WP 8, deliverable 8.1 | Release 1.0, 25/07/2025

GAPP-PRO D8.1
Update of the EUROGTPII guide: faecal microbiota and breast milk chapters

Date of submission	25/7/2025
Work Package	WP8
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Dissemination level	Public

Co-funded by the European Union

GAPP-PRO, Piloting GAPP model approach for assessing and authorizing novel substances of human origin preparation PROcess, is a project co-funded by the Heath Programme of the European Union.

Grant Agreement 101128035 – EU4H-2022-JA-07, February 2024 – June 2027. Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or HADEA. Neither the European Union nor the granting authority can be held responsible for them.

EuroGTP II OTHER SoHOs

Other Substances of Human Origin specific chapter

SPECIFIC GUIDANCE FOR THE USE OF METHODOLOGIES AND TOOLS

Co-funded by the Health Programme of the European Union

EURO GTP II
Good Tissue & cell Practices

GAPP PROJ

Table of Contents:

Acronyms:

CA – Competent Authorities

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

HM – Human Milk

HMB – Human Milk Banks

HMD – Human Milk Donor

IAT – Interactive Assessment Tool

IM – Intestinal Microbiota

KPI – Key Performance indicators

RCF – Relative centrifugal force

RCT – Randomized Controlled Trial

SARE – Serious Adverse Reaction and Event

SoHO – Substances of Human Origin

SED – Serum Eye Drops

Disclaimer:

The EuroGTP II (*Good Practices for demonstrating safety and quality through recipient follow-up)* Project, and the GAPP PRO (*Piloting GAPP (facilitatinG the Authorisation of Preparation Process for blood and tissues and cells Action) model approach for assessing and authorizing novel substances of human origin preparation PROcess*) Joint Action, developed this methodology and Interactive assessment tool, to provide recommendations and to improve the quality of healthcare delivery within the field of the Substances of Human Origin (SoHO). This tool represents the views of the EuroGTP II project and GAPP PRO 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 PRO partners has been obtained.

The aim of the methodologies and tools is to aid SoHO Entities, SoHO Establishments and healthcare professionals in the evaluation of safety, quality and effectiveness of SoHO and SoHO 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 PRO 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 considering the condition, circumstances, and in consultation with Competent Authorities (CA).

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Introduction:

Advances in technology and science continue to contribute to the development of novel Substances of Human Origin (SoHO) and novel preparation protocols/processes for new and existing SoHO.

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 SOHO may impact the quality of these therapies and therefore the safety of recipients. The EuroGTP II methodologies are specifically designed to evaluate risks to recipients, and not the risks to the donor arising from the collection process, for SoHOs donated by living individuals. However, it should be noted that in cases of autologous donation, the donor and recipient are the same individual.

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 from SoHO Entities who work with Human Milk (HM), Blood components for topical use or injection or Intestinal Microbiota (IM) (hereafter 'Other SoHO'), and other health professionals responsible for the clinical prescription (i.e. end users of these types of SoHOs) or assessment of its quality and safety (i.e. Competent Authorities).

The present methodologies align with the requirements of the Regulation (EU) 2024/1938, of the European Parliament and of the Council (SoHO Regulation)[2], particularly in what refers to the risk assessments associated with the implementation of novel SoHO Preparations, and the requirements defined in its articles 20(4), 21. It also aims to assist professionals and health authorities documenting a standardised process of identification, quantification and evaluation of any risks to SoHO recipients arising from the chain of activities performed for the SoHO preparation, as referred in the article 39 of the SoHO Regulation.

Regarding the Human Milk (HM), as it is established in the consideration number 27 of the Regulation (EU) 2024/1038, of the European Parliament and of the Council (SoHO Regulation)[2,] the feeding of one's own child with one's breast milk does not fall within the scope of the Regulation and neither on the scope of this Guidance. However, a mother's own milk is within the scope of the Regulation if it is processed, and in this case, it falls under the scope of this Guidance.

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

- Determine if the SoHO preparation or process has any novelty (**Step 1**)
- Assess the risks associated with the SoHO Preparation or its preparation process (**Step 2**)
- Determine the extent of any studies and/or follow up required to assure the safety and efficacy of the SoHO preparation/therapy. (**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 'Other SoHO'. It is suggested that chapters 1, 2 and 3 of the original 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 SoHO Preparations/therapies;
- Quality control personnel;
- Health care professionals

Please note that this list is not exhaustive. Appropriate stakeholders should be designated based on the nature of the change, and the type of SoHO. For example, where a SoHO is to be applied by the patient themselves rather than a clinician, a patient representative may need to be included to evaluate changes relating to packaging, or presentation.

iii) **The IAT may be used at any point in the preparation process/SoHO development cycle:** The initial process can be performed at an early stage in the development of new or revised SoHO; 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 SoHO, in order to re-evaluate the risks based on the current body of relevant information (by the studies performed and/or relevant references).
Much of the potential risk inherent to a new SOHO preparation 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 SOHO 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 SOHO 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 SOHO preparation which will contribute to its safety and efficacy,** to enable the risk assessment to be performed accurately. (All equipment and materials that may have direct contact with SoHO should be sterile, single use (where possible) and CE-marked for their intended purpose (where available))[3]. However, whenever materials are not tested for the specific / novel conditions or SoHO, 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 SOHO preparations, 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://tool.goodtissuepractices.site/staging/indexS.html).

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 SoHO Preparations/therapies) **and the EuroGTP II algorithm** (Annex III).

Define which type of SoHO you are evaluating

First it is important to define for which type of SOHO you are going to use the tool, as this will generate specific risk factors and risk consequences.
In case of 'Other SoHO', users may select 'Human Milk', 'Blood components for topical use or injection', or 'Intestinal Microbiota' and subsequently which type of SoHO Preparation is the subject of the process under evaluation.

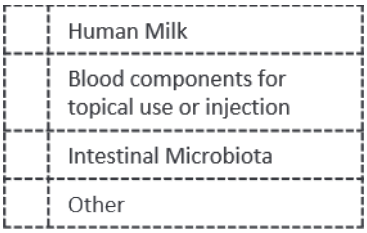

Figure 1: Diagram of Interactive Assessment Tool (IAT)

Evaluation of Novelty (Step 1)

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 SoHO 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 SoHO 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 SoHO 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 SoHO under evaluation.

If no novelty is identified, it can be concluded that there is no significant change or innovation in the SoHO 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 SOHO" (examples: HM, Intestinal Microbiota, Blood components for topical use, etc.) aims to ask if despite the novelty your SoHO Establishment has experience handling this SoHO.

