Brazilian Health Regulatory Agency

National Hemovigilance Guidelines
Brazil 2015

Brasília, 2015

Deputy director-president

Jaime César de Moura Oliveira

Directors

Ivo Bucaresky
José Carlos Magalhães Moutinho
Renato Alencar Porto

Superintendence of Surveillance, Control and Monitoring – Sucom
Eduardo Hage Carmo (superintendent)

General Management of Monitoring of Products Subject to Sanitary Surveillance
Maria Eugênia C. Cury (general manager)

Management of Risk Monitoring
Patrícia Fernanda Toledo Barbosa (manager)

Development:
Permanent Commission of Hemovigilance and subgroups

Andressa Honorato de Amorim
Auristela Maciel Lins (final draft)
Bárbara de Albuquerque Berçot
César de Almeida Neto
Eugênia M. Amorim Ubiali
Geni Neumann N. de Lima Camara
Gerson Fernando Mendes Pereira
Gil Cunha De Santis
Glória Regina Gama de Souza
José Francisco Comenalli Marques Júnior
Lydia Márcia de Melo França
Marcelo Addas Carvalho
Marcelo Augusto Nunes Medeiros
Maria Esther Jurfest Rivero Ceccon
Maria Eugênia C. Cury
Maria de Fátima Alves Fernandes
Maria Inês Vasconcelos Lopes Ferreira
Marília Rodrigues Mendes
Merula Steagall
Paulo Fernando de Oliveira Carneiro Leão
Regina Lúcia Cardoso Botega
Renato Vieira Alves
Rita de Cássia Azevedo Martins
Rita de Cássia de Jesus Rocha
Ronaldo de Almeida Coelho
Youko Nukui

TABLE OF CONTENTS

ACRONYMS

ALG	Allergic reaction
AHTR	Acute immune hemolytic reaction
ALLO/PAI	Alloimmunization/Positive irregular antibody screening
Anvisa	Brazilian Health Regulatory Agency
APTR	Acute pain transfusion reaction
APTT	Activated partial thromboplastin time
CGSH/MH	General Coordination of Blood and Blood Derivatives/Ministry of Health
DHTR	Delayed hemolytic reaction
FNHTR	Febrile non-hemolytic reaction
G-CSF	Granulocyte colony-stimulating factor
GVHD	Graft versus host disease
HEMOS	Hemosiderosis with organ impairment
HPC-BM	Hematopoietic progenitor cells from bone marrow
HPC-PB	Hematopoietic progenitor cells from peripheral blood
HTR	Hypotensive Transfusion reaction
ISBT	International Society of Blood Transfusion
MD	Metabolic disturbances
NAT	Nucleic Acid Amplification Test
NHRS	National Health Regulatory System
PTP	Post-transfusion purpura
TA	Transfusion Agency
TACO	Transfusion-associated circulatory overload
TTBI	Transfusion transmitted bacterial infection
TAD	Transfusion-associated dyspnea
TANIHR	Transfusion associated non-immune hemolysis reaction
TR	Transfusion reaction

TRALI	Transfusion-related acute lung injury
TTID	Transfusion Transmitted Infectious disease
PHS	Public Health Surveillance
Visa	Local Regulatory Authority

LIST OF FIGURES

LIST OF CHARTS

INTRODUCTION

Hemovigilance is defined as a set of surveillance procedures covering the entire blood cycle, with the aim of obtaining and providing information about adverse events occurred in its different steps to prevent their occurrence or recurrence, improve the quality of processes and products and increase donor and recipient's safety. This document describes the new conceptual and operational framework for the National Hemovigilance System in Brazil.

To date, hemovigilance in the country has been organized in a way to monitor the adverse reactions that occurred during or after a blood transfusion, in other words, it was limited to the surveillance of transfusion reactions. In many countries, hemovigilance encompasses all the steps of the blood cycle, from the beginning of the blood donation process until the investigation of possible reactions after transfusion.

The purpose of this document is to define guidelines in order to expand the scope of hemovigilance in the country, by including the surveillance of adverse events that may occur in the entire blood cycle.

By blood cycle, one can understand the process that comprises all the technical procedures related to the steps of donor recruitment, selection and qualification; of processing, storage, transportation and distribution of blood components; of pre-transfusion and transfusion procedures.

The extension of hemovigilance to all these steps is justified by the importance that the occurrence of nonconformances or adverse events may have in the product quality and in donor or recipient's safety.

This document is organized in order to present concepts and procedures of hemovigilance formulated for each one of these steps. It is based on the regulations in force for the technical and health procedures of hemotherapy[1], that predict organizational instruments for the planning, monitoring, and control of the good practices of hemotherapy and patient's safety, such as the institution of the transfusion committee, the committee for the control of nosocomial infection and the nucleus of patient's safety. It is expected that this guide constitutes an important tool for the institutional practice.

The definitions presented here are mostly based on documents by the International Society of Blood Transfusion (2008, 2011), in order to allow the comparative evaluation between different institutions and other hemovigilance systems.

[1] The respective quotations will appear in the development of this document.

CHAPTER I: DONOR HEMOVIGILANCE

Introduction

Although most of blood donations happen without any complication, occasionally some donors may present reactions. The adverse reaction to donation is defined as an unintentional response of the donor, associated with the collection of the blood unit, blood component or hematopoietic progenitor cells, which is life-threatening or results, or not, in death, deficiency or temporary disabling conditions, need for medical or surgical intervention, prolonged hospitalization or morbidity, among others.

These reactions can be classified in relation to:
1) time of occurrence;
2) severity;
3) Imputability to donation;
4) type of donation;
5) extension, local and systemic reactions, that will be commented within the classification related to the type of donation.

1. Classification of reactions related to time of occurrence

1.1. Immediate reaction

It is the one that occurs before the donor leaves the blood establishment.

1.2. Delayed reaction

It is the one that occurs after the donor has left the blood establishment.

2. Classification of reactions related to severity

The classification of adverse reactions related to donation can be seen in Chart 1.

Chart 1 – Classification of adverse reaction related to donation.

Classification	*Description*
Grade 1 - Mild	When there is a sign/local symptom, with no pain that stops donor from performing his/her habitual activities or that persists until two weeks; or systemic reactions with subjective symptoms with rapid recovery (less than 30 minutes), such as dizziness, nausea, discomfort, pallor.
Grade 2 - Moderate	When there is local symptom that stops donor from performing his/her habitual activities or that persists for more than two weeks; or systemic reactions with objective symptoms, such as loss of consciousness, hypotension with need for volume replacement and tetany.
Grade 3 - Severe	When there is need for hospitalization*, due to reaction, or need for intervention to prevent permanent damages, impairment of a body function or prevent death; or when there is the presence of symptoms that persist for more than one year after donation (long-term morbidity).
Grade 4 - Death	Death attributed to adverse reactions to donation.

*In the donation for allogeneic transplant, the following conditions that lead to hospitalization must be considered as severe reaction: (1) hospitalization for clinical/surgical reason at the collection of hematopoietic progenitor cells from peripheral blood; (2) prolongation of the donor's admission for more than 48 hours, for clinical/surgical reason, at the collection of hematopoietic progenitor cells from the bone marrow.

3. Classification of reactions related to the imputability to donation

The imputability between blood donations and reaction to donation can be seen in Chart 2.

Chart 2 - Imputability between donation and reaction to donation.

Imputability	Description
Confirmed (definite/certain)	When the investigation concluded that there is clear evidence (clinical/laboratory status, temporal relation) without a doubt about the imputability of the reaction to donation.
Likely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status, temporal relation) that indicates the imputability of the reaction to donation, but there are doubts for confirming it.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory/evolution status, temporal relation) that indicates the imputability of signs and symptoms to other causes, but the imputability of the reaction to donation cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status, temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.
Excluded*	When the investigation already concluded shows evidence (clinical/laboratory status, temporal relation) that clearly indicates the imputability of the adverse event to other cause(s) but not to donation.
Inconclusive	When the investigation already concluded has not found enough evidence (clinical/laboratory status, temporal relation) to confirm or exclude the imputability of the reaction to donation.

*Use this category to notify only in cases initially notified as other imputability, in which, after the conclusion of the investigation, the imputability to donation has been excluded.

4. Classification of adverse reactions related to the type of donation

4.1. Adverse reactions to whole blood donation

4.1.1. Local reactions

Local reactions present only local symptoms, directly caused by the insertion of the needle.

a) Reactions essentially characterized by blood extravasation

I. Hematoma

Definition: accumulation of blood in the tissues around the vessel punctured.

Signs and symptoms: local pain, discoloration, and edema. The higher the volume of extravased blood, the more intense the symptom.

II. Arterial puncture

Definition: results from the puncture of the artery at the time of the insertion of the needle.

Signs and symptoms: brighter red color of the blood donated, very rapid flow, time of collection in up to four minutes, pulsating movements in the needle, pain in the puncture site or weak referred pain in the elbow region.

Other possible complications of arterial puncture: hematoma, pseudoaneurysm, arteriovenous fistula, and compartment syndrome.

III. Post-donation bleeding

Definition: spontaneous beginning of bleeding from the puncture site, after the collection has been concluded and the bandage has been put on.

Signs and symptoms: bleeding from the puncture site.

b) Reactions mainly characterized by pain

I. Nerve irritation

Definition: irritation of a nerve by the pressure of the hematoma.

Signs and symptoms: radiating pain and/or paraesthesias associated with a hematoma. The hematoma may or not be visible when symptoms arise. Symptoms do not occur immediately after the insertion of the needle, but only when the hematoma reaches a sufficient dimension to compress the nerve.

II. Nerve injury

Definition: nerve injury by the needle at the insertion or withdrawal.

Signs and symptoms: sharp radiating pain, often associated with paraeshesia, occurring when the needle is inserted or withdrawn.

III. Tendon injury

Definition: tendon injury at the insertion or withdrawal of the needle.

Signs and symptoms: sharp pain in the insertion site, not radiating, beginning when the needle is inserted.

IV. Painful arm

Definition: mainly characterized by local sharp radiating pain in the arm used for donation, it arises during or hours after donation, but with no further details to allow its classification under one of the most specific categories mentioned above.

c) Other types of reactions with local symptoms

I. Thrombophlebitis

Definition: vein inflammation associated with thrombus.

Signs and symptoms: warmth, increased sensitivity, local pain, flushing, tumefaction, red firm subcutaneous cord with increased sensitivity.

II. Allergy

Definition: allergic reaction at the puncture site, caused by the solutions used in the procedures of antisepsis.

Signs and symptoms: skin rash, usually itching, at the puncture site.

4.1.2. Systemic reactions

Most of these are vasovagal reactions that can be triggered by psychological factors, such as anxiety, fear or apprehension, for seeing blood, or they can constitute a neurophysiological response to donation.

I. Vasovagal reaction

Definition: reaction secondary to the activation of the autonomic nervous system, stimulated by physiological factors, as well as by the volume of blood collected in relation to the total volume of donor's blood and by the speed of the collection.

Signs and symptoms: sensation of discomfort, anxiety and weakness, followed by dizziness, sweating, nausea with or without vomit, pallor, hyperventilation, decreased heart rate, slow pulse and hypotension. Depending on the severity of the reaction, symptoms can progress to loss of consciousness, tetany or convulsion. Accidents, often serious, may occur in consequence of the loss of consciousness.

II. Hypovolemia

Definition: decrease of the volume of circulating blood that may occur due to the excessive collection of blood, uncalibrated homogenizers and fails in the process, among others.

Signs and symptoms: hypotension, dizziness, malaise and weakness. The increase of heart rate is the main differential between hypovolemia and vagal reaction.

III. Fatigue

Definition: sensation of asthenia after donation. It is more frequently found in first-time donors and in women.

Symptoms: tiredness, weakness, and prostration.

4.2. Adverse reaction to donation of blood components by apheresis

The frequency of reactions among apheresis donors is lower than among whole blood donors. However, the rate of severe adverse reactions in apheresis donors is higher than in whole blood donors. Studies demonstrate a higher association of adverse events during donations by apheresis with low weight donor, with female donors and with the type of equipment used for collection.

The same reactions described for whole blood donation may occur in the donation by apheresis (item 4.1). Besides them, citrate toxicity, systemic allergic reaction and air embolism may occur. During the collection of granulocytes, reactions associated with the mobilization regimen and granulocyte sedimentation may also occur.

4.2.1. Adverse reactions exclusive to procedures of collection by apheresis

I. Citrate toxicity

Definition: reaction associated with adverse events of citrate, anticoagulant used in the collections by apheresis, associated with hypocalcemia, hypomagnesemia and increase of donor's blood pH.

Signs and symptoms: perioral paresthesia and in extremities, tingling, shivering, chills, abdominal pain, nausea and vomiting, hypotension, arrhythmia, tetany and convulsions, spams and muscle weakness, decrease of vascular tone and decrease of cardiac contractility and metabolic alkalosis.

II. Systemic allergy

Definition: systemic allergic reaction results from the release of vasoactive substances from mastocytes and basophils. It can be caused by ethylene oxide used in the sterilization of kits and by the sedimenting agent used for harvesting granulocytes.

Signs and symptoms: rash, periorbital edema, flushing, anaphylactic reaction, wheezing, lip swelling and hypotension.

III. Air embolism

Definition: reaction characterized by the infusion of air into the right ventricle and into the pulmonary artery, with obstruction of the right output and pulmonary vasoconstriction.

Signs and symptoms: cough, dyspnea, tachypnea, chest pain, tachycardia, psychomotor agitation, loss of consciousness, convulsions, hypotension, shock.

4.2.2. Adverse reactions resulting from cell mobilization in donors

Definition: adverse reactions related to the use of corticosteroids and/or granulocyte colony-stimulating factor (G-CSF) during the mobilization of donors for the collection of granulocytes.

Signs and symptoms: use of corticosteroids – headache, flushing, insomnia, euphoria, palpitations, epigastric hyperacidity and hyperglycemia; use of G-CSF – bone pain, myalgia, arthralgia, headache, fever, chills, gastrointestinal discomfort, paresthesia, chest pain and fatigue.

4.2.3. Adverse reactions related to the sedimenting agent

Definition: adverse reaction related to the use of hydroxyethyl starch which is used for the collection of granulocytes.

Signs and symptoms: itch, allergic reactions, hypertension and coagulopathies with decrease of fibrinogen and prolongation of activated partial thromboplastin time (APTT). It may provoke hyperamylasemia.

4.3. Adverse reactions to the collection of hematopoietic progenitor cells from peripheral blood and bone marrow for allogeneic or autologous use

The donation of hematopoietic progenitor cells from peripheral blood (HPC-PB) and from bone marrow (HPC-BM) are well-established procedures, performed by thousands of donors. Although donors and recipients are aware that these procedures are not risk free, all the community involved in the transplantation processes must maximize efforts in order to minimize risks to donors.

The collection of HPC-PB or HPC-BM can occur for allogeneic or autologous use. In the case of allogeneic transplantation, donor most of the time is a healthy individual. In autologous transplantation, donor and recipient fill in the same binomial. It is worth highlighting that, as being patients, underlying diseases and comorbidities may increase the occurrence of adverse reactions.

The Brazilian technical regulation establishes the operation of the laboratories of processing of hematopoietic progenitor cells from bone marrow and peripheral blood of placenta and umbilical cord blood banks for the purpose of conventional transplantation. However, it is worth underlining that the follow-up of donors in short, medium and long-term by the transplantation facility is necessary and desirable, particularly when it comes to those donors who have been mobilized with G-CSF, due to the oncogenic potential of this medication.

The adverse reactions of donors must be object of active search. Moreover, the informed consent must predict the potential risks of procedures of mobilization, collection and post-collection. The health regulation assigns to the blood establishement the responsibility to inform donor about the donation process, the risks involved, laboratory tests and other information needed for signing the informed consent term.

4.3.1. Types of adverse reactions related to the collection of HPC-PB

4.3.1.1. Related to cell mobilization: myalgia, fever, bone pain, thrombosis, cerebrovascular accident, myocardial infarction, splenic rupture or infarction, acute lung injury, and others.

4.3.1.2. Related to venous access

I. **Peripheral venous access:** comprises all the secondary reactions to the peripheral venous puncture, described in the previous item of this guide, regarding the whole blood donation.

II. **Central venous access:** infection, thrombosis, embolism, pneumothorax, hemothorax, other hemorrhages, etc.

4.3.1.3. Related to the apheresis procedure

The same ones described in this document for whole blood donation and the ones related to the procedures by apheresis.

4.3.2. Types of adverse reactions related to the collection of HPC-MO

The first point to be differentiated is whether the adverse reaction is related to the anesthetic or surgical procedure.

The adverse reactions related to the **anesthetic procedure** must be descriptive, in an open field.

The adverse reactions related to the **surgical procedure** must cover the following items: hypovolemia, acute anemia with need for blood transfusion, thrombosis, fat embolism, pathological fracture, nerve or vascular injury, infection, and others.

Chart 3 – Summary of possible adverse reactions to whole blood donation, donation of blood components by apheresis and of progenitor hematopoietic cells.

Whole blood donation	Donation by apheresis	HPC donation

1. Local reactions
• **Blood extravasation**
  • Hematoma
  • Arterial puncture
  • Post-donation bleeding
• **Pain**
  • Nerve irritation
  • Nerve injury
  • Tendon injury
  • Painful arm
• **Others with local symptom**
  • Thrombophlebitis
  • Allergy
2. Systemic reactions
• Vasovagal reaction
• Hypovolemia
• Fatigue
	1. The same as whole blood donation
	2. Exclusive to this procedure
	• Citrate toxicity
	• Systemic allergy
	• Air embolism
	3. Related to donor's cell mobilization
	• Signs and symptoms of G-CSF
	• Signs and symptoms of corticosteroid
	4. Related to the sedimenting agent
		1. HPC-PB
		• **Related to cell mobilization by G-CSF**
		• **Related to venous access**
		  • Peripheral: the same as whole blood donation
		  • Central:
		  • Systemic reaction (vasovagal, hypovolemia, fatigue)
		  • Infection
		  • Thrombosis
		  • Embolism
		  • Pneumothorax
		  • Hemothorax
		  • Other hemorrhages
		  • Others
		• **Related to the collection by apheresis (see donation by apheresis)**
		2. HPC-BM
		• **Anesthetic procedure**
		• **Surgical procedure**

5. Recording, communicating and notifying the adverse reaction associated with the collection of whole blood, blood components by apheresis, HPC-PB and HPC-BM for allogeneic and autologous use

The adverse reactions resulting from allogeneic or autologous donations, whether of whole blood or blood components by apheresis or hematopoietic progenitor cells, must be recorded at the facility where they occurred, as well as the corrective and preventive measures required (BRASIL, 2013a, art. 78, 165, 166 and 232; BRASIL, 2014a, art. 35, 36, 42, 45 and 146). Records shall be kept in compliance with the legislation in force and made available to competent authorities, whenever required (BRASIL, 2013a, art. 228 and 231; BRASIL, 2014a, art. 15).

