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La valutazione di efficacia dei nuovi prodotti alla luce del regolamento SoHO

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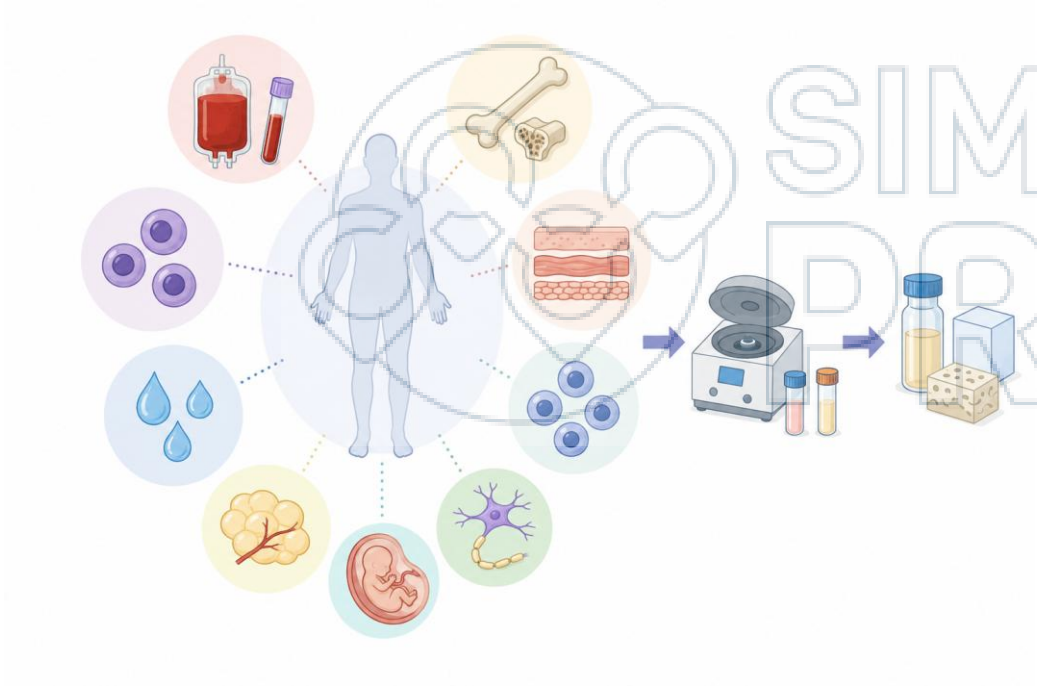
Il sottoscritto, in qualità di Relatore
dichiara che:

nell'esercizio della Sua funzione e per l'evento in oggetto, **NON** è in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le sue funzioni al fine di trarne vantaggio.

«**Sostanza di origine umana**» o «**SoHO**»: **qualsiasi sostanza raccolta dal corpo umano**, indipendentemente dal fatto che contenga o meno cellule e che tali cellule siano vive o meno, comprese preparazioni di SoHO risultanti dalla processazione di detta sostanza (Art. 3, EU SoHO Regulation)



- Sangue ed emocomponenti
- Eunt
- Cellule e tessuti
- Soho riproduttive
- Latte materno
- Microbiota fecale

Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC

Oggetto del Regolamento EU 2024/1938 (Art. 1)

Il presente regolamento stabilisce misure che fissano parametri elevati di **qualità e sicurezza** per tutte le sostanze di origine umana destinate all'applicazione sugli esseri umani e per le attività relative a tali sostanze.

Esso garantisce un livello elevato di protezione della salute umana, in particolare per i donatori di SoHO, **i riceventi di SoHO** e la progenie nata da procreazione medicalmente assistita, anche rafforzando la continuità dell'approvvigionamento di SoHO di importanza critica.

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Biological interaction drives regulation

Garantire la qualità e la sicurezza delle SoHO è fondamentale quando tali sostanze **interagiscono biologicamente con il corpo del ricevente di SoHO** o dei riceventi che ricevono prodotti fabbricati a partire da SoHO disciplinate da altre normative dell'Unione.

Tuttavia, il presente regolamento non dovrebbe contemplare l'applicazione di una sostanza sul corpo quando essa non ha alcuna interazione biologica con tale corpo

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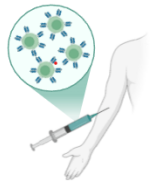
Soho Efficacy and Safety

« Efficacia delle SoHO»: la misura in cui l'applicazione sugli esseri umani di SoHO raggiunge l'esito biologico o clinico atteso nel ricevente di SoHO

- reazione attesa misurabile in gradi in un ricevente di SoHO, come l'attecchimento di cellule di midollo osseo a seguito di trapianto

- Un risultato atteso in un ricevente di SoHO che sia positivo o meno ma che non possa essere misurato in gradi, come la riuscita o meno di un trapianto di cornea od osseo



«Reazione avversa»: qualsiasi **incidente** che potrebbe essere ragionevolmente **associato alla qualità o alla sicurezza delle SoHO**, o alla loro raccolta da un donatore di SoHO o all'applicazione umana a un ricevente di SoHO, **che ha causato danni** a un donatore vivente di SoHO, a un ricevente di SoHO o alla progenie nata da procreazione medicalmente assistita → IMPUTABILITA', GRAVITA'

«Evento avverso»: qualsiasi incidente o errore associato alle attività relative a SoHO che può incidere sulla qualità o sulla sicurezza delle SoHO in modo tale da comportare il rischio di causare danni

Attività relative a SoHO: impatto diretto su sicurezza ed efficacia

- Registrazione di donatori di SoHO
- Anamnesi dei donatori di SoHO ed esame medico
- Controllo dei donatori di SoHO