"this SOHO Preparation" refers to the specific SoHO preparation or therapy under evaluation (Example: Frozen pasteurised Human Milk, Cryopreserved donor faeces capsules, Cryopreserved donor faeces suspension, etc.))

Table 1: Exercise for assessing novelty

	Yes	No	NA
A. Has this type of SOHO* 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 SoHO* for clinical use. It does not require that this type of SoHO* has been banked using the same process. (i.e. the question aims to ask if despite the novelty, your SoHO Establishment has experience handling this type of SoHO*)			
Examples for HM: **A1 –** Your establishment is already preparing HM, but you intend to revise the current processing method. In this case, you would answer "Yes" to this question, and there is no novelty. **A2 –** Your SoHO Establishment prepares corneas and amniotic membrane for clinical use, but intents to start preparing HM for distribution to patients. In this case, you would answer "No" to this question, as your establishment has no experience with this type of SoHO.			
Examples for Blood components for topical use or injection: **A1 –** Your establishment is already preparing Platelet-Rich Plasma (PRP), however you intend to change the process method. In this case, you would answer "Yes" to this question, and there is no novelty. **A2 –** Your establishment is already preparing Serum Eye Drops (SED) from blood, and wishes to start preparing eye drops from cord blood. In this case, you would answer "No" to this question, as your establishment has no experience with this type of SoHO.			
Examples for Intestinal Microbiota: **A1 –** Your establishment is already preparing Cryopreserved donor faeces capsules, but you intend to start preparing Cryopreserved donor faeces suspension. In this case, you would answer "Yes" to this question, as your establishment has prior experience with this type of SoHO. **A2 –** Your SoHO Establishment prepares Skin for clinical use, but intents to start preparing Cryopreserved donor faeces capsules. In this case, you would answer "No" to this question, as your establishment has no experience with this type of SoHO.			

* Should be interpreted as the type of SoHO (examples: examples: HM, Intestinal Microbiota, Blood components for topical use, Amniotic Membrane, Blood Component, etc.).

	Yes	No	NA
B. Will the starting material used to prepare this SOHO Preparation be obtained from the same donor population previously used by your establishment for this type of SOHO*?			
Explanation: This question aims to elicit if there may be differences in the SOHO preparation resultant from the donor population. Examples of changes that would create novelty are changing the age limits for donors of the SoHO, or changing specific aspects of the donor selection criteria applicable to the Human Milk. 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 SoHO.			
Examples for HM: **B1 –** Your establishment wishes to remove the limitations associated with the timeframe since birth to be allowed to donate, because it has been proven to not affect the quality of the HM and neither the safety of the mother. In this case, you would answer "Yes" to this question, and there is no novelty associated with the donor population. **B2 –** Your establishment wishes to include HM donors with alternative selection criteria (i.e., donors with strict diets, transgender donors, donors undergoing therapy, or other condition previously defined as exclusion criteria). In this case, you are changing your donor population, so you would answer "No" to the question, as there is novelty associated with the change.			
Examples for Blood components for topical use or injection: **B1 –** Your establishment wishes expand collection activities to a new donation site (i.e. different region), where blood will still be collected from allogenic donors. In this case, you would answer "Yes" to this question, and there is no novelty associated with the donor population. **B2 –** Your establishment wishes to include blood donors with alternative selection criteria (i.e., male or female donors, transgender donors, allogenic donors, donors undergoing therapy, or other condition previously defined as exclusion criteria). In this case, you are changing your donor population, so you would answer "No" to the question, as there is novelty associated with the change.			
Examples for Intestinal Microbiota: **B1 –** Your establishment wishes expand collection activities to a new donation site (i.e. different region, even if it involves longer transport time), where faecal samples will still be collected from voluntary donors. In this case, you would answer "Yes" to this question, and there is no novelty associated with the donor population. **B2 –** Your establishment wishes to add new limitation for donor selection (i.e. < 5 courses of antibiotic therapy throughout life or abstention from active and previous smoking habits). In this case you are changing the donor population, so you would answer "No" to the question, as there is novelty associated with the change.			
	Yes	**No**	**NA**
C. Will the starting material for this SOHO Preparation be collected using a procedure used previously by your establishment for this type of SOHO*?			
Explanation: The question is to determine if a change in the way in which the SoHO is collected from the donor may impact on its safety or quality			
Examples for HM: **C1 –**Your establishment aims to implement additional recommendations for the hygiene of donor's hands. In this case, you would answer "Yes" to this question, and there is no novelty associated with the collection procedure. **C2 –** Consider that your establishment wants to change the recommendations for the frequency or moment of HM collection by donors, the collection device, packaging, or the temperature of storage before preparation and the allowed storage time at home. In all these situations, you would answer "No" as there is novelty associated with the collection activities.			
Examples for Blood components for topical use or injection:			

C1 – Your establishment wants to change the collection device or packaging, to similar ones with the same specifications, but from other fabricant, in this case, you would answer "Yes" as there is no novelty associated with the collection activities.

C2 – Consider that your establishment wants to change the temperature of storage before preparation. In all these situations, you would answer "No" as there is novelty associated with the collection activities however it would be a novelty for processing.

Examples for Intestinal Microbiota:

C1 – Consider that you have a system in place where the collection of samples is implemented through specific transport that collects samples at home from donors. You want now to allow donors to bring their own samples to the processing laboratory in person maintaining the same transport conditions. In all these situations, you would answer "Yes" as there is no novelty associated with the collection activities.

C2 – Consider that your establishment wants to change the collection device / packaging (For example, changes from Fecotainer to GutAlive or vice-versa), the minimum amount of faeces collected or the temperature of storage before preparation. In all these situations, you would answer "No" as there is novelty associated with the collection activities

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

Explanation:

This question covers a wide range of protocols, essentially covering all processes applied to the SoHO Preparation between collection and preservation

Examples for HM:

D1 – Your establishment currently pasteurizes the HM, but the batch pasteurizer needs to be replaced with similar equipment that has the same specifications. In this case, it is unlikely there is any novelty, and you would answer "Yes" to the question.

D2 – Your establishment wants to change the decontamination procedure applied during the preparation, namely by changing the temperature of pasteurization, or add a nutritional supplement to HM. In these cases, you would answer "No" as there is novelty associated with the preparation process.

Examples for Blood components for topical use:

D1 – Your establishment currently prepares SED, however the centrifuge used in processing needs to be replaced with a very similar model that can accommodate the containers you currently use and can achieve the same Relative centrifugal force (RCF). In this case, it is unlikely there is any novelty, and you would answer "Yes" to the question.