Communication is the act of informing, by the fastest way, the parties interested in the adverse event and that need to initiate corrective and preventive actions. The communication of reactions to donation will be done to the health

authority and, when pertinent, to the suppliers of the inputs involved in the process (BRASIL, 2014a, art. 35).

Severe adverse reactions and deaths with confirmed, likely, possible, unlikely and inconclusive imputability, besides local record, shall also be notified to the health regulatory system (BRASIL, 2014a, art. 35 and 146). Excluded reactions will only be notified as rectification if they have been previously classified as other imputability to donation.

All the adverse events **related to process of mobilization with G-CSF, patient preparation and product collection** will be recorded at the facility where they occurred.

5.1. Deadlines for recording, communicating and notifying

Donor identification data, as well as the time elapsed between the adverse reaction and notification, must follow the notification protocols of other hemovigilance processes.

Records are internal and shall be performed according to the protocols of the facilities, when identifying any adverse event.

5.1.1. Communication and notification

Death: communication must be done within 24 hours from the occurrence, to the competent health authority and to suppliers of the inputs involved in the process, if any. The notification to the National Health Regulatory System must be given within until 72 hours (BRASIL, 2013b, art. 10, single paragraph).

Severe reactions: communication to the suppliers of the inputs involved in the process, when pertinent. The notification to the National Health Regulatory System must be given until the 15th business day of the month subsequent to the adverse event identification (BRASIL, 2013b, *caput* of art. 10). Flow chart 1 and Chart 4 present a summary of deadlines and actions.

Chart 4 – Actions and deadlines for recording, communicating and notifying severe adverse reactions and deaths resulting from the donation of whole blood, components by apheresis and HPC.

Actions	Recording	Communicating	Notifying
What	All events	• Death attributed to adverse reactions to donation.	• Severe reaction to donation with confirmed, likely, possible, unlikely and inconclusive imputability. • Death attributed to adverse reactions to donation with confirmed, likely, possible, unlikely and inconclusive imputability.
To whom	Internal records	To the competent health authority and, when pertinent, to suppliers of the inputs involved in the process.	National Health Regulatory System - SNVS
When	When detected	Within the first 24 hours.	Death: 72 hours (RDC 36/2013) Severe reaction: until **the 15th business day of the month subsequent** to the event identification.
How	Defined internally	Facsimile, telephone, electronic mean.	In a specific form, in the web based system of SNVS.

6. Post-donation information on adverse reaction

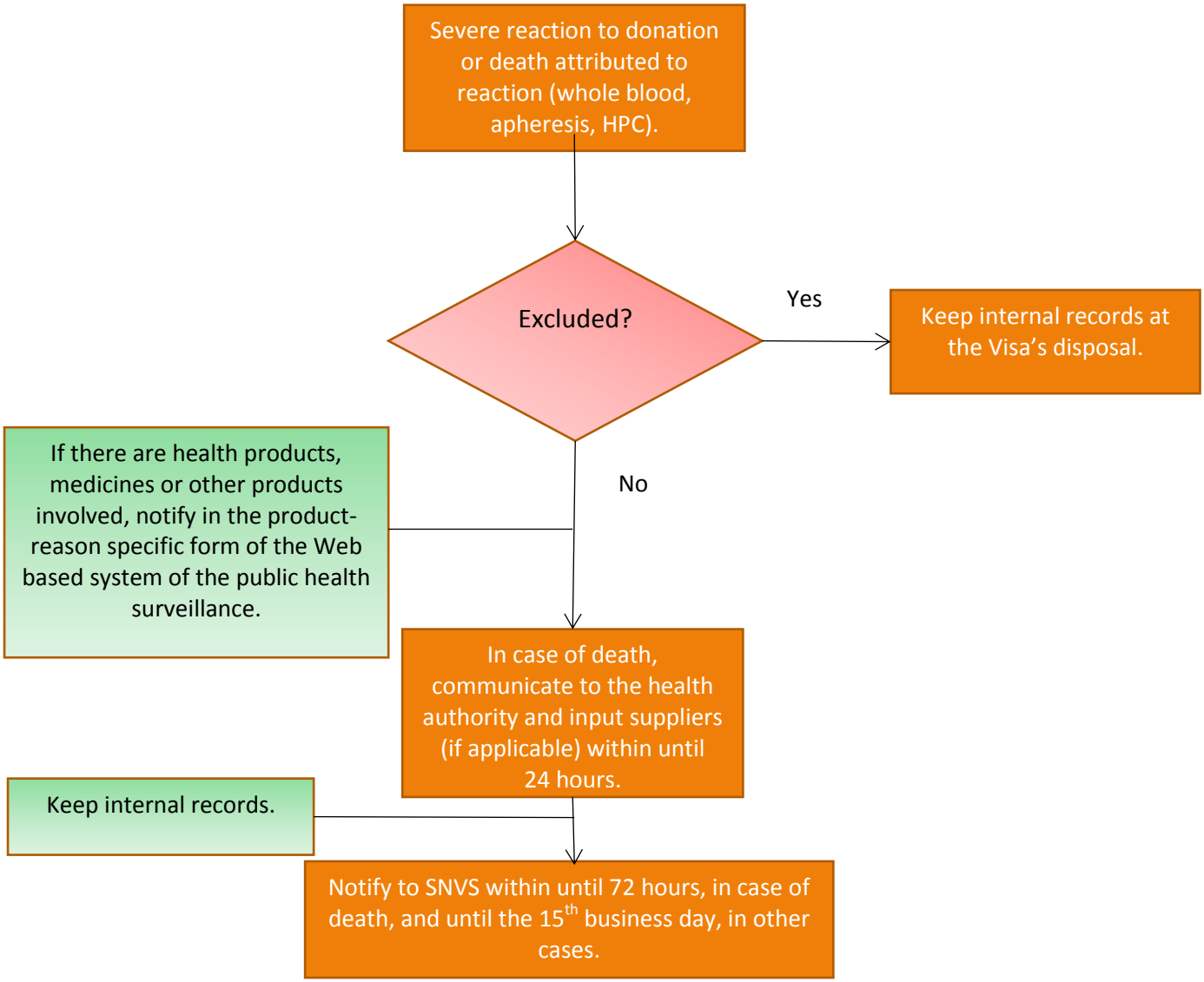
Blood establishments and bone marrow transplantation centers must provide information concerning the donation process (BRASIL, 2010, art. 38; BRASIL, 2013a, art. 33) and means for easy communication between donor and establishment. It is recommended that donors of whole blood, blood components by apheresis and hematopoietic progenitor cells from peripheral blood or bone marrow are advised to communicate to the blood or transplantation facility if they present any delayed adverse reaction, after the current donation. It is also important that the blood establishments include in their screening protocols questions for donors about they physical status on the days following the previous donation, especially for regular donors.

Blood and transplantation centers must record in the facility all the delayed adverse reactions related to the diverse donation processes, as well as the corrective and preventive measures applied. Records shall be kept, in accordance with the legislation in force, and made available to the competent authorities, whenever required.

Severe delayed adverse reactions and deaths correlated with donation, which can be confirmed, likely, possible, unlikely and inconclusive, in addition to local record, will be also subjected to notification to the public health surveillance system, in accordance with the standardization presented in this guide.

For allogeneic HPC donors, we recommend that a clinical evaluation is conducted according to the clinical guidelines of the National System of Transplantation.

Flow chart 1 – Communication and notification flow of the severe adverse reactions to the donation of blood, components by apheresis and hematopoietic progenitor cells and deaths attributed to donation.



CHAPTER II: ADVERSE EVENTS OF THE BLOOD CYCLE

Introduction

The adverse events of the blood cycle steps are covered in this chapter, with the exception of donation reactions and transfusion reactions, which are described in specific chapters.

It is considered adverse event of the blood cycle all and any adverse occurrence associated with their steps that may result in risk to donor or recipient's health, having or not as consequence an adverse reaction.

All adverse events of the blood cycle covered herein are:

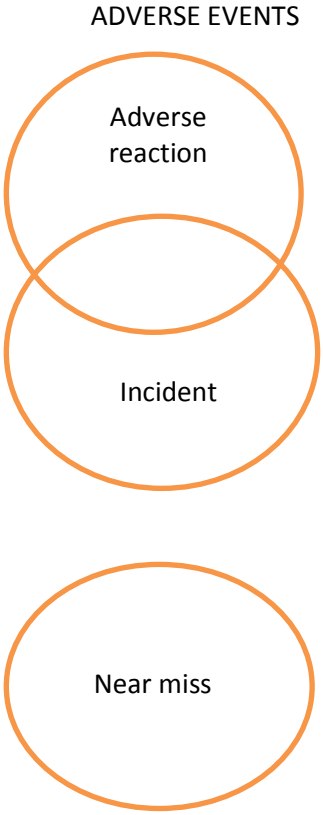
- **Incident** – the incidents are in the scope of the adverse events of the blood cycle, detected during or after transfusion or donation. They comprise, thus, deviations from operational procedures or from the individual's safety policies in the health or blood facilities, leading to inadequate transfusions or donations that may or not lead to adverse reactions. In case of transfusion, it occurs when an individual receives a blood component that does not meet all the requirements for a transfusion which is appropriate to him/her or that has been prescribed for someone else.

Therefore, the **incidents** can be classified as two types: those who led to adverse reactions and those that have not provoked them.

- **Near miss –** is the deviation from a standard procedure or policy detected before the start of the transfusion or donation, that could have resulted in a wrong transfusion, in a transfusion reaction or in a donation reaction.
- **Donation and transfusion reactions** – are damages, in varied grades, that affect the individuals of these actions. They may or not result from an incident of the blood cycle. The respective definitions are more particularized in the corresponding chapters.

Figure 1 makes a schematic representation of the adverse events of the blood cycle in which it is possible to visualize an intersection area between incidents and adverse reactions, representing the incidents that have led to them. This differentiation will be important for understanding the flow of record, communication and notification of the adverse events described later.

Figure 1 – Types of possible adverse events in the different steps of the blood cycle.



Source: ISBT, 2011.

The Brazilian legislation attributes to the blood and health facilities that perform transfusions the action of recording, investigating and reviewing the blood cycle procedures, as well as the corrective and preventive actions for all the nonconformances detected and their timely communication and notification to the health authority and to other parties involved (BRASIL, 2013a, art. 78, 116, 205, 239, 240, 246 and 247; BRASIL, 2014a, art. 9, 13, 15, 36, 69, 105, 106, 107, 119, 144, 146 and 147).

Therefore, the blood establishment must keep records of the adverse events detected in all the blood cycle steps, making it available for the analysis of the local regulatory authority or sending them, in a consolidated way, when required (BRASIL, 2013a, art. 231). With respect to hemovigilance, however, some serious adverse events have been selected for communication and notification to NHRS web based system (BRASIL, 2014a, art. 13).

For the purposes of this document, are classified as **serious adverse events of the blood cycle** the incident that has led to adverse reaction, the other incidents and near misses of repetitive and unusual nature and for which corrective and preventive actions have already been promoted.

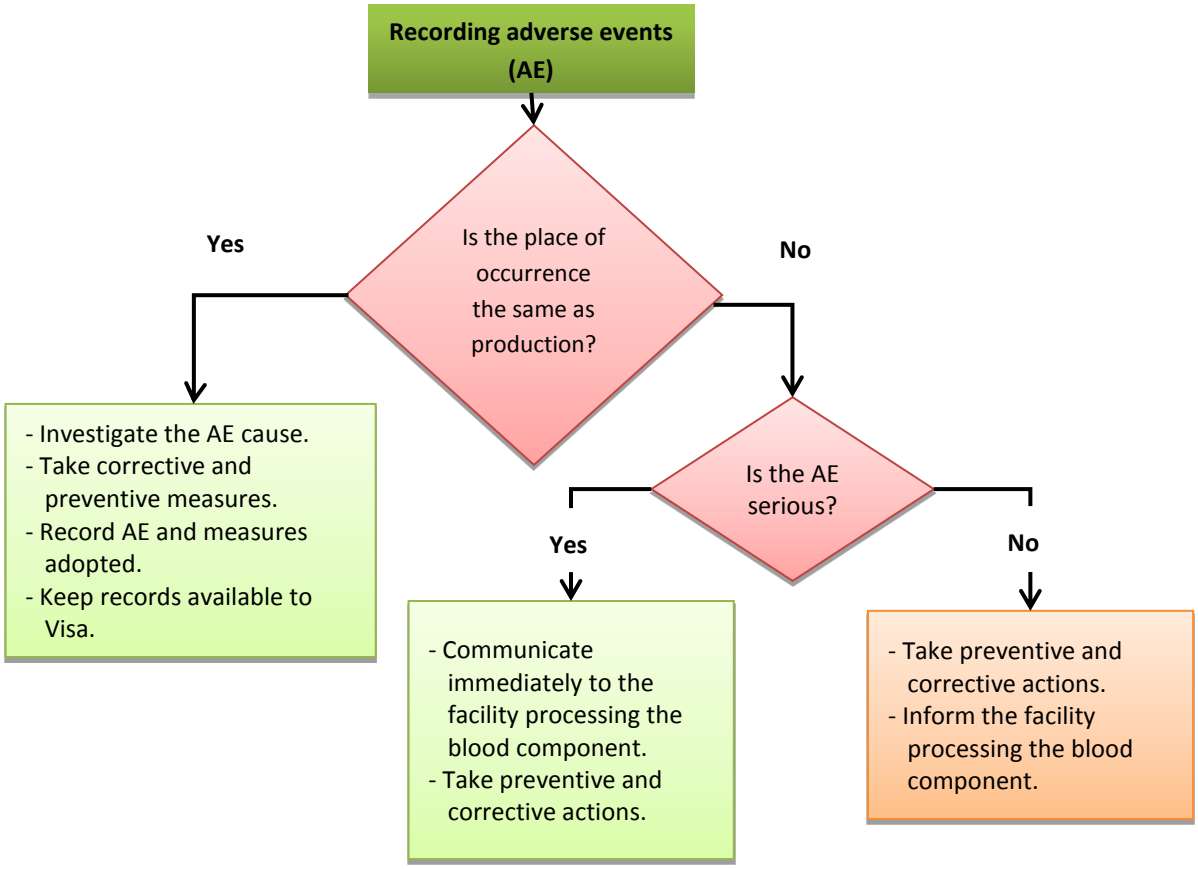
1. Flow of record, investigation, communication and notification of adverse events

1.1. Recording, investigating and communicating adverse events of the blood cycle

All the adverse events of the blood cycle must be recorded and investigated in the blood establishment or in the health facility where they occurred and must be available to the competent health authority (BRASIL, 2014a, art. 15). The local health authority will establish the periodicity for receiving the consolidated document containing the information. In case the event has not occurred in the establishment that produced the blood component, but in a health facility or in another establishment involved in the blood cycle, the blood component producer must be informed, including the corrective and preventive measures taken (BRASIL, 2013a, art. 205).

Serious adverse events shall be communicated within the first 72 hours to the blood establishment that produces the blood component. Flow chart 2 describes these procedures.

Flow chart 2 – Flow of the procedures of recording, investigating and communicating adverse events of the blood cycle.



1.2. Notification and communication of serious adverse events of the blood cycle

1.2.1. Notifying transfusion incidents

Incidents that provoke adverse reaction will be notified on the web based system of the health surveillance, in the scope of the notification of the reaction it has provoked. In these cases, the facility processing the blood component must also be communicated for taking appropriate corrective and preventive actions, as the case may be.

Serious incidents that have not provoked adverse reaction will be notified on the web based system of the health surveillance, in a specific form constructed and divulged by SNVS. Also in these cases, the facility processing the blood component will be equally communicated for taking appropriate corrective and preventive actions, as the case may be.

1.2.2. Notifying near misses

Serious near misses, in other words, those of repetitive or unusual nature or for which preventive and corrective actions have already been promoted, will be notified on the web based system of the health surveillance, in a specific form constructed and divulged by SNVS. The blood facility processing the blood component will be also communicated to review or take appropriate corrective or preventive actions, as the case may be.

Chart 5 summarizes the procedures for recording, communicating and notifying adverse events of the blood cycle, with the exception of the donation and transfusion reactions described in specific chapters.

Chart 5 – Guidelines for recording, communicating and notifying adverse events of the blood cycle.

<table>
<tr><th>Actions</th><th>Recording</th><th>Communicating</th><th colspan="3">Notifying</th></tr>
<tr><td rowspan="2">What</td><td rowspan="2">All events</td><td rowspan="2">Serious AE:
Incidents, in addition to repetitive and unusual near misses, for which corrective and preventive measures have already been taken.</td><td>Incident with adverse reaction</td><td>Serious incident with no adverse reaction</td><td>Serious near misses</td></tr>
<tr><td>All</td><td>Repetitive, unusual, for which corrective and preventive measures have already been taken.</td><td>Repetitive, unusual, for which corrective and preventive measures have already been taken.</td></tr>
<tr><td>To</td><td>Internal</td><td>To the competent</td><td>SNVS</td><td>SNVS</td><td>SNVS</td></tr>
</table>

whom	records	health authority and the processing facility.			
When	When detected	Within the first 72 hours of occurrence.	By the deadline for notifying the transfusion reaction	Until the 15th business day of the month subsequent to the event identification	Until the 15th business day of the month subsequent to the event identification
How	Defined internally – template proposed	Facsimile, telephone, electronic mean	In the act of notifying the transfusion reaction	In specific form of the SNVS web based system	In specific form of the SNVS web based system

Some examples of possible adverse events of the blood cycle are listed below. It is important to underline that the events listed below may include the said incidents and near misses of any severity. The aim is to help the process of identification and recognition of these adverse events. It is noteworthy to say that this is not a restrictive listing and other events might be identified by each establishment. All events shall be recorded, but the notification will follow the criteria established above.