- Raccolta
- Processazione
- Controllo sulla qualità

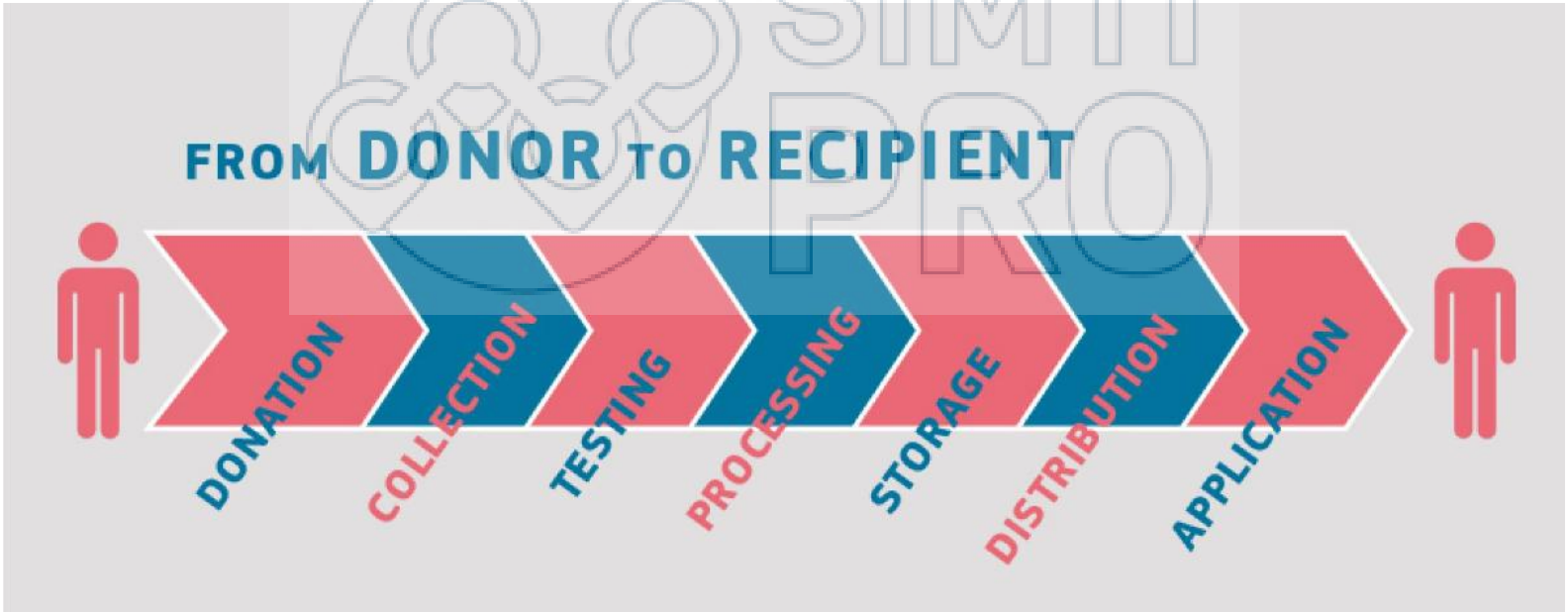
- Stoccaggio

- Rilascio, distribuzione, importazione, esportazione.

Attività relative a SoHO

- Applicazione sugli esseri umani: l'inserimento, l'impianto, l'iniezione, l'infusione, la trasfusione, il trapianto, l'ingestione, il trasferimento, l'inseminazione o la somministrazione in altro modo al corpo umano al fine di creare un'interazione biologica con tale corpo

- Registrazione degli esiti clinici



Nuove preparazioni Soho

«Il presente regolamento dovrebbe applicarsi… ..**qualsiasi altra SoHO che potrebbe essere applicata sugli esseri umani in futuro.**»

Normativa stringente

- Maggiore sicurezza per donatori e riceventi
- Migliore standardizzazione e qualità dei prodotti SoHO
- Evidenze cliniche più robuste prima dell'introduzione
- Maggiore tracciabilità e sorveglianza post-utilizzo
- Aumento della fiducia di clinici, pazienti e autorità

- Accesso più lento a prodotti innovativi, potenzialmente anche disease-modifying
- Costi regolatori elevati per centri e istituzioni
- Difficoltà per piccoli centri nel sostenere gli obblighi
- Possibile freno alla ricerca traslazionale
- Rischio di disuguaglianze tra paesi/centri con risorse diverse

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Normativa più flessibile

- Introduzione più rapida di nuove Soho
- Maggiore spazio per innovazione accademica
- Facilitazione di studi pilota e proof-of-concept
- Riduzione dei costi
- Migliore accesso precoce per pazienti senza alternative

- Evidenze cliniche limitate, rischio di utilizzo prematuro di approcci non consolidati (rischi per il paziente, spreco di risorse)
- Maggiore variabilità tra centri e scarsa comparabilità dei risultati
- Maggior complessità nella vigilanza
- Possibile riduzione della fiducia pubblica in caso di eventi avversi

Regolamento Soho: *approccio intermedio.*

Standard europei armonizzati, maggiore controllo di qualità e sicurezza, tracciabilità e vigilanza rafforzate, ma con **elementi di flessibilità garantiti da approccio risk-based**.

Approccio risk- based

(44) Poiché le preparazioni di SoHO possono essere soggette a una serie di **attività** relative a tali sostanze, svolte in conformità del metodo di processazione scelto, prima del loro rilascio e della loro distribuzione, **le autorità competenti per le SoHO dovrebbero valutare e autorizzare le preparazioni di SoHO al fine di verificare il conseguimento costante di un livello elevato di qualità, sicurezza ed efficacia in esito a tale specifica serie di attività**, svolte in tale specifica maniera (Art. 20)

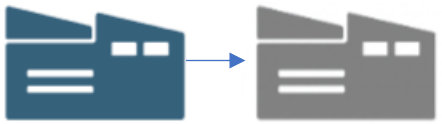
Quando le SoHO vengono preparate con metodi di raccolta, controllo o processazione di nuova messa a punto e validazione, **è opportuno dimostrare la sicurezza e l'efficacia nei riceventi di SoHO mediante la raccolta e il riesame dei dati sugli esiti clinici.**

La **portata** di tale monitoraggio richiesto sugli esiti clinici dovrebbe essere **correlata al livello di rischio** connesso alle attività svolte per la preparazione e l'uso delle SoHO in questione.

Rischio trascurabile

(44) Laddove una preparazione di SoHO nuova o modificata presenti **rischi trascurabili** per i riceventi di SoHO o laddove vi sia un elevato grado di certezza del fatto che il beneficio è predominante rispetto al rischio, sulla base delle prove fornite, gli **obblighi di vigilanza** previsti dal presente regolamento dovrebbero essere adeguati a verificare la **qualità e la sicurezza e l'efficacia**.

Ciò dovrebbe valere per le preparazioni di SoHO ben consolidate che sono introdotte presso un ente SoHO nuovo ma che si sono ampiamente dimostrate sicure ed efficaci attraverso il loro uso presso altri enti.



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Rischio non trascurabile > Piano di monitoraggio degli esiti clinici

Per quanto concerne le preparazioni di SoHO che presentano un rischio superiore a un rischio trascurabile e per le quali il beneficio atteso sia predominante rispetto a tale rischio, il **richiedente dovrebbe proporre un piano per il monitoraggio degli esiti clinici che dovrebbe soddisfare requisiti diversi adeguati al rischio in questione**.

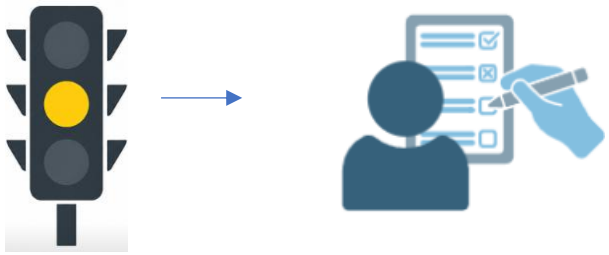
Ai fini della progettazione di piani di follow-up clinico proporzionati, in termini di portata e complessità, al livello di rischio individuato per la preparazione di SoHO, dovrebbero essere considerati pertinenti gli **orientamenti più aggiornati EDQM.**

- **L'autorità competente per le SoHO** approvare i piani prima della loro attuazione e valutare i dati sugli esiti nell'ambito dell'autorizzazione di preparazioni di SoHO.
- **Ruolo del Comitato Etico:** esprime parere riguardante gli **aspetti etici, giuridici e metodologici dello studio clinico** (*Art.40*)
- **Principi GCP:** Negli studi clinici sulle SoHO, i diritti, la sicurezza, la dignità e il benessere dei pazienti dovrebbero sempre essere prioritari e gli studi clinici sulle SoHO dovrebbero essere concepiti in modo da portare a dati e conclusioni affidabili e solidi

Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC

Rischio Basso

Follow-up clinico proattivo per un numero definito di riceventi.

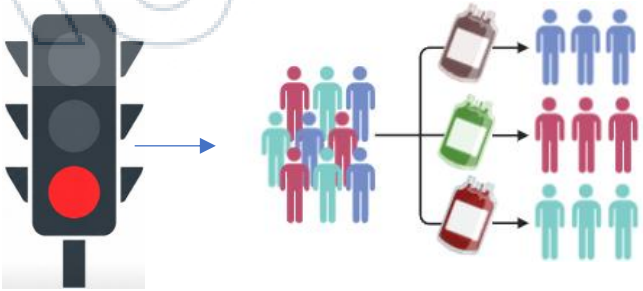


Rischio Moderato

Studio clinico con monitoraggio di endpoint clinici predefiniti.

