Guide to the preparation, use and quality assurance of blood components 22nd Edition

Change log and background documents

Contents

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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22nd Edition of the Blood guide – Change Log

A log of changes made to the standards and supporting non-standard text in the 22nd Edition of the *Guide to the preparation, use and quality assurance of blood components* (the *Guide*) is included in the tables below.

Good Practice Guidelines (GPG)

Section / Subsection	Standard	Change
1. General principles	1.2.4.	Minor change of wording to emphasise that the quality system also aims to ensure full traceability during collection, testing, preparation, distribution and issuance of blood components. Further wording was included to highlight the importance of developing appropriate contingency plans in order to ensure business continuity and avoid blood component supply shortage situations.

Chapter 1 - Introduction

Section / Subsection	Standard	Change
1.0. Overview	n/a	Terms of Reference specifically for the 22nd edition was prepared and approved by the GTS and CD-P-TS. The work on 22nd edition of the Guide followed the Terms of Reference.
1.0. Overview	n/a	The 22nd edition of the Guide refers to Directives 2002/98/EC and 2004/23/EC, which remain in force until 7 August 2027, in accordance with the transitional provisions of Regulation (EU) 2024/1938 of the European Parliament and the Council of 13 June 2024, concerning quality and safety standards for substances of human origin.

Chapter 2 – Donor selection

Section / Subsection	Standard	Change
2.1.4. Information to be provided to donors of blood or blood components	2.1.4.3.	New standard text specifying that the medical assessment is not a complete assessment of the donor's health (see Background Document 2.1).
2.2.2. Donor age	2.2.2.4.	Additional non-standard text specifying that donation under the age of 18 should not be recommended and increasing the upper age limit for first time and regular donors (see Background Document 2.2).

Section / Subsection	Standard	Change
2.2.4. Iron stores	n/a	Additional non-standard text on donors with insufficient iron absorption and on monitoring of haemoglobin and iron parameters.
2.3.2. Non-infectious medical conditions	n/a	Blood pressure: new text see "Blood pressure and pulse": Measurement of blood pressure or pulse is not needed for determination of donor eligibility (see Background Document 2.3).
	n/a	Pulse: new text see "Blood pressure and pulse": Measuring blood pressure or pulse is not needed for determination of donor eligibility (see Background Document 2.3).
	2.3.2.7.	New non-standard text describing situations in which the responsible physician may make exceptions for donors taking insulin.
	n/a	Thalassaemia: the last sentence about apheresis was deleted (see Background Document 2.4).
2.3.3. Infectious diseases	2.3.3.7. and 2.3.3.8.	Standard and non-standard text regarding Creutzfeldt-Jakob disease was replaced by these two standards (see Background Document 2.5).
	2.3.3.21. to 2.3.3.24.	The malaria text has been completely re-written and summarised in 4 standards (see Background Document 2.6).
2.4.2. Apheresis donation and specific standards for donors of different types of components and Table 2.3.	2.4.2.1. to 2.4.2.15.	Updated standards and non-standard text relating to apheresis donation and donors undergoing plasmapheresis. Table 2.3 was updated accordingly (see Background Documents 2.7 and 2.8).

Chapter 3 – Collection of blood and blood components

Section /Subsection	Standard	Change
Whole chapter	n/a	Updated standard and non-standard text to align terminology with definitions for blood bag systems and blood container.
3.8. Special requirements for apheresis	n/a	Updated non-standard text to clarify that there is no published evidence that a maximum plasmapheresis procedure time is required from a donor safety or product quality perspective. Blood establishments may choose to set a maximum procedure limit for donor experience and operational reasons, such as to assist with the timing of donor appointments (see Chapter 3 Background Document).

3.10.2. Prevention and treatment of adverse reactions in donors	n/a	Updated non-standard text to clarify that it is acceptable not to move the donor and instead manage the adverse reaction where it occurs; this reduces the potential for additional harm when moving a donor who is experiencing an adverse reaction to a specific space.

Chapter 4 – Processing, storage and distribution of blood and blood components

Section /Subsection	Standard	Change
4.0. Overview	n/a	Updated non-standard text to modify reference to use of whole blood in limited clinical settings.
4.1.1. General considerations	n/a	Updated non-standard text to remove "delays in preparation or unsuitable storage conditions may adversely affect the quality of final components."
4.1.2. Choice of blood bag system	n/a	Updated non-standard text to align terminology with definitions for blood bag systems and blood containers. Definition for blood container updated to read "A blood bag or bottle (or other medical device) which contains blood or blood components."
4.1.3. Assessing the impact of changes	n/a	New subsection assessing the impact of changes with an extended list of parameters to be considered for assessment.
4.1.4. Red cell and platelet preservation	n/a	Updated non-standard text on red cell preservation and microaggregates in red cells components
4.1.6. Leucocyte depletion	n/a	Updated non-standard text on leucocyte depletion of blood components including: • that pre-storage leucocyte depletion is considered superior to alternative approaches such as post-storage or bedside filtration. • that blood bag systems used in the preparation of blood components should ensure the final component contains less than 1×10^6 leucocytes. • that blood establishments should request relevant data from the manufacturers on the performance of leucocyte depletion filters within each system. • the addition of blood bag system defects and mishandling as reasons why inadequate leucocyte depletion, slow filtration or filter blockage may occur.
4.1.6. Leucocyte depletion	4.1.6.2.	Updated standard text to remove the term "residual" and include the requirement for appropriately sensitive and validated methods for counting leucocytes.
4.1.6. Leucocyte depletion	4.1.6.3.	New standard to align with blood component monographs that leucocyte depleted blood components should contain less than 1×10^6 leucocytes
4.1.7. Freezing and thawing of plasma for transfusion	n/a	Updated non-standard text related to the thawing and refreezing of plasma.

Section /Subsection	Standard	Change
4.1.9. Open and closed systems and sterile connection devices	n/a	Updated non-standard text recommending that any new developments in component preparation involving an open system should be subjected to intensive testing during the developmental phase to minimise the risk of bacterial contamination.
4.1.10. Component labelling and information	n/a	Updated non-standard text on the blood component label to clarify that it should include unique donation identification number and relevant blood groups.
4.2.1. General requirements	n/a	Updated non-standard text to remove reference to viability.
4.2.2. Equipment	n/a	Updated non-standard text related to alarm signals.
4.2.3. Storage of red cell components	n/a	Updated non-standard text to include reference to secondary processing.
4.2.4. Storage of platelet components	n/a	Updated non-standard text to include storage of buffy coats used in the preparation of pooled platelets
4.2.5. Storage of frozen plasma components	n/a	Updated non-standard text on the storage requirements from blood component monographs. The following text was removed and replaced with more general text; "The temperature on receipt can be monitored as in the following example: • Take two bags from the container; • Place a thermometer between the bags and fix them together with rubber bands; • Quickly place them back into the container and close the lid; • Read the temperature after 5 minutes. Alternatively an electronic sensing device may be used to take immediate measurements from the surface of a pack."
4.2.6. Storage of granulocyte components	n/a	Updated non-standard text to include the storage of buffy coats used in the preparation of granulocyte components.
4.2.7. Transportation of blood components – general requirements	n/a	Updated non-standard text.
4.2.9. Transportation of platelet components	n/a	Updated non-standard text to remove general requirements for monitoring the impact of transport conditions and moved to the general requirements for all blood components (Subsection 4.2.7)
4.3.2. Bacterial safety	n/a	Updated non-standard text related to bacterial safety to clarify that when PIT or rapid tests for platelet components are in place, for the purposes of process control, bacterial monitoring of collection and processing should still be performed at a frequency based on risk assessment.

Section /Subsection	Standard	Change
4.3.4. Pathogen Inactivation Technologies	n/a	Updated non-standard text related to pathogen inactivation technologies (PIT) to include reference to the efficacy of pathogen-reduced plasma components, loss of some Factor VIII and fibrinogen occurs compared to untreated control plasma.

Chapter 5 – Blood component monographs

Section	Monograph	Change
Part A. Whole blood components	A-2	Updated table to clarify that the volume specified excludes anticoagulant
Part B. Red cell components	B-3, B-4, B-5 and B-6	The following text has been removed in the monographs from the warnings of all non-leucocyte depleted red cell components: "Not for exchange transfusion in newborns, unless used within 5 days of donation and only if fresh frozen plasma is added on the day of use." and replaced with "Non leucodepleted components should not be transfused to newborns."
Part B. Red cell components	B9	Clarification of footnote b Extended to "Final suspending solution, as a process control for washing", to clarify that this quality control requirement is not replacing haemolysis measurements and not at the end of shelf life.
Part D. Plasma components	D-1	The following text has been removed: *From whole blood* "If FFP is to be prepared from a single-pack Whole Blood donation, adequate precautions should be adopted to avoid microbial contamination." *By apheresis* "Leucocyte depletion of the starting material and/or virus inactivation and/or quarantine is a requirement in some countries."
Part D. Plasma components	Table 5D-1	Reference changed from "clinical FFP" to "FFP for transfusion" Clarification added with regard to Factor VIII requirements. Average (after freezing and thawing): not less than 70 IU per 100 mL. It is clarified in footnoted that a minimum of 90 % of individual units tested should contain at least 50 IU/100 mL.
Part D. Plasma Components	D-1	Updated text in storage and transport to clarify that FFP should be thawed immediately after removal from storage, using a validated procedure in an environment that does not raise FFP temperature above + 37 °C.
Part D. Plasma Components	D-2	Updated text in storage and transport to clarify that Plasma, Fresh Frozen, PR should not be refrozen, unless approved by the manufacturer.

Section	Monograph	Change
Part D. Plasma Components	Table 5D-2	Footnote removed. "minimum of 90 % of units tested should meet the required value" is inconsistent with the requirement for an "average: not less than 50 IU per 100 mL".
Part D Plasma Components	D-3 and D-4	Updated text in storage and transport to clarify that Cryoprecipitate (and Cryo, PR) should be thawed immediately after removal from storage, using a validated procedure in an environment that does not raise the Cryoprecipitate temperature above + 37 °C.

Chapter 6 – Component monographs for intrauterine, neonatal and infant use

Section / Subsection	Monograph	Change
6.0. Overview	n/a	Updated non-standard text to align with monograph A.2 clarifying that platelet components from both apheresis and whole blood can be divided into satellite bags by using a closed system.
Part A. Component monographs used for intrauterine transfusion	A2	Updated technical information in Table to align with monograph text, clarifying that the storage time following secondary concentration of Platelets, IUT depends on the concentration factor and should be validated.

NEW: Chapter 7 – Blood components for topical use or injection

Monograph	NEW - Monograph for serum eye drops included (see Chapter 7 Background document)

Chapter 8 – Pre-deposit autologous donation

The number of this chapter is changed from **7** to **8**, due to introducing a new Chapter **7**.

Chapter 9 – Immunohaematology

The number of this chapter was changed from **8** to **9**, due to the introduction of a new Chapter **7**.

Section / Subsection	Standard	Change
9.1.3. Sample handling, retention and storage	n/a	Insertion of an introductory sentence: *Samples for immunohaematology testing of patients should be drawn in accordance with national requirements. Gross haemolysis and other factors such as lipemia that might affect test performance should be noted in the patient's records.*
9.1.3. Sample handling, retention and storage	9.1.3.1.	The standard has been reworded to include storage: Blood samples for immunohaematology testing should be used, handled and stored according to the reagent and/or device manufacturer's instructions.
9.4.1. Molecular testing	n/a	The following sentence was deleted from the introduction because it was opinion: In time, molecular testing may replace the need for routine serological testing.
	n/a	Testing can be undertaken on samples from blood,… Changed and expanded to Testing can be undertaken on genomic DNA isolated from validated samples such as blood, amniocentesis, biopsy of chorionic villi, buccal swabs and plasma.
9.4.2. ABO and RhD typing	9.4.2.6.	The highlighted text was deleted for clarity. If additional typing for non-ABO and RhD antigens is performed, before the result of the confirmed phenotype is printed on the label, a test should be done at least twice using two different samples collected from two different donations. The results should be linked to the donor record.
9.4.2. ABO and RhD typing Donors with antibodies	9.4.2.9.	Insertion of the following sentence: *The policy should be based on a risk assessment of the antibody specificity and strength.*
9.4.2. Positive direct antiglobulin test (DAT)	9.4.2.9.	Text insertion for clarity: A positive DAT result in donors will generate positive compatibility test results…
9.4.3. Blood group testing of patients ABO and RhD typing	9.4.3.1.	Text insertion for clarity: …the patient's blood sample before *selecting and issuing components for transfusion.*
		Addition of the following clarifying text: *The ABO and RhD blood group of patients tested for the first time should be based upon the results of two independent ABO and RhD tests. At least one of the ABO tests should include reverse grouping in patients ≥6 months old.*
	9.4.3.3.	Insertion of a clarifying sentence with regards to the required phenotype of antibody screening cells: *It may not be possible to include reagent red cells with the strongest expression where the phenotype is considered rare. Inclusion of a more common phenotype with a lower expression may be used, but should be noted as a limitation for detection of weaker antibodies.*

Section / Subsection	Standard	Change
9.5.1. Antiglobulin crossmatch	n/a	Highlighted text deleted for clarity: This test is the main component of a full serological crossmatch and is typically performed in patients with clinically significant red cell antibodies. To read: This test is typically performed in patients with clinically significant red cell antibodies.
9.5.3. Electronic release	9.5.3.2.	Insertion of a clarifying sentence with regards to the required phenotype of antibody screening cells: *It may not be possible to include reagent red cells with the strongest expression where the phenotype is considered rare. Inclusion of a more common phenotype with a lower expression may be used but should be noted as a limitation for detection of weaker antibodies.*
9.5.4. Selection of red cells	9.5.4.1.	Highlighted text deleted for clarity: …and an antiglobulin crossmatch, or equivalent procedure, between donor red cells and… To read: …and an antiglobulin crossmatch between donor red cells and…
9.5.5. Additional considerations Neonates and intrauterine transfusion (IUT)	n/a	Title inserted for clarity to: Infants less than 4 months of age and intrauterine transfusion (IUT)
		Text inserted for clarity: From: Red cell antigens to which the mother has been immunised have to be taken into account when selecting red cell components for the neonate or IUT. To: Red cell alloantibodies in the mother should be considered when selecting red cell components for the infant (< 4 months) or IUT. Postpartum, where the mother's red cell antibody status is not known and/or a maternal sample is not available, pre-transfusion testing should be performed on a sample from the infant.
Massive transfusion in immunised patients	n/a	Insertion of clarifying text: The decision to transfuse should be based on consultation between the patient's clinician and a transfusion medicine specialist/ laboratory director, taking into account the clinical significance of the antibody.

Section / Subsection	Standard	Change
9.6. Investigation of suspected haemolytic transfusion reactions	New section	If there are clinical symptoms of a haemolytic transfusion reaction, then a blood sample should be drawn from the patient and sent together with the blood bag in question to the laboratory for testing. Where possible, the pre-transfusion sample should be tested in parallel. Minimum testing should include ABO/RhD typing, DAT and antibody screening on the pre- and post-transfusion samples, ABO/RhD typing and a DAT on the blood unit. The crossmatch should be repeated with both the pre- and post-transfusion samples. The results should be reported to the treating physician without delay.

Chapter 10 – Screening for markers of transfusion-transmissible infections

The number of this chapter was changed from **9** to **10**, due to the introduction of a new Chapter **7**.

