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HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Directorate B - Health systems, medical products and innovation
B4 - Medical Products : quality, safety, innovation

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COMMON APPROACH
FOR DEFINITION OF REPORTABLE SERIOUS ADVERSE EVENTS AND REACTIONS AS LAID DOWN IN THE DIRECTIVE 2002/98/EC[1] *(THE BLOOD DIRECTIVE)* AND COMMISSION DIRECTIVE 2005/61/EC[2]
VERSION 5.2 (2016)

Article 8 of Directive 2005/61/EC provides that "*Member States shall submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse events and reactions received by the competent authority using the formats in Part D of Annex II and Part C of Annex III*."

However, precisely which serious adverse events and reactions (SARE) should be notified to the Commission may be interpreted differently. In 2007, the European Commission and Member States therefore agreed at a meeting of the competent authorities for blood and blood components[3] to define a common approach regarding the scope and definitions of the serious adverse events and reactions. This document was intended to inform the first annual reporting exercise completed in June 2008.

At the end of 2007, the Commission convened a first meeting of national experts where the initial common approach was laid down. Since 2009, several meetings of haemovigilance experts have taken place, and the current document reflects updates discussed in these meetings. These include:

- Meeting of national experts (19 December 2007),
- Working Group on "Common approach for definition of reportable serious adverse events and reactions Blood and blood components Directive 2002/98/EC and Commission directive 2005/61/EC" (29 April 2009),

[1] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8.2.2003, p. 30).
[2] Commission Directive 2005/61/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events (OJ L 256,1,10, 2005, p.32).
[3] DG Health and Consumers (DG SANCO). Summary report of the meeting of competent authorities for blood and blood components. Brussels: DG SANCO; 2007. http://ec.europa.eu/health/ph_threats/human_substance/documents/blood_mi_20071018_en.pdf (accessed 8 June 2015).

- Meeting of the Haemovigilance Working Group[4] (3 May 2011),
- Meeting of the Haemovigilance Working Group (26 March 2012), and
- Meeting of the Haemovigilance Working Group (27 February 2013)
- Meeting of the Haemovigilance Working Group (10 November 2015).

The common approach laid down here aims to facilitate comparisons between data sent to the Commission from Member States, and associated countries. The guidelines are meant to reduce the reporting burden on all parties concerned (reporting establishments, competent authorities, and the European Commission) by clarifying issues before data collection is undertaken each year.

It should be noted that this document is a **recommendation** for the completion of the electronic reporting template for serious adverse reaction(s) and event(s) (PDF version 2.5)**,** but is not legally binding for Member States. Furthermore, due to the complexity of data collection, annual reporting of serious adverse events and reactions has been and will continue to be a learning exercise over the coming years.

Please also note that the instructions in this document are still subject to clarifications, refinements and improvements.

The common approach is structured as follows:

1. **Scope of reporting.** This chapter addresses questions about what data should be reported to the Commission, and how this should be done. The chapter addresses those questions which have arisen to date, but may be subject to changes if future reporting exercises raise additional issues (subject to assessment by the Commission).

2. **Guidance on reportable serious reactions.** This chapter provides internationally agreed definitions of the serious adverse reactions terms listed in Directive 2005/61/EC Annex II, part D (Annual notification format for serious adverse reactions).

3. **Guidance on reportable serious adverse events.** This chapter gives indicative examples of serious adverse events, and how they should be classified according to the proposed format in Directive 2005/61/EC Annex III, part C (Annual notification format for serious adverse events).

In this revised edition of the document, the key changes from previous versions are in section 1 (p. 17) where authorities are asked to provide comments with information on serious adverse reactions that are fatal and section 2 (p. 19ff) as well as Annex 4 which aim to achieve greater standardisation in the reporting of serious adverse events.

[4] This is an Expert Sub-group of the Competent Authorities on Substances of Human Origin Expert Group.

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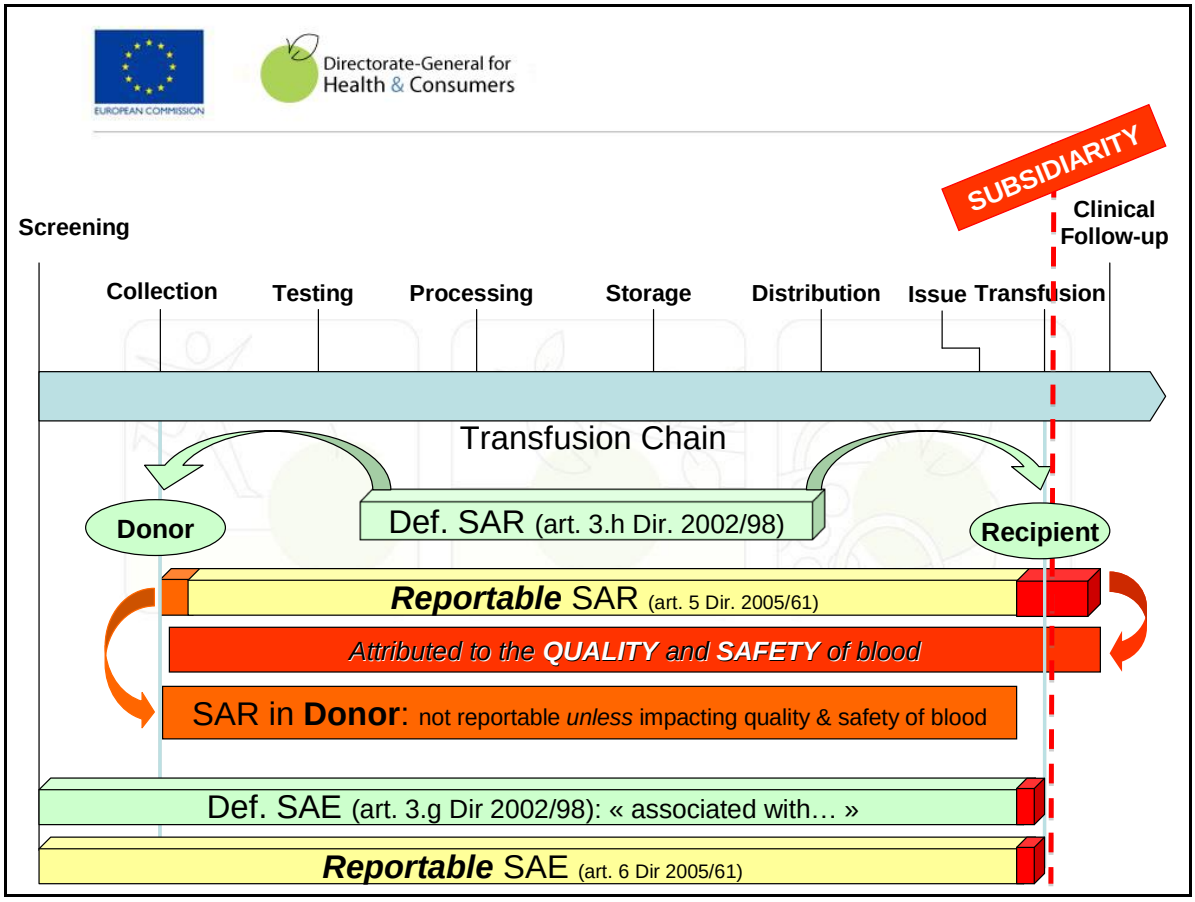
1. SCOPE OF REPORTING

EU legislation on blood states that reportable information concerns:

- *"any **serious** adverse reactions (SAR) observed in recipients during or after transfusion which may be attributable to the quality and safety of blood and blood components* (Directive 2005/61/EC Article 5(1))", and

- *"any **serious** adverse events (SAE) which may affect the quality or safety of blood and blood components* (Directive 2005/61/EC Article 6(1)."