2. Types of adverse events of the blood cycle

2.1. Related to donor recruitment, selection and qualification

2.1.1. Blood donor recruitment, register and selection

- Absence of policy with donors to minimize the risk of TRALI.
- Error in the identification of autologous for allogeneic donor.
- Error in the registration data of the candidates for donation.
- Not blocking the candidate considered definitely ineligible in previous donation.
- Inadequate/Insufficient guidance about donor selection criteria.
- Blood donor recruitment, register and selection out of the standards and rules not covered above.

2.1.2. Clinical and epidemiological screening

- Releasing the candidate to donation out of the requirements for donor selection.
- Not applying or partially applying the criteria established in the legislation.
- Not blocking the candidate ineligible in the screening.
- Not discarding the bag whose donor has self-excluded from the donation process.
- Clinical and epidemiological screening out of the standards and rules not covered above.

2.1.3. Donor blood collection

- Inadequate antisepsis at the puncture site in donor.
- Absence of homogenization of the blood component during collection.
- Collection of volume of blood and/or component out of the recommended for the preservative solution of the bag.
- Choice of inadequate site for the puncture.
- Lack of instructions to donor about post-donation care.
- Wrong identification of the unit of blood and/or samples for laboratory testing.
- Releasing donor after collection before the time recommended (at least 15 minutes).
- Handling of the puncture site after antisepsis.
- New puncture using the same material of the previous puncture.
- Exchange of labels containing the donation identification and donor's initials.
- Exchange of blood components and/or sample at the time of collection.
- Exceeded collection time.
- Blood collection out of the standards and rules not covered above.

2.1.4. Laboratory screening of the donor's sample

- Error in the input/record of results.
- Error in the identification of tubes collected and aliquots for the serum/plasma sample bank.
- Error in the identification of tubes received from other establishments.
- Error in the release of laboratory screening results.
- Error in performing the tests.
- Not blocking ineligible donors at the laboratory screening.
- Not performing immuno-hematological tests or performing these tests not complying with the legislation in force.
- Not performing immuno-hematological tests following the instruction manual of the reagent/kit manufacturer.
- Not performing serology/molecular biology tests in accordance with the legislation in force.
- Not performing serology/molecular biology tests following the instruction manual of the reagent/kit manufacturer.
- Use of inputs/reagents out of the standard (expiration, storage conditions, registration, and authorization).
- Laboratory screening of donor's sample out of the standards and rules not covered above.

2.2. Related to labelling, processing and qualification and storage

2.2.1. Labelling/Processing/Qualification

- Absence of a mechanism of traceability of units, including pool;
- Labels with no mandatory and visible information.
- Fail in the identification/labelling of irradiated/non-irradiated product.
- Fail in the quality control of the blood components produced.
- Fail in monitoring temperature throughout processing.
- Wrong identification of the donor's blood group in the blood components (labelling error).
- Processing out of the legal standards established.
- Other errors in labelling.

- Conducting the procedure using equipment in inadequate conditions: not qualified, no preventive/corrective maintenance and uncalibrated.
- Conducting the irradiation procedure in irradiator in inadequate conditions: not qualified, no preventive/corrective maintenance, no control of irradiation dosimetry.
- Labelling of the blood component with no double-checking or in a non validated electronic form.
- Use of inputs out of the standard (expiration, storage conditions, record, and authorization).

2.2.2. Storage of blood component

- Opening of the system.
- Storage of red blood cell concentrate in low temperatures.
- Storage in equipment in inadequate conditions: not qualified, no preventive/corrective maintenance and uncalibrated.
- Storage of blood component in temperatures not complying with the one recommended.
- Storage of inputs and reagents out of the legal standards established.
- Absence of specific areas for "released" and "not released" products.
- Discarded blood component not removed from the stock.
- Blood component returned and reintegrated into the stock without evaluating quality or not complying with the requirements established.

2.3. Related to transportation and distribution

2.3.1. Transportation of blood component

- Opening of the system.
- Time of transportation exceeding the capacity of the cold chain.
- Transportation of the capacity/packaging of blood components not complying with the legislation.
- Transportation in hygiene conditions out of the sanitary standards.
- Transportation with temperature monitoring not complying with the legislation.

2.3.2. Distribution of blood component

- Distribution of blood component after the expiration time.
- Distribution of blood component with wrong identification of the recipient.
- Distribution of blood component with other identification errors.
- Distribution of products without proper checking.
- Distribution of blood component with no monitoring of the entry and exit temperature.
- Distribution out of the legal standards established.
- Fail in the exit record of blood and/or blood component and in the identification of the destination sites in accordance with the legislation in force.
- Blood component reintegrated not complying with the procedures established.

2.4. Related to the transfusion procedure

2.4.1. Transfusion procedure

2.4.1.1. Order/prescription of blood component

- Wrong/illegible/incomplete identification data of the recipient at the transfusion order.
- Identification of the transfusion order not compliant with the identification of tubes of pre-transfusion samples.
- Prescription of blood components in volume and/or speed higher than the recipient's need or cardiac reserve.
- Prescription of non-irradiated blood components for recipient with indication to receive irradiated cell products.
- Order not compliant with the rules.
- Order with no data referring to the transfusion reactions that occurred in previous transfusions.

2.4.1.2. Recipient's identification

- Absence of mechanisms of positive identification in accordance with the legislation.
- Not performing recipient's positive identification at the time of sample collection/transfusion administration.

2.4.1.3. Collection and identification of recipient's sample

- Sample collected from wrong patient.
- Sample with patient's wrong/illegible/incomplete name.
- Sample without label.
- Sample without required information.
- Not performing recipient's positive identification at the time of sample collection.
- Other labelling errors.

2.4.1.4. Recipient's immuno-hematological tests

- Absence of register/alert mechanism for patients with results altered in previous tests.
- Errors in the input/record of results.
- Error in the interpretation of test results.
- Error in the release of immuno-hematological results.
- Technical error in performing tests.
- Not performing immuno-hematological tests in accordance with the legislation in force.
- Not performing immuno-hematological tests following the instruction manual of the reagent/kit manufacturer.
- Exchange of samples at the time of performing pre-transfusion tests.
- Use of reagents without performing daily quality control or at every lot/shipment
according to the parameter evaluated;
- Use of inputs/reagents out of the standard (expiration, storage conditions, registration and authorization).

2.4.1.5. Release of the blood component

- Fail in the inspection of the blood component, with release out of the parameters established.
- Release of the wrong type of blood component.
- Release of the wrong blood type.
- Release not compliant with the qualification order of the blood component (irradiation, leukoreduction, washing, aliquoting, apheresis, pool).
- Time of release of the blood component for transfusion out of the protocols pre-established in the institution, with damages to the recipient.

2.4.1.6. Pre-administration of the blood component

- Absence of a mechanism for checking the recipient's data with the identification data of the blood component.
- Inadequate thawing or warming of the blood component before transfusion.
- Not performing tests for recipient's phenotyping with alloantibody.

2.4.1.7. Administration of the blood component

- Administration of red blood cell concentrate under pressure.
- Administration of red blood cell concentrate inadequately warmed.
- Administration of red blood cell concentrate after expiration date.
- Administration of medication or non-physiological solution at the same venous line of the blood component.
- Administration of red blood cell concentrate irradiated 28 days after irradiation.

- Administration of red blood cell concentrate irradiated 14 days after collection and more than 48 hours after irradiation.
- Administration of hemolysed red blood cell concentrate.
- Administration of the blood component in high volume and high speed without monitoring/care to the levels of calcium.
- Administration of the blood component in a period of time longer than 4 hours.
- Wrong administration of the amount of blood component.
- Administration by wrong route.
- Absence of close follow-up in the first 10 minutes after the administration of the blood component and periodical monitoring until the end of the transfusion.
- Absence of records of vital signs before and after transfusion.
- Not performing recipient's positive identification at the time of transfusion administration.
- Not suspending the transfusion of the blood component in the presence of a severe transfusion reaction.
- Patient under chronic transfusion regimen without monitoring and/or without treatment of the iron overload.
- Autologous blood transfused into someone else.
- Transfusion of blood component not compliant with the order and/or transfused without order.
- Transfusion of blood component without indication, according to the organization protocols.
- Transfusion of blood component in which bacterial growth was detected.
- Transfusion of incompatible ABO blood component.
- Transfusion in wrong patient, but with compatible ABO.
- Transfusion in wrong patient, with incompatible ABO.
- Transfusion of co-component of blood component in which bacterial growth was detected.
- Transfusion of blood component with volume and/or speed higher than recipient's need or cardiac reserve.
- Transfusion of non-irradiated blood component to recipient with indication to receive irradiated cell products.
- Inadvertent transfusion of Rh incompatible blood component (Rh positive in Rh negative recipient).
- Inadvertent transfusion of other incompatible erythrocyte systems.
- Transfusion of the wrong blood product.
- Transfusion procedures out of the standards and rules not covered above.

CHAPTER III: HEMOVIGILANCE OF THE TRANSFUSION RECIPIENT

Introduction

Blood transfusion is a therapeutic method universally accepted and proved to be effective, especially if it is well-indicated. In relation to the type, transfusion can be classified as autologous and allogeneic, according to the definitions presented in Chart 6.

Chart 6: Classification and definition of transfusion types.

Type	Definition
Autologous	When the blood donor and the recipient are the same person.
Allogeneic	When the blood donor and the recipient are different people.

Even when properly indicated, blood transfusion may lead to adverse reactions. Transfusion reaction can be defined as a untoward effect or response observed in a person, timely associated with the administration of blood or blood component. It can be the result of an incident of the blood cycle or of the interaction between the recipient and the whole blood or blood component transfused, a biologically active product.

Transfusion reaction can be classified related to:

1. time of presentation of the clinical and/or laboratory picture;
2. severity;
3. imputability to transfusion;
4. reaction diagnosis.

1. Classification related to time up to the occurrence of clinical/laboratory status

The classification of the transfusion reaction (TR) related to time up to the occurrence of the clinical/laboratory status (signs and symptoms) is described and defined in Chart 7.

Chart 7 – Classification and definition of transfusion reactions related to time up to the occurrence of the clinical/laboratory status

Classification	Definition
Immediate	Occurrence of TR during transfusion or until 24 hours of its start.
Delayed	Occurrence of TR 24 hours after the start of the transfusion.

Besides the times of occurrence defined for each type of reaction addressed in this document, the maximum time to associate a certain clinical condition with transfusion is not determined. In general, reactions such as the transmission of diseases or sensitization to an alloantigen are only detected years after the suspected transfusion. There are works that show the occurrence of delayed hemolytic reactions until 90 days after transfusion. However, in the presence of clinical or laboratory status that may have as source a blood transfusion, the professional must use the diagnostic means available to clarify it, according to what was presented in the respective item of this document or in the medical literature.

2. Classification related to the severity of the transfusion reaction

The classification of the reaction related to severity is presented in Chart 8.

Chart 8 – Classification and definition of transfusion reactions related to severity.

Classification	***Definition***
Grade 1 – Mild	Not life-threatening. Medical intervention may be required, but the absence of intervention does not result in permanent damage or impairment of an organ or function.
Grade 2 – Moderate	Long-term morbidity. In consequence of the transfusion reaction there were: • need for hospitalization or prolongation of it **and/or** • persistent or significant deficiency or disability **or** • need for medical or surgical intervention to prevent permanent damages or impairment of an organ or function.
Grade 3 – Severe	Immediately life-threatening, in consequence of the transfusion reaction, no death attributed to transfusion. Medical intervention required to prevent death.
Grade 4 – Death [1]	Death attributed to transfusion.

[1]Grade 4 must be used only if death is attributed to transfusion, with its respective imputability grade. If there was a transfusion reaction and the patient died because of the underlying disease or other cause, the severity of the transfusion reaction must be classified as grade 1 - mild, 2 - moderate or 3 - severe.
Source: ISBT, 2011.

3. Classification related to the imputability to transfusion

The national hemovigilance system adopts the categories of imputability of clinical/laboratory status and/or temporal relation to transfusion, broadly described in Chart 9. In the case definitions, in the item referring to the classification of reactions related to diagnosis, charts will be presented containing the description of the imputability more adequate for each type of reaction, when pertinent.

Chart 9 – Classification and definition of reactions related to the imputability to transfusion.

Imputability	Description
Confirmed (definitive/certain)	When the investigation concluded that there is clear evidence (clinical/laboratory status, temporal relation), without a doubt about the imputability to transfusion.
Likely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status, temporal relation), which indicates the imputability to transfusion, but there are doubts for confirming it.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status, temporal relation), which indicates imputability of signs and symptoms to other causes, but the imputability to transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status, temporal relation), which indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.
Excluded*	When the investigation already concluded shows evidence (clinical/laboratory picture, temporal relation) which clearly indicates the imputability of the adverse event to other cause(s) and not to transfusion.
Inconclusive	When the investigation already concluded has not found enough evidence (clinical/laboratory picture, temporal relation), to confirm or exclude the imputability to transfusion.

*Use this category for notification only in cases initially notified as other imputability, in which, after the conclusion of the investigation, the imputability to transfusion was excluded.

4. Classification related to the diagnosis of transfusion reaction

The national hemovigilance system adopts, for notification purposes, the following diagnosis of transfusion reactions:

1. Febrile non-hemolytic reaction – FNHTR
2. Allergic reaction – ALG
3. Transfusion Transmitted bacterial infeccion -TTBI
4. Transfusion Transmitted Infeccion Diseases - TTID
5. Acute immune hemolytic reaction – AHTR
6. Transfusion-related acute lung injury – TRALI
7. Transfusion associated non-imune hemolysis reaction - TANIHR
8. Hypotensive transfusion reaction – HTR
9. Transfusion-associated circulatory overload – TACO
10. Transfusion-associated dypsnea – TAD
11. Transfusion-associated graft versus host disease– TA-GVHD
12. Delayed hemolytic reaction– DHTR
13. Alloimmunization/Delayed serologic reaction - DSRT
14. Post-transfusion purpura – PTP
15. Acute pain transfusion reaction – APTR
16. Hemosiderosis with organ impairment – HEMOS
17. Metabolic disturbances – MD
18. Other immediate reactions - OI
19. Other delayed reactions - OD

4.1. Definition of transfusion reaction case, according to reaction diagnosis

The criteria considered for the inclusion of diagnoses as a transfusion reaction case, in the list of reporting reactions, were: severity, incidence, existence of mechanism of prevention and minimization of the occurrence/recurrence and evaluation of differential diagnosis with other severe transfusion reactions.

It is important to highlight that the case definition for each one of the different types of transfusion reaction presented below represents the confirmed case, in accordance with the classification related to the imputability to transfusion already described.

4.1.1. Febrile non-hemolytic reaction – FNHTR

Case definition: fever (temperature ≥38 ^{o}C) with rise of at least 1^{o}C over the value before transfusion;

AND/OR

shivering and chills, during transfusion or until 4 hours after;

AND

absence of other causes such as bacterial contamination, hemolytic reaction or another underlying condition.

Nausea, vomiting and headache may occur. Symptoms may cease spontaneously.

Chart 10 – Classification of the imputability of febrile non-hemolytic reaction (FNHTR) cases to transfusion.

Grade of imputability	Criteria
Confirmed	Absence of other causes that can explain the signs and symptoms described in the case definition, such as bacterial contamination, hemolytic reaction or other underlying condition.
Likely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status, temporal relation), which indicates the imputability to transfusion, but there are other causes that can explain the signs and symptoms described in the case definition.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory/evolution status, temporal relation), which indicates the imputability of the signs and symptoms described in the case definition to other causes, but the imputability to transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows clear evidence (clinical/laboratory/evolution status, temporal relation), which indicates the imputability of the adverse event with other cause(s), but the imputability to transfusion cannot be excluded.
Inconclusive	There is not enough evidence (clinical/laboratory/evolution status, temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status, temporal relation) which clearly indicates the imputability of the adverse event to other cause (s), such as bacterial contamination, or other reactions, or even with the underlying disease.

4.1.2. Allergic reaction – ALG

Case definition: consists in the presentation of hypersensitivity (allergy) reaction during transfusion or even 4 hours after. The confirmed case must present two or more of the following signs and symptoms:

- papules;
- pruritus;
- urticaria;
- lip, tongue and uvula edema or periorbital/conjunctival edema;

- cough, hoarseness.

In anaphylactic reaction – severe case of allergic reaction –, signs and symptoms occur fast, in few seconds or minutes after the start of the transfusion. Respiratory disorders and the following symptoms are mandatorily observed:

- laryngeal edema;
- cyanosis;
- respiratory failure;
- bronchospasm;
- stridor.

Anxiety, tachycardia, loss of consciousness, hypotension and shock may also occur.

Chart 11 – Classification of the imputability of allergic reaction (ALG) cases to transfusion.

Grade of imputability	Criteria
Confirmed	When there is not evidence of other causes (environment, food or medication) that explain the symptoms described in the case definition.
Likely	There are other causes (environment, food or medication) that could explain the symptoms described in the case definition, but transfusion is the most likely cause.
Possible	There is evidence of other causes (environment, food or medication) that explain the symptoms described in the case definition, but the imputability to transfusion cannot be excluded.
Unlikely	There is clear evidence in favor of causes (environment, food or medication) other than the transfusion, but the imputability to transfusion cannot be excluded.
Inconclusive	A relation between the adverse event and transfusion is unknown or not defined.
Excluded	There is evidence that clearly indicates the imputability of the adverse event to other cause(s) (environment, food or medication).

4.1.3. Transfusion transmitted bacterial infection -TTBI

Case definition: presence of microorganism in the blood component transfused or in other blood component from the same donation (co-component);

AND

presence of the same microorganism in the recipient's blood, even with no clinical symptomatology;

AND/OR

fever (temperature ≥38^{o}C) with rise of at least 2^{o}C over the value before, during or until 24 hours after transfusion, with no evidence of previous infection.

It is common the occurrence of some of the following signs and symptoms:

- shivering;
- chills;
- hypotension;
- tachycardia;
- dyspnea;
- nausea, vomiting;
- shock.

Chart 12 – Classification of the imputability of transfusion transmitted bacterial infection (TTBI) cases to transfusion.

