EURO GTP II

Good Tissue & cell Practices

Good Practices for demonstrating safety and quality through recipient follow-up

Using the EuroGTP II methodologies and Interactive Assessment Tool (IAT)

Co-funded by the Health Programme of the European Union

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Project ‘709567 / Euro-GTP II’ received funding from the European Union’s Health Programme (2014-2020).

COLLABORATIVE PARTNERS

EATB – European Association of Tissue Banks

EBMT – European Society for Blood and Marrow Transplantation

ESHRE – European Society of Human Reproduction and Embryology

EEBA - European Eye Bank Association

EDQM, CoE - European Directorate for the Quality of Medicines & HealthCare, Council of Europe

Kliničkí Bolnički Centar Zagreb

Fondazione Banca dei Tessuti di Treviso - Onlus

Fondazione Banca degli Occhi del Veneto Onlus

Department of Experimental Medicine Medical Fisiopathology Division of the Rome La Sapienza University

Gruppo Italiano per il Trapianto di Midollo Osseo,cellule staminali emopoietiche e terapia cellulare

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BISLIFE Multi Tissue Centre

Sanquin Blood Supply Foundation

Instituto Português do Sangue e da Transplantação

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Key Question:

Any novel or changed preparation process creates the possibility of risk

How do we identify, quantify, and manage this risk?

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Objectives

- Develop methodologies for

  Identifying risks associated to novel tissues/cells

  Assessing these risks

- Develop methodologies for assessing the **extent of the studies needed to provide enough quality, safety and efficacy** data for the clinical use of novel tissues/cells

- Determining the **follow up programs necessary** to support the evaluation of clinical safety and efficacy

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Objectives

SCOPE:

- **Tissue Allografts**
- **Haematopoetic Stem Cells**
- **Assisted Reproductive Technology (ART)**

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- TEs / ART Centers
- ORHAs
- NCAs

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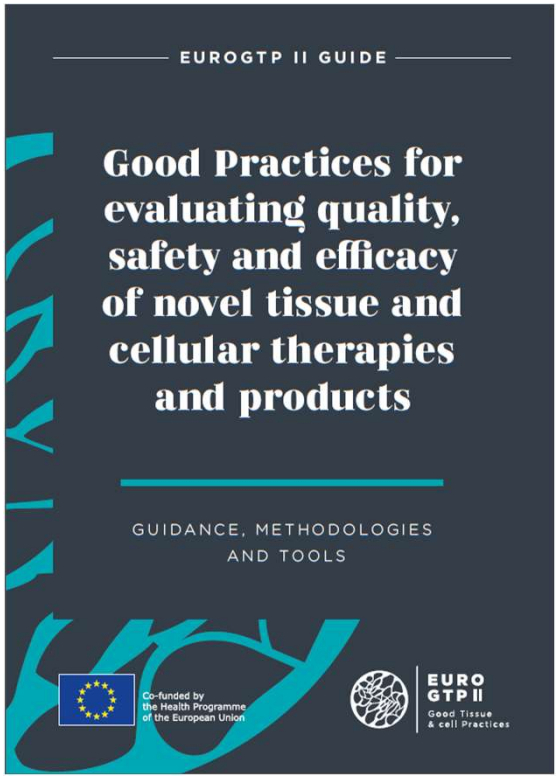
Guide

Definition of the **methodology to assess:**

- **Novelty grade** (risk value **Risk Based Approach**);
- Definition of the **validation studies, pre- clinical (*in vivo* and *in vitro*) studies, Clinical Evaluation procedures, and follow up programs**
- Sections: **Generic + Tissues + HSC + ART**



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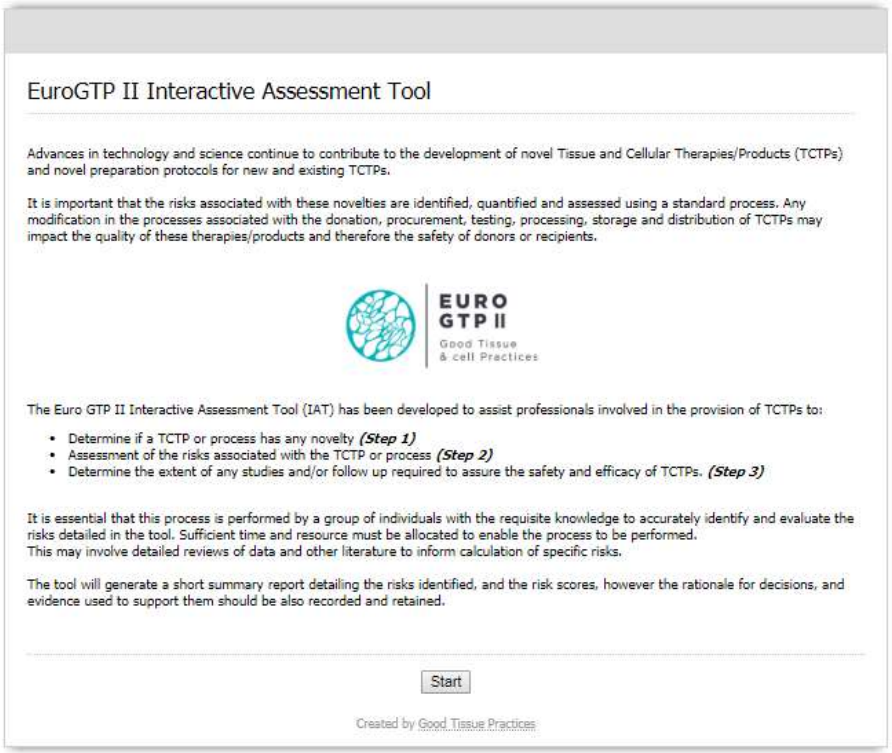
Interactive Assessment Tool