The legal coverage of these definitions means that there is no mandated requirement to report events or reactions in donors which do not influence the quality and safety of the blood components. Similarly, reactions in recipients which are not linked to the quality and safety of the blood components transfused are not reportable under this legal framework.



Note on the diagram *The stages in the transfusion chain where a serious adverse reaction or a serious adverse event may occur are shown above. The blue bar at the top illustrates the scope of the definitions in Directive 2002/98/EC. The lower part of the diagram shows which serious adverse events and reactions are subject to mandatory reporting as described by the specifications in 2005/61/EC.*

According to Article 168 of the Consolidated version of the Treaty on the Functioning of the European Union[5], the management of healthcare, i.e. the clinical use of blood and blood components, is not a competence for the European Union, and remains under the responsibility of the Member States. Serious adverse events occurring after the start of the medical act of transfusion are therefore not subject to mandatory reporting under the Blood Directive. Similarly, serious adverse reactions not attributable to the quality and safety of the blood or blood component are not subject to mandatory reporting under EU legislation.

As a general principle, the Commission cannot require Member States to report more information than specified in the Blood Directives. The Commission is, however, aware that there are some areas where Member States would like to report additional data, and in these cases the Commission agrees to consider wider reporting submitted on a voluntary basis. For example, many Member States require, and consider good practice, the reporting of all **serious adverse reactions in blood donors,** regardless of whether they have influenced the quality and safety of the blood components collected.

1.1. Reporting timeframe

Article 8 of Directive 2005/61/EC provides that *"Member States shall submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse reactions and events received by the competent authority using the formats in Part D of Annex II and Part C of Annex III."*

Tables in the legally-mandated format should be filled in by reporting establishments on an annual basis and sent to the national competent authorities. The competent authorities should then collate this information and complete the reporting template (sent by the Commission) with the aggregated data of **confirmed** cases per category over the previous year**.** The competent authorities should not forward individual forms sent by reporting establishments to the Commission.

The annual report to the European Commission aims to monitor ex-post the serious adverse events and serious adverse reactions that have occurred during the previous reporting year in the EU. Therefore **only those serious adverse events or reactions which have occurred prior to the 31 December of the reporting year, and for which investigations are finalised and confirmed before the cut-off date for reporting to the Commission (specified by the competent authority) should be included in the annual report of that reporting year**.

Serious adverse events and reactions that have occurred during the reporting year, but for which investigations are only completed after the cut-off date for reporting to the Commission should be reported in the subsequent year during which the investigation is finalised. This will result in a certain number of cases being attributed to a wrong year, but the general trend is not expected to be significantly affected, because on average a comparable number of cases will be concerned each year. This statistical bias is therefore considered acceptable.

[5] Consolidated version of the Treaty on the Functioning of the European Union (OJ C 326, 26.10.2012, p.47).

EXAMPLE

For the reporting year "Y", Member States *should report* to the Commission the serious adverse events and serious adverse reactions that:

Occurred *within* the calendar year Y and for which investigations were completed and confirmation agreed on before the cut-off date for compilation of national data for reporting to the Commission (e.g. 31 March Y+1),

and

Occurred *before* the calendar year Y, but have not been yet reported to the Commission before because investigations were completed - and confirmations agreed on – after the cut-off date for consolidation of the previous year(s) (e.g. 31 March Y-1 or 31 March Y-2).

For the reporting year "Y", Member States *should not report* to the Commission the Serious Adverse Events and Serious Adverse Reaction that:

Occurred during the calendar year Y, but for which investigations are still pending at the time of the cut-off date (e.g. 31 March Y+1). These cases should be reported as part of the calendar year during which the investigation is completed/final status confirmed (i.e. 31 March Y+2 or later).

1.2. Which organisations should report SAE/R to the competent authority?

Article 1(b) of Directive 2005/61/EC defines reporting establishments as *"the blood establishment, the hospital blood bank or facilities where the transfusion takes place that reports serious adverse reactions and/or serious adverse events to the competent authority."*

Directive 2005/61/EC Article 5 on serious adverse reactions and Directive 2005/61/EC Article 6 on serious adverse events state the responsibilities of the *reporting establishments*. The responsibilities of these different establishments as regards traceability and reporting are outlined below.

1.2.1. Blood establishments

According Directive 2002/98/EC[6] Article 3(e), a blood establishment (BE) "*shall mean any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage, and distribution when intended for transfusion. This does not include hospital blood banks.*"

Article 1(d) of the Directive 2005/61/EC extends the responsibilities of the blood establishment to issuing blood components: *"'issue' means the provision of blood or blood components by a blood establishment or a hospital blood bank for transfusion to a recipient."*

[6] Directive 2002/98/EC of the European Parliament and of the Council setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8,2,2003,p.30).

1.2.2. Hospital blood banks

According to Directive 2002/98/EC Article 3(f), *"hospital blood bank shall mean a hospital unit which stores and distributes and may perform compatibility tests on blood and blood components exclusively for use within hospital facilities, including hospital based transfusion activities."*

Similarly to BEs, hospital blood banks (HBBs) can issue blood components for transfusion (Directive 2005/61/EC Article 1(d)).

More details on serious adverse events reportable by the HBBs can be found in section 3.2.

1.2.3. Facilities

Article 1(f) of Directive 2005/61/EC provides that "*'facilities' means hospitals, clinics, manufacturers, and biomedical research institutions to which blood or blood components may be delivered"*.

These facilities also have reporting obligations towards the competent authority.

1.2.3.1. Facilities where the transfusion takes place

Article 5(1) of Directive 2005/61/EC on notification of serious adverse reactions requests that *"Member States shall ensure that those facilities where transfusion occurs have procedures in place to retain the record of transfusions and to notify blood establishments without delay of any serious adverse reactions observed in recipients during or after transfusion which may be attributable to the quality or safety of blood and blood components."*

Facilities where transfusion takes place are understood as hospitals, clinics and bio-medical research institutions that perform transfusions of blood components as established therapies or clinical trials.

More details on serious adverse events reportable by the facilities where the transfusion takes place can be found in section 3.2.

1.2.3.2. Facilities understood as "manufacturers of blood derived medicinal products"

Medicinal products originating from blood/plasma components are regulated by Directive 2001/83/EC[7]. However, collection and testing of the raw blood and plasma material used for the manufacturing of these products are regulated by the Blood Directive.

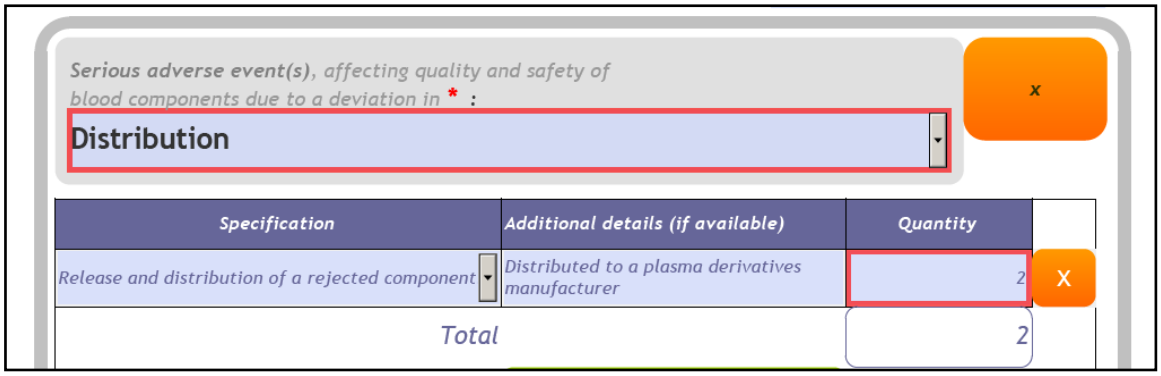
SAE/R related to blood/plasma derived medicinal products should be reported through the national pharmacovigilance systems. However, when these SAE/R are linked to a problem of quality/safety that occurred during collection and/or testing, manufacturers must forward this information to the haemovigilance chain (i.e. the blood establishment

[7] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28/11/2004, p. 67).

that distributed the components concerned). The blood establishment should then report all SAE/R relating to collection and testing to the competent authority. This interdependence requires that the pharmacovigilance and haemovigilance systems are closely interconnected. It is therefore recommended that authorities on pharmacovigilance and haemovigilance communicate directly with each other.