Section / Subsection	Standard	Change
10.4.1. General requirements	n/a	Updated non-standard text to note that a risk assessment may be performed to determine which previous donations are at risk and thereby Guide the extent of the look-back. For example, the availability of external negative test results, whether pathogen inactivation was in place, what type of testing was used (e.g. ID NAT versus serology), and whether the donor had a documented seroconversion illness.
10.5. Classification of TTI testing	n/a	Updated non-standard text to include a Classification of TTI testing, including Mandatory, Additional and Selective blood donor screening tests.
10.5.3. Additional screening	n/a	Updated non-standard text to clarify that additional screening refers to testing applied to all donors.
10.5.3. Anti-HTLV 1/2	n/a	Updated non-standard text to include information that Leucodepletion and PIT reduce the risk of HTLV 1/2 transfusion transmission.
10.5.3. Anti-HBc	n/a	Updated non-standard text to include information that this test is not required for plasma for fractionation.
10.5.4. Selective screening	n/a	Updated non-standard text to clarify that selective screening refers to testing applied to a subset of the overall donors.
10.5.4. Selective screening, CMV screening	n/a	Updated non-standard text to include information that leucodepletion reduces the risk of CMV transfusion transmission.
10.5.4. Selective screening, Malaria screening	n/a	Updated non-standard text to note that high-sensitivity molecular tests may represent a valuable complementary screening option for specific donor groups or in specific contexts, such as residents of non-endemic areas where autochthonous malaria cases are reported.

Section / Subsection	Standard	Change
10.5.4. Selective screening, Trypanosoma cruzi screening	n/a	Updated non-standard text to include the following information: In addition, if the donor's mother is from a country endemic for *T. cruzi,* selective screening may be considered in view of the risk of congenital transmission of *T. cruzi*.
10.5.4. Selective screening, West Nile virus screening	n/a	Updated non-standard text to note that this test should be able to detect all currently known WNV genotypes AND is not required for plasma for fractionation.

Chapter 11 - Elements for a quality system on the clinical use of blood

Section / Subsection	Standard	Change
11.4.2.	n/a	Added text: If possible, all relevant data (patient´s wristband, sample collection number and number of blood components to be transfused) should be monitored by an electronic system (complete transfusion chain).

Chapter 12 – Haemovigilance

The number of this chapter was changed from **10** to **12**, due to the introduction of a new Chapter **7** and moving this chapter after the chapter on Elements for a quality system on the clinical use of blood.

Section / Subsection	Standard	Change
	n/a	The chapter has been completely restructured. See background document for further explanation. The current text from the 21st edition of the Blood Guide has reused as far as possible. New text has been added (see Chapter 12 Background Document).
12.1. Introduction	12.1.0.1.	Standard text is not changed. Previous number in 21st edition is 10.0.0.1.
12.2. Traceability of blood components	12.2.0.1.	Standard text is not changed. Previous number in 21st edition is 10.1.1.1.
12.2. Traceability of blood components	12.2.0.2.	Standard text is not changed. Previous number in 21st edition is 10.1.1.2.
12.2. Traceability of blood components	12.2.0.3.	Standard text is not changed. Previous number in 21st edition is 10.1.1.3.
12.3. Definitions and categorisation	12.3.5.1.	New standard. The text is already in the 21st edition as non-standard text. It is considered standard to assess the severity and should therefore be set as a standard.
12.3. Definitions and categorisation	12.3.6.1.	Standard text is not changed. Previous number in 21st edition is 10.6.5.1.
12.4. Management of haemovigilance	12.4.0.1.	Standard text is not changed. Previous number in 21st edition is 10.1.3.1.

Section / Subsection	Standard	Change
12.4. Management of haemovigilance	12.4.0.2.	Standard text is not changed. Previous number in 21st edition is 10.1.3.2.
12.4. Management of haemovigilance	12.4.0.3.	Standard text is not changed. Previous number in 21st edition is 10.1.3.3.
12.4. Management of haemovigilance	12.4.0.4.	Standard text is not changed. Previous number in 21st edition is 10.1.3.4.
12.4. Management of haemovigilance	12.4.0.5.	Standard text is not changed. Previous number in 21st edition is 10.2.3.1.
12.4. Management of haemovigilance	12.4.0.6.	Standard text is not changed. Previous number in 21st edition is 10.3.1.1.
12.4. Management of haemovigilance	12.4.2.1.	Standard text is not changed. Previous number in 21st edition is 10.4.1.1.
12.4. Management of haemovigilance	12.4.2.2.	Standard text is not changed. Previous number in 21st edition is 10.4.1.2.
12.4. Management of haemovigilance	12.4.2.3.	Physician is replaced by blood establishment; otherwise, standard text is not changed. Previous number in 21st edition is 10.4.1.3.
12.4. Management of haemovigilance	12.4.2.4.	Standard text is not changed. Previous number in 21st edition is 10.4.1.4.
12.5. Data management	12.5.1.1.	Standard text is not changed. Previous number in 21st edition is 10.1.2.1.

Chapter 13 - Blood Supply Contingency and Emergency Planning

Section / Subsection	Standard	Change
New chapter on Blood Supply Contingency and Emergency Planning	n/a	In consideration of the new EU SoHO regulation, which also makes reference to general guidelines on emergency planning for SoHO of the EDQM, a new chapter has been included in the Guide summarising the high-level concept of contingency and emergency planning. It is important to point out that it is mainly the responsibility of the blood establishment and hospital blood banks to prepare contingency plans to ensure business continuity for many situations. An emergency plan on managing emergency situations on a national level is within the remit of the national health authority. The EDQM recently published their B-SCEP guideline, which served as a basis for the new Chapter 13 in the 22nd edition of the Guide.

Definitions

Definitions for the following terms were added for the 22nd Edition of the Blood Guide (in alphabetical order):

Blood supply, blood system, contingency planning, emergency preparedness, incident, near-miss event, regulatory oversight body, serious adverse event, serious adverse reaction, seriousness.

The following existing definitions were modified:

Adverse event, adverse reaction, blood container, imputability.

Appendices

Appendix 1 was revised and updated in accordance with proposed changes in Chapter 2.

Section / Subsection	Standard	Change
Appendix 1. Key criteria for donor eligibility	n/a	The introduction was updated and shortened.
	n/a	First-time & lapsed donors and regular donors' columns were revised, an additional column was added for plasma fractionation-only donors. The questions were revised and updated to reflect the changes in the updated standards in Chapter 2. Questions related to sexual risk behavior were replaced by the general guidance "to identify donors who are considered (based on national guidelines or legislation) to have increased risk for blood borne and sexually transmitted infections".

Chapter 2. Background Documents

Background Document 2.1. Additional information for donors

Prepared by Øystein Flesland. August 2023.

Text in the 21st edition of the Blood Guide

Information for donors

From 2.2.1.7 in the 21st edition of the Guide.

In practice, a complete medical and physical examination of the donor is not possible. It is necessary to rely on the donor's appearance, their answers to questions concerning their medical history, general health and relevant risk factors (e.g. risk behaviour, travel history, epidemiological factors), and on laboratory tests. Based on this information, a decision on the eligibility of the donor will be made using accepted guidelines. Conditions that are not covered by guidelines should be referred to the physician in charge with responsibility for making the final decision.

What the issues are

The aim of this guideline was to ensure that the donor will not suffer harm from donating blood and that the blood donated is safe for the recipient. The screening procedure may lead the donor to think that he or she has been through a general health screening, similar to what could be expected if the donor went to his or her own physician for a general health check or because of a specific health concern. This belief may be reinforced if the blood establishment decides to add tests to their screening procedure that are not required in this Guide.

If the donor believes that they recently "passed" a general health check, they may think it is unnecessary to see their own physician if they have symptoms of disease or worries about their health.

Recommendations (for the 22nd edition of the Guide)

The donor should be informed of the fact that the donor health screening performed in the blood establishment does not constitute a full health screening and that it is not a substitute for seeing their own physician.

This could be done by adding to

2.1.4.3. The following information must be provided:

- For both allogeneic and autologous donations: the reasons for requiring a medical assessment, health and medical history, the testing of donations and the significance of 'informed consent'.
- For allogeneic donations: the medical assessment is not a complete assessment of the donor's health and is not a substitute for seeing their own healthcare provider.
- For allogeneic donations: self deferral, temporary and permanent deferral and the reasons why individuals must not donate blood or blood components if there could be a risk for the recipient or the donor.

- For autologous donations: the possibility of deferral and the reasons why the donation procedure cannot take place in the presence of a health risk to the individual, whether as a donor or recipient of the autologous blood or blood components. (Directive 2004/33/EC, Annex II).

Background Document 2.2.
Donor age

GTS Ch2 document based on TRANSPOSE risk-based assessment tool

Prepared by Johanna Castrén and Joanne Pink. September 2023.

What the issues are

Donors under the age of 18 years and donors 65+ years of age

Text in the 21st edition of the Blood Guide

Age of the Donor

- The age limits for donation are a minimum of 18 years and maximum of 65 years.
- 17 to 18 years — unless classified as a minor by law, or with written consent of parent or legal guardian in accordance with law.
- Donation by first-time donors above the age of 60 years is at the discretion of the responsible physician.
- Donation by donors over 65 years is with permission of the physician in the blood establishment, given annually.
- Permission to continue donating after the age of 65 years should be given annually by the responsible physician, either individually to each donor or based on a medical risk assessment for a given donor population.

Severity and imputability

– Severity

grade of severity DONOR*				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
Elevated risk for iron deficiency (ID) (young donors)		X		
Elevated risk for vasovagal reactions (VVRs) (young donors)		X		
Potential for greater proportion of delayed and severe VVRs in older donors and hence greater risk of complications		X		
grade of severity RECIPIENT* ***NO***				

– Imputability

level of imputability DONOR risks*						
Risk(s)	*Definite/ Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
ID and VVRs (young)	X					
VVRs (elderly)		X				

Donors under the age of 18

Recommendations (for the 22nd edition of the Guide)

The recommended age limit for donation is a minimum of 18 years (based on medical risks related to younger age groups).

Justification

While new and inexperienced donors have a higher risk of VVRs in all age groups, data from Australian Red Cross Lifeblood show that the risk is highly age-dependent: the 16-17 age cohort has a higher risk than donors aged 18-20.

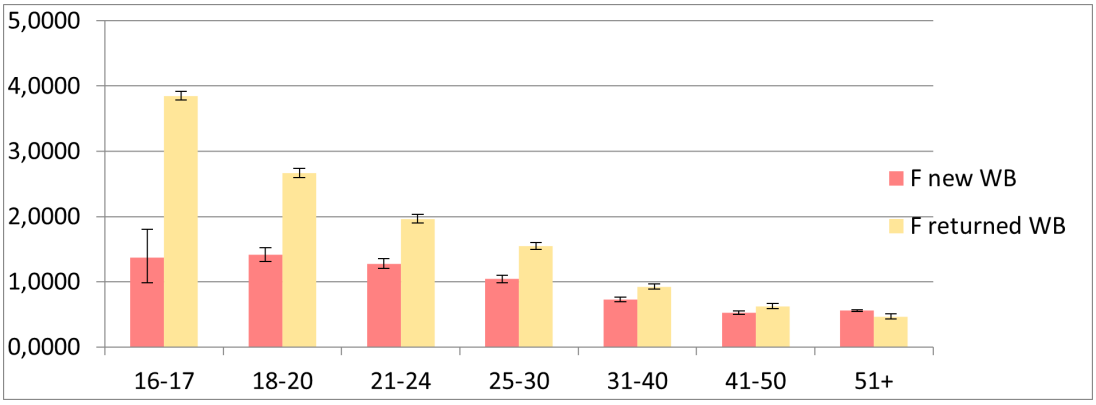
Vasovagal reaction rates – for youth donor comparisons (Australia)

VVR rates – provided as a % on the graph.

The tables show the odds ratios (OR) based on the overall rate for the population

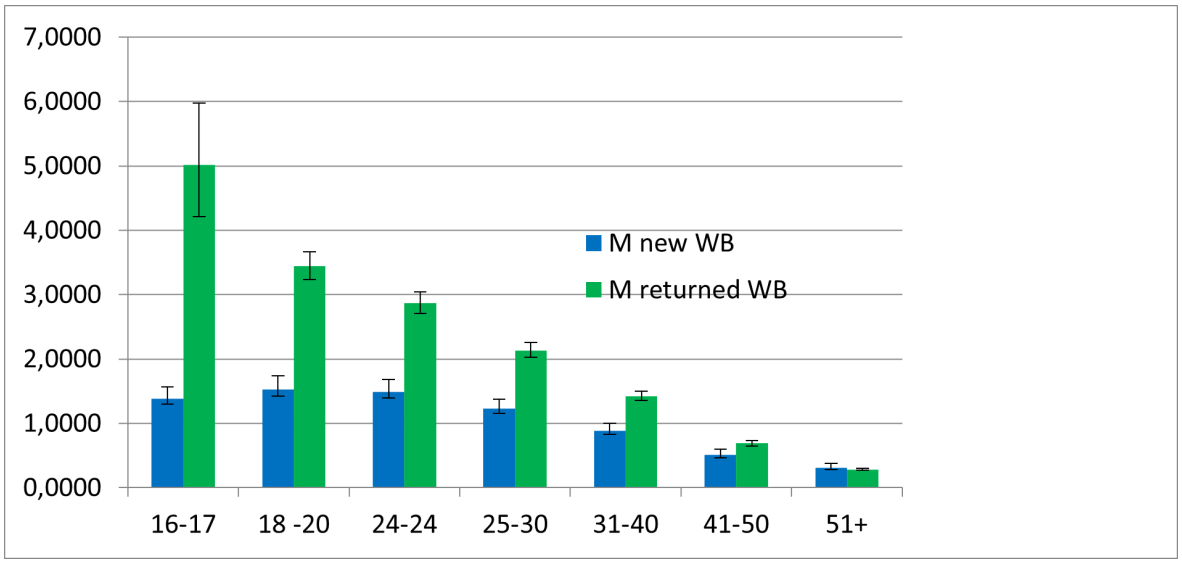
Females

Age	Donations	OR	95 % CI
16-17	3398	3.8498	3.4635-4.2791
18-20	40933	2.6611	2.5586-2.7676
21-24	53420	1.9620	1.8872-2.0399
25-30	72076	1.5474	1.4908-1.6062
31-40	88975	0.9227	0.8861-0.9608
41-50	107839	0.6253	0.5992-0.6525
51+	244462	0.4672	0.4523-0.4825



Males

Age	Donations	OR	95%CI
16-17	2046	5.0148	4.2117-5.9712
18 -20	26659	3.4396	3.2309-3.6619
21-24	36731	2.8706	2.7068-3.0442
25-30	63119	2.1345	2.0246-2.2503
31-40	102217	1.4239	1.3542-1.4973
41-50	126175	0.6874	0.6484-0.7287
51+	313407	0.2831	0.2692-0.2976



Permission for inclusion of above data from Australian Red Cross Lifeblood given by Dr Joanne Pink, Chief Medical Officer, Australian Red Cross Lifeblood.

A study from the US showed that young donors aged 16-17 have a higher risk for vasovagal reactions than older blood donors (Eder *et al.*, 2008).

Iron Deficiency

Data from Australian Red Cross Lifeblood show that the risk for iron deficiency is highly age-dependent: the 16-17 age cohort has higher rates of iron deficiency than donors in the older age cohorts.

Blood Service Prevalence Study (2012)

Prevalence of iron deficiency (ferritin < 15 ng/mL) in new female donors

	Number	Iron deficiency (%)	Confidence intervals
All	301	12.0	(8.3-15.7)
16-17	30	23.3	(8.2-38.4)
18-24	88	10.2	(3.9-16.5)
25-50	147	12.2	(6.9-17.5)
51+	36	5.6	(0.0-13.1)

Permission for inclusion of above data from Australian Red Cross Lifeblood given by Dr Joanne Pink, Chief Medical Officer, Australian Red Cross Lifeblood.

Prevalence of iron deficiency (ferritin < 30 ng/mL) in new male donors

	Number	Iron deficiency (%)	Confidence intervals
All	229	4.8	(2.0-7.6)
16-17	35	17.1	(4.6-29.6)
18-24	51	3.9	(0.0-9.2)
25-50	113	2.7	(0.0-5.7)
51+	30	0	(0-13.5)

Permission for inclusion of above data from Australian Red Cross Lifeblood given by Dr Joanne Pink, Chief Medical Officer, Australian Red Cross Lifeblood.