Practical **assessment to determine the extent of studies and follow-up programs** needed to implement, evaluate and authorise a novel T&C product, process or therapy.



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The Methodology

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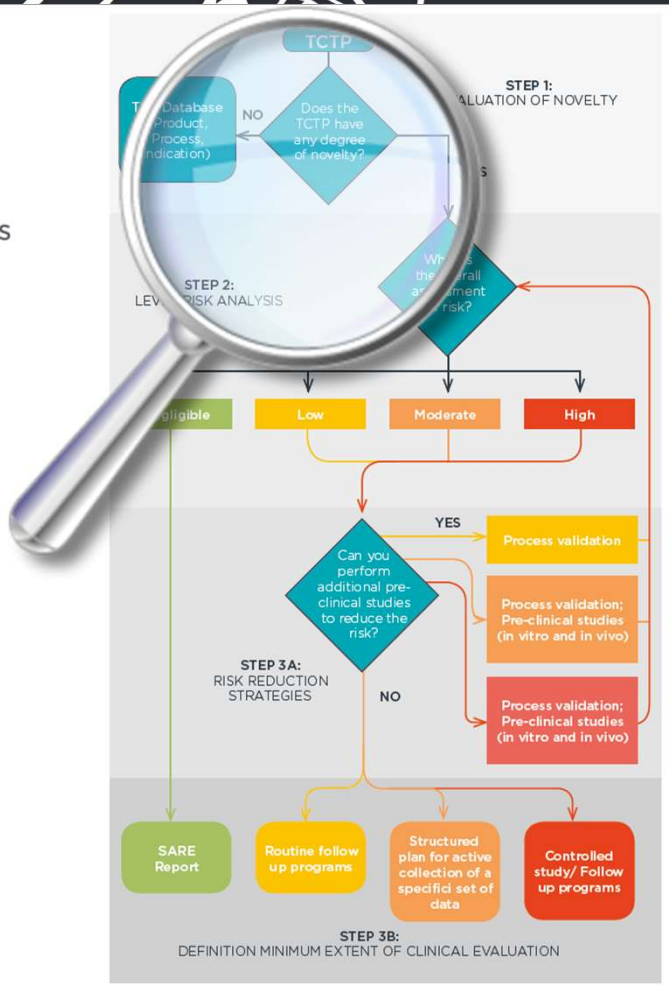

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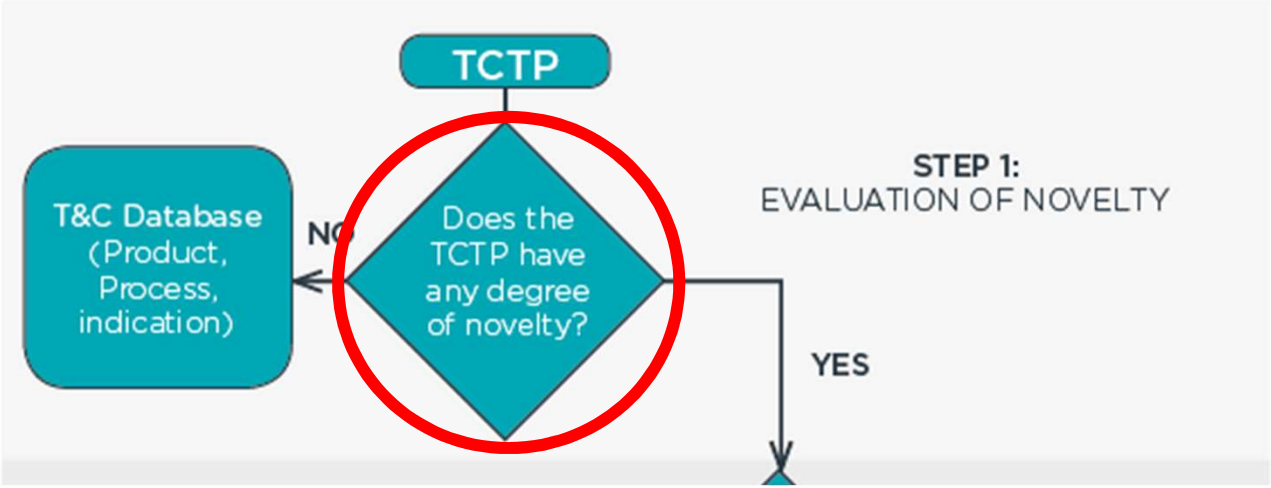