Rischio elevato

Nei casi in cui il rischio o il beneficio non siano valutabili a causa della mancanza di conoscenze o dati clinici e scientifici: gli studi clinici con confronto con una terapia standard, idealmente in uno studio con riceventi di SoHO assegnati a gruppi di verifica e di controllo in modo **randomizzato**.



In sintesi – Autorizzazione delle preparazioni SoHO (Art.39)

- Le preparazioni SoHO devono essere autorizzate dall'autorità competente nazionale
- La domanda deve includere:
  - descrizione di donatori, raccolta e processazione
  - materiali/dispositivi utilizzati
  - controlli qualità e validazione del processo
  - indicazioni cliniche e dati di efficacia/sicurezza

- Obbligatoria una valutazione **beneficio-rischio**
- Forte riferimento a standard e monografie EDQM
- Per preparazioni innovative o con evidenze limitate può essere richiesto:
  - monitoraggio clinico
  - autorizzazione condizionata

- Modifiche significative del processo richiedono nuova autorizzazione

Passaggio da una logica "centre-based" a una valutazione "product/process-based"

Ruolo del medico (Art. 50)

Il medico è responsabile dei compiti seguenti:

- Elaborazione, riesame e approvazione delle procedure per stabilire e applicare i criteri di idoneità dei donatori di SoHO, le procedure per la raccolta di SoHO e i criteri per l'assegnazione di SoHO
- Supervisione dell'attuazione delle procedure di cui al punto precedente quando sono svolte da enti SoHO incaricati dal centro SoHO

- Gli aspetti clinici dell'indagine sulle sospette reazioni avverse nei donatori di SoHO, nei riceventi di SoHO e nella progenie nata da procreazione medicalmente assistita dalla prospettiva del centro SoHO
- La progettazione, **in collaborazione con i medici curanti**, dei piani di monitoraggio degli esiti clinici al fine di produrre le prove richieste a sostegno delle domande di autorizzazione di preparazioni di SoHO a norma dell'articolo 39, nonché la sorveglianza su tali attività

- Altri compiti pertinenti per la salute dei donatori di SoHO, dei riceventi di SoHO e della progenie nata da procreazione medicalmente assistita in relazione raccolte o fornite dal centro SoHO.

The Regulation includes very LIMITED TECHNICAL RULES.

Instead, it makes reference to TECHNICAL GUIDELINES that, if followed, provide a presumption of compliance.

GOOD PRACTICE GUIDELINE TO AUTHORISATION ON PREPARATION PROCESSES IN BLOOD, TISSUES AND CELLS ESTABLISHMENTS

Preparation Process Dossier (PPD)

Module 1: Applicant information

- BE/TE data.
- Data of the responsible person for the PPD.

Modules 2 and 3: Novelty and risk assessment

- Description of BTC.
- Novelty Questions.
- Activity information.
- Risk Assessment.

Module 4: Quality

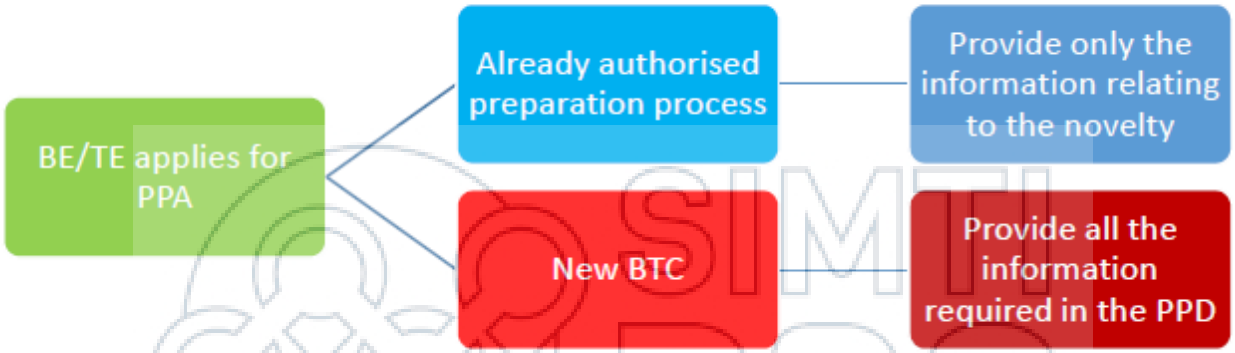
- Updated SOPs.
- Validation.

Module 5: Preclinical studies

- *In-vitro/In-vivo* studies
- Performed studies.
- Bibliography.

Module 6: Clinical information

- General clinical information.
- Clinical indication.
- CIP.
- CFUpP


BE/TE applies for PPA
Already authorised preparation process
New BTC
Provide only the information relating to the novelty
Provide all the information required in the PPD

The activities where the **novelty** can be implemented

1. **Donor Selection**
2. **Donation/Collection/ Procurement**
3. **Testing**
4. **Processing**
5. **Storage**
6. **Transport and delivery**
7. **Distribution/issue**
8. **Exportation/importation**
9. **New application/infusion method**
10. **New clinical indication**
11. **New anatomical site**

GAPP
PREPARATION PROCESS FOR BLOOD, TISSUES AND CELLS

Novelty questions	Yes	No	Sections to be fulfilled
Has this type of BTC previously been prepared and issued for clinical use by your establishment?			All sections as applicable
Will the starting material used to prepare this BTC be obtained from the same donor population previously used by your establishment for this type of BTC?			1 and 3 as applicable
Will the starting material for this BTC be procured/collected using a procedure used previously by your establishment for this type of BTC?			2 and 3 as applicable
Will this BTC be prepared by a procedure (processing/preparation, decontamination and preservation) used previously in your establishment for this type of BTC?			4
Will this BTC be packaged and stored using a protocol and materials used previously in your establishment for this type of BTC?			5
Will this type of BTC provided by your establishment be applied/ infused clinically using an application/infusion method used previously?			6, 7, 8 and 9 as applicable
Has your establishment provided this type of BTC for a same clinical indication or applied/infused into a same anatomical site?			10 and 11 as applicable

A **novelty** is 'any change that might affect the quality and/or the safety of the blood, tissues and cells and/or the safety of recipients '.
This change includes a new BTC, a new procedure designed by the BE/TE, a new procedure adopted from another centre that has shown scientific evidence or the application of the BTC to treat a new clinical indication.

• A **significant change** is a 'change that could significantly affect the quality and/or the safety of the BTC/or the safety of recipients and that is assessed as a 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 Euro GTPII.

GAPP
PREPARATION PROCESS FOR BLOOD, TISSUES AND CELLS

Tissues and Cells	Blood and Blood components
Identification of risk factors:	
Donor Characteristics	Donor Characteristics
Procurement process and environment	Collection process and environment
Processing and environment	Processing and environment.
Reagents	Reagents / Added component
Reliability of Microbiology Testing	Reliability of Testing
Storage Conditions	Storage Conditions
Transport Conditions	Transport Conditions
Presence of unwanted cellular material and/or graft vascularity	Presence of unwanted residues
	Clinical indications
Loss of viability and/or functionality	
Complexity of the immediate pre-implantation preparation and/or application method	

Identification of risk consequences	
Unexpected immunogenicity Implant failure / engraftment failure / pregnancy loss Disease transmission Toxicity / Carcinogenicity Other potential risks (can be associated with specific TC)	Unexpected immunogenicity Failure to perform clinically / Incremental failure Disease transmission Toxicity/Carcinogenicity Other
Quantification of risk	
The probability of the risk occurring. The severity of the consequences should the risk occur. The probability the source of the hazard for the risk consequences will be detected before the TC is applied.	The probability of the risk occurring. The severity of the consequences should the risk occur. The probability that the source of the harm for the risk consequences will be detected before the BC is transfused/applied. This does not refer to detection of the consequences of the risk post transfusion/application. Any existing evidence that can be used to mitigate the risk.

