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EUROPEAN COMMITTEE (PARTIAL AGREEMENT) ON BLOOD TRANSFUSION (CD-P-TS)

21st Edition of the Guide to the preparation, use and quality assurance of blood components ("the Blood Guide") – Background Documents

EDQM Responsible Scientific Officer: Richard Forde

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For information :

EDQM address : 7 allée Kastner, CS 30026, FR-67081 Strasbourg (France)

CONTENTS

Background Document 1

GTS Ch2 document based on TRANSPOSE risk-based assessment tool
(by J.Castrén. Last update 1.5.2022)

Sex and gender in blood donation and transfusion practices

a. What the issues are;

In blood donation and transfusion practices donors´ and patients´ sex/gender is traditionally determined binomial and based on heteronormative and biological/physiological general differences between male and female individuals.
In the current western society traditional division only in two alternatives (which would be a lifelong solution for all individuals) is no more always valid. Individuals may change their sex determined in birth during their life (trans people) or might identify themselves as not belonging neither to the male nor the female alternative (intersex) or refuse to inform anything about their sex/gender categorization.

In blood donation the traditional division into male and female donors is needed for
-Donor acceptance based on their Hb-value
-Donor deferral based on pregnancy or lactation
-Donor deferral based on MSM-activity
-Donor screening algorithm based on pregnancy or miscarriage (Red cell antibody screening)
-Donation interval rules
-Donation volume rules in plasma donation
-Estimation of total blood volume in order to accept donors for a certain fixed donation volume
-Donor acceptance for plasma donation based on risk for HLA-antibodies OR donor testing for HLA-antibodies

In transfusion practices patients´ sex/gender is used for the determination for need of Rh/Kell negative red cell products

In donor and patient registration/identification can also a system be used where the official ID determinates the official sex used in the society.

It is important that in the blood donation and blood transfusion practices all individuals should be evaluated according same appropriate rules and that unnecessary/ inappropriate boundaries due to sex, gender and sexual orientation should be removed.

Categorisation is needed for the safety of donors and patients there, where strong biological/physiological differences exist, and individuals need to be divided into two or more groups what it comes to acceptance criteria or transfusion recommendations. Also clear rules for the safety of look back processes might be needed in countries where the donor/patient ID is combined with the official sex/gender and the society has mechanisms in place where individuals may change their official ID if the sex/gender is changed.

In case there would not be specific rules and principles concerning the diversity of gender/sex related issues, but the donors and recipients would instead no more be categorized as male or female individuals; all the sex/gender-based rules would need to be taken to account by using the precautionary principle:

- All the donors must reach the higher required Hb value to accepted as donors
- The minimum intervals for female donors must apply to all donors
- All the questions in the DHQ must be asked for all donors
- All donors must be tested for HLA antibodies in order to be accepted as plasma donors (And/or some countries must change their general acceptance criteria (only male plasma is accepted) for plasma donation)
- All the donors can donate the plasma volumes determined by the weight and height for female donors

➔ this practice would cause a remarkable loss of potential donations and cause risk for a severe shortage of blood products

➔ There is need national rules and improvement of the practices in blood establishments and also generally in the health care with can ensure

1. the human rights and respect of all individuals
2. the safety of the donors
3. the safety of the recipients
4. the sufficiency of the blood products

b. Issues related to (select all that apply):

X donor X recipient

- Severity

*grade of severity*DONOR*				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
		X		

-

*grade of severity*RECIPIENT*				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
		X		

- Imputability

-

*level of imputability*DONOR risks*

Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
	X					

*level of imputability*Recipient risks*						
Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
	X					

c. Options to minimise each of the risks

d. Proposed text to the 20 Ed

Sex and gender

In blood donation and transfusion practices donors´ and patients´ sex/gender is traditionally determined binomial and based on heteronormative and biological/physiological general differences between male and female individuals.

In the donor selection, all individuals should be evaluated according same rules and criteria that serve best to protect the safety of donors and patients. To ensure donor or recipient safety, a categorization to sex based on biological, physiological, behavioral characteristics is required for certain donor selection criteria and should be applied accordingly. Such safety aspects include for example selection criteria based on donor haemoglobin values, total blood volume estimation, pregnancy related risks including risks for HLA/HNA-antibodies, or sexual risk behavior.

e. Justification (data/references);

Goldman M, Butler-Foster T, Lapierre D, O'Brien SF, Devor A. Trans people and blood donation. Transfusion. 2020 May;60(5):1084-1092. doi: 10.1111/trf.15777. Epub 2020 Apr 28. PMID: 32343438

f. Considerations (e.g., financials, etc.).

Background Document 2

GTS Ch2 document
Prepared by J. Rosochova and Ch2 group 2022

Iron stores, Hb requirements

Comments and answers to the comments from Stakeholder consultation:

1.

Shared classification	Chapter	Page
B1/B2	2	45

Comments:

Plasma apheresis b' - please clarify if this includes plasma for fractionation. This is not clear as the hemoglobin is in focus in this chapter. 'b' - Why was plasma apheresis included, when not explicitly required (see 'b' - 'when measured' - why was this included, if it is not a requirement?
In addition, if it is measured, do the rest of the subsequent requirements apply?
In addition, this section should allow the option of using hematocrit, in addition to hemoglobin.
Hemoglobin levels for plasmapheresis: What is the basis for this, given published literature showing that there is no iron loss with frequent plasma donation (The Ferritin Levels in Plasma Donor (FLIPD) study. Schreiber GB, Brinser R, Rosa-Bray M, Yu ZF, Simon T. Transfusion. 2018 Apr;58(4):951-959. doi: 10.1111/trf.14489. Epub 2018 Mar 9. PMID: 29520799)?

Text as it is in the 20th Edition:

2.2.3.1 Haemoglobin concentration must be determined each time the donor donates **whole blood or cellular components** (Directive/2004/33/EC Annex III).

2.2.3.2 Haemoglobin values at donation must not be lower than the values shown in the table:

	Female	Male
Whole blood and cellular components a	125 g/L or 7.8 mmol/L	135 g/L or 8.4 mmol/L
Double red cell apheresis	140 g/L or 8.7 mmol/L	140 g/L or 8.7 mmol/L
Plasma apheresis b	120 g/L or 7.5 mmol/L	130 g/L or 8.1 mmol/L

a Directive/2004/33/EC Annex III

b if measured

Individual donations may be accepted below these levels after consultation with the responsible physician or as established by a competent authority based on norms for their specific populations. Hemoglobin should be measured preferably before the donation, but always before donation when donors were deferred from

ANSWERS:

- Hb values for plasma apheresis were included in this text for a very simple reason - to bring together all the hemoglobin limits for the donation of all blood components. Countries are free to decide whether Hb should be checked before plasmapheresis and / or to define situations in which Hb should be checked before plasmapheresis.
- All low Hb donors must be treated equally. Especially if the plasma donors are also donors of blood, platelets or red blood cells.
- Hematocrit in addition to hemoglobin is not prohibited, it is allowed, it depends on the decision of the blood establishment. For some apheresis devices it is necessary to enter the hematocrit at the beginning of the procedure.

GTS ad hoc working group recommends to transfer the Hb limits for plasmapheresis, platelet apheresis and erythrocytopheresis to the relevant articles.

2.

Shared classification	Chapter	Page
B2	Chapter 2 - 2.2.4	46

Comment:

It should be useful to add in the sentence "individual tailoring of donation frequency and/or of type of blood component donation and /or interval between two blood donations based on iron status"

Text as it is in the 20th Edition:

Measures to prevent iron depletion and to protect donor health may include:

• provision of materials for donor education particularly in regard to the impact of blood donation on iron stores;

• individual tailoring of donation frequency and/or of type of blood component donation based on iron status.

ANSWER:

- "individual tailoring of donation frequency/interval between two blood donations and/or of type of blood component donation based on sex/age/Hb-values/iron status"

GTS ad hoc working group accepts proposal and adds "……. sex/age/Hb-values/……"

3.

Shared classification	Chapter	Page
B2	2 Donor selection	46

Comment:

Measures to prevent iron depletion and to protect donor health: Please add: for donation of plasma for fractionation: testing from test tubes obtained from the product (citrate plasma) instead of the donor (serum or EDTA plasma) can significantly contribute to the prevention of iron loss due to iatrogenic anemia

Text in the 20th Edition:

Measures to prevent iron depletion and to protect donor health may include:

• provision of materials for donor education particularly in regard to the impact of blood donation on iron stores;

• individual tailoring of donation frequency and/or of type of blood component donation based on iron status;

• use of tests to assess iron status, such as ferritin, soluble transferrin receptor, and RBC indices;

• iron supplementation taking into account the risk of delaying the diagnosis of unapparent underlying diseases and side effects of the iron preparations

ANSWER:

Point to be added to the text:

- In plasmapheresis donations destined for plasma for fractionation: Use of samples from plasma collection container (instead of whole blood samples) for mandatory laboratory screening tests in order to avoid of iron in testing samples (see also 3.6.2.2.).

GTS ad hoc working group accepts proposal.

4.

Comment:

We suggest to choose a definition of iron deficiency.

ANSWER:

There is no consensus in Europe on the definition of iron deficiency. Clinical signs or test results should be taken under consideration. Different tests may be used in different blood establishments to examine iron stores.

GTS ad hoc working group recommends not to make changes to the text.

5.

Shared classification	Chapter	Page
B2	2.2.4	46

Comment:
Minimizing iron depletion in frequent blood donors, can "frequent" be defined?

Text as it is in the 20th Edition:

2.2.4.1 Blood establishments must have measures in place to minimize iron depletion in frequent blood donors (Directive 2004/33/EC, Annex III).

This is a text from directive 2004/33 EC

ANSWER:

There is no consensus on the definition of frequent blood donor. Different countries apply different definitions. Situation is not clear when donor donate different blood components.

GTS ad hoc working group recommends not to make changes to the text.

6.

Shared classification	Chapter	Page
B2	2.2.4	46

Comment:

We suggest instead of "taking into account the risk of delaying the diagnosis of" use "it is recommended to investigate the possibility of unapparent underlying diseases associated with iron deficiency and it is suggested to take side effects of the iron preparations into consideration whenever iron supplement is proposed".

Text as it in the 20th Edition:

Measures to prevent iron depletion and to protect donor health may include:

• provision of materials for donor education particularly in regard to the impact of blood donation on iron stores;

• individual tailoring of donation frequency and/or of type of blood component donation based on iron status;

• use of tests to assess iron status, such as ferritin, soluble transferrin receptor, and RBC indices;

• iron supplementation taking into account the risk of delaying the diagnosis of unapparent underlying diseases and side effects of the iron preparations.

ANSWER:a

The need for an investigation follows from the current text and the investigation itself is not usually (in many countries) permitted the blood establishment.

GTS ad hoc working group proposes :

• iron supplementation taking into account the risk of delaying the diagnosis of unapparent underlying diseases and adverse effects of the iron preparations.

7.

Shared classification	Chapter	Page
B2	Chapter 2.2.4.1	46

Comment:

Change proposed:

"• use of tests to assess iron status, such as serum iron, ferritin, total iron-binding capacity, transferrin saturation, soluble transferrin receptor and RBC indices;"

Text as it in the 20th Edition:

133 • use of tests to assess iron status, such as ferritin, soluble transferrin receptor, and RBC indices;

ANSWER:

"Ferritin, soluble transferrin receptor, and RBC indices;" are considered as the most important, most objective and most frequently used tests to assess the iron status in different surveys . Others are not excluded, but not sufficient when perform alone.

GTS ad hoc working group recommends not to make changes to the text.

8.

Shared classification	Chapter	Page
B2	2	46

Comment:

Add young donors (until age 25)?

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ANSWER:

There is no consensus on unique definition of young donor. Blood donation under 18 years is not accepted in Europe. We do not see the reason to specify the young age as age under the 25 years.

GTS ad hoc working group recommends not to make changes to the text.

9.

Shared classification	Chapter	Page
C	2.2.4.1	46

Comments:

"Blood establishments must have measures in place to minimize iron depletion in frequent blood donors."

It is suggested to use "BEs should have measures in place…"

GTS ad hoc working group accepted the proposal

2.2.4.1 Blood establishments should have measures in place to minimize iron depletion in frequent blood donors

List of publications for 21st version of GUIDE

Revision of Chapter 2, article Hemoglobin and Iron stores

1. **Strategies on protection of iron stores in plasma donors**, George Schreiber PPTA, EDQM International symposium on plasma supply management, January 30, 2019

   Frequent source plasma donation is not associated with lower plasma ferritin values or reduced body iron stores

2. **International forum: an investigation of iron status in blood donors,** Vuk Tomislav et al, Blood Transfusion 2017, 15: 20-41

3. **The strategies to reduce iron deficiency in blood donors randomized trial: design, enrolment and early retention**, W. Bialkowski et al, Vox Sanguinis 2015, 108: 178–185

   USA STRIDE study: *two-year, randomized, placebo-controlled study in blood donors. 692 frequent donors were randomized into one of two educational groups or one of three interventional groups. Donors randomized to educational groups either received letters thanking them for donating, or, suggesting iron supplements or delayed donation if they had low ferritin. Donors randomized to interventional groups either received placebo, 19-mg or 38-mg iron pills.*

AIS and IDE were common in this population of frequent donors. AIS was present in 32,0% of females and 17,2% of males with a mean ferritin of 19,7 – 17,4 mg/l for females and 34,7 – 34,9 mg/l for males IDE was present in 746% of females and 527% of males with a mean log10sTfR/ferritin of 2,3 ± 0,4 for females and 2,1 ± 0,4 for males.

Donors asked to take tablets were more likely to withdraw from the two-year longitudinal study within the first 60 days of participation, whereas donors receiving a letter only (control or interventional) remained as active participants. Indicating that some donors will be resistant to taking a pill regularly.

4. **Iron deficiency in blood donors: a national cross-sectional study,** Hannah E. Salvin, Transfusion 2014, 54(10):2 434-44

Australian study: *Overall,* ***apheresis-only donors*** *did* ***not appear to be at increased risk of iron deficiency (ID)*** *(Ferritin <12) compared with new donors*.

The prevalence of ID in new female donors was 12.0% compared with 1.3% in males.
The ***prevalence of ID in female WB-only donors was 26.4%; it increased with donation frequency and decreased with age.*** *The prevalence in male WB-only donors was 6.3% with no evident change with age or donation frequency.*

The high burden of ID among premenopausal female WB donors, especially those who make frequent donations, indicates that strategies of iron supplementation should be initially targeted to this group.

5. **Iron deficiency in Canadian blood donors**, Goldman Mindi, Transfusion 2014, 54(3): 775-779

Canadian study: Iron deficiency *is common in our whole blood donors and* ***correlates strongly with sex and frequency of donation. For female donors, more than one-third of first-time or reactivated donors and approximately two-thirds of repeat donors have low or absent iron stores****. The presence of iron deficiency, even in first-time female donors, is concordant with data from Canadian nutrition surveys showing inadequate iron intake and low iron stores in more than 10% of women under age 50. Iron deficiency is rare in first-time and reactivated male donors, but* ***more than one-third of repeat male donors have low or absent iron stores.***

6. **High prevalence of subclinical iron deficiency in whole blood donors not deferred for low hemoglobin,** A. Mireille Baart, Transfusion 2013, 53(8): 1670-1677

Dutch study: *5280 Dutch whole blood donors, who passed the Hb criteria for donation. During donor screening, Hb levels were measured in capillary samples (finger prick), and venous blood samples were taken for measurements of zinc protoporphyrin (>100umol/mol heme) and other iron variables. These variables included ferritin, transferrin saturation, soluble transferrin receptor (sTfR), hepcidin, red blood cell mean corpuscular volume (MCV), and mean cell Hb (MCH).*
Subclinical iron deficiency was present in 6.9% of male donors and in 9.8% of female donors. Prevalence rates ranged from 4.8% (based on transferrin saturation) to 27.4% (based on hepcidin concentration) in men and from 5.6% (based on sTfR concentration) to 24.7% (based on hepcidin concentration) in women.
Results at subsequent visit indicate *that Hb levels in donors with subclinical iron deficiency do not fully return to the normal value within 56 days after a blood donation. Consequently, these donors are*

at high risk of developing iron deficiency anaemia after a blood donation and subsequently being deferred at the next visit to the blood collection canter. ***Prolongation of the donation interval for donors with subclinical iron deficiency might be useful to protect them from developing iron deficiency anaemia and to prevent them from being deferred for a subsequent donation.***
Using Hb measurement as a screening tool in blood donors, iron deficiency cannot be detected in the subclinical state.

7. **Clinical evaluation of iron treatment efficiency among non-anemic but iron-deficient female blood donors: a randomized controlled trial**, Sophie Waldvogel et al, BMC Medicine 2012, 1741-7015/10/8

Swiss study: One week after donation*, 154* ***female donors with iron efficiency*** *without anemia, aged below 50 years, were randomly assigned to a* ***four-week oral treatment of ferrous sulphate*** *versus a placebo. The main outcome was the change in the level of* ***fatigue before and after the intervention. Aerobic capacity, mood disorder, quality of life, compliance and adverse events were also evaluated. Hemoglobin and ferritin were used as biological markers****.*

Results: *The effect of the treatment from* ***baseline to four weeks of iron treatment was an increase in hemoglobin and ferritin levels to 5.2 g/L (P < 0.01) and 14.8 ng/mL (P < 0.01), respectively****.*** ***No significant clinical effect was observed*** *for fatigue (-0.15 points, 95% confidence interval -0.9 points to 0.6 points, P = 0.697) or for other outcomes. Compliance and interruption for side effects was similar in both groups. Additionally, blood donation did not induce overt symptoms of fatigue in spite of the significant biological changes it produces.*

Conclusions: *These data are valuable as they enable us to conclude that donors with iron deficiency without anemia after a blood donation would* ***not clinically benefit from iron supplementation.***

8. **Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors (Review),** Smith GA, Fisher SA, Doree C, Di Angelantonio E, Roberts DJ, Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

The effects of iron supplementation on iron deficiency and deferral in blood donors

Iron deficiency can cause symptoms of tiredness. The interval between blood donations is set by independent regulators to minimise iron deficiency in donors. Potential blood donors are screened each time they visit to give blood to see if they have iron deficiency.