A reaction associated with collection and testing can be captured within the associated component category. Such reactions i.e. associated, with blood /plasma material for manufacturing should always be highlighted within in the comment section of the template.

For SAEs, Member States can indicate that events concerning collection and testing relate to blood/plasma derived medicines in the "specification" box of the SAE section. Complementary descriptions can also be added in the "additional details" box, as illustrated below.



Guidance on reportable serious adverse reactions (SAR)

1.3. General information

At the beginning of the template, the following fields are available but not mandatory:

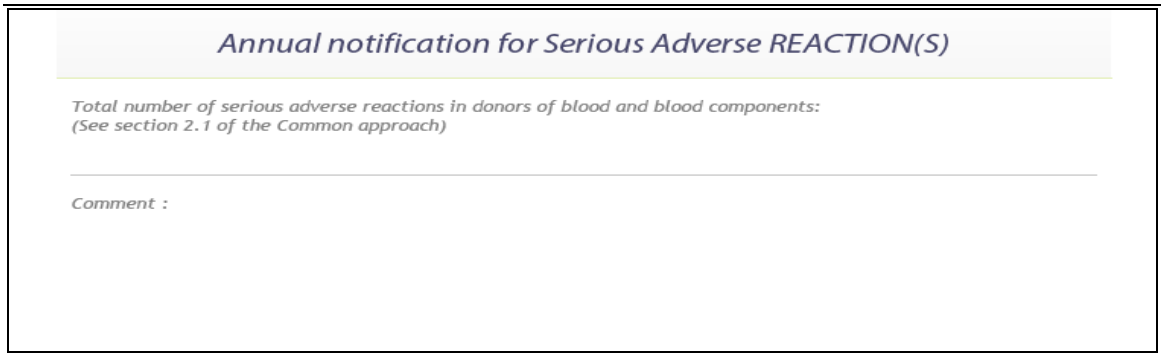
- **Serious adverse reactions in donors**

According to Article 3(h) of Directive 2002/98/EC, a serious adverse reaction is *"an unintended response in donor or in patient associated with the collection or transfusion of blood or blood components that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity."*

Article 5 of Directive 2005/61/EC provides a more limited definition of *reportable serious adverse reactions*, which relates **to recipients of blood and blood components.** Serious adverse reactions in donors are **not** reportable, unless they impact on the quality and safety of the blood component.

Several Member States collect information on serious adverse reactions in donors. The Commission recognises the value of this data and invites Member States to submit an annual report concerning donor reactions on a voluntary basis.

Accordingly, a specific box "SAR in donor of blood and blood components" can be found at the beginning of the SAR section of the PDF reporting template. See the illustration below.



- **Percentage of completeness of data.**

In March 2012, haemovigilance experts agreed to add a field on data completeness to the template. When data reported is partial data, competent authorities can indicate this by adding estimations of percentage data completeness in relation to expected values for four indicators: reports received, units issued, number of recipients transfused, and number of units transfused. Competent authorities who know they have received all possible reports with complete data should report 100 % completeness for the four fields. In 2013, the possibility to select NA when no data is available has been added.

- **Number of reporting establishments in your country.**

Article 26 of Directive 2002/98/EC requires Member States to submit to the European Commission, every 3 years, reports on the implementation of the provisions of the EU Blood Directives, including the number of reporting establishments. This non-mandatory question is also asked in the SARE template to ensure that this information is kept up-to-date and facilitate SARE analyses.

- **Total number of units issued** (see section 2.2.1)

Added in 2013, this is the total number of units issued **across** all blood components. For further information on how to report units issued please see section 2.2.1.

- **Total number of recipients transfused regardless the type of product** (see section 2.2.2)

- **Total number of units transfused** (see section 2.2.3)

Added in 2013, this is the total number of units transfused **across** all blood components. For further information on how to report units transfused please see section 2.2.3.

1.4. Denominators for serious adverse reactions

Annex II part D of Directive 2005/61/EC requires that Member States report information concerning denominators to permit detailed analysis of SAR related to blood components (for example, indicators on the number of SAR per type of blood component issued).

Three sets of information are sought per type of blood component:

This Table refers to [ ] **Whole blood** [ ] **Red blood cells** [ ] **Platelets** [ ] **Plasma** [ ] **Other** *(use separate table for each component)*	Number of units issued (total number of units issued with a given number of blood components)
	Number of recipients transfused (total number of recipients transfused with a given number of blood components) *(if available)*
	Number of units transfused (the total number of blood components (units) transfused over the reporting period) *(if available)*

Member States are required to set up a traceability system which is able to record all the processes and potential serious adverse events and reactions associated with a particular unit of blood/blood component from collection to transfusion (Directive 2005/61/EC Articles 2, 3, and 4). Member States are, therefore, expected to keep good records of their overall transfusion activity.

However, due to differences in the organisation of Member State transfusion systems, collection of denominator data may raise difficulties or result in non-comparable figures. Some clarifications of the definitions for these three denominators are required in order to ensure that comparable and reliable data is reported.

1.4.1. Number of units issued

According to Article 1(d) of Directive 2005/61/EC, "*issue*" means the provision of blood or blood components by a BE or a HBB for transfusion to a recipient.

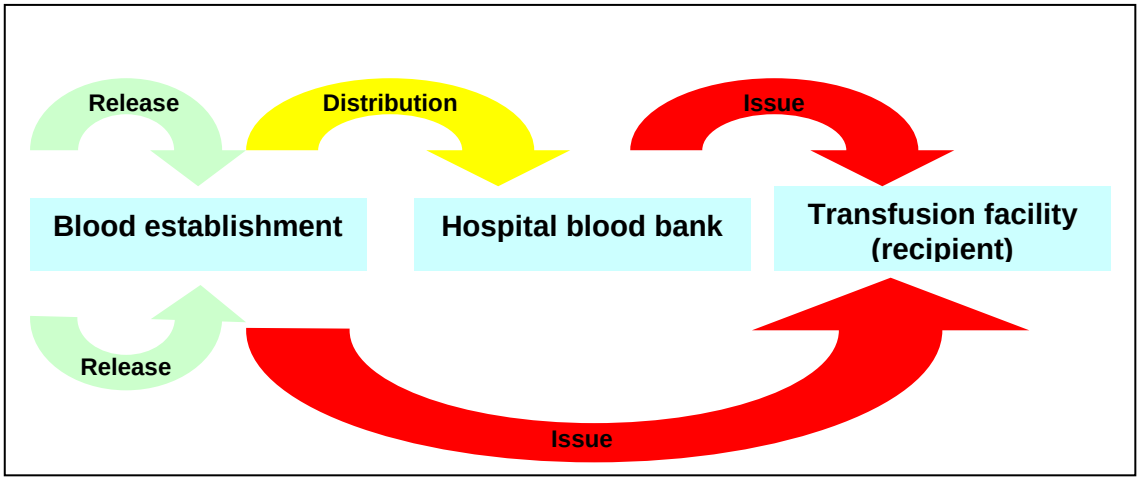
"*Issue*" differs from "*distribution*", which is *"the act of delivery of blood and blood components to other blood establishments, hospital blood banks and manufacturers of blood and plasma derived products. It does not include the issuing of blood or blood components for transfusion* (Article 3(k) of Directive 2002/98/EC)."