D2 – Your establishment wants to change the reagents used to dilute during the eye drops preparation (i.e plasmalyte to ophthalmic solutions). In these cases, you would answer "No" as there is novelty associated with the preparation process.

Examples for Blood components for injection:

D1 – Your establishment currently prepares PRP, however the centrifuge used in processing needs to be replaced with a very similar model that can accommodate the containers you currently use and can achieve the same RCF. In this case, it is unlikely there is any novelty, and you would answer "Yes" to the question.

D2 - Your establishment wants to change the reagents used to dilute during the PRP preparation. In these cases, you would answer "No" as there is novelty associated with the preparation process**.**

Examples for Intestinal Microbiota:

D1 – Your establishment currently uses sterile saline to dilute product. Your currently supplier has discontinued this product and you intend to switch to a new one who provides the reagent to the same specification. On this case you would answer "Yes" to the question.

D2 – Your establishment currently prepares IM by manual homogenization and you are considering to use a new device (i.e. Stomacher). In this case you are introducing a novel process which could have significant implication on safety and quality of the product. In these cases, you would answer "No" as there is novelty associated with the preparation process.

	Yes	No	NA
E. Will this SOHO Preparation be packaged, stored and distributed using a protocol and materials used previously in your establishment for this type of SOHO*?			
Explanation: This question seeks to elicit whether there are any significant changes in how the SoHO Preparation is packaged, stored, and distributed prior to application/ingestion.			
Examples for HM: **E1 –** Your establishment aims to distribute HM units with less volume to avoid waste. In this case, you would answer "Yes". There is unlikely to be novelty as the change does not seem to impact the quality and safety of the SoHO preparation. **E2 –** Your establishment wishes to change the storage packaging from plastic containers to glass bottles for storing HM units. In this case, you would answer "No" as there is novelty associated with the storage procedures.			
Examples for Blood components for topical use or injection: **E1 –** Your establishment aims to change the courier provider, who has confirmed they will meet your requirements for transport specifications and procedures. In this case, you would answer "Yes". It is unlikely to be novelty as the change does not seem to impact the quality and safety of the SoHO preparation. **E2 –** Consider that your establishment wishes to change the minimum storage temperature of your SoHO preparation. In this case, you would answer "No" as there is novelty associated with the storage method.			
Examples for Intestinal Microbiota: **E1 –** Consider your establishment stores faecal suspensions in specific plastic bags at -80ºC. You now consider either using a double bag system, a larger bag, or a single plastic bag from another supplier. In this case, you would answer "Yes". There is unlikely to be novelty as the change does not seem to impact the quality and safety of the SoHO preparation. **E2 –** Your establishment wishes to change the minimum storage time of your IM preparation (from 1 year to 2 year at -80°C). In this case you are making a change that could affect the safety and quality of your product. you would answer "No" as there is novelty associated with the storage method.			
	Yes	**No**	**NA**
F. Will this type of SOHO* provided by your establishment be applied clinically using an application method used previously?			
Explanation: This question seeks to elicit whether there is any significant change in how the SoHO Preparation is clinically applied/infused/ingested.			
Examples for HM: **F1 –** Your establishment aims to extend the criteria to distribute HM to bigger or older infants than previously defined. In this case, you would answer "Yes", as there is no novelty associated with the application method. **F2 –**Your establishment currently provides HM units to feed premature new born patients but wishes to start issuing them for topical use such as eye drops or to treat diaper dermatitis. In this case, you would answer "No" as there is novelty associated with the application method.			
Examples for Blood components for injection: **F1 –** Your establishment currently provides PRP derived gels with specific hydrophobic dress, which is not available anymore and you use similar dressing from other Producer, in this case, you would answer "Yes", as there is no changes in your SoHO or its application method. **F2 –** Your establishment currently provides PRP for topical use but wishes to distribute PRP units for intraarticular injection. In this case, you would answer "No", as there is novelty associated with the application method.			
Examples for Intestinal Microbiota: **F1 –** Consider your establishment produces faecal microbiota capsules using 00 size. Your establishment now considers increasing the size of the capsules while preserving otherwise the same method of production. in this case, you would answer "Yes", as there are no changes in your SoHO or its application method. **F2 –** Your establishment currently provides IM to be applied by colonoscopy and wishes to distribute the product by oral capsule. . In this case, you would answer "No", as there is novelty associated with the application method			

	Yes	No	NA
G. Has your establishment provided this type of SOHO* for the same clinical indication or for application into a same anatomical site?			
Explanation: This question seeks to elicit whether the SoHO Preparation will be applied for a new clinical indication or for patients with a clinical indication never used before.			
Examples for HM: **G1 –** Your establishment aims to allow the use of colostrum to be applied with bottle or enterally to feed new born babies. In this case, you would answer "yes" as there is no novelty associated with the clinical indication and application method of the SoHO preparation. **G2 –** Your establishment currently provides HM units to feed premature new born patients but wishes to start issuing them for topical use as SED in patients with ocular pathologies. In this case, you would answer "No" as there is novelty associated with the clinical indication and anatomical site of application of the SoHO preparation.			
Examples for Blood components for topical use or injection: **G1 –** PRP are being used in leg ulcers and your Establishment aims to start issuing the preparation to be used in pressure ulcers on the back, you would answer "Yes" as there is no novelty associated with the clinical indication and application method. **G2 –** Your establishment currently issues SED for topical use in patients with different dry eye syndromes but wishes to start issuing SED for persistent epithelial defects, ocular burns, and/or intra-articular and other injections. In this case, you would answer "No" as there is novelty associated with the clinical indication and/ or anatomical site of application of the SoHO. **G3** – PRP is currently being used intra-articular and we aim to applied in intra-bone injections to treat a non-healing fracture site. In this case, you would answer "No" as there is novelty associated with the clinical indication and application method.			
Examples for Intestinal Microbiota: **G1 –** Your establishment performs FMT in patients with recurrent C. difficile infection (second recurrence), and it is now considering performing FMT for patients with first recurrence with associated risk factors for recurrence. In this case, you would answer "Yes" as there is no novelty associated with the clinical indication and application method. **G2 –** IM is currently being used for C. difficile infection and you aim to use FMT for the treatment of Inflammatory Bowel Disease. In this case, you would answer "No" as there is novelty associated with the clinical indication.			