Assessment of risk reduction	
It may be possible to adjust the overall risk score taking into account external sources of information. The data that should be taken into account when assessing the risk reduction are: • Published data in peer reviewed literature. • Unpublished data from external sources. • Advice and information from external experts. • Clinical outcome data from external sources (e.g. registries).	For blood the assessment of the risk reduction is performed within the quantification of the risk step.

EuroGTP II Interactive Assessment Tool

Advances in technology and science continue to contribute to the development of novel Tissue and Cellular Therapies/Products (TCTPs) and novel preparation protocols for new and existing TCTPs.

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, procurement, testing, processing, storage and distribution of TCTPs may impact the quality of these therapies/products and therefore the safety of donors or recipients.

EURO GTP II
Good Tissue & cell Practices

The Euro GTP II Interactive Assessment Tool (IAT) has been developed to assist professionals involved in the provision of TCTPs to:

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

It is essential that this process is performed by a group of individuals with the requisite knowledge to accurately identify and evaluate the risks detailed in the tool. Sufficient time and resource must be allocated to enable the process to be performed.
This may involve detailed reviews of data and other literature to inform calculation of specific risks.

The tool will generate a short summary report detailing the risks identified, and the risk scores, however the rationale for decisions, and evidence used to support them should be also recorded and retained.