Grade of imputability	Criteria
Confirmed	One or more of the following evidence: • bacteria in the product transfused; • bacteria in donor in the period of the donation; • bacteria in other component from the same donation (co-component); • bacteria in recipient of other blood component from the same donation (co-component); **AND** presence of the same bacteria in the recipient's blood; **AND** evidence that the recipient was not infected with the same bacteria before the transfusion; **AND** no other evidence of contamination of the recipient by the same bacteria by any mean other than transfusion.
Likely	**One or more** of the following evidence: • bacteria in the product transfused; • bacteria in donor in the period of the donation; • bacteria in other component from the same donation (co-component); • bacteria in recipient of other blood component from the same donation (co-component);

	AND presence of the same bacteria in the recipient's blood; **AND** evidence that the recipient was not infected with the same bacteria before the transfusion; **OR** no other evidence of contamination of the recipient by the same bacteria by any mean other than transfusion.
Possible	Presence of bacteria in the recipient's blood; **AND** signs and symptoms of sepsis with no other cause; **AND** not performing the culture of the blood component; **AND** exclusion of contamination of the blood sample or laboratory contamination.
Unlikely	Clear evidence in favor of any causes of contamination other than transfusion, but the imputability to transfusion cannot be excluded.
Inconclusive	The relation between reaction and transfusion is unknown and not established.
Excluded	There is evidence that clearly indicates the correlation of the adverse event to other cause.

4.1.4. Transfusion transmitted infectious diseases - TTID

Case definition: the recipient presents post-transfusion infection (virus, parasites or other infectious agents, except for bacteria), with no evidence of existence of this infection before the transfusion;

AND

absence of an alternative source of the infection;

AND

donor of blood component transfused in recipient shows evidence of the same infection;

OR

blood component transfused in recipient shows evidence of the same infectious agent.

Chart 13 – Classification of the imputability of transfusion transmitted infectious diseases (TTID) cases to transfusion.

Grade of imputability	Criteria
Confirmed	**One or more** of the following criteria: • evidence of infectious agent in the *blood component* transfused; • evidence of infectious agent in *donor* at the time of donation; • evidence of infectious agent in other *blood component* from the same donation (co-component); • evidence of infectious agent in other *recipient* of blood component from the same donation; **AND** evidence that the recipient did not present the infection by the infectious agent before the transfusion; **AND** absence of other potential exposure of the recipient to the infectious agent.
Likely	**One or more** of the following criteria: • evidence of infectious agent in the *blood component* transfused; • evidence of infectious agent in *donor* at the time of donation; • evidence of infectious agent in other *blood component* from the same donation (co-component); • evidence of infectious agent in other *recipient* of blood component from the same donation; **AND** evidence that the recipient did not present the infection by the infectious agent before the transfusion; **OR** absence of other potential exposure of the recipient to the infectious agent.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory/evolution status, temporal relation), which indicates the imputability of signs and symptoms to other causes, but the imputability to transfusion cannot be excluded.
Unlikely	Laboratory evidence that the recipient was infected by the infectious agent before the transfusion; **OR** Evidence clearly in favor of other source, but transfusion cannot be excluded.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status, temporal relation), to confirm or exclude the imputability to the transfusion.
Excluded	**All** the following ones (where applicable): • evidence that the *blood component* transfused was free from the

	infectious agent at the time of the transfusion; • evidence that the *donor* was free from the infectious agent at the time of donation; • evidence that *other blood components* from the same donation were free from the infectious agent; • evidence that *other recipients* of blood components from the same donation were free from the infectious agent; **OR** evidence clearly in favor of any source other than transfusion.

4.1.5. Acute immune hemolytic reaction – AHTR

Case definition: reaction characterized by a rapid destruction of erythrocytes during transfusion or until 24 hours after, by ABO incompatibility or other erythrocyte system.

Presence of any of the following signs and symptoms:

- anxiety;
- agitation;
- feeling of impending death;
- shivering/chills;
- flushing;
- fever;
- pain at the venipuncture site;
- abdominal, lumbar and flank pain;
- hypotension;
- epistaxis;
- oliguria/anuria, kidney failure,
- hemoglobinuria;
- disseminated intravascular coagulation (DIVC);
- bleeding at the venipuncture site, shock;

AND

positive hemolysis test in the patient's sample;

AND

two or more of the following results:

- direct antiglobulin test positive for anti-IgG or anti-C3;
- positive elution test;
- elevated lactate dehydrogenase;
- elevated indirect bilirubin;
- drop of hemoglobin and hematocrit;
- low haptoglobin;
- hemoglobinuria;
- low fibrinogen or increased free hemoglobin.

Chart 14 - Classification of the imputability of acute immune hemolytic reaction (AHTR) cases to transfusion.

Grade of imputability	Criteria
Confirmed	Laboratory confirmation of ABO incompatibility or other erythrocyte systems, according to definition and case; OR presence of acute immune-mediated hemolysis exclusively related to transfusion.
Likely	Evidence (clinical/laboratory status, temporal relation), that indicates the imputability to transfusion, but there are other causes that can explain acute hemolysis.
Possible	Evidence (clinical/laboratory status, temporal relation), that indicates the imputability of acute hemolysis to other causes, but the imputability to transfusion cannot be excluded.
Unlikely	Clear evidence in favor of other causes of acute hemolysis, but the imputability to transfusion cannot be excluded.
Inconclusive	The relation between reaction and transfusion is unknown or not established.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status, temporal relation), which clearly indicates the correlation of the adverse event to other cause(s).

4.1.6. Transfusion-related acute lung injury – TRALI

Case definition: syndrome characterized by acute respiratory distress that occurs during transfusion or until six hours after it, with no previous evidence of lung injury;

AND

chest imaging exam showing bilateral pulmonary infiltrate with no evidence of circulatory overload;

AND

hypoxemia with oxygen saturation < 90% at ambient air and/or Pa02 / Fi02 < 300 mmHg.

Patient may present dyspnea, fever, tachycardia, hypertension/hypotension and cyanosis.

Chart 15 – Classification of the imputability of transfusion-related acute lung injury (TRALI) cases to transfusion.

Grade of imputability	Criteria
Confirmed	Clear evidence of the imputability to transfusion, according to case definition; **AND** absence of other causes or factors that can explain lung injury.
Likely	Evidence (clinical/imaging/laboratory status, temporal relation) that indicates the imputability to transfusion, but there are other causes that can explain acute lung injury, such as: aspiration, pneumonia, toxic inhalation, pulmonary contusion, near-drowning, severe sepsis, polytrauma, shock, burn, acute pancreatitis, cardiopulmonary bypass, and drug overdose.
Possible	Evidence (clinical/imaging/laboratory status, temporal relation) of other causes that explain acute lung injury, but the imputability to transfusion cannot be excluded. Examples of other causes: aspiration, pneumonia, toxic inhalation, pulmonary contusion, near-drowning, severe sepsis, polytrauma, shock, burn, acute pancreatitis, cardiopulmonary bypass, and drug overdose.
Unlikely	When the investigation already concluded, or still ongoing, shows clear evidence (clinical/laboratory/evolution status and temporal relation) that indicate the imputability of the adverse event to other cause(s), but the imputability to transfusion cannot be excluded.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status, temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status, temporal relation), which clearly indicates the correlation of the adverse event to other cause(s).

4.1.7. Transfusion associated non-immune hemolysis reaction – TANIHR

Case definition: is characterized by hemolysis, during or until 24 hours after transfusion, with or without significant clinical symptoms, with no evidence of immune cause;

AND

presence of free hemoglobin in plasma (hemoglobinemia) and/or in urine (hemoglobinuria).

Chart 16 – Classification of the imputability of transfusion associated nonimmune hemolysis reaction (TANIHR) cases to transfusion.

Grade of imputability	Criteria
Confirmed	Cause of acute hemolysis related only to transfusion with no evidence of immune cause.
Likely	There are other potential causes that could explain nonimmune acute hemolysis, but transfusion is the most likely cause.
Possible	Other causes of nonimmune acute hemolysis are possible, but transfusion cannot be dispelled.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status, temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.8. Hypotensive transfusion reaction – HTR

Case definition

Over 18 years of age:

A drop higher or equal to 30 mmHg and records lower or equal to 80 mmHg of systolic arterial blood pressure, within until one hour after the transfusion;

OR

between 1 to 18 years of age:

drop higher than 25% of the baseline systolic arterial blood pressure, within until one hour after the transfusion;

OR

in children younger than 1 year or with body weight lower than 12 kg:

a drop higher than 25% of the baseline value of systolic, diastolic or average arterial blood pressure, within until one hour after the transfusion;

AND

exclusion of all other causes of hypotension;

patient responds quickly to discontinuation of the transfusion and to support treatment.

Chart 17 - Classification of the imputability of hypotensive transfusion reaction (HTR) cases to transfusion.

Grade of imputability	Criteria
Confirmed	The condition described in the case definition occurs at least 15 minutes after the start of the transfusion; **AND** patient responds quickly (10 minutes) after the interruption of the transfusion and support treatment; **AND** exclusion of other conditions that explain hypotension.
Likely	Presentation of the condition described in the case definition between 15 minutes after the start of the transfusion and 1 hour after its interruption; **OR** patient does not respond quickly (within 10 minutes) to the interruption of the transfusion and support treatment; **OR** there are other potential causes that can explain hypotension, but the transfusion is the most likely cause.
Possible	There are other conditions that can explain arterial hypotension.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.9. Transfusion-associated circulatory overload – TACO

Case definition: is characterized by the presentation of pulmonary edema during the transfusion or until six hours after, showing at least four of the following characteristics:

- acute respiratory failure (orthopnoea, dyspnea and cough);
- tachycardia;
- hypertension;
- imaging findings of pulmonary edema;
- evidence of positive water balance;
- increase of central venous pressure;
- left ventricular failure;
- increase of B-type natriuretic peptide (BNP).

Chart 18 - Classification of the imputability of transfusion-associated circulatory overload (TACO) cases to transfusion.

Grade of imputability	Criteria
Confirmed	Clear evidence of the imputability to transfusion, according to the case definition: **AND** absence of other causes or factors that can explain circulatory overload.
Likely	Evidence that indicated the imputability to transfusion; **AND** recipient received other fluids; **OR** recipient has history of cardiac and/or kidney failure that can explain circulatory overload.
Possible	Recipient has history of pre-existing cardiac failure that can better explain the circulatory overload, but the transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.

Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.10. Transfusion-associated dyspnea – TAD

Case definition: characterized by acute respiratory distress within the first 24 hours of the transfusion, that does not meet the criteria of TRALI, transfusion-associated circulatory overload, and allergic reaction. Respiratory distress is the most prominent clinical symptom;

AND

cannot be explained by the patient's underlying condition or by other cause.

Chart 19 – Classification of the imputability of transfusion-associated dyspnea (TAD) cases to transfusion.

Grade of imputability	Criteria
Confirmed	When the investigation concluded that there is clear evidence (clinical/laboratory status and temporal relation), without any doubt, of the imputability to transfusion, according to the case definition.
Likely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability to transfusion, but there are other causes that can explain the signs and symptoms described in the case definition.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the signs and symptoms described in the case definition to other cause(s), but the imputability to transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows clear evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but the imputability to transfusion cannot be excluded.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.11. Transfusion-associated graft versus host disease – (TA-GVHD)

Case definition: is a clinical syndrome that occurs between two and six weeks after the blood component infusion, it is characterized by:

- fever;
- diarrhea;
- erythema with maculopapular rash that spreads to the extremities and can, in severe cases, progress to generalized erythroderma and formation of hemorrhagic blisters;
- hepatomegaly;
- alteration of the liver function (increase of alkaline phosphatase, transaminases and bilirubin);
- pancytopenia;
- bone marrow aplasia;

AND

biopsy of the skin or other compromised organs compatible with TA-GVHD;

OR

presence of leukocyte chimerism.

Chart 20 – Classification of the imputability of transfusion-associated graft versus host disease (TA-GVHD) cases to transfusion.

Grade of imputability	Criteria
Confirmed	Presence of leukocyte chimerism in the absence of other diagnoses.
Likely	Presence of leukocyte chimerism **BUT** there other potential causes.
Possible	Absence of leukocyte chimerism or the exam has not been done; **OR** other potential causes are more likely.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.

Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.12. Delayed hemolytic reaction– DHTR

Case definition: the condition is related to the development of antibodies against erythrocyte antigen(s) after the transfusion. The clinical signs of hemolysis generally are present between 24 hours and 28 days after the transfusion.

The patient can be asymptomatic, with discreet clinical signs and often unnoticeable. The classical clinical picture, however, is composed of fever, jaundice and anemia, it may present other symptoms similar to the ones of the acute immune hemolytic reaction;

AND

positive direct antiglobulin test;

AND

positive elution test or erythrocyte alloantibody newly-identified in the recipient's serum;

AND

insufficient increase of the post-transfusion hemoglobin level **or** rapid drop of hemoglobin to levels prior to transfusion **or** inexplicable appearance of spherocytes.

Chart 21 – Classification of the imputability of delayed hemolytic reaction (DHTR) cases to transfusion.

Grade of imputability	Criteria
Confirmed	No other explanation for the symptoms described in the case definition; **OR** identification of a new erythrocyte antibody.
Likely	There is an alternative explanation for the symptoms described in the case definition or the identification of a new erythrocyte antibody, but transfusion is the most likely cause.
Possible	There are other explanations for the symptoms described in the case definition or the identification of a new erythrocyte antibody, but transfusion cannot be dispelled.

Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.13. Alloimmunization/Delayed serologic reaction – ALLO/DSRT

Case definition: development in the recipient of a clinically significant new antibody, against erythrocyte antigens detected by the positive direct antiglobulin test (DAT) or screening of irregular antibodies;
AND
absence of clinical or laboratory signs of hemolysis.

Chart 22 – Classification of the imputability of alloimmunization/delayed serologic reaction (ALLO/DSRT) cases to transfusion.

Grade of imputability	Criteria
Confirmed	New antibody is identified between 24 hours and 28 days after transfusion; **AND** transfusion done in the same institution is the only possible cause for the development of irregular antibodies.
Likely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability to transfusion, but there are other causes that can explain the signs and symptoms.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the signs and symptoms to other cause(s), but the imputability to transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.

Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to the transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.14. Post-transfusion purpura – PTP

Case definition: is an episode of thrombocytopenia (fall in the platelet count to levels lower than 20% of the pre-transfusion count) which occurs from 5 to 12 days after the blood transfusion;

AND

presence of antiplatelet antibody in the recipient.

It can be asymptomatic, self-limited, but can also present cutaneous and mucosal gastrointestinal, and genitourinary bleeding and of the central nervous system.

Chart 23 – Classification of the imputability of post-transfusion purpura (PTP) cases to transfusion.

Grade of imputability	Criteria
Confirmed	The condition described in the case definition occurs from 5 to 12 days after the transfusion; **AND** recipient with no other conditions that explain thrombocytopenia.
Likely	The condition described in the case definition occurs in less than 5 days or more than 12 days after the transfusion; **OR** there are other potential causes that could explain thrombocytopenia, but transfusion is the most likely cause.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory/evolution status and temporal relation) that indicates the imputability of the signs and symptoms to other cause(s), but the imputability to transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.

Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.15. Acute pain transfusion reaction – APTR

Case definition: acute short-term pain (until 30 minutes), mainly in the lumbar and chest region and in the upper limbs, during or until 24 hours after the transfusion, with no other explanation.

It is common the occurrence of some of the following signs and symptoms: hypertension, uneasiness, flushing, chills, tachypnea, dyspnea, and tachycardia. The pain experienced in this reaction is more intense compared to the pain of other reactions.

Chart 24 – Classification of the imputability of acute pain transfusion reaction (APTR) cases to transfusion.

Grade of imputability	Criteria
Confirmed	Acute short-term pain (until 30 minutes), excluding other conditions that explain it; **AND** conclusive evidence that the adverse reaction can be attributed to transfusion.
Likely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability to transfusion, but there are other causes that can explain the signs and symptoms.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory/evolution status and temporal relation) that indicates the imputability of the signs and symptoms with other cause(s), but the imputability to transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event with other cause(s), but there are doubts for excluding it.

Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.16. Hemosiderosis with organ impairment – HEMOS

Case definition: presence of blood ferritin level higher or equal to 1,000 microgram/L in the setting of multiple transfusions of red blood cell concentrates;
AND
organ dysfunction.

Chart 25 – Classification of the imputability of hemosiderosis with organ impairment (HEMOS) cases to transfusion.

Grade of imputability	Criteria
Confirmed	When the investigation concluded that there is clear evidence (clinical/laboratory status and temporal relation), without a doubt, of the imputability to transfusion, according to the case definition.
Likely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability to transfusion, but there are other causes that can explain the signs and symptoms described in the case definition.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory/evolution status and temporal relation) that indicates the imputability of the signs and symptoms described in the case definition to other cause(s), but the imputability to transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.

Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.17. Metabolic disturbances – MD

Case definition: clinical evidence of metabolic disturbances (for example: hypocalcimia, hyperkalemia, metabolic alkalosis) in the absence of the same disturbances in the underlying disease;
AND
laboratory confirmation.

Chart 26 – Classification of the imputability of metabolic disturbances (MD) cases to transfusion.

Grade of imputability	Criteria
Confirmed	Laboratory confirmation of the metabolic disturbance attributed to transfusion in the absence of this disturbance in the underlying disease.
Likely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability to transfusion, but there are other causes that can explain the signs and symptoms described in the case definition.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory/evolution status and temporal relation) that indicates the imputability of the signs and symptoms described in the case definition to other cause(s), but the imputability to transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.18. Other immediate reactions – OI

Case definition: clinical/laboratory status with presentation during or until 24 hours after the transfusion, which after investigation could not be classified as none of the transfusion reactions described, and having been excluded other causes not related to the transfusion.

Chart 27 – Classification of the imputability of other immediate reactions (OI) cases to transfusion.

Grade of imputability	Criteria
Confirmed	When the investigation concluded that there is clear evidence (clinical/laboratory status and temporal relation), without a doubt, of the imputability to transfusion, according to the case definition.
Likely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability to transfusion, but there are other causes that can explain the signs and symptoms described in the case definition.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory/evolution status and temporal relation) that indicates the imputability of the signs and symptoms described in the case definition to other cause(s), but the imputability to transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

4.1.19. Other delayed reactions – OD

Case definition: clinical/laboratory status with presentation 24 hours after the transfusion, which after investigation could not be classified as none of the transfusion reactions described, having been excluded other causes not related to transfusion.

Chart 28 – Classification of the imputability of other delayed reactions (OD) cases to transfusion.

