EUROGTP II BLOOD

Blood components specific chapter

SPECIFIC GUIDANCE FOR THE USE OF METHODOLOGIES AND TOOLS

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EURO GTP II
Good Tissue & cell Practices

GAPP

Blood components specific chapter

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Acronyms

BC	Blood Component(s)
BE	Blood Establishment
BTC	Blood component, Tissue or Cells
CA	Competent Authorities
CFUpP	Clinical Follow-up Plan
CIP	Clinical Investigational Plan
CPPs	Critical Process Parameters
CQAs	Critical Quality Attributes
GAPP	Facilitating the Authorisation of Preparation Process for Blood and Tissues and Cells
HBB	Hospital Blood Banks
IAT	Interactive Assessment Tool
JPAC	Joint United Kingdom Blood Transfusion Services Professional Advisory Committee
KPI	Key Performance indicators
PPA	Preparation Process Authorisation
SARE	Serious Adverse Reaction and Event
TE	Tissue Establishment

Disclaimer

The *Good Practices for demonstrating safety and quality through recipient follow-up Project* (hereinafter referred to as 'EuroGTP II project'), and the *facilitating the Authorisation of Preparation Process for blood and tissues and cells Action* (hereinafter referred to as 'GAPP Joint Action'), developed this methodology and Interactive assessment tool, to provide recommendations and to improve the quality of healthcare delivery within the field of human tissues, cells and blood components. This tool represents the views of the EuroGTP II project and GAPP Joint Action, which were achieved after careful consideration of the scientific evidence available at the time of preparation. In the absence of scientific evidence on certain aspects, a consensus between the EuroGTP II and GAPP partners has been obtained.

The aim of the methodologies and tools is to aid tissue and blood bankers and healthcare professionals in the evaluation of safety, quality and efficacy of Blood, Tissue and Cells (BTC) and BTC therapies, therefore providing for effective care of their patients.

However, adherence to guidance does not guarantee a successful or specific outcome, nor does it establish a standard of care.

EuroGTP II and GAPP outcomes do not override the healthcare professional's clinical judgment and treatment of patients. Ultimately, healthcare professionals must make their own clinical decisions on a case-by-case basis, using their clinical judgment, knowledge, and expertise, and taking into account the condition, circumstances, and in consultation with Competent Authorities.

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Introduction

Advances in technology and science continue to contribute to the development of novel Blood Components, Tissues and Cells (BTC) and novel preparation protocols/processes for new and existing BTC.

It is important that the risks associated with these novelties are identified, quantified and assessed using a standard process. Any modification in the processes associated with the donation, collection, testing, processing, storage and distribution of BTC may impact the quality of these therapies and therefore the safety of donors or recipients.

The *Good Practices for demonstrating safety and quality through recipient follow up Project* (hereinafter referred to as 'EuroGTP II') project, developed the tools and methodologies to aid tissue bankers and healthcare professionals in the evaluation of safety, quality and efficacy of tissue and cellular therapies and products - Good Practices for evaluating quality, safety and efficacy of novel tissue and cellular therapies and products[1] - therefore providing effective care of their patients. The current guidance aims to provide similar aid to professionals of Blood Establishments (BE), Hospital Blood Banks (HBB), and other health professionals responsible for the clinical use or assessment of quality and safety of Blood Components (BC) (i.e. Competent Authorities (CA)).

The Euro GTP II Methodologies (Annex I. Methodologies Wall Chart) and Interactive Assessment Tool (IAT) have been developed to assist professionals involved in the provision of BC to:

- Determine if a BC or preparation process has any novelty **(Step 1)**
- Assess the risks associated with the BC or preparation process **(Step 2)**
- Determine the extent of any studies and/or follow up required to assure the safety and efficacy of BC **(Step 3)**

This document is intended to be used as reference, as it provides specific guidance for the use of tools and methodologies applied to blood and BC. It is suggested that chapters 1, 2 and 3 of the EuroGTP II Guide[1] be read in their entirety before attempting to use the methodologies proposed in this guide.

KEY PRINCIPLES FOR EFFECTIVE USE OF THE EUROGTP II METHODOLOGIES AND IAT

The value of the outputs from the IAT will be determined by the accuracy, comprehensiveness and relevance of the information that is put into it. It is therefore advised that:

i) The **process should be treated as a long term exercise:** The intention is that the IAT will provide the framework for a detailed assessment of risk. It is important that the **rationale for these decisions is recorded and documented**.

ii) It is unlikely that a single individual will have sufficient knowledge and expertise to complete the whole process at one go with no support. Ideally, the **assessment should be performed by a group of individuals selected for their knowledge and experience** who will consider all available information to generate an accurate assessment of risk. The process should be performed by a team selected to provide the requisite knowledge and experience to fully identify and evaluate all potential risks. This may include all professionals involved in the activities, namely:

- Operational staff;
- Scientists developing BTCs;
- Quality control personnel;
- Health care professionals

Please note that this list is not exhaustive.

iii) **The IAT may be used at any point in the preparation process/BTC development cycle:** The initial process can be performed at an early stage in the development of new or revised BTC; this may identify areas of high risk that could be addressed by pre-clinical development work. The exercise can be repeated at different stages of the development and implementation of the BTC, in order to re-evaluate the risks based on the current body of relevant information (studies performed and/or relevant references).
Much of the potential risk inherent to a new BTC or preparation process can generally be eliminated or ameliorated by well-planned and focussed pre-clinical studies. It can therefore be useful to use the IAT at a very early stage, where it can pinpoint areas where there is a high level of risk that could be addressed with pre-clinical in vitro studies, or review of the appropriate literature. Often at this stage, potential risk must be assessed as high, purely due to lack of data. The IAT can be re-run during the development cycle to evaluate how ongoing work is contributing to ameliorating the overall risk, and identify areas where further effort should be focussed. If used in this manner, the final use of the IAT prior to providing BTC for clinical use will identify the residual risk that can only be addressed with clinical evaluation or follow up. This

final output, along with all associated documentation and evidence, can be used to support submissions to CA to seek approval to provide the BTC for clinical use, either in a routine or restricted setting as indicated by the level of residual risk.

iv) There must be a clear **understanding of the critical quality attributes of the BTC which will contribute to its safety and efficacy**, to enable the risk assessment to be performed accurately. (As determined in the Commission Directive 2005/62/EC materials shall be CE-marked, which warrants a certain level of safety (for example biocompatibility). However, whenever materials are not tested for the specific/novel conditions or BC, additional risk assessment and risk mitigation shall be carried out).

Note also that the IAT should only be **used to assess new risks resulting from the novelty**. It is assumed that for existing BTC, which are being provided for clinical use, the existing risks have been evaluated and are adequately controlled.

ACCESSING THE IAT

The IAT is accessible on-line (**https://bloodtool.goodtissuepractices.site/**).

Due to the significant volume of data that can be introduced in the IAT for each individual assessment, and the need to reassess data, the **tool allows users to save their data**:
To do this, users need to use the "save" option available in the report page of IAT (results). After selecting this option, a file (.gtptool) will be downloaded. This document can be further used to "restore" the assessment in a new session.

The assessment methodologies proposed can also be applied on paper using the available template (Annex II. Template form: Methodologies for Assessing the Risks associated to novel BC) and the EuroGTP II algorithm (Annex III).

DEFINE WHICH TYPE OF BC YOU ARE EVALUATING

First it is important to define for which type of BTC you are going to use the tool, as this will generate specific risk factors and risk consequences.

In case of BC, choose 'Blood' and subsequently which type of component is the subject of the process under evaluation.