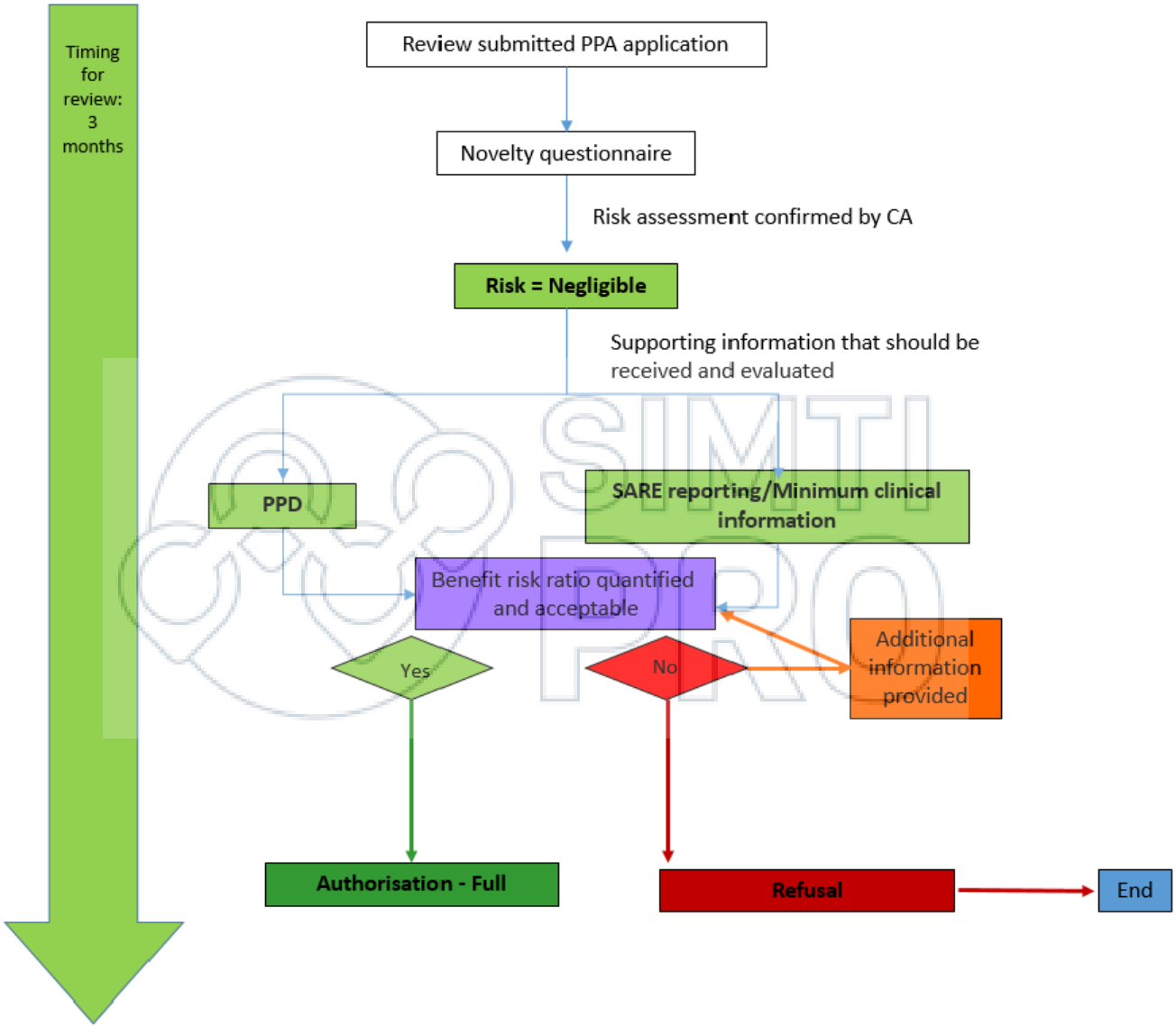
Restore Start

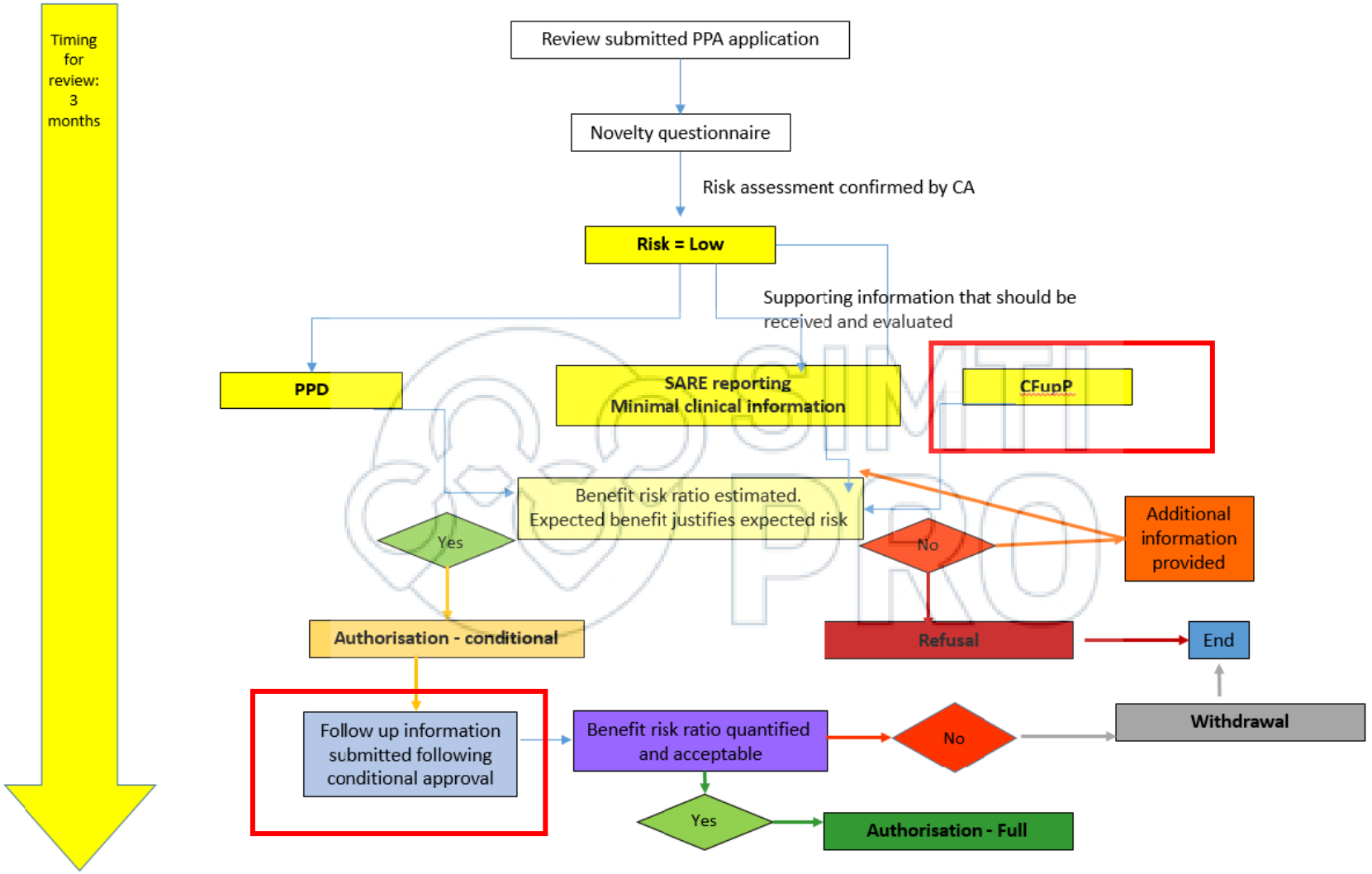
Created by EURO GTP II

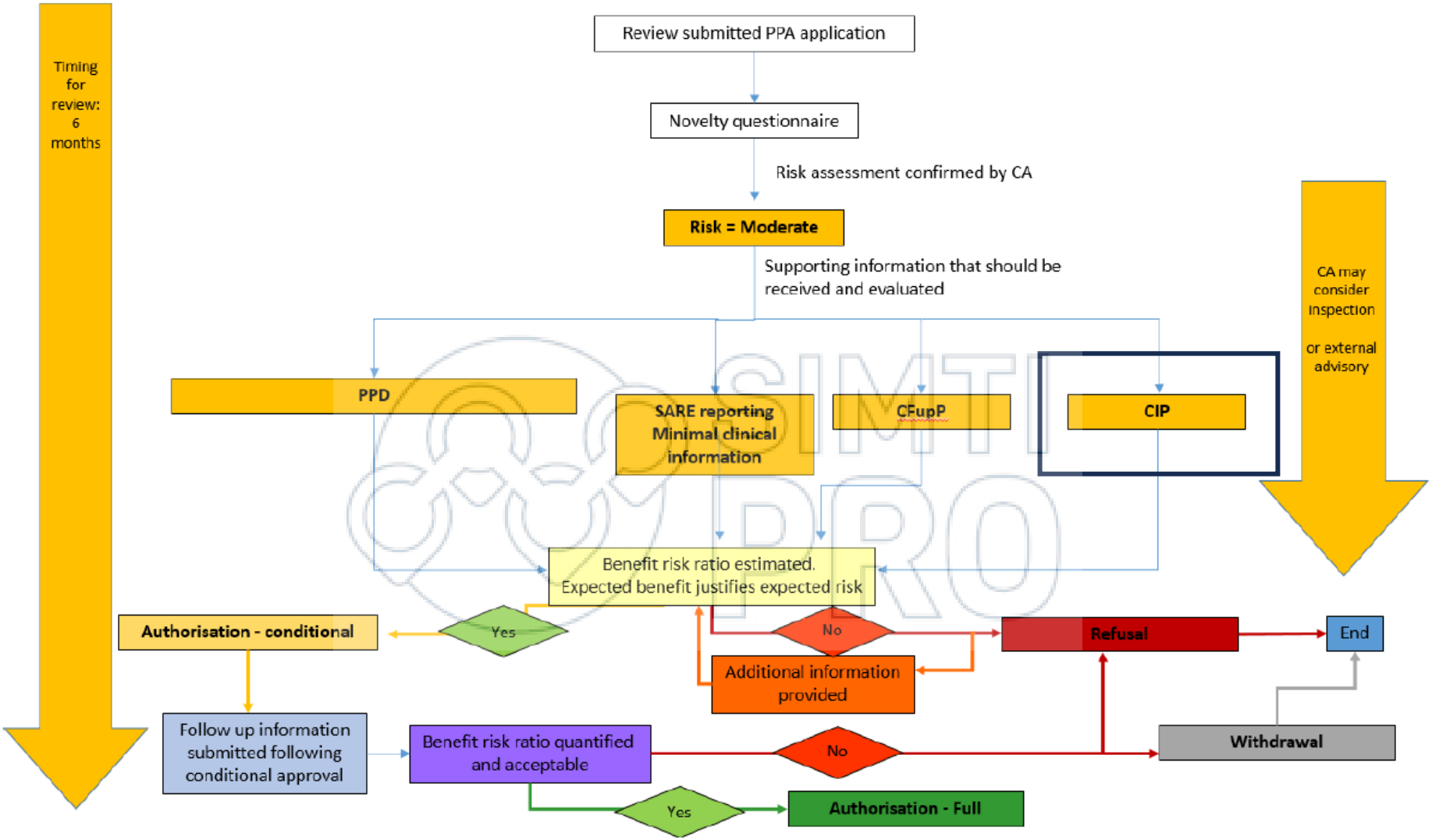
Risk assessment → Livello di evidenza clinica richiesto