Donors who do not pass this screening test and so cannot give blood are deferred and asked to delay giving blood, but many of these donors do not return. If blood donors take iron tablets, then the risk Of becoming iron deficient may be reduced. However, the balance between the benefits of giving iron and the possible side effects is not clear. We have reviewed all the randomised trials testing the benefits of giving blood donors iron. The evidence is current up to November 2013. We found 30 randomised trials of iron supplementation in blood donors with a total of 4704 participants. We found that some of the studies did not report details of their design very well and people in some of the studies left the study early and did not contribute data.

Combining the results from four studies, we have shown that around 3% of donors who were given Iron supplements were unable to give blood when they next came to donate because the levels of ir in their blood were too low, compared with 10% of donors who did not take iron. More than this, 4% of iron-supplemented donors were unable to give blood at any future donation due to low iron levels,

compared with around 20% of donors not given iron supplementation. However, 29% of donors who took iron tablets experienced side effects compared with 17% of donors who were given dummy

tablets. Combined data from two studies showed that the iron-supplemented donors had nearly five times the chance of stomach upsets and changes in their taste compared to donors who did not take these tablets. Due to the issues around how reliable the studies were, the quality of evidence is moderate and these results could change with more research.

Donors can benefit from iron tablets, but the rate of side effects is high, which means in practice that giving all donors iron tablets is unlikely to be acceptable and we do not know whether giving iron causes extra problems over a long period of time. Blood services may target iron supplementation at groups or individuals who are at risk of iron deficiency or may try to reduce deferral by adjusting donation intervals to suit the donor's ability to give blood without becoming iron deficient or to give specific dietary advice to donor.

9. **Prediction of low haemoglobin levels in whole blood donors, Baart** AM, de Kort WL, Moons KG, Vergouwe Y, Vox Sanguinis 2011, 100(2):204-11

Individual data from 5191 whole blood donors were analysed.

143 donors had a low Hb level. Eleven candidate predictors were considered in logistic regression models to predict low Hb levels. The performance of the prediction model was studied with the receiver operating characteristic (ROC) curve. Internal validity was assessed with a bootstrap procedure.

Strong predictors were sex, seasonality, Hb level measured at the previous visit, difference in Hb levels between the previous two visits, time since the previous visit, deferral at the previous visit, and the total number of whole blood donation in the past 2 years.

Conclusion: The developed prediction model provides accurate discrimination between donors with low and appropriate Hb levels. The model predictions may be valuable to determine whether donors can be invited for a next donation, or whether some interventions such as postponement of the invitation are warranted. Potentially, this could decrease the number of donor deferrals for low Hb levels.

10. **Demographic correlates of low hemoglobin deferral among prospective whole blood donors,** Alan E. Mast, Karen S. Schlumpf, David J. Wright, Brian Custer, Bryan Spencer, Edward L. Murphy, and Toby L. Simon for the NHLBI Retrovirus Epidemiology Donor Study-II, Transfusion 2010, 50(8):1794-802

Low Hb deferrals were tracked in more 715,000 whole blood donors at six blood canters across the United States.

Demographic factors significantly associated with low Hb deferral include female sex (11 times greater odds than males), increasing age in men (men over 80 have 29 times greater odds than men under20), African American race (2-2.5 times greater odds than Caucasians), Hispanic ethnicity in women (1.29 times greater odds than Caucasian women), and weight in men (men under 124 pounds have 2.5 times greater odds than men over 200 pounds). Interestingly, increasing donation frequency is associated with decreased odds for low Hb deferral (women with one donation in the previous 12 months have two times greater odds than those with six donations).

Conclusion: Low Hb deferral is associated with female sex, older age, African American

race/ethnicity, and lower body weight in men. An inverse association with donation frequency suggests a selection bias in favour of donors able to give more frequently. These data provide useful

information that can be utilized to manage blood donors to limit low Hb deferrals and assist in policy decisions such as changing the Hb cut off or permissible frequency of donation.

11. **Iron deficiency in blood donors: analysis of enrollment data from the REDS-II Donor Iron Status Evaluation (RISE) study**, NHLBI **Retrovirus Epidemiology Donor Study-II:** Cable RG, et al, Transfusion 2010 and 2011, 51(3):511-522.

A total of 2425 red blood cell donors, either first-time (FT) or reactivated donors (no donations for 2 years) or frequent donors, were recruited for follow-up.

At enrolment, ferritin, soluble transferrin receptor (sTfR), and hemoglobin were determined. Donor variables included demographics, smoking, dietary intake, use of iron supplements, and menstrual and/or pregnancy history.

Models to predict two measures of iron deficiency were developed: Absent iron stores (AIS) were indicated by a ferritin level of less than 12 ng/mL and iron-deficient erythropoiesis (IDE) by a log(sTfR/ferritin) value of 2.07 or greater.

A total of 15.0% of donors had AIS and 41.7% IDE. In frequent donors, 16.4 and 48.7% of males had AIS and IDE, respectively, with corresponding proportions of 27.1 and 66.1% for females.

Donation intensity was most closely associated with AIS and/or IDE (odds ratios from 5.3 to 52.2 for different donation intensity compared to FT donors). Being female, younger, and/or menstruating also increased the likelihood of having AIS and/or IDE, as did having a lower weight.

Marginally significant variables for AIS and/or IDE were being a non-smoker, previous pregnancy, and not taking iron supplements. Dietary variables were in general unrelated to AIS and/or IDE, as was race and/or ethnicity.

Investigated the prevalence of iron depletion (defined as ferritin levels <12 ng/mL) and of iron-deficient erythropoiesis (defined as log[sTfR/ferritin] 2.07) in whole blood donors that met the Hb criteria for blood donation. Hb cut off levels for donation used in the RISE study were 12.5 g/dL (7.8 mmol/L) for both men and women.

Based on the used definitions of iron deficiency, the RISE study showed that in male frequent donors (at least three donations in the past year) the prevalence of iron depletion and iron-deficient erythropoiesis was 47 and 18%, respectively. Among female frequent donors (at least two donations in the past year) these prevalence rates were 62 and 27%, respectively.

Conclusion: A large proportion of both female and male frequent blood donors have iron depletion. Donation intensity, sex and/or menstrual status, weight, and age are important independent predictors of AIS and/or IDE. Reducing the frequency of blood donation is likely to reduce the prevalence of iron deficiency among blood donors, as might implementing routine iron supplementation.

12. **The effect of blood donation frequency on iron status,** Røsvik AS, Ulvik RJ, Wentzel-Larsen T, Hervig T. Transfusion and Apheresis science 2009, 41(3):165-9.

Haemoglobin (Hb) and serum ferritin were analysed in 893 donors over 1 year. Serum transferrin receptor (sTfR) was measured at the first and last donation.

Prolonged intervals prevented decrease in Hb in women and in ferritin for both genders. In women, a high TfR-F index (sTfR/log ferritin) predicted fall in Hb.

Conclusion: Adjusting the donation intervals is a way to prevent iron deficiency in blood donors.

13. **Effect of iron supplementation on iron status during the first week after blood donation,** Røsvik AS, Hervig T, Wentzel-Larsen T, Ulvik RJ. Vox Sanguinis 2010, 98(3 Pt 1): e249-56.

Compare the short time changes in iron status after donation in two groups randomized to iron supplementation or no additional iron. Evaluate the effect of iron supplementation in donors having HFE-variants compared to HFE wild types.

199 women and 200 men were randomized to receive iron supplementation or no additional iron after donation. Iron status, defined by the concentration of haemoglobin, serum ferritin, soluble transferrin receptor, concentration of haemoglobin in reticulocytes (CHr) and percent hypochromia mature red blood cells, was determined at the start of donation and 8 +/- 2 days after donation. HFE genotyping was performed at reappearance.

There was a significant difference between the two study groups on all the iron status parameters. CHr was an efficient, early marker of ongoing synthesis of haemoglobin. Heterozygosity for the HFE variants C282Y and H63D had no statistically significant influence on the iron status. The donor's baseline serum ferritin value may be basis for an individual iron supplementation regimen, as donors with serum ferritin >50 microg/l do not seem to utilize the iron supplementation but prefer endogenous iron to restore the loss of haemoglobin.

Conclusion: Iron supplementation had a significant positive impact on the restoration of iron status one week after donation.

14. **Post-donation iron supplementation with 45 mg carbonyl iron is effective and well tolerated**, Marks DC, et al, Transfusion 2011,51:98A.

Australian study showed that post donation carbonyl iron supplementation to premenopausal female WB donors reduced the incidence of anemia and associated deferrals after 12 weeks.

15. **Iron replacement therapy in the routine management of blood donors,** Bryant BJ, Transfusion 2012,52(7):1566-1575.

Post donation iron replacement has been shown to effectively reduce the prevalence of ID

16. **A pilot Iron Substitution Programme in female blood donors with iron deficiency without anaemia,** C. Pittori, A. Buser, U. E. Gasser, J. Sigle, S. Job, M. Rüesch, A. Tichelli & L. Infanti, Vox Sanguinis 2011, 100(3):303-11. Controlled clinical trial

Women aged below 50 with haemoglobin levels adequate for donation and serum ferritin below 10 ng ml were offered iron supplementation. Substitution lasted 16 weeks and the donation interval was extended. History collection including iron deficiency–related symptoms, whole blood count and serum ferritin determination was performed at baseline and after 2 and 6 months.

Significant results were serum ferritin increase (from a mean value of 7,12 to 25,2 ng ml), resolution of prostration, fatigue, sleep disturbances, tension in the neck, hair loss and nail breakage. 60% of the women completed the programme and donated again.

Conclusion: Targeted iron substitution prevents the development of anaemia and enhances donation return in premenopausal female blood donors with iron deficiency.

17. **Iron stock diminution in absence of anemia in blood donors,** Rosochova J, Pizzi-Bosman L, Scemama-Clergue J, Descombes M, Rigal E, ISBT poster presentation (2010)

9,261 donors were screened, out of which 2,784 were retained as new donors. A total of 19,296 donations of whole blood were performed. The hemoglobin (Hb) level before each donation is measured from capillary blood by Hemocue (Hc). Ferritin level measurement performed if:
HcHb <125 g/l in females or <135 g/l in males (+ blood count),
anemia diagnosed at previous visit (+ blood count),
symptoms of fatigue, RBC anomalies (e.g. microcytosis),
medical history of anemia or hypoferritinaemia or history of iron treatment.

Anemia was found in 184 (1,9%) donors: 163 females and 21 males. Hypoferritinaemia in absence of anemia was detected in 140 (1,5%) donors. These were 117 females and 23 males and can be classified in 4 groups:
1. 18 new donors (12.9%) with low HcHb level before donation but normal Hb in blood count,
2. 60 regular donors without history of anemia (42.9%) with low HcHb level before donation but normal in blood count,
3. 27 regular donors with anemia at last visit (19.3%) - 17 of these with normal HcHb level before donation were accepted for donation,
4. 35 regular donors presenting with other anemia-related conditions (microcytosis…) (25%) had normal HcHb levels before donation -blood was collected from 28 of them.

Conclusion: Blood donation contributes to the development of hypoferritinaemia. Hypoferritinaemia can be present also in first time donors. Most of donors with hypoferritinaemia are women. Blood is often collected from donors with iron depletion among donors with anemia detected at previous visit and among donors presenting with anemia-related conditions (microcytosis...) but normal HcHb.

18. **Transferrin receptor in serum. A new tool in the diagnosis and prevention of iron deficiency in blood donors,** O. Flesland, A.-K. Eskelund, A.B. Flesland, D. Falch, B.G. Solheim, J. Seghatchian, Transfusion and Apheresis science 2004, 31(1):11-6.

Transferrin receptor mediates cellular uptake of iron, and the expression on cells reflects iron needs and erythropoietic activity. The results of measuring transferrin receptor in serum (sTfR) in blood donors are presented.

Haemoglobin, serum-ferritin and sTfR were measured in 172 female and 174 male donors that had donated whole blood six or more times during the previous 3 years and in 96 female and 56 male new donors.

Haemoglobin and sTfR were not significant different in new and repeat donors. New donors had significantly higher s-ferritin than repeat donors. Twenty donors had a Hb above the low limit for normal, but below the determined cut-off for donation. Only three of these had high sTfR and/or low serum-ferritin. Hence, of the total 492 donors 3.5% were below the Hb cut-off, but having Hb, s-ferritin and sTfR within normal ranges. 11.6% of new female donors belonged in this category.

Conclusion: STfR is better than s-ferritin as a screening for iron deficiency. Most donors with low tissue iron neither have high sTfR, nor anaemia. There is probably no need to have a separate, higher than the lower normal range, requirement for Hb in donors. STfR measurements are probably most valuable in a setting where most donors are repeat.

19. **Predictors of iron levels in14,737 Danish blood donors: results from the Danish Blood Donor Study,** Rigas, A., Sørensen, C., Pedersen, O., Petersen, M.S., Thørner, L.W., Kotze, S., Sørensen, E.,Magnussen, K., Rostgaard, K., Erikstrup, C. &Ullum, H. Transfusion 2014, 54(3 Pt 2):789–796.

    In the Danish study of nearly 15 000 donors, ***ID (defined asF≤15lg/l) was strongly associated with female sex, menopausal status, blood donation frequency and the time since the previous donation.*** *The risk of ID was only weakly associated with body weight, menstrual blood loss, and dietary and supple-mental iron intake.*

20. **Iron deficiency among blood donors: experience from the Danish Blood Donor Study and from the Copenhagen ferritin monitoring scheme,** A. S. Rigas, O. B. Pedersen, K. Magnussen, C. Erikstrup, H. Ullum, Transfusion medicine 2019, 29 Suppl. 1:23-27.

    *The authors of the article present summaries of various iron deficiency studies in blood donors as well as the Danish experiences from their previous studies. Iron deficiency is both a global health issue and a specific problem for blood donors. I****n general, either guided iron supplementation with screening for iron deficiency through ferritin measurements or adjusting the inter-donation intervals may alleviate the high proportion of iron-deficient donors. The experience from Copenhagen, the Capital Region of Denmark, is that guided iron supplementation is an effective strategy for avoiding iron depletion.***

21. **How do we manage iron deficiency after blood donation?** Joseph E. Kiss and Ralph R. Vassallo British Journal of Haematology 2018, 181(5):590-603.

    The authors of the article present summaries of various iron deficiency studies in blood donors as well as the American experience with mitigating of iron deficiency in blood donors.

    ID is not unique to donors of RBC units. Plateletpheresis donors may be prone to iron depletion because of the increased donation frequency allowed (up to 24 times/year in the US) which results in a higher number of smaller RBC losses with each procedure (50–80 ml in samples and tubing), in individuals often recruited from the ranks of repeat whole blood donors.

    Accordingly, AABB and others in North America have recommended that blood collectors implement an effective strategy to mitigate donation-induced ID. These may include blood collector-facilitated access to iron supplements, meaningful extension of the inter-donation interval, or measurement of ferritin as a basis for motivating donors to take iron supplements.

    Over the next few years, they expect to see programmes implement one or more strategies that will impact donor iron status, including low dose iron supplementation, ferritin testing with donor action in response to knowledge of iron status, and/or lengthening the inter-donation interval.

    The donor risk, stratification is clear, with adolescent donors, pre-menopausal females, and frequent donors, in that order, being the most susceptible to the potential harms of ID.
    Healthcare providers should be familiar with guidelines, on donors who are repeatedly deferred for low hb and/or anaemia that does not improve with iron supplement, when to undertake GI endoscopy and just as importantly, when not to do so.

22. **In contrast to whole blood donation, no significant loss of RBC if the device is rinsed and the suspension reinfused at the end of the session** Fischer T et al., Transfusion and Apheresis Science 2013, 49(1):80-83

The aim of this study was to determine the loss of red cell mass during a plasma donation. If the donor undergoes plasmapheresis 45 times within one year without rinsing the tubing system and reinfusing this normal saline into the donor at the end of the donation, the result is a loss of red cell mass of 11.01 ml per donation. This result translates into an accumulated loss of red cell mass of up to 495.63 ml per year. The loss of blood induced by plasma donations can be reduced to 58.01 ml per year, if the disposable tubing is rinsed with normal saline and reinfused into the donor at the end of each plasma donation.