More data can be found in Salvin *et al.*(2014). Iron deficiency in blood donors: a national cross-sectional study. *Transfusion*. Publications from the US showed that donors under 18 years old have a higher risk for iron deficiency than older donors (Spencer *et al.*, 2019, Spencer *et al.*, 2022). Younger individuals may also be especially susceptible to iron deficiency and therefore iatrogenic iron deficiency should be avoided (Mast, 2017).

Donors over the age limit of 65 years, first-time donation only up to 60 years

Recommendations (for the 22nd edition of the Guide)

The upper age limit for regular donors is 70 years and the limit for first-time donors is 65 years.

These limits are based on the increase in the life expectancy in Europe since the 1980s.

While a number of countries allow people over the age of 70 years to continue as blood donors, the available evidence, particularly for donors over the age of 80 years, is relatively limited.

If donation is allowed for healthy individuals over the given upper age of 70 years or for first-time donors after the age 65 years, national donor adverse event data, life expectancy and general health data should be utilised to set a national upper age limit policy. In addition, a more stringent upper age limit can be justified based on national data and conditions.

Justification

The current upper age limits in the EU Directive and the Blood Guide have been in use since at least the 1980s. Since that time, life expectancy in Europe has increased remarkably, and peaked at 79.1 years in 2019, before the COVID-19 pandemic (https://www.statista.com/statistics/1258347/life-expectancy-at-birth-in-europe/). Even when the exceptional pandemic years are taken into account, life expectancy in Europe has increased from around 71 years to 77 years. On the basis of this demographic change in Europe, a general increase in the upper age limit of 5 years can be justified.

Besides this theoretical model, there are several publications from Canada, New Zealand, England, the United States, Australia and Germany showing that healthy individuals up to the age of 70 or 80 can safely donate and make a significant contribution to the blood supply (Goldman *et al.*, 2019, Müller-Steinhardt *et al.*, 2012, Zeiler *et al.*, 2014).

In the UK, a medical review was performed in 2008 to gather evidence for updating the upper age limit rules for regular blood donors (Stainsby and Butler, 2008). The UK recommendation concluded that donation for regular donors beyond 70 years is safe without any specific upper age limit and or pre-screening processes. The age limit for first-time and lapsed donors was recommended as 66 years.

The donor adverse event (DAE) data from many countries and publications show that elderly donors do not have higher rates of DAE compared with younger donors. Typically, the VVR rate decreases with increasing age and relates in part to increasing donor experience and self-deferral if the donor no longer considers themself sufficiently fit to donate.

While the rate of VVRs appears to be lower in the older/oldest donor cohorts, there is some evidence based on more detailed analysis that the proportion of VVRs that are categorised as severe may be higher in these donor cohorts.

While risk factors for an increase in the proportion of severe reactions are not clear, it is recognised that there are cardiac and blood vessel changes as we age. Baroreceptors become less sensitive with ageing and there is an increased risk of orthostatic hypotension. With increasing age our ability to compensate for blood loss decreases because of reduced physiological reserves. The consequences

of falling due to feeling faint may be more severe because older donors are at greater risk of bone loss and osteoporosis.

Data from Finland:

The Finnish Red Cross Blood Service (FRCBS) has an upper age limit for donors of 71 years. The DAE statistics show that donation for the oldest age cohort is safe, but there are weak signals showing that in the oldest age cohort (66-70 years) the proportion of VVRs with loss of consciousness (LOC) is much higher than in the younger age groups.

FRCBS Donor DAE Statistics 2014-2022 (n = 1 798 425 donations, of which 97 193 were from the age group "over 65")

	VVR with LOC	VVR all	%
under 56	2442	26615	9 %
56-60	112	666	17 %
61-65	75	405	19 %
over 65	28	104	27 %

Permission for inclusion of above data from Finnish Red Cross Blood Service given by Dr Johanna Castrén, Medical Director, Finnish Red Cross Blood Service.

Data from Australian Red Cross Lifeblood:

While females aged over 60 years have significantly lower rates of VVRs overall and lower rates of VVRs with LOC when compared with females aged less than 30 years, they have significantly higher rates of delayed VVRs (38.3 vs 28.71 per 10 000) and delayed VVRs with LOC (8.9 vs 4.86 per 10 000). They also have significantly higher rates of VVRs requiring outside medical care (9.72 vs 5.91 per 10 000).

In the older group, the event was more likely to have occurred off-site (73 %, 11/15) when compared with the younger age group (26 %, 10/38), and the injuries appeared to be generally more severe, but the small numbers do not allow definitive conclusions to be drawn.

It is postulated that older females who faint may be more likely to suffer more severe injuries due to osteopenia and sarcopenia.

References

1. Eder AF, Hillyer CD, Dy BA *et al.* Adverse reactions to allogeneic whole blood donation by 16- and 17-year-olds. *JAMA* 2008;**299**(19):2279-86. doi: 10.1001/jama.299.19.2279. PMID: 18492969.
2. Spencer BR, Bialkowski W, Creel DV *et al.* Elevated risk for iron depletion in high-school age blood donors. *Transfusion*. 2019;59(5):1706-16. doi: 10.1111/trf.15133. PMID: 30633813; PMCID: PMC6499707.
3. Spencer BR, Mast AE. Iron status of blood donors. *Curr Opin Hematol* 2022;29(6):310-16. doi: 10.1097/MOH.0000000000000733. PMID: 35916553; PMCID: PMC9547853.
4. Mast AE. Putting donor health first in strategies to mitigate donor iron deficiency. *Transfusion* 2017;**57**(3):495-8. doi: 10.1111/trf.14074. PMID: 28297079; PMCID: PMC5453175.
5. Goldman M, Germain M, Grégoire Y *et al.* Safety of blood donation by individuals over age 70 and their contribution to the blood supply in five developed countries: a BEST Collaborative group study. *Transfusion* 2019;**59**(4):1267-72. doi: 10.1111/trf.15132. PMID: 30609060.
6. Müller-Steinhardt M, Müller-Kuller T, Weiß C *et al.* Safety and frequency of whole blood donations from elderly donors. *Vox Sang* 2012;**102**:134-9. https://doi.org/10.1111/j.1423-0410.2011.01531.x.
7. Zeiler T, Lander-Kox J, Alt T. Blood donation by elderly repeat blood donors. *Transfus Med Hemother* 2014;**41**(4):242-50. doi: 10.1159/000365401. PMID: 25254019; PMCID: PMC4164071.

8. Stainsby D, Butler M. Recommendations for removal of the upper age limit for regular whole blood and component donors November 2008. URL: https://www.transfusionguidelines.org/document-library/documents/recommendations-for-removal-of-the-upper-age-limit-for-regular-whole-blood-and-component-donors-november-2008.

* 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 hospitalisation or prolongation of hospitalisation 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 the 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 2.3. Blood pressure and pulse

GTS Ch2 document based on TRANSPOSE risk-based assessment tool

Prepared by Frederic Bigey and Johanna Castrén. September 2023.

What the issues are

Directive 2004/33/EC does not recommend blood pressure or pulse measurement.

Text in the 21st edition of the Blood Guide

Blood pressure. A person with a systolic blood pressure of 180 mm Hg or higher, or a diastolic blood pressure of 100 mm Hg or higher should be temporarily deferred.

Pulse. A person with a pulse under 50 beats per minute (bpm), or above 100 bpm or presenting with an irregular pulse should be deferred. Exceptions may be made to accept donors with a lower pulse rate following individual medical review, e.g. athletes.

- **Risks for the donor**:
  - Cardiovascular complication:

    BP or pulse rate out of normal range, combined with blood loss or a vasovagal reaction, might theoretically lead to a lowered vascular irrigation – risk of cerebrovascular accident or myocardial infarction?
  - Hypertension treatment: risk of impaired adaptation to a vasovagal reaction?
- **Risks for the recipient**
  - none

Recommendations (for the 22nd edition of the Guide)

Measuring blood pressure and/or pulse is not needed for determination of donor eligibility, and it can be deleted as a donor selection criterion.

The review of available literature about adverse reactions in blood donors (vasovagal reactions or cardiac ischaemia) shows no relevant data for blood pressure (BP) and pulse as specific risk factors. Several countries around the world do not measure these parameters before donation. If these are measured, they should be classified as a health service/information provided to the donor or as part of the non-specific general assessment of the donor's health.

Justification (data/references)

Eder A. Evidence-based selection criteria to protect blood donors. *J Clin Apher* 2010;**25**:331-7. DOI: 10.1002/jca.20257.

Blood pressure (BP): 1778 adverse reactions for 72 000 WB donations in 1997 were reanalysed in ARC. Diastolic BP was not correlated with donor reactions, systolic BP was not significantly associated after adjustment for age, sex, first time donation or weight. Eder's conclusion was: "There is no evidence to suggest that measurement of BP and exclusion of individuals with 'unacceptable' BP contributes to donation safety."

Pulse: > 100 or 110 BPM showed a higher risk but accounted for only 1 % of total reactions. Age and sex were predominant causes.

Germain M, Delage G, Grégoire Y *et al.* Donation by donors with an atypical pulse rate does not increase the risk of cardiac ischaemic events. *Vox Sang* 2013;**104**(4):309-16. DOI: 10.1111/vox.12002.

Pulse: no difference found in incidence of hospitalisations and deaths for coronary disease 1 year after deferral for pulse < 50 or > 100 BPM.

Donald SJ, McIntyre WF, Dingwall O *et al.* Is donating blood for the faint of heart? a systematic review of predictors of syncope in whole blood donors. *Transfusion* 2019;**59**(9):2865-9. DOI: 10.1111/trf.15442.

Systematic review, 11 relevant studies.

BP: One showed a protective effect of BP > 150. No effect of diastolic BP. One study showed a slightly higher mean systolic BP in the adverse reaction group, but within normal range.

Pulse: one paper showed an increased risk if out of 70-79 range.

The studies identified the main risk factors as being female sex, low estimated blood volume, young age, low weight, new donor status, previous history of symptoms at blood donation.

Pauwels NS, Cusack L, De Buck E *et al.* The effect of pre-donation hypotension on whole blood donor adverse reactions: a systematic review. *J Am Soc Hypertens* 2014;**8**:429-36. DOI: 10.1016/j.jash.2014.03.332.

Systematic review, 10 relevant papers.

BP: "…no evidence that hypotensive blood donors have a greater risk for donor adverse events compared with their normotensive counterparts."

Salvadori U, Sandri M, Cemin R *et al.* Effect of a liberal versus a restrictive pre-donation blood pressure policy on whole-blood donor adverse reactions. *Vox Sang* 2019;**114**(4):317-24. DOI: 10.1111/vox.12772.

Incidence of vasovagal reactions compared in two groups of ca. 22 000 donations each in 2015 and 2016, before and after a change of policy from restrictive to liberal regarding BP. Donors with hypertensive treatment were definitively excluded.

Multivariate logistic regression: no effect of low or high BP was shown. Low weight, number of donations, age and collection centre were identified as risk factors for reactions.

Severity and imputability

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

- Severity

grade of severity DONOR*				
Risk(s)	*Non-Severe*	*Severe*	*Life-threatening*	*Death*
Fainting		X		
Cardiovascular or cerebral attack			X	

- Imputability

level of imputability DONOR*						
Risk(s)	*Definite/ Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
Fainting				X		
Cardiovascular or cerebral attack				X		

– *Options to minimise each of the risks*
  - Assessment and prevention of other risk factors of vasovagal reactions
  - General investigation of cardiovascular risks

Considerations (e.g. financial)

In countries where BP and pulse are measured and associated with eligibility rules, these parameters are one of the two most frequent deferral causes.

The measurement of BP and pulse can be considered as a secondary benefit, comparable to non-mandatory biological tests performed in some blood centres for donors as a loyalty method (e.g. glycaemia, cholesterol).

** 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 hospitalisation or prolongation of hospitalisation 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 the 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 2.4.
Apheresis donation for thalassaemia trait carriers

TRANSPOSE risk-based assessment tool

Prepared by Massimo La Raja. March 2024.

Text in the 21st edition of the Blood Guide

This recommendation appears on page 139:

Thalassemia

Donors with thalassaemia should be deferred permanently if they are not in good health or if the haemoglobin levels are below acceptable values. Individuals with thalassaemia trait may give whole blood provided they are in good health and have a haemoglobin level within acceptable values. **Platelet or plasma collection by apheresis is not recommended as the process may cause mechanical haemolysis.**

What the issues are

With reference to the statement regarding collection by apheresis, two risks are possible:

1. Risk for the donor: possible decrease in haemoglobin due to haemolysis in the case of frequent donations;
2. Risk for the recipient: transfusion of plasma or platelets with free haemoglobin.

Arguments and summary of the literature

The statement "**Platelet or plasma collection by apheresis is not recommended as the process may cause mechanical haemolysis**." was not present in the 20th edition of the Guide, and there is no discussion on its inclusion in the available Change Log of the 21st edition.

The change was made based on the stakeholder consultation in 2022. It was proposed not to accept beta thalassemia trait donors as plasma donors, as their red cells are not suitable for repetitive centrifugation. No literature or scientific evidence was provided. The Chapter 2 group decided to accept this proposal and it was supported by the GTS.

Based on our experience in Italy, we disagree with this recommendation against plasma/platelet donations by apheresis from thalassemia trait donors. Thalassaemia trait, or minor, is a non-pathological carrier state characterised by microcitaemia and slightly lower Hb levels, and it is distinguished from thalassemia major, which is usually associated with very low levels of haemoglobin and overt disease that make the situation incompatible with any donation. In Italy we have many beta-thalassemia (ßT) trait plasma donors, as ßT is common in some regions of our country. Additionally, our selection criteria favour plasma donation for ßT trait carriers, with lower eligibility limits of haemoglobin of 11.0 and 12.0 for female and male donors, respectively. Following the EDQM recommendation in the 21st edition of the Guide, we consulted public databases, including PubMed and Scopus, using the search terms "blood donors", "blood donation" and "plasma donation" combined with "thalassemia", and were unable to find scientific evidence with reference to any contraindication or any side effect in donors or recipients of plasma by apheresis collected from these donors. Nor did we find any observation of deviation of laboratory parameters (bilirubin, free haemoglobin, etc) in plasma donors with ßT trait. Moreover, experimental laboratory tests on ßT trait RBC show that they demonstrate a higher resistance to both osmotic and, interestingly, mechanical stress [1, 2]. This makes it even less likely that haemolysis will occur during plasma donations. Based on the experience of our blood

donation centres with both centrifuge and filter-based blood separators, we do not have any reports in the haemovigilance system of visible haemolysis of RBC from ßT trait donors during or after collection.

Free haemoglobin becomes visible in plasma at a concentration between 0.1 and 0.3 g/L [3]. So, if we consider a donation with a donor Hb concentration of 133 g/L (40 % HCT) yielding a standard plasmapheresis of 700 mL of plasma (including 100 mL anticoagulant) with a mean 1800 mL of blood processed, visible haemolysis with a Hb concentration of 0.3 g/L becomes apparent in collected plasma when only 0.2 % of processed RBCs are destroyed during the procedure. So absence of visible coloration of plasma is a reliable criterion to exclude significant haemolysis (i.e. < 0.2 %) during apheresis procedures and, as it is in practice, it is a release and acceptance criterion of the product both for clinical and industrial utilisation.

1. Anastasiadi AT, Paronis EC, Arvaniti V-Z *et al.* The post-storage performance of RBCs from beta-thalassemia trait donors is related to their storability profile. *Int J Mol Sci* 2021;**22**(22):12281. DOI: 10.3390/ijms222212281. PMID: 34830162. PMCID: PMC8619127.
2. Tzounakas VL, Anastasiadi AT, Stefanoni D *et al.* Beta thalassemia minor is a beneficial determinant of red blood cell storage lesion. *Haematologica* 2022;107(1):112-25. doi: 10.3324/haematol.2020.273946. PMID: 33730845; PMCID: PMC8719105
3. Guder WG. Haemolysis as an influence and interference factor in clinical chemistry. *J Clin Chem Clin Biochem* 1986;**24**(2):125-6. PMID: 3711796.