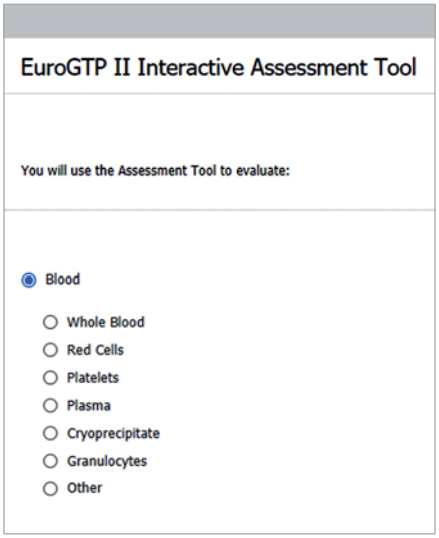


Figure 1: Diagram of Interactive Assessment Tool (IAT): different types of BC

If selecting Blood, you will be asked to choose a specific BC:

- Whole Blood
- Red Cells
- Platelets
- Plasma
- Cryoprecipitate
- Granulocytes
- other

Step 1

Evaluation of Novelty

It is important that the definition of 'novelty' within the context of this process is clearly established. It is not intended to encompass every change to a BC or process, regardless of how minute the change is; rather it intends to capture any change that could **significantly** affect the quality and/or safety of the BC and/or the safety of recipients.

The first stage of the tool is the assessment of novelty. This involves answering a series of seven questions, shown in Table 1 below, covering all aspects of the BC supply chain from donation to clinical application. This stage is intended to generate a simple 'yes' or 'no' answer; there is either novelty or not, irrespective of the degree of novelty.

Additionally, a third option – 'Not Applicable/Not relevant' (NA) – is provided to cover situations that are not addressed for the BC under evaluation.

If no novelty is identified, it can be concluded that there is no significant change or innovation in the BC being assessed; in this case, there is no need to proceed with the rest of the IAT.

This section outlines the questions asked when the tool is being used, a brief explanation of the information that the question is intended to elicit, and some examples to demonstrate when novelty may or may not be present, are shown in Table 1 below.

When performing this exercise please note the following definitions:

"this type of BTC" should be interpreted as the type of BC (example: platelets, red cells, plasma).

"this BTC" refers to the specific BC or therapy under evaluation (example: Red cells Leucocyte-depleted or Red Cells apheresis).

Table 1: Exercise for assessing novelty

	YES	NO	NA
A. Has this type of BTC* previously been collected, processed/ prepared and issued for clinical use by your establishment?			
Explanation: The purpose of this question is to determine if your establishment has previously prepared, collected, banked or provided this type of BC* for clinical use. It does not require that this type of BC* has been banked using the same process. (i.e. the question aims to ask if despite the novelty, your BE has experience handling this type of BC*). **Examples:** **A1.** Your establishment is already preparing plasma, but you intend to transfuse your routinely manufactured plasma collected from convalescent COVID-19 patients, for a different clinical application. In this case you would answer "Yes" to the question, and there is no novelty. **A2.** Your establishment is already preparing platelets pools, but you intended to store them at 4°C and transfuse cold platelets in acute bleeding patients. In this case you would answer "Yes" to the question, and there is no novelty. **A3.** Your establishment aims to start processing platelets for the first time. In this case you would answer "No" to the question, and there is novelty.			
	YES	**NO**	**NA**
B. Will the starting material used to prepare this BTC be obtained from the same donor population previously used by your establishment for this type of BTC*?			
Explanation: This question aims to elicit if there may be differences in the BC resultant from the donor population. Examples of changes that would create novelty are changing the age limits for donors of the BC, or changing specific aspects of the donor selection criteria applicable to the BC. Note that this does not apply to generic changes to donor selection criteria; for example if screening requirements for blood borne infections are amended, rather it should be considered when making specific changes to donor selection criteria that impact on specific BCs. **Examples:** **B1.** Your establishment will start preparing lyophilized platelets, without implementing any changes in the donor population. In this case you would answer "Yes" to the question, and there is no novelty. **B2.** Your establishment wants to issue plasma from convalescent COVID-19 patients. In this case the donor characteristic must have specific anti-spike antibodies (IgG), which is not a prior characteristic of your donor population. In this case you would answer "No" to the question, and there is novelty.			
	YES	**NO**	**NA**
C. Will the starting material for this BTC be procured/collected using a procedure used previously by your establishment for this type of BTC*?			
Explanation: The question is to determine if a change in the way in which the BC is procured/collected from the donor may impact on its safety or quality. **Examples** **C1.** Your establishment wants to implement an established collection protocol in a different location. This does not represent a change in the collection procedure, in this case you would answer "Yes" to the question, and there is no novelty. **C2.** Your establishment decides to implement apheresis procedure (not previously performed) in the BE, to collect platelets. In this case you would answer "No" to the question, and there is novelty.			

* Should be interpreted as the type of BC (examples: platelets, red cells, plasma).
It aims to ask if despite the novelty your Blood Establishment (BE) has experience handling this BC.

	YES	NO	NA
D. Will this BTC be prepared by a procedure (processing/preparation, decontamination/pathogen reduction and preservation) used previously in your establishment for this type of BTC*?			

Explanation:
This question covers a wide range of protocols, essentially covering all processes applied to the component between retrieval and preservation.

Examples:
D1. Your establishment wants to issue your routinely manufactured plasma collected from convalescent COVID-19 patients. In this case the preparation method does not change, and you would answer "Yes" to the question, as there is no novelty.
D2. Your establishment wants to implement a new pathogen reduction method. In this case you would answer "No" to the question, and there is novelty.

	YES	NO	NA
E. Will this BTC be packaged, stored and distributed using a protocol and materials used previously in your establishment for this type of BTC*?			

Explanation:
This question seeks to elicit whether there are any significant changes in how the BC is packaged, stored, and distributed prior to transfusion.

Examples:
E1. Your establishment is adding a new container to protect the blood units during transport. The new container and associated handling conditions have been previously validated by your BE, to maintain the designated temperature range. In this case the change does not represent a modification of the storage temperature/conditions, you would answer "Yes" to the question, as there is no novelty.
E2. Your establishment currently stores platelets at 20ºC (+-2ºC) and is considering implementing a new protocol to store them at 4ºC. In this case you would answer "No" to the question, and there is novelty.

	YES	NO	NA
F. Will this type of BTC* provided by your establishment be applied/infused clinically using an application/transfusion/infusion method used previously?			

Explanation:
This question seeks to elicit whether there are any significant changes in how the BC is clinically applied/infused.

Example:
F1. Your establishment wants to issue leucocyte-depleted red cells produced by apheresis for transfusion, for the first time. In this case you would answer "Yes" to the question, and there is no novelty.
F2. Your establishment aims to issue for the first time, platelet lysate for ocular application (topical use). In this case you would answer "No" to the question, and there is novelty.

* Should be interpreted as the type of BC (examples: platelets, red cells, plasma).
It aims to ask if despite the novelty your Blood Establishment (BE) has experience handling this BC.

	YES	NO	NA
G. Has your establishment provided this type of BTC* for the same clinical indication or for application/transfusion/infusion into a same anatomical site?			

Explanation:
This question seeks to elicit whether the BC will be applied for a new clinical indication or for patients with a clinical indication/new anatomical site never used before.

Examples:
G1. Your establishment wants to issue platelets leucocyte-depleted produced for the first time by apheresis. In this case you would answer "Yes" to the question, and there is no novelty.
G2. Your establishment has been issuing platelet concentrates for transfusion, and now wants to transfuse it to absorb antibodies in the recipients. In this case you would answer "No" to the question, and there is novelty.