"*Distribution*" differs from "*release*" which means "*a process which enables a blood component to be released from a quarantine status by the use of systems and procedures to ensure that the finished product meets its release specification* (Directive 2002/98/EC Article 3(i))." A product which is *released* remains in the remit of the BE as it has not yet been *distributed*.

Therefore, a unit of blood/blood component can be *issued* by either:

- a hospital blood bank,
- a BE responsible for providing blood components for transfusion to a specific recipient directly to a transfusion facility into a hospital or a clinic, or
- a BE with its own transfusion facility.

The diagram below summarises the different release/distribution/issue scenarios:



The first annual report in 2008 highlighted difficulties for several Member States to obtain reliable and robust figures on issuing of blood components. Particular difficulties arise at the level of the hospital blood banks due to among others:

- difficulties in monitoring the final issue of blood components due to multiple cross matching tests done on the same blood bag that do not result in actual issue (e.g. a negative cross-match result, or lack of provision by the BE/HBB of units designated for a patient due to cancellation or postponement of a planned surgery);

- difficulties in monitoring multiple issues of a single blood bag (e.g. blood issued for surgery and returned due to cancellation/postponement of the surgery);

- differences in administrative organisation that complicate reporting of information from a clinical unit or HBB to BEs.

Feedback from hospital blood banks indicates that the vast majority of blood components received by them (i.e. distributed by blood establishments) are issued at least once, even if they are not actually transfused. "Units distributed" is therefore a good estimate of the "number of units issued".

For this reason, experts consulted by the European Commission in April 2009 agreed that an acceptable approximation for the number of units *issued* for transfusion is the following:

Number of units issued =	Units distributed by blood establishments to the hospital blood banks + Units issued by blood establishments directly for transfusion.

Units distributed or issued several times over a year period should only be counted one time. Handling of a unit for compatibility testing within the BE/HBB is not considered issue or a distribution, but should rather be considered as remaining in the inventory.

The units distributed by one BE to another BE should not be counted.

1.4.2. Number of recipients transfused

This definition is to be understood as the number of individual patients who are transfused with at least one unit of blood/blood component during the reporting year in a given country. This definition aims to aggregate the number of individual patients transfused over a year in the country, not specifying whether they received single or multiple transfusions during the period.

If a Member State is able to link recipients to blood components, it should put these figures in the "number of recipients transfused" section of the PDF reporting template (for each individual blood component).

However, the first annual report demonstrated that there are difficulties for the majority of Member States to conclusively link each individual recipient to a precise set of blood components (which is why this information is only optional). This is due to several reasons including:

- in many cases, patients are transfused with several blood components during a single transfusion episode;

- administrative and organisational differences inside hospitals, and between hospitals and BEs, make it difficult to report precisely the number of patients transfused, and how many blood components they receive.

For these reasons, the experts consulted by the Commission in April 2009 agreed that a good approximation for the number of recipients transfused with a given number of blood components is:

Number of recipients transfused =	overall number of recipients transfused at least once over a year period, without linking these transfusion episodes to specific types of blood components.

If it is only possible to report aggregated data, as outlined in the formula above, because it is not possible to obtain recipients transfused per blood component or partial data, then this should be completed in the field "Number of recipients transfused regardless the type of product" at the beginning of the PDF template.

Although this does not allow the "number of recipients/type of blood components" to be calculated, the overall number of recipients can be used as a satisfactory approximation denominator.

If it is not possible to trace patients/recipients at the national level (e.g. lack of unique national ID/reference number in the Member State), this calculation should at minimum be done at the hospital or clinic level, in order to limit statistical bias or possible overestimations caused by some patients having several transfusions episodes in different places during a year.

1.4.3. Number of units transfused

This definition is the total number of individual units transfused in hospitals/reporting establishments independently of hospitalisation episodes or patients.

Home transfusions should be included in the hospital/reporting establishment's activity.

Member States should endeavour to introduce traceability systems that facilitate the collection of information on "units transfused", as this is the 'gold-standard' denominator when analysing SAR data.

1.5. Imputability of reportable SAR (due to the quality and safety of the blood and blood components)

Directive 2005/61/EC Article 5(3)(a) requires that *"Member States shall ensure that reporting establishments notify to the competent authority all relevant information about* ***serious adverse reactions of imputability level 2 or 3****, as referred to in Part B of Annex II,* ***attributable to the quality and safety of blood and blood components.****"*

Imputability levels are defined by Annex II part B as follows:

PART B

Serious adverse reactions — imputability levels

Imputability levels to assess serious adverse reactions.

Imputability level		Explanation
NA	Not assessable	When there is insufficient data for imputability assessment.
0	Excluded	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes.
	Unlikely	When the evidence is clearly in favour of attributing the adverse reaction to causes other than the blood or blood components.
1	Possible	When the evidence is indeterminate for attributing adverse reaction either to the blood or blood component or to alternative causes.
2	Likely, Probable	When the evidence is clearly in favour of attributing the adverse reaction to the blood or blood component.
3	Certain	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the blood or blood component.

Article 5(3)(f) requires that reporting establishment submit a **complete report on serious adverse reactions to the competent authorities on an annual basis** using the format set out in part D of Annex II. This format requires reporting of serious adverse reactions with imputability levels NA to 3.

Article 5(3) raises questions regarding the relationship between the two sub-sections mentioned above (i.e. how to identify, and report on an annual basis, imputability with the link to quality and safety). The common approach outlined below is recommended.

The core goal of the EU legislation on blood is to set rules which guarantee a high level of quality and safety for blood components transfused within the EU. As explained previously, the Blood Directive is essential for ensuring the safety of the transfusion chain, but cannot be solely relied upon for this purpose as clinical practical lies outside of its scope due to the principle of subsidiarity.

In this context, the goals of the annual reporting of serious adverse reactions to the Commission are:

(1) identifying and keeping a record of confirmed general trends on the safety of blood transfusion, which complements information gathered through other European or international sources and channels, and

(2) measuring as precisely as possible the proportion of the total number of serious adverse reactions during the reported year which are related to unsafe and/or bad quality blood components.

This information is crucial for identifying areas where adaptations or improvements to EU blood legislation may be required. It also enables the collection of data on the impact of quality and safety increases for blood components on the safety and efficiency of the whole transfusion chain.