Severity and imputability

There is a theoretical risk of damage to donor or patient due to free haemoglobin present in the plasma and the theoretical reduction in haemoglobin level in frequent plasma donors. However, there is no evidence in the medical literature of damage to the donor or to the patient from plasma or platelets donated by apheresis by ßT trait donors, nor evidence of abnormal haemolysis in the product, so neither severity or imputability to donor or recipient can be measured for this practice.

Recommendations (for the 22nd edition of the Guide)

The complete absence of clinical and experimental evidence of any haemolytic complications during apheresis donations by ßT trait donors justifies, in our opinion, the removal from the 22nd edition of the Guide the statement: "Platelet or plasma collection by apheresis is not recommended as the process may cause mechanical haemolysis."

Justification (data/references)

There is no scientific evidence or data on possible haemolysis during apheresis from ßT trait donors.

Considerations (e.g. financial)

If the recommendation is adopted in regions where thalassemia is common, the exclusion of ßT trait subjects from plasma/platelet donation could cause a substantial loss in donations.

Background Paper 2.5. Variant Creutzfeldt-Jakob disease

GTS Ch2 document based on TRANSPOSE risk-based assessment tool

Prepared by Joanne Pink and the GTS Chapter 2 Group. March 2024.

Text in the 21st edition of the Guide

Standard

2.3.3.7 Deferral of donors as a preventative measure for vCJD should be based on appropriate risk assessment.

Variant Creutzfeldt-Jakob disease (vCJD) was first described in the UK in 1996. Estimating the potential size of the vCJD epidemic has been very difficult. Transfusion transmission of vCJD has been documented in animal studies and in humans. Endogenous risk of vCJD differs between countries. Therefore, the need for different measures to reduce risk will depend on each country's own risk assessment, balancing risk with sufficiency of supply.

Many countries outside the UK defer donors who have lived in the UK for a minimum defined period between 1980 and 1996; the European Medicines Agency (EMA) mandates 1 year of UK residence for donors of plasma for fractionation. In some instances, the deferrals have been extended to include donors from other countries with a significant number of cases.

What the issues are

Transfusion-transmitted vCJD has been documented in animal studies and humans. To mitigate the risk of transfusion transmission of vCJD, many countries implemented a precautionary deferral for cumulative UK residence for a minimum defined period between 1980 and 1996; subsequently there were four cases of transfusion-transmitted vCJD and hence the deferral could be considered as preventative. The implicated product for the four reported cases was non-leucodepleted red cells (detailed in Table 1, below). Recipients of blood transfusion in high-risk countries were also permanently deferred. Many blood establishments no longer provide non-leucodepleted red cells. To date, there have been no confirmed cases of vCJD transmission associated with fractionated plasma products, and no clinical vCJD cases reported in UK haemophilic patients. There is a single report of possible transmission of vCJD by factor VIII; this asymptomatic patient was exposed to multiple potential sources of infection.

Real-world data demonstrates that the initial estimates of the size of the vCJD epidemic are not plausible. With the passage of time this risk is now known to be significantly lower than initial estimates. Data from Appendix study II estimated a rate of abnormal prions of about 1 in 2 000. However, only 233 cases of vCJD have occurred worldwide and no dietary exposure cases since 2016. In addition, while the median and mean incubation period of the transfusion-transmitted cases is 7.8 and 7.6 years, respectively, there have been no cases of transfusion-transmitted vCJD in the UK since 1999 when universal leucodepletion was implemented, despite some 50 million transfusions in the UK during this period. There are 44 cases of primary vCJD identified in people residing in 10 other countries who have not spent a cumulative time in the UK of 6 months (with France estimated to have 10 % of the UK risk). If it is assumed that the appendiceal studies are representative of the true risk, then those countries would be expected to have a prevalence of vCJD proportional to that risk and this has not held true. There are also significant issues interpreting cross-sectional studies, such as Appendix I and II, without a valid control group. Regulatory agencies such as the Therapeutic Goods

Administration (the medicine and therapeutic regulatory agency of the Australian Government) and United States Food and Drug Administration (FDA) have now accepted that the risk estimates based on the Appendix studies are not plausible.

Based on the epidemiological data of the waning vCJD epidemic (with the last recorded dietary-associated case in 2016), scientific evidence and probabilistic risk assessment modelling as well as reputational risk from maintaining an unjustified exclusion, some regulatory agencies have approved the removal of this restriction. For example, in July 2022 the Australian Red Cross Lifeblood removed the restriction based on a risk assessment which estimated a 1 in 1.45 billion risk of a clinical case of vCJD per transfused unit (McManus *et al.*, 2022). Other reviews have been undertaken in the CBS and HemaQuebec, USA, Hong Kong, UK Medicines and Healthcare products Regulatory Agency, Ireland and New Zealand, which have led to the removal of the geographical deferral. The UK risk model and its outputs were reviewed and supported by independent experts on the Advisory Committee on Dangerous Pathogens - Transmissible Spongiform Encephalopathies (ACDP TSE) Sub Group.

People who received blood or blood products in the UK between 1980 and 1996 are usually indefinitely deferred. The risk of acquiring vCJD through transfusion of blood donated by a donor who has received a transfusion of blood or blood product in the UK during the risk years is lower than for those who lived in the UK during the height of the bovine spongiform encephalopathy (BSE) epidemic. Assuming that the risk of clinical vCJD will increase with the addition of the risk of accepting UK transfusion recipients (potentially double), because the overall modelled risk is tiny, any increase in risk would not be significant.

The vCJD outbreak centred in the UK (178 of 232 cases worldwide) and therefore the risk of transfusion-transmitted vCJD in the rest of Europe (and the world) is lower than in the UK. It was not feasible for the UK to implement a geographical restriction for transfusable/labile blood components (e.g. red cell components) and for this reason the residual risk for these components was accepted in the UK. The residual risk attributed to removing the vCJD geographical restriction in countries outside the UK now will be significantly lower than the peak risk that occurred in the UK during the at-risk years. The fact that there have been no cases of transfusion-transmitted vCJD in the UK since 1999 when universal leucodepletion was implemented, despite some 50 million transfusions in the UK during this period, supports the initial deferral as being precautionary.

Comprehensive and peer-reviewed risk assessments performed by multiple countries and the FDA demonstrate that the residual risk of transfusion-transmitted vCJD is trivial and the results can reasonably be extrapolated to all countries outside the UK. Risk assessments take into consideration the percentage of donors who may be exposed to the infective pathogen and the number of cases of confirmed vCJD. The donor exposure rate and vCJD prevalence for all countries outside the UK are significantly lower than that seen in the UK and, for this reason, should a risk assessment be performed, it is reasonable to expect that the residual risk would be acceptable. The preparation of quantitative risk assessments requires modelling expertise and the availability of data; many countries will not have access to the required data and hence will not be able to prepare a risk assessment. Taking into consideration the availability of a number of qualitative risk assessments and other available data, it is now possible to prepare a common qualitative assessment for non-UK European countries, which can be used as the basis to support a change in the donor eligibility criteria for vCJD.

The removal of the geographical deferrals will expand the donor pool and assist with collection sufficiency. The experience from Australian Red Cross Lifeblood is that about 8 % of the total donor panel is now individuals who were previously deferred because of a risk of vCJD.

Although the primary epidemic peak appears to have passed, there remains some concern about further cases due to different *PRNP* genotypes (MV and VV at codon 129) that may have a longer incubation period compared to the MM genotype. Of 161 UK vCJD cases that have been

genotyped, 160 definite or probable vCJD cases were methionine homozygous (MM) at codon 129 of the *PRNP* gene and one case of definite vCJD was methionine/valine (MV) heterozygous. In addition, a case of probable vCJD with an MV heterozygous genotype has been reported. MV heterozygous individuals with either subclinical infection or exposure that is not an infection have been identified by retrospective testing of tonsil/appendix tissues, as well as one case who was the recipient of non-leucodepleted RBCs and died five years later from unrelated causes. The last case of vCJD identified in the UK (2016) was heterozygous at *PRNP* codon 129. That said, the risk of a second peak remains theoretical and the benefits of removing the geographical deferral outweigh the theoretical risk.

Remaining uncertainties, such as the potential for a delayed second wave of vCJD, need to be considered. There should be ongoing surveillance and reassessment of risk if new cases of the disease emerge in the future.

Severity and imputability

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

– Severity

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

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

– Imputability

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

level of imputability* Recipient risks						
Risk(s)	*Definite/ Certain*	*Likely/ Probable*	*Possible*	*Unlikely*	*Excluded*	*Not assessable*
Transfusion-transmission of vCJD	*X, but modelled risk is now extremely low.*					

– Options to minimise each of the risks

Donor risk: NA

Recipient risks: The residual risk of transfusion-transmitted vCJD has been estimated by a number of countries to be trivial.

Recommendations (for the 22nd edition of the Guide)

Standard

2.3.3.7 There is no requirement to defer donors because of travel to or residency in geographical areas where cases of BSE or vCJD were identified.

2.3.3.8 There is no requirement to impose any additional restrictions for donors who received transfusions in geographical areas where cases of BSE or vCJD were identified.

Variant Creutzfeldt-Jakob disease (vCJD) was first described in the UK in 1996. The justification for a vCJD geographical deferral was in part influenced by uncertainty in the initial modelling of future cases. The worst-case prediction in case numbers has not been realised and there have been no new cases of vCJD in the UK since 2016. Despite continued collection of blood in the UK over the past two decades, and more than 50 million transfusions in the UK, there have been no further reported cases of transfusion-associated vCJD. In response to the waning of the vCJD epidemic and the reputational risk from maintaining an unjustified exclusion, several regulatory agencies have approved the removal of this restriction based on risk assessments which estimate the residual risk to be acceptable. Risk assessments take into consideration the percentage of donors who may be exposed to the infective pathogen and the number of confirmed cases. The donor exposure rate and vCJD prevalence for all countries outside the UK are significantly lower than that seen in the UK.

The requirement to perform a risk assessment has been removed because it is reasonable to expect that the residual risk assessed in any non-UK European country would be minimal and considered acceptable. The four reported cases of transfusion-transmission of vCJD involved non-leucodepleted red cells. Sheep model research suggests that leucodepletion reduces the transmission rate of vCJD by 71%. Blood establishments could consider performing a risk assessment if non-leucodepleted products are supplied.

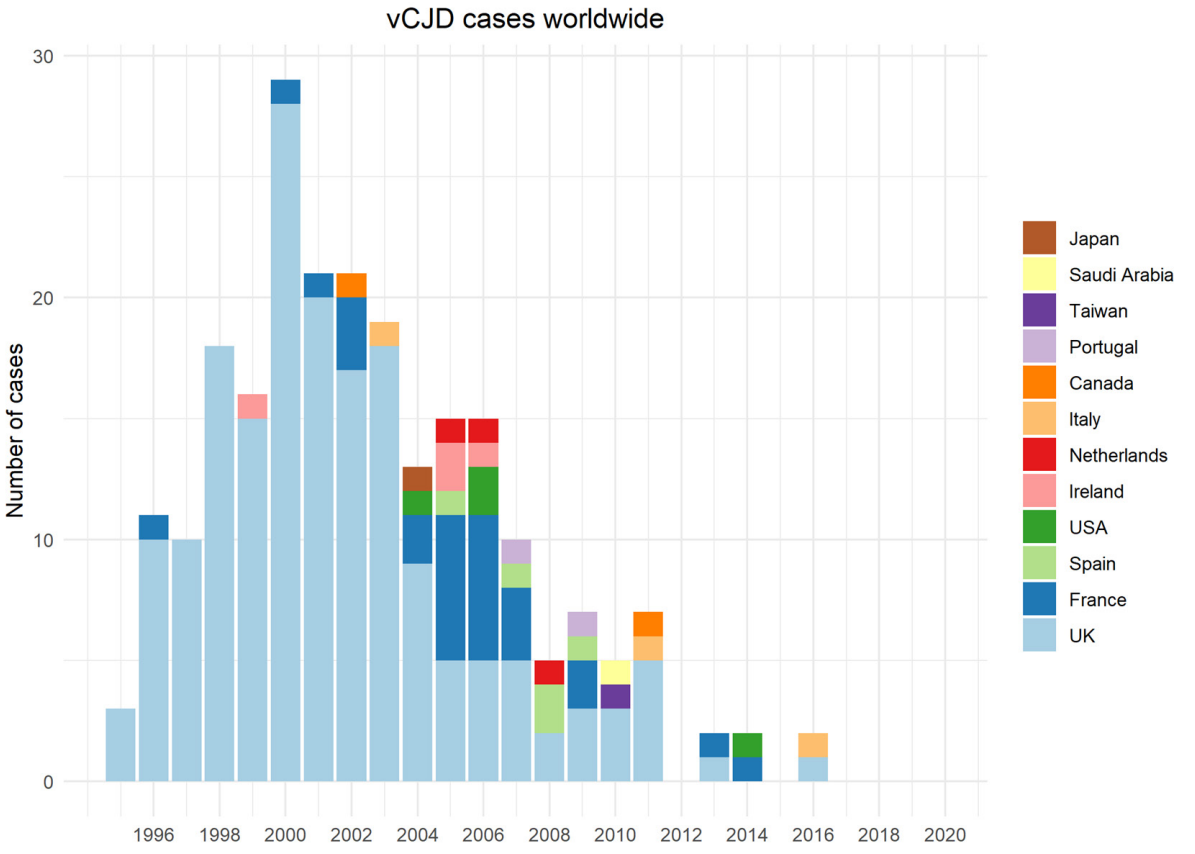
Justification (data/references)

1. The implicated product for all reported cases of transfusion-transmission of vCJD was non-leucodepleted red cells. Many blood services no longer provide non-leucodepleted red cells.

Table 1. Characteristics of reported cases of transfusion-associated vCJD

Reference	Date transfused	Implicated blood component	Date symptom onset	Time from transfusion to symptom onset (or preclinical detection)	Recipient genotype at codon 129 of PRNP
Llewelyn 2004[3]	1996	Red cells (non-LD)	2002	6.5 years	MM
Peden 2004[6]	1999	Red cells (non-LD)	None (preclinical detection at autopsy)	5 years	MV
Wroe 2006[4]	1997	Red cells (non-LD)	2005	7.5 years	MM
Eurosurveillance 2007[5]	between 1996-1999	Red cells (non-LD)	?2006	8.5 years	MM

2. The total cases of vCJD were much lower than initially expected and there has not been a dietary-associated case diagnosed since 2016.



Source: McManus H, Seed CR, Hoad VC, Kiely P, Kaldor JM, Styles CE, *et al*. Risk of variant Creutzfeldt–Jakob disease transmission by blood transfusion in Australia. *Vox Sang*. 2022; **117**(8): 1016–1026.

A number of countries have made the decision to remove the vCJD geographical deferral based on risk assessments, including:

1. Australian Red Cross Lifeblood – Risk of variant Creutzfeldt Jacob Disease transmission by blood transfusion in Australia (McManus *et al.*, 2022).
2. FDA – Recommendations to reduce the risk of transmission of Creutzfeldt Jacob Disease and variant Creutzfeldt Jacob Disease by blood and blood components. Guidance for Industry May 2022. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-reduce-possible-risk-transmission-creutzfeldt-jakob-disease-and-variant-creutzfeldt).
3. Hong Kong – removed their deferral, announced via X (formerly Twitter).
4. Ireland (IBTS (https://www.giveblood.ie/can-i-give-blood/keeping-blood-safe/vcjd/)).
5. UK – Critical risk assessment report – use of UK plasma for the manufacture of immunoglobulins and vCJD risk (UK government Department of Health and Social Care 2021).
6. Canada
7. Israel
8. New Zealand

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Scientific guideline from the EMA

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Considerations (e.g. financial)

There is a cost to recruit and maintain blood donor panels. Expanding donor eligibility based on evidence takes pressure off the resources required to recruit 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 hospitalisation or prolongation of hospitalisation 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 the 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 2.6. Malaria

GTS Ch2 document "Prevention of TRANSFUSION-TRANSMITTED MALARIA" based on TRANSPOSE risk-based assessment tool

Prepared by Massimo La Raja. March 2024.