23. **Frequent source plasma donors are not at risk of iron depletion: the Ferritin Levels in Plasma Donor (FLIPD) study**, Schreiber et al., Transfusion 2018, 58: 951-959

A total of 1254 SP donors were enrolled in four frequency groups determined by donations in the prior 12 months: no donations and 1 to 24, 25 to 69, and 70 or more donations. Ferritin was determined for each donor. Donors with ferritin levels of less than 12 ng/mL were classified as having absent iron stores (AIS). Results: Compared to new donors, ferritin for females was higher in each successive frequency group. For 70 or more donations, ferritin was 13 ng/mL higher than in new donors (p = 0.02). For males, 1 to 24 donations had the highest ferritin levels. Compared to new donors, highest-frequency donors had lower ferritin levels, 114 ng/mL versus 100 ng/mL (p = 0.14). Age for females and males increased with each successive frequency group. Age adjustment resulted in smaller ferritin differences for females and larger differences for males in the high-frequency groups; AIS for females was highest in new donors (7%) and lowest in the highest-frequency group (1%). In aggregate, AIS occurred in less than 1% of all male donors. Male new and highest-frequency donors had 1% AIS with none in the other groups. ***Conclusion: Few SP donors have iron depletion, and it is not higher in frequent donors. Frequent SP donation does not adversely impact iron stores. Thus, monitoring donor iron status or iron supplementation is not necessary*** *(not clear how samples were taken from donors – from plasma product or whole blood?)*

24. **Impact of informing donors of low ferritin results**, Mindy Goldman , Samra Uzicanin , Jenna Scalia , Vito Scalia , Sheila F O'Brien Transfusion 2016, 56(9):2193-8.

Informing donors of low ferritin results decreased return rate in first-time and repeat donors, and the median number of donations declined from three to two donations/year in returning donors with low ferritin on index donation compared to an increase from 1.5 to 2.5 donations/year in donors with normal ferritin. An electronic questionnaire demonstrated that approximately 60% of low ferritin donors saw their primary medical practitioner, and half of this group started iron. Qualitative interviews revealed suboptimal understanding of iron needs and poor compliance with iron supplementation.

Conclusion: Providing donors with results of ferritin testing may reduce return rates and donation frequency in the 2 years after testing. Simply providing donors with ferritin results and an information sheet is often inadequate to improve donors' understanding of iron needs and may not lead to a substantive increase in iron intake over time.

25. **Study of iron stores in regular plateletpheresis donors,** Page EA, Coppock JE, Harrison JF, Transfusion Medicíne 2010, 20(1):22-9

Plateletpheresis donors will lose up to 100 mL of blood at each donation*, leading to concern that they may become iron deficient, particularly if donating at the maximum allowed frequency under National Blood Service policy of every 2 weeks. The serum ferritin levels of 508 regular plateletpheresis donors*

and 101 non-donors were measured to indicate the level of their iron stores. About 33.9% (156/460) of platelet donors had depleted iron stores compared with 3.1% (3/97) non-donors. Results for male and post-menopausal female donors were similar with 36.2% (131/362) of males and 37.7% (20/53) of post-menopausal females showing iron depletion. There was clear correlation with donation frequency in males with 63.9% (46/72) of males donating at 2 weekly intervals found to be iron depleted. The percentage of iron depleted male subjects decreased as donation intervals increased. Correlation with lifetime donations of platelets was not demonstrated, although no donor who had given fewer than 14 blood and/or platelet donations was found to be iron depleted. In males there was a clear correlation between iron depletion and frequency of donation. There appeared to be no correlation with lifetime number of platelet donations. ***As a result of this study, we have advised that volunteers should not donate platelets more than 15 times per year, so that red cell loss is no more than the equivalent of three whole blood donations (1500 mL).***

26. **Serum ferritin in plateletpheresis and whole blood donors,** Frances Duggan , Kathleen O'Sullivan , Joan P Power , Michael Healy , William G Murphy, Transfuision and Apheresis Science 2016, 55(1):159-63

Prospective analysis of iron status in plateletpheresis donors, using whole blood donors as a control group, to assess the haematinic effects of regular anti-coagulated extracorporeal circulation and platelet collection was performed.
Ferritin levels were measured in samples from 31 regular male plateletpheresis donors and from 14 first time male whole blood donors, immediately before and immediately after donation, and immediately before the next donation. An additional 33 regular male plateletpheresis donors and 17 first time male whole blood donors had serum ferritin levels checked pre-donation.
Male plateletpheresis donors had a statistically significant fall in serum ferritin after donation (P = 0.005). In addition, male platelet donors had significantly lower serum ferritin levels than first time male blood donors: ferritin <20 µg/L was found in 6/64 (9%) of regular platelet donors and 1/31 (3%) of first time blood donors (P < 0.001)*.*
This studies support the value of serum ferritin measurement in apheresis donor management.

Background Document 3

GTS Ch2 document based on TRANSPOSE risk-based assessment tool

(by J.Castrén, R.Lehtisalo (FIN), Consultation: Prof Mika Mäkelä, Helsinki University Hospital. Comments: O.Garrau. Last update April 2022)

Allergy and anaphylaxis

Guide 20th Ed text
Allergy
Individuals with a documented history of anaphylaxis should not be accepted as donors.

- ➔ no criteria (in other words: no deferral?) for mild allergy
- ➔ permanent deferral for anaphylaxis

a. What the issues are;

A donor with an allergic condition may have IgE antibodies that could cause a severe allergic reaction in the recipient
A donor with an allergic condition may not be healthy to donate (e.g. Allergic asthma)
A donor with an allergic condition may have an allergic reaction caused by materials used during the donation process (e.g. arm disinfection)

Serious transfusion-associated allergic / anaphylactic reactions are rare, but number of case reports have been published since 1919 (Arnold 2007, Cheung 2015, Jacobs 2011, Poisson 2014, Ponnampalam 2014, Ramirez 1919, Routledge 1976). The risk is highest by using fresh frozen plasma (FFP) plasma from one donor to recipient and by platelet products rich in plasma.

The half time life for IgE in plasma is short, only up to 2-3 days, while allergen-specific IgE with captured allergen can last for months once bound to mast cells and eosinophils. As a consequence, only a small proportion of total IgE is free in the plasma (Dati 1982, Normansell 2014, Laffer 2008). Because of the stringent leukoreduction of labile blood components, IgE that can cause allergic reactions in recipients is likely to originate from plasma: therapeutic plasma, plasma rich platelet components and the small part of residual plasma of red blood cell components.
Considering biomarkers of allergy, tryptase return to base line within ca. one day after symptoms of anaphylaxis (Beck 2019, Passia 2020); and histamine has an extremely short half-life, estimated at20 minutes (Beck 2019, Laroche 1995).

Besides the theoretical risk reduction there is data to show that the risk of an anaphylactic reaction in the recipient can be reduced by reducing the amount of plasma in transfusion components (Tobian 2011).

Donor health questionnaires have been shown to have a low sensitivity to identify donors with high IgE levels in order to mitigate the recipient risk to manifest anaphylaxis. However, deferring donors with the very common phenomena of atopy or allergic symptoms would have a remarkable impact on the size of donor population (Goldman 2011, Johansson 2005, Stern 1995, Wilhelm 1995). Deferral policies in the western countries have a large variation; from deferring donors from all allergic symptoms and signs and medications to liberal policies where only present severe allergic symptoms are cause for deferral (Garraud 2017).

Recent studies have demonstrated that an atopic condition in the recipient stands for the major risk of anaphylactic reactions (Savage 2011, Savage 2011);next, donor screening is an ineffective measure to prevent from anaphylaxis in the recipient (Goldman 2011, Johansson 2005, Stern 1995, Wilhelm 1995).

Donors with known allergies to material used in blood donation should not be put at risk of developing symptoms due to donation (general ethical principle) and neither donors not feeling well due to their allergic symptoms.

Deferring donors with recurrent severe allergic reactions to commonly consumed food or antibiotics in their adult life might be considered especially if blood products with high amounts of plasma from a single donor is used for in transfusion (Cheung 2015, Wilhelm 1995).

Allergic reactions mediated by IgE has also been described in IVIG products originating from plasma for fractionation (PFF). This type of patient reactions cannot be mitigated by known donor selection processes but can be treated effectively in patients (Zdiarski 2017). Therefore, no specific donor policies to PFF donors are needed.

Summary from consultation with Professor Mika Mäkelä, Helsinki University Hospital
100% risk mitigation of risk for recipient anaphylaxis is not possible
100% identification of high risky donors is not possible via interview and health questionnaire
The major risk in transfusion related anaphylactic and severe allergic reactions is the patient; or combination of recipient and patient related factors, not known
Risks can be mitigated by using in blood components reduced in plasma content, or when plasma can be pooled from different donors
The half time life of IgE + other effectors/mediators in anaphylactic/severe allergic reactions is very short; due to it would be enough (recipient safety) to have a very short deferral, hours -days. While taking to account also the donor safety; a 2 weeks deferral is to be considered

It is – for donor safety – logic to defer donors in need for systemic corticosteroids and other immunosuppressive medicines as treatment for their allergy/anaphylaxis
Donors with severe, widespread atopic eczema should be deferred; both for the recipient safety due to risk for bacterial contamination (disinfection in skin with serious atopic lesions on the upper limits is not effective) as well as for the risk of continuing high levels of IgE
No need for long or permanent deferral for donors undergoing sensibilization therapy; they don’t have constant high IgE levels after the treatment

For FFP24 in use for transfusion; more stringent criteria for donors can be considered.

Rare disease, mastocytocis individuals have a high risk to anaphylactic reactions; they should be deferred in order to defer the high risky donors. This is a haematological disease and therefore not needed in the allergy and anaphylaxis donor selection criteria

- Issues related to (select all that apply): donor and recipient

- Severity

*grade of severity*DONOR*				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
Exacerbation of symptoms	*X*	*X*		

*grade of severity*RECIPIENT*				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
Reactions caused by transferred IgE (or other biomarker)	*X*	*X*	*X*	*(X)*

- Imputability

*level of imputability*DONOR risks*						
Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
Exacerbation of symptoms	*X*	*X*				

*level of imputability*Recipient risks*						
Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
Reactions caused by transferred	*X*	*X*				

IgE (or other biomarker)						

- *Options to minimise each of the risks*

Donor risk: Deferring donors with known allergies against reagents / materials used in blood donation procedures
Recipient risks: Reducing the amount of plasma in cell products. Deferring high risk donors from all donations OR deferring high risk donors from donations where larger amounts of plasma is transfused (fresh frozen plasma for clinical use)

b. Recommendations;

- General principle:
  The donor should be deferred if not feeling well

- Local / non-generalized allergic symptoms which are controlled with/without medication:
  No reason for deferral
  *Exception: Any **known allergy** to agents used in blood collection (skin disinfection, other material used in the process)*

- Anaphylactic or generalized severe allergic reactions:
  Literature does not support general rule of permanent deferral for all donors with a history of anaphylaxis; no general permanent deferral for all types of anaphylaxis and for all types of donations is needed.

  Proposed text for the 21st Ed:
  2.1.2.X Donors with local / non-generalized allergic symptoms, which are controlled with medication (except of oral corticosteroids, or other immunosuppressive medical treatment)or without medication are accepted as donors.(Evidence level C,E)

  2.1.2.X Donors with anaphylaxis or severe allergic reaction should be deferred for two weeks after recovery. (Evidence level C,E)

  Permanent deferral should be considered for donors of FFP for clinical use and platelets in plasma in case of several anaphylaxis or severe allergic reactions in the adulthood and if the causal allergen cannot be eliminated from the environment (for example pollen) / treatment of the recipients (for example antibiotics)
  Donors with severe, widespread atopic eczema should be temporary deferred until cessation of the symptoms. (Evidence level C,E)
  Donors requiring oral corticosteroids, or other immunosuppressive medical treatment should be deferred temporary until such treatment has stopped. (Evidence level C,E)

Donors with any known allergy to agents used in blood collection (skin disinfection agent, other material used in collection process) if there is no alternative material available should be deferred (Evidence level E)

c. Justification (data/references);

Transpose final report:
For severe allergy, it was not possible to reach a consensus based on current literature, as it mostly consisted of single cases and lacked more extensive studies investigating the effect of passive IgE transfer on recipient mortality.

Defined gaps: Allergy to medication/anaphylaxis_risk to recipient_Deferral period
Severe allergy_risk to donor_Deferral period

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d. Considerations (e.g., financials, etc.)

The current deferral policy (Guide 20th Ed.) leads to unnecessary deferrals and therefore permanent loss of donors; a single anaphylactic reaction in childhood is quite common and there is no data showing that all these donors need to be deferred lifelong.

* definitions for severity grade

Grade 1	*Non-Severe*	*the recipient may have required medical intervention (e.g. symptomatic treatment) but lack of such would not result in permanent damage or impairment of a body function.*

Grade 2	*Severe*	*the recipient required in-patient hospitalization or prolongation of hospitalization directly attributable to the event; and/or – the adverse event resulted in persistent or significant disability or incapacity; or – the adverse event necessitated medical or surgical intervention to preclude permanent damage or impairment of a body function.*
Grade 3	*Life-threatening*	*the recipient required major intervention following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death*
Grade 4	*Death*	*the recipient died following an adverse transfusion reaction Grade 4 should be used only if death is possibly, probably or definitely related to transfusion.*

If the patient died of another cause, the severity of the reaction should be graded as 1, 2 or 3.

* definitions for imputability level

NA	*Not assessable*	*When there is insufficient data for imputability assessment.*
0	*Excluded*	*When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes.*
	Unlikely	*When the evidence is clearly in favour of attributing the adverse reaction to causes other than the quality/safety of tissues/cells*
1	*Possible*	*When the evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissues/cells or to alternative causes.*
2	*Likely, Probable*	*When the evidence is clearly in favour of attributing the adverse reaction to the quality/safety of tissues/cells.*
3	*Definite, Certain*	*When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues/cells.*

Background Document 4

GTS Ch2 document based on TRANSPOSE risk-based assessment tool
Updated: Stefano Fontana, and Ch2 group 4/2022

Cancer and malignancies

a. what the issues are;

Risk for the donor:
Does blood donation increase the risk of cancer? Based on listed literature (Racila 1998, Ishii 2016, Zhao 2020): no risk
Do sequela (signs or symptoms) of cancer or treatment increase the risk of blood donation?

Risk for recipient:
Is there a risk of transmitting malignant disease? Based on the listed literature (Yang 2010, Edgren 2007, Hjagrim 2015) and on references listed as additional literature 1-12: globally **no risk,** discrepant study results for non-Hodgkin Lymphoma.

Arguments and summary of the literature

No transmission of cancer though transfusion of blood components has been shown to date. This is true even though cancer is a frequent disease with a variable, but generally relatively long occult phase before diagnosis. Cancer incidence in Switzerland is about 400 cases / 100'000 inhabitants / year (Schweizerischer Bundesamt für Statistik, 2015), this means +/- 1:250 inhabitants/year. Assuming an occult phase before diagnosis of 3 to 6 months, this means that 1:500 to 1:1,000 “healthy donors” are carriers of malignant tumour cells at the moment of their blood donation. Thus, in at least 1:1,000 donations cancer cells may potentially be collected with a blood component and thus contaminate a blood product.

On this background, the risk for recipients of blood donated by individuals with a history of malignant disease may be acceptable if 2 assumptions are met.

First, the estimated risk of cancer persistence or relapse in individual in remission after a diagnosis of cancer should not be significantly higher than the risk in a healthy individual. We assume that this condition is fulfilled in individual in complete remission from malignant disease after a relapse-free time interval of several years (for example 5 years), and under regular follow up. Those individuals do not have a significantly higher risk of being carrier of cancer cells compared to healthy individuals with no history of cancer.

Second, the literature available does not document an increased risk for patients if they are transfused with products collected from donors with cancer disease. Studies performed on this topic have investigated if cancer is transmitted through direct transfusion of malignant blood cells, if transfused patients have a higher risk of developing cancer, or if patients receiving blood from donors developing cancer have a higher risk to develop themselves a malignant disease. Studies

are all negative for both transmission of haematological and non-haematological malignant diseases, apart from non-Hodgkin Lymphoma patients, where the results are controversial. Globally, studies strongly suggest that cancer is not transmitted by transfusion of blood components [see additional references 1-12].

The situation is different for solid organ transplantation, where an increased risk of cancer for recipient is well documented, although transplantation is performed less frequently than transfusion. Many reasons may explain the difference between transfusion and transplantation: the immunosuppression of the patient, the HLA-identity, the high tumour burden, the direct implantation of the tumour within the recipient, and a prolonged exposure of the recipient to the malignant cells in transplantation.

Issues related to (select all that apply): X donor X recipient

Severity

grade of severity* DONOR				
Risk(s)	Non-Severe	Severe	Life-threatening	Death
Increased risk of cancer		X		
grade of severity* RECIPIENT				
Risk(s)	Non-Severe	Severe	Life-threatening	Death
Transmission of malign disease			X	

Imputability

level of imputability*DONOR						
Risk(s)	Definite/Certain	Likely/ Probable	Possible	Unlikely	Excluded	Not assessable
Increased risk of cancer					X	
level of imputability*RECIPIENT						
Risk(s)	Definite/Certain	Likely/ Probable	Possible	Unlikely	Excluded	Not assessable

Transmission of malign disease				X		

Options to minimize each of the risks

Donor: deferral of individuals with residual symptoms or signs of disease or treatment.

Recipient: deferral of donors without documented remission, leucodepletion of cell components.

b. Proposed criteria;

Premalignant conditions: no deferral.

Cancers with negligible metastatic potential (e.g. basal cell carcinoma and carcinoma in situ of the cervix): accept immediately following successful removal and cure

Malignant diseases in general: a minimum deferral period of 5 years after end of treatment and cessation of all symptoms should be considered, because after this time interval most cancer diseases are considered as cured. Persisting or new symptoms, the risk of relapse and the risk of secondary malignancies should be part of the medical evaluation.