* Should be interpreted as the type of BC (examples: platelets, red cells, plasma).
It aims to ask if despite the novelty your Blood Establishment (BE) has experience handling this BC.

If step 1 establishes that a new or changed BC has significant novelty, a systematic risk assessment must be undertaken to identify and quantify the risks associated with it. This must be a comprehensive process that considers all aspects of BC supply chain: from donor selection through to transfusion or other method of clinical application of the BC. This is the second step of the novelty and risk evaluation process.

Step 2

Level Risk Analysis

STEP 2A. IDENTIFICATION OF RISK FACTORS

If, after completing step 1, you determine that there is some novelty resulting from your proposed change, you should now proceed to step 2 to identify and quantify the potential risks resulting from this novelty. The risks have been subdivided into 9 factors:

i) Donor Characteristics

ii) Collection process and environment

iii) Processing and environment

iv) Reagents/Added components*

v) Reliability of Testing

vi) Storage Conditions

vii) Transport Conditions

viii) Presence of unwanted residues

ix) Clinical indications

You must first determine which of these risk factors are relevant to the aspect or aspects of your proposed change which result in novelty. Worked examples are provided later in this document to demonstrate how the process works.

* Any substance(s) added in any step of the process: from collection to storage of the BC.

STEP 2B. IDENTIFICATION OF RISKS

Having identified the appropriate risk factor(s), you should then determine which specific risk consequences are applicable. A standard set of risk consequences is applied to each factor, with an open, 'other' category for any risks not covered in the four main categories.

i) Unexpected immunogenicity

ii) Failure to perform clinically*

iii) Disease transmission

iv) Toxicity/Carcinogenicity

v) Other

Examples of the combination of risk factors and specific risk consequences that may need to be considered are provided in table 2. The purpose of the exercise is to systematically consider each risk factor and risk consequences in turn against the nature of the change. Note that for certain combinations of risk factor and specific risk, there may be no relevant examples. It is recognised that the IAT cannot anticipate all potential types of risk; the four specific risk consequences listed are those which it is generally agreed will be most commonly related to BC therapies. For any risks not covered by these four categories, an open, 'other' category may be used, and is provided in the IAT.

The overall process requires that firstly, specific risks relating to the potential risk factors and risk consequences be identified.

* See definition of *Clinical Peformance*; e.g. Platelet incremental failure

Table 2. Identification of the risk factors and risks associated with BC/therapies

	Risks factors	Explanation	Risks	Examples/Explanations
Donation	**Donor Characteristics**	This factor requires that you consider whether the novelty in your donor population represents any new risk for recipients, and/or increases the previously existing residual risk. (The assessment of risks for donors are not in the scope of this methodology.)	Unexpected immunogenicity	Could adjustment of donor selection criteria (age, specific antigens, or condition/anti-body), induce an unexpected immune response (e.g. donor anti-HLA antibodies, or anti-HNA antibodies)?
			Failure to perform clinically	Could certain aspects of a donor's medical history impact on the quality of the component?
			Disease transmission	Is the risk for transmission of infectious diseases increased if you accept donors who travelled in endemic areas for some known diseases? In terms of selection of donors with specific characteristics to cover the patient needs. Does this situation introduce risks for the patients?
			Toxicity/ Carcinogenicity	Could certain aspects of a donor's medical history (e.g.: medication) impact on the safety of the component?
			Other	No example provided: Consider other risks if applicable
Collection	**Collection process and environment**	Consider where and how the BC is collected currently and whether the changes proposed with the novel method changes collection time, complexity, mixing, etc? For example, how long does the process take, how complex is it, and how does the collection devices affect the quality of the BC?	Unexpected immunogenicity	Could changes to the collection process result in elevated quantities of immunogenic material being present in the BC? (e.g. Use of collection bags system which contain bio-compatible plasticizer materials).
			Failure to perform clinically	Could the use of new collection procedure affect the composition of the BC, and result in failure to perform clinically?
			Disease transmission	Could changes to the collection process result in an increased risk of donor-recipient disease transmission? (e.g.: Can a change in the disinfection solution cause a microbiological contamination of the BC during the collection process)
			Toxicity/ Carcinogenicity	Could any chemicals (e.g. new composition of anticoagulant solutions) used in the collection process be transferred to the BC?
			Other	No example provided: Consider other risks if applicable

	Risks factors	Explanation	Risks	Examples/Explanations
Processing/storing/transport	**Processing and environment**	Consider the current processing method, and how the novelty in processing can affect the final BC. Consider if the novel preparation process is more complex (and for instance, it includes steps preformed in an open system) and this may have an impact on the risk of contamination, or cell characteristics that may not be consistent with BC specifications.	Unexpected immunogenicity	Could the process change lead to the introduction of unwanted cellular components.
			Failure to perform clinically	Could the complexity of the process result in significant reduction of clinical efficacy? Could the environmental conditions applied during processing (e.g. temperature) affect the quality of the component?
			Disease transmission	Could the length, complexity or environment where the processing takes place affect the risk of environmental contamination? (e.g. splitting/open system used for preparation of components in paediatric preparations)
			Toxicity/ Carcinogenicity	Could the BC degrade during processing, generating toxic compounds? (e.g. after changes in the irradiation process)
			Other	No example provided: Consider other risks if applicable
	Reagents/ Added Components	Consider any reagent (and in vitro diagnostic products) used during processing (e.g. washing, pathogen reduction, freezing), and storage of the BC. Could they damage the BC in any way, or could residual traces of reagent remain in the BC that could cause toxic or immunogenic effects in recipients.	Unexpected immunogenicity	Could change of anticoagulant induce an unwanted immunogenic reaction in the recipient?
			Failure to perform clinically	Could change of anticoagulant affect the ability of the BC to perform clinically?
			Disease transmission	Could the use of reagents lead to contamination of the BC?
			Toxicity/ Carcinogenicity	Could the use of pathogen reduction systems cause toxic effects in the recipient?
			Other	No example provided: Consider other risks if applicable
	Reliability of Testing	Consider the risk that the testing methodology and/or presence of residual processing reagents in the BC, may impact the accuracy (sensitivity and specificity) of any testing (e.g. microbiology controls, quality controls, accuracy of validation, etc.). This risk factor does not relate to blood tests performed on immediate post-donation samples..	Unexpected immunogenicity	The use of a new leucodepletion filter, which changes the membrane of red blood cells, and cannot be effectively detected in the quality controls, cause a stimulation of antibody production in the recipients?
			Failure to perform clinically	Could the sampling method not allow the detection of the correct platelet content of the BC?
			Disease transmission	Could the change of sampling method (e.g. new sample size and/or type) cause a suboptimal detection of contaminants of current microbiology testing?
			Toxicity/ Carcinogenicity	It is unlikely this combination of risk and risk factor could occur associated with BC.
			Other	No example provided: Consider other risks if applicable