		YES	NO	NA
A.	Has this type of TCTP previously been prepared and issued for clinical use by your establishment?			
B.	Will the starting material used to prepare this TCTP be obtained from the same donor population previously used by your establishment for this type of TCTP?			
C.	Will the starting material for this TCTP be procured using a procedure used previously by 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?			
E.	Will this TCTP be packaged and stored using a protocol and materials used previously in your establishment for this type of TCTP?			
F.	Will this type of TCTP provided by your establishment be applied clinically using an implantation method used previously?			
G.	Has your establishment provided this type of TCTP for implantation or transplantation into the intended anatomical site before?			

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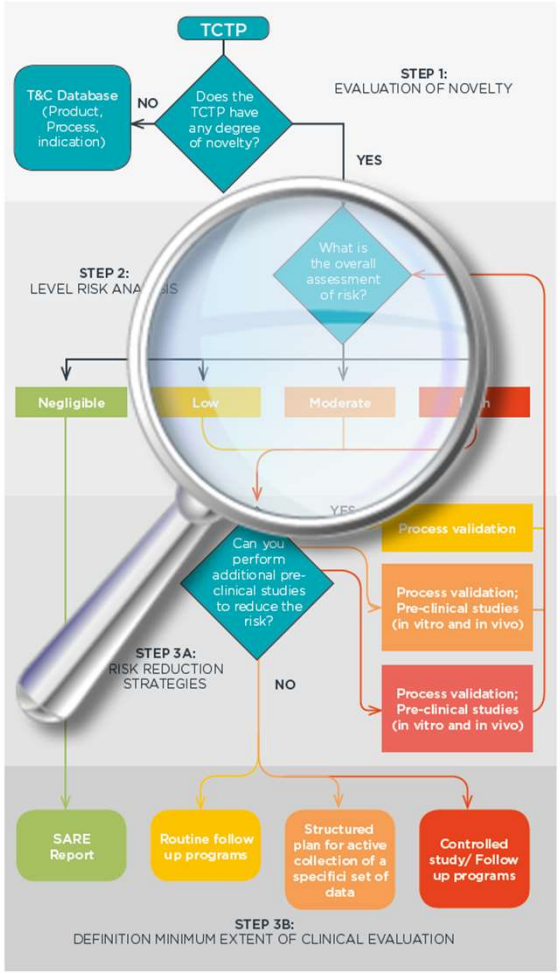

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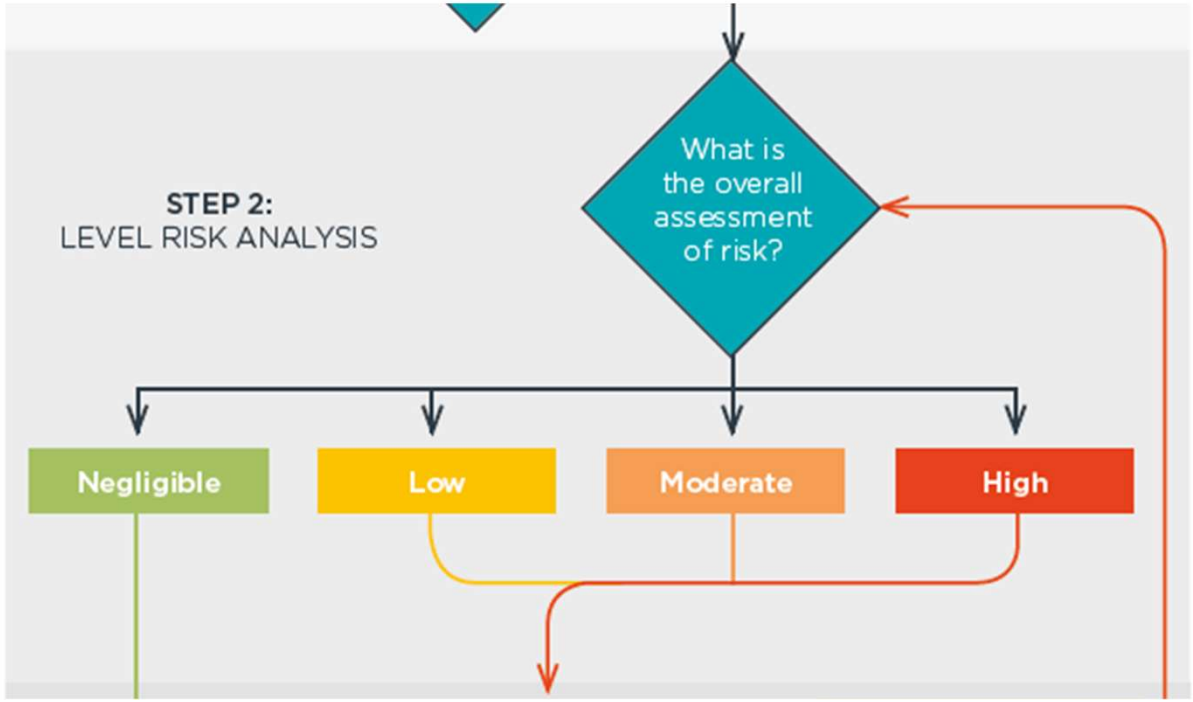