Grade of the imputability	Criteria
Confirmed	When the investigation concluded that there is clear evidence (clinical/laboratory status and temporal relation), without a doubt, of the imputability to transfusion, according to the case definition.
Likely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability to transfusion, but there are other causes that can explain the signs and symptoms described in the case definition.
Possible	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory/evolution status and temporal relation) that indicates the imputability of the signs and symptoms described in the case definition to other cause(s), but the imputability to transfusion cannot be excluded.
Unlikely	When the investigation already concluded, or still ongoing, shows evidence (clinical/laboratory status and temporal relation) that indicates the imputability of the adverse event to other cause(s), but there are doubts for excluding it.
Inconclusive	When the investigation already concluded did not find enough evidence (clinical/laboratory/evolution status and temporal relation) to confirm or exclude the imputability to transfusion.
Excluded	When the investigation already concluded shows evidence (clinical/laboratory/evolution status and temporal relation) that clearly indicates the correlation of the adverse event to other cause(s).

5. Communication and notification of adverse events in hemotherapy

The national hemovigilance system defines **communication** as the exchange of information about the occurrence of adverse events related to the products of health interest and to technical and therapeutic procedures in donors and recipients of blood and components. This communication must be done to the blood establishment, to the local health authority (in municipal, state/district setting) and to other health facilities, companies or product manufacturers (BRASIL, 2013a, art. 205, 208, 210; BRASIL, 2014a, art. 35, 101, 103 and 104), where applicable[2]. The immediate means to

[2] Technovigilance is also competence of the company processing products/materials/equipment involved in hemotherapy. In this sense, the communication of adverse event to the processing facility/importer is stimulated when these products are involved, being its obligation to report to SNVS.

communicate are by telephone, electronic mean, text messaging, and facsimile. Subsequently, the communication must be formally recorded.

Notification is the information to the competent authority of the national hemovigilance system, by its web based system, about the occurrence of an adverse event related to the products of health interest and to the technical and therapeutic procedures in donors and recipients, as defined in standards (BRASIL, 2013a, art. 205, 206, 209 and 247; BRASIL, 2014a, art. 13, 35, 100, 147 and 147). In exceptional circumstances, it can be done by other documentary mean (facsimile, electronic mean, physical mean or other).

The Brazilian standards establish as mandatory the notification of all transfusion reactions to the National Health Regulatory System. The transfusion reactions of confirmed, likely, possible, unlikely, and inconclusive imputability must be notified. The excluded imputability will only be notified if the same reaction has been previously notified with another grade of imputability and, after investigation, it had its grade changed to excluded imputability.

The communication of the transfusion reaction to the processing blood facility and/or to the health authority will be conditioned to the type of transfusion reaction or to its severity. Chart 10 describes the deadlines defined to communicate and notify transfusion reactions.

6. Investigation of transfusion reactions

The Brazilian legislation attributes to the establishment, where the transfusion reaction occurred, the investigation, proper report in medical records, the communication and notification, as described. The blood facility processing the blood component has sympathetic responsibility, mainly in cases of transfusion-transmitted infectious diseases. In these cases, it is duty of the processing facility to perform look-back, whose concepts and procedures are described below.

Chart 29 – Deadlines for notifying the occurrence of the transfusion reaction to SNVS, from its occurrence.

Actions	Communicating	Notifying		
What	• Transfusion transmitted bacterial infection. • Transfusion transmitted infectious diseases. • Transfusion-related acute lung injury. • Acute immune hemolytic reaction. • Death attributed to transfusion, related to any type of transfusion reaction.	• **Death** attributed to any adverse reactions to transfusion.	• Transfusion transmitted bacterial infection. • Transfusion transmitted infectious diseases. • Transfusion-related acute lung injury. • Acute immune hemolytic reaction. • Acute nonimmune hemolytic reaction.	• Transfusion-associated graft versus host disease. • Hemosiderosis with organ impairment. • Transfusion-associated circulatory overload. • Febrile non-hemolytic reaction. • Allergic reaction. • Hypotensive transfusion reaction. • Transfusion-associated dyspnea. • Delayed hemolytic reaction. • Alloimmunization/Delayed serologic reaction. • Post-transfusion purpura. • Acute pain transfusion reaction. • Metabolic disturbances. • Other immediate reaction. • Other delayed reaction.
To whom	To the local health authority (municipal, state or district Health Surveillance, according to the local	SNVS (Notivisa or other backup system).	SNVS (Notivisa or other backup system).	SNVS (Notivisa or other backup system).

	agreements) and facility processing the blood component.			
When	Within the first 72 hours.	Within the first 72 hours. (BRASIL, 2013b).	Until the 15th business day of the month subsequent to the identification of the event (BRASIL, 2013b).	Until the 15th business day of the month subsequent to the identification of the event (BRASIL, 2013b).
How	Facsimile, telephone, electronic mean.	In specific form, in the respective web based system of SNVS.	In specific form, in the respective web based system of SNVS.	In specific form, in the respective web based system of the SNVS.

CHAPTER IV: LOOK-BACK INVESTIGATION

Introduction

Look-back is understood as the part of hemovigilance that deals with the retrospective investigation related to the traceability of bags of prior donations of a donor who presented seroconversion or related to a blood recipient that started to present positive marker for a communicable disease. This term is also applicable in cases of detection of positivity in microbiological analyses of blood components and investigation of infectious bacterial pictures in recipients, with no immediate manifestation, but potentially imputed to transfusion, such as for example the investigation of cases by *Yersinia enterocolitica* in thalassemic patients.

The steps for the look-back investigations whose index cases are donors or recipients or even notified by the industry of blood derivatives are shown below.

1. Look-back from repeat/sporadic donor seroconversion/laboratory turning

1.1. Donor identified as reagent for one or more markers evaluated

The legislation of hemotherapy procedures and the health regulation in hemotherapy define as mandatory for establishments to perform high sensitivity laboratory testing for each donation to detect markers of syphilis, Chagas disease, hepatitis B, hepatitis C, Aids and HTLV 1 and 2. They add that, in endemic areas of malaria with active transmission, regardless of the parasite incidence of the disease, a test must be performed for the detection of plasmodium or plasmodial antigens (BRASIL, 2013a, art. 129; BRASIL, 2014a, art. 89).

1.2. Steps of investigation of blood components donated at the seroconversion of repeat/sporadic donor

When the screening tests are reagent (positive or inconclusive) in a blood donor who, in previous donations, presented non-reagent test (seroconversion/laboratory turning), the blood establishment will adopt look-back procedures, which start by: a) checking the stock to identify if there are blood components of this donation, discarding them, if that is the case; and b) retesting the same sample of the donation to confirm the initial result[3], when the seroconversion is detected only by serological test[4].

[3] Also in accordance with the current standards, retesting must be done using kits of different manufacturers or applying different methodology to dispel problems of false positive as a result of the technical qualification of the test or characteristic of the sample/individual. When the tests performed

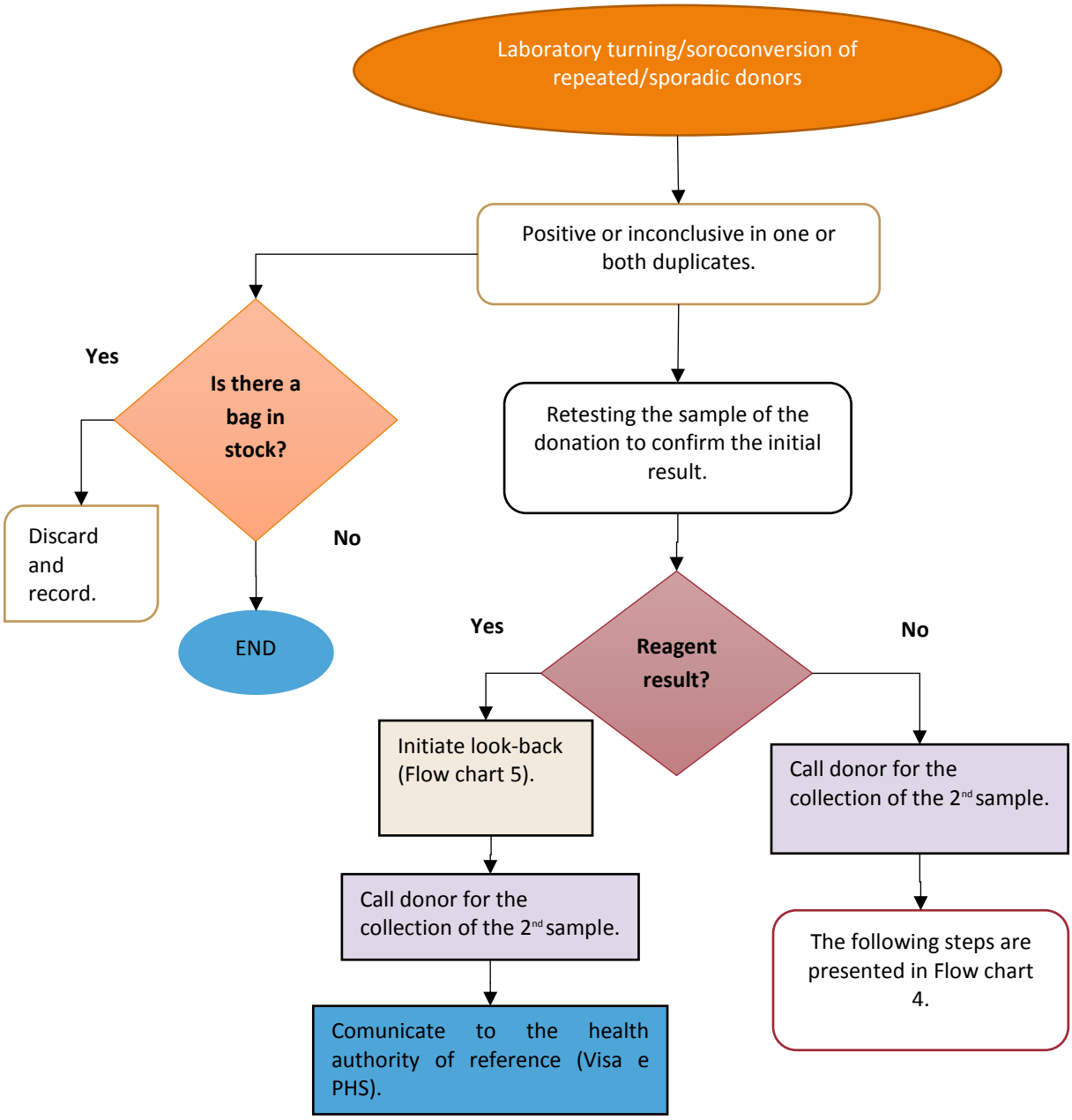
The technical procedures for retesting the same sample are described by the rules mentioned. When the test for confirmation of the initial result points towards a reagent result (positive or inconclusive), the blood establishment will check the fate of all the blood components from prior donations, with deadlines for verification and according to the reagent marker (Flow chart 5).

Flow chart 3 represents the initial steps, from the viewpoint of look-back procedures, at the detection of seroconversion of a repeat donor for any of the markers.

have different nature, for example: Elisa/Chemiluminescence and NAT, this need for test differentiation has been already addressed.

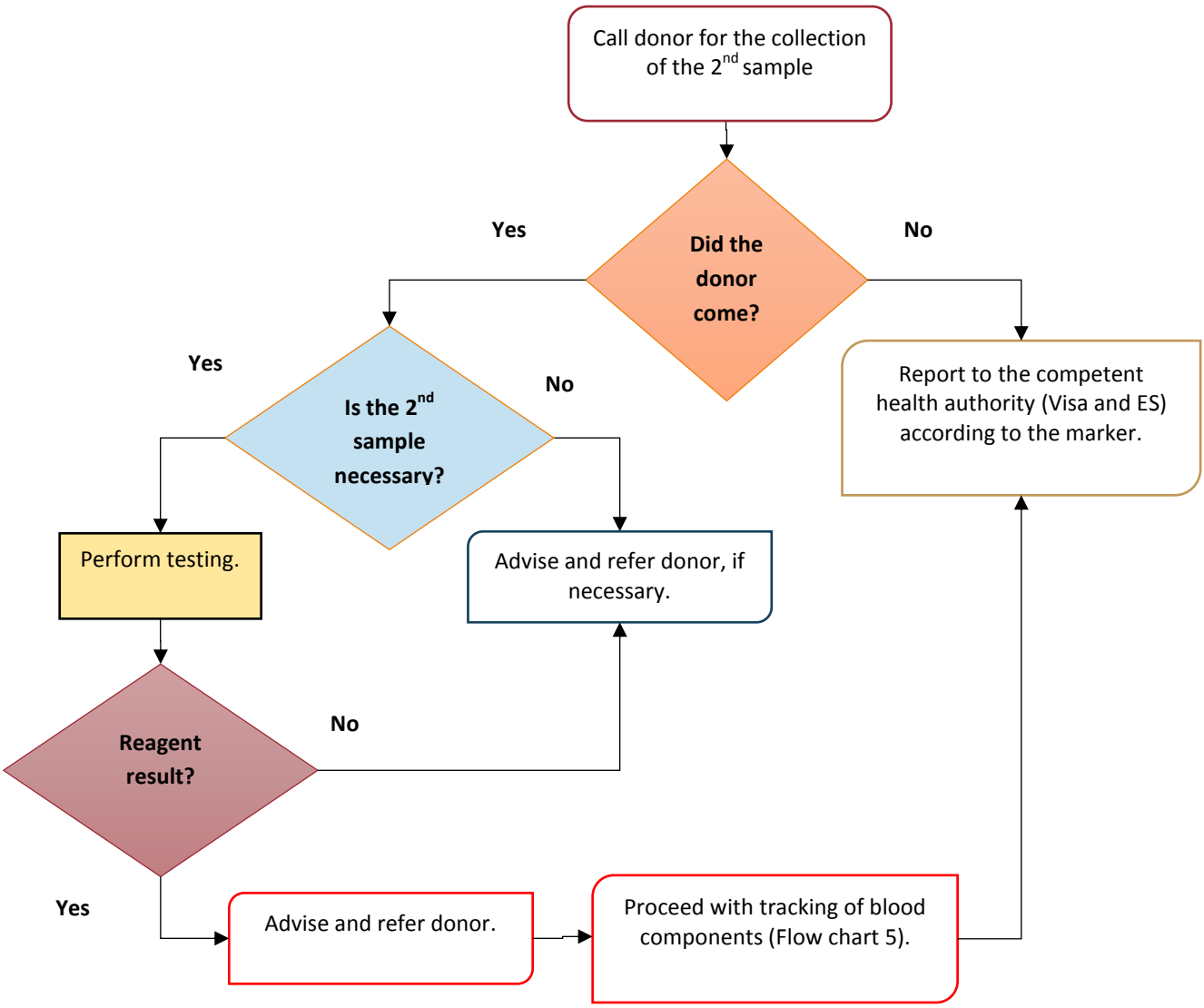
[4] In case of seroconversion detection by NAT for HIV and/or HCV in isolation or associated with the serological test, it will not be necessary to perform the test to confirm the initial result.

Flow chart 3 – Initial look-back procedures by the facility processing the blood component, from the seroconversion/laboratory turning of a repeat or sporadic donor.



The result of the test to confirm the initial result also triggers different actions: a) if negative, donor must be called for the collection of a second sample; b) if positive, the retrospective investigation of all the blood components of prior donations is initiated and donor is called for the collection of a second sample and/or guidance according to the positive marker. This flow is presented in Flow chart 4.

Flow chart 4 – Look-back procedures by the facility processing the blood component, from the confirmation of a positive or inconclusive initial result.



1.3. Steps for calling donor for the collection of the second sample

Depending on the marker, the legislation for the control of diseases predicts the compulsory notification of disease or positivity of a test which is characterized as a confirmed and/or suspected case of communicable disease (BRASIL, 2014b).

Among the diseases cited in this rule, the following diseases potentially transmitted by blood transfusion are important for hemovigilance and form part of the exams for donor qualification: viral hepatitis (B and C); acute Chagas disease; infection by HIV/Aids; infection by HIV in pregnant women and children exposed to the risk of

vertical transmission; infection by HIV; malaria in the Amazon and extra-Amazon region; and acquired, congenital syphilis or in pregnant women. Among them, acute Chagas disease and malaria in the extra-Amazon region must be immediately notified or no later than 24 hours from the initial suspicion. The other diseases must be notified on a weekly basis. In case of Chagas disease, once the blood establishment does not possess ideal conditions to make the diagnosis and classify the stage of the disease, this guide proposes the surveillance of Chagas disease or suspected case, without specifying if it is acute or chronic.