Should be interpreted as the type of SoHO (examples: examples: HM, Intestinal Microbiota, Blood components for topical use, Amniotic Membrane, Blood Component, etc.).

If step 1 establishes that a new or changed SoHO Preparation 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 HM supply chain: from donor selection through to ingestion. This is the second step of the novelty and risk evaluation process.

Level risk analysis (Step 2)

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 and/or application method

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 (in the Annexes IV, V and VI) to demonstrate how the process works.

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.

a) Unexpected immunogenicity
b) Failure to perform clinically[‡]
c) Disease transmission
d) Toxicity/Carcinogenicity
e) Other

Examples of the combination of risk factors and specific risk consequences that may need to be considered are provided in the 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 risks consequences listed are those which it is generally agreed will be most commonly related to SoHO Preparations and 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 risks consequences be identified.

[†] Any substance(s) added in any step of the process: from collection to storage of the SoHO.
[‡] See definition of *Clinical Performance*

Table 2. Identification of the risk factors and risks associated with 'Other SoHO' preparations/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 induce an unexpected immune response?
			Failure to perform clinically	Could certain aspects of a donor's medical history (namely donors with strict diets, or work in contact with toxic chemicals (i.e. cleaning products, paint, etc)) impact on the quality of the SoHO? Example: Consider if a change to permit donation from female donors for allogeneic SED, as they are currently excluded due to the potential risk of alloimumisation, may impact the quality of the SED and it ability to perform clinically.
			Disease transmission	Is the risk for transmission of infectious diseases increased if you accept donors who travelled in endemic/outbreak 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, nicotine, use of insecticides) impact on the safety of the SoHO? Examples: Autologous donors may be taking strong/toxic medication that may damage the ocular surface, for example Graft-versus-host disease (GVHD) patients.
			Other	No example provided: Consider other risks if applicable

Collection	**Collection process and environment**	Consider where and how the SoHO 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 SoHO?	Unexpected immunogenicity	Could the collection process lead to the introduction of unwanted content (i.e. other SoHO content like Red Blood Cells, White Blood Cells, etc…). May the components present in the collection devices be also present in the final SoHO preparation and have impact in the immune response of recipients.
			Failure to perform clinically	Could the use of new collection procedure affect the composition of the SoHO, and result in failure to perform clinically? Examples: The fat content of HM varies significantly depending on the collection period. Per instance, collecting the leakage of HM from the breast that is not feeding/being expressed, does not comply with the acceptance quality criteria for donation. The quality of the environment shall be a factor to consider when it can impact in the quality of SoHO may be a factor, e.g. excess heat, causing degradation of active components.
			Disease transmission	Could changes to the collection process result in an increased risk of donor-recipient disease transmission? (Example: Can a change in the cleaning procedure (e.g. arm or breast) prior to collection cause a microbiological contamination of the SoHO during the collection process)
			Toxicity/Carcinogenicity	Consider if the new kits used for SoHO collection contain extractable and/or leachable substances which may be transferred to the SoHO. Example: Can DEHP (Bis(2-ethylhexyl) phthalate) be present in the collection systems?
			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 SoHO Preparation. 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 other proprieties/characteristics that may not be consistent with SoHO preparation' specifications.	Unexpected immunogenicity	Could the process change lead to the introduction of unwanted content (i.e. other SoHO content) in the SoHO? Example: Can a change to the serum separation protocol result in more donor cellular content being retained in the prepared eyedrops?
			Failure to perform clinically	Could the complexity of the process result in significant reduction of clinical effectiveness? Could the environmental conditions applied during processing (e.g. temperature, air quality, pressure) affect the quality of the SoHO preparation? Examples: Can changes to the clotting time or hold temperature may impact on the composition of the serum? For SED, a change in the dilution factor may impact clinical performance.
			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 SoHO) Example: The time held at ambient temperature prior to freezing may facilitate proliferation of any micro-organisms present in the SoHO.
			Toxicity/Carcinogenicity	Consider if the new kits used for SoHO preparation contain extractable and/or leachable substances which may be transferred to the SoHO preparation. Example: Consider if a new the source of water used for pasteurization may contain extractable and/or leachable substances which may be transferred to the SoHO preparation.
			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, freeze drying), and storage of the SoHO. Could they damage the SoHO's proprieties in any way, or could residual traces of reagent remain in the SoHO preparation that could cause toxic or immunogenic effects in recipients.	Unexpected immunogenicity	Could the process change lead to the introduction of unwanted content (i.e. drugs like antibiotics, supplements or other substances) in the SoHO?
			Failure to perform clinically	Could the added reagents (i.e. fortifiers such as protein or lipids added in some HM preparations) change the clinical properties/biological characteristics (i.e. viscosity, ability to be absorbed or digested) of the SoHO preparation?
			Disease transmission	Could the use of reagents lead to contamination of the SoHO? Example: For SED any change in the source of diluent, or how the diluent is produced/added to the serum may introduce a risk of contamination.
			Toxicity/Carcinogenicity	Could the use of pathogen reduction systems cause toxic effects in the recipient?
			Other	No example provided: Consider other risks if applicable

	Risk factors	Explanation	Risks	Examples / Explanations
Processing/ storing /transport	**Reliability of Testing**	Consider the risk that the testing methodology and / or presence of residual processing reagents in the SoHO preparation, 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 donors' samples.	Unexpected immunogenicity	Examples: Inability to detect the presence of irregular antibodies in Cord Blood preparations could lead to an immunogenic reaction in the recipient. Example: Can the inability to detect specific globulins in HM lead to an immunogenic reaction in the recipient.
			Failure to perform clinically	Could the sampling method not allow the detection of certain content in the specific quality controls performed on the SoHO preparation (i.e. small size of batch, reduced volume available for sampling)?
			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, according to our current knowledge. As knowledge of the underlying rationale of healing mechanisms develops, we may discover certain components that need to be screened for.
			Other	No example provided: Consider other risks if applicable
	Storage Conditions	Consider any potential risk arising from how the SoHO is stored, between collection and processing, during processing, and between processing and application.	Unexpected immunogenicity	Can a change in the plastics (e.g. DEHP) of primary packaging cause enhanced immunogenic material in the SoHO? Example: Can cross contamination (i.e. with food storage in the same freezer as HM, or other products) occur during storage, and can this cause a further reaction in the recipients?
			Failure to perform clinically	Could the storage temperature affect the quality of the SoHO preparation?
			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 SoHO?
			Other	No example provided: Consider other risks if applicable
	Transport Conditions	Consider any potential risk arising from how the SoHO are transported. For example, between the sites of collection (donors' homes) and processing, and between the sites of storage and patients home/storage.	Unexpected immunogenicity	Can the transport conditions damage the properties of the SoHO preparation and produce an unexpected immunogenic reaction in the recipient?
			Failure to perform clinically	Can the duration of the transport/shipment influence the quality of the SoHO?
			Disease transmission	Could the duration of the transport induce the risk of an extant contamination? Could transport conditions (e.g. heavy shaking) lead to damage of the packaging and lead to microbiological contamination of the SoHO preparation.
			Toxicity/Carcinogenicity	Could new transport conditions (e.g. heavy shaking or heating) lead to damage of the packaging and/or chemical contamination of the SoHO preparation.
			Other	Could transport conditions (e.g. heavy shaking or heating) lead to damage of the packaging and the irreparable loss of SoHO.