For some forms of solid cancer there is a residual risk of relapse over 5 years (e. g. breast cancer, see Moreau-Bachelard 2020 and Lee 2020). This risk is small, considering that donors are readmitted 5 years after end of aromatase inhibitor treatment, lasting itself up to 5 years. Considering the low risk inputability (negative consequences are excluded for the donor and very improbable for the recipient, s. above), the residual risk is acceptable and not higher than the risk that occult cancer cells circulate in a healthy donor.

For malignancies of hematopoietic tissues and cells the literature does not suggest a higher risk than for solid cancer, neither for the donor, nor for the patient. A minimum deferral period of 5 years after end of treatment and cessation of all symptoms should also be considered. Because of the risk of minimal residual disease and of the theoretical higher risk of collection of malignant cells by relapsing hematological diseases than for solid cancers, the risk of recurrence should become a higher weight in the assessment. Depending on the history of the hematological disease, a longer deferral interval may be applied by the responsible doctor of the blood establishment.

For malignacies known to be associated with viraemic conditions; based on current evidence no specific rules are needed. (1. The definition, respectively the kind of association between

cancer and viremic condition is not clear. 2. A viremic condition per se is a reason for donor deferral, so this risk is already addressed for viral diseases representing a risk (for example HIV). 3. There is no evidence that cancers associated with viruses represent a higher risk for the donor or for the patient.)

TEXT PROPOSAL FOR THE GUIDE

Standard 2.1.2.2: Individuals with a malignant disease, or a history of such, are usually permanently deferred, except donors with carcinoma in situ with complete recover (Directive 2004/33/EC Annex III).

There is a lack of evidence to support the theoretical concerns that cancer is transmitted via blood. Large observational studies have provided convincing evidence that the risk of transmitting cancer via blood transfusions is undetectable or not significant. (Evidence level C)

Therefore, the responsible physician may make other exceptions than carcinoma in situ exceptions if the donor has fully recovered with no expectation of recurrence (i.e. cured) and the following conditions apply: subject to the follow- ing rules:– for cancers with negligible metastatic potential (for example basal cell carcinoma), the donor may be accepted immediately following successful removal and cure;

– for other cancers, at least 5 years should have elapsed since completion of treatment.

(Evidence level: C,D,E)

c. Justification (data/references);

Ref1: Yang H, Lee J, Seed CR, Keller AJ: Can blood transfusion transmit cancer? A literature reviews. Transfus Med Rev. 2010 Jul;24(3):235-43. doi: 10.1016/j.tmrv.2010.03.005

Ref2: Edgren G, Hjalgrim H, Reilly M, Tran TN, Rostgaard K, Shanwell A, Titlestad K, Adami J, Wikman A, Jersild C, Gridley G, Wideroff L, Nyrén O, Melbye M.: Risk of cancer after blood transfusion from donors with subclinical cancer: a retrospective cohort study. Lancet. 2007 May 19;369(9574):1724-30

Ref3: Hjalgrim H, Rostgaard K, Vasan SK, Ullum H, Erikstrup C, Pedersen OB, Nielsen KR, Titlestad KE, Melbye M, Nyrén 2, Edgren 8: No evidence of transmission of chronic lymphocytic leukemia through blood transfusion. Blood 2015 126:2059-2061; doi: https://doi.org/10.1182/blood-2015-03-632844

Ref4: Edgren G, Reilly M, Hjalgrim H, Tran TN, Rostgaard K, Adami J, Titlestad K, Shanwell A, Melbye M, Nyrén O: Donation frequency, iron loss, and risk of cancer among blood donors. J Natl Cancer Inst. 2008 Apr 16;100(8):572-9. doi: 10.1093/jnci/djn084. Epub 2008 Apr 8

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[2] Hunter KW et al. Host genetics and tumour metastasis. Br J Cander 2004; 90:752-5.

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[8] Greenwald P et al. Morbidity and mortality among recipients of blood from preleukemic and prelymphomatous donors. Cancer 1976; 38:324-8.

[9] Vamvakas EC. Allogeneic blood transfusion as a risk factor for subsequent development of non-Hodgkin's lymphoma. Transfus Med Rev 2000; 14:258-68.

[10] Cerhan JR et al. Blood transfusions and risk of non-Hodgkin's lymphoma subtypes and chronic lymphocytic leukemia. Canc Epidemiol Biomarkers Prev 2001; 10:361-8.

[11] Edgren G et al. Risk of cancer after blood transfusion from donors with subclinical cancer: A retrospective cohort study. Lancet 2007; 369:1724-30.

[12] Penn I. Transmission of cancer from donor organs. Ann Transpl 1997; 2:7-12.

[13] Zhao J et al. Zhao J, Dahlén T, Brynolf A, Edgren G. Risk of hematological malignancy in blood donors: A nationwide cohort study. Transfusion. 2020;60:2591–2596. https://doi.org/10.1111/trf.16020

[14] Ishii K, Birmann BM, Zhang X, Giovannucci E, Bertrand KA. A prospective analysis of blood donation history and risk of non-Hodgkin lymphoma. Leuk Lymphoma. 2016;57(6):1423-1428. doi:10.3109/10428194.2015.1091928

[15] Moreau-Bachelard et al. Development of a Prognostic Tool to Guide the Decision to Extend Adjuvant Aromatase Inhibitors for up to Ten Years in Postmenopausal Early Breast Cancer Patients. Cancers 2020, 12, 3725; doi:10.3390/cancers12123725.

[16] Lee et al. Validation of C linical Treatment Score post-5 years (CTS5) risk stratification in premenopausal breast cancer patients and Ki-67 labelling index. Scientific Reports 2020 (https://doi.org/10.1038/s41598-020-74055-3)

17 Personal communication by clinical haematologists: Prof. Duchosal of the University of Lausanne and Prof. Stüssi of the Regional Hospital in Bellinzona / University of the Svizzera Italiana (4/2022 Stefano Fontano)

d. Considerations (e.g., financials, etc.).

Deferring individuals with a history of any malignancy (even cured) causes many deferrals (about every third individual suffers from a malignancy during his/her lifetime).

Deferring individuals who have been told they are cured and discharged from follow up means they get a conflicting message from the blood establishment of still being “ill”.

The literature does not support a different policy between haematological and solid malignant diseases. A minimal deferral for all kind of cancer (5 years) is reasonable, longer deferral in special cases should be at discretion of the responsible doctor of the blood establishment.

Background Document 5

GTS Ch2 document based on TRANSPOSE risk-based assessment tool
Prepared by O. Flesland and Ch2 group 2022

Interventions and treatments. Acupuncture, tattooing, body piercing, and aesthetic medical procedures.

a. What the issues are;

1. Risk for the donor:
   - For Acupuncture the reason for having acupuncture may be a risk

2. Risk for the recipient
   1. Acupuncture
      - Transmission of infectious agents (6 (4) months deferral (current standard 2.3.4.1)
      - The reason for the acupuncture may be a risk
   2. Tattooing
      - Transmission of infectious agents (6 (4) months deferral (current standard 2.3.4.1)
   3. Body piercing
      - Transmission of infectious agents (6 (4) months deferral (current standard 2.3.4.1)
   4. Aesthetic medical procedures (E.g., face and lip fillers, dermal fillers); substances injected into face or other parts of the body, botox injections for cosmetic purposes, eyeliner tattoo, permanent eyeliner.
      - Transmission of infectious agents, no rules in the current directive or Guide

Severity and immutability

- Issues related to (select all that apply): donor / recipient

- Severity

*grade of severity** DONOR				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
	X			

*grade of severity** RECIPIENT

Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
Infection			*x*	

- Imputability

*level of imputability** DONOR						
Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
			x			

- Imputability

*level of imputability** RECIPIENT						
Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
Infection	*x*					

- *Options to minimise each of the risks*

b. Recommendations;

Arguments and summary of the literature

The literature is not conclusive (no risk: Prinsze et al 2019, still a risk: Van Remoortel 2019) and for aesthetic medical procedures literature is sparse or missing.

A risk-based approach in each country is recommended.

If no risk-based approach is done the following rule applies:
Individuals having acupuncture, tattooing, body piercing and/or aesthetic medical procedures must be deferred for 6 months (or 4 months, provided a NAT test for hepatitis C is negative) (unless performed by a qualified practitioner and with sterile single used needles).

Factors to be considered in a risk-based approach are:

- Background epidemiology in each country.
    - For procedures performed outside the country stricter rules may apply due to less knowledge.
- The testing requirements in each country (e.g. no NAT, NAT pooled or NAT single donor)
- The setting in which the procedure is performed.
- Education of the person performing the procedure (e.g. Medical or non-medical)
- National regulations for e.g. acupuncture.
- Body parts involved (e.g. mucus membranes)

- For acupuncture; single or multiple use needles
- For Aesthetic procedures, method used for skin penetration

When data is not available the precautionary principle should apply. It may be helpful to look at rules for procedures with "similar" risk such as endoscopy with flexible instruments and not having less strict rules.

Text for the Guide 21 Ed:

Acupuncture, tattooing, body piercing and aesthetic medical procedures

Standard

2.3.1.1. Individuals having acupuncture (unless performed by a qualified practitioner and with sterile single use needles), tattooing or body piercing must be deferred for 6 months (or 4 months, provided a NAT test for hepatitis C is negative) (Directive 2004/33/EC Annex III).

There is evidence, that using a risk-based approach based on national TTI disease prevalence and incidence, exceptions of the standard 2.1.4.1 can be accepted and more liberal rules for acupuncture, tattooing, body piercing, or skin/mucosal penetrating aesthetic medical procedures can be implemented nationally or by the decision of the responsible physician (Evidence level C,E).

If more liberal rules are implemented, following aspects should be considered specific for each donor that fulfil general requirements:

Consider the reason for acupuncture and complications of acupuncture, tattooing, body piercing, and other aesthetic procedures. Concerning local complications; inspect for/ask about open/infected wounds

c. Justification (data/references);

Brook I: Recovery of Anaerobic Bacteria from 3 Patients with Infection at a Pierced Body Site. Clinical Infectious Diseases, Volume 33, Issue 1, 1 July 2001, Pages e12–e13. URL: https://academic.oup.com/cid/article/33/1/e12/318173

Chan MWC, Wu XY, Wu JCY, Wong SYS, Chung VCH. Safety of Acupuncture: Overview of Systematic Reviews. Sci Rep. 2017 Jun 13;7(1):3369. doi: 10.1038/s41598-017-03272-0. PMID: 28611366; PMCID: PMC5469776.

Ernst E, Sherman KJ. Is acupuncture a risk factor for hepatitis? Systematic review of epidemiological studies. J Gastroenterol Hepatol. 2003 Nov;18(11):1231-6. doi: 10.1046/j.1440-1746.2003.03135.x. PMID: 14535978.

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Hoad VC, Guy RJ, Seed CR, Harley R. Tattoos, blood-borne viruses and blood donors: a blood donor cohort and risk assessment. Vox Sang. 2019 Oct;114(7):687-693. doi: 10.1111/vox.12832. Epub 2019 Aug 8. PMID: 31396975.

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Prinsze FJ, van de Laar T, Slot E, de Jong M, Bokhorst A, de Kort W, Zaaijer H, van den Hurk K. No increased risk of transfusion-transmissible infections after tattooing, body piercing, or acupuncture among blood donors in the Netherlands. Transfusion. 2019 Aug;59(8):2575-2583. doi: 10.1111/trf.15421. Epub 2019 Jun 22. PMID: 31228271.

Public health Ontario. Personal Services and Infection Risks. 2019. URL: https://www.publichealthontario.ca/-/media/documents/a/2018/at-a-glance-ipac-pss-infection-risks.pdf?la=en

Urbanus AT, van den Hoek A, Boonstra A, van Houdt R, de Bruijn LJ, Heijman T, Coutinho RA, Prins M. People with multiple tattoos and/or piercings are not at increased risk for HBV or HCV in The Netherlands. PLoS One. 2011;6(9):e24736. doi: 10.1371/journal.pone.0024736. Epub 2011 Sep 14. PMID: 21935447; PMCID: PMC3173466.

Van Remoortel H, Moorkens D, Avau B, Compernolle V, Vandekerckhove P, De Buck E. Is there a risk of transfusion-transmissible infections after percutaneous needle treatments in blood donors? A systematic review and meta-analysis. Vox Sang. 2019 May;114(4):297-309. doi: 10.1111/vox.12780. Epub 2019 Apr 10. PMID: 30972765.

Wong Samson Sai-Yin, Wong Sally Cheuk-Ying, Yuen Kwok-Yung: Infections associated with body modification, Journal of the Formosan Medical Association, Volume 111, Issue 12, 2012, Pages 667-681 ,ISSN 0929-6646, https://doi.org/10.1016/j.jfma.2012.10.016. URL: https://www.sciencedirect.com/science/article/pii/S0929664612005141

Yang S, Wang D, Zhang Y, Yu C, Ren J, Xu K, Deng M, Tian G, Ding C, Cao Q, Li Y, Chen P, Xie T, Wang C, Wang B, Yao J, Threapleton D, Mao C, Ruan B, Li L. Transmission of Hepatitis B and C Virus Infection Through Body Piercing: A Systematic Review and Meta-Analysis. Medicine (Baltimore). 2015 Nov;94(47):e1893. doi: 10.1097/MD.0000000000001893. PMID: 26632685; PMCID: PMC5058954.

d. Considerations (e.g., financials, etc.).

Loss of safe donors if unnecessary long deferral periods, but Goldman did not get many donors from reducing deferral from 12 to six months.

Acupuncture, tattooing, piercing, and aesthetic procedures are common in the donor population. Evaluation of eligibility of a donor must be quick, and easy to perform in a consistent way.

* definitions for severity grade

Grade 1	*Non-Severe*	*the recipient may have required medical intervention (e.g. symptomatic treatment) but lack of such would not result in permanent damage or impairment of a body function.*
Grade 2	*Severe*	*the recipient required in-patient hospitalization or prolongation of hospitalization directly attributable to the event; and/or – the adverse event resulted in persistent or significant disability or incapacity; or – the adverse event necessitated medical or surgical intervention to preclude permanent damage or impairment of a body function.*
Grade 3	*Life-threatening*	*the recipient required major intervention following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death*
Grade 4	*Death*	*the recipient died following an adverse transfusion reaction Grade 4 should be used only if death is possibly, probably or definitely related to transfusion.*

If the patient died of another cause, the severity of the reaction should be graded as 1, 2 or 3.

* definitions for imputability level

NA	*Not assessable*	*When there is insufficient data for imputability assessment.*
0	*Excluded*	*When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes.*
	Unlikely	*When the evidence is clearly in favour of attributing the adverse reaction to causes other than the quality/safety of tissues/cells*
1	*Possible*	*When the evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissues/cells or to alternative causes.*
2	*Likely, Probable*	*When the evidence is clearly in favour of attributing the adverse reaction to the quality/safety of tissues/cells.*
3	*Definite, Certain*	*When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues/cells.*

Background Document 6

GTS Ch2 document based on TRANSPOSE risk-based assessment tool
(by O.Flesland, F. Bigey, J. Castrén. Last update on 9.3.2022)

Surgery

a. What the issues are.

- **Risk for the donor:**
  - Blood loss
    - 500 ml blood loss equals one donation. One donation in a healthy adult gives 2-3 months deferral (standard 2.4.1.4). A double unit red cell apheresis gives 4-6 months deferral (standard 2.4.2.18)
    - Predonation measurement of haemoglobin/iron parameters
  - Illness/condition that was reason for surgery
  - Wound healing
    - Open wounds are reason for deferral
    - Delayed wound healing because of blood donation? No evidence.
    - Large open wounds cause loss of fluid and protein
  - Blood transfusion
    - Deferral for 6 (4) months (standard 2.3.4.9)
  - Anaesthesia : no evidence of risk
  - Medication
    - As for medication
  - Donor waiting for major surgery

- **Risk for the recipient**
  - Illness that were reason for surgery
    - Refer to the relevant condition.
  - Infection – bacteria
    - Wounds
    - Hospital acquired infections
  - Infection – viruses
    - Surgeon-to-patient viral transmission
    - Blood transfusion
      - Deferral for 6 (4) months (standard 2.3.4.9)
    - Endoscopy using flexible instruments
      - Deferral for 6 (4) months (standard 2.3.4.4)
  - Implants
    - vCJD : refer to the origin of implant

Arguments and summary of the literature

Current standard states that “After surgery, persons must not donate until they have fully recovered (typically about 6 months for major surgery).”

Wound healing

The healing process consists in 3 phases :

- The first phase referred to as the inflammatory stage, spans the first 3 to 5 days of healing.
- The second phase, known as the proliferative phase, lasts approximately 5 to 25 days and is characterized by re-epithelialization, angiogenesis, fibroblast migration, and collagen deposition.
- The third and final phase, known as the remodeling phase, lasts up to 1 year and involves collagen cross-linking and replacement of the disorganized type III collagen by organized type I collagen.

The 3 stages of healing are overlapping, and their duration depends on several factors. Most of the factors significantly affecting wound healing are de facto exclusion criteria for blood donation (ischemia, chronic diseases, jaundice, uremia, medications, immunocompromised conditions, malnutrition…).

No data was found about the time when the wound can be considered tight enough to be protected against bacterial infection. Patient-oriented information and counselling state that most of surgical wound would heal within 6 to 8 weeks (St Joseph Healthcare Hamilton) or 3 months (John Hopkins Medicine).