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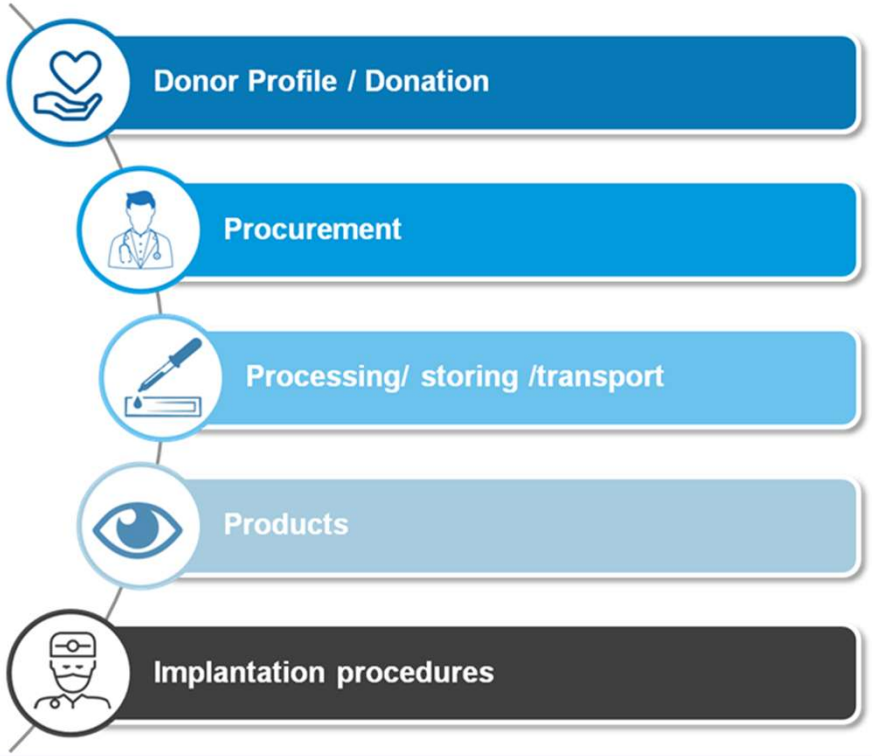
Donor Characteristics

Recovery process and environment'

Processing and environment'
Reagents
Reliability of Microbiology Testing'
Storage conditions
Transport conditions

Loss of viability and or functionality
Presence of unwanted cellular material and/or graft vascularity

Complexity of the immediate pre-implantation preparation and/or application method



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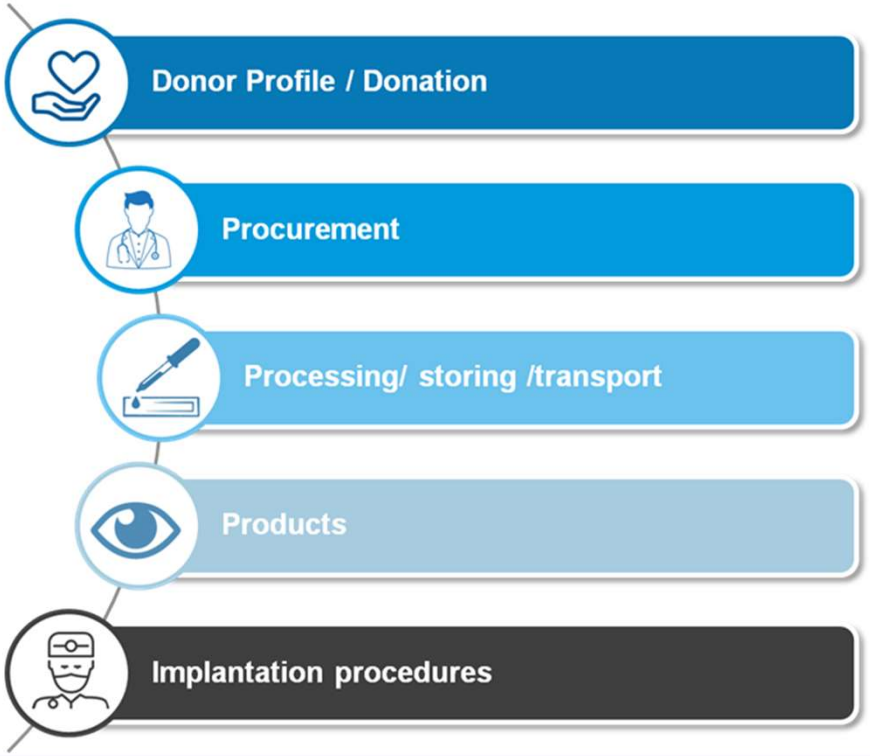
Unexpected immunogenicity

