered as screening strategy benefits.

Evaluated at a one-year and at a five-year time-horizon, for male donors the proposed screening strategy was found to effectively dominate the current screening strategy. For male donors, the proposed strategy was found to result in lower screening costs (a 6% decrease) and higher benefits (a 2% increase), when evaluated at a one-year time-horizon. Substantial reductions in male screening costs were found when evaluated at a five-year (a 21% cost reduction), and at a ten-year (a 24% cost reduction) time-horizon. Simultaneously at these same time-horizons, proposed

strategy benefits were effectively equal to current strategy benefits (equal at a five-year, and 2% lower at a ten-year horizon).

Between a one to ten year time-horizon, for female blood donors the proposed screening strategy was found to consistently result in higher total screening costs, and lower total benefits. For female donors, the proposed screening strategy was hence found to be dominated by the current screening strategy at all time-horizons modeled.

The current Dutch donor population gender composition would result in de proposed screening strategy generating increased screening costs and decreased screening benefits over the current screening strategy. Depending on donor population distribution between male and female donors male donor efficiency gains could at least partly offset female donor efficiency losses. Indeed, at a five-year time-horizon, this study found a donor population gender composition of 49.4% female donors, to result in equal current and proposed strategy screening costs.

Robustness of model results was assessed by multiple univariate and multivariate sensitivity analyses. For both female and male donors, realistic variation of model parameters never altered final deterministic costs results (increased screening costs for female donors, and costs-savings for male donors).

For both female and male donors, sensitivity analyses revealed that, all else equal, decreasing the probability a low-risk donor becomes inactive results in increased proposed strategy benefits. Likewise, increasing this probability resulted in decreased proposed strategy benefits. However, it arguably is not likely the respective transition probability as included in the model is underestimated. According to the proposed screening strategy, low-risk donors are exempted from pre-donation hemoglobin measurement, and its associated finger-prick and potential donor deferral. As donor return rates are negatively influenced by negative donation experiences, the proposed screening strategy might result in decreased probabilities of low-risk donors becoming inactive. This potential effect was however not incorporated in the deterministic analysis. Therefore, for both female and male donors, the deterministic results arguably reflect a minimum of benefits that could be generated by the proposed screening strategy.

All deterministic analyses revealed female proposed screening strategy benefits lower than current strategy benefits. However as low-risk donors might be less likely to become inactive under the proposed strategy than assumed, and as low-risk donors less likely to become inactive result in higher female benefits, implementing the proposed screening strategy among female donors might be less unattractive than as would be concluded based on the deterministic results derived by this study. For female proposed screening strategy benefits to become equal to those of the current screening strategy, all else equal, the probability a low-risk donor becomes inactive as used in deterministic analyses, had to be decreased with 3.10 percentage points (a relative reduction of

28.0%). At that point, female proposed strategy costs were still 38.1% higher than costs incurred according to the current strategy.

A second main analysis, in addition to the main costs and benefits analysis, revealed the proposed strategy to be associated with increased proportions of lost donors. In particular among female donors, the proposed strategy caused more donors to become lost. This increase is due to proposed strategy associated forced termination of donor careers, in case too low threshold ferritin levels are revealed. Where according to the current strategy donors can only terminate their donor career, and hence become lost donors, on their own initiative, according to the proposed strategy donors can additionally be forced to terminate their donor career, and hence be forced to become lost donors, in case too low ferritin levels are revealed. In order to maintain an adequate supply of donor blood, the proposed strategy might require donation facilities to compensate additional loss of donors and to hence recruit additional new donors.

The need for recruitment of new donors due to additional proposed strategy donor loss might be offset by proposed strategy increased retention of low-risk donors. Retention of low-risk donors higher than expected would offset the loss of donations due to lost donors, limiting the need for new donor recruitment. Determining the exact need for recruitment of new donors, and determining associated recruitment and new-donor screening costs was considered to be beyond the scope of the present study, and these costs were hence not included in the analyses conducted. However, these costs should be considered by donation facilities when implementing a new screening strategy.

The present study focused on gains and losses potentially associated with the proposed screening strategy in terms of screening costs and the number of approved blood donors. Potential donor health benefits associated with the proposed screening strategy were not quantified by the present study. Accordingly, differences between the current and proposed strategy in donor health, or the degree of donor health protection, were not included in the efficiency analysis conducted. However, minimizing risk of inflicting donation-induced harm on the health of donors, might be considered a worthwhile aim. In philanthropically driven donation settings, such as the Dutch, even more value might be attributed to this aim, as donors do not receive any compensation for their blood donations. If quantified by any future research, donor health gains associated with the proposed screening strategy could be used to further improve the model developed by the present study, incorporating the value of protecting donor health.

To the best of our knowledge, no previous research quantifies health gains associated with improved blood donor screening strategies. However, previous research does indicate donor safety improvements to result from screening strategy advancements the proposed screening strategy was based on. E.g., Magnussen et al. (2015) reported a reduction of the prevalence of low hemoglobin

levels among blood donors after implementing a strategy including ferritin screening. Would the proposed screening strategy indeed be found to result in donor health gains, for male donors, the proposed screening strategy would hence result in safety gains and in efficiency gains over the current screening strategy. Female donor health gains, once quantified, may justify the efficiency losses associated with the proposed screening strategy, as found in the present study.

To the best of our knowledge, this study is the first to fully focus on economic aspects associated with blood donor screening strategies. To some extent, distinct proposed screening strategy aspects have been subjected to economic remarks before. In Germany, post-donation hemoglobin measurement for low-risk donors has previously been reported to save time and expenditures (Lotfi et al., 2005). In Denmark, donor iron store surveillance has previously been reported to be complicated by high screening costs associated with ferritin measurements (Magnussen & Ladelund, 2015). This study however, is the first to provide insight in final economic consequences of an integrated screening strategy.

In addition to derived inferences regarding proposed strategy efficiency, this study delivers a comprehensive model, designed for evaluation of the blood donor screening strategies evaluated in this study. This model could easily be adjusted in order to reflect potential future developments in blood donor screening strategies. Hence, the model developed by the present study could provide guidance in conducting economic evaluations of potential future screening proposals.

In terms of the strategy costs and benefits evaluated, this study concludes the proposed strategy to be disadvantageous compared to the current strategy for female donors, and advantageous for male donors. The current Dutch donor population gender composition results in female donor disadvantages outweighing male donor advantages. Hence, from this study's perspective, based on the current Dutch donor population gender composition, the current Dutch screening standard should not be replaced with the proposed screening strategy. Retention of low-risk donors higher than expected potentially increases proposed screening strategy benefits for both female and male donors. The present study focused on screening costs and the number of approved donors only. In order to thoroughly assess the effect of implementing the proposed screening strategy, results derived by the present study should be complemented with donor health effects of the proposed screening strategy, once quantified by future research.