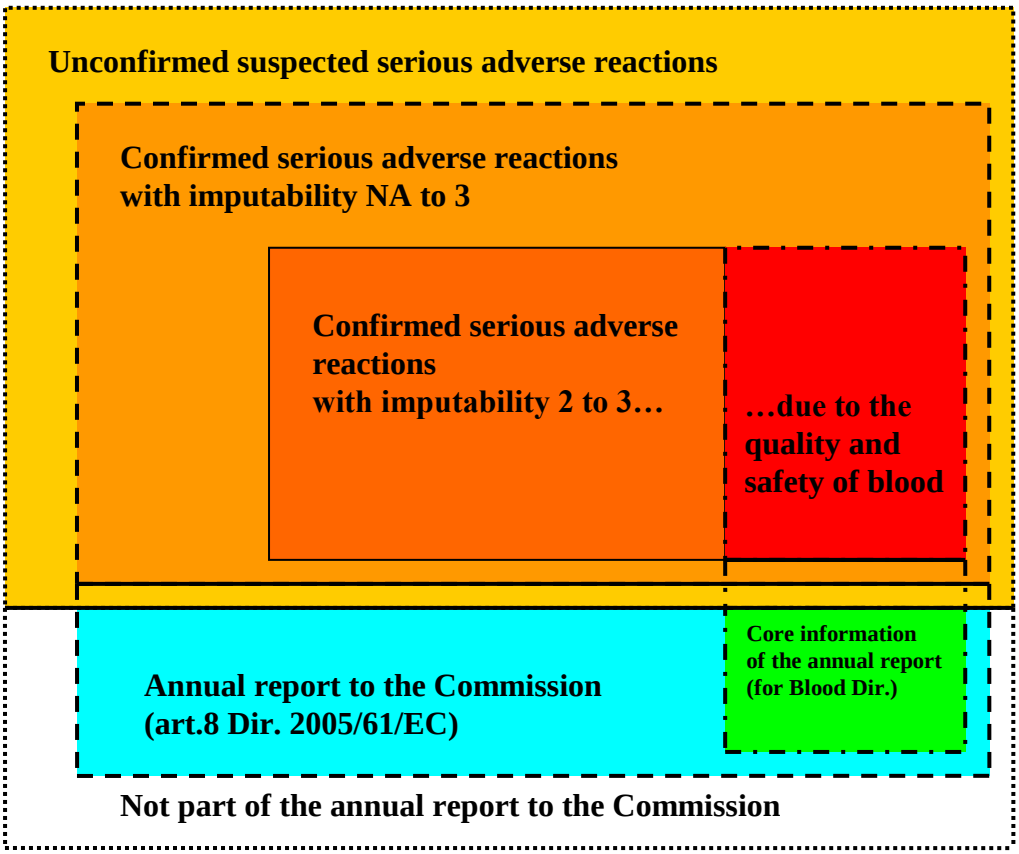
It is therefore crucial to specifically identify and report those cases which are clearly part of the Blood Directive's scope as opposed to other reported serious adverse reactions. For this reason article 5(3)(a) requires that clear-cut, confirmed serious adverse reactions linked to the quality and safety of the blood component are flagged and documented specifically.

"Clear-cut" means that they meet the following two conditions:

- they are likely, probable or certain (imputability 2 to 3), and
- they are attributable to a problem in quality and safety of the blood component.

In summary, the diagram below illustrates the reasoning developed above, and lays down the scope of the annual reporting to the Commission.

Scope of the annual report of serious adverse reactions to the European Commission



It should be noted that Member States are free to design their national reporting systems in a more stringent manner than that outlined in EU legislation (for example requiring that relevant information for all confirmed cases regardless their imputability and/or link to quality and safety be reported).

The Commission is aware that identifying a causal link between a serious adverse reaction and the quality or safety of the blood is often challenging. However, the interest in collecting data on "not assessable" and "level 0" reactions is questionable due to both its limited interest and the resources necessary for its collection. In 2012, it was therefore decided that only confirmed serious adverse reactions of imputability level 1 to 3 should be reported to the Commission. It was also decided that it is acceptable to exclude serious adverse reactions at imputability level 1 from the report. **The annual report should therefore at least include information on the number of serious adverse reactions at imputability 2 to 3 attributable to a problem in the quality and safety of the component, in line with article 5(3)(a) of Directive 2005/61/EC.**

In the PDF reporting template, the data should be transcribed as illustrated below. It should be noted that in 2013, A/B categories were removed for imputability levels 2 and 3. It is currently possible to report SAR for those transfused with whole blood, red blood cells, plasma, platelets, and 'more than one component.'

For ‘more than one component’, denominators should be counted under “per component” figures. For example, if there is a transfusion transmitted bacterial infection in a patient

transfused with two units of plasma and one unit of platelets, the reaction should be reported under 'more than one component', and the number of units transfused under the sections for plasma (two units) and platelets (one unit).

Imputability level after confirmation of the Serious Adverse Reaction(s)			Level 1	Level 2	Level 3	Total
Immunological Haemolysis	Due to ABO incompatibility	Total no death				0
		Total deaths				0
	Due to other allo-antibody	Total no death				0
		Total deaths				0
			Level 1	Level 2	Level 3	Total
Non-immunological Haemolysis		Total no death				0
		Total deaths				0
			Level 1	Level 2	Level 3	Total
Transfusion-transmitted bacterial infection		Total no death				0
		Total deaths				0
			Level 1	Level 2	Level 3	Total

Note on the diagram

Total no death	Total number of confirmed reports of serious adverse reactions related to transfusion of blood or blood components that did not result in the death of the recipient.
Total deaths	Deaths which occurred as an outcome of a serious adverse reaction associated to the transfusion of blood or blood components. Deaths associated with a patient's underlying conditions or any other cause should not be included in this category. In other words, only deaths which are definite, highly likely or certain attributable to the transfusion should be reported.

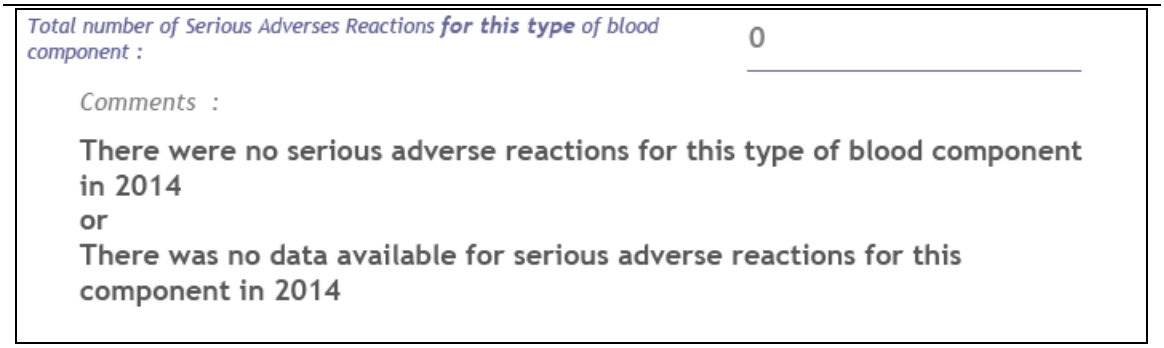
SAR linked to transfusion transmitted bacterial, viral, parasitic, prion and other infectious diseases with imputability 2 or 3 should be reported, as they are due to the quality and safety of the blood component.

SAR linked to SAE at the BE/HBB should be reported systematically as SAR, as they are due to quality and safety of the blood component. For instance, an error at a HBB resulting in a patient developing immunological haemolysis due to ABO incompatibility is a reportable SAR.

Multiple reactions in the same recipient should each be reported as one SAR.

Based on the experiences gained from the first reporting exercises, methods to improve targeted reporting of serious adverse reactions caused by problems in safety and quality could be developed. Methodologies for collecting serious adverse reactions with imputability NA to 1 in a resource efficient manner may also be further discussed.

In case there is no reportable SAR for a particular component, this should be indicated in the comments box for that component. In case there is no available data for a particular component, this should also be indicated in the comments box.



Concerning reports where an SAR is confirmed to be fatal, any relevant information should be reported in the comments box, such as:

- a brief description of patient details (if possible: gender, age, initial illness, clinical indications for transfusion etc.)
- a brief description of occurancies that led to the fatality,
- list of transfused units of blood/blood components; for each unit, any relevant information regarding the preparation of the implication component(s) (leukodepletion, apheresis ..),
- the conclusions and follow-up actions (corrective and preventive), if appropriate.