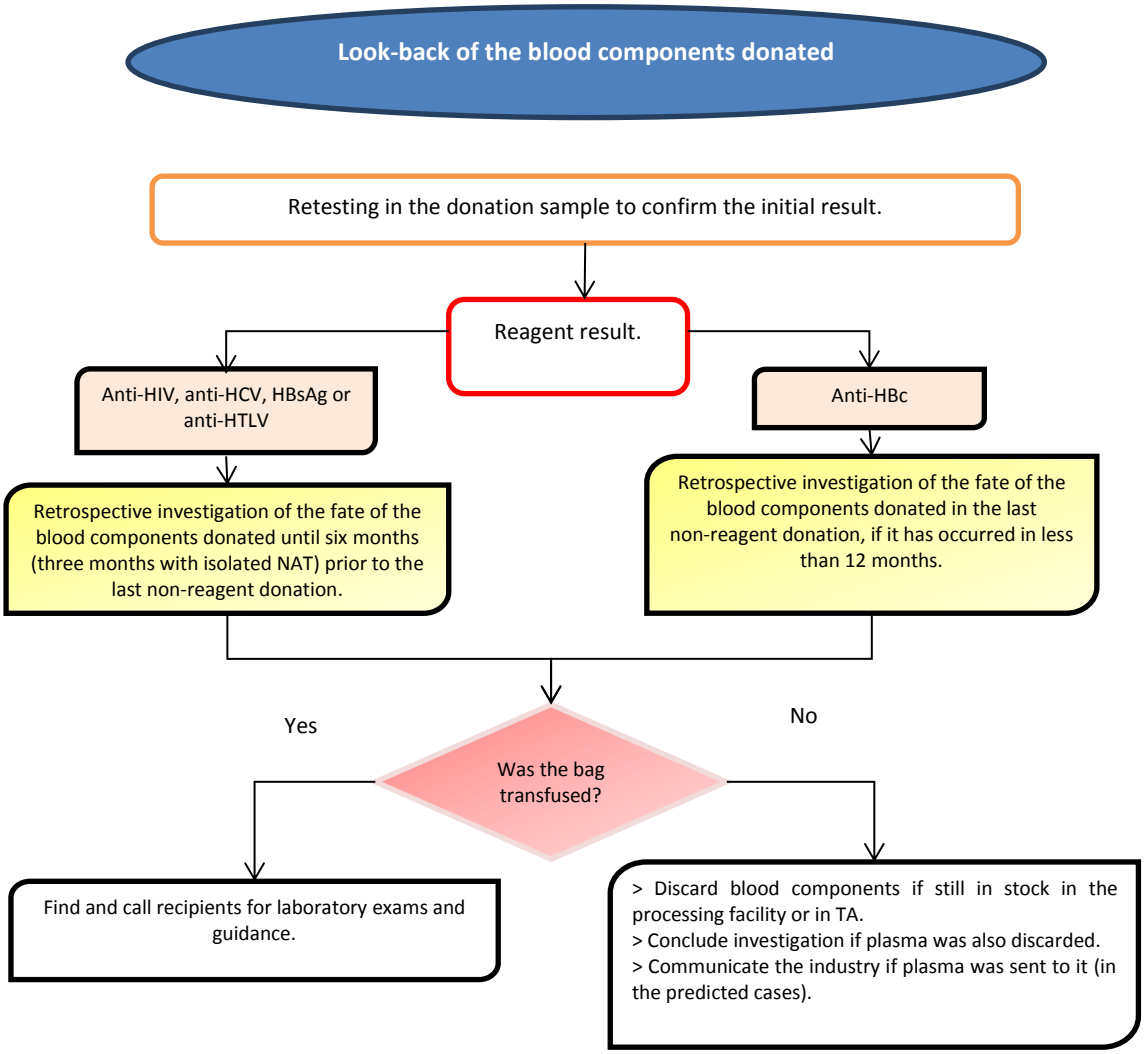
The donor who does not come to the blood establishment for the collection of the second sample is considered as a “suspected case” of the disease whose marker was positive or inconclusive in the initial test, and the legislation cited defines the mandatory nature of the notification of confirmed or suspected cases of these diseases. Therefore, the objectives of the need to notify or communicate to the health (sanitary and public health) surveillance consist in counting on the support of this team for the active search for “suspected” donors; collaborating with the protection of the individual and community; and complying with the legislation. Flow chart 4 elucidates the need to communicate or notify the suspected cases of the corresponding diseases to the health surveillance.

1.4. Retrospective investigation of the blood components donated

The legislation of technical procedures and health regulation in hemotherapy defines the steps to investigate the fate of the blood components donated in prior donations (BRASIL, 2013a, art. 134; BRASIL, 2014a, art. 101). The time of the retrospective investigation depends on the marker that turned into positive. For the cases of seroconversion with the confirmation of initial results reagent for anti-HIV, anti-HCV, HBsAg or anti-HTLV 1 and 2, in a donor who has a prior donation, the retrospective investigation must go through the blood components donated until the period of six months prior to the last non-reagent testing, if the test is by serology, then the period is three months if isolated NAT was used for HIV and HCV. In other words, the index data for the investigation of the blood components, resulting from previous donations, retroact for six months or three months from the last donation whose tests were negative. All the blood components resulting from all the donation of this period must be tracked, with the identification of the establishment that transfused it and/or of the recipient.

For the case of confirmation of the initial tests reagent for anti-HBc, in donor who possesses prior donation, the retrospective investigation must be conducted in blood components donated in the last non-reagent donation, if it has occurred in less than 12 months. Flow chart 5 describes this flow.

Flow chart 5 – Look-back procedures and investigation deadlines from the confirmation of the initial reagent results.



1.5. Finding and calling recipients of the blood components

The legislation of technical procedures and health regulation in hemotherapy defines the responsibilities shared between the blood establishment and the healthcare facility that performed the transfusion to find and call the recipients (BRASIL, 2013a, art. 136; BRASIL, 2014a, art. 101).

According to the local organization of the establishment, the step to be followed will be:

1.5.1. Healthcare facility with transfusion agency (TA) belonging to the facility processing the blood component: the information about the suspected blood component is given by the processing facility to the responsible technician (RT) of the TA that, together with the healthcare facility, identifies the recipient and undertakes the investigation of positivity or not for the same marker as donor's.

1.5.2. Healthcare facility with TA not belonging to the facility processing the blood component: as in the previous item, the information about the suspected blood component is given to the RT of the TA that, together with the healthcare facility, identifies the recipient and undertakes the investigation of positivity or not for the same marker as donor's.

1.5.3. Healthcare facility with no TA: the information about the suspected blood component is given preliminarily to the RT of the TA that prepared the blood component to identify the recipient and, later, to the clinical director of the establishment that transfused, that undertakes the investigation of positivity or not for the same marker as donor's.

In all the cases above, the healthcare facility that performed the transfusion keeps the follow-up of the recipient and reports about the conclusion of the investigation to the facility processing the blood component.

1.6. Follow-up of the recipient

The follow-up of the recipient refers to the process that follows his/her identification. It comprises the location, invitation to come to the health facility, tests to confirm or exclude the possibility of transmission, referral to proper reference establishments for clinical follow-up, notification of the case or suspected case to the health (sanitary and public health) surveillance and return of the result of the tests to the facility processing the blood component.

It is up to the health establishment where the transfusion occurred the effort to identify, find, and follow the recipient of the blood component under investigation.

The chart below presents the minimum periods for the follow-up of the recipient with laboratory exams so it can be excluded the transmission by transfusion.

Chart 30 – Definition of the time for following the recipient up for each of the markers in order to identify or exclude transfusion-transmitted diseases, in the case of blood donor seroconversion.

Exam that showed donor seroconversion	Testing to be done in the recipient	Minimum time to exclude the infection transmission by transfusion
HBsAg (reagent)	• HBsAg	6 months after transfusion
Anti-HBc (reagent)	• HBsAg	6 months after transfusion
Anti-HCV (reagent), NAT HCV (-)	• Anti-HCV	6 months after transfusion
	• NAT HCV	3 months after transfusion
Anti-HIV (reagent), NAT HIV (-)	• Anti-HIV and NAT HIV	3 months after transfusion
Anti-HTLV1/2 (reagent)	• Anti-HTLV 1/2	12 months after transfusion
NAT HCV (+) and/or NAT HIV (+)	• NAT • HCV and/or NAT HIV	3 months after transfusion
	• Anti-HCV or Anti-HIV	6 months after transfusion

The periods described must be analyzed according to other contamination sources, including other transfusions. The investigation of other sources is very important and the health surveillance can contribute to this investigative work.

1.7. Steps for information to the industry of blood derivatives

The relevant markers for reporting seroconversion to the industry (BRASIL, 2013a, art. 135) are the ones referring to the infection by hepatitis B (HBsAg, anti-HBc and/or NAT HBV), by hepatitis C (anti-HCV and/or NAT HCV) and by HIV (anti-HIV and/or NAT HIV). It is recommended that the communication is done within seven days after that the confirmation test of the initial results points towards a reagent (positive or inconclusive) result.

This communication must be done simultaneously and in writing to the industry that received the plasma, to Anvisa and to the General Coordination of Blood and Blood Derivatives/MH, when the plasma units of the donations involved had been sent for industrial fractionation.

To open an investigation process in the industry, the notification of seroconversion issued by the blood establishment must contain at least the following data: a) name of the blood center; b) date of donation; c) number of the bag provided;

d) serological marker; e) date of seroconversion/reagent donation; f) date of shipment of the plasma to industry.

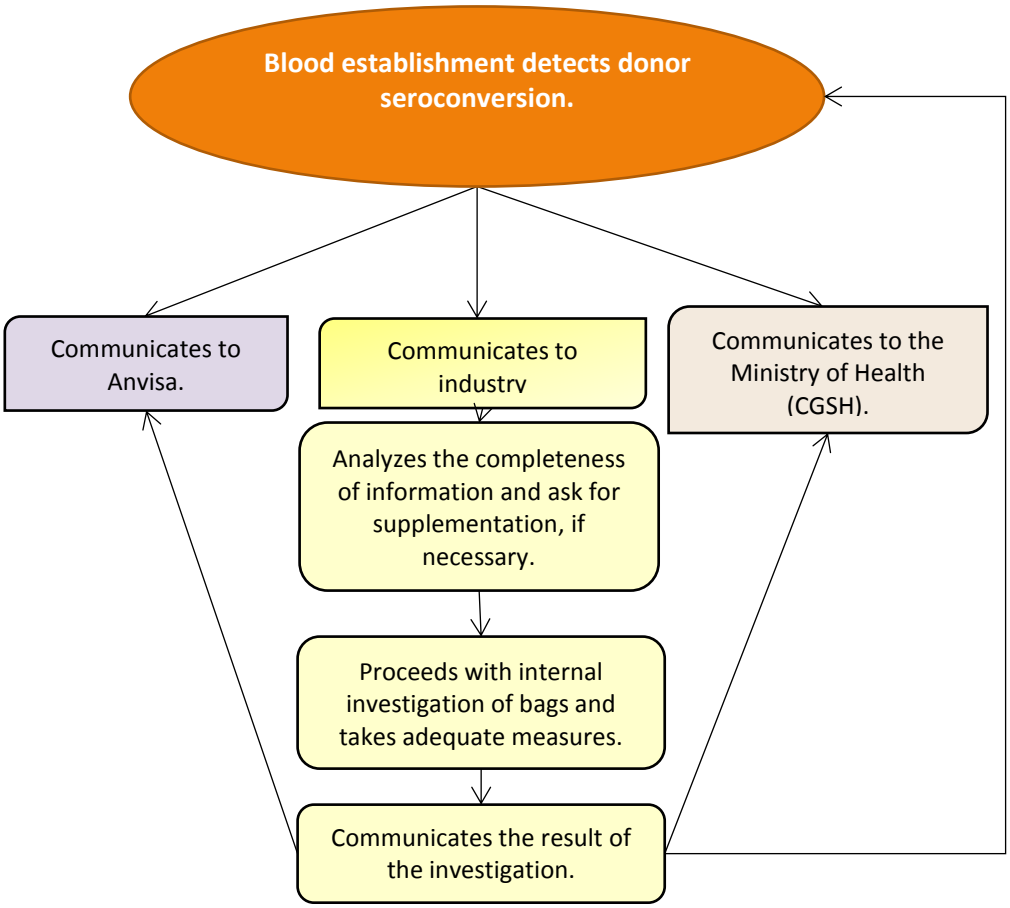
Other supplementary data that help throughout the procedure include: i) donor number; ii) technique of the kit employed in the screening; iii) confirmatory tests, and if that is the case, the technique employed.

In case of absence of critical information, the industry will contact the blood establishment to collect necessary information. A notification template can be found in Annex II.

1.8. Communicating and notifying the competent health authority

The communication of donor seroconversion and notification of transfusion reaction is predicted in the legislation of technical procedures and health regulation in hemotherapy (BRASIL, 2013a, art. 25, 136, 205, 210; BRASIL, 2014a, art. 100, 146, 147). In relation to donor seroconversion, the blood establishment shall communicate to Visa the onset of the look-back process and, later, its conclusion (BRASIL, 2013a, art. 68; BRASIL, 2014a, art. 104). This communication is standardized – with minimal content, markers, fate of the blood components collected, recipients involved and result of recipients' follow-up – in Annex 2 of this guide.

Flow chart 6 – Step for information about the plasma bag sent to industry when the seroconversion of repeat or sporadic donor occurs.

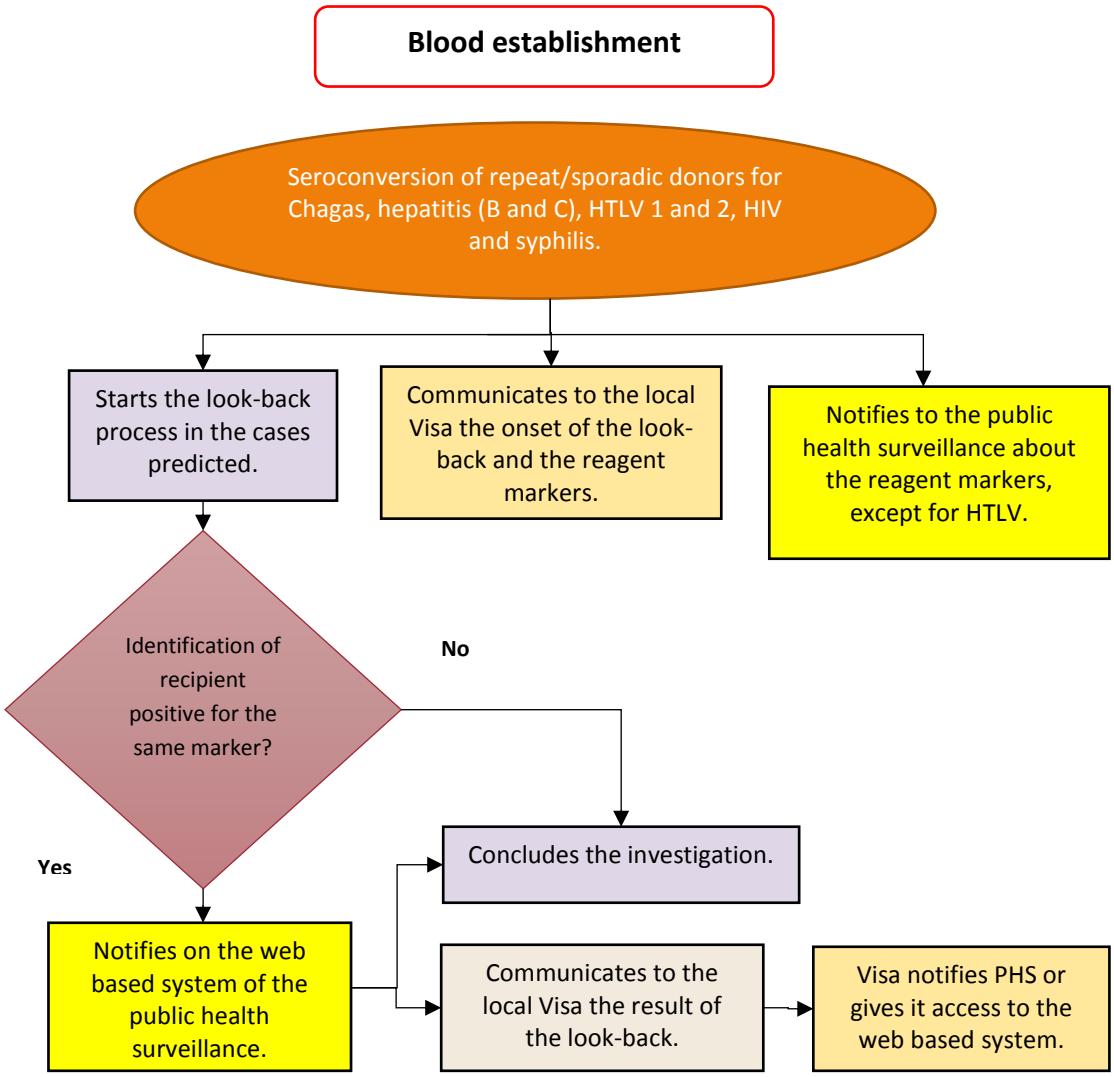


The notification follows two steps: a) notification to the public health surveillance within what is established in the legislation for the control of diseases, for the positivity of a marker in donor; and b) notification to the health regulatory system, when look-back detects the recipient who is also positive for the same marker, by the web based system used for notifying transfusion reactions.

Therefore, the blood establishment reports to the local public health surveillance the detection of positivity for one or more markers in donors, because they will not receive the notification by the web based system of the National Health Regulatory System. But the positivity, if it detected in a recipient, will be notified in this system. The Visa will be in charge of reporting to the public health surveillance or giving it access to its web based system.

The record of the notification in the System of Information for Disease Notification (Sinan) must be under the responsibility of the local public health surveillance, which will search for the supplementary information needed to complete the notification form. Flow chart 7 summarizes this communication step.

Flow chart 7 – Procedures to communicate and notify to the health surveillance about the seroconversion/laboratory turning of a repeat/sporadic donor by the blood establishment.



1.9. Articulation needed between the parties involved (blood establishment, health facility, and public health surveillance)

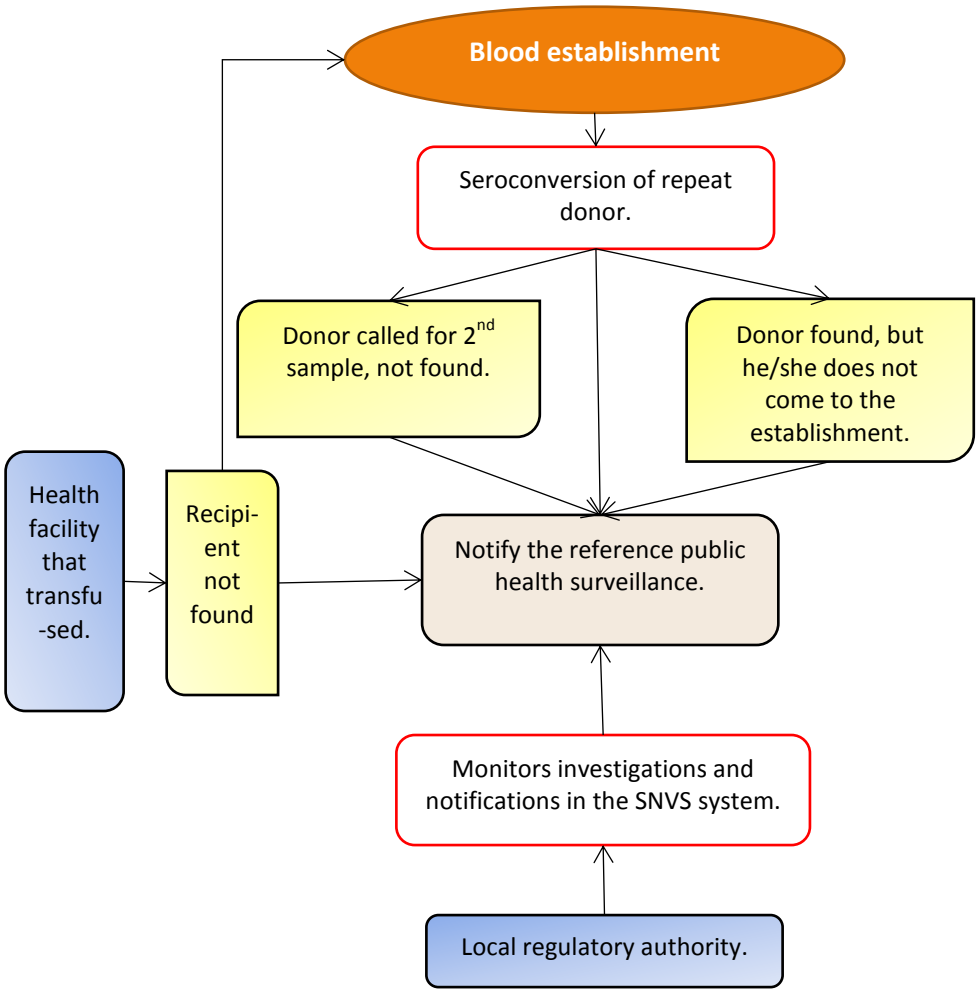
In this articulation between the parties involved, there are some possible situations to which actions are described, in addition to the ones already mentioned for the case where donor does not come when invited for the collection of the second sample and/or guidance.