	Risks factors	Explanation	Risks	Examples / Explanations
SoHO Preparation	**Presence of unwanted residues**	Consider the risk of the presence of unwanted/excess cells/cellular residues/content originating from the donated SoHO.	Unexpected immunogenicity	Can the presence of some unwanted SoHO residues (i.e. cell population, haemoglobin) induce an immunogenetic reaction in the recipient?
			Failure to perform clinically	Can the presence of some unwanted SoHO residues (i.e. high lipid content) reduce the ability of the SoHO preparation to perform clinically?
			Disease transmission	No example provided
			Toxicity/Carcinogenicity	Can the presence of some unwanted SoHO residues (i.e. heavy metals, antibiotics or other medicines) induce toxic reaction in the recipient?
			Other	No example provided: Consider other risks if applicable
Clinical Indication	**Clinical indications and/or application method**	Consider if a different clinical application or the Complexity of the immediate pre-implantation preparation and/or application method of a SoHO Preparation can represent a risk for the recipient. This risk factors should include the risk associated to 'patient acceptability', where the patient would apply and/or handle the SoHO themselves.	Unexpected immunogenicity	Can a different clinical application of a SoHO represent a new immunogenic risk for the recipient?
			Failure to perform clinically	Example: For SED, there are multiple different clinical indications that cause dry eye disease, and these may impact on how SED perform for an individual patient.
			Disease transmission	Example: For SED, some patients may be more susceptible to infection due to the underlying disease process and other medications (e.g. patients with GVHD).
			Toxicity/Carcinogenicity	No example provided
			Other	No example provided: Consider other risks if applicable

Step 2C: Quantification of risks 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 SoHO Preparation is transfused/applied/ingested. This does not refer to detection of the consequences of the risk post transfusion/application/ingestion.
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 risks 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 SoHO Preparation, preparation process or procedure. These methodologies provide a standardised process of identification, quantification and evaluation of any risks to SoHO recipients arising from the chain of activities performed for the SoHO preparation, as required in the SoHO Regulation[2] and EDQM Guide[4].

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 alevel of risk).

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

It is important to state that the SOHO Entities and Establishments should be prepared to discontinue treatment should negative outcomes become apparent (in terms of safety and effectiveness) even when a novelty of negligible risk was implemented. SOHO Entities and Establishments 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 term of the level of risk determined (adjusted according to Provoost V. et al. 2014[5] and JPAC - Trial Component Specifications 2019[6]).

Table 3. Review of Extent of Studies needed

Level of Risk[i]	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-centred 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 SoHO Establishment 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 SoHO preparations 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 effectiveness, 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 SoHo Preparation in a SoHO Establishment that might be in routine use elsewhere internationally, but has never been performed in the SoHO Establishment. 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 SoHO Preparation 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 SoHO Preparation/therapy might be restricted in the first instance to pilot sites. Safety might be monitored through biovigilance which might be enhanced above standard based on risk. Follow up procedures should also focus on assessing effectiveness, comparing the clinical followup with the results obtained before the implementation of the change in the process and in relation to the results published in scientific literature.

[i] Overall risk arising from the novelty

Level of Risk[ii]	Extend 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 effectiveness at least in pre-clinical data shows normal incremental or response. The studies that have published this data should have a sound methodology andpublished 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 Critical Process Parameters (CPPs), Critical Quality Attributes (CQAs), and the impact of the implemented HM 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. Safety might be monitored through biovigilance which might be enhanced above standard based on risk. **Clinical Investigation**, where implemented, should assess reassuring mid-term safety including data on psychological 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 effectiveness. Likely to have to further define some critical variables in SoHO quality An **extensive validation** including (where relevant) animal models, and including and a range of **additional quality controls** performed to monitor Critical Process Parameters (CPPs), Critical Quality Attributes (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 SoHO preparation should only be used clinically in the context of a 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 SOHO[7] (adapted from Good Clinical Practices[8] principles) must be adhered to. The clinical use of novelties is likely to require a Clinical Investigational Plan (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. Hospital Blood Banks should only offer experimental treatments or treatments based on experimental procedures after approval by a commission of medical ethics.

[ii] overall risk arising from the novelty

Worked examples demonstrating the whole process from novelty assessment to the definition of extent of studies are provided in the Annexes IV, V and VI.

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 **Good Practice Guideline to authorisation on preparation processes in blood, tissues and cells establishments[7].** This Good Practice Guideline will be updated as it is one of the expected outcomes of the GAPP PRO Joint Action.

The design of clinical evaluation programs must be planned in close cooperation between the SoHO Establishment and the clinicians responsible for the clinical use of the SoHO Preparation. The collaboration between SoHO Establishment 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 effectiveness.

The design of the clinical evaluation should consider:

a) The nature of the risk;

b) 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.

The Annex VII provides guidance for the definition of clinical evaluation and follow up plans for the human application of Blood components for topical use or injection.

Additional guidance on the risk mitigation strategies associated with the various SoHO discussed in this guide can also be found in the dedicated chapters and monographs of the EDQM Guide[3], and the guidelines of the scientific societies (namely, the European Milk Bank Association and the European Society of Neurogastroenterology and Motility)

Definitions

Additive Solution - Solution specifically formulated to maintain beneficial properties of cellular components during storage[10].

Application - means being inserted, implanted, injected, infused, transfused, transplanted, ingested, transferred, inseminated or otherwise added to the human body in order to create a biological interaction with that body[2].

Clinical Evaluation - A systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a SoHO Preparation/Therapy in order to verify the safety and performance, including clinical benefits, of the SoHO Preparation/Therapy when used as intended by the SoHO establishment[8].