1.6. Table of reportable serious adverse reactions

The table in Annex I provides common definitions for the serious adverse reactions terms listed in the Directive 2005/61/EC Annex II part D (Annual notification format for serious adverse reactions).

The International Society of Blood Transfusion (ISBT)[8] views and interpretation of haemovigilance are widely recognised in the blood transfusion community. It has therefore been agreed with ISBT, that ISBT definitions for serious adverse reactions should be used as starting point references when available. It should be noted that these definitions may be subject to further refinement in the future, which will be reflected in this document.

ISBT definitions related to surveillance of non-infectious adverse transfusion reactions were agreed by the ISBT in 2011 at the working party on haemovigilance. Complete

[8] http://www.isbt-web.org/ (accessed 8 June 2015)

definitions are available in endnotes of the annex I. It should be noted that this list may not cover all reportable reactions, which should be reported under 'other'.

As of yet there are no ISBT definitions for transmission transmitted infections. The United Kingdom has suggested that SHOT (Serious Hazard of Transfusion) definitions be used in the meantime. Details of these definitions can be found in the table in Annex 1 and on the SHOT website[9].

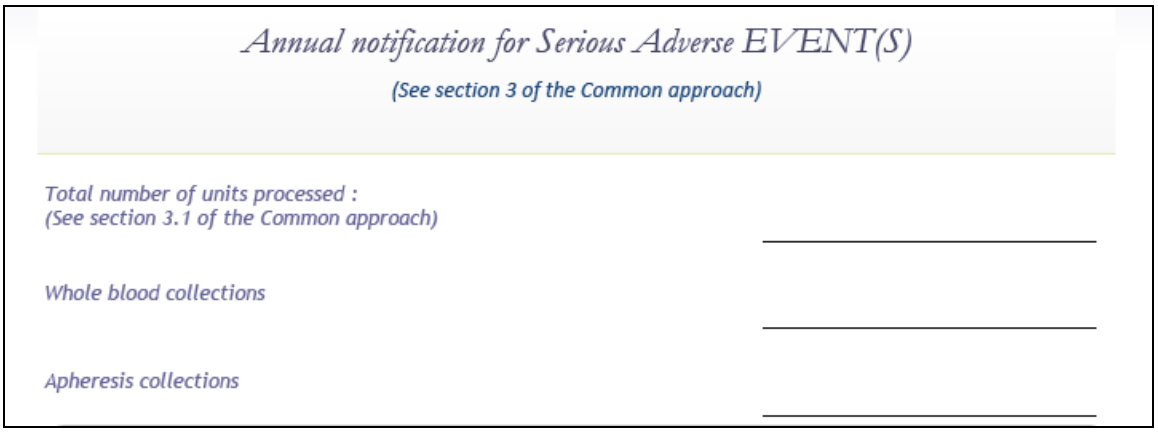
2. GUIDANCE ON REPORTABLE SERIOUS ADVERSE EVENTS (SAES)

2.1. Denominator: *Total number of blood and blood component units processed*

Annex III part C of Directive 2005/61/EC (Notifications of Serious Adverse Events) requires that Member States report the "total number of blood and blood components processed" prior to providing data on the occurrences of serious adverse events.

Reporting establishment	
Reporting period	1 January-31 December *(year)*
Total number of blood and blood components processed:	

This information can be reported in the PDF template as illustrated below:



Collecting this information aims to provide a general understanding of the overall parameters of blood component processing that can be used as denominators for detailed analysis (e.g. "number of SAEs per number of blood components processed").

Article 1(j) of Directive 2005/62/EC[10] on quality systems for blood establishments states that "*'processing' means any step in the preparation of a blood component that is carried out between the collection of blood and the issuing of a blood component."* According to Articles 3(e) and 3(f) of Directive 2002/98/EC, only blood establishments carry out "processing".

[9] http://www.shotuk.org/home/ (accessed 8 June 2015)

[10] Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments (OJ L 256, 1.10.2005, p. 41).

Activities of hospital blood banks are limited to storage, distribution and compatibility testing. Hospital blood banks are not involved in the preparation of blood components, hence are not involved in "processing." This interpretation is maintained for this year's reports to the European Commission.

Due to the complex nature of calculating the number of units processed from single donations, the experts consulted by the European Commission in March 2012 agreed that the number of units processed should be given as the number of individual collections performed by blood establishments. Where possible, whole blood and apheresis collections should be reported separately in the template. Where a single collection produces two or more components, it should be counted as one collection, and therefore one unit processed.

2.2. SAE that occur in the clinical sphere

Article 1(b) of Directive 2005/61/EC requires that blood establishments, hospital blood banks or facilities where the transfusion takes place report serious adverse reactions and/or serious adverse events to competent authorities.

According to Article 152(5) of the EC Treaty[11], the clinical act of transfusion is a legal barrier beyond which the Blood Directive cannot intervene (the principle of subsidiarity). EU legislation on blood applies up to the *issue* of the blood component for transfusion, after which the clinical legal sphere applies. Bedside treatment, prior and after transfusion, is therefore the exclusive responsibility of Member States. As a result, a SAE occurring at the bedside before, during or after transfusion (e.g. the use of an infected needle) is not reportable to the Commission.

However, practical experience demonstrates that this boundary can be blurred because the two legal spheres are closely interconnected in operational terms. For example, blood components may be received by clinical staff at the hospital, and stored minutes or even hours prior to the transfusion in a fridge next to the clinical area that is monitored by the HBB. These grey zones cause uncertainty over which SAE should be reported under the Blood Directives.

Experts consulted by the European Commission in 2012 agreed that acts of storage and distribution, even after issue to a clinical area, lie within the remit of the Blood Directive, and any SAEs that occur during this time are therefore reportable. For example, a unit of blood may be stored incorrectly on a ward and then returned to the blood fridge for use at a later time, or a unit of blood may be incorrectly packaged for distribution to another hospital when a patient is transferred.

2.3. Criteria for inclusion of serious adverse events in the annual notification

Not all adverse events are considered 'serious'.

In the sense intended in this reporting exercise, adverse events are considered serious and reportable to the European Commission, when they may put in danger blood donors or

[11] Consolidated version of the Treaty establishing the European Community (OJ C 321E, 29.12.2006, p. 37).

recipients of blood or blood components, or they may have a negative impact on blood donation or on transfusion of patients.

Deviations from standard operating procedures in reporting establishments, or other adverse events which have implications for the quality and safety of blood/blood components, should be reported to the Commission only when one or more of the following criteria applies:

1. Inappropriate blood/blood components have been issued/distributed for use, even if not used.
For instance, - blood components distributed for use with incorrect blood group labels - blood components distributed for use without the mandatory donor testing results - blood components issued with incorrect cross-matching information - blood components distributed for use despite a post-donation notification from the donor implying a disease transmission risk - blood components distributed/issued for use despite having been stored at temperatures outside the required range - blood components issued by the HBB without specific characteristics requested by the treating physician (e.g. irradiation, CMV negative)
2. The adverse event resulted in loss of any irreplaceable highly matched (i.e. recipient specific) blood/blood component,
For instance, - Blood components prepared for a patient with highly specific and urgent needs lost due to a storage or processing error - Blood components of a very rare group collected for a specific recipient and lost due to a storage or processing error
3. The adverse event resulted in the loss of a significant quantity of unmatched blood or blood components – a significant quantity is considered a loss that will have a negative impact (delay or cancellation) on treatment or surgery,
For instance, - In a BE, an undetected cold-room break-down with the consequent discard of number of red cell concentrates creating a problem to respond to requests for RCC from hospitals - A failure of the virology testing equipment results in 50% of a large blood establishment (supplying many hospitals) platelet stock expiring without being cleared for issue

4. The adverse event could have implications for other patients or donors because of shared practices, services, supplies or donors (e.g. repeat event inside or outside the BE/HBB),
For instance, - A defect is detected in a haemoglobin testing device known to be used by other blood establishments – no harm caused to donors due to parallel testing by a different method[12]
5. The adverse event could significantly impact the blood transfusion system (e.g. by jeopardising the confidence of blood donors or recipients).
For instance, - Confidential donor information is accidentally made publically accessible - Donations are collected, in error, from underage donors.