	Risks factors	Explanation	Risks	Examples/Explanations
Processing/storing/transport	**Storage Conditions**	Consider any potential risk arising from how the BC are stored, between collection and processing, during processing, and between processing and transfusion.	Unexpected immunogenicity	Can a change in the plastics (e.g. DEHP) of primary packaging cause enhanced immunogenic material in the BC
			Failure to perform clinically	Could the storage temperature affect the functionality of the BC (cells, factor VIII, etc.)?
			Disease transmission	Could the storage temperature increase the risk of an extant contamination? (e.g. Room temperature vs Cooling)
			Toxicity/ Carcinogenicity	Can the material of the primary container cause toxic reactions in the recipient of the BC?
			Other	No example provided: Consider other risks if applicable
	Transport Conditions	Consider any potential risk arising from how the BC are transported. For example, between the sites of collection and processing, and between the sites of storage and transfusion.	Unexpected immunogenicity	Can the transport conditions damage the cells and produce an unexpected immunogenic reaction in the recipient?
			Failure to perform clinically	Can the duration of the transport/shipment influence the quality/number of relevant cells present in the component?
			Disease transmission	Could the duration of the transport induce the risk of an extant contamination?
			Toxicity/ Carcinogenicity	Could transport conditions (e.g. heavy shaking) lead to damage of the packaging and chemical contamination of the BC.
			Other	No example provided: Consider other risks if applicable
Blood Component	**Presence of unwanted residues**	Consider the risk of the presence of unwanted/ excess cells/cellular residues originating from the donated component.	Unexpected immunogenicity	Do centrifugation forces during apheresis cause the presence of cell debris?
			Failure to perform clinically	Could the presence of inactivated cells lead to failure to perform clinically?
			Disease transmission	It is unlikely this combination of risk and risk factor could occur associated with BC
			Toxicity/ Carcinogenicity	It is unlikely this combination of risk and risk factor could occur associated with BC.
			Other	No example provided: Consider other risks if applicable
Clinical Indication	**Clinical indications**	Consider if a different clinical application of a BC can represent a risk (e.g. volume overload) for the recipient.	Unexpected immunogenicity	Can the use of convalescent plasma as prophylaxis treatment cause unwanted immunogenicity in the recipients?
			Failure to perform clinically	Could convalescent plasma in non-immune compromised patients be efficacious or will it solely distract the immune system without any beneficial effect?
			Disease transmission	Could the transfusion of a BC increase the probability of disease transmission in case of an unusual clinical administration?
			Toxicity/ Carcinogenicity	Could the new clinical indication cause risk to the recipient due to age or weight?
			Other	No example provided: Consider other risks if applicable

STEP 2C. QUANTIFICATION OF RISK CONSEQUENCES

When the risk factors are selected and the potential risks are identified, the potential impact of this risk analysis needs to be determined **according to the definitions summarized in Annex I - Methodologies Wall Chart**.

Each of these must be individually risk assessed to determine the residual risk of implementing the change, by considering:

i) The probability of the **risk occurring**.

ii) The **severity of the consequences** should the risk occur.

iii) The probability that the source of the harm for the risk consequences will be detected **before** the BC is transfused/applied. This does not refer to detection of the consequences of the risk post transfusion/application.

iv) Any **existing evidence** that can be used to mitigate the risk.

Step 3

Interpretation of the outcomes of risk analysis and definition of extent of studies needed based on the risk quantified

Using the EuroGTP II methodologies you will be able to perform a risk analysis, determine the risk profile and the level of risk associated with the novel BC, preparation process or procedure.

As a result the tools (IAT/EuroGTP II algorithm) will provide the value of the individual risks and the *Final Risk Score* which is proportional to the number of risks evaluated (in the form of a level of risk).

Applicants may need to share the results of the risk assessments with CA when requesting authorisation.

It is important to state that the BE and HBB should be prepared to discontinue treatment should negative outcomes become apparent (in terms of safety and efficacy) even when a novelty of negligible risk was implemented. BE and HBB should collect data and record follow up in a systematic way and make them available to the scientific community and CA regardless of the success of the treatment: not withholding results that point to a negative outcome or that turn out to be inconclusive. Therefore it is important in all processes, regardless of the level of risk, to monitor and register serious adverse reactions and events (SARE).

The table below (table 3) provides general guidance on the follow up studies needed in terms of the level of risk determined (adjusted according to Provoost V. et al. 2014[2] and JPAC - Trial Component Specifications 2019[3]).

Table 3. Review of Extent of Studies needed

Level of Risk*	Extend of Studies needed
Negligible	**Step 3A. Risk reduction strategies** A change in process could have a negligible level of risk because it is part of a therapy or procedure that is considered the standard and supported by widespread clinical experience from routine use. In this case multi-centre clinical investigations are published in peer-reviewed journals and the procedures are performed according to a validated, standard protocol. **Minimal process validation** is needed. The technical performance of staff should be monitored and compared with other BE or published studies, therefore standard Key Performance indicators (KPI) should be monitored related to the technical quality of the staff performing the procedures. Unsatisfactory KPIs indicating poor performance or protocol drift must lead to investigation of both the procedural steps and/or the possibility to re-train staff.
	Step 3B. Extent of clinical investigation The clinical use of the novel BC or therapy should be done as defined in clinical guidelines. A **routine/safety follow up program** incorporating serious adverse reaction and event (SARE) reporting, is sufficient as the good practices states. Ideally, follow up procedures should be focused on assessing efficacy, comparing the clinical follow up with the results obtained before the implementation of the change in the process.
Low	**Step 3A. Risk reduction strategies** Implementing a standard procedure or treatment in a BE that might be in routine use elsewhere internationally, but has never been performed in the BE. This procedure requires an **intensive validation**. Training of staff is necessary in order to reach the outcomes published in scientific literature. A learning curve might be expected and should be part of the validation report. When implementing the procedure, additional quality controls must be performed to **monitor Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs)**.
	Step 3B. Extent of clinical investigation The clinical use of the novel BC or therapy should be done as defined in clinical guidelines. A **safety Clinical Follow-up Plan (CFUpP)**, proportionate to the level of risk, should be implemented. The use of the novel BC/therapy might be restricted in the first instance to pilot sites. Safety might be monitored through haemovigilance which might be enhanced above standard based on risk. Follow up procedures should also focus on assessing efficacy, comparing the clinical follow up with the results obtained before the implementation of the change in the process and in relation to the results published in scientific literature.

* Overall risk arising from the novelty.

Level of Risk*	Extent of Studies needed
Moderate	**Step 3A. Risk reduction strategies** Novel procedures or treatments that exert a moderate risk and are considered innovative. The treatment has shown proof of principle and there is reassuring data in literature in terms of both safety and efficacy at least in animal studies and pre-clinical data shows normal incremental response. The studies that have published this data should have a sound methodology and published in peer-reviewed journals. In order to implement an innovative treatment, an **enhanced validation** is necessary including and a range of **additional quality controls** performed to monitor CPPs, CQAs, and the impact of the implemented Blood therapy should be carefully monitored. Since reassuring data of this innovative treatment is already available, a more specific monitoring of the published critical parameters can be performed instead of a registration of all critical parameters.
	Step 3B. Extent of clinical investigation Use might either be considered a change in clinical practice or as part of an approved research study, to be determined based on clinical usage/data to date. Use might be restricted in first instance to small scale pilot studies. A CFUpP to monitor safety through haemovigilance may be enhanced above standard based on risk. **Clinical Investigation Plan (CIP)**, where implemented, should assess reassuring mid-term safety including data on patients' wellbeing.
High	**Step 3A. Risk reduction strategies** A new procedure can be offered to patients in an experimental design aiming at showing proof of principle, short-term safety and/or efficacy. Likely to have to further define some critical variables in BC quality. An **extensive validation including** (where relevant) animal models, and including a range of **additional quality controls** performed to monitor CPPs, CQAs, and the impact of the implemented changes is required. This extensive validation should include: **Non clinical studies:** preferably there should be studies showing the experimental procedure is safe in animals. **Pre-clinical Studies:** when experimental treatments encompass a laboratory phase, then at least the viability of cells should be looked at in detail, monitored and registered.
	Step 3B: Extent of clinical investigation The BC should only be used clinically in the context of an Clinical Investigation approved by an independent Ethics Committee and compared to standard therapy (where applicable) until the residual risks have been adequately mitigated. The good practices of clinical setting for BTC[4] (adapted from Good Clinical Practices[5] principles) must be adhered to. The clinical use of novelties is likely to require a CIP and CA approval. It cannot to be used outside of an approved study. **Follow up program:** experimental treatments should only be offered to a selected and limited patient cohort and these patients should be clearly informed on the experimental status and should receive information about possible risks, alternative treatments etc. HBB should only offer experimental treatments or treatments based on experimental procedures after approval by a commission of medical ethics.