Clinical Follow-up Plan (CFUpP) – The plan for monitoring the novel SoHO recipient for a given time after clinical application/administration; may comprise of medical visits, tests, diagnostic procedures, samples etc.[8] (adapted from VISTART JA[12])

Clinical Investigation Plan (CIP) - A document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation[25], prepared by the applicant(s) in the context of the authorisation request for clinical use of novel SoHO therapies/SoHO resulting from novel preparation process[8].

Clinical performance - The ability of a SoHO Preparation 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)[13].

Critical Quality Attributes (CQAs) – a CQA is a physical, chemical, biological, or microbiological property or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality (adapted) [14].

Critical Process Parameters (CPPs) – is a process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality (adapted)[14].

Effectiveness – The extent to which the human application of SoHO achieves the intended biological or clinical outcome in the SoHO recipient[2].

Efficacy - Presence of desired (clinical) effects/patient outcomes[8].

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

Human Milk - Human milk expressed by a donor mother, stored frozen and processed in a human milk bank, following specific recommendations, for use by a recipient that is not the mother's own infant[4].

Novelty - Any change to an established/consolidated blood, tissue or cell preparation process that may or may not result in a new SOHO or to the mode of application of this SOHO[2] (adapted).

Other SoHO – for the purpose of the current guidance, means a category of SoHO which encompasses Human Milk (HM), Blood components for topical use or injection and/or Intestinal Microbiota (IM).

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[12].

Recipient - Person to whom human SoHO are applied[12].

Significant change: Change that could significantly affect the quality and/or the safety of the SoHO, or the safety of recipients and that is assessed as moderate or high risk. A significant change will have been identified through initial identification as a novelty and the subsequent risk assessment process described in EuroGTP II (adapted)[7].

SoHO entity - means an organisation legally established in the Union that carries out one or more of the SoHO activities: (i) donor registration; (ii) donor history review and medical examination; (iii) testing of SoHO donors or of persons from whom SoHO are collected for autologous use; (iv) collection; (v) processing; (vi) quality control; (vii) storage; (viii) release; (ix) distribution; (x) import; (xi) export; (xii) human application; (xiii) clinical outcome registration[2].

SoHO Establishment - means a SoHO entity that carries out any of the following SoHO activities: (a) both processing and storage; (b) release; (c) import; (d) export[2].

Substance of human origin' (SoHO) - means any substance collected from the human body, whether it contains cells or not and whether those cells are living or not, including **SoHO preparations** resulting from the processing of that substance[2.]

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[15].

Transport – the act of transferring a SoHO between distributing or receiving facilities under the control of trained personnel [11] (adapted).

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 SOHO 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. The level of validation should be according to the level of risk.[16] (adapted).

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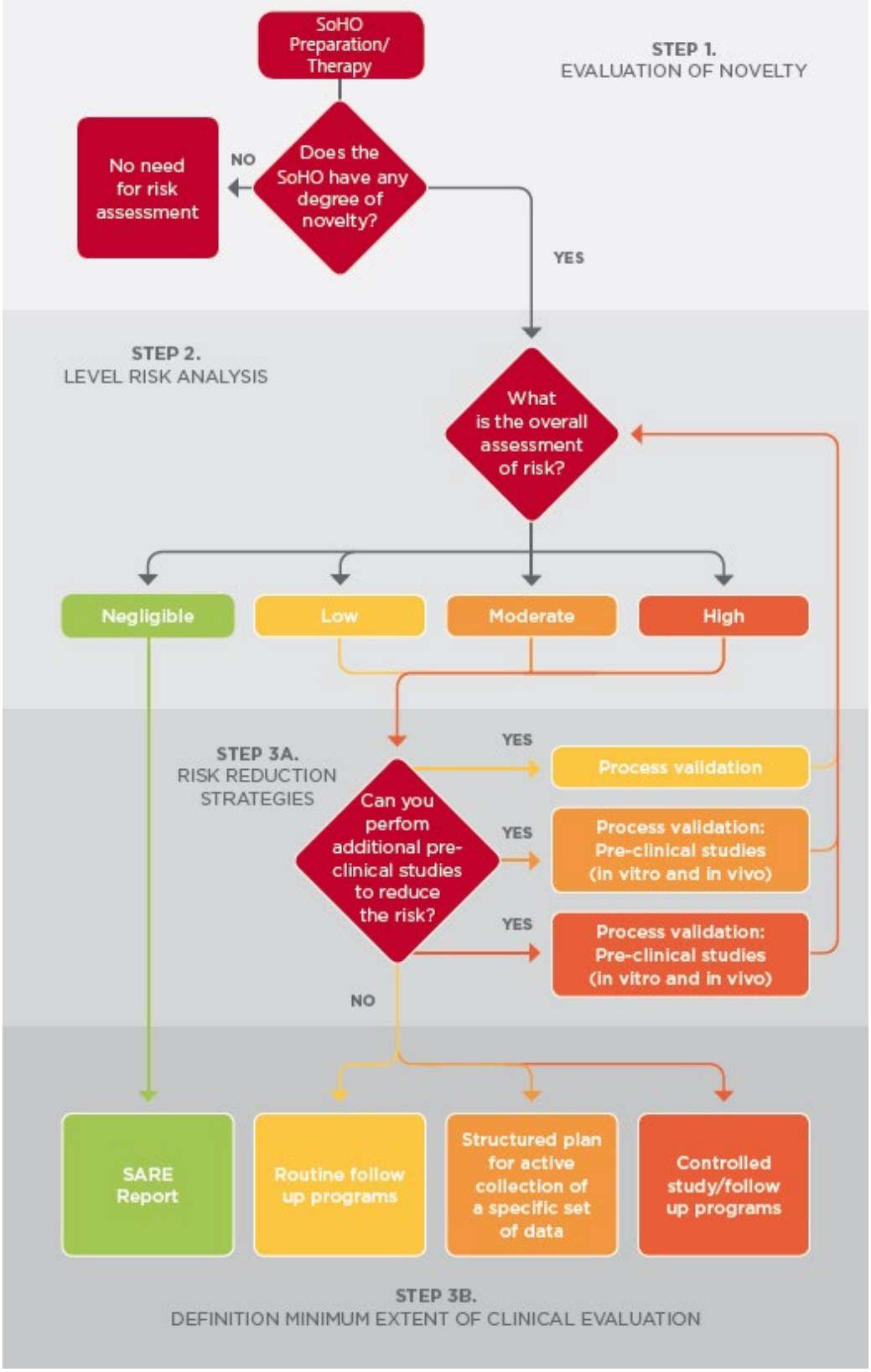
Annex I
Methodologies Wall Chart


SoHO Preparation/ Therapy
STEP 1.
EVALUATION OF NOVELTY
Does the SoHO 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 SoHO is transfused/applied/ingested. This does not refer to detection of the consequences of the risk post transfusion/application/ingestion.