Text in the 21st edition of the Blood Guide

Standards

2.3.3.21

Blood establishments should have access to a current map or list **of endemic areas and seasonal risk periods** at the site of blood collection.

2.3.3.22

The following rules should apply for individuals who give a **history of malaria**:

- They should be deferred for a period of at **least 4 months** following departure from a malarial area and 4 months following cessation of treatment/last symptoms. They may then be accepted if the result of a v**alidated immunological test for** antibodies to the malaria parasite is negative.
- If the test is repeatedly reactive, the donor should be deferred and may be re evaluated after a suitable period when the antibody test may have reverted to negative (a period of 3 years is suggested).
- **If the test is not performed**, the donor should be deferred until the test is performed and negative.

2.3.3.23

The following rules should apply for individuals who report **an undiagnosed febrile illness** consistent with malaria during a visit to or within 6 months following departure from a malarial area:

- They should be deferred for a period of **at least 4 months following departure** from a malarial area and 4 months following cessation of treatment/last symptoms. They may then be accepted if the result of a validated immunological test for antibodies to the malaria parasite is **negative**.
- If the test is repeatedly reactive, the donor should be deferred and may be re evaluated after a suitable period when the antibody test may have reverted to negative (a period of 3 years is suggested).
- **If the test is not performed**, the donor should be deferred until the test is performed and negative.

2.3.3.24

The following rules should apply for individuals **who have lived in a malaria endemic area for a continuous period of 6 months or more at any time in their life at the time of their first donation and after each return** from a malarial area:

- They may be accepted as blood donors if the result of a validated immunological test for antibodies to the malaria parasite, performed at least 4 months after leaving the malarial area, is negative.
- If the test is repeatedly **reactive**, the donor should be deferred and may be re evaluated after a suitable period when the antibody test may have reverted to negative (a period of 3 years is suggested).
- If **the test is not performed**, the donor should be deferred until the test is performed and negative.

2.3.3.25

The following rules should apply for all other individuals who **have visited a malarial area without reporting any clinical symptoms consistent with malaria**:

- They should be deferred for a period of 4 months following departure from the malarial area and may then be accepted as blood donors if the result of a validated immunological test for antibodies to the malaria parasite is negative.
- **If the test is not performed**, the donor may be accepted once a period of **12 months** has elapsed following departure from the malarial area.
- If the test is repeatedly **reactive**, the donor should be deferred and may be re evaluated after a suitable period when the antibody test may have reverted to negative (a period of 3 years is suggested).

Malaria screening (page 340)

At present, only a few reliable and robust malaria antibody tests are commercially available. Any malarial antibody-testing requirement necessitates integration within local approaches to the taking of donor histories. Users need to be aware that assays may depend on the detection of heterotypic antibodies. Users should ensure that the assay detects antibodies to the *Plasmodium* species prevalent in their donor panel. This test is not required for plasma for fractionation. Currently, NAT for malaria cannot be recommended for use in screening of blood donors because it may fail to detect the small number of parasites in a blood donation that can infect a transfusion recipient.

Standard

9.5.4.2

If malaria **antibody testing** is used to determine donor acceptance or rejection, the test employed should be shown to detect antibodies to the malaria parasite types that are likely to pose a risk of transfusion transmission and to the *Plasmodium* species prevalent in their donor panel.

Other reference criteria in EU

Commission Directive 2004/33/EC of 22 March 2004

Malaria (duration of deferral period)

— individuals who have lived in a malarial area within the first five years of life: 3 years following return from last visit to any endemic area, provided person remains symptom free; may be reduced to 4 months if an immunologic or molecular genomic test is negative at each donation

— individuals with a history of malaria: 3 years following cessation of treatment and absence of symptoms. Accept thereafter only if an immunologic or molecular genomic test is negative

— asymptomatic visitors to endemic areas: 6 months after leaving the endemic area unless an immunologic or molecular genomic test is negative

— individuals with a history of undiagnosed febrile illness during or within six months of a visit to an endemic area: 3 years following resolution of symptoms; may be reduced to 4 months if an immunologic or molecular test is negative

What the issues are

Risk for the donor: no risk for the donor

Risk for the recipient: transfusion-transmitted malaria (TTM) from an asymptomatic donor travelling from malaria-endemic countries.

With reference to the present criteria for TTM prevention, the issues at stake are:

- Sensitivity and specificity of immunological screening tests
- Sensitivity of molecular tests (DNA copies/mL)
- Minimal number of plasmodia (copies/mL) in the RBC units for malaria transmissibility
- Stratification of malaria risk for travellers according to geographic areas (high risk, low risk) and to duration of stay in endemic areas
- Duration of asymptomatic carrier state according to different *Plasmodium* species (*falciparum, malariae, vivax, ovale, knowlesi*) and the possibility of immunologically silent long incubation times for *P. ovale* and *P. vivax*.

Arguments and summary of the literature

In non-endemic countries before the year 2000, different deferral times and no laboratory screening tests were in use to prevent TTM. Since the beginning of the millennium, the majority of non-endemic countries have implemented more stringent selection criteria. In many European countries anti-malaria antibody testing was added to identify exposed donors and potential asymptomatic carriers. This resulted in a significant reduction in incidence of TTM cases in non-endemic countries [2, 15]. The review of breakthrough TTM cases in the last two decades in non-endemic countries and the magnitude of donors deferred helps us assess the safety and consequences, in terms of blood availability, of these strategies. For the purpose of this document, we searched the available reports and reviews published in medical library databases, with specific reference to cases and studies conducted in Europe, North America and Australia [2-4, 7, 12-14, 21].

A total of 22 cases of TTM were reported from 2000 to 2022: 11 in Europe (out of approximately 20 million RBC transfusions per year), 11 in the USA (out of about 10 million RBC transfusions per year), and one in Canada. Of these, 16 TTM cases were due to *Plasmodium falciparum* (Pf), five to P*lasmodium malariae* (Pm), and one to *Plasmodium ovale* (Po). Four cases were fatal, all caused by *Plasmodium falciparum*. In fact, in the entire history of all TTM cases as reported in medical literature, only one fatality attributable to plasmodia other than *Plasmodium falciparum* has been described to date: a *Plasmodium malariae* case in 1938 [12].

Only two donors were short-term visitors to tropical areas, one was a long-term expatriate (missionary) and the remaining 19 were former residents and natives of endemic countries, all but one from Sub-Saharan Africa (SSA). Out of the three donors that were born in non-endemic countries, only one was a *Plasmodium falciparum* case, and was due to unreported very recent travel. The implicated donor developed full-blown malaria soon after donation. The other two were *Plasmodium malariae* cases, one acquired in Sub-Saharan Africa and the other in an Eastern Asian country.

As regards TTM cases in Europe, based on present standards (deferral and immunologic testing) and available information, only three can be considered breakthrough cases, i.e. unreactive to anti-malaria immunological tests after proper deferral. The other eight were either due to incorrect travel history reporting or to non-application of present standards, i.e. not tested with immunological screening tests. In all cases where the immunological test was performed in the look-back on stored samples, a

positive result was obtained. So, they were all ineligible according to the standards. However, it must be mentioned that deferrals that preceded implicated donations were, on average, much longer than the 4 months indicated by the EDQM Guide. This may be due to the fact that some European countries, and Italy among them, still apply a 3-year deferral for former residents of endemic countries vs. 4 months as indicated in the Guide.

As far as the USA and Canada are concerned, immunological tests have not been adopted so far in the selection process, but a longer deferral period (3 years) is required for former residents of endemic countries and for previous cases of malaria. After review of the 11 cases, five were ineligible according to US and Canada criteria because the time elapsed since the last exposure was shorter than 3 years. All donors in North American TTM cases were former residents and natives of Sub-Saharan African countries, and, according to the EDQM Guide standards, they should have been screened with immunological tests regardless of the deferral time. All US TTM cases were enzyme immunoassay (EIA) or indirect fluorescent antibody test (IFAT) positive when tested retrospectively on stored donor or recalled donor samples. Based on this information, it is likely that few, if any, North American cases would have been missed by the immunological test, if performed.

Discussion of findings and evaluation of the residual risk

Concerning the prevention of TTM, when assessing the residual risk there are essentially two distinct groups of donors: the occasional visitors to malaria-endemic countries who were not previously and repeatedly exposed to malaria infection, and the former residents of malaria-endemic countries, considered semi-immune and potentially silent chronic carriers. Other critical elements to be taken into consideration in evaluating preventive strategies are the sensitivity and the specificity of immunological and molecular tests and the deferral periods, according to the time and intensity of exposure in endemic areas.

Former residents in malaria-endemic countries

Except for two cases, all documented cases of TTM in the last 22 years in non-endemic countries were caused by blood donations from individuals born in or former long-term residents of endemic countries. Most of these donors were exposed to malaria risk in Sub-Saharan Africa, and only one case occurred in Eastern Asia. These donors were actually asymptomatic chronic carriers, a known clinical situation due to a semi-immunity acquired over years of repeated exposure to infectious mosquito bites, usually in the first years of life. Many natives of endemic areas do not recall a history of previous malaria episodes, as they likely occurred in early childhood [6]. In some cases, the asymptomatic carrier state exceeded 3 years from last exposure, including cases of *Plasmodium falciparum* [1-3, 7]. As expected, all fatal TTM cases were caused by *Plasmodium falciparum* [12, 14]. After review of TTM cases from semi-immune individuals, the majority were attributable to failures in correct history taking/reporting, and they were ineligible according to the current EDQM Guide selection standards. TTM cases originating from semi-immune donors who tested negative in the immunological test (EIA), i.e. breakthrough cases, have been reported in only two cases: one *Plasmodium falciparum* and one *Plasmodium malariae* [2]. In both these cases, molecular tests performed on stored samples or recalled donor samples were weakly reactive. Among immunologically reactive TTM implicated donors, whose reactivity was assessed retrospectively, only one case caused by *Plasmodium falciparum* was unreactive in the molecular test performed on a stored sample [4]. However, according to the case report, the stored sample was described as being of poor quality.

Considering the specificity side of the screening strategy, donors who were born and/or resided for a long time in areas with high malaria prevalence are also "long-term" (> 3 years) and often lifelong carriers of anti-malaria antibodies, as detected by standard screening tests [5]. Yet the vast majority (> 99 %) of immunologically reactive donations are not reactive for plasmodia DNA or RNA with molecular methods [6, 20]. This is because of the permanent exclusion of many donors that are likely not infectious, leading to a significant reduction in the donor pool especially from specific ethnic groups. This issue is particularly relevant for donors from Sub-Saharan Africa who carry specific red

blood cell antigenic profiles that are relatively rare in Europe and are increasingly required due to the growing number of patients of African ancestry, and especially those with hemoglobinopathies who are transfusion-dependent and easily immunised against common blood antigens. The uncertain cut-off between molecular test sensitivity and minimal infectious dose of malaria parasites in donated blood is the major issue for the effective introduction of these tests in the selection process.

Non-immune visitors

Non-immune visitors are defined as individuals who were not former residents of or born in malaria-endemic countries and who spent less than 6 months continuously in malaria-endemic regions. These individuals are considered non-immune and, if exposed to infectious mosquito bites, they are expected to develop symptoms and signs, often severe, of malaria after the normal incubation time. This incubation time is invariably shorter than 3 months for *Plasmodium falciparum*. For *Plasmodium ovale* and *Plasmodium vivax*, the clinical incubation period may be longer due to hypnozoite-related relapse. In rare cases of P*lasmodium ovale/Plasmodium vivax* infections, particularly if anti-malaria prophylaxis was administered during the travel, the first clinical episode may occur many months after exposure [11]. In these cases, it is not known whether the donor is carrying plasmodia in the bloodstream during the long asymptomatic "window period" or the plasmodia in the form of hypnozoites are confined only in the liver. However, so far, no case of Transfusion-Transmitted Malaria (TTM) due to *Plasmodium ovale* or *Plasmodium vivax* has been documented originating from non-immune donors who had *Plasmodium ovale/Plasmodium vivax* malaria following the expected 4-month deferral. Two recent cases in Australia [17] were classified as near misses as the malaria attack occurred 4 months after returning from the endemic countries: the antibody tests in these two cases were negative. However, the blood units donated before malaria symptoms were not transfused, and it is therefore unknown whether they were infectious or not. Overall, only one case of *Plasmodium ovale* TTM was reported in Western non-endemic countries in the last 20 years, and it was from a semi-immune donor unit.

In Europe and North America, only two cases of Transfusion-Transmitted Malaria caused by non-immune visitors have been documented since the year 2000. The most recent and fatal case [14] resulted from a failure to report recent travel in Sub-Saharan Africa (< 1 month), and the donor developed symptomatic *Plasmodium falciparum* malaria soon after the implicated donation. The second case [13] occurred more than a decade ago and involved a *Plasmodium malariae* transmission. It resulted from a blood unit collected from a non-immune visitor who did not report any malaria-like symptoms during the 5 years since their last travel to malaria-endemic countries (Sub-Saharan Africa and Southeast Asia for two distinct periods). Interestingly, during these years, this person donated whole blood more than 10 times without transmitting malaria before the implicated donation. On stored samples and subsequent controls, the donor tested negative by anti-malaria EIA, weakly positive by immunofluorescence assay (IFA), and weakly positive by polymerase chain reaction (PCR). This represents the third breakthrough case of the immunological test barrier together with the two from semi-immune donors described above.

After almost 20 years since the introduction of immunological screening tests for malaria, a small minority of non-immune "travellers" without a history of malaria were found to be reactive to immunological tests after the deferral period. Among these reactive cases, there was no documented evidence of malaria episodes in the follow-up, or reactivity to molecular tests that were reported in the medical literature. Based on this information, the current standards in the EDQM Guide that recommend a longer (12 months) deferral for non-immune asymptomatic "travellers" in case of unavailability of immunological tests do not seem to add any improvement to blood safety. This was also the conclusion of a recent risk assessment conducted by the Australian Red Cross [18].

Selective immunological testing

Since their introduction immunological tests for the detection of anti-malaria antibodies have contributed to the reduction of TTM cases in countries where they were adopted [2, 15]. The gold

standard for immunological tests is considered to be the immunofluorescence assay (IFA [8], which is more sensitive and specific [21] than immunoenzymatic assays. However, IFA is not practical as a screening test due to limited commercial availability and for being operator dependent. Therefore, enzyme immunoassay (EIA tests and other automated technologies were adopted and validated in recent decades for TTM prevention.

In the last 20 years, only in rare cases enzyme immunoassays (EIA failed to detect chronic malaria carriers only in rare cases [2, 15]. Three breakthrough donations, i.e. EIA negative, have been reported to date: two *Plasmodium malariae* and one *Plasmodium falciparum* TTM cases [2].

Utilisation of molecular tests

Molecular tests for malaria diagnosis have been in place for decades, but there is still no kit with proven sensitivity for the prevention of Transfusion-Transmitted Malaria. This is because the minimal infectious *Plasmodium* DNA copies in transfused blood are not known, and so it cannot be ruled out that they are lower than the threshold of detection of many tests utilised to date. However, in TTM cases where molecular tests were applied to stored samples, all but one [4] were positive in molecular tests. This false-negative molecular test was obtained from a suboptimal quality stored sample and in a case of *Plasmodium ovale* transmission [4]. Based on this real-world evidence, current molecular tests appear predictive and sensitive enough to prevent TTM. Moreover, molecular test sensitivity for plasmodia detection has increased in recent years, due to developments in molecular targets (ribosomal RNA), methods (nested PCR) and the volume of processed samples. Recently, a sensitive molecular test, based on transcription-mediated nucleic acid amplification and targeting *Plasmodium* rRNA, has been proposed [19] as a unique universal screening strategy for all donations in the US, also considering the possibility of autochthonous cases in some areas of the country. In the past it has been hypothesised that a sensitivity threshold of 1 parasite per mL could be sufficient to detect all cases of infectious parasitaemic donations [10]. Today some commercial molecular tests are approaching this level [19].