* Overall risk arising from the novelty.

A worked example demonstrating the whole process from novelty assessment to the definition of extent of studies is provided in the Annex IV.

RISK REDUCTION STRATEGIES TO MITIGATE THE IDENTIFIED RISKS (STEP 3A), AND DEFINITION OF EXTENT OF PRE-CLINICAL (IN VITRO) AND CLINICAL STUDIES TO EVALUATE THEIR EFFECTIVENESS (STEP 3B)

Guidance on how to evaluate and mitigate the risks through an application of risk mitigation strategies (pre-clinical and clinical evaluations) can be found in the GAPP deliverables:

- **GAPP Technical Annex 1:** Authorisation of changes in donation, procurement and collection, processing, preservation, storage and distribution.
- **GAPP Technical Annex 2:** Assessing the quality and safety of donor testing, microbial inactivation and sterilization steps as part of Preparation Process Authorisation (PPA);
- **GAPP Technical Annex 3:** Assessing clinical data as part of PPA.

The design of clinical evaluation programs must be planned in close cooperation between the BE and the clinicians responsible for the clinical application of the BC. The collaboration between BE and end users is critical to identify suitable design parameters, risk mitigation strategies, clinical indications, number of patients, type of follow up proportionate to the residual risks identified, and to ensure that comprehensive data is gathered to evaluate efficacy.

The design of the clinical evaluation should consider:

i) The nature of the risk;

ii) The number of patients required to obtain statistically significant data, where applicable. If the number needed is too high because the disease is a rare disease or the follow up period is very long then alternative solutions must be proposed.

Definitions

Additive Solution: Solution specifically formulated to maintain beneficial properties of cellular components during storage[6].

Allogenic Donation: Blood and blood components collected from an individual and intended for transfusion to another individual, for use in medical devices or as starting material/raw material for manufacturing into medicinal products[7].

Apheresis: A medical technique in which peripheral blood of a donor or patient is passed through an apparatus that separates one or more blood components and returns the remaining constituents to the donor or patient[8].

Blood: Whole blood collected from a donor and processed either for transfusion or for further manufacturing[9].

Blood Component (BC): Therapeutic components of blood (red cells, white cells, platelets, plasma) that can be prepared by centrifugation, filtration and freezing using conventional methodologies in blood establishment[6].

Blood Establishment (BE): 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[9].

Clinical Evaluation: A systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a BC (Blood component, Tissue or Cells) therapy in order to verify the safety and performance, including clinical benefits, of the BC therapy when used as intended by the blood and tissue establishment[10].

Clinical Follow-up Plan (CFUpP): The plan for monitoring the novel BC recipient for a given time after clinical application/administration; may comprise of medical visits, tests, diagnostic procedures, samples etc.[4] (adapted from VISTART JA[11]).

Clinical Investigation Plan (CIP): A document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation, prepared by the applicant(s) in the context of the authorisation request for clinical use of novel BC therapies/BC resulting from novel preparation process[4].

Clinical performance: The ability of a BC to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user (Adapted)[12].

Efficacy: Presence of desired (clinical) effects/patient outcomes depending on the mode of action of the BC[11].

Follow-up : Subsequent evaluation of the health of a recipient for the purpose of monitoring the results of the BC application, maintaining care and initiating post-application interventions[8].

Novelty: Any change to an established/consolidated blood, tissue or cell preparation process that may or may not result in a new BTC or to the mode of application of this BTC[11].

Preservation: The use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of blood or blood components[6].

Recipient: Person to whom human BC are applied[11].

Transmissible disease: Comprises all clinically evident illnesses (i.e. characteristic medical signs and/or symptoms of disease) resulting from the infection, presence and growth of micro-organisms in an individual or the transmission of genetic conditions to the offspring. In the context of transplantation, malignancies and autoimmune diseases may also be transmitted from donor to recipient[8].

Transport: To transfer or convey blood and blood components, tissues and cells from one place to another[1].

Validation: Means establishing documented evidence that provides a high degree of assurance that a specific process, SOP, piece of equipment or environment will consistently produce a BTC meeting its predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use[13].

Bibliography

1. EuroGTPII (GA n.º 709567) - Good Practices for demonstrating safety and quality through recipient follow-up. *EuroGTP II Guide - Good Practices for evaluating safety, quality and efficacy of tissue and cellular therapies and products.* (2019). (http://goodtissuepractices.eu).

2. Provoost, V. et al. *Beyond the dichotomy: A tool for distinguishing between experimental, innovative and established treatment.* Hum. Reprod. 29, 413–417 (2014).

3. *Trial Component Specifications. Standing Advisory Committee on Blood Components (SACBC) of JPAC (Joint United Kingdom Blood Transfusion Services Professional Advisory Committee).* 22nd February 2019. (2019).

4. GAPP JA. *Technical Annex 3 to overall guidance: assessing clinical data as part of Preparation Process Authorisation (PPA).* (2020). (https://www.gapp-ja.eu).

5. *ICH E6: Good Clinical Practice:* Consolidated guideline. Good Clinical Practice 50 (1997).

6. The European Directorate for the Quality of Medicines & HealthCare (EDQM) Council of Europe European Committee on Blood Transfusion (CD-P-TS). *Guide to the Preparation, Use and Quality Assurance of Blood Components.* 20th edition 2020.

7. Commission Directive 2004/33/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.

8. The European Directorate for the Quality of Medicines & HealthCare (EDQM) Council of Europe. *Guide to the quality and safety of Tissues and Cells for human application.* (2019).

9. Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.

10. European Parliament & Council of the European Union. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices. Off. J. Eur. Union 60, 1–175 (2017).