Assuming that no standard healing timeline can be designed, clinical criteriae could be considered : a closed wound (stitches removed), no anaemia, and a reasonable time period for the patient to have fully recovered. **A 3 months deferral could be a minimal reasonable time for major surgery.**

Major/minor surgery

Despite their common use in scientific literature, there is no evidence-based/official definition of these categories, thus a difficulty to classify borderline procedures.
Webster's definition for major surgery is : *surgery involving a risk to the life of the patient - specifically **:** an operation upon an organ within the cranium, chest, abdomen, or pelvic cavity.*

The most recent attempts refers to patient condition, and pre/post operation features, more than to any specific category of procedure. Some teaching and training handbooks list cases of major surgery, but with no clear explanation for this designation.

NOMESCO Classification of surgical procedures provides an extensive list of codified procedures, including a specific paragraph for minor procedures.

For minor surgery, one factor to be considered could be the removal of the stitches.

Transmission of infectious agent

The probability of transmission of HCV from surgeon to patient has been estimated between 0,004 and 0,007 for 2005-2020 in France, i.e 0,3 to 7 cases per year during that period of time. This risk has been described as significantly higher in open heart surgery compared to other vascular surgery, but these condition lead to permanent deferral for blood donation. Therefore, this viral risk should not be taken into account as a selection criteria per se.

vCJD : refer to the list of procedures identified as "at risk".

Issues related to (select all that apply): donor / recipient

- Severity

*grade of severity** DONOR				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
Anaemia and iron deficiency	*X*			
Reduced wound healing			X	

*grade of severity** RECIPIENT				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
Transmission of infectious agents		X		

- Imputability

*level of imputability** DONOR						
Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
Anaemia and iron deficiency	*X*					
Reduced wound healing			X			

- Imputability

*level of imputability** RECIPIENT						
Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
Transmission of infectious agents				*X*		

- *Options to minimise each of the risks*
    - Blood loss : pre-donation Hb measurement is to be performed according to national procedures.
    - Iron stores : ferritin measurement can be suggested at the first donation following major surgery
    - Would healing : pre-donation questioning

b. Recommendations;

2.0.3.7. After major surgery, donors must be deferred for 6 months, or for 4 months provided a NAT test for hepatitis C is negative. (Directive 2004/33/EC Annex III).

2.0.3.8. After minor surgery, donors must be deferred for 1 week. (Directive 2004/33/EC Annex III).

There is no clear evidence supporting the exact deferral periods of 4 to 6 months after major surgery and for 1 week after minor surgery. Based on current literature the following policy concerning surgery can be implemented (C,E):

The relevant illness/condition should first be evaluated regarding donation criteria. Transfusion of labile blood products needs to be investigated (refer to specific rules). Pre-donation haemoglobin measurement should be performed after major surgery.

After major surgery, persons should not donate until they have fully recovered (typically about 6 months). A shorter deferral period is possible with medical advice after medical evaluation, if the donor has totally recovered from the surgery:

- wound healed
- no signs of post-operative infection
- healthy condition. (C, E)

Planned major surgery: homologous whole blood donation should be avoided at for an appropriate time interval before major surgery. (E)

Minor surgery: deferral until wound healed (stitches removed, no signs of infection). (C,E)

c. Justification (data/references)

- Commander SJ, Chamata E, Cox J, Dickey RM, Lee EI. Update on Postsurgical Scar Management. Semin Plast Surg. 2016 Aug;30(3):122-8

- Guo S, Dipietro LA. Factors affecting wound healing. J Dent Res. 2010 Mar;89(3):219-29

- Solimeno LP, Escobar MA, Krassova S, Seremetis S. Major and Minor Classifications for Surgery in People With Hemophilia: A Literature Review. Clin Appl Thromb Hemost. 2018 May;24(4):549-559

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d. Considerations (e.g., financials, etc.).

Distinguish between minor and major surgery is sometimes difficult.

Surgery, in itself, will cause a temporary deferral of the donor with limited consequences for the transfusion services.

The reason for surgery may result in permanent deferral of the donor.

Need for surgery may motivate the donor to continue donation or motivate non-donors to become donors.

* definitions for severity grade

Grade 1	*Non-Severe*	*the recipient may have required medical intervention (e.g. symptomatic treatment) but lack of such would not result in permanent damage or impairment of a body function.*
Grade 2	*Severe*	*the recipient required in-patient hospitalization or prolongation of hospitalization directly attributable to the event; and/or – the adverse event resulted in persistent or significant disability or incapacity; or – the adverse event necessitated medical or surgical intervention to preclude permanent damage or impairment of a body function.*
Grade 3	*Life-threatening*	*the recipient required major intervention following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death*
Grade 4	*Death*	*the recipient died following an adverse transfusion reaction Grade 4*

		should be used only if death is possibly, probably or definitely related to transfusion.

If the patient died of another cause, the severity of the reaction should be graded as 1, 2 or 3.

* definitions for imputability level

NA	*Not assessable*	*When there is insufficient data for imputability assessment.*
0	*Excluded*	*When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes.*
	Unlikely	*When the evidence is clearly in favour of attributing the adverse reaction to causes other than the quality/safety of tissues/cells*
1	*Possible*	*When the evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissues/cells or to alternative causes.*
2	*Likely, Probable*	*When the evidence is clearly in favour of attributing the adverse reaction to the quality/safety of tissues/cells.*
3	*Definite, Certain*	*When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues/cells.*

Background Document 7

GTS Ch2 document based on TRANSPOSE risk-based assessment tool
(by J.Castrén. Latest update on 11.1.2022)

Dental treatment

a. What the issues are;

Risk for the recipient: bacteraemia in the donor due to dental care may be a risk for sepsis in the recipient.
For donors who have received bovine bone filling material please refer to Variant Creutzfeldt-Jacob Disease.

Issues related to (select all that apply): ☐ donor X recipient

- Severity

*grade of severity*RECIPIENT*				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
Transmission of infection		*X*	*X*	

- Imputability

*level of imputability*Recipient risks*						
Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
Transmission of infection			*X*			

- *Options to minimise each of the risks*

Options to minimize each of the risks

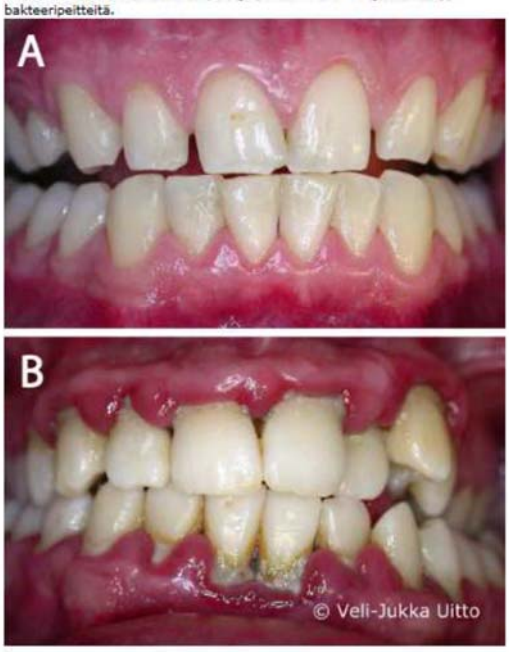
b. proposed criteria;

• Minor dental treatment:
Based on literature: bacteraemia with microbes of dental/oral origin is common after a variety of oral activities and all kind of gum and tooth irritation. Bacteraemia is typically time related to the irritation (0-30 min) and detected after tooth extraction, root scaling, periodontal probing, suture removal, orthodontic treatment, tooth restoration, non-surgical root canal treatment. The risk for bacteraemia is **oral health dependent**: the risk for bacteraemia is high – even with chewing or tooth

brushing in patients with periodontitis (picture B) – but almost zero with persons with only gingivitis or with healthy periodontium (picture A).
Conclusion:
60 minutes' deferral is enough for donors who have undergone small dental procedures including root scaling and dental restoration. 1-week deferral for small surgery and tooth extraction. For donors with acute oral infections: deferral period as for infections in general.

A. Terve parodontium. Ikenet ovat vaaleat ja kiinnittyvät tiiviisti hampaiden pintaan.

B. Parodontiitti. Ikenet ovat turpeat ja punoittavat. Ienrajoissa näkyy bakteeripeitteitä.



Artikkelin tunnus: ima02126 (070.028)

• Major dental treatment:
Deferral until the healing process is at a stage where the risk of secondary infection is over; at least one week.

c. justification (data/references);

- Update on bacteraemia related to dental procedures. Olsen I. Transfusion and Apheresis Science, 2008; 39(2):173-78.
- Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. Forner L, Larsen T, Kilian M, Holmstrup P. J Clin Periodontol. 2006; 33:401-7.

d. considerations (e.g., financials, etc.).

Dental care procedures are very common; healthy people visit dentists; unnecessary deferrals for one day can be avoided by shortening the minimum deferral period of 1 day to one hour.

Background Document 8

GTS Ch2 document based on TRANSPOSE risk-based assessment tool
(by O.Flesland, J.Castrén. Latest update on 1.3.2022)

Blood components for topical use or injections

a. What the issues are;

This document describes risks/selection criteria in cases where the prospective blood donor has received topical or injection treatment with blood components.

(To be noted: The preparation of blood components for topical use or injection is described in the Chapter 35 of the Guide to the quality and safety of TISSUES AND CELLS for human application 4th ed.)

The risk connected with receiving topical or injection treatment with blood components depends on the source of the blood component. If the blood component is from an autologous donation, it is a risk of the blood component being contaminated with bacteria or fungi during storage, i.e. before treatment. If the blood component is from an allogeneic donation there is in addition a risk of transmission of other blood born infections.

1. Risk for the donor coming to the blood establishment to donate whole blood for transfusion:
    - Same risk as for all other donors; no specific risk due to the treatment they received.
    - In addition, the reason for needing the treatment may be a risk.

2. Risk for the recipient of blood components for transfusion

    - Transmission of infectious agents. The same risk as for any recipient receiving blood components from a donor that has been transfused. Such donors already have a deferral period (6 (4) months deferral (standard 2.3.4.1).

Arguments and summary of the literature

Current guidelines for donor selection will prevent donors that have a bacterial of fungal infection after using blood components for topical use or injections from donating.

Current guidelines for donor selection will prevent donors that have received allogeneic blood components for topical use or injections from donating for 6 or 4 months (standard 2.3.4.1).

In donor selection allogeneic blood components for topical use or injections should be treated like blood ***components for transfusion***.

There is a small risk of bacterial and fungal infections from blood components for topical use or injections when stored.

The literature show that platelet rich plasma may have antibacterial properties.

Severity and immutability

- Issues related to (select all that apply): donor / recipient

- Severity

*grade of severity** DONOR				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
The possible risk due to the reason for treatment, so specific risks due to the treatment as such	*X*			

*grade of severity** RECIPIENT				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
Infection		*X*		

- Imputability

*level of imputability** DONOR						
Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
The possible risk due to the reason for treatment, so specific risks due to the treatment as such			*X*			

- Imputability

*level of imputability** RECIPIENT						
Risk(s)	*Definite/Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*

Infection	*X*					

- *Options to minimise each of the risks*

b. Recommendations;

The preparation of blood components for topical use or injection should be as described in Guide to the quality and safety of TISSUES AND CELLS for human application 4th ed.

The donor selection should be according to the current Guide to the preparation, use and quality assurance of BLOOD COMPONENTS.

In donor selection allogeneic blood components for topical use or injections should be treated like blood components for transfusion.

c. Justification (data/references);

Eye drops

Thanathanee O, Phanphruk W, Anutarapongpan O, Romphruk A, Suwan-Apichon O. Contamination risk of 100% autologous serum eye drops in management of ocular surface diseases. Cornea. 2013 Aug;32(8):1116-9. doi: 10.1097/ICO.0b013e3182910036. PMID: 23665646.

Yang Y, Zhu X, Yang J, Shi A, Jiang M, Peng Y, Li M, Wang Y, Yuan H. An Environmental Control Experiment for Contamination of the Production and Storage of 20% Autologous Serum Eye Drops. Curr Eye Res. 2020 Nov;45(11):1364-1368. doi: 10.1080/02713683.2020.1741008. Epub 2020 Mar 23. PMID: 32150475.

Sauer R, Blüthner K, Seitz B. Sterilitätskontrolle von unkonservierten Eigenserumtropfen bei therapieresistenten Hornhautepitheldefekten. Eine prospektive Studie [Sterility of non-preserved autologous serum drops for treatment of persistent corneal epithelial defects]. Ophthalmologe. 2004 Jul;101(7):705-9. German. doi: 10.1007/s00347-003-0962-4. PMID: 14999414.

Platelet rich plasma, platelet gel etc.

Piccin A, Di Pierro AM, Canzian L, Primerano M, Corvetta D, Negri G, Mazzoleni G, Gastl G, Steurer M, Gentilini I, Eisendle K, Fontanella F. Platelet gel: a new therapeutic tool with great potential. Blood Transfus. 2017 Jul;15(4):333-340. doi: 10.2450/2016.0038-16. Epub 2016 Jul 25. PMID: 27483482; PMCID: PMC5490729.

https://uscenterforsportsmedicine.com/what-are-the-side-effects-of-platelet-rich-plasma-therapy/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6589492/

d. Considerations (e.g., financials, etc.).

Loss of safe donors if unnecessary long deferral periods.

The use of blood components for topical use or injections is still not common in the donor population but the use is increasing.

Evaluation of eligibility of a donor must be quick, and easy to perform in a consistent way.

The clinicians using these treatments might not understand/be aware that the practicing this treatment should be regulated according to the blood donation rules and requirements

* definitions for severity grade

Grade 1	*Non-Severe*	*the recipient may have required medical intervention (e.g. symptomatic treatment) but lack of such would not result in permanent damage or impairment of a body function.*
Grade 2	*Severe*	*the recipient required in-patient hospitalization or prolongation of hospitalization directly attributable to the event; and/or – the adverse event resulted in persistent or significant disability or incapacity; or – the adverse event necessitated medical or surgical intervention to preclude permanent damage or impairment of a body function.*
Grade 3	*Life-threatening*	*the recipient required major intervention following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death*
Grade 4	*Death*	*the recipient died following an adverse transfusion reaction Grade 4 should be used only if death is possibly, probably or definitely related to transfusion.*

If the patient died of another cause, the severity of the reaction should be graded as 1, 2 or 3.

* definitions for imputability level

NA	*Not assessable*	*When there is insufficient data for imputability assessment.*
0	*Excluded*	*When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes.*
	Unlikely	*When the evidence is clearly in favour of attributing the adverse reaction to causes other than the quality/safety of tissues/cells*
1	*Possible*	*When the evidence is indeterminate for attributing adverse reaction either to the quality/safety of tissues/cells or to alternative causes.*
2	*Likely, Probable*	*When the evidence is clearly in favour of attributing the adverse reaction to the quality/safety of tissues/cells.*
3	*Definite, Certain*	*When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the quality/safety of tissues/cells.*

Background Document 9

Plasmapheresis, Ch2 2021

GTS Ch2 document based on TRANSPOSE risk-based assessment tool

(by P. Radziwon, J.Castrén. Last update on 11.1.2022)

Apheresis donation

a. What the issues are;

- **Low level of vital human proteins is the main known long term adverse event among plasma donors**
- **Donors should be protected against too low IgG levels as well as too low levels of total proteins**
- **How often and how many times per year is it safe to donate?**

Current criteria in the 20 Ed of the Guide

- The maximum number of plasma donations allowed is 33 per year (2.4.2.10.)
- The donation interval must be at least 96 hours. (2.4.2.11.)
- Total proteins must be measured at least annually and must not be less than 60 g/L. (2.4.2.12)

Additional requirements for donors undergoing plasmapheresis – measurement of IgG concentration

- Serum-IgG levels must be within reference values of the normal population and should not fall below 6.0 g/L. (2.4.2.13.)
- Serum-IgG must be measured at least annually and at every 5th donation, whichever comes first. (2.4.2.14.)

- Issues related to (select all that apply): donor / recipient

- Severity

grade of severity DONOR*				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
hypoglobulinaemia			*X*	
hypocalcaemia		*X*		
hypomagnesemia		*X*		
decrease in bone density		*x*		
osteoporosis		*X*		
vascular calcifications		*X*		

- Imputability

level of imputability DONOR*						
Risk(s)	*Definite/ Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
hypoglobulinaemia	*X*					
hypocalcaemia	*X*					
hypomagnesemia	*X*					
decrease in bone density	*X*					
osteoporosis		*X*				
vascular calcifications			*X*			

- *Options to minimise each of the risks*

Donor: deferral of individuals with IgG concentration below 6 g/L; measurement of serum IgG concentration; adjustment of the frequency of plasma donation to the concentration of IgG in the donor.

b. Recommendations;

- *The maximum number of plasma donations allowed is 33 per year.*
- *The donation interval must be at least one week.*
- *Serum IgG should be measured annually and at every 26th donation, whichever comes first.*
- *The maximum donation frequency for an individual donor should be guided by the results of the testing. An approach for the calculation of the maximum donation frequency for an individual donor based on its IgG levels could be as follows:*
    - *IgG < 6.0 g/L results in a deferral from plasmapheresis of at least 3 weeks. Repeated measurements of < 6.0 g/L should lead to either a significant increase in the inter-donation interval or permanent deferral from plasmapheresis;*
    - *IgG 6.0–8.0 g/L supports donations with a minimum interval of two weeks*
    - *IgG > 8.0 g/L supports donations with a minimum interval of one week*

c. Justification (data/references);

1. **There are no data supporting safety of more than 33 plasmapheresis per year.**
2. **There are data reporting significant effect of multiple apheresis and citrate contributing to hypocalcemia, hypomagnesemia, hyperparathyroidism. The experience from haemodialysis may suggest that chronic exposure to citrate may also have an effect on formation of vascular calcifications(1-6).**

2. There are no data supporting safety of plasmaphereses on more than a weekly basis justified IgG concentration > 10 g/L. (20th edition of the Guide)

3. There are no valuable data supporting measurement of IgG concentration every 5th plasma donation. (20th edition of the Guide)

3.1. No statistically significant difference from the initial concentrations was observed during monthly measurements of IgG, IgA and IgM levels among groups donating plasma at weekly or bi-weekly intervals (7).