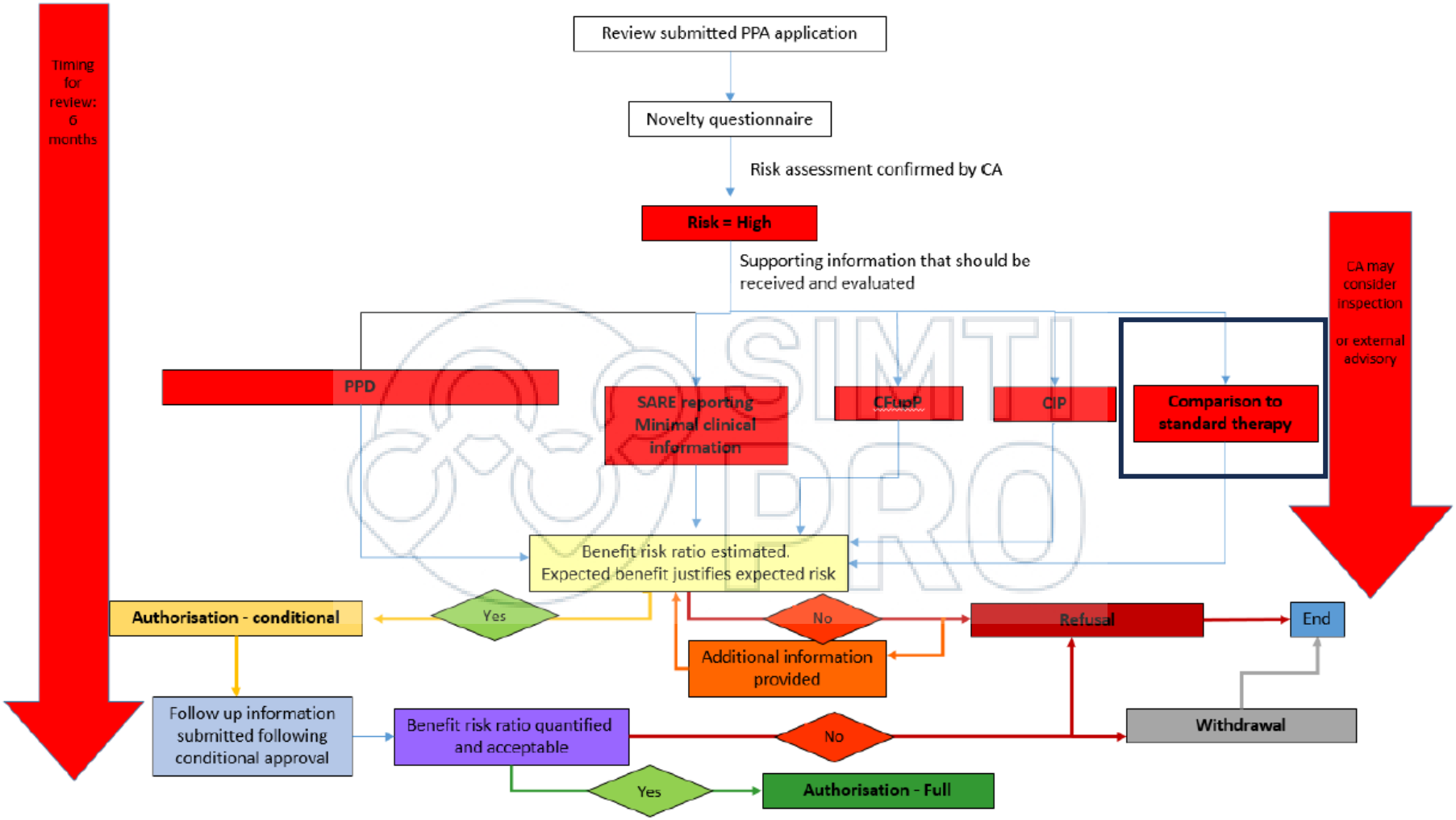
Select the risk level assigned after performing the EuroGTPII risk assessment and provide the completed EuroGTPII tool template	**The information below is required based on the indicated risk. To submit the required information proceed to module 4, 5 and 6 as appropriate.**
Negligible □	Quality SARE reporting*
Low □	Quality Preclinical information SARE reporting* CFUpP
Moderate □	Quality Preclinical information SARE reporting* CFUpP CIP
High □	Quality SARE reporting* Preclinical information CFUpP CIP Comparison Study

Table 2: risk level assigned after performing EuroGTPII risk assessment and the corresponding required information.

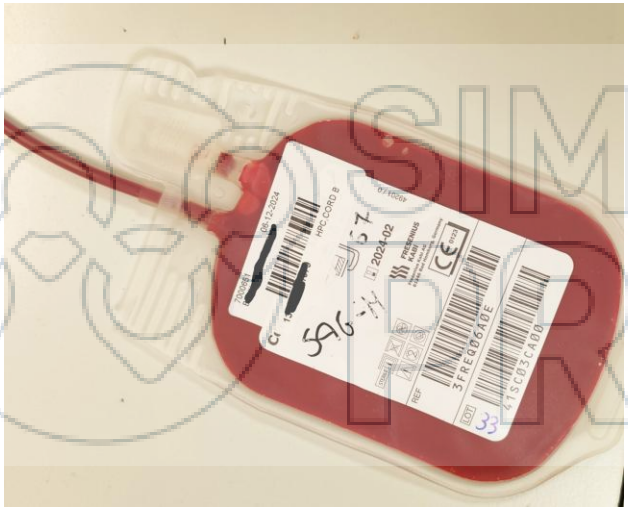

Timing for review: 3 months
Review submitted PPA application
Novelty questionnaire
Risk assessment confirmed by CA
Risk = Negligible
Supporting information that should be received and evaluated
PPD
SARE reporting/Minimum clinical information
Benefit risk ratio quantified and acceptable
Yes
No
Additional information provided
Authorisation - Full
Refusal
End


Timing for review: 3 months
Review submitted PPA application
Novelty questionnaire
Risk assessment confirmed by CA
Risk = Low
Supporting information that should be received and evaluated
PPD
SARE reporting
Minimal clinical information
CFupP
Benefit risk ratio estimated.
Expected benefit justifies expected risk
Yes
No
Additional information provided
Authorisation - conditional
Refusal
End
Follow up information submitted following conditional approval
Benefit risk ratio quantified and acceptable
No
Withdrawal
Yes
Authorisation - Full