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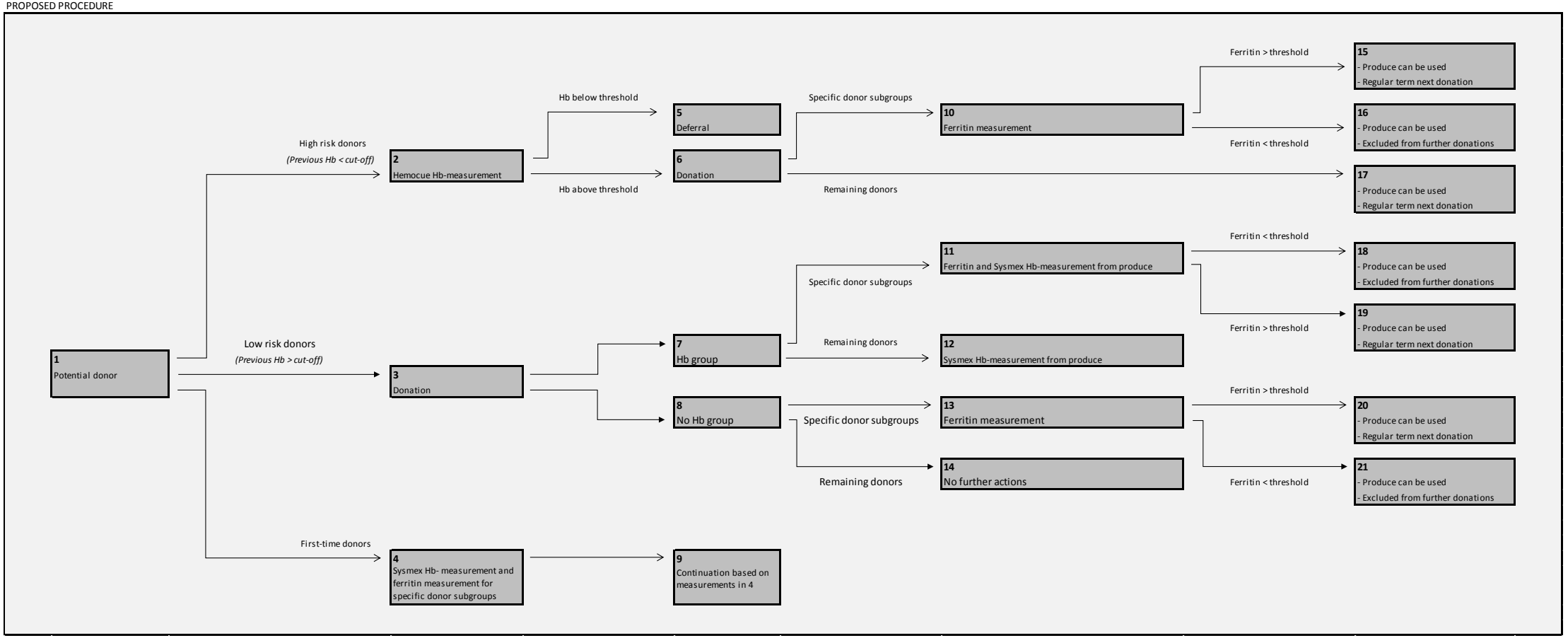
Thomson, R. A., Bethel, J., Lo, A. Y., Ownby, H. E., Nass, C. C., & Williams, A. E. (1998). Retention of "safe" blood donors. The Retrovirus Epidemiology Donor Study. *Transfusion, 38*(4), 359-367.

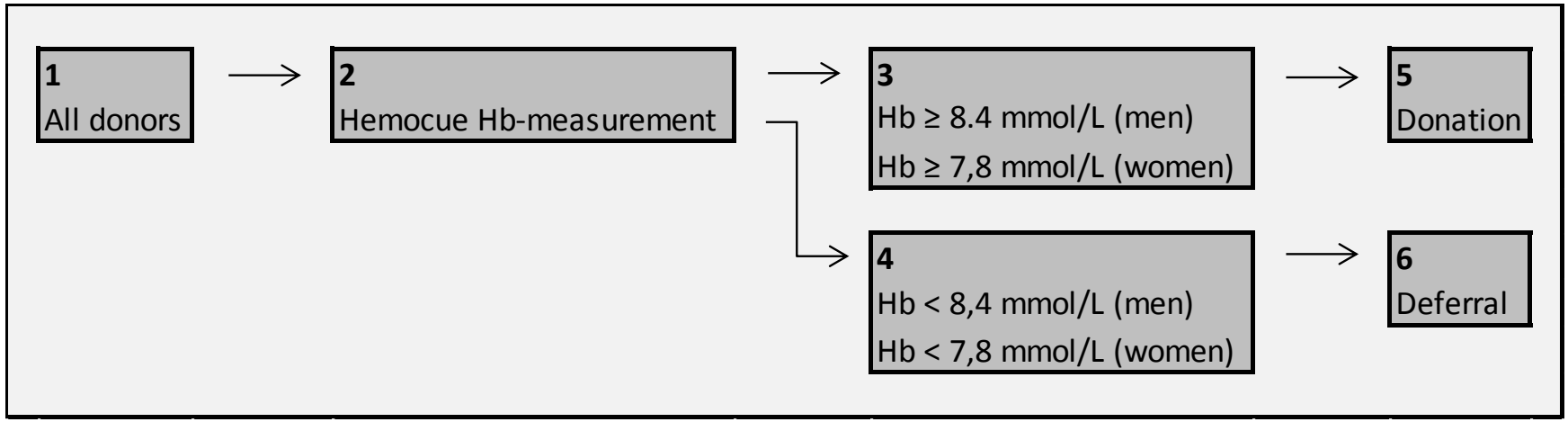
Ziemann, M., Steppat, D., Brockmann, C., Washington, G., Kirchner, H., & Schlenke, P. (2006). Selection of whole-blood donors for hemoglobin testing by use of historical hemoglobin values. *Transfusion, 46*(12), 2176-2183. doi: 10.1111/j.1537-2995.2006.01049.x

APPENDIX 1: Decision tree proposed screening strategy

PROPOSED PROCEDURE



APPENDIX 2: Decision tree current screening strategy



APPENDIX 3: Cutoff value low/high-risk donor division

Post-donation anemia screening of blood donors has previously been prospectively evaluated by Lotfi et al. (2005) and Ziemann et al. (2006), in their German donation centers. While Lotfi et al. (2005) were the first to evaluate a strategy exempting donors with a high previous hemoglobin level from pre-donation hemoglobin measurement, Ziemann et al. (2006) extended the validity of their results to include donors with lower yearly donation frequencies. Between May 2003 and November 2005, Ziemann et al. (2006) assessed 81913 consecutive donors. In order to enhance accuracy, Ziemann et al. (2006) set the hemoglobin cutoff value granting donors to be high or low-risk donors, 4 g/L above the minimum hemoglobin level required for donation. Hence, for females the cutoff level was set at 129 g/L, for males the cutoff level was set at 139 g/L. Minimum hemoglobin levels required for blood donation are equal in Germany and the Netherlands, at 125 g/L for females and 135 g/L for males. Based on Ziemann et al. (2006), cutoff levels granting blood donors to be high or low-risk donors were set at 129 g/L for female donors, and at 139 g/L for male donors, for the purpose of the present study.

APPENDIX 4: Donor subgroup selection for ferritin screening

Developing the screening strategy proposed by the present study, selection of donor subgroups for ferritin screening was made based on evidence presented by previous literature. In the donor subgroup selection process, several consecutive steps taken. These steps, the decisions made during these steps, and the evidence these decisions were based on, are discussed in this section.

1. FERRITIN THRESHOLD FOR IRON STORE DEPLETION

For both men and women, the World Health Organization (WHO) defines depletion of iron stores in otherwise healthy individuals to occur at a serum ferritin level of < 15 μg/L. Table 7 and Table 8 list several studies assessing prevalence of iron store depletion among blood donors and the general population. Indeed, all

Table 7 and Table 8 studies regard a serum ferritin level of 15 μg/L or slightly less as the threshold below which iron stores are considered to be depleted. Based on the definition of iron store depletion adopted by relevant previous studies and the WHO, this study assumed iron store depletion to occur at serum ferritin levels < 15 μg/L. In order to prevent blood donors from donation induced iron store depletion, whilst simultaneously avoiding unnecessary donor deferral, the blood donor screening strategy proposed by this study was set to exclude blood donors from further future donations in case serum ferritin levels < 15 μg/L are revealed.

2. PREVALENCE OF IRON STORE DEPLETION

Currently, prevalence of below 15 μg/L ferritin levels among Dutch blood donors and the Dutch general population is not known. Table 7 provides an overview of several previous studies assessing prevalence of below 15 μg/L ferritin for males in other donor populations. Table 8 does the same for females. From Table 7 and Table 8 it could be derived that for both males and females, blood donation is associated with bodily iron store depletion.

For the present study, iron store depletion prevalence among Dutch blood donors was based on the studies listed in Table 7 and Table 8. Differences in blood donation legislation and general characteristics of blood donors across countries might exist. These differences might influence the prevalence of below 15 μg/L ferritin levels among donor populations. Higher donation frequencies allowed per year might for example result in a higher prevalence of iron store depletion among blood donors. In order to account for potential uncertainty in the true prevalence of iron store depletion among Dutch blood donors, influence of this prevalence on final study results was assessed in a sensitivity analysis.

Based on Table 7 and Table 8, prevalence of low depleted iron stores was assumed to average at 10.0% for female first-time donors, and at 0% for male first-time donors. For non-first-

time donors, prevalence of depleted iron stores was assumed to average at 28.5% for female donors, and at 15.0% for male donors. Influence of uncertainty incorporated in these prevalence numbers on final study results, was assessed in a sensitivity analysis.