3.2. Serum levels of total protein, albumin, and immunoglobulins, monitored at intervals in first-time and long-term plasmapheresis donors over 10 years showed no significant differences (8).

3.3. There are reports concluding that removal of 500-600 ml of plasma at weekly intervals involves little, if any, risk of total protein or immunoglobulin depletion in donors (7).

3.4. Total serum protein, IgG, Hb, ferritin, transferrin, cardiovascular risk markers and parameters of blood coagulation did not change significantly during the observation period of 3 years of intensive plasmapheresis (9).

3.5. Like non-donors, all plasma donors had normal humoral and cellular immunity (10).

4. There are data justifying measurement of IgG concentration in plasma donors.

4.1. Donors had significantly lower total serum protein, albumin and IgG levels than non-donors (9,10).

4.2. Seven percent of regular donors had low IgG levels on at least one occasion and level of IgG fluctuate throughout of regular donations (11).

4.3. Low IgG concentration is a risk factor for dropping out of donors (12).

4.4. Donors' IgG levels during apheresis shows a steady decrease (13).

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1. Amrein, Karin & Dimai, Hans & Dobnig, H. & Fahrleitner-Pammer, Astrid. (2016). Plasmapheresis and Osteoporosis: The absence of evidence is not the evidence of absence. 23. 44-47.
2. Amrein K, Katschnig C, Sipurzynski S, et al. Apheresis affects bone and mineral metabolism." Bone. 2010;46(3):789-795. doi:10.1016/j.bone.2009.11.00
3. Bialkowski W, Blank RD, Zheng C, Gottschall JL, Papanek PE. Impact of frequent apheresis blood donation on bone density: A prospective, longitudinal, randomized, controlled trial. Bone Rep. 2018;10:100188. Published 2018 Dec 12. doi:10.1016/j.bonr.2018.100188
4. Bialkowski W, Bruhn R, Edgren G, Papanek P. Citrate anticoagulation: Are blood donors donating bone?. J Clin Apher. 2016;31(5):459-463. doi:10.1002/jca.21438
5. Boot CL, Luken JS, van den Burg PJ, de Kort WL, Koopman MM, Vrielink H, van Schoor NM, den Heijer M, Lips P. Bone density in apheresis donors and whole blood donors. Vox Sang. 2015 Nov;109(4):410-3. doi: 10.1111/vox.12299. Epub 2015 May 29. PMID: 26031345.
6. Rodríguez-García M, Gómez-Alonso C, Naves-Díaz M, et al. Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. Nephrol Dial Transplant. 2009;24(1):239-246. doi:10.1093/ndt/gfn466
7. Ciszewski TS, Ralston T, Acteson D, Wasi S, Strong SJ. Protein levels and plasmapheresis intensity. Transfus Med. 1993;3:59-65.
8. Wasi S, Santowski T, Murray SA, Perrault RA, Gill P. The Canadian Red Cross plasmapheresis donor safety program: changes in plasma proteins after long-term plasmapheresis. Vox Sang. 1991;60:82-7.
9. Bechtloff S, Tran-My B, Haubelt H, Stelzer G, Anders C, Hellstern P. A prospective trial on the safety of long-term intensive plasmapheresis in donors. Vox Sang. 2005;88:189-95.
10. Tran-Mi B, Storch H, Seidel K, Schulzki T, Haubelt H, Anders C, Nagel D, Siegler KE, Vogt A, Seiler D, Hellstern P. The impact of different intensities of regular donor plasmapheresis on humoral and cellular immunity, red cell and iron metabolism, and cardiovascular risk markers Vox Sang. 2004;86:189-97.
11. Burgin M, Hopkins G, Moore B, Nasser J, Richardson A, Minchinton R. Serum IgG and IgM levels in new and regular long-term plasmapheresis donors. Med Lab Sci. 1992;49:265-70.
12. Schulzki T, Seidel K, Storch H, Karges H, Kiessig S, Schneider S, Taborski U, Wolter K, Steppat D, Behm E, Zeisner M, Hellstern P, SIPLA study group. A prospective multicentre study on the safety of long-term intensive plasmapheresis in donors (SIPLA). Vox Sang. 2006;91:162-73.
13. Burkhardt T, Rothe R, Moog R. Immunoglobulin G levels during collection of large volume plasma for fractionation Transfus Apher Sci. 2017;56:417-420.
14. Salvaggio et al. (1971); Int. Arch. Allergy 41: 883-894
15. Friedman et al., (1975); Transfusion15 (5): 467-472
16. Grgičević, D. (1983); Ric Clin Lab: 21-31
17. Matthes et al. (1992); Infusionstherapie 19: 29-31

18. Möller, Anke (2012) PhD Thesis “Der Einfluss der präparativen Plasmapherese auf Immunglobulin G-, Gesamteiweiß- und Flüssigkeitshaushalt des Plasmaspenders“ (The influence of preparative plasmapheresis on immunoglobulin G, total protein and fluid balance of the plasma donor.) (In German, English summary for the GTS by Piotr Radziwon
19. Hellstern P, Bach J, Haubelt H, Hitzler WE, Mathis S, Vogt A. The impact of the intensity of serial automated plasmapheresis and the speed of deep-freezing on the quality of plasma. Transfusion. 2001 Dec;41(12):1601-5. doi: 10.1046/j.1537-2995.2001.41121601.x. PMID: 11778078.
20. Rezvan H, Ahmadi J, Mirbod V: The Iranian Blood Transfusion, Donor Safety Program: Effect of Long-term Plasmapheresis on Plasma Proteins. Iran JMed Sci 2003; 28(1):33-36

d. Considerations (e.g., financials, etc.).

Frequent measurement of IgG concentration does not add value to the donor protection or to the product quality according to available literature.

CITATIONS FROM REFERENCES

1. Amrein, Karin & Dimai, Hans & Dobnig, H. & Fahrleitner-Pammer, Astrid. (2016). Plasmapheresis and Osteoporosis: The absence of evidence is not the evidence of absence. 23. 44-47.

“Plasma and the products derived from it are indispensable to modern medicine, e. g. for immunoglobulins, coagulation factors, and albumin. Apheresis donations allow for selective collection of plasma with minimal loss of red blood cells. However, reliable anticoagulation - usually with citrate - is required because of the length and method of the donation procedure. Citrate complexes calcium and therefore leads to acute hypocalcemia, hyperparathyroidism, and prolongation of the QT interval. Apheresis donors also experience exposure to "endocrine disrupting chemicals" such as pthalates, which leak from the plastic donation sets during the donation and have been implicated with potential adverse effects on fertility and endocrine function. Repetitive apheresis might therefore be a previously unknown risk factor for impaired bone health. The existing data are however sparse and insufficient to confirm or reject this hypothesis.”

2. Amrein K, Katschnig C, Sipurzynski S, et al. Apheresis affects bone and mineral metabolism.” Bone. 2010;46(3):789-795. doi:10.1016/j.bone.2009.11.008

Conclusions: Exposure to citrate during the apheresis procedure acutely affects mineral and bone metabolism. Regular donations of blood components compromised BMD at the lumbar spine. If confirmed, strategies to prevent long-term effects on bone need to be formulated.

3. Bialkowski W, Blank RD, Zheng C, Gottschall JL, Papanek PE. Impact of frequent apheresis blood donation on bone density: A prospective, longitudinal, randomized, controlled trial. Bone Rep. 2018;10:100188. Published 2018 Dec 12. doi:10.1016/j.bonr.2018.100188

The longitudinal, randomized, controlled ALTRUYST trial (NCT02655055) was undertaken to determine whether BMD declined following high frequency apheresis blood donation over 1 year.

Donors randomized to the apheresis arm were asked to make between 20 and 26 apheresis blood donations during the subsequent one year period. Donors in the apheresis arm experienced a median of 20 apheresis blood donations during the one year study period with the amount of citrate exposure by donation type ranging from 164 mL to 657 mL. The duration of each donation ranged from just under 30 min to more than

two hours in length. High frequency apheresis induced clinically meaningful positive change in some donors and clinically meaningful negative change in others, particularly at the lumbar spine.

Interpretation: ALTRUYST is the first longitudinal trial to demonstrate that apheresis blood collection guidelines in the United States adequately protect the skeletal health of male volunteer blood donors.

4. Bialkowski W, Bruhn R, Edgren G, Papanek P. Citrate anticoagulation: Are blood donors donating bone?. J Clin Apher. 2016;31(5):459-463. doi:10.1002/jca.21438

Results from a bone density study of 102 apheresis platelet donors with a lifetime average of 85 apheresis procedures (range 16 – 633) as compared to non-blood donor controls demonstrated significantly lower bone density at the lumbar spine (Z-score P=0.038) for apheresis donors as compared to controls [38]. The lumbar spine is rich in metabolically active trabecular bone that requires 14 days or longer to replenish serum calcium, a period over which some have shown evidence of bone remodeling [45]. The opportunity exists to fully catalog apheresis blood donor physiology in the weeks following IV citrate exposure. Making use of the available data in predicting long term effects on bone health in this donor population is challenging, though a prospective study at the National Institutes of Health (NCT00073060) is incorporating a longitudinal assessment of bone density to address this.

5. Boot CL, Luken JS, van den Burg PJ, de Kort WL, Koopman MM, Vrielink H, van Schoor NM, den Heijer M, Lips P. Bone density in apheresis donors and whole blood donors. Vox Sang. 2015 Nov;109(4):410-3. doi: 10.1111/vox.12299. Epub 2015 May 29. PMID: 26031345

In this study, the BMD of 20 postmenopausal apheresis donors (mean donation number 115 times in up to 15 years) was compared with that of 20 whole blood donors (for 15 years or more) aged 55-70. BMD in the lumbar spine was not lower in apheresis donors than in blood donors (mean ± SD 1.00 ± 0.18 vs. 0.92 ± 0.12, P = 0.09). In the hip, BMD was not different between the groups.

6. Rodríguez-García M, Gómez-Alonso C, Naves-Díaz M, et al. Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. Nephrol Dial Transplant. 2009;24(1):239-246. doi:10.1093/ndt/gfn466

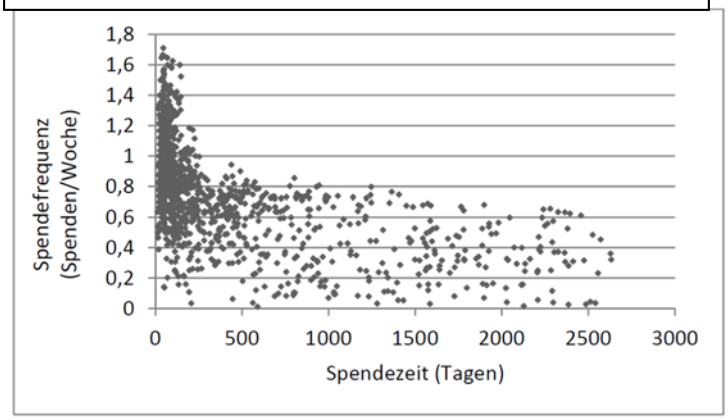
A total of 193 HD patients were followed up to 2 years. Positive associations between vascular calcifications, vertebral fractures and mortality have been found in patients on HD

Summary of main results of the Ph.D. Thesis Möller 2021:

"Der Einfluss der präparativen Plasmapherese auf Immunglobulin G-, Gesamteiweiß- und Flüssigkeitshaushalt des Plasmaspenders" (The influence of preparative plasmapheresis on immunoglobulin G, total protein and fluid balance of the plasma donor.) by Anke Möller (2012)

The Author analysed retrospectively the data concerning IgG and total serum protein (TSP) metabolism in plasma donors as well as drop outs of plasmapheresis donors and researched for parameters estimating the time needed for recovery and donor suspension.
The study was performed in Germany where 45 plasmaphereses per year are allowed with minimal interval of 48 hours. The data set of multiple donors donating plasma from 2001 to 2009 in blood centres of HAEMA AG contained 6667 donors who were suspended at least once due to low IgG (≤ 6,0 g/L), or TSP (≤60 g/L) concentration.
Plasmapheresis frequency was in a range from 0.01 to 1.71 per week; median 0.73 per week. Plasmapheresis frequency negatively correlated with the time to the drop out due to low IgG concentration or TSP concentration. At the high frequency plasmapheresis the above mentioned correlation was very strong. At low frequency plasmapheresis the dependence of the time window to the first drop out was very week. According to the fig. 23 the borderline high and low frequency donations is between 0.6-0.8 donations per week, which means 31-41.6 donations per year.

Figure 23: Donation frequency vs donation time.



The impact on the plasma protein management caused by plasmapheresis becomes significant. As part of the donation activity, the TSP was reduced by 18%, the IgG by 38%. As expected, the IgG regeneration rate was well below the TSP regeneration rate.
Donors no longer reach the total protein concentration as well as IgG serum concentration determined before the start of the donation activity.

The most important conclusions of the thesis are as follows:
1. IgG and TSP behave independently of each other. While the TSP concentration can be very good influenced by diet, the IgG concentration is the limiting factor of plasmapheresis.

2. IgG and TSP concentrations and regeneration rates are subject to large individual differences.

3. IgG concentrations of less than 5 g/L must be avoided. To avoid very low plasma concentrations, the donation frequency should be set individually depending on the initial level of IgG and regeneration

rate. High plasma concentrations and high regeneration rates allow high donation frequencies. Low IgG concentrations and low regeneration rates require low donation frequencies.

4. Rapid onset of volume shifts justify the low risk of collapse during and after plasmapheresis. The extracorporeal volume should therefore not be included in the calculation of the maximum donation volume.

The Ph.D. thesis by Anke Möller presents the background for the recommendations of the "Guide…":

The (high) frequency of plasmapheresis above 0.6-0.8 donations per week exceeds the regeneration rate for IgG or TSP in significant number of donors thus presents a risk factor for donors. The (low) frequency donations can not exclude the risk of drop out due to low concentration of IgG or TSP however the risk is mostly donor dependent rather than plasmapheresis frequency dependent. – *recommendation 2.4.2.10.*

The individual assessment of the plasmapheresis frequency according to the initial IgG concentration decreases the risk of low IgG concentration in donor – *recommendation 2.4.2.14. (partially)*.

Summary of the Ph.D. Thesis Möller 2012:

"Der Einfluss der präparativen Plasmapherese auf Immunglobulin G-, Gesamteiweiß- und Flüssigkeitshaushalt des Plasmaspenders" by Anke Möller (2012)
(The influence of preparative plasmapheresis on immunoglobulin G, total protein and fluid balance of the plasma donor.)

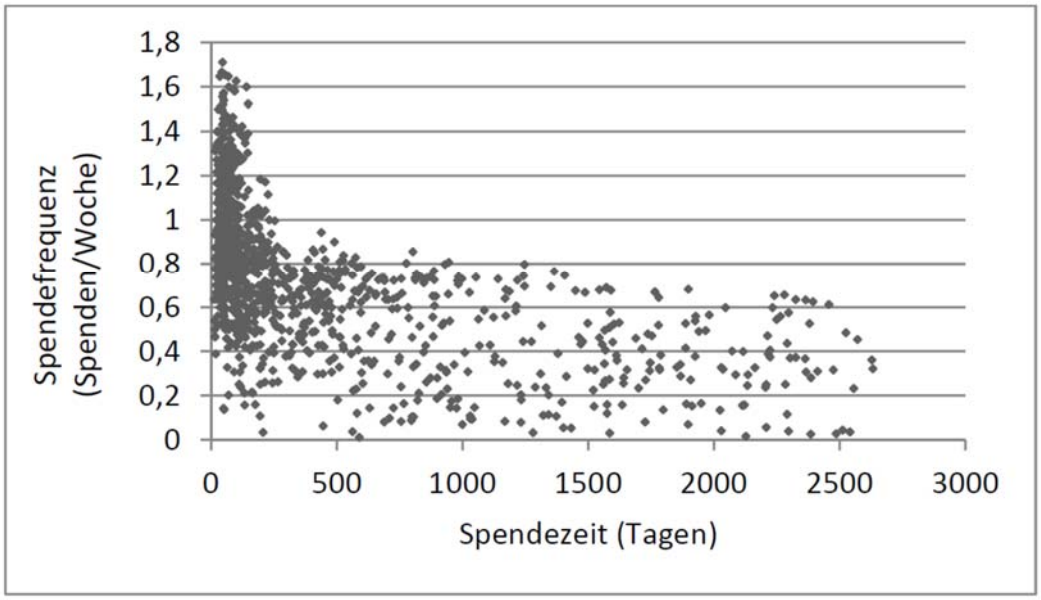
Aim
One of the aim was retrospective analysis of the data concerning IgG and total serum protein metabolism in plasma donors as well as drop outs of plasmapheresis donors and research for parameters estimating the time needed for recovery and donor suspension.