1.9.1. Donor with suspected or confirmed seroconversion for Chagas, syphilis, hepatitis (B and C) and HIV: the reference health (public health and sanitary) surveillance of the blood establishment that performed the blood collection must be notified. The suspicion or confirmation of HTLV (1 and 2) must be informed to the public health surveillance, in the scope of the reports that will inform the onset of the look-back process.

1.9.2. Donor not found or that, despite invitation, does not come to collect the second sample: the reference health surveillance (PHS and Visa) of the blood establishment that performed the blood collection must be notified about this donor as being a "suspected case".

1.9.3. The recipient is identified and found, but does not come to the health facility where he/she received the transfusion: the reference health surveillance (PHS and Visa) of the blood establishment that performed the blood collection must be notified about this recipient as being a 'suspected case', in accordance with the procedures already mentioned in the legislation for the control of diseases. In this case, the public health surveillance can help to find and convince the recipient, apart from contributing to individual and collective protection measures. The notification on the web based system (Notivisa) must only be done when the recipient shows result compatible with the transmission by transfusion and according to the classification of the imputability to transfusion (except for the imputability 'excluded').

Flow chart 8 – Summary of the articulation between blood establishment, health facilities and public health surveillance from the seroconversion of repeat/sporadic donor.



1.9.4. The recipient is identified by the blood establishment, but he/she cannot be found by the health facility where he/she received the transfusion: the health surveillance will be informed by the blood establishment to check the conformance of the procedures followed by the health facility where the transfusion occurred. Notification on the web based system will only be done when the recipient shows result compatible with the transmission by transfusion and according to the classification of the imputability to transfusion (in accordance with the type of imputability).

1.9.5. The recipient is not identified, because the health facility does not inform the recipient of the blood component: the health authority must be informed by the blood establishment to check the conformance of the procedures followed by the health facility where the transfusion occurred.

1.9.6. The recipient comes and is confirmed with the same marker as donor: notify on the web based system of the health authority the adequate imputability with transfusion, until the conclusion of investigations.

1.9.7. The recipient comes and, at that moment, does not present positivity for the same marker as donor: wait the minimum time of follow-up to exclude the transmission by transfusion (Chart 11).

1.9.8. Recipient's death: death ends the investigation in relation to this recipient and does not generate a notification form on the web based system of the health surveillance, except if there is evidence that the death occurred as a consequence of a disease possibly transmitted by transfusion.

In all the cases where donor and recipient do not come, the initial effort to find and convince them is up to the respective blood and health establishments that received the donation and/or performed the transfusion. The notification to the public health surveillance reinforces the actions of active search and control, in addition to the legal need already mentioned. The health surveillance follows all the process to identify possible nonconformances and act as a link between the different establishments.

2. Look-back from marker positivity in blood recipient

This individual is that one who was diagnosed not based on the discovery of a repeat donor with seroconversion, but by virtue of an exam requested for any reason.

2.1. Steps for retrospective investigation of the bags of blood components transfused

The specific standards do not address directly the responsibilities of establishments in cases of positivity detection in transfusion recipients, but there articles in the legislation of technical procedures and health regulation in hemotherapy that can be applied to those cases (BRASIL, 2013a, art. 179, 205 and 210; BRASIL, 2014a, art. 146 and 147). The step proposed for look-back in cases of suspected transmission by transfusion is presented below:

2.1.1. If the facility that detected positivity for one or more markers in the individual who has also undergone a blood transfusion is not the same where the transfusion was performed:

a) Local (public health and sanitary) surveillance must be notified about a confirmed case of disease having blood transfusion as a possible source.

b) The public health surveillance compiles information about the health facility where the transfusion occurred and communicates to the health surveillance. The notifications will be done by the respective notification systems – Sinan and Notivisa.

c) The health surveillance communicates to the facility where the transfusion occurred so it can identify the blood components transfused and the processing facility.

d) The health establishment where the transfusion occurred must communicate immediately to the processing blood facility the list of blood components involved.

e) The processing facility initiates the look-back process, identifying the donors of these blood components and conducting the investigation of seroconversion, according to the deadlines and tests identified in Chart 12.

f) If the donor(s) has not made new donations or tests for this infection within the deadlines established in Chart 12, he/she must be called immediately to collect a new sample for diagnostic tests.

2.1.2. If the health establishment that detected positivity is not the same that performed the transfusion:

a) Local (public health and sanitary) surveillance must be notified about a confirmed case of disease having blood transfusion as a possible source. The notifications will be done by the respective notification systems – Sinan and Notivisa.

b) The health establishment where the transfusion occurred must communicate immediately to the processing facility the list of blood components involved.

c) The processing facility initiates the look-back process, identifying the donors of these blood components and conducting the investigation of seroconversion, according to the deadlines and tests identified in Chart 12.

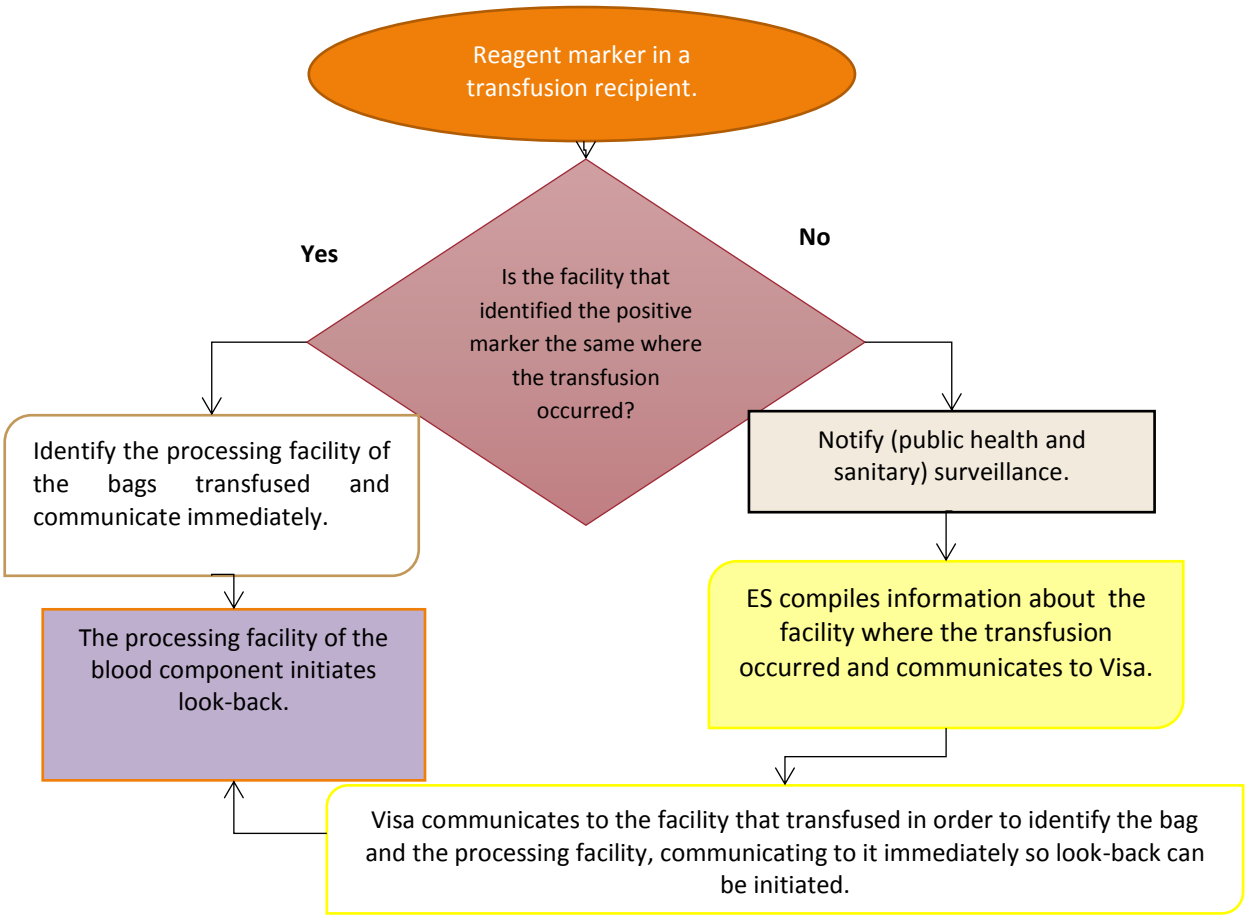
d) If the donor(s) has not made new donations or tests for this infection within the deadlines established in Chart 12, he/she must be called immediately to collect a new sample for diagnostic tests.

2.1.3. If the public health surveillance receives a notification of positivity for one of these markers in which there is the possibility of a blood transfusion being the source of contamination:

a) communication will be done to the health surveillance that will promote the initial investigation of the health facility where the transfusion occurred, triggering the other procedures.

It is up to the health surveillance the follow-up of all the investigative process by the health and blood establishments, until its conclusion.

Flow chart 9 – Look-back procedures from the identification of the reagent marker in a transfusion recipient.



2.2. Calling donors and identifying the fate of the blood components donated

The step and procedures related to location, to donor invitation and his/her presence or not, to research on the fate of other blood components donated, to invitation of possible recipients and to the articulation with the industry of blood

derivatives are the same already predicted for the detection of seroconversion of the repeat donor.

It is important to highlight that only the employment of new tests in the material of the serum/plasma sample bank, possibly still existing in the blood establishment, **is not** enough to rule out the possibility of disease transmission by transfusion, once the sample will be subjected to the same technical circumstances of the collection and clinical and epidemiological circumstances of the donor.

2.3. Deadlines for excluding the possibility of infection/disease transmission by transfusion

Chart 12 presents the timeline and actions needed along with donor for the adequate analysis of possibility that the case detected has had blood transfusion as a possible source of transmission. Naturally, the investigation of the existence of other sources is fundamental to the conclusion of the imputability to transfusion.

Chart 31 – Definition of the minimum time between the index donation and the subsequent non-reagent sample to exclude the possibility of infection/disease transmission by transfusion.

Cause of investigation (disease or positive marker)	Subsequent non-reagent test	Minimum time between index donation and the subsequent non-reagent sample
Hepatitis B	HBsAg/Anti-HBc	6 months
Hepatitis C	Anti-HCV/HCV combo	6 months
	NAT HCV	3 months
HIV	Anti-HIV/Ag p24	3 months
	NAT HIV	3 months
HTLV 1/2	Anti-HTLV	12 months

Note: 1) The results to be evaluated correspond to the ones obtained in donation subsequent to the index donation or of samples collected later.
2) Index donation: donation whose blood component(s) is(are) involved in the look-back process under investigation.

2.4. Notifications and articulation of the parties involved with the public health surveillance

The legislation for the control of diseases defines the list of the diseases whose notification to the health surveillance by professionals and health establishments is

obligatory (BRASIL, 2014b). Thus, if any individual is identified as positive or suspected for one of the diseases in the list, the notification to the public health surveillance is also mandatory. If this individual is also a blood recipient and if there is any possibility that the source of contamination has been blood transfusion, other actions must be taken, besides those already explained in the items above in terms of look-back which concern to the articulation between the health facility, the blood establishment, the local health authority, and the public health surveillance.

These actions include:

a) The blood establishment reports to the local Visa about the onset of the look-back process with minimal information needed, contained in the report template (Annex 2).

b) The health facility that detected the positivity conducts a joint investigation with the public health surveillance and tries to define the existence of other possible sources of contamination.

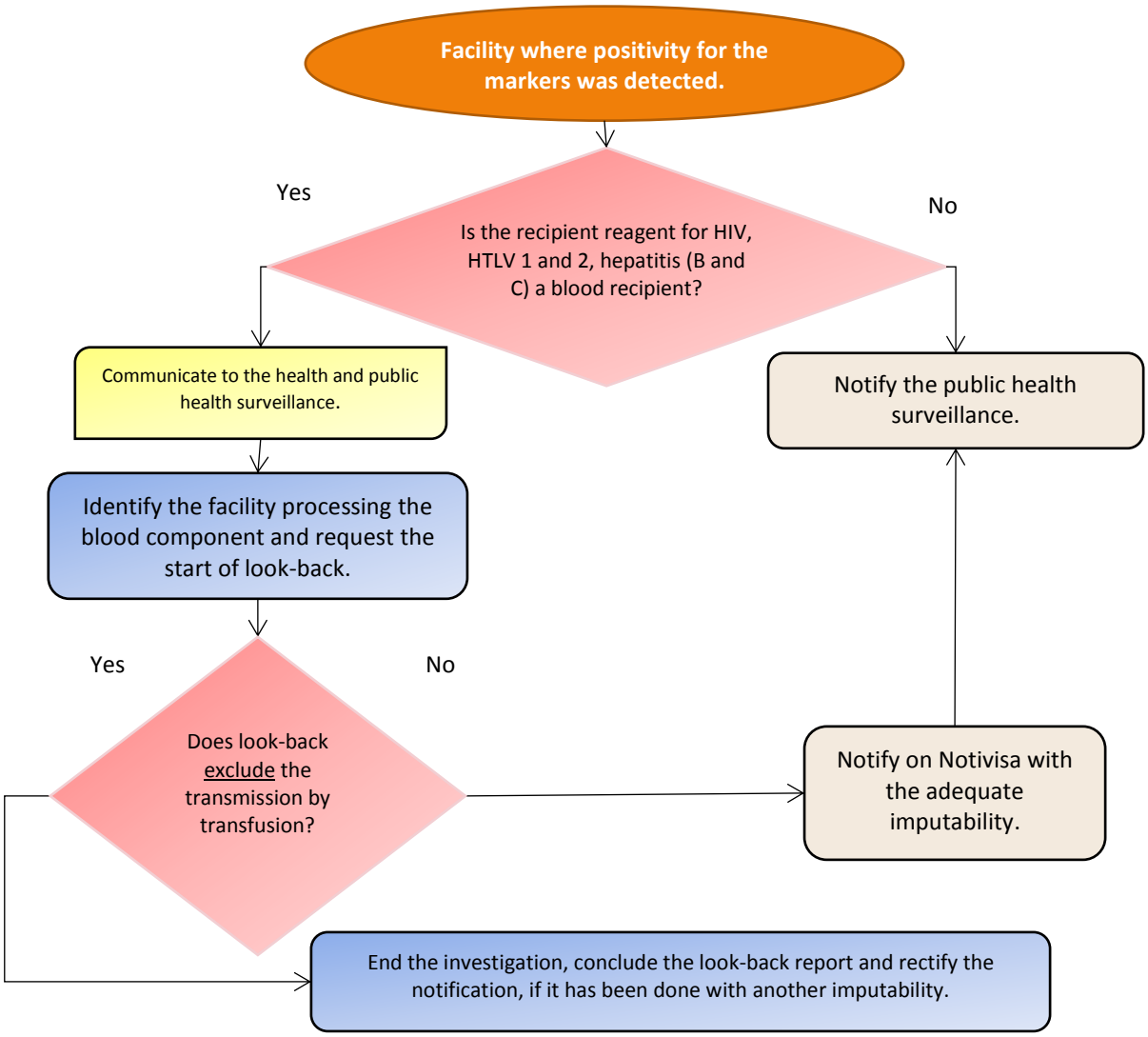
c) The health (or blood) establishment notifies the case on the web based system of the health authority, when concluded the look-back and process of investigation of possible sources, if the contamination has any grade of imputability to transfusion.

If look-back investigaion identifies all donors and concludes by the impossibility of blood transmission, the case is closed and the notification in the respective system is not done, or it is rectified to be excluded if it had already been notified.

d) The blood establishment mentions, in the final look-back report, the case excluded, when blood transmission was not the cause.

e) The health (or blood) establishment ends the investigation and communicates to the public health surveillance or notifies the occurrence on Sinan.

Flow chart 10 – Procedures of look-back, communication and notification from the identification of positivity in a transfusion recipient.



3. Look-back actions by the industry of blood derivatives from the notification received

From the data contained in the notification received, the industry will track the bag and take proper actions, according to the situation. Every bag will fit in one of the four measures as they follow:

1. Bag already destroyed before the notification receipt of seroconversion to the industry: no measure in particular.

2. Bag in stock for fractionation (at the time of the notification receipt the bag was in stock): blocked for fractionation and forwarded to discard.
3. Fractionated bag (in case of investigation of probable infection of donor by HTLV, syphilis, malaria, Chagas disease, microbial contamination or increased risk of STD): no measure in particular.
4. Fractionated bag (in case of investigation of probable infection by HBV, HCV and HIV, the results of biological control tests are analyzed, tests performed in the raw material during the first homogeneous plasma pool and, when necessary, in the final product): supplementary analysis.

After the tracking actions of the bag, the industry must report simultaneously to the blood establishment, to Anvisa and to CGSH its result, the following data for each bag: a) name of the notifying blood center; b) number of the bag under investigation; c) registration number linked to the industry during screening, where applicable; d) measures adopted.

The production of blood derivatives requires a series of technical procedures that jointly aim to assure safety to blood derived products in relation to the transmission of viruses currently known. However, if by the end of the investigation it is verified that any lot of blood derived medication poses risk to the recipient, the industry shall notify immediately the parties involved, providing the identification and the number of the lots of final products. The holder of the registration of the medication in Brazil must notify to Anvisa and CGSH and initiate the recollection measures, where applicable. In the context of Anvisa, the notification of blood derived products is framed as notification of medications, out of the hemovigilance scope, but in the actions of pharmacovigilance.