TABLE 7
Prevalence of low ferritin levels among males, assessed by several studies

			Prevalence low ferritin (%)	
Study	**Country**	**Definition low ferritin**	**First-time donors**	**Donors**
Cable et al., 2011	U.S.	< 12 µg/L	0	16.4
Alvarez-Ossorio, 2000	Germany	< 15 µg/L	0	24
Simon, 1981	U.S.	< 12 µg/L	0	8
Kiss, 2013	U.S.	< 12 µg/L	0	16.9
Finch, 1977	U.S.	< 12 µg/L	0	-
Milman, 1991	Denmark	< 15 µg/L	0.4	3.3

TABLE 8
Prevalence of low ferritin levels among females, assessed by several studies

FEMALES			Prevalence low ferritin (%)	
Study	**Country**	**Definition low ferritin**	**First-time donors**	**Donors**
Cable et al., 2011	U.S.	< 12 µg/L	6.4	27.1
Alvarez-Ossorio, 2000	Germany	< 15 µg/L	11	30
Simon, 1981	U.S.	< 12 µg/L	12	23
Kiss, 2013	U.S.	< 12 µg/L	6.2	29.2
Finch, 1977	U.S.	< 12 µg/L	5.9	-

3. DONOR SUBGROUPS SUBJECT TO FERRITIN SCREENING: SELECTION BASED ON DONATION HISTORY

Several studies have developed and prospectively evaluated blood donor screening strategies including measurement of blood donor ferritin levels. Table 9 lists these studies, and the donor subgroups they subjected to ferritin measurements.

TABLE 9
Donor subgroups subject to ferritin screening, as proposed by several studies

Study	Country	Donor subgroups subject to ferritin screening
O'meara et al. (2011)	Switzerland	All presenting blood donors
Stern et al. (2012)	Switzerland	- Once yearly for repetitive blood donors - For every donor with a hemoglobin level of < 128 g/L (females) or < 138 g/L (males)
Alvarez-Ossorio et al. (2000)	Germany	- All first-time female donors - After five donations for every donor
Ziemann et al. (2006)	Germany	All donors at every tenth donation
Magnussen et al. (2015)	Denmark	- All first-time donors at their first donation - All donors at every tenth donation
Bravo et al. (unpublished)	U.S.	Ferritin screening based on hemoglobin level at presentation - Female donors: Hb 12.5 - 12.9 g/dL (7.8 - 8.0 mmol/L) - Male donors: Hb 12.5 - 13.4 g/dL (7.8 - 8.3 mmol/L)

One study included in Table 9 measured ferritin among all presenting donors, at every donation. All other studies in the table selected specific subgroups for ferritin screening. As is the case at our facility, subgroups selection for ferritin screening might be subject to economic constraints. Magnussen and Ladelund (2015), indeed mention financial motives for not performing a ferritin measurement at every donor presentation.

Two studies included in Table 9 selected donors for ferritin measurement based on their hemoglobin level at presentation for donation. A second study partly did so. All other studies included in the table selected donors for ferritin screening based on their donation history. In previous literature, yearly donation frequency and the absolute number of historical blood donations, have been reported to be negatively correlated with donor ferritin levels (Alvarez-Ossorio et al., 2000; Cable et al., 2011; Finch et al., 1977; Simon et al., 1981). Additionally, hemoglobin levels are no adequate measure of donor iron stores. Anemia, as defined by a below threshold hemoglobin level, is a late consequence of depleted bodily iron stores. Effectively, at any level of hemoglobin, bodily iron stores may be depleted. Therefore, blood donor deferral based on below threshold hemoglobin levels helps to prevent donation induced anemia, but does not help to prevent donation induced depletion of bodily iron stores (Eder, 2010; Kiss et al., 2013).

Given the limited adequacy of hemoglobin screening in prevention of blood donor iron store depletion, this study argued it to be ineffective to relate qualification of blood donors for ferritin measurement to their hemoglobin level. A single blood donation extracts a substantial amount of iron from the donor's bodily iron stores (Alvarez-Ossorio et al., 2000). Indeed, a higher yearly donation frequency, and a higher absolute number of donations in a donor's donation history, have

been reported to result in lower, and potentially depleted, donor iron stores. Therefore, this study argued donors should be selected for ferritin measurements based on their donation history.

First-time donors

In the donor screening strategy presented by Magnussen and Ladelund (2015), all first-time donors are subjected to a ferritin measurement. However, based on Table 7, prevalence of below 15 µg/L ferritin levels among male first-time donors could be considered negligible. Ferritin screening of male first-time donors would thus not result in exclusion of any donors. Therefore, this study argued there is little rationale for a routine ferritin measurement of all male first-time donors. However, based on Table 8, among female first-time donors, below 15 µg/L ferritin levels definitely are present. First-time donors who before their first donation present with low iron stores, generally are not capable of successfully maintaining a regular donation scheme (Garry et al., 1995). Therefore, ferritin screening of all female first-time donors might arguably result in early exclusion of unsuccessful donors. Indeed, Alvarez-Ossorio et al. (2000) recommended ferritin screening of first-time donors to be directed towards females only.

Regular donors

Table 9 includes four studies that selected blood donors for ferritin measurement based on their donation history. Two of these studies measured donor ferritin levels at every tenth donation of every donor. One study measured donor ferritin levels at every fifth donation of every donor, and one study measured donor ferritin levels once yearly for all repetitive donors.

Using data on blood donors enrolled at their Lübeck, Germany based donation center, Alvarez-Ossorio et al. (2000) retrospectively assessed donor ferritin levels in relation to donation frequency and absolute number of donations. Donors were stratified based on their number of historical donations, with the lowest stratum consisting of donors with at least ten historical donations. Alvarez-Ossorio et al. (2000) reported donors with at least ten historical donations to have substantially lower ferritin levels than their first-time donor peers. However, ferritin levels were reported not to decrease further among strata with an even higher number of historical donations. As concluded by the authors themselves, this could suggest donation impact on ferritin levels at an even earlier stage. Finally, Alvarez-Ossorio et al. (2000) recommend a ferritin measurement for all new donors, after their first five donations.

Alvarez-Ossorio et al. (2000) showed blood donor ferritin levels not to substantially decrease further among donors with more than ten historical donations. Pedersen and Morling (1978) already reported ferritin levels of new blood donors to plateau after the first donations, for both male and female donors. A similar result was found by Garry et al. (1995) in a randomized, controlled, clinical

trial among people aged ≥ 65. Given this evidence of plateauing blood donor ferritin levels, blood donor ferritin levels could be measured at a lower frequency, following the ferritin measurement after the first five donations.

A blood donor ferritin measurement after the first five donations, provides an early identification of those donors that due to their donation of blood, suffer from iron store depletion. As blood donor ferritin levels are reported to plateau, those donors that are not iron depleted after the first five donations can thereafter be subjected to ferritin measurements at a lower frequency. Based on the studies included in Table 9, this lower frequency was set on every tenth donation for the present study.

APPENDIX 5: Markov model sub states

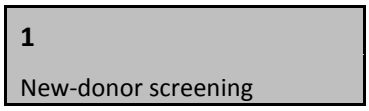
In this section, sub states included in Markov model main states are graphically presented. Current strategy Markov sub states are presented first.

1. CURRENT STRATEGY

State W: New donor

First-time donors are subjected to a comprehensive set of screening tests in order to assess their suitability to donate blood. As part of this set of screening tests, a hemoglobin measurement is performed. According to the current Dutch screening strategy, no ferritin tests are conducted for any donor. During their first visit, first-time donors are not allowed to actually donate blood. Sub states included in the main state *New donor* are depicted in Figure 8.

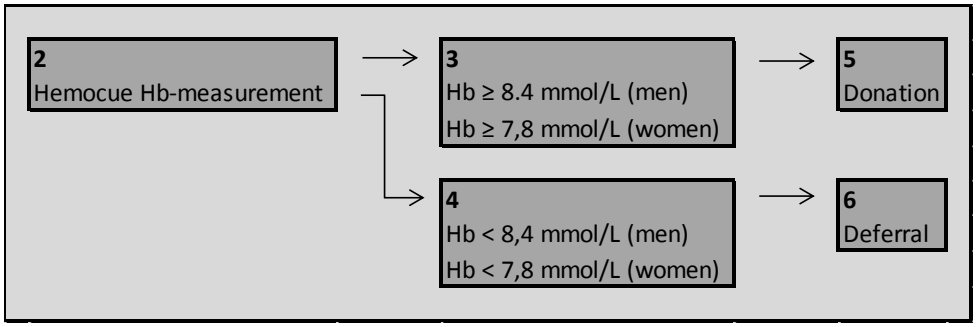
FIGURE 8
Sub states Markov state W: New donor



State X: Donor

According to the current standard screening strategy, no differentiated Markov states are developed based on historical hemoglobin values. If a donor presented to donate in the applicable model cycle, that donor is included in model state X for that model cycle. Sub states included in the Markov main state *Donor* are depicted in Figure 9. Hemoglobin threshold depicted in Figure 9 are derived from donation legislation, as enforced in the Netherlands (Council of Europe, 2009).