Methods
The study was performed in Germany where 45 plasmaphereses per year are allowed with minimal interval of 48 hours.
The data set of multiple donors donating plasma from 2001 to 2009 in blood centres of HAEMA AG (Chemnitz, Erfurt, Freiberg, Gera, Jena, Plauen, Weimar und Zwickau) contained 6667 donors who were suspended at least once due to low IgG (>/= 6,0 g/L), or TSP (>/= 60 g/L) concentration.

Results
The median time to the first drop out was 143 days, plasmapheresis frequency was in a range from 0.01 to 1.71 per week; median 0.73 per week.
The needed time for re-entry into the plasma donation was very variable and strongly donor dependent.
Total protein concentration at the first plasmapheresis was 72 g/l and dropped to 58 g/l. After donation brake increased to 67 g/l.
IgG concentration also dropped as a result of plasmapheresis and did not reached initial values after donation brake.
Plasmapheresis frequency negatively correlated with the time to the drop out due to low IgG concentration or TSP concentration. (Fig.23)
At the high frequency plasmapheresis the above mentioned correlation was very strong. At low frequency plasmapheresis the dependence of the time window to the first drop out was very week.

Figure 23: Donation frequency vs donation time.

Abbildung 23: Spendefrequenz versus Spendezeit



As part of the donation activity, the TSP was reduced by 18%, the IgG by 38%. As expected, the IgG regeneration rate was well below the GEW regeneration rate.

In both groups, however, the impact on the plasma protein balance caused by plasmapheresis becomes significant. Donors no longer reach the total protein concentration as well as IgG serum concentration determined before the start of the donation activity.

Conclusions

1. IgG and TSP behave independently of each other. While the TSP concentration can be very good

influenced by diet, **the IgG concentration is the limiting factor of plasmapheresis.**

2. IgG and TSP concentrations and regeneration rates are subject to large individual differences.

3. The currently practiced IgG and TSP donor suspension practice is not in line with an individual

Donor management.

• Very low plasma concentrations, which pose a donor hazard, will not be prevented.

• The fixed provision period does not reliably correspond to the actually required

individual deferral period.

4. IgG concentrations of less than 5 g/L must be avoided. To avoid very low plasma concentrations, the donation frequency should be set individually depending on the initial level of IgG and regeneration rate. High plasma concentrations and high regeneration rates allow high donation frequencies. Low IgG concentrations and low regeneration rates require low donation frequencies.

5. The control regime should be individually set depending on the initial level and regeneration rate. Low output IgG concentration and low regeneration rate requires lower donation frequency.

6. The implementation of the individual regeneration rate calculated by a forecast model in

the blood bank IT system is another way to individualize and optimize donor protection. The forecast model developed in the context of this study for determining the timing of a successful re-entry after suspension should be incorporated after further examination into the suspension practice.

7. Rapid onset of volume shifts justify the low risk of collapse during and after plasmapheresis. The extracorporeal volume should therefore not be included in the calculation of the maximum donation volume.

8. The volume shifts from the extravascular to the intravascular compartment lead to a significant dilution of the plasma proteins IgM, IgG, albumin and total protein.

9. Improving donor safety requires individualization. The German Medical Association guidelines of the flat-rate requirements with regard to the IgG and TSP dependent suspension time do not meet this requirement.

10. Donor management is the means of choice in order not to decrease donor safety on the one hand, on the other hand, to be able to encourage donors with optimal conditions to make additional donations.

Comment PR: *In my opinion the results of the study (particularly the figure 23) strongly support the allowed number of plasmapheresis set in CoE Guideline.*

Background Document 10

CHAPTER 3 REVISION

Prepared by	Joanne Pink Sarah Morley Vera Bogdanova

SUMMARY OF CHANGE

3.6.2.5

There is now scientific evidence that supports extending the bleeding time from 12 minutes to 15 minutes (Dirk de Korte et al, Evaluation of platelet concentrates prepared from whole blood donations with collection times between 12 and 15 minutes: The BEST Collaborative study. Vox Sang 2022:1-7).

The authors conclude " This study provides evidence that 12-15 min donations should not be excluded for PC preparation and justifies the guidelines to <15 min instead of <12 min of collection in line with current practice in some countries".

The bleeding time has been changed to 15 minutes. This standard has also been clarified such that it only applies to whole blood collections.

3.6.2.6

There is an old publication (Huh et al Effect of donation time on platelet concentrates and fresh frozen plasma. Vox Sang 1989; 56, 21-24) that showed a correlation between a higher fibrinopeptide A level with a longer donation time, indicating a greater degree of thrombin generation. However, assays of factor V and VIII:C did not show decreased activity.

The authors conclude that "the degree of thrombin generation during the blood collection does not appear to be significant enough to degrade FV and VIII:C. The higher activity of FVIII:C in units collected over a prolonged period may have resulted from activation of thrombin, as others have suggested. The stability of these labile factors remains to be determined by plasma fractionation study."

We have concluded that there is insufficient evidence to support an extension of the collection time to 20 minutes for platelets or plasma. We have recommended that this be explored by a study by the BEST Collaborative.

This standard has also been clarified such that it only applies to whole blood collections.

References:

- Dirk de Korte et al, Evaluation of platelet concentrates prepared from whole blood donations with collection times between 12 and 15 minutes: The BEST Collaborative study. Vox Sang 2022:1-7
- Huh et al Effect of donation time on platelet concentrates and fresh frozen plasma. Vox Sang 1989; 56, 21-24

Background Document 11

Andre Rapaille and Dirk de Korte

pH measurement versus glucose measurement as a tool of quality monitoring in PCs stored in PAS E / Plasma

Objective.

Replacement of pH measurement at the end of the shelf life of platelet concentrates (PC) used as a tool of quality monitoring by glucose measurement in PC stored in PAS containing phosphate with different percentages of plasma.

Introduction

Glucose in platelet concentrates (PC) is metabolized to lactic acid by the glycolytic pathway resulting in decreasing pH levels. Depletion of glucose is generally preceded by change in platelet metabolism in terms of increased rate of glycolysis and fall in pH levels. Those results suggested that depletion of glucose, not the pH level alone, may be detrimental to platelets during storage (Gulliksson, Vox sang 2014).

The expected decrease in pH with storage was evident after day 6 in PCs suspended in plasma. This is generally attributed to the consumption of bicarbonate, which acts as the principal buffer in plasma. Platelet concentrates with a $pH_{22°C}$ less than 6.2 have been poor recoveries and survival (Murphy Blood 1970, Kikson Blood 1984).

The 90s years saw the arrival of different platelet additive solutions (PAS). The use of these solutions became widespread in the years 2000 - 2010. One of the benefits, in addition to the increase in plasma for fractionation, is the reduction of some transfusion reactions. Many studies have been conducted to evaluate the in vitro quality of platelet concentrates stored in these PAS with different amount of plasma.

To improve the plasma reduction, efforts to increase buffering capacity by addition of phosphate in PAS have been made. And the metabolism of acetate in PAS also stabilizes the pH levels.

Literature review.

PAS E solutions is widespread used in European countries in combination with pathogen inactivation method or not to store PC up to 7 days in some countries. PAS E solution contains 69 mmom/L NacCl, 5 mmol/L KCl, 1,5 mmol/L $MgCL_2$, 10 mmol/L Na_3-citrate, 26 mmol/L NaH_2PO_4/Na_2HPO', 30 mmol/L Na-acetate with a pH level of 7.2. The amount of plasma added to PAS E vary between 30 to 40%. Some studies has been suggested to reduce the amount to 20%.

Level of pH In PC stored in PAS E/plasma solution stay stable over 6.4 up to day 7 and up to day 14 in some publications (Table 1).

Saunders suggested in his 2011 publication to review the usefulness of pH measurement as a quality indicator for PCs stored in PAS/plasma solution. This study concerned PCs stored in PAS E/plasma solution up to day 14.

Proposition from Sanquin resulting in this white paper

Guide : pH measured (+22°C) at the end of the recommended shelf-life, value > 6.4.

"This is only valid for platelet concentrates in plasma or in older types of additive solutions. With the currently used PAS-E (SSP+, TPAS+, PASIIIM as trade names) in a ratio of 30-40 plasma and 60-70% platelet additive solution pH will not decrease much further than 6.8, due to the buffering capacity in the PAS-E (partly by phosphate, partly formed from acetate metabolism). Also units with too much platelets in the bag (passing the capacity of the storage bag) and absence of swirl still have a pH > 6.8 in our QC data, from which we conclude that pH measurement as a process control check is not valid for platelets in PAS-E. Instead, the absence of glucose is a better predictor for absence of swirl 1-2 days after running out of glucose. If glucose at end of shelf life is still available (> 0.5 mM or > 1 mM) it seems to correlate with the presence of swirl. Suggestion to change the recommendation for QC and to skip pH measurement if PAS-C or PAS-E is used and to look for a better parameter, for which glucose seems to be a good candidate"

Discussion

To be considered in a routine use, the QC assay must be fast, straightforward (ideally without the need of sample preparation), robust, reliable, and applicable to all blood components treated (Abonnenc Transfusion2016).

We can see in the literature review that the pH remains stable up to 14 days in PCs suspended in solution combined PAS E and plasma unlike PCs suspended in 100% plasma solution.

The pH results of Sanquin study and CRB-SFS QC data described upper don't' say otherwise.

Sanquin's proposition to use the glucose level for QC monitoring of PCs stored in PAS with phosphate seems a good proposition. The level of glucose is well correlated with pH measurement and with swirl status of PCs in PAS E solution. Measurement of glucose answers the requirements for a QC parameter.

Minimal level of glucose needed: several data sets from GTS members showed that as long as there is some glucose present the units usually have good swirl. This is in line with research from Sanquin with measuring glucose every day; in this study the swirl disappeared roughly one day after glucose being 0. This means that as long as the glucose is quantifiable at the end of storage there would be no problem. Because there are different methods to quantify with different detection limits we suggest the term Limit of Quantification (LoQ: lowest level that can be determined accurate and reproducible). If we want a number this will be different per method/device used, and to cover all methods it should be 0.5 mM (whereas in practice lots of devices will be able to measure lower), resulting in unnecessary failure for units between 0.1 and 0.5 mM.

Conclusion.

1. pH measurement at the end of the shelf life is not recommended as quality monitoring on PCs stored in PAS E (or phosphate containing PAS). All results were above 6.4, the lower limit, in 2 home data analyses and in many articles.
2. If glucose at end of shelf life is still available (> LoQ) it seems to correlate with the presence of swirl.

Recommendation.

Measurement of glucose in PCs stored in PAS containing phosphate (expel: PAS E) can be an alternative as a process control check.

Limit of 0.5 / 1 mmol/L seems a good alternative.

Table 1

Authors	Publication date	Method	Plasma / PAS %		day 1	day 2	day 3	day 5	day 6	day 7	day 8	day 9	day 10	day 12	day 14
Gulliksson	2002	BC	30/70	pH (37°C)	6,98+/-0,01		7,15+/-0,01	7,17+/-0,02		7,13+/-0,02					
			20/80	pH (37°C)	6,98+/-0,01		7,11+/-0,01	7,12+/-0,02		7,07+/-0,02					
		Aph	30/70	pH (37°C)	7,29+/-0,02		7,35+/-0,03	7,29+/-0,03		7,16+/-0,09					
			20/80	pH (37°C)	7,23+/-0,03		7,23+/-0,04	7,16+/-0,03		7,16+/-0,09					
van der Meer	2004	BC	30/70	pH (37°C)	7,03+/-0,02			7,01+/-0,03							
			20/80	pH (37°C)	7,05+/-0,05			6,95+/-0,05							
Ringwald	2005	Aph	30/70	pH (37°C)	7,17+/-0,03			7,21+/-0,04		7,17+/-0,06					
			20/80	pH (37°C)	7,14+/-0,02			7,13+/-0,04		7,12+/-0,04					
Hornsey	2006	BC	25/75	pH (37°C)		7,08+/-0,03		7,1+/-0,03		7,09+/-0,03		7,05+/-0,05		6,97+/-0,06	7,02+/-0,05
Saunders	2011	BC	30/70	pH (22°C)	7,06	7,12	7,17		7,22		7,2		7,16		7,29
Gulliksson	2012	BC	30/70	pH (37°C)	6,97+/-0,03		7,05+/-0,04	7,10+/-0,03		7,11+/-0,03					
Nogawa	25013	Aph	35/65	pH (37°C)	7,08+/-0,01		7,15+/-0,02	7,19+/-0,06							

Sanquin data.

Platelets, recovered, pooled in additive solution and plasma.

From Whole blood-derived buffy coats with 35% of plasma and 65% of PAS E.

30 PC

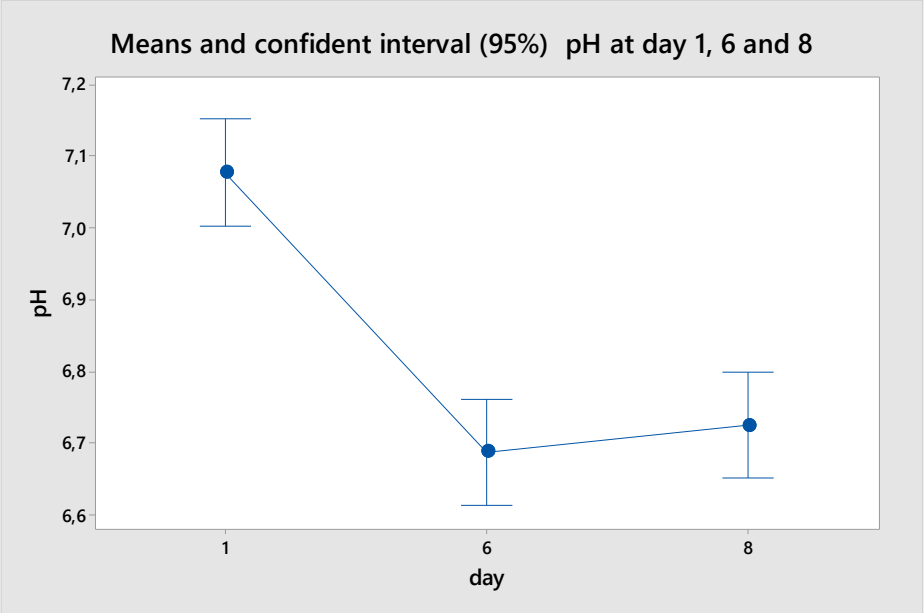
Sampling at day 1 day 6 and day 8

1. pH versus Glucose

Table 2. pH and glucose measurement.

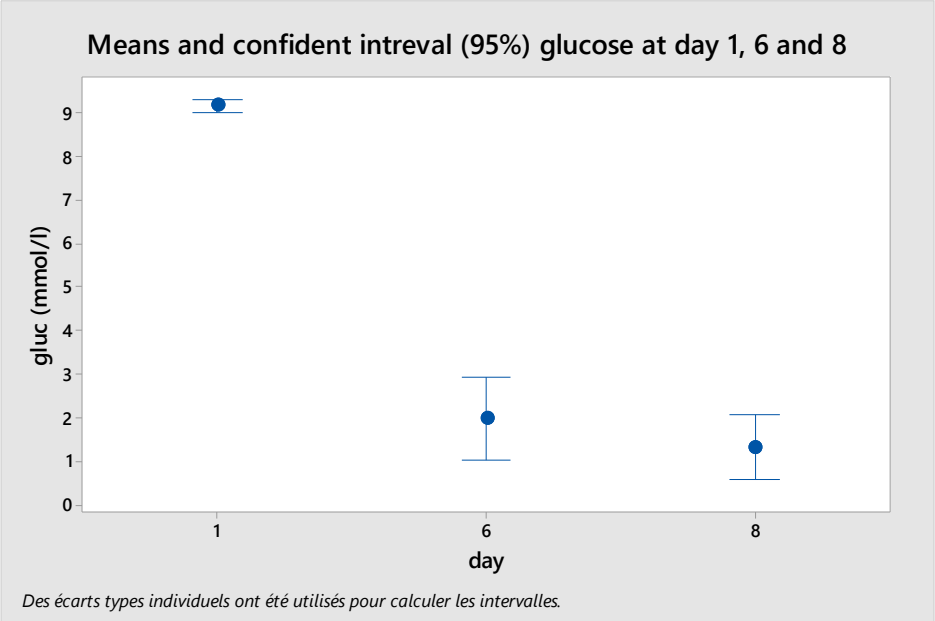
Variable	day	N	Mean	SD	Minimum	Median	Maximum
pH at 37°C	1	30	7.08	0.01	7.06	7.07	7.10
	6	30	6.69	0.27	6.41	6.54	7.19
	8	30	6.72	0.23	6.48	6.61	7.19
Glu (mmol/L)	1	30	9.16	0.41	8.30	9.30	9.80
	6	30	1.99	2.58	0.00	0.10	6.50
	8	30	1.33	1.96	0.00	0.05	5.50

Fig 1. Graph of pH expressed as means and confident interval at day 1, 6 and 8.



There is a statistical difference of pH measurement between days results (ANOVA: p<0.001).

Fig 2. Graph of glucose expressed as means and confident interval at day 1, 6 and 8.



There is a statistical difference of pH measurement between days results (ANOVA: $p<0.001$).

The correlation between pH and glucose measurement is high ($R^2 = 0.736$).

Regression: Glucose= - 87.22 + 13.40 pH

Fig 3. Graph of regression (linear model) between pH and glucose.