Implant failure/Engraftment failure/ Pregnancy loss

Disease transmission

Toxicity / Carcinogenicity

Other potential risks (can be associated with specific TCP/therapy)



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Each of these must be individually risk assessed to determine the residual risk of implementing the change, assessed 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 hazard for the risk consequences will be detected** before the TCTP is applied. This does not refer to detection of the consequences of the risk post implantation.

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

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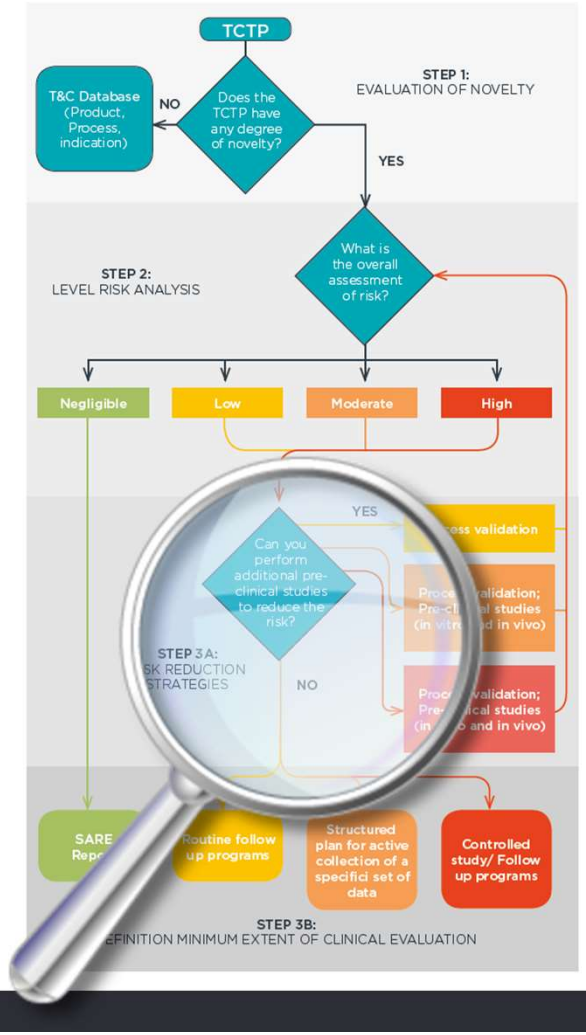

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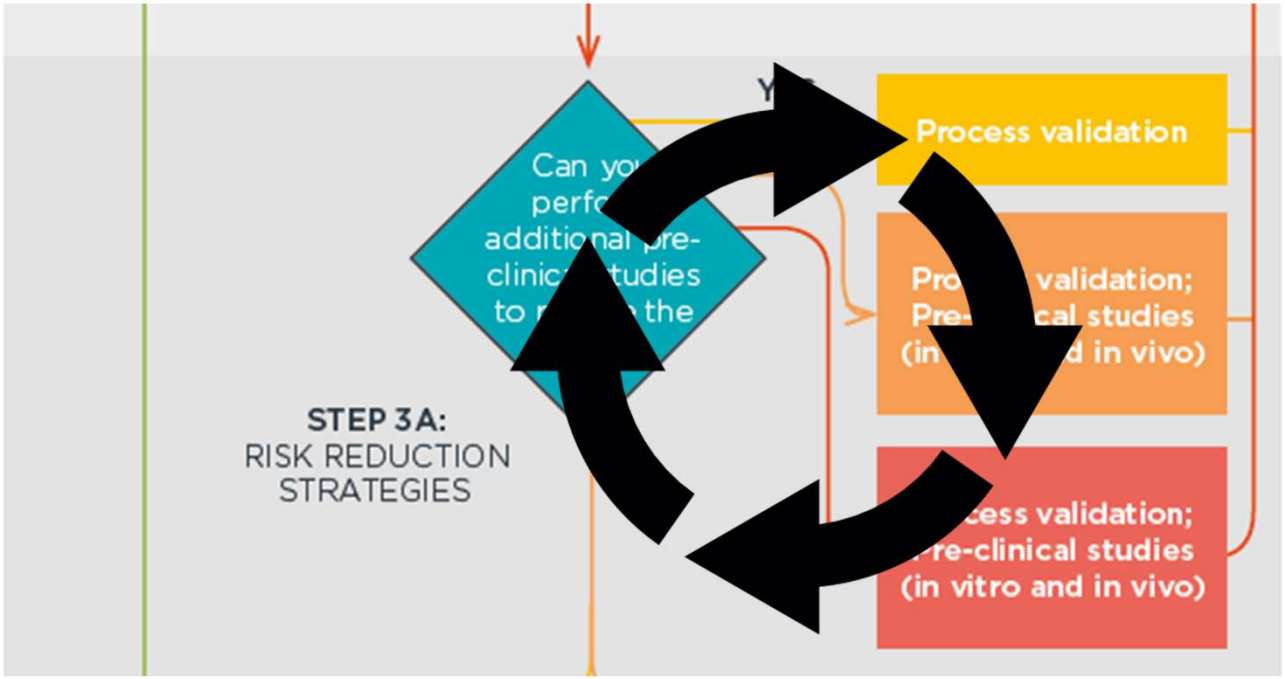