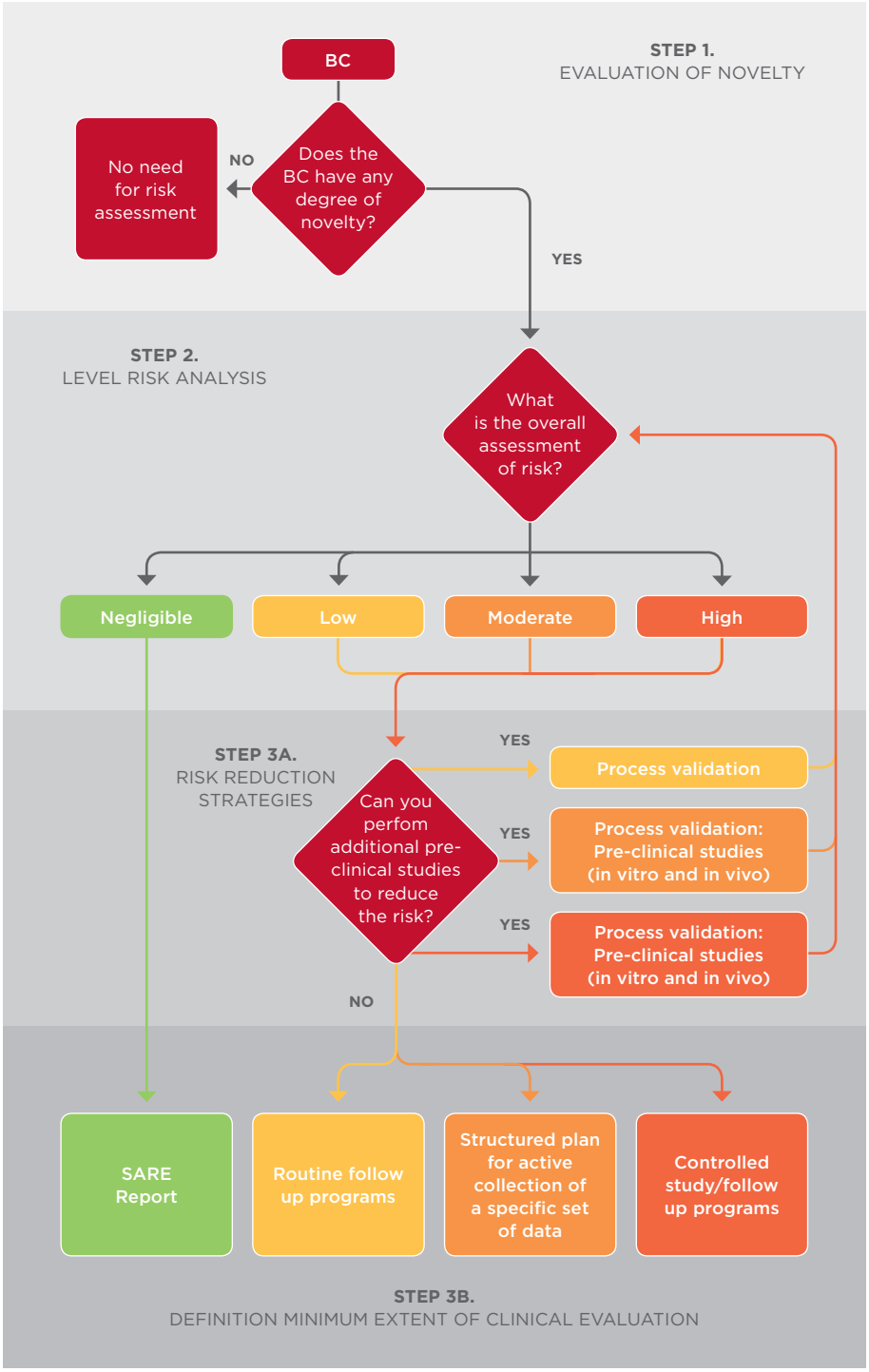
11. Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation (VISTART- GA n.º 676969). *Principles for Competent Authorities for the evaluation and approval of Clinical Follow Up Protocols for Blood, Tissues and Cells prepared with newly developed and validated processing methods.* 1–32 (2018). (https://vistart-ja.eu).

12. REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

13. COMMISSION DIRECTIVE 2006/17/EC, implementing Directive 2004/23/EC of the European Parliament and of the Council as regards. (2006).

— Annex I —

Methodologies Wall Chart


BC
STEP 1.
EVALUATION OF NOVELTY
Does the BC have any degree of novelty?
NO
No need for risk assessment
YES
STEP 2.
LEVEL RISK ANALYSIS
What is the overall assessment of risk?
Negligible
Low
Moderate
High
STEP 3A.
RISK REDUCTION STRATEGIES
Can you perfom additional pre-clinical studies to reduce the risk?
YES
Process validation
YES
Process validation: Pre-clinical studies (in vitro and in vivo)
YES
Process validation: Pre-clinical studies (in vitro and in vivo)
NO
SARE Report
Routine follow up programs
Structured plan for active collection of a specific set of data
Controlled study/follow up programs
STEP 3B.
DEFINITION MINIMUM EXTENT OF CLINICAL EVALUATION

Probability levels (definitions from V&S SoHO Project)*

Level of Probability	Definition
1. Rare	Difficult to believe it could happen
2. Unlikely	Not expected to happen but possible
3. Possible	May occur occasionally
4. Likely	Probably but not persistent
5. Almost certain	Likely to occur on many occasions

* The probability of the risk occurring.

Severity levels (definitions from V&S SoHO Project)*

Level of Severity	Definition
1. Non-serious	Mild clinical or psychological consequences for the recipient, however with no hospitalisation, or anticipated long term consequences/disability
2. Serious	Hospitalisation and/or: Persistent/significant disability or incapacity Intervention to preclude permanent damage Evidence of a serious transmitted infection Significant decrease in the expected treatment success Birth of a child with an infectious or genetic disease following ART with donor gametes or embryos
3. Life-threatening	Major intervention necessary to prevent death Evidence of a live threatening transmissible infection Birth of a child with life threatening genetic disease following ART with donor gametes or embryos
4. Fatal	Death of the patient

* The severity of the consequences should the risk occur.

Detectability levels*

Level of Detectability	Definition
1. Very high	The potential defect will almost certainly be detected before clinical application in the recipient
2. Moderately high	There is a reasonable chance that the potential defect will be detected before clinical application in the recipient
3. Low	There is a low chance that the potential defect will be detected before clinical application in the recipient
4. Very low	It is unlikely that the potential defect will be detected before clinical application in the recipient
5. Cannot be detected	The potential defect will be detected only after clinical application in the recipient

* The probability that the source of the harm for the risk consequences will be detected before the BC is transfused/applied. This does not refer to detection of the consequences of the risk post transfusion/application.

Percentage risk reduction definitions*

Percentage Risk Reduction		Definition
0	**None**	There is no relevant data available to support reducing the calculated risk score
25	**Limited**	There is a moderate relevant data available to support reducing the calculated risk score, based predominantly on unpublished data
50	**Moderate**	There is moderate amount of good quality relevant data available to support reducing the calculated risk score, including published and unpublished data from external sources, and some data which has been through and independent peer review process
75	**Substancial**	There is high quality relevant data to support reducing the calculated risk score, including data that has been peer reviewed and published
95	**Extensive**	There is an extensive amount of high quality relevant data, including multiple peer reviewed publications, that demonstrates that the probability of the risk occurring, having a significant impact, and/or being undetected is negligible

* Any existing evidence that can be used to mitigate the risk.

— Annex II —

Template form: Methodologies for Assessing the Risks associated to novel BC

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Methodologies for Assessing the Risks
associated to novel Blood Components (BC)

Please follow the guidance in order to correctly evaluate your BC

Define which type of BC you are evaluating

The evaluation of the level of novelty and the risks associated, should start with a characterization of the novel process or BC.

	Whole Blood
	Red Cells
	Platelets
	Plasma
	Cryoprecipitate
	Granulocytes
	Other

Name of the BC, therapy or process under evaluation:

Description of BC, therapy or process under evaluation:
(Describe the relevant aspects of the BC, detailing the modifications/novelties associated with **donation**, **processing** and **clinical** application under evaluation)

Step 1

Please answer the following questions in order to determine if the BC, process or therapy is novel. This process represents the first stage of the overall procedure for evaluating novelty and risk.

	Yes	No	Not Applicable/ Not Relevant
A. Has this type of BTC* previously been collected, processed/ prepared and issued for clinical use by your establishment?			
Justify:			
B. Will the starting material used to prepare this BTC be obtained from the same donor population previously used by your establishment for this type of BTC*?			
Justify:			
C. Will the starting material for this BTC be procured/collected using a procedure used previously by your establishment for this type of BTC*?			
Justify:			
D. Will this BTC be prepared by a procedure (processing/preparation, decontamination/pathogen reduction and preservation) used previously in your establishment for this type of BTC*?			
Justify:			
E. Will this BTC be packaged, stored and distributed using a protocol and materials used previously in your establishment for this type of BTC*?			
Justify:			
F. Will this type of BTC* provided by your establishment be applied/ infused clinically using an application/transfusion/infusion method used previously?			
Justify:			
G. Has your establishment provided this type of BTC* for the same clinical indication or for application/transfusion/infusion into a same anatomical site?			
Justify:			

* Should be interpreted as the type of BC (examples: platelets, red cells, plasma).