FIGURE 9
Sub states Markov state X: Donor



State Y: Temporarily inactive

State Y includes all blood donors that did not donate in the applicable model cycle, yet are not member of the donor group of permanently lost donors in model state Z. No screening costs, nor donation benefits are associated with donors included in state Y.

State Z: Permanently lost

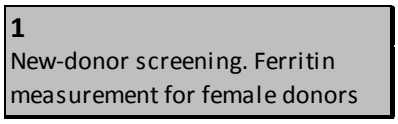
State Z contains all blood donors that were either first-time donor (state W) or donor (state X) during at least one model cycle, but never presented to donate thereafter. Donors are considered to be permanently lost if they did not present to donate for at least two years. As costs and effects are arguably equal to zero for all permanently lost donors, no distinction is made based on reason of donor loss.

2. PROPOSED STRATEGY

State A: New donor

In concordance with the current screening strategy, according to the proposed screening strategy first-time donors are subjected to a comprehensive set of screening tests in order to assess their suitability to donate blood. As part of this set of screening tests, a hemoglobin measurement is performed, and for female donors, an additional ferritin measurement. Based on these hemoglobin and ferritin measurements, first-time donors potentially transition to Markov model states *High-risk*, *Low-risk*, or *Excluded on ferritin*. During their first visit, first-time donors are not allowed to actually donate blood. Sub states included in the Markov main state *New donor* are depicted in Figure 10.

FIGURE 10
Sub states Markov state A: New donor



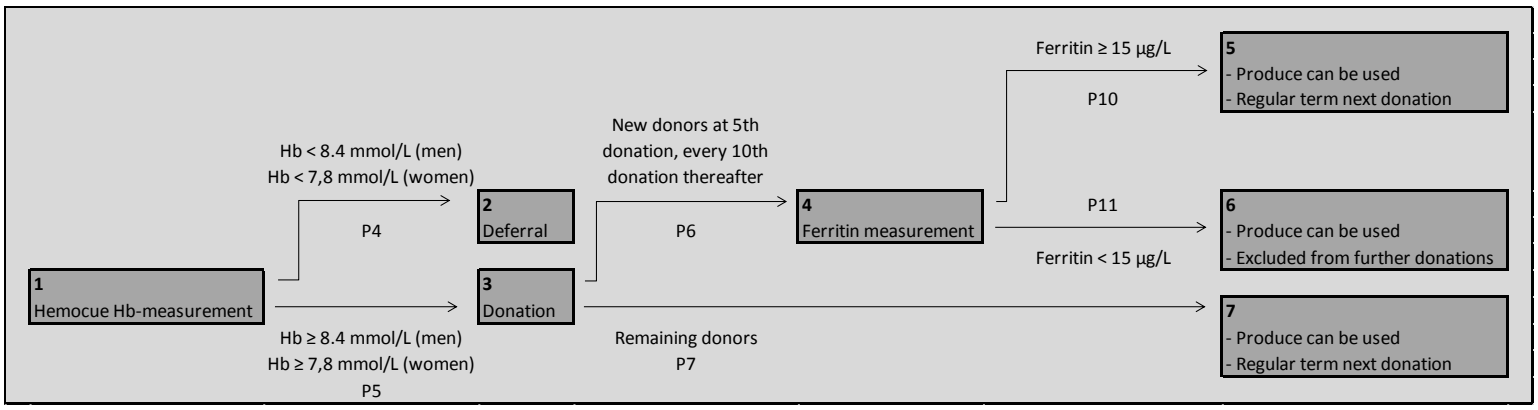
State B: High-risk

Blood donors were proposed to be high-risk donors in case their hemoglobin level showed to be below a certain threshold at their previous donation attempt. New donors who revealed below threshold hemoglobin levels in Markov state *New donor* also move to Markov state *High-risk*, at their subsequent donation attempt.

Sub states included in the Markov main state *High-risk* are assembled in the decision tree depicted in Figure 11. All high-risk donors are subjected to pre-donation capillary hemoglobin measurement. Those with hemoglobin levels above the legal threshold are allowed to donate. Of

those donors, specific donor subgroups (see Figure 11) are subjected to additional ferritin measurement. For the purpose of this study, donors with a ferritin level < 15 µg/L are excluded from making any further future donations.

FIGURE 11



Sub states Markov state B: High-risk

State C: Low-risk, Hb & State D: Low-risk, no Hb

Blood donors were proposed to be low-risk donors in case their hemoglobin level showed to be above a certain threshold at their previous donation attempt. New donors who revealed at or above threshold hemoglobin levels in Markov state *New donor* move to Markov state *low-risk, Hb*, at their subsequent donation attempt.

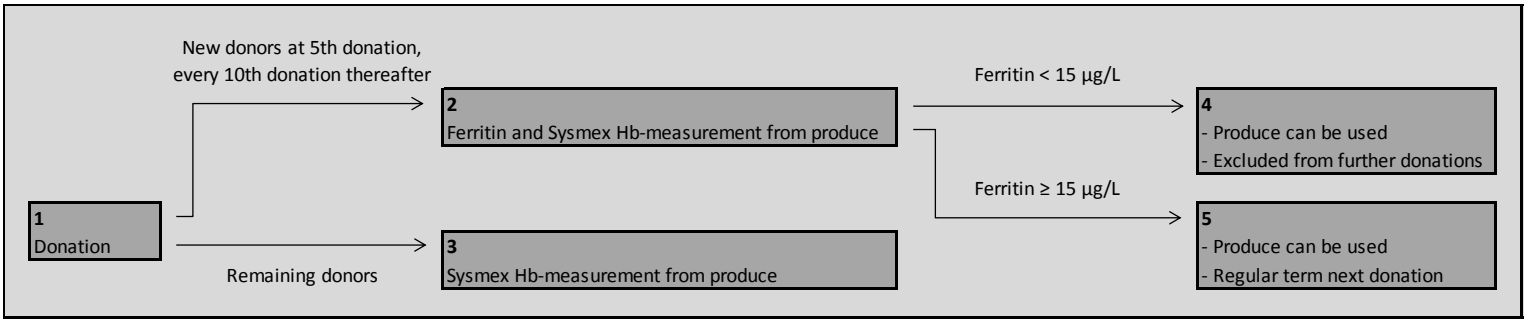
Sub states included in the Markov main state *Low-risk, Hb* are assembled in the decision tree depicted in

Figure *12*. Sub states included in the Markov main state *Low-risk, no Hb* are assembled in the decision tree depicted in Figure 13. All low-risk donors are allowed to donate without pre-donation hemoglobin measurement. For low-risk donors in state *Low-risk, Hb*, hemoglobin levels are measured post-donation, from the donation produce. For low-risk donors in state *Low-risk, no Hb*, hemoglobin levels are never measured. Those low-risk donors that were low-risk donors during their previous donation, and did receive a hemoglobin measurement (thus were member of the *Low-risk, Hb* state), are incorporated in state *Low-risk, no Hb*. Hence, donors, consecutively donating as low-risk donors, are exempted from any hemoglobin measurement every second, consecutive low-risk donation.

For specific donor subgroups (see

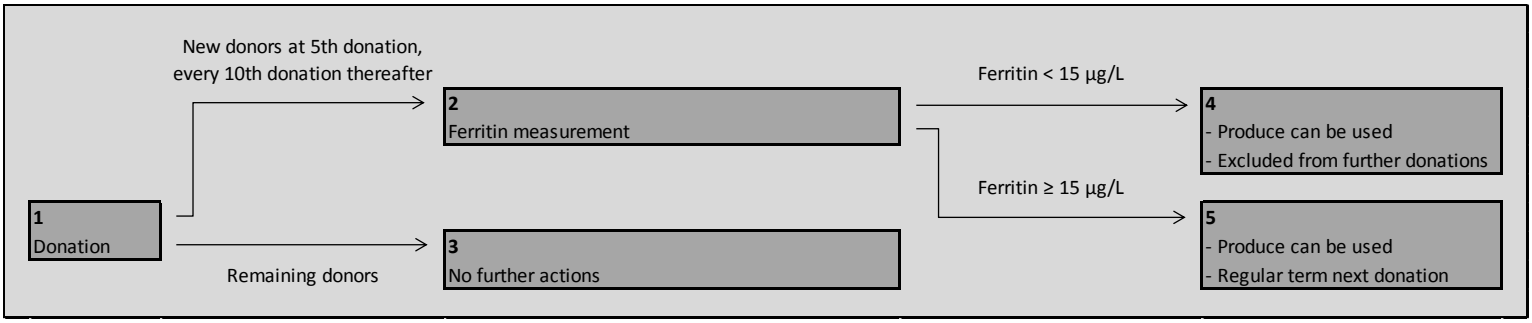
Figure *12* and Figure 13), both in state *Low-risk, Hb* and in state *Low-risk, no Hb*, ferritin levels are measured. Similar to high-risk donors, low-risk donors who reveal below threshold ferritin levels, are excluded from making any further future donations for the purpose of this study.