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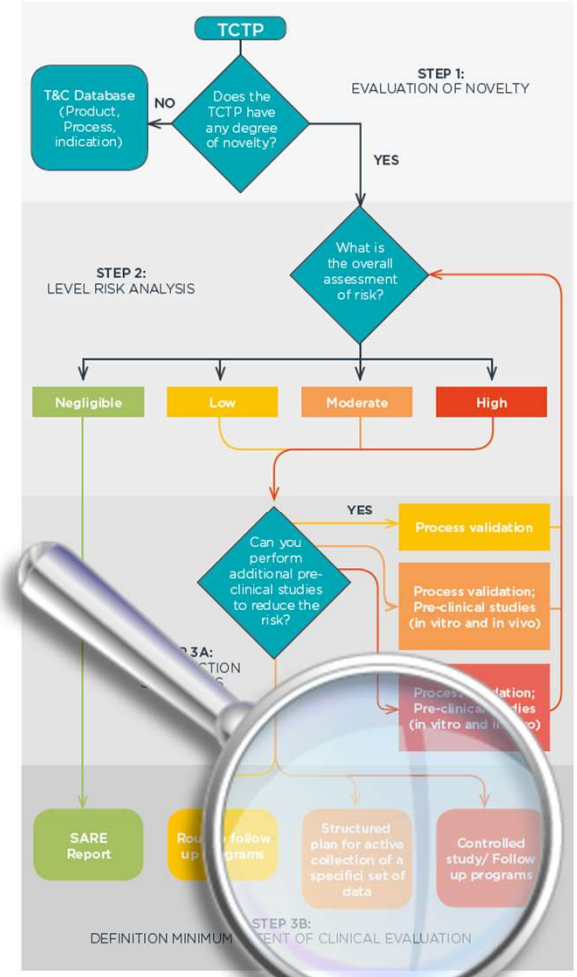

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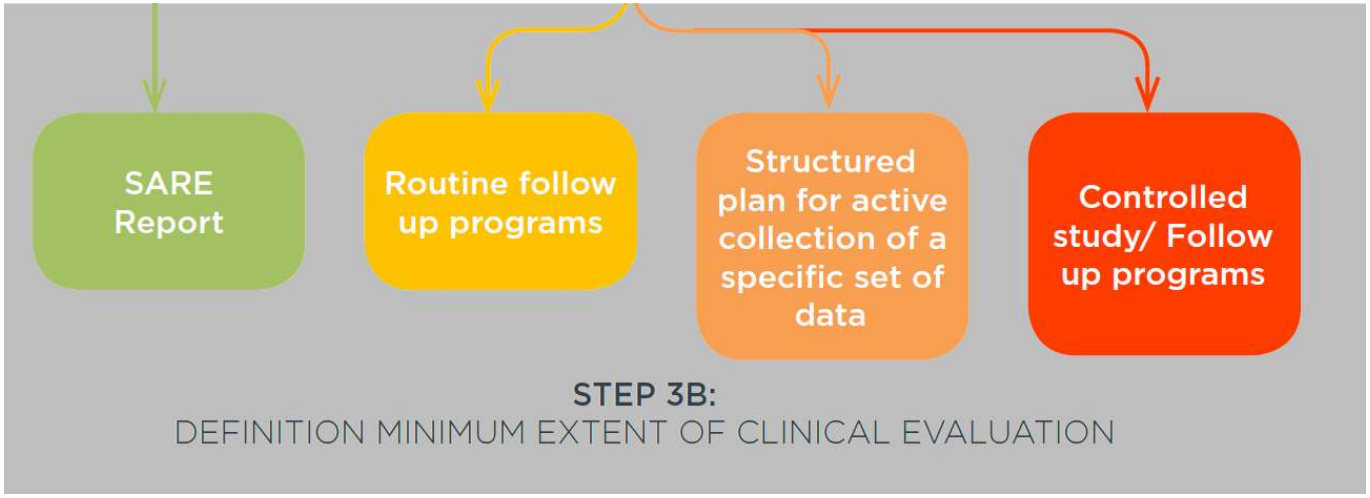

STEP 3B:
DEFINITION MINIMUM EXTENT OF CLINICAL EVALUATION

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Practical Case

Heart Valve Decontamination

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What is your current process?