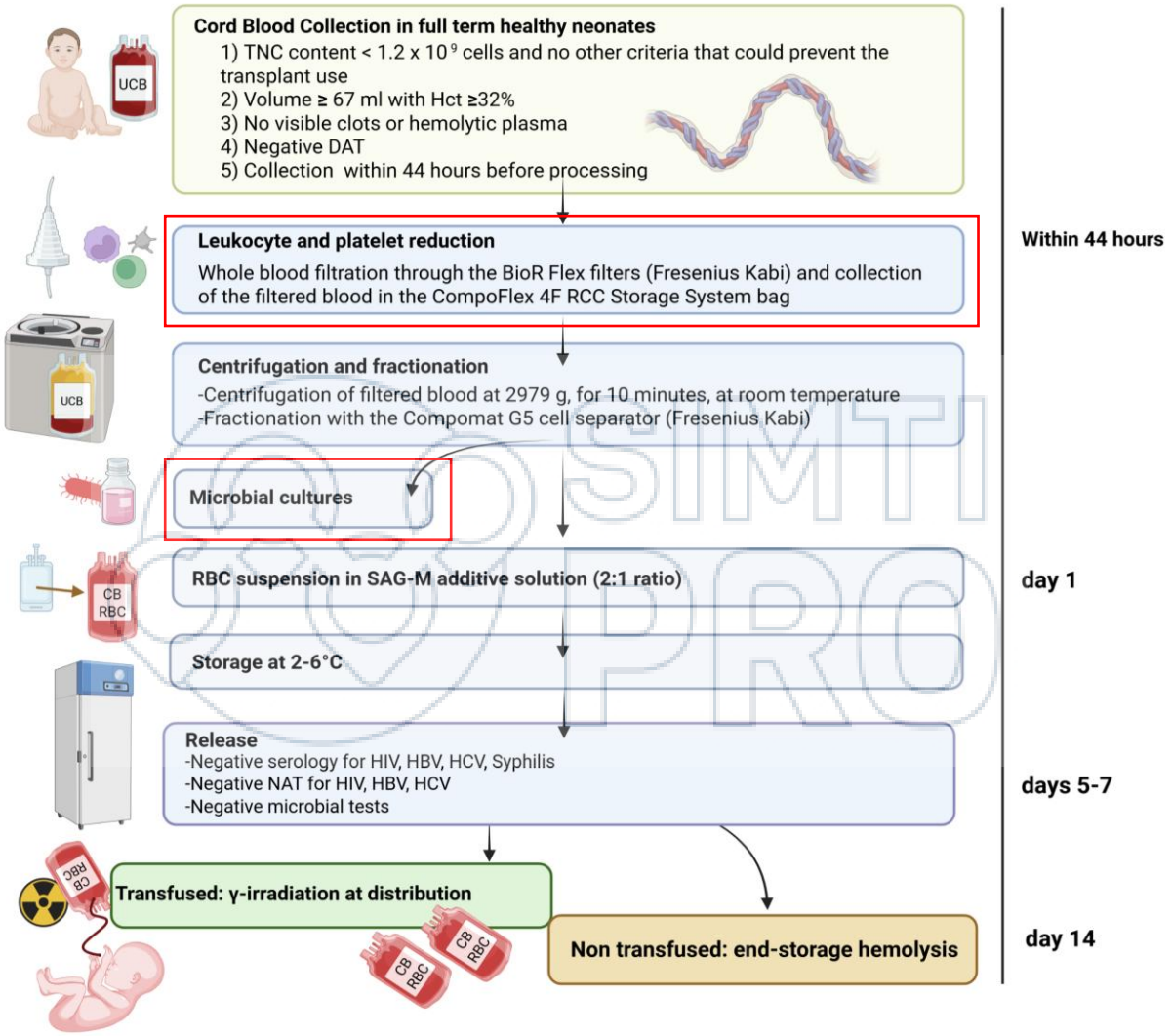

Timing for review: 6 months
Review submitted PPA application
Novelty questionnaire
Risk assessment confirmed by CA
Risk = Moderate
Supporting information that should be received and evaluated
CA may consider inspection or external advisory
PPD
SARE reporting Minimal clinical information
CFupP
CIP
Benefit risk ratio estimated. Expected benefit justifies expected risk
Authorisation - conditional
Yes
No
Refusal
End
Additional information provided
Follow up information submitted following conditional approval
Benefit risk ratio quantified and acceptable
No
Withdrawal
Yes
Authorisation - Full


Timing for review: 6 months
Review submitted PPA application
Novelty questionnaire
Risk assessment confirmed by CA
Risk = High
Supporting information that should be received and evaluated
CA may consider inspection or external advisory
PPD
SARE reporting Minimal clinical information
CFuoP
CIP
Comparison to standard therapy
Benefit risk ratio estimated. Expected benefit justifies expected risk
Authorisation - conditional
Yes
No
Refusal
End
Additional information provided
Follow up information submitted following conditional approval
Benefit risk ratio quantified and acceptable
No
Withdrawal
Yes
Authorisation - Full

CB-RBC: nuova preparazione SoHo



Cord Blood Red Cells, Leukocyte-depleted, in additive solution (CB-RBCs)



Guide to the preparation, use and quality assurance of BLOOD COMPONENTS

European Committee on Blood Transfusion (Partial Agreement) (CD-P-TS)

EDQM

22nd Edition

2025

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

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B-2. Red Cells, Leucocyte-Depleted in Additive Solution

Definition and properties

Red Cells, Leucocyte-Depleted in Additive Solution (LD-AS) is a red cell component derived from *Whole Blood* by removing the leucocytes, removing the majority of the plasma and adding an additive solution, or from leucocyte filtration of *Red Cells, AS or Red Cells, Buffy Coat Removed-AS (BCR-AS).*

Red Cells, LD-AS contains a minimum haemoglobin content of 40 g. The haematocrit is 0.50 to 0.70.

Red Cells, LD-AS contains less than 1×10^6 leucocytes.

Preparation

Generally, a filtration technique is used to produce *Red Cells, LD-AS.* Leucocyte depletion should be performed within 48 hours after donation.

Red Cells, LD-AS can be produced:

- By leucocyte filtration of *Whole Blood*, with subsequent centrifugation and removal of the plasma and immediate addition of the additive solution, followed by careful mixing;
- By leucocyte filtration of *Red Cells, AS or Red Cells BCR-AS.*

Requirements and quality control

As indicated for *Whole Blood, LD* except for the parameters specified in Table 5B-2.

Table 5B-2

Parameter to be checked	Requirements	Frequency of control
Volume[a]	To be defined for the system used	as determined by SPC
Haematocrit[a]	0.50–0.70	as determined by SPC
Haemoglobin per final unit[a]	Minimum 40 g	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

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

EuroGTP II Interactive Assessment Tool

You will use the Assessment Tool to evaluate:

- ○ Tissues
- ◉ Hematopoietic Cells
  - ○ Bone Marrow
  - ○ Peripheral Blood
  - ○ Cord Blood
  - ◉ Other
- ○ Assisted Reproductive Techniques

Select the category of Substance of Human Origin (SoHO) under evaluation

Back Next

A: Has this type of SoHO previously been prepared and issued for clinical use by your establishment?

A. Has this type of TCTP previously been prepared and issued for clinical use by your establishment?

- (●) Yes
- ( ) No
- ( ) Not Applicable / Not relevant

Justify

B. Will the starting material used to prepare this TCTP be obtained from the same donor population previously used by your establishment for this type of TCTP?

- ( ) Yes
- ( ) No

The purpose of this question is to determine whether your institution has previously prepared, and issued the specific, anatomical type of TCTP in clinical application for a specific indication. It does not require that the TCTP has been issued and administered before for a different indication.

Examples:
A1 – Your establishment is already performing T-cell depletion on haematopoietic grafts, but you intend to revise the processing. In this case you would answer 'Yes' to this question, and there is no novelty.
A2 - Your establishment is performing haematopoietic stem cell transplantation (HSCT) using bone marrow (BM) and peripheral stem cell (PBSC) grafts. It is decided to start a cord blood transplantation programme. In this case you answer 'No'; you have no experience in handling and issuing cord blood.

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?

B. Will the starting material used to prepare this TCTP be obtained from the same donor population previously used by your establishment for this type of TCTP?

- ○ Yes
- ◉ No
- ○ Not Applicable / Not relevant

Justify

This question aims to elicit possible differences in the characteristics of the TCTP caused by a change in the donor population. Examples of changes that would create novelty are changing the age limits for donors of the TCTP, or changing specific aspects of the donor selection criteria applicable to the TCTP. Note that this does not apply to generic changes to donor selection criteria; for example if screening requirements for blood borne infections are amended. It , rather should be considered when making specific changes to donor selection criteria that has an impact on specifications of the TCTP's.

C: Will the starting material for this SoHO be procured/collected using a procedure used previously by your establishment for this type of SoHO

C. Will the starting material for this TCTP be procured/collected using a procedure used previously by your establishment for this type of TCTP?

- ○ Yes
- ◉ No
- ○ Not Applicable / Not relevant

Justify

The question is to determine whether a change in the way in which the TCTP is procured from the donor (or patient) may impact on its safety or quality.

Examples:
C1 – Your establishment is currently administering filgrastim (G-CSF) for the mobilization of haematopoietic stem cells in donors. It is decided to start using a biosimilar for this purpose. In this case, there may be a novelty; because the nature of the cells and composition of the graft could have been changed in a way that it influences the quality and

D: Will this TCTP be prepared by a procedure (processing, decontamination and preservation) used previously in your establishment for this type of TCTP?

D. Will this TCTP be prepared by a procedure (processing, decontamination and preservation) used previously in your establishment for this type of TCTP?

- ○ Yes
- ◉ No
- ○ Not Applicable / Not relevant

Justify

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

Examples:
D1 – Your establishment currently storing autologous PBSC grafts in liquid nitrogen storage, after controlled-rate freezing. You are considering changing to mechanical freezing and storage. There would clearly be novelty here, as you are introducing a novel process which could have significant implications for graft safety and quality.
D2 – Your establishment currently used buffered

E. Will this TCTP be packaged , stored , and distributed using a protocol and materials used previously in your establishment for this type of TCTP?