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Step 2

Novelties represent different risks with distinct impact in the quality and safety.

Select the specific risks consequences that apply to this risk factor (note that some risk factors may not apply to your BC/therapy).

Risk Factor: Donor Characteristics

This factor requires that you consider whether the novelty in your donor population represents any new risk for recipients, and/or increases the previously existing residual risk (the assessment of risks for donors are not in the scope of this methodology).

Applicable ☐ **Yes** ☐ **No**

Justify:

Risks					
Unexpected immunogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial (75%) ☐	Extensive (95%) ☐
Failure to perform clinically				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial (75%) ☐	Extensive (95%) ☐
Disease transmission				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐
Toxicity/Carcinogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐
Other _____				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐

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Step 2

Novelties represent different risks with distinct impact in the quality and safety.

Select the specific risks consequences that apply to this risk factor (note that some risk factors may not apply to your BC/therapy).

Risk Factor: Collection process and environment

Consider where and how the BC is collected currently and whether the changes proposed with the novel method changes collection time, complexity, mixing, etc? For example, how long does the process take, how complex is it, and how does the collection devices affect the quality of the BC?

Applicable ☐ **Yes** ☐ **No**

Justify:

Risks					
Unexpected immunogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Failure to perform clinically				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Disease transmission				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Toxicity/Carcinogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Other _____				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐

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Step 2

Novelties represent different risks with distinct impact in the quality and safety.

Select the specific risks consequences that apply to this risk factor (note that some risk factors may not apply to your BC/therapy).

Risk Factor: Processing and environment

Consider the current processing method, and how the novelty in processing can affect the final BC. Consider if the novel preparation process is more complex (and for instance, it includes steps preformed in an open system) and this may have an impact on the risk of contamination, or cell characteristics that may not be consistent with BC specifications.

Applicable ☐ **Yes** ☐ **No**

Justify:

Risks					
Unexpected immunogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial (75%) ☐	Extensive (95%) ☐
Failure to perform clinically				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial (75%) ☐	Extensive (95%) ☐
Disease transmission				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐
Toxicity/Carcinogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐
Other _____				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐

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Step 2

Novelties represent different risks with distinct impact in the quality and safety.

Select the specific risks consequences that apply to this risk factor (note that some risk factors may not apply to your BC/therapy).

Risk Factor: Reagents/Added Components

Consider any reagent (and in vitro diagnostic products) used during processing (e.g. washing, pathogen reduction, freezing), and storage of the BC. Could they damage the BC in any way, or could residual traces of reagent remain in the BC that could cause toxic or immunogenic effects in recipients.

Applicable ☐ **Yes** ☐ **No**

Justify:

Risks					
Unexpected immunogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial (75%) ☐	Extensive (95%) ☐
Failure to perform clinically				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial (75%) ☐	Extensive (95%) ☐
Disease transmission				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐
Toxicity/Carcinogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐
Other _____				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐

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Step 2

Novelties represent different risks with distinct impact in the quality and safety.

Select the specific risks consequences that apply to this risk factor (note that some risk factors may not apply to your BC/therapy).

Risk Factor: Reliability of Testing

Consider the risk that the testing methodology and/or presence of residual processing reagents in the BC, may impact the accuracy (sensitivity and specificity) of any testing (e.g. microbiology controls, quality controls, accuracy of validation, etc.). This risk factor does not relate to blood tests performed on immediate post-donation samples.

Applicable ☐ **Yes** ☐ **No**

Justify:

Risks					
Unexpected immunogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Failure to perform clinically				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Disease transmission				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Toxicity/Carcinogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Other _____				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐

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Select the specific risks consequences that apply to this risk factor (note that some risk factors may not apply to your BC/therapy).

Risk Factor: Storage Conditions

Consider any potential risk arising from how the BC are stored, between collection and processing, during processing, and between processing and transfusion.

Applicable ☐ **Yes** ☐ **No**

Justify:

Risks					
Unexpected immunogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Failure to perform clinically				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Disease transmission				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Toxicity/Carcinogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Other _____				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐

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Novelties represent different risks with distinct impact in the quality and safety.

Select the specific risks consequences that apply to this risk factor (note that some risk factors may not apply to your BC/therapy).

Risk Factor: Transport Conditions

Consider any potential risk arising from how the BC are transported. For example, between the sites of collection and processing, and between the sites of storage and transfusion.

Applicable ☐ **Yes** ☐ **No**

Justify:

Risks					
Unexpected immunogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Failure to perform clinically				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Disease transmission				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Toxicity/Carcinogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Other _____				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐

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Novelties represent different risks with distinct impact in the quality and safety.

Select the specific risks consequences that apply to this risk factor (note that some risk factors may not apply to your BC/therapy).

Risk Factor: Presence of Unexpected residues

Consider the risk of the presence of Unexpected/excess cells/cellular residues originating from the donated component.

Applicable ☐ **Yes** ☐ **No**

Justify:

Risks					
Unexpected immunogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial (75%) ☐	Extensive (95%) ☐
Failure to perform clinically				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial (75%) ☐	Extensive (95%) ☐
Disease transmission				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐
Toxicity/Carcinogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐
Other _____				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None (0%) ☐	Limited (25%) ☐	Moderate (50%) ☐	Substantial (75%) ☐	Extensive (95%) ☐

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Step 2

Novelties represent different risks with distinct impact in the quality and safety.

Select the specific risks consequences that apply to this risk factor (note that some risk factors may not apply to your BC/therapy).

Risk Factor: Clinical Indications

Consider if a different clinical application of a BC can represent a risk (e.g. volume overload) for the recipient.

Applicable ☐ **Yes** ☐ **No**

Justify:

Risks					
Unexpected immunogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Failure to perform clinically				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None ☐	Limited ☐	Moderate ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Disease transmission				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Toxicity/Carcinogenicity				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐
Other _____				Applicable ☐	NA ☐
Probability	**1** Rare ☐	**2** Unlikely ☐	**3** Possible ☐	**4** Likely ☐	**5** Almost certain ☐
Severity		**1** Non serious ☐	**2** Serious ☐	**3** Life-threatning ☐	**4** Death ☐
Detectability	**1** Very high ☐	**2** Moderately high ☐	**3** Low ☐	**4** Very low ☐	**5** Cannot be detected ☐
Risk Reduction	None **(0%)** ☐	Limited **(25%)** ☐	Moderate **(50%)** ☐	Substantial **(75%)** ☐	Extensive **(95%)** ☐

— Annex III —

EuroGTP II Algorithm for the calculation of Final Risk Score

EuroGTP II Algorithm for the calculation of Final Risk Score

1. Estimate the Preliminary Score associated with the BC:

$$\text{Preliminary Score} = \Sigma \text{ risks} = \Sigma ((S \times P \times D) - ((S \times P \times D) \times (\% \text{ risk reduction}))$$

P = Probability
S = Severity
D = Detectability

The combined risk is determined following the described steps:

$$\text{Combined Risk Value} = \frac{\text{Preliminary Score} \times \text{Highest Possible Score}}{(\text{Max S} \times \text{Max P} \times \text{Max D} \times \text{Number of Applicable Risks Consequences})}$$

Max P = 5
Max S = 4
Max D = 5

Applicable Number of Risks Consequences = Range from: 1 to 45

Highest Possible Risk Score = (Max S × Max P × Max D × Number of Risks) × Risk Factors = 4500

$$\text{Final Risk Score} = \frac{\text{Combined Risk Value} \times 100}{\text{Highest Possible Score}}$$

Two ancillary rules have been implemented in the algorithm to ensure that individual highly scored risks are not masked by adding various low risk scores. Thus, independently of the determined Final Risk Score, individual risks with scores higher than 30, result in “moderate risks” and, individual risks with scores higher than 50, result in “high risks”.