FIGURE 12



Sub states Markov state C: Low-risk, Hb

FIGURE 13



Sub states Markov state D: Low-risk, no Hb

State E: Temporarily inactive

State E includes all blood donors that did not donate in the applicable model cycle, yet are not member of the donor group of permanently lost donors in model state F, nor of the group of excluded donor in model state G. All temporarily inactive donors are incorporated in model state E, regardless of the specific reason of their inactivity. In case a donor is temporarily inactive for multiple consecutive model cycles, that donor remains in model state E for all those consecutive cycles of inactivity.

State F: Permanently lost

State F contains all blood donors that were either first-time donor (state A), high-risk donor (state B) or low-risk donor (states C and D) during at least one model cycle, but never presented to donate

thereafter. Donors are treated as first-time donors if they did not donate for at least two years (De Kort & Veldhuizen, 2010). Therefore, donors are considered to be permanently lost if they did not present to donate for at least two years. No further distinction is made regarding reason of donor loss.

State G: Excluded on ferritin

This paper proposes it to be beneficial to screen specific donor subgroups for ferritin levels. Below threshold ferritin levels results in exclusion of the applicable donor from any further future donations. These donors, excluded from future donations based on their ferritin level, occupy Markov state G.

APPENDIX 6: Transition and branch probabilities current strategy Markov model

In this section, calculation of the current screening strategy Markov state transition probabilities and Markov sub state branch probabilities is discussed. Transition probabilities are discussed first.

1. TRANSITION PROBABILITIES

Transitioning to *Donor*

Transition probabilities towards Markov state *Donor* were established by determining the proportion of donors in Markov states *New donor*, *Donor* and *Temporarily inactive*, attempting to donate in the subsequent model cycle. I.e., transition probabilities towards *Donor* were established by determining the proportion of donors in the donation database that, after being in model state *New donor*, *Donor* or *Temporarily inactive* for one model cycle, subsequently attempted to donate in the subsequent model cycle.

Transitioning to *Temporarily inactive*

Transition probabilities towards *Temporarily inactive* were established by determining the proportion of donors in Markov states *New donor*, *Donor* and *Temporarily inactive*, not attempting to donate in the subsequent model cycle, whilst not being permanently lost. I.e., transition probabilities towards *Temporarily inactive* were established by determining the proportion of donors in the donation database that, after being in model state *New donor*, *Donor* or *Temporarily inactive* for one model cycle, did not make a donation attempt in the subsequent model cycle, whilst simultaneously were not permanently lost.

Transitioning to *Permanently lost*

Transition probabilities towards *Permanently lost* were established by determining the proportion of donors in Markov states *New donor* and *Donor*, never attempting to donate again following the current model cycle. As donors are considered to be permanently lost after two years of inactivity, and the donation dataset contains information on 2012, 2013, and 2014, transition probabilities towards Markov state *Permanently lost* could be based only on those donors who donated in 2012.

2. BRANCH PROBABILITIES

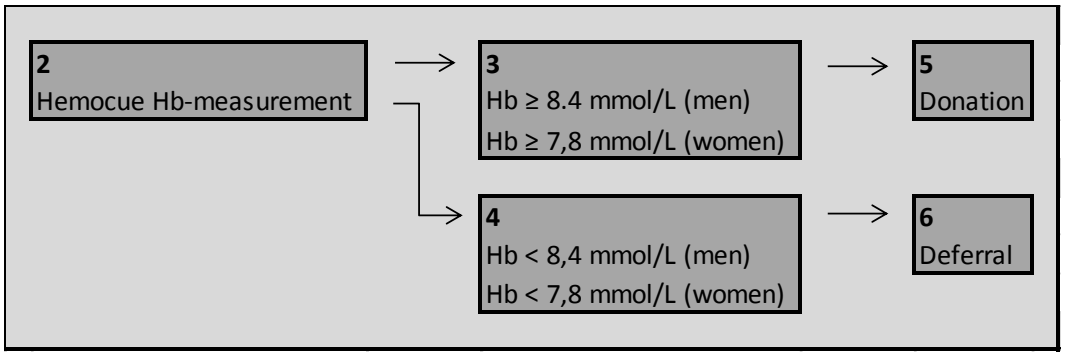
State X: *Donor*

Sub states included Markov state *Donor*, are depicted in Figure 14. According to the current screening strategy, all donors presenting to the donation facility are subjected to a pre-donation, capillary hemoglobin measurement. Based on their revealed hemoglobin levels, presenting donors are allowed to actually donate blood, or are deferred from donation. Based on the donation dataset

available to this study, Dutch female donors were estimated to have a 6.1% probability of donation deferral due to below 7.8 mmol/L hemoglobin levels at donor presentation. For Dutch male donors, the chance of donor deferral due to below 8.4 mmol/L hemoglobin levels at donor presentation was estimated to equal 2.8%.

Donor deferral due to below threshold hemoglobin levels has been reported to subsequently result in significantly lower donor return rates, compared to accepted donors (Boulton, 2008; Newman et al., 2006). Indeed, based on the donation dataset available to this paper, 18.0% of female donors who experienced a hemoglobin deferral in 2012, did not return to donate within two years, whilst 11.1% of approved 2012 female donors did not return to donate within two years. For male donors, these proportions amounted to 9.8% and 6.7%, respectively.

FIGURE 14
Sub states Markov state *Donor*



APPENDIX 7: Transition and branch probabilities proposed strategy Markov model

In this section, calculation of the proposed screening strategy Markov state transition probabilities and Markov sub state branch probabilities is discussed. Transition probabilities are discussed first.

1. TRANSITION PROBABILITIES

Proposed strategy transition probabilities were derived from the current strategy transition probabilities depicted in Table 1. These current strategy transition probabilities were adjusted based on evidence presented in relevant literature and the proposed strategy Markov model structure, in order to accurately effect the proposed strategy. Several steps were conducted adjusting the current strategy transition probabilities. These steps are discussed in the subsections below.

1.1 RATIO BETWEEN HIGH-RISK AND LOW-RISK

In the current screening strategy Markov model, one donation state is included: state X: *Donor*. In the proposed strategy, a division is made between high-risk and low-risk donors. Hence, current strategy transition probabilities towards and from Markov state *Donor*, are split between the high-risk and low-risk states according to the proposed strategy Markov model. Based on the donation dataset available to this paper, a ratio was calculated, reflecting this split between transition probabilities towards and from the high-risk and low-risk (including both Markov state *Low-risk, Hb* and Markov state *Low-risk, no Hb*) Markov states. These ratios are stated in Table 10 and Table 11.

All ratios stated in Table 10 and Table 11 were estimated retrospectively examining the dataset available to this paper, containing all donation attempts made in the Netherlands, in 2012, 2013 and 2014. Hence, blood donors were retrospectively divided in a high-risk and a low-risk group. It was assumed that this division, and the differences in screening methodology between the donor groups, would not impact donor behavior in a real-life donation setting.

TABLE 10
High-risk / low-risk donor transition probability ratios, applicable to female donors

	Transition to	
Transition from	**High risk**	**Low risk**
New donor	0.0599	0.9401
High risk donor	0.4076	0.5924
Low risk donor	0.1533	0.8467
Temporarily inactive	0.1950	0.8050

TABLE 11
High-risk / low-risk donor transition probability ratios, applicable to male donors

	Transition to	
Transition from	**High risk**	**Low risk**
New donor	0.0000	1.0000
High risk donor	0.3133	0.6867
Low risk donor	0.0914	0.9086
Temporarily inactive	0.1333	0.8667

1.2 Division Low-risk, Hb and Low-risk, no Hb

The only difference in events taking place in Markov states *Low-risk, Hb* and *Low-risk, no Hb*, derives from post-donation hemoglobin measurement. This post-donation hemoglobin measurement is conducted in Markov state *Low-risk, Hb* only. As this post-donation hemoglobin measurement is conducted on a blood sample taken from the donation produce itself, for blood donors effectively no difference is perceived between the two low-risk Markov states. Hence, no differences in donor behavior should occur.