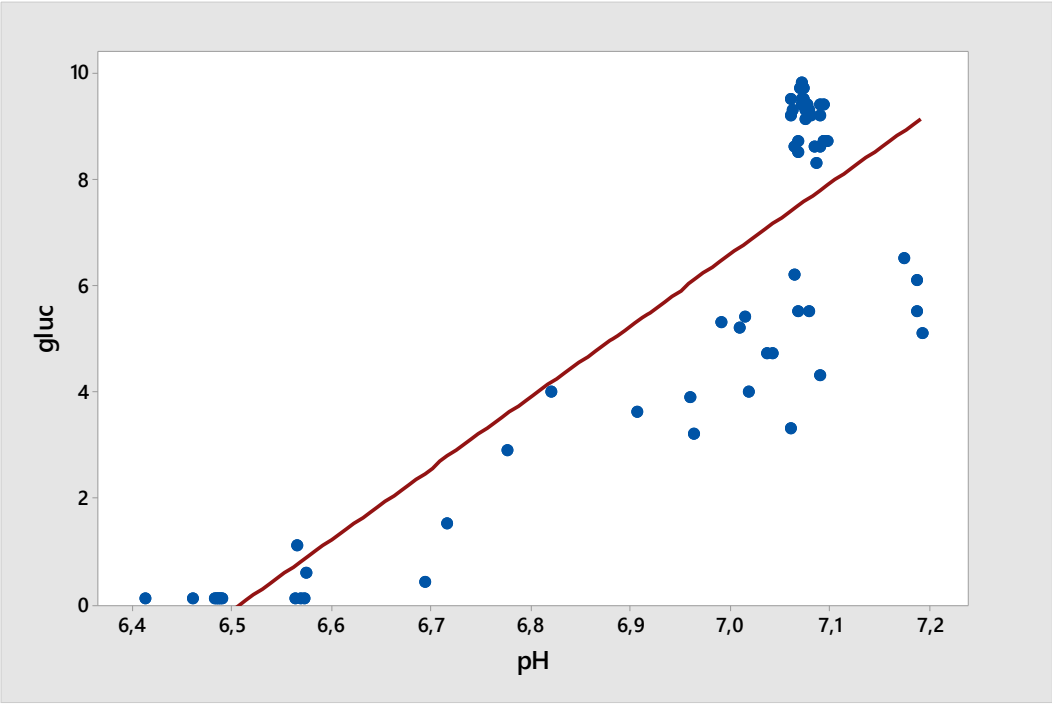


Table 3. pH and glucose Conformity data.

Variable	day	N	N conformity	% conformity

pH>6,4	1	30	30	100%
	6	30	30	100%
	8	30	30	100%
Gluc>0,5	1	30	30	100%
	6	30	13	43%
	8	30	10	33%
Gluc> 1	1	30	30	100%
	6	30	12	40%
	8	30	10	33%

1st option: glucose > 0.5 mmol/L

Table 4. pH related to glucose conformity (>0.5 mmol/L).

Gluc>0,5	N	Mean	SD
no	37	6.54	0.07
yes	53	7.03	0.13

There is a statistical difference between pH with glucose >0.5 et pH with glucose <0.5 (t'Student test P<0.001).

2d option: glucose > 1 mmol/L

Table 5. pH related to glucose conformity(>1 mmol/L)

Gluc>1	N	Mean	SD
no	38	6,54	0,07
yes	52	7,04	0,11

There is a statistical difference between pH with glucose >1 and pH with glucose <1 (t'Student test P<0.001).

2. glucose versus swirling

Table 6.glucose (mmol/L) measurement related to swirl status.

Swirling	N	Mean	SD	Minimum	Median	Maximum
0	15	0.0	0.0	0	0	0.1
1	19	0.1	0.1	0	0	0.6
2	11	2.1	2.0	0	1.5	5.3
3	45	7.8	2.1	3.2	8.7	9.8

Fig 4. Graph of glucose expressed as means and confident at different swirl status.

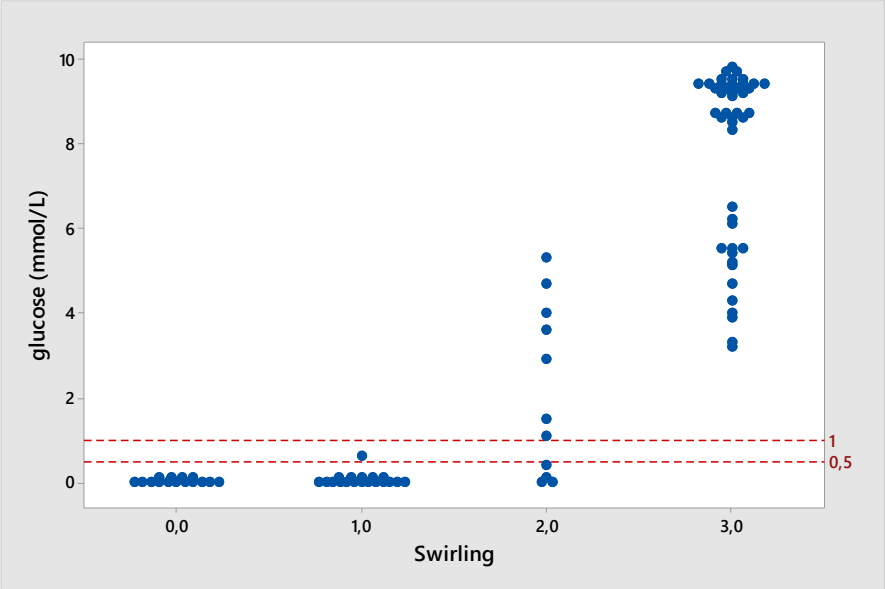


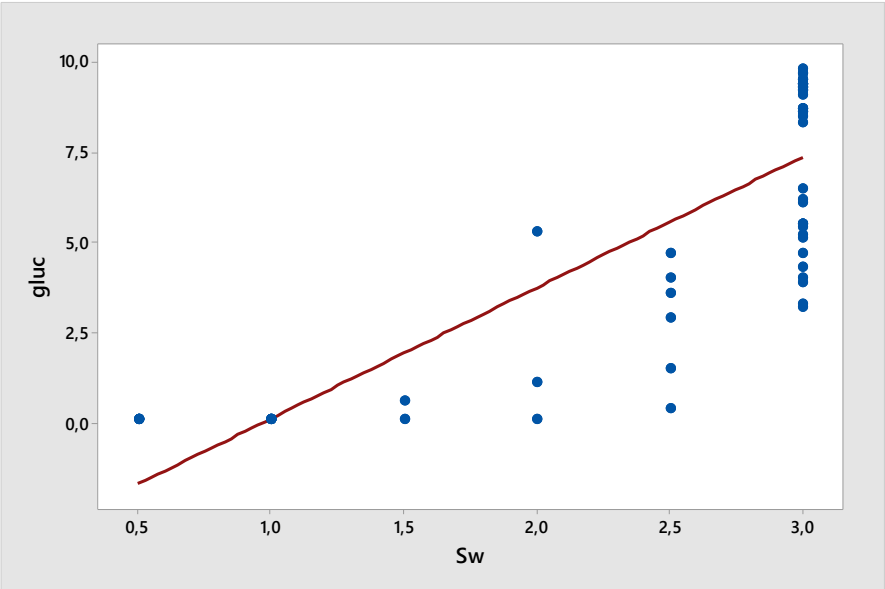
Table 7. Swirl status related to glucose conformity

Swirling	N Glu < 0.5	N Glu > 0.5	N Glu < 1	N Glu > 1
0	15	0	15	0
1	18	1	19	0
2	4	7	4	7
3	0	45	0	45

The correlation between swirling and glucose measurement is high ($R^2 = 0.628$).

Regression: Glucose= - 3,501 + 3,626 Swirling.

Fig 5. Graph of regression (linear model) between swirl status and glucose.



BRC-SFS data

- Platelets, Recovered, Pooled, Pathogen-Reduced

From Whole Blood-derived buffy coats with 35 % of plasma and 65 % of PAS E.

- Platelets, Apheresis, Pathogen-Reduced
- All PCs are pathogen reduced with Intercept method.
- pH measurement at 22°C in close system (pH and gases analyser).
- Swirl have been evaluated at different steps of PC preparation.

1) Quality Control results

Table 8. Results of pH measurements between 2015 and 2020 years with conformity.

			pH (day 7)						
Year	Type	N	Mean	SD	Minimum	Median	Maximum		N pH>6.4
2015	Aph	25	6.91	0.09	6.68	6.90	7.05		25
	BC	29	6.97	0.07	6.79	6.98	7.09		29
2016	Aph	71	6.90	0.12	6.42	6.90	7.11		71
	BC	80	6.95	0.08	6.75	6.96	7.10		80
2017	Aph	49	6.94	0.11	6.65	6.96	7.13		49
	BC	101	6.95	0.08	6.79	6.95	7.12		101
Total									355
			pH (day 5) *						
2018	Aph	52	7.02	0.09	6.80	7.04	7.20		52
	BC	91	7.04	0.06	6.82	7.04	7.16		91
2019	Aph	77	7.02	0.09	6.80	7.03	7.18		77
	BC	198	7.07	0.07	6.86	7.07	7.80		198
2020	Aph	136	7.02	0.10	6.78	7.03	7.25		136
	BC	164	7.06	0.05	6.91	7.07	7.19		164
Total									718

Table 9. Swirl status at the end of the shelf life of PC.

	Swirl at day 7			
Year		3	2	1

2015	Aph	23	1	1
	BC	29	0	0
2016	Aph	66	3	2
	BC	76	4	0
2017	Aph	44	5	0
	BC	97	4	0
	Swirl at day 5 *			
2018	Aph	52	0	0
	BC	91	0	0
2019	Aph	77	0	0
	BC	197	1	0
2020	Aph	134	2	0
	BC	164	0	0
Total		1050	20	3

*: shelf life of PC have been reduced from 7 days to 5 days at the beginning of 2018 year.

All pH measurements at the end of the shelf life, 7 or 5 days, are higher than 6.4 from 2015 to 2020 years.

2) pH, glucose and swirl in QC data 2020 (Jan->Oct).

Table 10. pH and glucose measurements and swirl status from January to October 2020.

Variable	Type	N	Mean	SD	Minimum	Median	Maximum
pH	Aph	99	7.04	0.08	6.81	7.04	7.25
	BC	142	7.07	0.05	6.93	7.07	7.19
glucose (mmol/L)	Aph	99	2.5	0.9	0.5	2.5	4.6
	BC	142	2.9	0.7	0.8	2.9	4.3
Swirl		3	2	1	0		
	Aph	98	1	0	0		
	BC	142	0	0	0		

All PCs had a pH >6.8.

1st option: glucose > 0.5 mmol/L

All PCs had a glucose > 0.5 mmol/L.

2d option: glucose > 1 mmol/L.

Aph: 95 had a glucose > 1 mmol/L (96%)

BC: 140 had a glucose > 1 mmol/L (99%)

3) PC without swirl at different days (2017-2018).

Table 11. pH measurements at different days in PC without swirl.

day	N	Mean	SD	Minimum	Median	Maximum
2	4	6.57	0.14	6.45	6.55	6.75
3	8	6.69	0.16	6.50	6.68	6.97
4	5	6.63	0.05	6.57	6.62	6.70
5	9	6.78	0.13	6.59	6.82	6.98
6	4	6.73	0.08	6.67	6.70	6.85
8	1	6.74	*	6.74	6.74	6.74

All PCs without swirl had a pH level above 6.4.

Table 12. Glucose (mmol/L) measurements at different days in PC without swirl.

day	N	Mean	SD	Minimum	Median	Maximum
2	4	0.48	0.52	0.00	0.41	1.10
3	8	1.19	1.40	0.00	0.91	4.20
4	5	0.08	0.13	0.00	0.04	0.30
5	9	1.57	1.52	0.00	1.70	4.50
6	4	0.10	0.08	0.00	0.11	0.18
8	1	0.00	*	0.00	0.00	0.00

1st option: glucose > 0.5 mmol/L

18 PC without swirl had a glucose level lower than 0.5 mmol/L.

13 PC without swirl had a glucose level higher than 0.5 mmol/L.

Table 13. pH related to glucose conformity (>0.5 mmol/L).

Gluc>0,5	N	Mean	SD
no	18	6.65	0.11
yes	13	6.77	0.14

There is a statistical difference between pH with glucose >0.5 and pH with glucose <0.5 (t'Student test P<0.012).

2d option: glucose > 1 mmol/L.

21 PC without swirl had a glucose level lower than 0.5 mmol/L.

10 PC without swirl had a glucose level higher than 0.5 mmol/L.

Table 14. pH related to glucose conformity (> 1 mmol/L).

Gluc>1	N	Mean	SD
no	21	6.65	0.10
yes	10	6.81	0.14

There is a statistical difference between pH with glucose >1 and pH with glucose <1 (t'Student test P<0.007).

4) Lotens' article (2018)

BC PCs and Aph (Trima and Amicus devices) PCs treated with 2 Intercept kits.

Table 15. pH and glucose measurement at different days.

Variable	day	N	Mean	DS	Minimum	Median	Maximum
pH	1	36	6.96	0.10	6.73	6.97	7.09
	3	36	7.04	0.12	6.80	7.04	7.27
	5	36	7.00	0.14	6.75	7.01	7.25
	7	36	6.94	0.13	6.62	6.92	7.15
gluc (mmol/L)	1	36	5.5	1.3	3.3	5.5	7.2
	3	36	4.1	1.5	12	4.3	6.4
	5	36	2.5	1.7	0.0	2.7	4.9
	7	36	1.1	1.1	0.0	0.8	3.0

All PCs pH were > 6.4.

All PCs had a swirl score of 3 at day 7.

Fig 6. Graph of individual values of pH at different days.

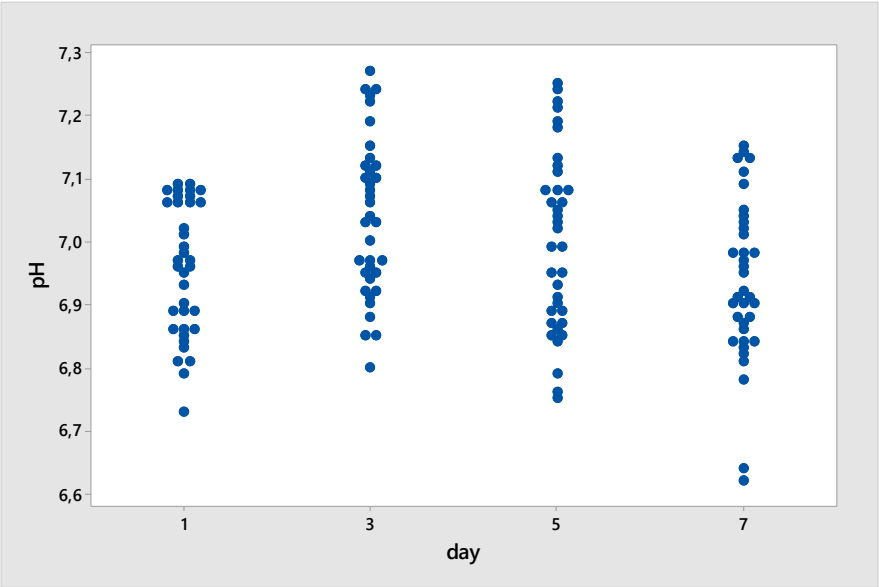


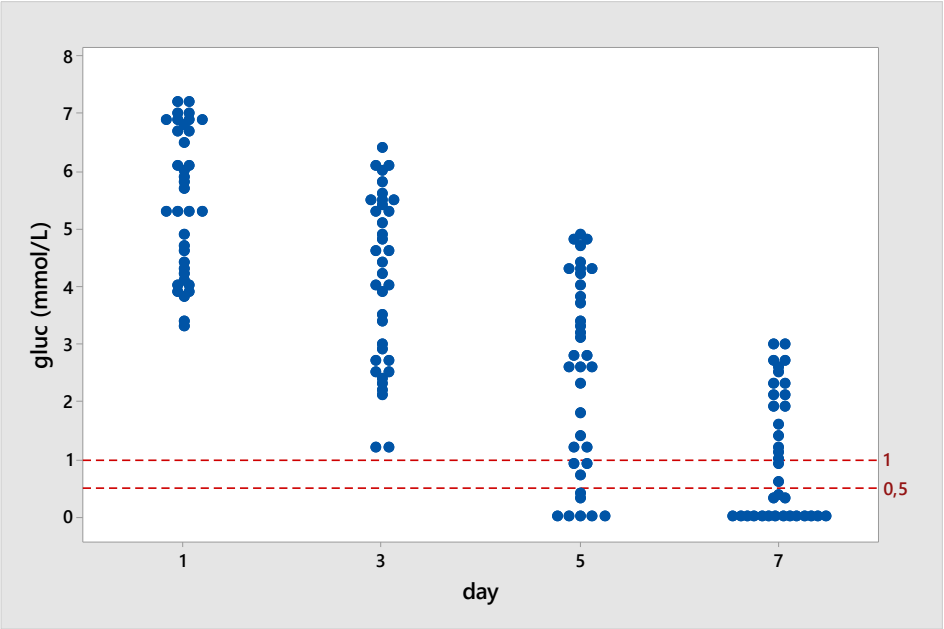
Table 16. 1st option: Glucose > 0.5 mmol/L

day	N	Glu > 0.5	Conformity
1	36	36	100%
3	36	36	100%
5	36	29	81%
7	36	19	53%

Table 17. 2d option: glucose > 1 mmol/L.

day	N	Glu > 1	Conformity
1	36	36	100%
3	36	36	100%
5	36	26	72%
7	36	16	44%

Fig 7. Graph of individual values of glucose at different days.



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Tables and Figures

Sanquin data

BRC-SFS data