You obtain whole hearts from deceased donors either in hospital mortuaries, or directly from organ transplant surgeons. These hearts are aseptically packaged and sent to your tissue bank, where you dissect out the aortic and pulmonary valves. These are then decontaminated with an antibiotic solution at a temperature of 2-8ºC for 18-24 hours, and cryopreserved. Prior to and after decontamination, you take biopsies and swabs from each graft. Based on the outcome of these tests, your microbiologist will advise if the grafts are suitable for clinical use.

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What are the changes being evaluated?

1. You can no longer obtain one of the antibiotics that makes up your solution. Your microbiologist has advised a suitable replacement.

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What relevant information do you already have? (1)

•Your current antibiotic solution contains 5 antibiotics. The manufacturing of one of these antibiotics has been discontinued. You are replacing this with another antibiotic;

• It is known from prior studies that traces of the antibiotics used in the solution can be retained in the tissue following decontamination in quantities sufficient to affect microbiology testing.

•There is also a risk that the new antibiotic may cause allergies. Manufacturer guidance suggest that 1/10 000 patients may have allergic reactions.

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What relevant information do you already have? (2)

•You are aware that other heart valve banks have been using this antibiotic for the decontamination of heart valves for several years.

•Your microbiology advisor has advised that the new antibiotic is an effective substitute for the former antibiotic, but there is no evidence as to how it's efficacy may be compromised in combination with the other components of the solution.

•Information from the manufacturer suggests there is no evidence of carcinogenic or toxic effects associated with the antibiotic

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Evaluation of Novelty

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Using EuroGTP II Methodology:
Summary of novelty outcome

	Yes	*No*	*NA*
A. Has this type of TCTP previously been prepared and issued for clinical use by your establishment?			
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?			
C. Will the starting material for this TCTP be procured using a procedure used previously by 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?			
E. Will this TCTP be packaged , stored , and distributed using a protocol and materials used previously in your establishment for this type of TCTP?			
F. Will this type of TCTP provided by your establishment be applied clinically using an application method used previously?			
G. Has your establishment provided this type of TCTP for implantation or transplantation into the intended anatomical site and/or same clinical indication before?			

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Identification of Risk factors

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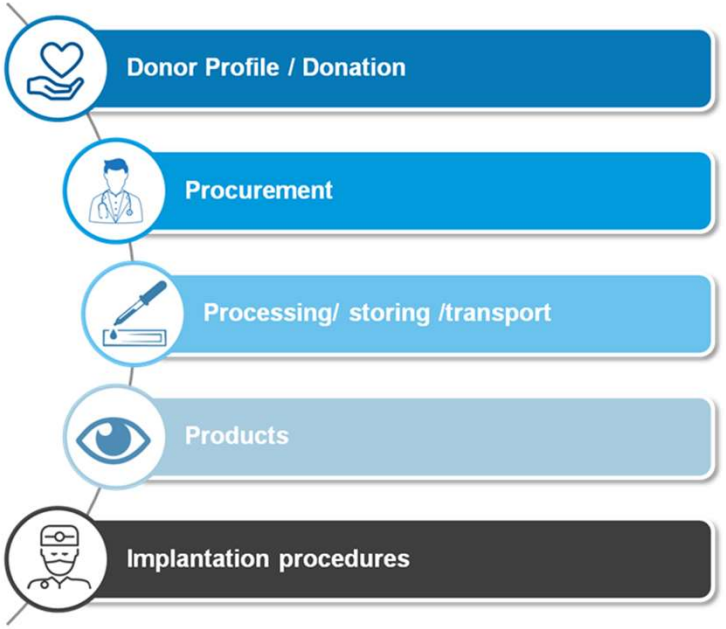
- x Donor Characteristics
- x Recovery process and environment'
- x Processing and environment'
- ✓ Reagents
- ✓ Reliability of Microbiology Testing'
- x Storage conditions
- x Transport conditions
- x Loss of viability and or functionality
- x Presence of unwanted cellular material and/or graft vascularity
- x Complexity of the immediate pre-implantation preparation and/or application method



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Which Risk Factors did we select?

- **Reagents** – We are changing the formulation of the antibiotic solution
- **Reliability of Microbiology Testing** – The presence of the new antibiotic may impact on this

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Risk Consequences

Consider the risk consequences associated with

"**Reagents**"

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Reagents

Unexpected immunogenicity	✓
Implant failure/Engraftment failure/ Pregnancy loss	✓
Disease transmission	✓
Toxicity / Carcinogenicity	✓
Other potential risks (can be associated with specific TCP/therapy)	x

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Which Risk Consequences did we Select?