For these reasons, molecular tests of validated sensitivity may represent a safe option for the readmission of long-lasting, clinically silent, antibody-positive donors. In these cases, however, molecular tests should be applied for all subsequent donations, as fluctuation of parasite numbers in peripheral blood, and thus the infectivity, may change over time.

Additionally, in cases of autochthonous malaria outbreaks in non-endemic countries, molecular tests may represent a unique option to reduce to a minimum malaria transmission without a massive restriction on blood donations [19].

Deferral time from exposure

According to the situation, deferral from blood donation is calculated from the last day of stay in malaria-endemic countries, or from the last day of effective treatment for malaria, or of symptoms of confirmed/suspected malaria.

The EDQM Guide standards have somewhat simplified the deferral of malaria-exposed donors with a flat 4 months deferral for any of the previous conditions, for all categories of donors, non-immune or semi-immune, provided that validated immunological tests are unreactive. An exception is given for visitors (non-immune donors) that can donate blood after 12 months, also without immunological test.

In the US, a 3-year deferral is applied for former residents and previous malaria cases, without the need for immunological tests. On the contrary, for short-time visitors the deferral in the US is limited to only 3 months after travel.

Directive 2004/33/EC requires 3 years deferral and negative immunological or molecular tests after a cured malaria infection. On the other hand, and in part contradictory, the directive indicates only 4

months of deferral in the case of residence in the first 5 years of life, i.e. native of endemic countries, again with a non-reactive immunological or molecular test.

It is known that the risk of being asymptomatic chronic carriers, and in particular for *Plasmodium Falciparum*, decreases over time from exposure. However, some cases of *Plasmodium Falciparum* TTM were also described after 3 years of deferral. It is also true that chronic carriers that were exposed to several malaria episodes in the past are, with few exceptions, reactive to sensitive immunological tests. Therefore, for potentially semi-immune individuals a sensitive immunological test performed after 4 months deferral, as recommended by the EDQM Guide, can be considered, a safe approach, and this is also the conclusion of the recent risk assessment published by the Australian Red Cross [18].

Conclusions

According to available evidence that emerged during the last two decades, the current EDQM Guide standards for the prevention of TTM have proven to be a safe and cost-effective strategy. The main arguments that have emerged are on the specificity side of the strategy, i.e. the possible excessive rate of exclusion of non-infected donors and unnecessary testing, after deferral, of asymptomatic visitors. From this perspective, immunological testing for non-immune asymptomatic visitors does not appear to offer any additional safety after the current deferral period and could be safely omitted in the future. Additionally, in the absence of clinical manifestations, high-sensitivity molecular tests can be considered for the readmission of antibody-positive donors after a given period of deferral. High-sensitivity molecular tests may also represent a viable option for TTM prevention in cases of autochthonous malaria outbreaks in non-endemic countries. As a final remark, the correct and complete travel history remains the mainstay of blood safety when any selective deferral and testing approach is in place, and it should never be overlooked.

Recommendations (for the 22nd edition of the Guide)

Standards

Blood establishments should have access to a current map or list **of endemic areas and seasonal risk periods** at the site of blood collection.

The following rules should apply for:

- individuals **who have lived in a malaria endemic area for a continuous period of 6 months or more at any time in their life at the time of their first donation and after each return** from a malarial area;
- individuals who give a **history of malaria**;
- individuals who report **an undiagnosed febrile illness** consistent with malaria during a visit to or within 6 months following departure from a malarial area.

Such individuals should be deferred for a period of at **least 4 months** following departure from a malarial area and 4 months following cessation of treatment/last symptoms. They may then be accepted if the result of a **validated immunological test for** antibodies to the malaria parasite is negative. If the test is repeatedly reactive, the donor should be deferred and may be re evaluated after a suitable period when the antibody test may have reverted to negative (a period of 3 years is suggested). **If the test is not performed**, the donor should be **deferred** until the test is performed and negative.

The following rules should apply for all other individuals who **have visited a malarial area without reporting any clinical symptoms consistent with malaria**:

Such individuals should be deferred for a period of **4 months** following departure from the malarial area and may then be accepted as blood donors if the result of a validated immunological test for antibodies to the malaria parasite is **negative**. If the test is repeatedly **reactive**, the donor should be

deferred and may be re evaluated after a suitable period when the antibody test may have reverted to negative (a period of 3 years is suggested). **If the test is not performed**, the donor may be accepted once a period of **6 months** has elapsed following departure from the malarial area.

Malaria screening

Any malarial antibody-testing requirement necessitates integration within local approaches to the taking of donor histories. Users need to be aware that assays may depend on the detection of heterotypic antibodies. Users should ensure that the assay detects antibodies to the Plasmodium species prevalent in their donor panel. This test is not required for plasma for fractionation. Currently, NAT for malaria cannot be recommended as **a unique strategy in screening of blood donors** because it may fail to detect the small number of parasites in a blood donation that can infect a transfusion recipient.

However high-sensitivity molecular tests may represent a valuable complementary screening option for specific donor groups or in specific contexts, such as residents of non-endemic areas when autochthonous malaria cases are reported.

Standard

If malaria **antibody testing** is used to determine donor acceptance or rejection, the test employed should be shown to detect antibodies to the malaria parasite types that are likely to pose a risk of transfusion transmission and to the Plasmodium species prevalent in their donor panel.

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Background Document 2.7.
Plasmapheresis new proposal rationale

Ch2 Plasma_new proposal for the 22nd edition of the Blood Guide

Prepared by Johanna Castrén. March 2024.

What the issues are

We are proposing a new approach to the criteria/standards that recognises the current variability in collection practice, with appropriate safeguards built in. This includes two options. The first is a Standard plasma collection approach, which is based on the current Guide criteria and is supported by the results of the European plasma project (SUPPLY). The second is an Individualised donor assessment plasma collection approach, which requires more frequent monitoring of the donor´s IgG level with adjustment of the donation interval based on the IgG levels, to ensure ongoing donor safety. The requirement for more frequent monitoring when the donor plasma collection frequency is individualised is to ensure that the level of donor safety is increased to the same level as a standard plasma collection approach.

A number of matters were taken into consideration when drafting this proposal:

1. The plasma criteria are the most debated ones.
    - The reason for this is that there is a **significant variation in practice**, both within Europe and internationally, and there is very little published evidence to confirm that the practices are safe.
    - This is especially **true when it comes to the maximal allowed annual number** of plasma donations.
2. There are **knowledge gaps**.
    - We need to encourage publication of available data and research to address knowledge gaps, particularly for the longer-term theoretical risks such as the consequences of long-term citrate exposure.
3. Our **priority is donor health and well-being**. Plasma quality is also important.
    - We acknowledge that it is not possible to have a set of rules where we can guarantee absolute safety for every donor.
    - We know that some donors will faint when the needle is first inserted or after a very small volume of plasma is collected and others will tolerate large collection volumes without any problem.
    - We know that the time required for donors to replace the amount of IgG removed with plasma collection varies significantly because the IgG production (or synthesis) and IgG breakdown (or catabolism) rates for each individual donor vary considerably.
    - We need rules that are suitable for the vast majority of donors and to have appropriate processes in place to ensure good care of donors who experience a donation complication, such as feeling faint or a reduction in IgG levels.
4. The **demand for Ig continues** to increase and many blood establishments are expanding collection capacity.

- We agree that we need to have a set of rules that provide safe and sustainable plasma collection, which are easy to understand, as simple as possible to implement and support the need to increase plasma collections.

5. Plasmapheresis removes plasma proteins.
   - We all agree that **measuring IgG levels to monitor donor health is important**, but there were some differences in opinion with regard to how frequently this should be done.
   - An acute decrease in plasma protein levels is expected immediately post-donation, in line with the content collected.
   - The available literature indicates that overall, IgG levels tend to return to the baseline with time, usually after several months, presumably because there is an IgG feedback loop which signals that an increase in the production rate of IgG is required.
   - Donors are not always predictable with their donation frequency – in any given year they may donate regularly for a period of time and very infrequently at other times, depending on what is happening in their lives.

Recommendations

We propose a **new approach to the criteria/standards that recognises the current variability in collection practice**, with appropriate safeguards built in. This approach allows two options:

a. ***Standard* plasma collection approach**
   - These criteria are based on the current Guide criteria – plasma donation no more frequently than 2 weeks with an annual assessment of IgG level.
   - There is published evidence that supports that this approach is safe.
   - The current results from the European plasma project (SUPPLY) also support this.

b. ***Individualised donor assessment* plasma collection approach**
   - This approach requires approval by the local competent authority.
   - It requires more frequent monitoring of the donor.
   - It allows the inter-donation interval to be reduced to 1 week with more frequent monitoring of IgG levels (every 6th donation). The individualised donor monitoring allows the donation interval to be adjusted based on the donor's IgG levels, to ensure ongoing donor safety.
   - Donors must not donate more frequently than weekly.
   - There are additional requirements – the need to capture, monitor and report on donor adverse events. Publication is encouraged to grow the evidence base.

We have intentionally not included an annual upper limit of collections, because the focus is on ensuring the health and well-being of the donors, rather than aiming for a maximal number of donations.

Background Document 2.8. Plasmapheresis

GTS Ch2 document based on TRANSPOSE risk-based assessment tool

Prepared by Piotr Radziwon and Johanna Castrén. October 2022.
Updated by Veerle Compernolle and Johanna Castrén. October 2024.

Apheresis donation

What the issues are

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

Text in the 21st edition of the Blood Guide

- The maximum number of plasma donations allowed is 33 per year. (2.4.2.6.)
- The donation interval must be at least 1 week. (2.4.2.10.)
- 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 should be within local population reference values and should not fall below 6.0 g/L. (2.4.2.13.)
- Serum-IgG should be measured at least annually and at every 26th donation, whichever comes first. (2.4.2.14.)

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 their 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 2 weeks;
- IgG > 8.0 g/L supports donations with a minimum interval of 1 week.

Severity and imputability

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 calcification		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 calcification			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 donation interval to avoid too low IgG levels

Recommendations (for the 22nd edition of the Guide)

- Total proteins must be measured at least annually and must not be less than 60 g/L (Directive 2004/33/EC, Annex III).
- IgG levels should be measured at least annually and within local population reference ranges and should not fall below 6.0 g/L.
- The minimum interval is recommended to be at least 2 weeks.
- Where the competent authority approves a plasma programme where the donation interval is less than 2 weeks, there are additional requirements.
- There should be enhanced monitoring of donors to ensure that the programme is safe and sustainable. Where a donation interval between 1 and 2 weeks is allowed, additional monitoring is required to determine the health impact of frequent donation on the individual donor. As a minimum this should include the following:
  1. Donor adverse events should be captured and regularly monitored to allow for the identification of adverse donor health trends and concerns with donor loss. Concerning health trends should be reported to the national authority and corrective action taken to mitigate the donor health safety concern.
  2. IgG levels should be measured at least every sixth donation to determine a donation frequency that allows the donor's IgG level to be maintained within the normal range.
- The donation interval should not be less than one week.

Justification (data/references)

IgG and Donation interval

1. A randomised, controlled trial demonstrated that, in cases where donation frequency is limited to once/month, the effect on IgG is limited to 5 % [1].
2. Two randomised, controlled trials demonstrated a 16 % reduction in IgG levels in donors donating 3 times/month [1] and biweekly [2].
3. The same randomised controlled trials demonstrated a large impact on IgG levels in donors donating more than once per week: donors donating twice per week displayed a 38 % IgG reduction [1] and donors donating 3 times/2 weeks displayed an IgG reduction of 34 % [2] in IgG levels. Moreover, Mortier *et al.* [1] demonstrated that IgG levels dropped below 6 g/L in 56 % of the donors exposed to a twice per week plasmapheresis programme.
4. A Canadian study [3] demonstrated that switching regular donors from a biweekly to a weekly regimen did not result in a statistically significant difference in IgG, although IgG levels were ± 1 g/L lower in the weekly donation group compared to the biweekly group. Finally, in two observational studies allowing up to 60 plasmapheresis donations per year, the drop out rate due to low IgG was significant: 12.4 % of donors dropped out of the SIPLA study due to IgG levels below 5.8 g/L [4], whereas in the SIPLA II study the drop out rate due to IgG was 27 % [5].
5. Hauben *et al.* [2] demonstrated that recovery of IgG levels is incomplete 4 weeks after the last plasma donation. In addition, the consequences of induced hypo-IgG are not well understood. Therefore, efforts should be made to avoid inducing hypo-IgG in donors.
6. A workgroup within the SUPPLY project conducted a systematic review on the impact of the plasmapheresis frequency for the donor. This systematic review concluded that a very high-frequency donation (twice per week) may result in a clinically relevant decrease in ferritin and bring IgG levels below the lower threshold of 6 g/L. As a precautionary measure they recommend, in the absence of more evidence, a maximum donation frequency of 2 times per month. [6]
7. Based upon these results
   - A minimum donation interval of 2 weeks is recommended. A donation interval of 2 weeks or more should be accompanied by (at least) yearly monitoring of IgG levels.
   - A donation interval of less than one week is not justified.
   - Due to a lack of published evidence on safety of donation intervals between 1 and 2 weeks, plasmapheresis programmes allowing for more than biweekly donation should be approved by the local competent authority. To ensure the health of donors and the sustainability of such more intensive plasmapheresis programmes, additional monitoring and data capturing is required whenever the donation interval is below 2 weeks. Such monitoring should include at least the following:
     - Donor adverse events should be captured and regularly monitored:
       - to allow for the identification of adverse donor health trends;
       - to understand the reasons for donor loss and to identify any associated risk for the donor.
     - IgG levels should be measured at least every 6th donation to determine a donation frequency that allows the donor's IgG level to be maintained within the normal range.
     - Red cell loss should be monitored (blood samples and residual red blood cells in the apheresis set) to ensure annual red cell loss does not exceed that of a whole blood donor.

Long-term effects of apheresis

There are data reporting significant effects of multiple apheresis and citrate contributing to hypocalcaemia, hypomagnesemia and hyperparathyroidism. The experience from haemodialysis may suggest that chronic exposure to citrate may also have an effect on the formation of vascular calcifications [7-12].

The main knowledge gap is the long-term potential risks, such as the consequences of repeated protein depletion, notably immunoglobulins. Monitoring Ig levels and adjusting donation frequencies based on the IgG level are warranted. However, such monitoring does not resolve the issue of potential risks associated with repeated protein depletion. The following aspects of long-term effects are not covered by IgG guided donation approaches:

a. How long will the low plasma protein (such as IgG) level persist in donors who are deferred and do not come back (or do come back, but not in a timely fashion with regard to this issue)?
b. The potential long-term effects resulting from repeated protein depletion, notably IgG.
c. The potential long-term effects resulting from repeated increased synthesis of the depleted proteins (such as increased B-cell and plasmacyte activation and proliferation).

Therefore, large-scale studies, including prospective randomised studies as well as epidemiological studies, linking blood establishment databases and public health databases to assess long-term health outcomes in plasma donors are needed.

Considerations (e.g. financial)

The consequences of induced hypo-IgG are not well studied. Preventing the occurrence of low IgG levels is therefore important to protect the donor. The risk of inducing hypo-IgG increases when donation intervals are shorter than 2 weeks. Therefore, monitoring of IgG can be restricted to the first donation and a yearly follow up when the donation interval is 2 weeks or more. Donation intervals of less than 1 week should be avoided because of the risk of inducing hypo-IgG. In contrast, when donation intervals are less than 2 weeks, more intensive IgG monitoring is required to protect the donor.

Red cell loss should be monitored (blood samples and residual red blood cells in the apheresis set) to ensure annual red cell loss does not exceed that of a whole blood donor.