Transition probabilities towards, from and between Markov states *Low-risk, Hb* and *Low-risk, no Hb*, were derived from Table 10 and Table 11, where just one low-risk Markov state was assumed.

1.3 Transition probability New donor → Excluded on ferritin

According to the proposed screening strategy, male first-time donors are not routinely subjected to a ferritin measurement. Therefore, the probability that males, occupying Markov state *New donor*, will transition to the Markov state *Excluded on ferritin*, was assumed to be zero. Female first-time donors are set to be routinely subjected to a ferritin measurement at their first presentation. Based on related literature included in Table 8, this study assumed the probability that females, occupying Markov state *New donor*, will transition to the Markov state *Excluded on ferritin* to equal 10.0%.

1.4 Transition probabilities High-risk → Excluded on ferritin & Low-risk → Excluded on ferritin

As severely decreased hemoglobin levels are a late manifestation of depleted iron stores, low ferritin levels might effectively be present at any hemoglobin level (Eder, 2010; Kiss et al., 2013). However, Alvarez-Ossorio et al. (2000) do indicate blood donor anemia to be caused by depleted donor iron stores in the majority of cases. Detection of, and donor exclusion based on too low donor ferritin levels, can thus be argued to be more likely among donors occupying Markov state *High-risk*. Table 7 and Table 8 in appendix 4, however, provide information on prevalence of low ferritin levels among

the general male and female blood donor populations respectively. Average prevalence is stated, and no distinction is made based on donor hemoglobin levels. Additionally, this study proposes ferritin measurements to be performed regardless of donor hemoglobin levels. I.e., ferritin measurements are assumed to be performed for blood donors occupying Markov states *High-risk* and *Low-risk* in equal frequency. In real-life circumstances, it is highly likely transition probabilities towards Markov state *Excluded on ferritin* will be above the general blood donor population average for donors occupying Markov state *High-risk*, and below that same average for donor occupying Markov state *Low-risk*. However, for the purpose of this study, only the total number of donors excluded due to too low ferritin levels, and thus the average transition probability towards Markov state *Excluded on ferritin*, is relevant. Therefore, a simplifying, but non-distorting, assumption was made, granting transition probabilities towards Markov state *Excluded on ferritin* to be equal, and at the population average, for both donors occupying Markov state *High-risk*, and donors occupying Markov state *Low-risk*. The subsections below consecutively discuss the probability a donor qualifies for a ferritin measurement, and the probability a below 15 μg/L ferritin level is revealed if a ferritin measurement is performed. Subsequently, transition probabilities are derived.

Probability a ferritin measurement is performed

This study argues it to be appropriate to screen all new blood donors at their fifth donation. Based on the donation dataset available to this study, for female donors, the average yearly frequency of successful donations was estimated to be 1.75 (SE 0.0022). Based on the same dataset, this frequency was estimated to be 2.50 (SE 0.0040) for male donors. Hence, on average, female new donors were estimated to make their fifth donation after 2.85 years. Male new donors were estimated to make their fifth donation after 2.0 years, on average.

Calculated based on the donation dataset, each year, 14.6% of all successful female donations are made by new donors. Based on the same dataset, each year, 8.5% of all successful male donations are made by new donors. Given their respective yearly donation frequency and model cycle length, at the end of each model cycle, female donors occupying Markov states *High-risk* and *Low-risk* were estimated to have a 1.71% chance of making their fifth donation as a new donor, and thus of qualifying for a ferritin measurement. For male donors this chance was estimated to amount to 0.85% per model cycle.

Those new donors who, following their fifth donation, are not excluded from further donations due to a below 15 μg/L ferritin level, receive a ferritin measurement every tenth successful donation thereafter. Among the Dutch blood donor population, 85.4% of successful female blood donation are performed by females who have made more than five previous donations. Among Dutch male donors, 91.5% of all successful donations are performed by donors who have made more

than five previous donations. In total, given their respective yearly donation frequency and model cycle length, female donors occupying Markov states *High-risk* and *Low-risk* were estimated to have a 5.15% chance of making their tenth donation after their previous ferritin measurement, and thus of qualifying for a renewed ferritin measurement. For male donors this chance was estimated to amount to 4.42%.

Both for male and female donors occupying Markov states *High-risk* and *Low-risk,* the total probability of qualifying for a ferritin measurement results from combining the probability a new donor is making his or her fifth donation, with the probability a non-new donor is making a tenth donation after his or her previous ferritin measurement. Hence, for females occupying Markov state *High-risk* or *Low-risk* the probability a ferritin measurement is performed, was estimated to amount to 6.86%, each model cycle. For male donors, this probability was estimated to amount to 5.27%, each model cycle.

Probability a < 15 µg/L ferritin level is revealed at fifth donation new donors

According to the screening strategy proposed by this study, for male first-time donors, no routine ferritin screening is performed at the donor's first presentation to the blood bank. Therefore, prevalence of below 15 µg/L ferritin levels among male new donors at their fifth donation, can be directly derived from Table 7. As discussed in section 2, prevalence of below 15 µg/L ferritin levels is estimated to range between 5.0% and 25.0% for male, non-new donors.

As discussed in section 1.3, between 5.0% and 15.0% of all female first-time donors are estimated to be excluded from blood donations based on below 15 µg/L ferritin levels at initial presentation. As discussed earlier, an individual's ferritin level decreases as his or her number of blood donations made increases. Therefore, the 5.0% to 15.0% of female first-time donors who reveal below 15 µg/L ferritin levels at their first presentation to a blood bank, will arguably also have below 15 µg/L ferritin levels after five blood donations, if they are allowed to donate. However, according to the screening strategy proposed in this study, female first-time donors are routinely subjected to a ferritin measurement at their first presentation to the blood bank. Hence, according to the screening strategy proposed, the 5.0% to 15.0% of first-time female donors who present with below 15 µg/L ferritin levels, are excluded from any blood donation beforehand. Arguably, this will decrease the prevalence of below 15 µg/L ferritin levels among new female donors at their fifth donation. However, females with below 15 µg/L ferritin levels at their first presentation might experience more iron-deficiency related complications after donation, or might have a higher probability of being deferred from donation based on below threshold hemoglobin levels. They therefore might be discouraged to make further blood donations. Females with below 15 µg/L ferritin levels might thus be underrepresented among new donors making their fifth donation, even

without ferritin screening strategies. This underrepresentation would dilute the effect of the proposed screening strategy in decreasing the prevalence of below 15 µg/L ferritin levels among female donors, making their fifth donation. Taking into account the possible effects of the proposed screening strategy, based on Table 8, prevalence of below 15 µg/L ferritin levels among new, female donors, making their fifth donation, is assumed to range between 16.0% and 25.0%.

Probability a < 15 µg/L ferritin level is revealed at tenth donation after previous ferritin measurement

Table 7 and Table 8 depict prevalence of low ferritin levels among blood donors in a situation without donor exclusion based on ferritin levels, and without iron supplementation. As previously discussed, blood donor ferritin levels have been reported to plateau after the first few donations (Alvarez-Ossorio et al., 2000; Garry et al., 1995; Pedersen & Morling, 1978). Hence, the ferritin levels of those donors who show above 15 µg/L ferritin levels at their fifth donation, can generally be expected not to decrease below the 15 µg/L threshold at subsequent donations. The screening strategy evaluated in this study can thus be expected to filter out most donors at risk of iron deficiency at their fifth donation. Therefore, prevalence of below 15 µg/L ferritin levels can be expected to be substantially lower among donors at their tenth-donation measurements, than for new donors at their fifth-donation measurement. While exact prevalence numbers were not readily available from previous studies, this study assumed prevalence of below 15 µg/L ferritin levels at every tenth donation to equal 15.0% for female donors, and 7.5% for male donors. Influence on study result of uncertainty incorporated in these assumptions, was evaluated in a sensitivity analysis.

Transition probabilities

Probabilities of blood donors occupying Markov states *High-risk* and *Low-risk* transitioning to Markov state *Excluded on ferritin*, were ultimately derived combining the probability a ferritin measurement is performed, with the probability a below 15 µg/L ferritin level is revealed by that measurement. These two probabilities have been discussed above in this section. Ultimately, for female donors occupying Markov state *High-risk* or *Low-risk*, the probability of transitioning to Markov state *Excluded on ferritin* for the next model cycle, was estimated to equal 1.10%, each model cycle. For males, this probability was estimated to equal 4.7%, each model cycle.