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.

EURO GTP II
Good Tissue & cell Practices

GAPP PROJ

Co-funded by the Health Programme of the European Union

— Annex II —

Template form: Methodologies for Assessing the Risks associated to novel 'Other SoHO'

EURO GTP II
Good Tissue & cell Practices

Co-funded by the Health Programme of the European Union

Methodologies for Assessing the Risks associated to novel Other SoHO

(Namely, Human Milk (HM), Blood components for topical use or injection or Intestinal Microbiota (IM))

Please follow the guidance in order to correctly evaluate your process and/or SoHO Preparation.

Define which type of SoHO you are evaluating

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

	Human Milk
	Blood components for topical use or injection
	Intestinal Microbiota
	Other

Name of the SoHO Preparation, therapy or process under evaluation:

Description of SoHO Preparation, therapy or process under evaluation :
(Describe the relevant aspects of the SoHO, 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 SoHO preparation, 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 SOHO* previously been collected, processed /prepared and issued for clinical use by your establishment?			
Justify:			
B. Will the starting material used to prepare this SOHO Preparation be obtained from the same donor population previously used by your establishment for this type of SOHO*?			
Justify:			
C. Will the starting material for this SOHO Preparation be collected using a procedure used previously by your establishment for this type of SOHO*?			
Justify:			
D. Will this SOHO Preparation be prepared by a procedure (processing/preparation, decontamination/pathogen reduction and preservation) used previously in your establishment for this type of SOHO*?			
Justify:			
E. Will this SOHO Preparation be packaged, stored and distributed using a protocol and materials used previously in your establishment for this type of SOHO*?			
Justify:			
F. Will this type of SOHO* provided by your establishment be applied clinically using an application 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 SoHO (examples: examples: HM, Intestinal Microbiota, Blood components for topical use, Amniotic Membrane, Blood Component, etc.).

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%) ☐

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 SoHO 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 SoHO?

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%) ☐

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 SoHO Preparation. 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 other proprieties/characteristics that may not be consistent with SoHO preparation' 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%) ☐

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, freeze drying), and storage of the SoHO. Could they damage the SoHO's proprieties in any way, or could residual traces of reagent remain in the SoHO preparation 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%) ☐

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 SoHO preparation, 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 donors' 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%) ☐

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: Storage Conditions

Consider any potential risk arising from how the SoHO is stored, between collection and processing, during processing, and between processing and application.

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%) ☐

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: Transport Conditions

Consider any potential risk arising from how the SoHO are transported. For example, between the sites of collection (donors' homes) and processing, and between the sites of storage and patients home/storage.

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%) ☐

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: Presence of Unwanted residues

Consider the risk of the presence of unwanted/excess cells/cellular residues/content originating from the donated SoHO..

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%) ☐

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 and/or Application Method

Consider if a different clinical application or the Complexity of the immediate pre-implantation, preparation and/or application method of a SoHO Preparation can represent a risk for the recipient.
This risk factors should include the risk associated to 'patient acceptability', where the patient would apply and/or handle the SoHO themselves.

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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— 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).

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— Annex IV —

Worked Example for Human Milk

EuroGTP II Interactive Assessment Tool

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SoHO: *Other SoHO - Human Milk*

The following information refers to SoHO: *Pasteurised Human Milk (HM)*

Evaluation performed on: *2024-10-22 16:38:39*

Description of SoHO under evaluation:

In the present scenario, we aim to assess the risk associated with reducing the pasteurization temperature from 62.5º to 60ºC. The goal of this charge is to improve the preservation of protein content in HM. For this assessment, no prior bibliographic search was conducted.

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

	Justification provided for Evaluation of Novelty questions
D.	We will introduce a change in the temperature of pasteurisation during the preparation process.

Risk Factor	Risk	Probability	Severity	Detectability	Potential Risk	Risk Reduction	Risk
Processing and environment	Disease transmission	2	2	2	8	25%	6

Risk Factor	*Applicable*	*Comment*
Processing and environment	Y	By reducing the temperature of pasteurisation from 62.5°C to 60°C, it is possible the decontamination process may not be as efficient as with the previous preparation process. All the current stage, we consider it possible that an inefficient reduction of bioburden could result in a final SoHO preparation that is contaminated and capable of inducing disease transmission such as encephalitis in the newborn recipient. Due to the routine performance of microbiological tests on each batch of pasteurized HM, the detectability of contamination is considered moderately high. At his stage, we have not performed validation nor introduced additional quality controls: these may be implemented later. There are some publications documenting the efficacy of a lower pasteurisation temperature, such as the study by Michael A. Pitino, Deborah L. O'Connor, Allison J. McGeer and Sharon Unger (2021), which reviewed the impact of thermal pasteurisation on viral load and detectable live viruses in human milk and other matrices. This study, published in Applied Physiology, Nutrition and Metabolism, allows us to reply on previous findings to mitigate the risks associated with this innovation (Pitino et al., 2021 https://doi.org/10.1139/apnm-2020-0388). There are no reports of serious adverse reactions associated with this processing method in the Notify Library.

Your assessment has Final Risk Score of: **6**

This suggests that your SoHO falls into the Level of Risk:

Level of Risk	*Extent of Studies needed*
Low	**Step3A: Risk reduction strategies** Implementing a standard procedure or SoHo Preparation in a SoHO Establishment that might be in routine use elsewhere internationally, but has never been performed in the SoHO Establishment. 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 SoHO Preparation 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 SoHO Preparation/therapy might be restricted in the first instance to pilot sites. Safety might be monitored through biovigilance 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.

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— Annex V —

Worked Example for Blood components for topical use

EuroGTP II Interactive Assessment Tool

SoHO: *Other SoHO - Blood components for topical use or injection*

The following information refers to SoHO: *Serum Eye Drops (SED)*

Evaluation performed on: *2024-10-22 13:30:33*

Description of SoHO under evaluation:

Longer expiration of the vials: patients have reported that the volume of the current vials is sufficient for treatment for more than one day. To avoid wasting the BTC, we aim to extend the expiration time from one day to two days after the vial has been opened. In the current scenario we did not considered the adoption of alternative packaging, or any relevant bibliography, which could be considered for risk reduction.