The term "near miss event"[13] is not defined in the Blood Directive but is a commonly used term. Near miss events are adverse events and, if they meet the criteria listed above, they reportable as SAEs.

SAE which are not reportable include:

- An incorrect result of compatibility testing performed by the BE/HBB due to a misidentification of the recipient's blood sample (e.g. wrong blood in tube from a clinical area and detected in the lab) is not reportable as the error falls within the "clinical practice" scope and is not covered by the Blood Directives.

- Correctly cross-matched and labelled blood components that are issued by the HBB for the correct patient and transfused to the wrong patient are not reportable as the error falls within the "clinical practice" scope and is not covered by the Blood Directives.

2.4. Categorisation of serious adverse events

Annex II provides definitions of activity steps and specifications to assist with categorisation of reportable serious adverse events (affecting the quality and safety of blood components) according to the format in Directive 2005/61/EC Annex III, part C (Annual notification format for serious adverse events).

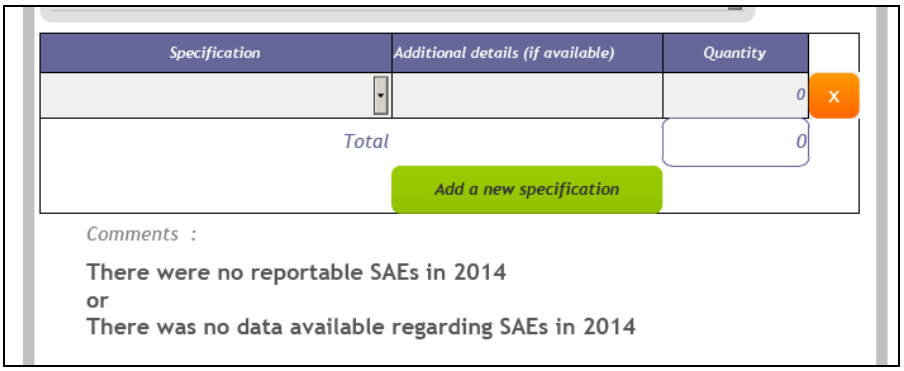
It is acknowledged that more than one specification can be associated to a specific event, but request that for the purpose of collating data for the annual report the dominant

[12] This should also be reported via the medical devices reporting system.

[13] According to SHOT, near miss events are "an error or deviation from standard procedures or policies that is discovered before the start of the transfusion and that could have led to a wrongful transfusion or a reaction in a recipient if transfusion was to have taken place." http://www.shotuk.org/wp-content/uploads/2010/03/SHOT-definitions-Nov012-final.pdf (accessed 08 June 2015)

specification be selected. Further comments can be provided regarding other possible selections in the "additional details" box.

In case there are no reportable SAEs for this reporting year, this should be indicated in the comments box for SAEs. In case there is no available data for this year, this should also be indicated in the comments box.



3. ANNEX I: TABLE OF REPORTABLE SERIOUS ADVERSE REACTIONS

Directive 2005/61/EC categories	Reportable reactions
Immunological haemolysis due to ABO incompatibility	Acute haemolytic transfusion reaction (AHTR according to ISBT[I]) due to ABO-incompatibility
Immunological haemolysis due to other allo-antibody	Acute haemolytic transfusion reaction (AHTR according to ISBT[I]) due to irregular antibodies Delayed haemolytic transfusion reaction (DHTR according to ISBT[II]) due to irregular antibodies
Non-immunological haemolysis	Acute haemolytic transfusion reaction (AHTR according to ISBT) due to physical, chemical or biological (but non-immune) reasons (for example mechanical stress, temperature, osmotic pressure, pH, drugs etc.)
Anaphylaxis / hypersensitivity	Severe allergic reaction (according to ISBT[III])
Transfusion related acute lung injury (TRALI)	TRALI (according to ISBT[IV])
Transfusion transmitted bacterial infection	Sepsis due to T-t BI (according to SHOT definition of transfusion transmitted infections[V])
Transfusion-transmitted viral infection (HBV, HCV, HIV-1/2, others)	T-t viral infection (according to SHOT definition of transfusion transmitted infections[V])
Transfusion-transmitted parasitical infection (malaria, others)	T-t parasitical infection (according to SHOT definition of transfusion transmitted infections[V])
Post-transfusion purpura	Post transfusion purpura (PTP according to ISBT[VI])
Graft versus host disease	Transfusion associated graft versus host disease (TA-GVHD according to ISBT[VII])
Other serious reactions (specify)	• Febrile non haemolytic transfusion reactions (FNHTR according to ISBT[VIII]) • Severe reaction due to transfusion associated circulatory overload (TACO according to ISBT[IX]) as well as cases occurring after 6 hours if clinically confirmed • Severe reaction due to transfusion associated dyspnea (TAD according to ISBT Definition[X]) • Transfusion-transmitted prion infection • Others[XI] (including previously uncategorised complications of transfusions)

I Acute haemolytic transfusion reaction (AHTR) (ISBT definition)

An AHTR has its onset within 24 hours of a transfusion. Clinical or laboratory features of hemolysis are present.

Common signs of AHTR are:

- Fever
- Chills/rigors
- Facial flushing
- Chest pain
- Abdominal pain
- Back/flank pain
- Nausea/vomiting
- Diarrhea
- Hypotension
- Pallor
- Jaundice
- Oligoanuria
- Diffuse bleeding
- Dark urine

Common laboratory features are:

- Hemoglobinemia
- Hemoglobinuria
- Decreased serum haptoglobin
- Unconjugated hyperbilirubinemia
- Increased LDH an AST levels
- Decreased hemoglobin levels

Not all clinical or laboratory features are present in cases of AHTR.
Blood group serology usually shows abnormal results but absence of immunological findings does not exclude AHTR. AHTR may also be due to erythrocyte auto-antibodies in the recipient or to non immunological factors like mechanical factors inducing hemolysis (malfunction of a pump, of a blood warmer, use of hypotonic solutions, etc.).

II A DHTR (ISBT definition) usually manifests between 24 hours and 28 days after a transfusion and clinical or laboratory features of hemolysis are present. Signs and symptoms are similar to AHTR but are usually less severe. AHTR may sometimes manifests as an inadequate rise of post-transfusion hemoglobin level or unexplained fall in hemoglobin after a transfusion. Blood group serology usually shows abnormal results.