(Demonstration of the algorithm with practical examples - Annex IV)

The Preliminary and *Combined Risk Scores* resulting from the risk assessment doesn't have a direct correspondence with the *Final Risk Score*.

The calculation of the *Final Risk Score* must be proportional to the number of risk consequences evaluated in the assessment of the BTC.

Table 2.1. Levels of risk based in the Final Risk Value determined by the algorithm

0 – 2	Negligible Risk
>2 – 6	Low Risk
>6 – 22*	Moderate Risk
>22*	High Risk

* Lower values may result in moderate and high risk scores due to the application of the ancillary rules (described in the algorithm).

— Annex IV —

Worked Example

EuroGTP II Interactive Assessment Tool

BTC: Blood - Plasma

The following information refers to BTC: Covid Convalescent Plasma (CCP)

Evaluation performed on: 2021-10-04 09:18:24

Description of BTC under evaluation:
The present evaluation refers to the preparation of fresh frozen plasma, collected by apheresis from donors recovered from COVID-19. Our Blood establishment has experience with the collection and preparation of fresh frozen plasma for transfusion, but has not issued this blood component to treat viral infections.

	Yes	No	NA
A. Has this type of BTC previously been prepared and issued for clinical use by your establishment?	x		
B. Will the starting material used to prepare this BTC be obtained from the same donor population previously used by your establishment for this type of BTC?		x	
C. Will the starting material for this BTC be procured/collected using a procedure used previously by your establishment for this type of BTC?	x		
D. Will this BTC be prepared by a procedure (processing, decontamination and preservation) used previously in your establishment for this type of BTC?	x		
E. Will this BTC be packaged, stored, and distributed using a protocol and materials used previously in your establishment for this type of BTC?	x		
F. Will this type of BTC provided by your establishment be applied/infused clinically using an application/infision method used previously?	x		
G. Has your establishment provided this type of BTC for a same clinical indication or applied/infused into a same anatomical site?		x	

	Justification provided for Evaluation of Novelty questions
A	Our Blood establishment has experience with the collection and preparation of fresh frozen plasma for transfusion.
B	In addition to the donor selection criteria defined on the EU Blood Directives and CoE Guide, previously defined for plasma donors, CCP donors shall have recovered from COVID-19 infection, and are selected based on their COVID-19 antibody level.
C	Same procedure as for fresh frozen plasma collected by apheresis.
D	Same procedure as for processing fresh frozen plasma.
E	Same procedure as for fresh frozen plasma.
F	Same procedure as for fresh frozen plasma.
G	CCP will be issued to treat COVID-19 patients.

Risk Factor	Risk	Probability	Severity	Detectability	Potential Risk	Risk Reduction	Risk
Clinical indications	Unexpected immunogenicity	3	2	2	12	50%	6
Clinical indications	Failure to perform clinically	3	2	2	2	50%	6

Risk Factor	Applicable	Comment
Donor Characteristics	**N**	Despite the changes implemented in the donor selection criteria, the donor characteristics are not expected to represent any additional risk for the recipients, because donors will be required a negative PCR test before donation. The levels of antibodies shall also be tested for every donation.
Collection process and environment	**N**	Collection procedure is the same as for fresh frozen plasma collected by apheresis, and has been previously validated by our BE.
Processing and environment	**N**	Processing procedure is the same as for fresh frozen plasma collected by apheresis, and has been previously validated by our BE.
Reagents/Added components	**N**	There are no additional reagents/added components associated in the new therapy.
Reliability of Testing	**N**	Changes in donation and clinical indication do not suggest any additional risk associated with the reliability of the tests performed in the Blood Component.
Storage conditions	**N**	Storage procedure is the same as for fresh frozen plasma collected by apheresis, and has been previously validated by our BE.
Transport conditions	**N**	Transport procedure is the same as for fresh frozen plasma collected by apheresis, and has been previously validated by our BE.
Presence of unwanted residues	**N**	Changes in donation and clinical indication do not suggest any additional residues in the Blood Component.
Clinical indications	**Y**	The depending on the title of antibodies presented in the blood component, it can potentially cause an immunogenic reaction, or fail to perform clinically after being transfused. However, the title of antibodies in each unit are tested and there is currently a significant amount of publications documenting the safety of CCP to treat COVID-19 patients.

Preliminary Score: **12**
Number of Applicable Risks Consequences: **2**
Number of Risks Consequences: **5**
Max individual Risk value = **6**

Highest Possible Risk Score = 5 * 4 * 5 * 5 * 9 = **4500**
Applicable Risk Score = 5 * 4 * 5 * 2 = **200**

Combined Risk Value = (Risk Value * Highest Possible Risk Score) / Number of Applicable Risks = (12 * 4500) / 200 = **270**
Final Risk Score = (Final Risk Score * 100) / Highest Possible Risk Score = (270 * 100) / 4500 = **6**

Your assessment has Final Risk Score of: **6**
This suggests that your BTC falls into the Level of Risk:

Level of Risk	Extent of Studies needed
Low	Step3A: Risk reduction strategies Implementing a standard procedure or treatment in a BE that might be in routine use elsewhere internationally, but has never been performed in the BE. This procedure requires an intensive validation. Training of staff is necessary in order to reach the outcomes published in scientific literature. A learning curve might be expected and should be part of the validation report. When implementing the procedure, additional quality controls must be performed to monitor Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs).
	Step 3B: Extent of clinical evaluation The clinical use of the novel BC or therapy should be done as defined in clinical guidelines. A safety Clinical Follow-up Plan (CFUpP), proportionate to the level of risk, should be implemented. The use of the novel BC/therapy might be restricted in the first instance to pilot sites. Safety might be monitored through haemovigilance which might be enhanced above standard based on risk. Follow up procedures should also focus on assessing efficacy, comparing the clinical follow up with the results obtained before the implementation of the change in the process and in relation to the results published in scientific literature.

Annex V

Authors and Experts

Working Group	
Banc de Sang i Teixits (BST) www.bst.cat	Jaime Tabera Rita Piteira
National Health Service – Blood and Transplant (NHSBT) www.nhsbt.nhs.uk	Akila Chandrasekar Richard Lomas
Istituto Superiore di Sanità (ISS-CNT-CNS) www.iss.it	Claudia Carella Livia Cannata Maura Mareri Paola Di Ciaccio Simonetta Pupella
Organització Catalana de Trasplantaments (OCATT) www.trasplantaments.gencat.cat	Ruth Barrio
Health Products Regulatory Authority www.hpra.ie	Laura Hickey
Agence de la biomédecine www.agence-biomedecine.fr	Samuel Arrabal Petra Hesky Nigel Strang
Agence nationale de sécurité du médicament et des produits de santé (ANSM) - French National Agency for Medicines and Health Products Safety https://ansm.sante.fr/	Sandid Imad
European Blood Aliance (EBA) www.europeanbloodalliance.eu	Cristina Caeiro
Azienda Ospedaliera Universitaria Integrata Verona www.aovr.veneto.it	Aurora Vassanelli
Experts	
Saints Anargyroi Hospital Greece	Anthi Gafou
Etablissement Français du Sang France	Stéphane Bégué
Paul-Ehrlich-Institut Germany	Meri Tanner Winfried Kammer
Sanquin The Netherlands	Dirk de Korte
Österreichisches Rotes Kreuz Austria	Simone Hennerbichler
Centro Hospitalar do Porto Portugal	Margarida Amil

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