1.5 REMAINING TRANSITION PROBABILITIES

Apart from the occasional donor that is excluded from further donations based on below 15 µg/L ferritin levels, from the donor's perspective no differences with the current screening strategy arise from the proposed screening strategy. The blood sample needed for a ferritin measurement would

be obtained from part of the donation produce itself, no additional blood collection would be required. According to the current screening strategy, part of the donation produce is used for screening measurements already, e.g. for screening on viral infections. The ferritin measurement introduced by the proposed screening strategy would not increase the amount of test blood collected from the donation produce.

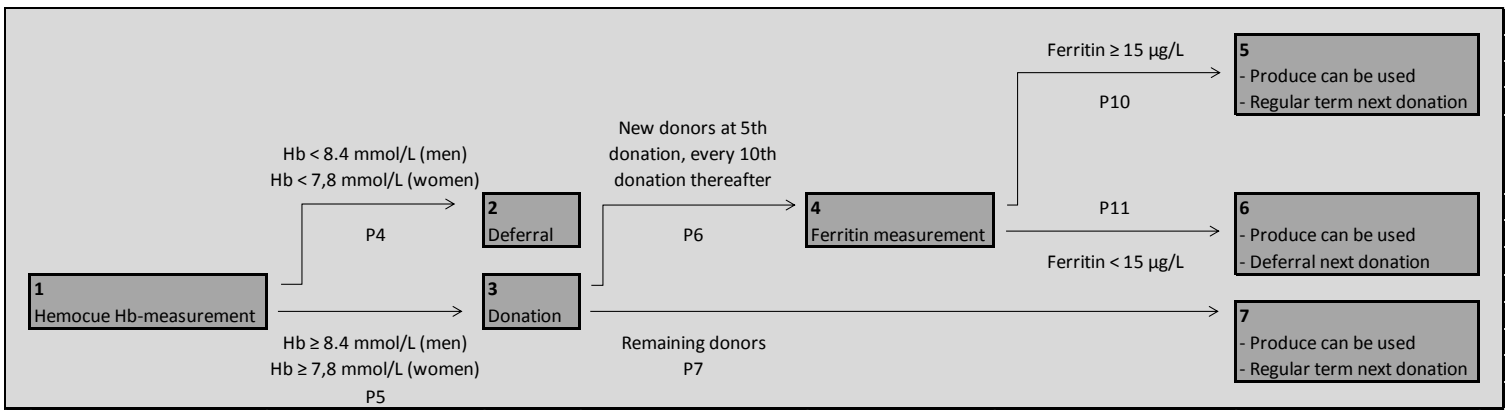
As the introduction of an occasional ferritin measurement effectively would not alter the donor's donation experience, the introduction of ferritin measurements was assumed not to influence donor behavior. Therefore, after establishment of transition probabilities towards *Excluded on ferritin*, remaining transition probabilities from Markov states *High-risk*, *Low-risk* and *Temporarily inactive*, towards Markov states *High-risk*, *Low-risk*, *Temporarily inactive* and *Permanently lost*, were assumed to maintain the same ratio as the current strategy transition probabilities included Table 1.

2. BRANCH PROBABILITIES

State B: High-risk

Sub states included in Markov state *High-risk*, are depicted in Figure 15. According to the screening strategy proposed in this study, high-risk donors are subjected to a pre-donation hemoglobin measurement. Retrospectively applying the proposed high-risk / low-risk division to the three-year Dutch donation dataset available to this paper, it was estimated female high-risk donors have a 17.8% chance of being deferred from donation, due to too low pre-donation hemoglobin levels. Male high-risk donors were estimated to have a 13.2% chance of being deferred from donation, due to too low pre-donation hemoglobin levels. The probability a high-risk donor is subjected to a ferritin measurement, and the subsequent probability the revealed ferritin level is above or below 15 µg/L, are discussed in appendix 7.

FIGURE 15
Sub states included in Markov state *High-risk*



State C: *Low-risk, Hb* & State D: *Low-risk, no Hb*

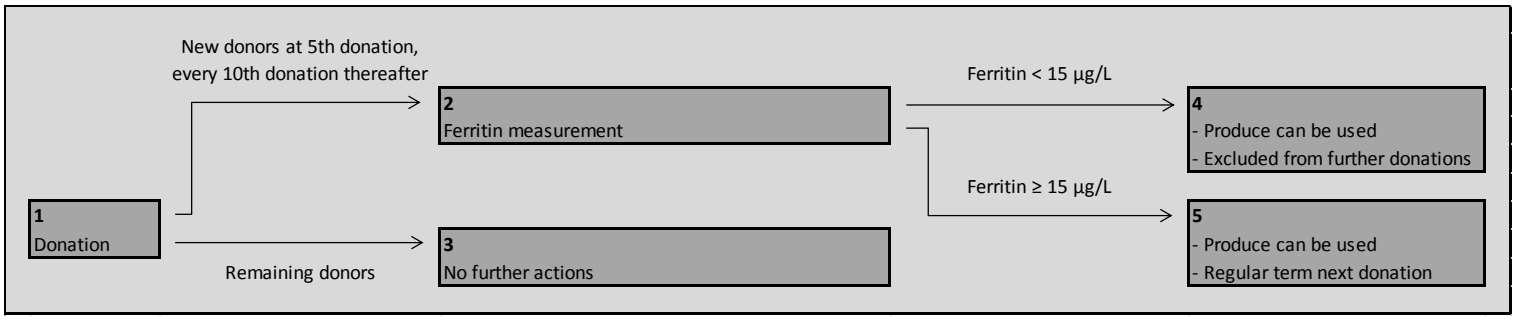
Sub states included in Markov state *Low-risk, Hb*, are depicted in Figure 16. Sub states included in Markov state *Low-risk, no Hb* are depicted in Figure 17. According to the screening strategy proposed in this paper, low-risk donors are allowed to donate without pre-donation hemoglobin measurements. The probability a low-risk donor is subjected to a ferritin measurement, and the subsequent probability the revealed ferritin level is above or below 15 µg/L, are discussed in appendix 7.

Retrospectively applying the high-risk / low-risk division to the three year Dutch donation dataset available to this paper, it was estimated female low-risk donors have a 96.0% probability of revealing an above 7.8 mmol/L hemoglobin level. Male low-risk donors were estimated to have a 97.9% probability of revealing an above 8.4 mmol/L hemoglobin level. As low-risk donors do not receive a hemoglobin measurement prior to their donation, low-risk donors cannot be deferred from donating based on too low hemoglobin levels. Therefore, retrospectively evaluated over the three years covered by the Dutch donation dataset available to this study, exemption of low-risk donors from pre-donation hemoglobin screening would have had resulted in blood collection from donors with below threshold hemoglobin levels in 4.0% of female low-risk donors, and in 2.1% of male low risk donors.

In the three-year donation dataset available to this study, hemoglobin levels are determined using the current standard Hemocue technique. However, according to the screening strategy proposed by this study, hemoglobin levels of low-risk donors are measured on venous blood samples. Therefore, a simplifying assumption associated with the above approach is that the Hemocue determined hemoglobin levels in the donation dataset, are mirrored by the hemoglobin measurements on venous blood samples.

FIGURE 16
Sub states included in Markov state *Low-risk, Hb*

FIGURE 17
Sub states included in Markov state *Low-risk, no Hb*



APPENDIX 8: Costs per screening test

Three screening tests are associated with the screening strategies evaluated in this study. Costs of these screening tests are discussed in the subsections below.

1. FERRITIN MEASUREMENT

Currently, no ferritin measurements are conducted among any blood donors presenting to any Dutch donation facility. Therefore, costs of ferritin measurements cannot be derived from the Dutch current practice. Table 12 lists several studies that implemented a ferritin measurement at their related donation facility, and published the costs per ferritin measurement they incurred. Based on Table 12 and in-house expert opinion, the cost of a single ferritin measurement was assumed to equal EUR 2.00, for the purpose of this study.

TABLE 12

Study	Study period	Country	Price
Magnussen et al. (2015)	February, 2012 – February, 2014	Denmark	USD 1.80
O'Meara et al. (2011)	January, 2004 – December, 2009	Switzerland	USD 5.85
Bravo et al. (unpublished)	March, 2013 – February, 2014	U.S.	USD 2.75

2. HEMOGLOBIN MEASUREMENT ON CAPILLARY BLOOD

Capillary hemoglobin measurements are currently routinely performed in the Dutch donation practice, using the Hemocue technique. Hence, for the purpose of this study, costs of (Hemocue) capillary hemoglobin measurements were based on current experience, and were set at EUR 1.00 per single capillary hemoglobin measurement.