III Allergic reaction (ISBT definition)

An allergic reaction may present only with mucocutaneous signs and symptoms:

- Morbilliform rash with pruritus
- Urticaria (hives)
- Localized angioedema
- Edema of lips, tongue and uvula
- Periorbital pruritus, erythema and edema
- Conjunctival edema

occurring during or within 4 hours of transfusion. In this form it usually presents no immediate risk to life of patient and responds quickly to symptomatic treatment like anti-histamine or steroid medications. This type of allergic reaction is called ‘minor allergic reaction’ in many hemovigilance systems. ***For the purpose of classification this type of allergic reaction would be graded as 1, i.e. non-severe.***

An allergic reaction can also involve respiratory and/or cardiovascular systems and present like an anaphylactic reaction. There is anaphylaxis when, in addition to mucocutaneous systems there is airway compromise or severe hypotension requiring vasopressor treatment (or associated symptoms like hypotonia, syncope). The respiratory signs and symptoms may be laryngeal (tightness in the throat, dysphagia, dysphonia, hoarseness, stridor) or pulmonary (dyspnea, cough, wheezing/bronchospasm, hypoxemia). Such a reaction usually occurs occurring during or very shortly after transfusion. ***For the purpose of classification this type of allergic reaction would be graded as 2 (severe), 3 (life-threatening) or 4 (death) depending on the course and outcome of the reaction.***

An allergic reaction classically results from the interaction of an allergen and preformed antibodies. A rise of mast cell tryptase can support the diagnosis of an allergic reaction. IgA deficiency and/or anti-IgA in the recipient has been associated with severe allergic reactions but is only one infrequent cause out of many others.

IV TRALI (ISBT definition incorporating 2013 correction)

In patients with no evidence of acute lung injury (ALI) prior to transfusion, TRALI is diagnosed if a new ALI is present:

- Acute onset
- Hypoxemia
    - Pa02 / Fi02 < 300 mm Hg or
    - Oxygen saturation is < 90% on room air or
    - Other clinical evidence
- Bilateral infiltrates on frontal chest radiograph
- No evidence of left atrial hypertension (i.e. circulatory overload)
- No temporal relationship to an alternative risk factor for ALI during or within 6 hours of completion of transfusion.

Alternate risk factors for ALI are:

- Direct Lung Injury
    - Aspiration
    - Pneumonia
    - Toxic inhalation
    - Lung contusion
    - Near drowning
- Indirect Lung Injury
    - Severe sepsis
    - Shock
    - Multiple trauma
    - Burn injury
    - Acute pancreatitis
    - Cardiopulmonary bypass
    - Drug overdose

It has been suggested by the Toronto TRALI Consensus Panel to add a category of possible TRALI that would have the same definition as TRALI except for the presence of a temporal relationship to an alternative risk factor for ALI (as described above). In such a circumstance TRALI should be indicated with a possible imputability to transfusion.

TRALI is therefore a clinical syndrome and neither presence of anti-HLA or anti-HNA antibodies **in donor(s)** nor confirmation of cognate antigens **in recipient** is required for diagnosis.

V Transfusion transmitted infection (SHOT definition)

A report was classified as a transfusion transmitted infection if, following investigation:

- The recipient had evidence of infection post-transfusion, and there was no evidence of infection prior to transfusion and no evidence of an alternative source of infection

and, either

- At least one component received by the infected recipient was donated by a donor who had evidence of the same transmissible infection,

or

- At least one component received by the infected recipient was shown to contain the agent of infection

reference: Annual Report 2006 of the Serious Hazards of Transfusions (SHOT). Available at http://www.shotuk.org/home.htm

VI PTP (ISBT definition)

PTP is characterized by thrombocytopenia arising 5-12 days following transfusion of cellular blood components with findings of antibodies in the patient directed against the Human Platelet Antigen (HPA) system.

VII TA-GVHD (ISBT definition)

TA-GVHD is a clinical syndrome characterised by symptoms of fever, rash, liver dysfunction, diarrhea, pancytopenia and findings of characteristic histological appearances on biopsy occurring 1-6 weeks following transfusion with no other apparent cause. The diagnosis of TA-GVHD is further supported by the presence of chimerism.

VIII FNHTR (ISBT definition)

There is a FNHTR in the presence of one or more of:

- fever ($\geq 38^{o}$C oral or equivalent and a change of $\geq 1^{o}$C from pretransfusion value),
- chills/rigors

This may be accompanied by headache and nausea occurring during or within four hours following transfusion without any other cause such as hemolytic transfusion reaction, bacterial contamination or underlying condition.
FNHTR could be present in absence of fever (if chills or rigors without fever).

For the purpose of international comparisons, only the most serious cases of FNHTR should be accounted for: fever ($\geq 39^{o}$C oral or equivalent and a change of $\geq 2^{o}$C from pretransfusion value) and chills/rigors

IX TACO (ISBT definition)

TACO is characterized by any 4 of the following:

- Acute respiratory distress
- Tachycardia
- Increased blood pressure
- Acute or worsening pulmonary edema on frontal chest radiograph
- Evidence of positive fluid balance

occurring within 6 hours of completion of transfusion. An elevated BNP is supportive of TACO.

X TAD (ISBT definition)

TAD is characterized by respiratory distress within 24 hours of transfusion that do not meet the criteria of TRALI, TACO, or allergic reaction. Respiratory distress should not be explained by the patient's underlying condition or any other known cause.

XI Others (including previously uncategorized reported complication of transfusion). Reports of new previously unreported signs and symptoms temporally related to transfusion and with no other risk factor other than transfusion e.g like the red eye syndrome associated with some leucodepletion filters or in future if new reactions occur related to psoralene or prion filters.

4. ANNEX II: DEFINITIONS OF ACTIVITY STEPS AND SPECIFICATIONS FOR REPORTABLE SERIOUS ADVERSE EVENTS (AFFECTING THE QUALITY AND SAFETY OF BLOOD COMPONENTS)

ACTIVITY STEPS WHERE A DEVIATION MAY OCCUR[14]

I. **Whole blood and apheresis collection** refers to the act of collection of whole blood or apheresis donations (exclusive to blood establishments).

II. **Testing of donations** refers to the act of testing blood donations in the blood establishments to meet the requirements of Directive 2002/98/EC Annex IV, as well as supplementary national requirements (exclusive to blood establishments).

III. **Processing** is the process of transforming donations of whole blood and apheresis donations into issuable components intended for transfusion. This also involves secondary processing such as irradiation.

IV. **Storage** refers to the act of storing blood or blood components at blood establishments or hospital blood banks. Annex IV of Directive 2004/33/EC lays down requirements for both storage temperature and length.

V. **Distribution** is the act of delivery of blood and blood components to other blood establishments, hospital blood banks and manufacturers of blood and plasma derived products. It does not include the issuing of blood or blood components for transfusion.

VI. **Materials** refers to equipment (machines, bags, preservation solutions, etc.) used in the transfusion process. It should be noted that medical device defects should be reported under Medical Device legislation.

VII. **Other** refers to any other activity or parameter in the process which can affect the quality and safety of the component which may harm a patient.

SPECIFICATIONS[15]

Product defect	Equipment failure	Human error	Other (specify)
An SAE, meeting the criteria defined in section 3.3 of this document, should be included in the **Product Defect** category when the blood or a blood component that has been issued for use does not meet the quality and safety requirements set in annex V of the Directive 2004/33/EC due to an undetectable parameter.	An SAE, meeting the criteria defined in section 3.3 of this document, should be included in the **Equipment Failure** category when it was caused by any material, instruments or machinery that did not function as required at any stage from the collection to the distribution of blood and blood components If the equipment failed because of inappropriate use, or the failure was not detected/ prevented by incorrect human action, these should be reported as human error. **Note:** Failures of medical devices, whether or not they met the criteria for serious adverse event notification, should be reported via the medical devices reporting procedure.	An SAE, meeting the criteria defined in section 3.3 of this document, should be included in the **Human error** category when it resulted from an inappropriate or undesirable human decision or behaviour that reduces, or has the potential of reducing, effectiveness, quality, safety, or system performance.	Any SAE, meeting the criteria defined in section 3.3 of this document, should be included in the **Other** category when it cannot be classified in the already listed specifications.

[14] Please note that these are not legal definitions but rather aimed at facilitating reporting.
[15] Please note that these are not legal definitions but rather aimed at facilitating reporting.