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> *"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."*

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> *"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."*

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> *"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 *et al.* Citrate anticoagulation: Are blood donors donating bone?. *J Clin Apher* 2016;**31**(5):459-63. 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 *et al.* Bone density in apheresis donors and whole blood donors. *Vox Sang* 2015;**109**(4):410-3. DOI: 10.1111/vox.12299. 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) [13]

The author retrospectively analysed IgG and total serum protein (TSP) metabolism data in plasma donors as well as drop outs of plasmapheresis donors, and searched 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 a minimum 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 the range of 0.01 to 1.71 per week; median 0.73 per week. **Plasmapheresis frequency negatively correlated with the time to drop out due to low IgG concentration or TSP concentration. With high frequency plasmapheresis, the above-mentioned correlation was very strong**. With low frequency plasmapheresis, the correlation of the time window with the first drop out was very weak. **According to Figure 23, the borderline between 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**

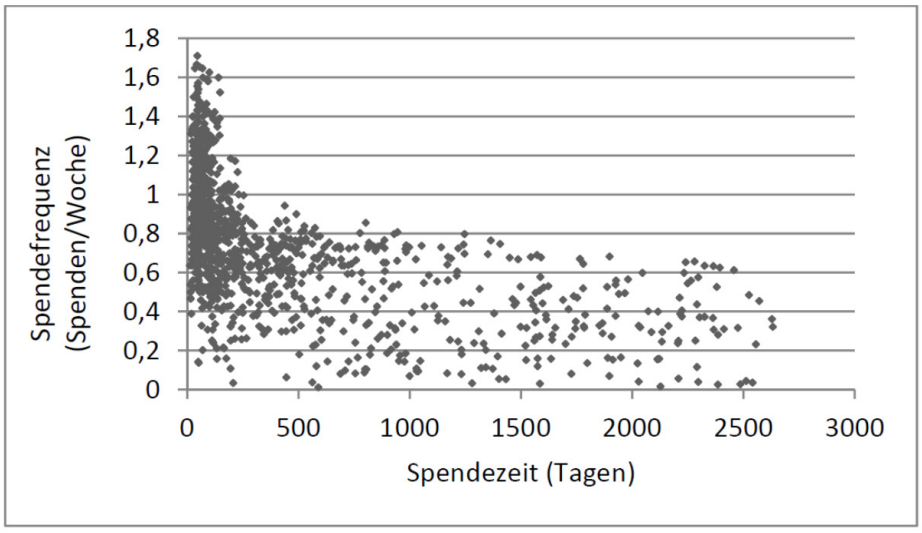

Figure sourced from"Der Einfluss der präparativen Plasmapherese auf Immunglobulin G-, Gesamteiweiß- und Flüssigkeitshaushalt des Plasmaspenders" (The influence of preparative plasmapheresis on immunoglobulin G, total protein and fluid balance of the plasma donor – PhD thesis) by Anke Möller (2012) [13]

The impact on plasma protein management caused by plasmapheresis becomes significant. Donation led to reductions in TSP and IgG by 18 % and 38 %, respectively. As expected, the IgG regeneration rate was well below the TSP regeneration rate.

Donors no longer reach the total protein or IgG serum concentrations determined before the start of donation.

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 influenced by diet, IgG concentration is the limiting factor for 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 IgG level 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.

Chapter 3. Background Document

Collection of blood and blood components

Prepared by Sarah Morley and Joanne Pink. March 2024.

1. **Minor word inconsistencies with the Directive wording**

A review was undertaken of the wording of the GPG and the Directive in the 21st edition and some small inconsistencies were identified. The text was aligned with the GPG / Directive and, where feasible, the additional text (which had previously been included) was added at the end of the standard text.

2. **Should there be an upper limit for plasmapheresis collections?**

Long collection time whole blood donations are more likely to contain clots which will consume platelets and clotting factors, and for this reason it is important to have an upper collection time limit.

The plasmapheresis collection process is different because citrate is administered in a volume that is proportional to the volume of whole blood in the extracorporeal circuit. There are no published product quality concerns related to the length of the procedure; feedback was also sought from a number of commercial plasma collectors who do not consider that the length of the collection procedure impacts product quality.

For this reason, the main considerations are donor experience and potentially donor safety.

Factors which influence the duration of the procedure include the target plasma volume to be collected and the draw rate, as well as donor attributes (calibre of the vein, haemoglobin/haematocrit, total blood volume, hydration status).

Australian Red Cross Lifeblood conducted a review on whether donors with a longer collection time have a higher rate of adverse events. Data were analysed for females, noting that females in general have a higher rate of vasovagal reactions. These data did not support a need to terminate the collection on the basis of time specifically. The analysis found that 0.72 % of collections had a procedural length time that was more than 3SD above the mean collection time. This group accounted for 0.6 % of vasovagal reactions.

In conclusion, there is no convincing evidence that a maximum plasmapheresis procedure time is required from a donor safety or product quality perspective.

The following words were added:

"There is no published evidence that a maximum plasmapheresis procedure time is required from a donor safety or product quality perspective. Blood establishments may choose to set a maximum procedure limit for donor experience and operational reasons, such as to assist with the timing of donor appointments."

3. **Management of adverse reactions in donors**

The Guide currently states the following: "In each collection facility, a specific space should be available for dealing with donors who have an adverse reaction".

There is the potential for additional donor harm if a donor who is experiencing an adverse reaction is moved to a dedicated area, for example, they may faint and fall.

For this reason, the following amendment was made:

In each collection facility, a specific space should be available for dealing with donors who have an adverse reaction. *"It is acceptable not to move the donor and instead manage the adverse reaction where it occurs; this reduces the potential for additional harm when moving a donor who is experiencing an adverse reaction to a specific space"*.

Chapter 7. Background Document

Blood components for topical use or injection

Prepared by Richard Forde. March 2024.

What the issues are

In recent years, novel preparations originating from blood components (autologous or allogeneic) have been used in various clinical situations. Examples include serum eye drops (SED) and several platelet preparations.

These blood components for topical use or injection have been described in the EDQM *Guide to the quality and safety of tissues and cells for human application* (Tissues and Cells Guide), but have not previously been considered for inclusion in the Blood Guide.

Recommendation for the 22nd edition of the Guide

It is proposed to include a new chapter on blood components for topical use or injection in the 22nd edition of the Blood Guide.

SED have become a commonly used therapy for dry eye treatment, as they offer potential advantages over traditional therapies. Using the 5th edition of the EDQM Tissues and Cells Guide[1] as a basis, a component monograph for SED has been included in this edition of the Blood Guide.

Platelet preparations, including platelet-rich plasma (PRP), platelet gel, platelet-rich fibrin (PRF) and platelet lysate eye drops are emerging products but their clinical efficacy remains uncertain. Furthermore, several techniques for the manufacture of platelet preparations are available, with each method yielding a different product with different composition of biologically active substances and potential uses.[1]

As a result, at this time, specific monographs for platelet preparations are not included in this edition of the Blood Guide. The description of platelet preparations provided in the 5th edition of the Tissues and Cells Guide is included in this background document for reference.

Reference

1. The Guide to the quality and safety of tissues and cells for human application (5th edition), European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM)[1]

1 https://www.edqm.eu/en/guide-to-the-quality-and-safety-of-tissues-and-cells-for-human-application1

Platelet preparations – 5th edition of the *Guide to the quality and safety of tissues and cells for human application*

Introduction

Platelet preparations are used in regenerative medicine as source of growth factors and cytokines for the treatment of soft and hard tissue lesions. Each growth factor is involved in a phase of the healing process, such as inflammation, collagen synthesis, tissue granulation and angiogenesis, collectively promoting tissue restitution.

The use of platelet preparations is an emerging field and its efficacy remains controversial. Several techniques for the preparation of platelet preparations are available; however, the results of applications have been confusing because each preparation method yields a different product with different composition of biologically active substances and potential uses. Platelet preparations have been prepared as platelet-rich plasma (PRP), platelet gel, platelet-rich fibrin (PRF) and platelet lysate eye drops, and they vary in consistency and in composition, for example in the concentration of growth factors and cytokines. Depending on the leukocyte and fibrin content, platelet preparations could be classified into four categories: pure platelet-rich plasma (P-PRP), leukocyte- and platelet-rich plasma (L-PRP), pure platelet-rich fibrin (P-PRF), and leukocyte- and platelet-rich fibrin (L-PRF) [1].

They are usually used in an autologous setting and can be prepared at the time of application. When they are prepared in advance and stored for future application, this should be done by a blood or tissue establishment. Allogeneic platelet preparations can be collected from healthy donors or produced from umbilical cord blood.

PRP is a concentrated source of autologous platelets, and it contains several different growth factors and other cytokines, in concentrations 5 to 10 times higher than in standard plasma; PRP is used to stimulate healing of soft tissue by injecting this concentrated plasma in the tissue where the healing effect is desired. There are primarily 3 isomers of platelet-derived growth factor (PDGF), namely αα, ββ and αβ, 2 transforming growth factors, TGF-β1 and TGF-β2, endothelial growth factor (EGF) and vascular epidermal growth factor (VEGF). PRP also contains proteins responsible for cell adhesion: fibrin, fibronectin and vitronectin [2]. The content of bioactive molecules depends on the production protocol [3]. All the products of this family can be used as liquid solutions or in an activated gel form. It can therefore be injected, for example in sports medicine, or placed during gelling on a skin wound or suture.

PRP is used to promote healing of injured tendons, ligaments, muscles and joints, and can be applied to various musculoskeletal problems. In addition to orthopaedics, other uses include dermatology, ophthalmology, plastic surgery and dentistry, including oral and maxillofacial surgery. As of 2020, no large-scale randomised, controlled trials have confirmed the efficacy of PRP as a treatment for musculoskeletal or nerve injuries, the accelerated healing of bone grafts or the reduction of androgenic hair loss.

The main advantages so far identified in platelet gel derived from umbilical cord blood (CBPG), as compared with platelet gel from adult platelets, relate to a different profile of growth factor concentrations, such as a higher content of VEGF and lower content of TGF-β in CBPG. Recent developments have led to a procedure in which cord blood platelet gel can be prepared, stored in a cryopreservation bag and applied to the skin ulcer without breaking the sterility chain [4].

Platelet-rich fibrin (PRF) is a second-generation PRP where autologous platelets and leukocytes form a strong natural fibrin matrix or three-dimensional scaffold. This 'scaffolding' helps localise the growth factors, essentially increasing their concentration at the desired location to guide tissue regeneration [5]. PRF has a dense fibrin network with leukocytes, cytokines and structural glycoproteins, as well as growth factors (e.g. TGF β1, PDGF, VEGF) and glycoproteins, such as thrombospondin-1. Leukocytes that are concentrated in PRF scaffold play an important role in growth factor release, immune

regulation, anti-infectious activities and matrix remodelling during wound healing. In addition, due to their elasticity and viscosity, these membranes adhere to the bone surface, acting as mechanical barriers against the penetration of the epithelium, which has faster regeneration potency than connective tissues [6].

Topical application of a platelet lysate, administered as eye drops, is an alternative therapeutic option for treatment of ocular surface disorders that do not respond to standard treatment [7]. The plasma component contains proteins essential for surface lubrication, whereas platelets provide growth factors (PDGF, EGF and TGF-β) and fibronectin that can promote ocular re-epithelialisation [8]. Eye drops comprising PRP have been used to treat dry eye syndrome for patients with Sjögren disease, and ocular chronic graft-versus-host disease (cGvHD) [9], and are used during macular hole surgery. So far, only studies of small case series have been published exploring the use of platelet preparations in ophthalmology, and further large-scale studies are necessary to demonstrate efficacy.

Donor evaluation

In the case of autologous donation, special attention should be paid to the status of donor's coagulation systems. The use of autologous platelet preparations avoids the ethical and legal implications of exposing the patient to the risks (albeit low) of transmission of blood-borne pathogens, although the risk of infection related to contamination during collection and handling still remains. Disadvantages of autologous products include a larger individual variability in the quality of platelet preparations compared with allogeneic products that are prepared from healthy donor blood through standardised working procedures.

Procurement and processing

Depending on the type of platelet preparations, they can be prepared from whole blood or from apheresis product, or by using other methods of collection, such as small volume bags, tubes or various types of medical devices. Different blood volumes can be used, but the volume of anticoagulant should be proportional to the amount of blood collected. All manipulations during processing carried out in open system must be performed under aseptic processing.

Procurement and processing of platelet-rich plasma

For the preparation of PRP, the blood is drawn with the addition of an anticoagulant, such as citrate dextrose A (ACD-A), to prevent platelet activation prior to its use. The platelets are separated from other blood cells using the two-step centrifugation method. A 30 mL venous blood draw will yield 3-5 mL of PRP, depending on the patient's baseline platelet count, the device used and the technique employed. An initial centrifugation separates red blood cells from PRP, and is followed by a second centrifugation that concentrates platelets in 3-5 mL of the final plasma volume.

After the first centrifugation step, the whole blood is separated into three layers: an upper layer that contains mostly platelets and white blood cells, an intermediate thin layer that is known as the buffy coat and is rich in white blood cells, and a bottom layer that consists mostly of erythrocytes. To produce pure PRP, the upper layer and superficial buffy coat are transferred to an empty sterile tube. The second centrifugation process should be adequate to generate the formation of soft platelet pellets at the bottom of the tube. The upper portion of the volume, composed mostly of platelet-poor plasma, is removed. Platelet pellets are re-suspended in the lower third part of plasma to create the PRP.

Many automated systems for the preparation of PRP facilitate the preparation of ready-to-apply platelet-rich suspensions in a reproducible manner and are commercially available. These systems widely differ in their ability to collect and concentrate platelets, depending on the method and time of its centrifugation. As a result, suspensions of different concentration of platelets and leukocytes are

obtained. Differences in the concentrations in platelets and white blood cells influence the diversity of growth factors concentration.

Procurement and processing of platelet-rich fibrin

For the preparation of PRF, a sample of blood is collected from the patient in tubes without anticoagulant and the blood is immediately centrifuged. During centrifugation, the platelets are activated when the blood contacts the tube wall.

The duration of time between blood collection and centrifugation is an important factor affecting the success and clinical outcome of this procedure. The majority of PRF preparation protocols recommend immediate (within 2 minutes of collection) centrifugation after blood collection. Delay in centrifugation will result in diffuse polymerisation of fibrin, leading to the formation of a small blood clot with irregular consistency. Therefore, a reproducible protocol for PRF production should be followed to obtain a clinically usable fibrin clot with substantial enmeshment of platelets.

After centrifugation, the uppermost of the three layers consists of acellular platelet-poor plasma, the PRF clot is in the middle layer and red blood cells are at the bottom of the tube. After centrifugation, the fibrin clot is removed from the tube and any attached red blood cells are scraped off and discarded.

PRF can also be applied as a membrane; the membrane can be formed in different shapes by squeezing out the fluids present in the fibrin clot using, for example, the stainless steel PRF compression device composed of two spoon-shaped parts [10].

Procurement and processing of platelet lysate eye drops

Platelet lysate eye drops are prepared using PRP after freezing–thawing at a final dilution of 30 %. A volume of 40 to 60 mL of peripheral blood anticoagulated with anticoagulant citrate dextrose solution A (ACD-A) is collected and centrifuged to obtain an autologous PRP. The platelet preparation is afterwards exposed to thermal shock by freezing at – 60 ° to – 80 °C for at least 60 min and then thawing to induce platelet lysis. The lysate can be diluted with sterile saline solution, and aliquoted into defined doses. A sample for microbiological control must be taken at the end of the processing (see Chapter 11 – 5th edition of Tissues and Cells Guide). The final product is then frozen again at – 15 °C and stored in a freezer. Patients are usually provided with a monthly supply of doses and trained how to thaw the dose, store it for the day from to 2 to 8 °C and safely instil eye drops.

Quality control

The quality of platelet preparations could be evaluated according to platelet recovery and growth factor contents. Further investigations are required to define standardised protocols for the preparation of high-quality platelet preparations suitable for different clinical applications, thus making it possible to compare results [11].

It is recommended that, if the platelet preparations are going to be stored, tissue establishment should have a microbiological testing protocol and acceptance/rejection criteria, similar to other cell and tissue products.

Biovigilance

Studies that have evaluated the topical use of platelet preparations have shown that the application is safe, and no serious adverse events were observed [12, 13]. According to a current literature search on platelet preparations use, there is no evidence of systemic effects that might limit the use of platelet preparations, provided that the possible risk of infections is excluded [1]. Few randomised controlled trials have reported adverse events after injection of platelet product; where these occur, they are mostly local side effects related to venepuncture required for blood collection or (rarely) bad scarring or calcification at the application sites after injection of platelet product.