3. HEMOGLOBIN MEASUREMENT ON VENOUS BLOOD

Currently, no venous blood hemoglobin measurements are conducted on blood donors presenting to a Dutch donation facility. Therefore, costs of venous blood hemoglobin measurements cannot be derived from the Dutch current practice. However, two clinical chemists connected to our donation facilities, estimated for this study total costs of a single hemoglobin measurement on a venous blood sample to amount to approximately EUR 1.10.

APPENDIX 9: Costs and benefits current screening strategy

In the subsections below, costs and benefits associated with each current screening strategy Markov state are discussed.

State W: *New donor*

New donor are subjected to a comprehensive set of screening test. According to the current strategy, the only test conducted relevant for this study, is a capillary blood hemoglobin test. This hemoglobin test is obligatory for all new donors. As new donors do not actually donate blood at their first visit, no benefits are associated with Markov state *New donor*.

State X: *Donor*

According to the current donor screening strategy, all donors presenting to donate are subjected to a capillary blood hemoglobin measurement. As stated in section 2, currently 6.1% of Dutch female donors are deferred from donation due to a below threshold pre-donation hemoglobin level. Among Dutch male blood donors, hemoglobin deferral occurs in 2.8% of all donation attempts. Hence, for female donors occupying Markov state *Donor*, the probability of being approved for donation is 93.9%. For male donors occupying Markov state *Donor*, this probability equals 97.2%.

State Y: *Temporarily inactive* & State Z: *Permanently lost*

Donors occupying Markov states *Temporarily inactive* and *Permanently lost* do not present to donate during the applicable model cycle. Hence, no screening costs, nor donation benefits, are associated with those donors.

APPENDIX 10: Costs and benefits proposed screening strategy

In this section, costs and benefits associated with each proposed screening strategy Markov state are discussed. These costs and benefits were based on current screening strategy costs and benefits, and adjusted by relevant literature where appropriate. First, this relevant literature and associated adjustments are discussed. Subsequently, proposed strategy costs and benefits are derived.

1. BRAVO ET AL.

In their U.S. based donation facility, Bravo et al. implemented a donor screening strategy, increasing donation intervals based on donor ferritin levels. Donors were selected for ferritin measurements based on their hemoglobin level at presentation. Hemoglobin levels of 12.5 – 12.9 g/dL for females and 12.5 – 13.4 g/dL for males triggered ferritin measurement. Donors who subsequently revealed ferritin levels of <12 μg/L were postponed from their next donation for a 24-week period. Between a 12-month period before ferritin measurement implementation (November 26, 2011 – November 25, 2012) and a 12-month period after ferritin measurement implementation (March 1, 2013 – February 28, 2014), Bravo et al. compared the proportions of donors that were deferred from donation due to a below threshold hemoglobin level. As opposed to the blood donation practice in the Netherlands, in the U.S. the hemoglobin deferral threshold is equal for male and female donors, and is set at 12.5 g/dL. In the period before their screening strategy implementation, 853,656 blood donors were tested for hemoglobin levels at their donation facility. In the period after screening strategy implementation, 808,117 blood donors were tested. Compared with the period before strategy implementation, Bravo et al. report their screening strategy to result in a statistically significant ($p<0.0001$) decrease of the proportion of donors deferred from donation due to below threshold hemoglobin levels, both for male and female donors. For female donors this proportion is reported to decrease with 17.5%, from 12.0% to 9.9%. Among male donors, hemoglobin deferral was reported to decrease with 38.5%, from 1.3% to 0.8%. Additionally, Bravo et al. observed a statistically significant decrease in the proportion of male donors for whom a ferritin measurement was required. For male donors this proportion decreased from 6.3% to 5.4%, while for female donors no statistically significant decrease was observed.

2. APPLICATION RESULTS BRAVO ET AL. TO THE PRESENT STUDY

According to the screening strategy proposed by this study, donor deferral based on below threshold hemoglobin levels can occur among high-risk donors only. According to Bravo et al., exclusion of donors with below threshold ferritin levels will result in less high-risk donors deferred from donation due to too low hemoglobin levels. Additionally, it could be argued exclusion of iron store depleted donors might result in a higher share of blood donors classified as low-risk donors. However, for

simplicity, and due to a lack of evidence in support of this latter theory, this study merely focusses on the decreased share of deferred high-risk donors.

As discussed in appendix 7, based on the three-year Dutch donation dataset available to this study, it was estimated application of the high-risk/low-risk division would have had resulted in 17.8% of female high-risk donors and 13.2% of male high-risk donors being deferred from donation due to below threshold hemoglobin levels. Applying the results reported by Bravo et al. to the deferral rates derived from the Dutch donation dataset, this study assumed the exclusion of low-ferritin donor to result in donation deferral due to below threshold hemoglobin values to occur in 14.7% of female high-risk donors, and in 8.1% of male high-risk donors. That is, this study assumed, in concordance with Bravo et al., the screening strategy it proposes to result in a decrease of donation deferral due to below threshold hemoglobin levels of 17.5% among female high-risk donors, and of 38.5% among male high-risk donors.

3. COSTS AND BENEFITS PER MARKOV STATE

State A: *New donor*

New donors are subjected to a comprehensive set of screening test. According to the proposed strategy, all new donors receive a hemoglobin measurement on a venous blood sample. This hemoglobin measurement is obligatory for all new donors. All female new donors additionally receive a ferritin measurement. As new donors do not actually donate blood during their first visit, no benefits are associated with Markov state *New donor*.

State B: *High-risk*

According to the screening strategy proposed by this study, all high-risk donors are subjected to a pre-donation capillary blood hemoglobin measurement. Additionally, as derived in appendix 7, among 6.86% of female high-risk donors, and among 5.27% of male high-risk donors, a ferritin measurement is conducted, and 14.7% of female high-risk donors and 8.1% of male high-risk donors were assumed to reveal below threshold pre-donation hemoglobin levels. Hence, 85.3% of female high-risk donors, and 91.9% of male high-risk donors were assumed to be approved to donate.

State C: *Low-risk, Hb* & State D: *Low-risk, no Hb*

According to the screening strategy proposed by this study, low-risk donors are allowed to donate without prior hemoglobin measurement. Hence, as no low-risk donors are deferred due to too low hemoglobin levels, 100% of low-risk donors are approved for donation. From the donation produce of *low-risk, Hb* donors, hemoglobin levels are measured conducting a venous blood hemoglobin test.

Additionally, as derived in appendix 7, among 6.86% of all female low-risk donors, and among 5.27% of all male low-risk donors, a ferritin measurement is conducted.

State E: *Temporarily inactive*, state F: *Permanently lost*, and state G: *Excluded on ferritin*

Donors occupying Markov states *Temporarily inactive*, *Permanently lost* and *Excluded on ferritin*, do not present to donate during the applicable model cycle. Hence, no screening costs, nor donation benefits, are associated with those donors.

APPENDIX 11: Results, costs per screening technique

		COSTS (EUR)			
		Capillary Hb	**Venous Hb**	**Ferritin**	**TOTAL**
Female donors					
1	Current	1672	0	0	1672
	Proposed	66	1494	2081	3641
	Increment	-1606	1494	2081	**1969**
5	Current	3890	0	0	3890
	Proposed	365	2478	2337	5179
	Increment	-3525	2478	2337	**1289**
10	Current	5109	0	0	5109
	Proposed	520	2964	2468	5951
	Increment	-4588	2964	2468	**843**
Male donors					
1	Current	2233	0	0	2233
	Proposed	81	1882	133	2096
	Increment	-2152	1882	133	**-137**
5	Current	6079	0	0	6079
	Proposed	456	3825	539	4820
	Increment	-5623	3825	539	**-1259**
10	Current	8480	0	0	8480
	Proposed	681	4976	781	6438
	Increment	-7799	4976	781	**-2042**
Donor population (weighted average female and male donors)					
1	Current	1845	0	0	1845
	Proposed	70	1614	1479	3163
	Increment	-1775	1614	1479	**1318**
5	Current	4566	0	0	4566
	Proposed	393	2894	1781	5068
	Increment	-4173	2894	1781	**502**
10	Current	5109	0	0	5109
	Proposed	520	2964	2468	5951
	Increment	-4588	2964	2468	**843**