- (●) Yes
- ( ) No
- ( ) Not Applicable / Not relevant

Justify [ ]

F. Will this type of TCTP provided by your establishment be applied/infused clinically using an application/infision method used previously?

- (●) Yes
- ( ) No
- ( ) Not Applicable / Not relevant

Justify [ ]

G. Has your establishment provided this type of TCTP for a same clinical indication or applied/infused into a same anatomical site?

- (●) Yes
- ( ) No
- ( ) Not Applicable

Justify [ ]

	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		

Risk Factor	Risk	Probability	Severity	Detectability	Potential Risk	Risk Reduction	Risk
Collection process and environment	Disease transmission	3	2	1	**6**	75%	**1.5**
Processing and environment	Unwanted immunogenicity	1	3	1	**3**	95%	**0.15**

Risk Factor	Applicable	Comment
Donor Characteristics	N	Donor selection is performed according to the criteria used for cord blood collection for transplant use, in agreement with current regulations on cord blood donation.
Collection process and environment	Y	In contrast to blood collected by venipuncture of adult donors, blood collected from the umbilical cord has a higher risk of microbial contamination. For this reason, all collected units are subjected to bacterial and fungal culture testing and distributed after negative results are provided.
Processing and environment	Y	The initial volume of cord blood is significantly lower than that of an adult donor's whole blood unit. To recover a satisfactory amount of red blood cells, cord blood is filtered before fractionation using a "small volume" filter originally designed for red blood cell concentrates. The filtration efficiency has been validated. Cord blood processing occurs in a closed system, using a semiautomated method.

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 **routine/safety follow up program** incorporating serious adverse reaction and event (SARE) reporting, is sufficient as the good practices states. Ideally, follow up procedures should be focused on assessing efficacy, comparing the clinical follow up with the results obtained before the implementation of the change in the process.

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Cord blood red cell concentrates for preterm neonate transfusion: Insights from the multicenter BORN trial

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TABLE 2 Pre-study validation of leukodepletion.

	CB units *N* 40
Pre-filtration volume, mL	77.1 (70.4–94.3)
Pre-filtration Hct, %	37.3 (34–7-39.2)
Pre-filtration RBC mass, mL	29.0 (24.8–34.3)
Pre-filtration WBCs, 10^6/unit	754 (606–998)
Pre-filtration PLT, 10^9/unit	17.4 (14.4–20.7)
Post-filtration volume, mL	55.7 (47.6–72.9)
Volume loss, %	27.3 (22.9–32.0)
Post-filtration Hct, %	36.0 (34.2–38.9)
Post-filtration RBC mass, mL	21.0 (16.7–27.2)
RBC mass recovery, %	72.3 (67.0–77.1)
Post-filtration WBCs, 10^6/unit[a]	0.014 (0.005–0.036)
WBC removal, %[a]	99.9 (99.9–99.9)
Compliant for residual WBC[a]	30 (96.8)
Post-filtration PLT, 10^9/unit	1.8 (1.4–2-9)
PLT removal, %	88.8 (84.1–90.7)

Abbreviations: CB, cord blood; Htc, hematocrit; RBC, red blood cells; WBC, white blood cells.

[a]Data relative to 31 CB units. Data are expressed as median (25th to 75th percentile range) or *n* (%).

TABLE 3 Processing data and quality controls of CB-RBC units produced during the BORN study.

	A (*n* 30)	B (*n* 47)	C (*n* 30)	D (*n* 20)	E (*n* 98)	F (*n* 14)	G (*n* 25)	I (*n* 84)	H (*n* 103)	TOT 451
Interval form collection, hours	30.5 (20.7–38.8)	28.3 (26.0–30.4)	25.8 (24.0–32.6)	22.6 (17.0–37.9)	31.8 (21.1–37.9)	21.8 (1.0–40.6)	23.0 (19.2–29.5)	24.6 (18.4–32.0)	24.1 (18.8–36.0)	26.0 (20.4–35.8)
CB-RBC volume, mL	39.5 (30.7–48.5)	44.0 (34.0–50.0)	53.0 (44.5–61.0)	35.0 (29.0–40.2)	32.5 (28.0–44.0)	32 (29.3–39.0)	46.5 (30.2–57.0)	42.0 (30.2–50.0)	38.0 (30.5–45.5)	39.0 (30.0–50.0)
Hct, %	57.6 (54.2–60.7)	58.0 (56.0–59.5)	47.5 (44.3–52.7)	57.0 (52.4–58.5)	56.0 (52.0–59.0)	53.9 (37.9–61.8)	49.0 (41.4–52.6)	55.0 (52.6–56.6)	58.3 (55.4–61.9)	56.1 (52.3–59.4)
RBC mass, mL	22.0 (18.0–27.5)	25.0 (20.0–29.0)	27.0 (20.0–32.0)	20.5 (15.3–22.0)	18.0 (14.0–24.0)	16.0 (10.5–22.0)	18.5 (13.5–26.25)	22.0 (16.2–28.0)	22.0 (17.0–27.0)	21.6 (17.0–27.0)
RBC mass recovery, %	68.6 (63.4–75.7)	65.8 (62.2–69.6)	84.4 (69.3–96.2)	57.5 (50.0–64.5)	59.4 (53.7–69.4)	64.0 (53.0–71)	62.4 (48.0–83.3)	62.8 (58.4–69.9)	67.7 (60.8–73.1)	64.6 (58.4–72.0)
Hb/unit, g	6.9 (5.5–8.6)	8.2 (6.4–9.4)	8.3 (6.2–10.3)	6.4 (5.3–7.2)	5.6 (4.3–7.6)	5.5 (4.7–6.9)	6.0 (4.0–8.9)	7.3 (5.3–9.1)	6.9 (5.2–8.5)	6.8 (5.2–8.5)
Platelets, 10^9/unit	2.3 (1.3–3.3)	3.9 (2.7–5.1)	2.3 (0.8–4.1)	1.6 (0.9–2.5)	1.7 (0.9–3.0)	2.6 (1.0–53.7)	1.2 (0.9–2.6)	2.4 (1.5–4.4)	1.0 (0.5–1.9)	1.9 (0.9–3.2)
Platelet removal, %	87.4 (83.9–91.5)	82.5 (77.9–85.5)	87.8 (82.9–94.7)	90.4 (86.6–94.5)	89.7 (84.3–93.1)	87.0 (81.8–91.4)	90.9 (86.1–95.0)	88.2 (84.7–92.6)	94.1 (91.5–96.6)	89.6 (84.8–93.6)
Compliant for Htc values[a]	29 (96.7)	47 (100)	10 (33.3)	18 (90.0)	85 (86.7)	9 (64.2)	9 (36.0)	78 (92.8)	94 (91.2)	379 (84.0)
Compliant for residual WBC	30/30 (100)	45/46 (97.8)	29/29 (100)	20/20 (100)	95/95 (100)	9/9 (100)	24/24 (100)	76/76 (100)	9/9 (100)	337/338 (99.7%)
End-stage hemolysis	0.23 (0.01–0.47)	0.24 (0.17–0.35)	0.39 (0.31–0.63)	0.51 (0.41–0.65)	0.33 (0.28–0.62)	NR	NR	0.45 (0.40–0.51)	0.29 (0.22–0.41)	0.39 (0.25–0.51)
Compliant/tested for end storage hemolysis[a]	10/10 (100)	7/8 (87.5)	20/22 (90.9)	16/17 (94.1)	17/17 (100)	NA	NA	18/19 (94.7)	30/30 (100)	117/123 (94.3)

Cord red blood cell transfusions for severe retinopathy in preterm neonates in Italy: a multicenter randomized controlled trial

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