References

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2. Lacci KM, Dardik A. Platelet-rich plasma: support for its use in wound healing. *Yale J Biol Med* 2010;**83**(1):1-9.
3. De Pascale MR, Sommese L, Casamassimi A *et al.* Platelet-derivatives in regenerative medicine: an update. T*ransfus Med Rev* 2015;**29**(1):52-61.
4. Rebulla P, Pupella S, Santodirocco M *et al.* Italian Cord Blood Platelet Gel Study Group. Multicentre standardisation of a clinical grade procedure for the preparation of allogeneic platelet concentrates from umbilical cord blood. *Blood Transfus* 2016;**14**:73-9.
5. Naik B, Karunakar P, Jayadev M *et al.* Role of platelet rich fibrin in wound healing: a critical review. *J Conserv Dent* 2013;**16**(4):284-93.
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8. Hartwig D, Harloff S, Liu L *et al.* Ephiteliotrophic capacity of a growth factor preparation produced from platelet concentrate on corneal epithelial cells: a potential agent for the treatment of ocular surface defects? *Transfusion* 2004;**44**:1724-31.
9. Zallio F, Mazzucco L, Monaco F *et al.* A single-center pilot prospective study of topical application of platelet-derived eye drops for patients with ocular chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2016;**22**:1664-70.
10. Kobayashi M, Kawase T, Horimizu M *et al.* A proposed protocol for the standardized preparation of PRF membranes for clinical use. *Biologicals* 2012;**40**(5):323-9. https://doi.org/10.1016/j.biologicals.2012.07.004.
11. Aprili G, Gandini G, Guaschino R *et al.* SIMTI Working Group. SIMTI recommendations on blood components for non-transfusional use. *Blood Transfus* 2013t;**11**:611-22.
12. Picardi A, Lanti A, Cudillo L *et al.* Platelet gel for treatment of mucocutaneous lesions related to graft-versus-host disease after allogeneic hematopoietic stem cell transplant. *Transfusion* 2010 Feb;**50**(2):501-6.
13. Pezzotta S, Del Fante C, Scudeller L *et al.* Long-term safety and efficacy of autologous platelet lysate drops for treatment of ocular GvHD. *Bone Marrow Transplant* 2017 Jan;**52**(1):101-6.

Chapter 12. Background Document

Haemovigilance

Prepared by Betina Samuelsen Sørensen and Rada M. Grubovic Rastvorceva. March 2024.

Introduction

Chapter 12 in the Blood Guide provides guidance on haemovigilance. The chapter was generally revised and updated.

Proposal

The chapter has been totally restructured. The new structure of the chapter is as follows:

- 12.1 Introduction
  - 12.1.1 Setting up an effective haemovigilance system
  - 12.1.2 Guiding principles of haemovigilance
  - 12.1.3 Haemovigilance co-operation and communication
- 12.2 Traceability of blood components
- 12.3 Definitions and categorisation
  - 12.3.1 Definitions
  - 12.3.2 Adverse reactions
  - 12.3.3 Adverse events
  - 12.3.4 Near misses
  - 12.3.5 Severity information
  - 12.3.6 Imputability information
- 12.4. Management of haemovigilance
  - 12.4.1 Detection/identification
  - 12.4.2 Initial reporting/notification
    - Standardisation of reporting
    - Post-transfusion infection reported to the blood establishment
  - 12.4.3 Investigation
    - Root-cause analysis
  - 12.4.4 Corrective and preventive actions
  - 12.4.5 Final report/Final notification to competent authorities
  - 12.4.6 Rapid alert system for blood and blood components
- 12.5 Data management
  - 12.5.1. Data collection
- 12.6 Epidemiology and surveillance

The purpose of the new structure is to provide a more logical pathway for a guideline on haemovigilance. In the revision of the chapter the text from the 21st edition of the Blood Guide has been reused as far as possible. New topics have been added to the chapter and some topics were further elaborated. Standards from the 21st edition of the Blood Guide have not changed. One new standard has been added (see the Change Log for more details). The number of this chapter was changed from 10 to 12, due to the introduction of a new Chapter 7 and moving this chapter after the chapter on *Elements for a quality system on the clinical use of blood*.

Supporting evidence

1. World Health Organization. User guide for navigating resources on stepwise implementation of haemovigilance systems, WHO, 2022 https://iris.who.int/bitstream/handle/10665/360060/9789240047860-eng.pdf?sequence=1.

   Justification:

   Used in section 12.1.

   This document gives guidance on developing a haemovigilance system and outlines the necessary steps in that regard. This is the background for 12.1.2.

2. World Health Organization. A guide to establishing a national haemovigilance system, WHO, 2016 https://iris.who.int/bitstream/handle/10665/250233/9789241549844-eng.pdf?sequence=1.

   Justification:

   Used in sections 12.1 and 12.4.

   This document provides a good overview of elements in haemovigilance and can be helpful for strengthening an existing system.

3. Global Consultation on Haemovigilance, WHO, SBTRC and Government of UAE, IHN, ISCT, 2022 https://cdn.who.int/media/docs/default-source/biologicals/blood-products/document-migration/conceptpaperglobalhaemovigilanceconsultationnov2012.pdf?sfvrsn=34523366_3.

   Justification:

   Used in sections 12.1 and 12.4.

   The introductory text in this document is used as the background for section 12.1 as an introduction to haemovigilance and in section 12.4 as an introduction to the different stakeholders in the management of haemovigilance.

4. Incident Analysis Collaborating Parties. Canadian Incident Analysis Framework. Edmonton, AB: Canadian Patient Safety Institute; 2012. https://www.healthcareexcellence.ca/media/gilnw3uy/canadian-incident-analysis-framework-final-ua.pdf.

   Justification:

   Used in sections 12.1 and 12.4.

   This is a resource document to learn from patient safety incidents with the goal of increasing the effectiveness of analysis in enhancing the safety and quality of patient care. Lessons from this document are also useful in haemovigilance.

5. European Union: Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. Official Journal of the European Union 8.2.2003:L33/30.

   Justification:

   Used in sections 12.1, 12.4 and 12.5.

   Legally binding document for EU member states.

6. European Union: Commission Directive 2005/61EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events. Official Journal of the European Union 1.10.2005: L256/32.

Justification:

Used in sections 12.2, 12.3, 12.4 and 12.5.

Legally binding document for EU member states.

7. Standard for Surveillance of Complications Related to Blood Donation, Working Group on Donor Vigilance of the International Society of Blood Transfusion Working Party on Haemovigilance. ISBT, IHN and AABB, 2014

https://www.aabb.org/docs/default-source/default-document-library/resources/donor-standard-definitions.pdf.

Justification:

Used in section 12.3.

This is a commonly accepted standard, written and published by ISBT, IHN and AABB. It is therefore mentioned in the Guide as one possible standard for definitions, among several that can be used.

8. Severity Grading Tool for Blood Donor Adverse Events, AABB Donor Hemovigilance Working Group. AABB, 2018

https://www.aabb.org/docs/default-source/default-document-library/resources/severity-grading-tool-for-donor-adverse-events.pdf?sfvrsn=ff563263_4.

Justification:

Used in section 12.3.

These definitions are easy to use and follow. In comparison to severity grading designed for patients, which are commonly referenced, this grading tool is specifically designed for donors. Donors are healthy as a prerequisite and therefore any impact, even if minor, should be considered when grading severity.

9. ISBT, Proposed standard definitions for surveillance of non-infectious adverse transfusion reactions, ISBT, 2011. EN 2011 ISBT PROPOSED STANDARD DEFINITIONS FOR SURVEILLANCE OF Non-infectious adverse transfusion reactions | The International Society of Blood Transfusion (ISBT) (isbtweb.org).

Justification:

Used in section 12.3.

This is a commonly accepted standard, written and published by ISBT, IHN and AABB. It is therefore mentioned in the Guide as one possible standard for definitions, among several that can be used.

10. Land KJ, Townsend M, Goldman M *et al*. International validation of harmonized definitions for complications of blood donations. *Transfusion* 2018;58(11):2589-95. DOI:10.1111/trf.14948.

Justification:

Used in section 12.3.

The definitions from ISBT (ref. 5) provide adequate coverage of donor reactions; however, some terms require clarification. Severity grading and imputability and other optional terms need clear and objective definitions and instructions on when and how to use them.

11. Common approach for definition of reportable serious adverse events and reactions (SARE) as laid down in the Blood Directive 2002/98/EC and Commission Directive 2005/61/EC, version 2023, European Commission Directorate-General for Health and Food Safety, Brussels, Belgium.

Publicly available at: https://health.ec.europa.eu/system/files/2023-10/btco_2023_blood_common-approach_en.pdf

Justification:

Used in section 12.3 and Table 12-1.

This document is a recommendation for EU member states but is not legally binding. It gives guidance on the reporting of SARE and is structured as follows: scope of reporting, guidance on reportable serious adverse reactions and guidance on reportable serious adverse events.

12. Aide-mémoire produced by the Service Organization and Clinical Interventions unit, Department of Service Delivery and Safety, World Health Organization, Geneva, Switzerland (WHO/HIS/SDS/2015.10).

Justification:

Used in section 12.4.

Provides guidance on effective leadership and governance for the development of a sustainable national blood system.

13. European Commission Directorate General for Health and Food Safety. Rapid Alert system for human Tissues and Cells (RATC) and for human Blood and Blood Components (RAB), Summary of 2022 activities, European Commission.

Justification:

Used in section 12.4.

Legally binding document for EU member states.

14. National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol, CDC, February 2023.

Justification:

Used in section 12.4.

Provides an overview of haemovigilance practices used in the USA.

15. Investigating Incidents: a systems-based approach, SHOT Bite No.1(a), February 2021, SHOT, www.shotuk.org.

Justification:

Used in section 12.4.

Provides a good overview of investigating incidents.

16. Biovigilance, Guide to the quality and safety of tissues and cells for human application, EDQM, 5th edition, 2022.

Justification:

Used in sections 12.1, 12.3 and 12.4.

Chapter 17 in the Tissues and Cells Guide provides general guidance on implementation of good vigilance. For categorisation and definitions, blood and tissues/cells are similar in that they are both substances of human origin and within a few years will be covered by the same EU legislation.

17. Biovigilance, Guide to the quality and safety of organs for transplantation, EDQM, 8th edition, 2022.

Justification:

Used in sections 12.4 and 12.6.

An active surveillance system should monitor all follow-up, not only some specific expected serious reactions or events. When a surveillance system is implemented, periodic analyses can show if there is an upward trend of SAREs, AEs or ARs, more or less systematically occurring and expected. Those should be reported to the Health Authority, a root-cause analysis should be initiated and corrective measures should be implemented.

18. Politis C, Vuk T, Richardson C *et al.* The role and importance of epidemiology in transfusion medicine. *Transfus Clin Biol* 2024, ISSN 1246-7820, https://doi.org/10.1016/j.tracli.2024.01.004.

Justification:

Used in section 12.6.

For the blood transfusion field, surveillance systems include not only transfusion-transmissible infections and donor behaviour posing a risk to blood safety, but also the serious adverse reactions and events associated with blood donation and blood transfusion.

19. Laperche S, Pillonel J. Influence of epidemiological factors on blood transfusion. ISBT Science Series. 2007;2:78-84. https://doi.org/10.1111/j.1751-2824.2007.00064.x.

Justification:

Used in section 12.6.

The prevalence, incidence and risk factors of infectious diseases observed in the general population have been described to directly influence transfusion medicine, especially blood selection. The objective is to ensure blood safety. The characterisation of modes of transmission influences donor selection: the risk factors of the main blood-borne infections have permitted the pre-donation questionnaire to be adapted to exclude at-risk donors. The prevalence of infections also has an impact on the blood screening strategy.

20. Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European centre for disease prevention and control, amended on 26/12/2012.

Justification:

Used in section 12.6.

Eurosurveillance is a European peer-reviewed scientific journal published by ECDC, with weekly publication, not a result of ECDC's daily activities in monitoring trends in communicable diseases.

Chapter 13. Background Document

Blood supply contingency and emergency plan

Prepared by Richard Forde. March 2024.

What the issues are

Contingency planning and emergency preparedness are key elements of a blood system. It is essential to ensure that when faced with emergencies, a safe and adequate supply of blood can be maintained and made available for all essential transfusions.

Contingency planning ensures that, when faced with disruptions, the capability of the blood system to continue the delivery of blood, blood components and associated services is maintained.

Emergency preparedness is the retaining of plans through which a blood system manages the impact of an unexpected event, which enables it to provide the required blood, blood components and associated services to the healthcare community throughout the ongoing emergency/disruption.

Contingency planning and emergency preparedness are fundamental for blood establishments to be able to react in an efficient and adequate way to a sudden emergency situation or an emerging issue that may result in a disruption of the blood supply. Having defined plans in place can ensure a shortened response time and enable fast and accurate mitigation strategies that lay the foundations for blood supply continuity in emergency situations to be put in place.

The inclusion of standards and supporting guidance in the Blood Guide is of the utmost importance to facilitate contingency arrangements and blood supply back-up with the aim of ensuring the continuity of blood supply.

Recommendations (for the 22nd edition of the Guide)

It was proposed to utilise the deliverables of the EDQM Blood Supply Contingency and Emergency Plan (B-SCEP) Project [1, 2] to include a new chapter in the Blood Guide, which will include supporting guidance on contingency and emergency planning.

Specifically, the new chapter will integrate the general recommendations for establishing, implementing and maintaining a B-SCEP and the specific recommendations for member states, blood establishments and hospital blood banks. A reference to the B-SCEP Model Preparedness Plan will also be included to assist national bodies, blood establishments and hospital blood banks in the development of appropriate blood supply contingency and emergency plans.

Blood Supply Contingency and Emergency Plan (B-SCEP) Project[1]

The EDQM B-SCEP Project was started in 2019 with final deliverables produced in 2022. It aimed to strengthen national plans to ensure the continuity of the blood supply in emergency situations, developing strategies to support European countries in this regard.

1 https://www.edqm.eu/en/blood-supply-contingency-and-emergency-plan-b-scep-

The objectives were to identify and assess the existing interventions and actions implemented at national level to ensure continuity of the blood supply in an emergency and establish the need for guidance or a standardised toolkit on contingency planning and emergency preparedness.

The project produced three deliverables: a **Survey Report**, a set of **Recommendations** and a **Model Preparedness Plan**.

The survey was conducted among the members of the European Committee on Blood Transfusion (CD-P-TS) and representatives of the National Competent Authorities for blood of the EU member states via DG-SANTE. It aimed to gather information on the existing national-level frameworks and contingency/emergency measures in place for the blood supply among European countries.

The recommendations aim to provide support for European countries in establishing, implementing and maintaining a B-SCEP. They include general recommendations on the key aspects of a B-SCEP, followed by specific recommendations for key stakeholders of the national blood system in order to ensure preparedness when faced with emergency situations.

The Model Preparedness Plan aims to assist in the development of a B-SCEP by:

- providing a template which aids in the structuring of key elements of the blood system in relation to an emergency response;
- assisting in defining the organisational structure and the blood supply chain of the blood system;
- providing a guided risk assessment tool to:
  - help define relevant key risk scenarios (what);
  - identify key stakeholders (who) for each key risk scenario;
  - decide how and when the key stakeholders should operate and interact with each other.

From this, action and mitigation plans based on the overall impact on the blood supply can be tailored accordingly, to accommodate individual blood systems.

The Model Preparedness Plan can be applied to any blood system, irrespective of its organisational setting, and it can be inclusive of all main stakeholders. The standardised B-SCEP format provided by the Model Preparedness Plan facilitates intercountry, interregional and local contingency collaboration between different blood systems.

References

1. European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe. Blood Supply Contingency and Emergency Plan (B-SCEP) Survey Report
2. European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe. Blood Supply Contingency and Emergency Plan (B-SCEP) Recommendations and Model Preparedness Plan