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

	Justification provided for Evaluation of Novelty questions
F.	The SED will be handled differently by patients, as they will be able to use it for a longer period and will need to handle the preparation more than once.

Risk Factor	Risk	Probability	Severity	Detectability	Potential Risk	Risk Reduction	Risk
Storage conditions	Implant failure	3	1	5	15	0%	15
Storage conditions	Disease transmission	3	2	5	30	0%	30
Storage conditions	Toxicity / Carcinogenicity	1	2	5	10	0%	10

Risk Factor	Applicable	Comment
Storage conditions	Y	The vial, once opened, will be stored in the patient's fridge for a longer period: During this process, three things may occur; –The preparation can be contaminated by microorganisms. –The preparation can be contaminated by other substances present in the patient's fridge. –The content of the preparation could be damaged by the unsuitable temperature of a domestic fridge.

Your assessment has Final Risk Score of: **18**

This suggests that your SoHO falls into the Level of Risk:

Level of Risk	Extent of Studies needed
Moderate	**Step3A: 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 pre-clinical data shows normal incremental or 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 Critical Process Parameters (CPPs), Critical Quality Attributes (CQAs), and the impact of the implemented HM 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 evaluation 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. Safety might be monitored through biovigilance which might be enhanced above standard based on risk. **Clinical investigation** , where implemented, should assess reassuring mid-term safety including data on psychological wellbeing.

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— Annex VI —

Worked Example for Intestinal Microbiota

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SoHO: *Other SoHO - Intestinal Microbiota*

The following information refers to SoHO: *Intestinal Microbiota (IM) preparation*

Evaluation performed on: *2024-10-22 17:18:52*

Description of SoHO under evaluation:

Our establishment wishes to change the minimum storage time of your IM preparation (from 1 year to 2 years at -80ºC). This change aims to increase the availability of IM preparations for more patients, thereby optimizing the use of donations from selected donors which are not issued for clinical application within one year. The present assessment is performed prior to any validation studies performed by our SoHO Establishment.

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

	Justification provided for Evaluation of Novelty questions
E.	We intend to extend the storage period of IM preparation from 1 to 2 years.

Risk Factor	*Risk*	*Probability*	*Severity*	*Detectability*	*Potential Risk*	*Risk Reduction*	*Risk*
Storage conditions	Implant failure	1	2	2	4	75%	1
Storage conditions	Disease transmission	1	2	2	4	75%	1

Risk Factor	Applicable	Comment
Storage conditions	Y	Based on the infomation currently available, it is not possible to ensure that a longer storage period does not impact the viability of microbiota components and the functions. Morover, changes in the microbiota population during the storage period could also result in desease transmision. Additional studies suggest that a longer storage period does not impact the quality of the IM, and "Faecal suspensions for rCDI treatment can be stored at -80°C for up two years, without a loss of efectiveness". The following reference studies have been considered to reduce the risk associated with this risk/change in the procedure: – Cammarota G., Ianiro G., Kelly CR., et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. Gut 2019;68:2111-2121. – Keller JJ. et al. A standardised model for stool banking for faecal microbiota transplantation: a consensus report from a multidisciplinary UEG working group. United European Gastroenterol J. 2021 Mar;9(2)229-247. – Elisabeth M Terveer, Karuna EW Vendrik, Rogier E Ooijevaar, Emilie van Lingen, Eline Boeije-Koppenol, Els van Nood, Abraham Goorhuis, Martijn P Bauer, Yvette H van Beurden, Marcel GW Dijkgraaf, Chris JJ Mulder, Christina MJE Vandenbroucke-Grauls, Jos FML Seegers, Joffrey van Prehn, Hein W Verspaget, Ed J Kuijper and Josbert J Keller. Faecal microbiota transplantation for Clostridioides difficile infection: Four years' experience of the Netherlands Donor Feces Bank. January 2020. https://doi.org/10.1177/2050640620957765

Your assessment has Final Risk Score of: **1**

This suggests that your SoHO falls into the Level of Risk:

Level of Risk	Extent of Studies needed
Negligible	**Step3A: Risk reduction strategies** A change in process could have a negligible level of risk because it is part of a therapy orprocedure that is considered the standard and supported by widespread clinical experience from routine use. In this case multi-centred clinical investigations are published in peerreviewed 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 SoHO Establishment 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 evaluation The clinical use of the novel SoHO preparations or therapy should be done as defined in clinical guidelines. A **rotine/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.

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Annex VII

Definition of clinical evaluation for blood components for topic use and injection

STEP 3B: Definition of Clinical evaluation and follow up plans for:

Blood Components for Topical use of Injection

	Clinical Indication	
	PRP for injections	**Ocular surface healing**
Test category	**Detailed investigational options**	
Physical investigation (functional)	1. Range of Motion 2. Daily living activities functionality	1. Assessment of visual acuity 2. Eye movements 3. Visual field
Physical investigation (Anatomical)	1. MRI	1. Observation of external structures (cornea, eye lid, sclera, conjunctiva, pupil and iris, etc.) 2. Presence of defects, pathologies, inflammation, etc. 3. Topography 4. Pachymetry 5. Optical Coherence Tomography for cornea/retina
Overall Clinical outcome measures	1. Alloimunisation 2. Standard articular functionality scales	1. Severe Adverse Reactions and events 2. Best corrected visual acuity 3. Topography 4. Infection 5. Optical Coherence Tomography 6. Schirmer test 7. Measurement of mechanical sensation (esthesiometry - Cochet Bonnet anaesthesiometer)

Patient Reported outcome measures	1. Oxford Elbow Score 2. Lysholm Knee Score 3. Functional Knee Score 4. Activity Level	1. EQ-5D (QoL - https://euro-qol.org/) 2. Proceedings of Patient Reported Outcome Measure's (PROMs) which are more specific for Ophthalmology treatments and that are available in the UK at https://onlineproms.co.uk/ , such as: • Patient-reported outcomes are measured using questionnaires (CatQuest) • QIRC • VAS satisfaction • Numeric Rating Scale (NRS) to assess pain • 12-Item Short Form Health Survey (SF-12) or 36-Item Short Form Health Survey (SF-36) 3. Ocular surface disease index (OSDI)
Procedure failure	1. Infection 2. Pain	1. Confocal microscopy 2. Infection 3. Optical Coherence Tomography
Examples of Clinical Application	1. PRP injection for lateral epicondylitis 2. PRP injection for osteoarthritis of the knee	Ophthalmology - promote healing of the ocular surface

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Annex VIII

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