3.1. Look-back actions, by the industry, from the identification of a positivity blood component

3.1.1. Important markers, steps and deadlines for notification or communication to the facility processing the blood component

a) Markers that do not implicate in pool opening for bag identification

Parvovirus, hepatitis A and positive screening of irregular antibody: will not be communicated individually. Information will be sent in an aggregate way, every six months, to CGSH/MH and to Anvisa. Such information shall be included in the reports sent to the blood establishments and in bulletins. The flow shall be: industry contracted > CGSH and Anvisa > blood establishments.

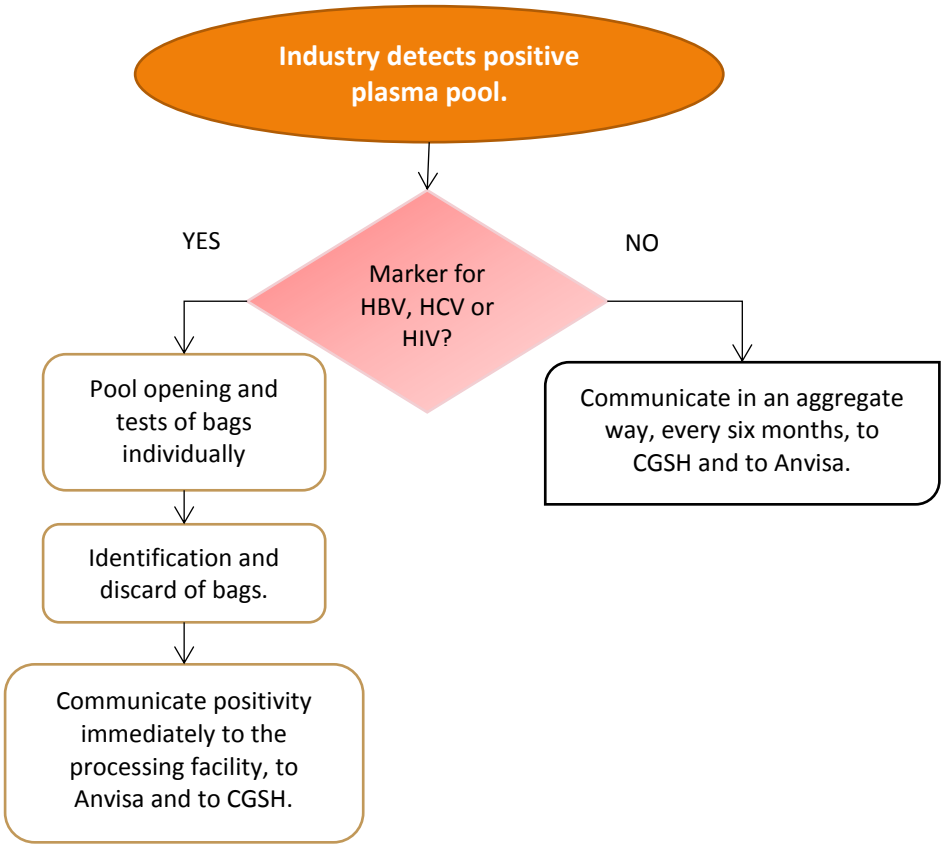
b) Markers that implicate in pool opening and bag identification (HCV, HBV and HIV)

Once detected the positivity, industry will communicate immediately to Anvisa, to CGSH and to the blood establishment supplier of the plasma bag (BRASIL, 2014a, art. 103), by electronic mean and, within seven days by physical mean, in order that

they can take appropriate measures so the blood establishment can proceed with the look-back investigation and with the active donor search. To do so, the communication will provide the following information about the bag with positive result: i) name of the supplier blood establishment; ii) registration number linked to the industry, where applicable; iii) the bag number provided by the blood center, at the time of pool opening; iv) serological marker/virus detected; v) date of positivity detection; vi) measures adopted by the industry.

The facility processing the blood component shall notify to SNVS as a serious near miss until the 15th business day of the month subsequent to the event identification and the look-back process of the co-components must be triggered.

Flow chart 11 – Look-back actions by the industry from the detection of positivity in pools.



3.2. Articulation of industry and blood establishment with the public health surveillance

In addition to the articulation of the blood establishments, the General Coordination of Blood and Blood Derivatives and Anvisa with the industry producing blood derivatives, the look-back developed from a communication of a plasma bag reagent for makers for hepatitis B and C and HIV will trigger actions of articulation between these entities and the public health surveillance, similar to the ones already treated in the items corresponding to the seroconversion of a repeat donor.

4. First-time donor identified with one or more positive markers

Although it does not need the onset of look-back procedures, this donor must be advised and referred to care and the case must be notified to the reference public health surveillance of the blood establishment that performed the blood collection (BRASIL, 2013a, art. 136; BRASIL, 2014a, art. 99), according to the disease or positivity detected, within the list of the legislation for the control of diseases (Chagas, hepatitis B and C, Aids and positive HIV, syphilis and malaria – see item 1.3).

5. Information about the occurrence of disease in donor detected after donation

It is encouraged that the blood establishment organizes its own system to receive donor's information about the occurrence of signs and symptoms of infectious disease that appear within 7 days after donation and that donor is advised to report them to the establishment where the donation was made. The detection positive exam for infectious disease must also be informed, regardless the time elapsed from the donation.

The following possibilities can be approached:

1. Donor himself/herself or a health facility informs to the blood establishment that, after the donation, a test was positive/reagent for a disease possibly transmitted by blood or provides new information omitted during the screening.

a) Period for receiving information after donation: consider any time and investigate on a case to case basis.
b) Action of the blood establishment: perform another exam for the marker identified, if necessary, and consider the onset of the look-back process.

2. Donor himself/herself reports signs and symptoms compatible with infectious disease to the blood establishment where he/she made the donation.

a) Period for receiving information: seven days after the donation for diseases in general and 30 days for malaria.

b) Action of the blood establishment: analysis on a case to case basis, keeping or not the blood components in quarantine or discarding them, apart from evaluating the need for intervention in the recipient, if any blood component from that donation has been transfused.

6. What to do when there is a suspected infection in donor or recipient by donor's qualification markers and other markers not approached

Brazil is one country of great dimensions and different social, demographic, epidemiological realities and different health team training. Doubts may raise in relation to the conduct to be adopted when alterations appear in the other markers, used to qualify the blood donor, which are not addressed in the content of these technical guidelines.

This is the case, for example, of Chagas disease, for which it should also be conducted an investigation of the recipients who have been transfused with the blood components from donors with confirmed seroconversion (screening testing and reagent confirmatory testing) or whose screening exam for Chagas in prior donation has revealed as a false negative for this marker.

Still in what concerns to other transfusion transmitted diseases, which are not in the list of the markers for donor qualification, recent research studies the probability of transmission by this route. It is important that the professional analyzes on a case to case basis in light of recent knowledge and employs the most adequate measures for the safety of donors and recipients. Hemovigilance manuals, the Guide of Public Health Surveillance and other technical bibliographies may help in this decision making.

7. Monitoring patients with frequent need for multiple transfusions

Very often blood and health establishments have under their responsibility the treatment of patients who need to undergo multiple transfusion or frequent transfusions, such as the carriers of hereditary coagulopathies. These multiple transfusion recipients are those more exposed to the risk of transfusion reactions, particularly transfusion transmitted diseases.

The national hemovigilance system recommends that establishments that perform blood transfusion, and mainly those that also process blood components, include in their protocols vigilance actions of occasional seroconversion for the markers of the diseases predicted in donor qualification. The periodicity of laboratory monitoring may be linked to the epidemiological characteristics of each one of the respective diseases and to the periodicity of transfusions.

The detection of reagent markers for these diseases among the polytransfused patients shall trigger immediate look-back procedures and health care to recipients, promoting actions to minimize risks and morbimortality among the individuals of this group.

DEFINITIONS

Adverse event of the blood cycle: all and any adverse occurrence associated with the blood cycle steps that may result in risk to donor or recipient's health, having or not as consequence an adverse reaction.

Adverse reaction: effect or untoward response to donation or to the therapeutic use of blood or blood component that occurs during or after donation or transfusion and is related to them. It may or not result from an incident of the blood cycle.

Adverse reaction to donation: donor's unintentional response, associated with the collection of blood unit, blood component or hematopoietic progenitor cells, that results in death or life-threating situation, deficiency or temporary or permanent disabling conditions, need for medical or surgical intervention, prolonged hospitalization or morbidity, among others.

Adverse reaction to transfusion or transfusion reaction: effect or untoward response observed in someone, timely associated with the administration of blood or blood component. It may be the result of an incident of the blood cycle or of the interaction between a recipient and blood or blood component, a biologically active product.

Allogeneic or homologous donation: donation occurs among individuals of the same species, however, donor and recipient are different individuals.

Autologous donation: previous collection of a blood bag from someone for his/her own use in a scheduled transfusion procedure, in other words, donor and recipient are the same individual.

Blood component: product originated from whole blood or plasma, obtained by physical processing.

Blood cycle: process that comprises the technical procedures related to the steps of donor recruitment, selection and qualification, and to the processing, storage, transportation and distribution of blood components, to pre-transfusion procedures and to the transfusion act.

Blood establishment: facility that conducts any kind of the blood cycle activities. **Corrective action**: activity performed to eliminate the cause of an existing nonconformance or other untoward situation with the aim of preventing recurrence.

Blood processing facility: public or private blood establishment responsible for the collection and processing of blood/blood component.[5]

Communication: exchange of information, by telephone, facsimile, electronic mean, physical mean or other, to the competent authority of the national health regulatory system, to the blood establishment, to other health facilities, companies or product manufacturers, where applicable, about the occurrence of adverse events and their consequences, related to products of health interest and to technical and therapeutic procedures in donors and recipients.

Distribution: supply of blood and components by a blood establishment for stock/storage, matched or not, for transfusion or industrial purposes.

Health facility: all the services related to health care.

Hemovigilance: set of vigilance procedures that cover all the blood cycle, with the aim of obtaining and providing information on adverse events occurred in its different steps to prevent their appearance or recurrence, improve the quality of processes and products, and enhance donor and recipient's safety.

Index donation: donation whose blood component(s) is(are) involved in the look-back process under investigation.

Preventive action: action taken to reduce the potential of nonconformances or other untoward situations.

Serious adverse event of the blood cycle: is described as the incident that led to the adverse reaction, and other incidents and near misses of repetitive and unusual nature for which corrective and preventive actions have already been promoted.

Supplier: natural or legal person that supplies a product or service to the organization. It can be or not the same one processing blood and blood components.

Incident: incidents are within the scope of the adverse events of the blood cycle, discovered during or after transfusion or donation. They comprise, thus, deviations from operational procedures or individual's safety policies in the health facility, leading to inadequate transfusions or donations that may lead or not to adverse reactions. In case of transfusion, it occurs when an individual receives a blood component that does not meet all the requirements for a transfusion that is adequate for him/her or that has been prescribed for someone else.

[5] In Brazil, there are several categories of blood establishments, from the ones that perform all the blood cycle actions to those that only collect or only transfuse.

Look-back: part of the hemovigilance that deals with the retrospective investigation related to the traceability of bags from a prior donation of a donor who showed seroconversion for a marker or related to a blood recipient who came to present a positive marker for a communicable disease. This term is also applicable in cases of positivity detection in microbiological analyses of blood components and investigation of bacterial infectious pictures in recipients, with no immediate manifestation, but potentially imputed to transfusion.

Near miss: deviation from a standard procedure or from a policy that is detected before the start of a transfusion or donation and that could have resulted in a wrong transfusion, in a reaction to transfusion or to donation.

Nonconformance: fail in complying with requirements previously specified.

Notification: information to the competent authority of the national health regulatory system, by its web based system, about the occurrence of adverse event related to products of health interest and to technical and therapeutic procedures in donors and recipients, as defined in standards. In exceptional cases, it can be done by other documentary mean (facsimile, electronic mean, physical mean or other).

Reagent marker: laboratory marker tested and whose result showed to be reagent, including positive and inconclusive results.

Record: administrative procedure that keeps accessible and traceable information about technical acts to which donors, recipients and products of health interest were subjected, with or without provision in rules.

Seroconversion: result of the serological seroconversion for markers of blood transmitted infections identified in the laboratory screening of a donor who, in prior donation, had non-reagent/negative result for the same marker. In the case of test by molecular biology methodology the term is not applicable, because the marker is not investigated in blood serum but in the cells, although there is nonreagent to reagent 'seroconversion'.

REFERENCES

BRASIL. Agência Nacional de Vigilância Sanitária. **Manual Técnico para Investigação da Transmissão de Doenças pelo Sangue**. 1. ed. Brasília: Anvisa, 2004. Disponível em: <http://portal.anvisa.gov.br/wps/wcm/connect/912de50047457fc18b7adf3fbc4c6735/manual_doenca.pdf?MOD=AJPERES>. Acesso em: 13 jan. 2015.

_____. Agência Nacional de Vigilância Sanitária. **Hemovigilância: manual técnico para investigação das reações transfusionais imediatas e tardias não infecciosas.** Brasília: Anvisa, 2007. Disponível em: <http://portal.anvisa.gov.br/wps/wcm/connect/17386000474581698db3dd3fbc4c6735/manual_tecnico_hemovigilancia_08112007.pdf?MOD=AJPERES>. Acesso em: 8 jan. 2015.

_____. Agência Nacional de Vigilância Sanitária. Resolução da Diretoria Colegiada - RDC nº 56, de 16 de dezembro de 2010. Dispõe sobre o regulamento técnico para o funcionamento dos laboratórios de processamento de células progenitoras hematopoéticas (CPH) provenientes de medula óssea e sangue periférico e bancos de sangue de cordão umbilical e placentário, para finalidade de transplante convencional e dá outras providências. **Diário Oficial da União**, Brasília, DF, 17 dez. 2010.

_____. Agência Nacional de Vigilância Sanitária. Resolução da Diretoria Colegiada - RDC nº 36, de 25 de julho de 2013. Institui ações para a segurança do paciente em serviços de saúde e dá outras providências. **Diário Oficial da União**, Brasília, DF, 26 jul. 2013b.

_____. Agência Nacional de Vigilância Sanitária. Resolução da Diretoria Colegiada - RDC nº 34, de 11 de junho de 2014. Dispõe sobre as boas práticas do ciclo do sangue. **Diário Oficial da União**, Brasília, DF, 16 jun. 2014a.

_____. Ministério da Saúde. **Guia de Vigilância Epidemiológica**. 7. ed. Brasília: Ministério da Saúde, 2009.

_____. Ministério da Saúde. **Aspectos Hemoterápicos Relacionados a TRALI** (Lesão Pulmonar Aguda relacionada à Transfusão) - Medidas para redução do risco. Brasília: Ministério da Saúde, 2011. Disponível em: <http://bvsms.saude.gov.br/bvs/publicacoes/aspectos_hemotrapicos_relacionados_trali.pdf>. Acesso em: 13 jan. 2015.

_____. Ministério da Saúde. Portaria nº 2.712, de 12 de novembro de 2013. Redefine o regulamento técnico de procedimentos hemoterápicos. **Diário Oficial da União**, Brasília, DF, 13 nov. 2013a.

_____. Ministério da Saúde. Portaria nº 1.271, de 6 de junho de 2014. Define a Lista Nacional de Notificação Compulsória de doenças, agravos e eventos de saúde pública nos serviços de saúde públicos e privados em todo o território nacional, nos termos do anexo, e dá outras providências. **Diário Oficial da União**, Brasília, DF, 9 jun. 2014b.

CENTERS FOR DISEASE CONTROL AND PREVENTION. National Healthcare Safety Network. Biovigilance Component. **Hemovigilance Module Surveillance Protocol**. Aug. 2013. Disponível em: <http://www.cdc.gov/nhsn/PDFs/Biovigilance/BV-HV-protocol-current.pdf>. Acesso em 12 jan. 2015.

HALTER, J. et al. Severe events in donors after allogeneic hematopoietic stem cell donation. **Haematologica**, v. 94, n. 1, p. 94-101, Jan. 2009. Disponível em: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2625420/>. Acesso em: 13 jan. 2015.

INTERNATIONAL SOCIETY OF BLOOD TRANSFUSION. **Definições para a vigilância de complicações relacionadas com a dádiva de sangue**. 2008 [updated 2008; cited 2012 10/04]. Disponível em: <http://www.hemovigilancia.net/docs/Standard_DOCO_%202008%20_V%20P_12022009.pdf>. Acesso em: 12 jan. 2015.

INTERNATIONAL SOCIETY OF BLOOD TRANSFUSION; INTERNATIONAL HEMOVIGILANCE NETWORK. **Proposed standard definitions for surveillance of noninfectious adverse transfusion reactions.** July 2011. Disponível em: <http://www.ihn-org.com/wp-content/uploads/2011/06/ISBT-definitions-for-non-infectious-transfusion-reactions.pdf>. Acesso em: 12 jan. 2015.

KAMEL, H. et al. Delayed adverse reactions to blood donation. **Transfusion**, v. 50, p. 556-65, Mar. 2010.

NEWMAN, B. H. Blood donor complications after whole-blood donation. **Curr Opin Hematol**, v. 11, n. 5, p. 339-45, Sept. 2004.

_____. Blood donor suitability and allogeneic whole blood donation. **Transfus Med Rev**, v. 15, n. 3, p. 234-44, July 2001.

_____. Donor reactions and injuries from whole blood donation. **Transfus Med Rev**, v. 11, n. 1, p. 64-75, Jan. 1997.

NEWMAN, B. H et al. Adverse effects in blood donors after whole-blood donation: a study of 1000 blood donors interviewed 3 weeks after whole-blood donation. **Transfusion**, v. 43, n. 5, p. 598-603, May 2003.

WINTERS, J. L. Complications of donor apheresis. **J Clin Apher**, v. 21, n. 2, p. 132-41, July 2006.

PUBLIC HEALTH AGENCY OF CANADA. Guideline for Investigation of Suspected Transfusion Transmitted Bacterial Contamination. **Canada Communicable Disease Report**, v. 34S1, Jan. 2008. Disponível em: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08pdf/34S1-eng.pdf>. Acesso em: 13 jan. 2015.

PULSIPHER, M. A. et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. **Blood**, v. 113, n. 15, p. 3604-11, Apr. 2009.

SERIOUS HAZARDS OF TRANSFUSION (SHOT). **Definitions of Current SHOT Categories & What to Report**. United Kingdom, Mar. 2011. Disponível em: <http://www.shotuk.org/wp-content/uploads/2011/03/SHOT-Categories-2010-v13.pdf>. Acesso em: 13 jan. 2015.