- **Unwanted Immunogenicity** – Could residuals of our new antibiotic remain in the tissue, and provoke an allergic reaction in recipients?
- **Implant Failure** – Could the new antibiotic damage the tissue matrix?
- **Disease Transmission** – Is the reformulated antibiotic solution as effective as our current solution?
- **Toxicity/ Carcinogenicity -** effects in the recipient due to the new chemical itself or the interaction with other reagents in the antibiotic solution?

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Quantification of Risk Scoring

the risk consequences

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Which is the scoring for “Unexpected Immunogenicity” associated with “Reagents“ ?

LEVEL OF PROBABILITY
1 - Rare
2 - Unlikely
3 - Possible
4 - Likely
5 - Almost certain

LEVEL OF SEVERITY
1- Non-serious
2- Serious
3- Life-threatening
4 - Fatal

LEVEL OF DETECTABILITY
1 - Very high
2 - Moderately high
3- Low
4 – Very low
5 - Cannot be detected

PERCENTAGE RISK REDUCTION	
0	None
25	Limited
50	Moderate
75	Substantial
95	Extensive

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Which is the scoring for “Implant Failure” associated with “Reagents“ ?

LEVEL OF PROBABILITY
1 - Rare
2 - Unlikely
3 - Possible
4 - Likely
5 - Almost certain

LEVEL OF SEVERITY
1- Non-serious
2- Serious
3- Life-threatening
4 - Fatal

LEVEL OF DETECTABILITY
1 - Very high
2 - Moderately high
3- Low
4 – Very low
5 - Cannot be detected

PERCENTAGE RISK REDUCTION	
0	None
25	Limited
50	Moderate
75	Substantial
95	Extensive

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Which is the scoring for “Disease Transmission” associated with “Reagents“ ?

LEVEL OF PROBABILITY
1 - Rare
2 - Unlikely
3 - Possible
4 - Likely
5 - Almost certain

LEVEL OF SEVERITY
1- Non-serious
2- Serious
3- Life-threatening
4 - Fatal

LEVEL OF DETECTABILITY
1 - Very high
2 - Moderately high
3- Low
4 – Very low
5 - Cannot be detected

PERCENTAGE RISK REDUCTION	
0	None
25	Limited
50	Moderate
75	Substantial
95	Extensive

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Which is the scoring for “Toxicity” associated with “Reagents“ ?

LEVEL OF PROBABILITY
1 - Rare
2 - Unlikely
3 - Possible
4 - Likely
5 - Almost certain

LEVEL OF SEVERITY
1- Non-serious
2- Serious
3- Life-threatening
4 - Fatal

LEVEL OF DETECTABILITY
1 - Very high
2 - Moderately high
3- Low
4 – Very low
5 - Cannot be detected

PERCENTAGE RISK REDUCTION	
0	None
25	Limited
50	Moderate
75	Substantial
95	Extensive

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Risk Consequences

Consider the risk consequences associated with

"**Reliability of Microbiology Testing**"

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Reliability of Microbiology Testing

Unexpected immunogenicity	x
Implant failure/Engraftment failure/ Pregnancy loss	x
Disease transmission	✓
Toxicity / Carcinogenicity	x
Other potential risks (can be associated with specific TCP/therapy)	x

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Which Risk Consequences did we Select?

- **Disease Transmission –** Could we have ‘false negative’ microbiology results in post-decontamination samples due to antibiotic carry-over?

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Quantification of Risk Scoring the risk consequences

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Which is the scoring for “Disease Transmission ” associated with “Reliability of Microbiology Testing“ ?

LEVEL OF PROBABILITY
1 - Rare
2 - Unlikely
3 - Possible
4 - Likely
5 - Almost certain

LEVEL OF SEVERITY
1- Non-serious
2- Serious
3- Life-threatening
4 - Fatal

LEVEL OF DETECTABILITY
1 - Very high
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PERCENTAGE RISK REDUCTION	
0	None
25	Limited
50	Moderate
75	Substantial
95	Extensive

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Initial Risk Score

IAT Results

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Risk Factor	*Risk*	*Probability*	*Severity*	*Detectability*	*Potential Risk*	*Risk Reduction*	*Risk*
Reagents	Unwanted immunogenicity	3	2	4	**24**	0%	**24**
Reagents	Implant failure	2	3	4	**24**	50%	**12**
Reagents	Disease transmission	3	3	2	**18**	50%	**9**
Reagents	Toxicity / Carcinogenicity	1	2	4	**8**	75%	**2**
Reliability of Microbiology Testing	Disease transmission	3	3	4	**36**	0%	**36**

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Your assessment has Final Risk Score of: **17**

Level of Risk	*Extent of Studies needed*
Moderate	**Step3A: Risk reduction strategies** The assessment indicates that more evidence is needed to support safe and effective use of this TCTP and mitigate risk. Process validation should be performed, however if the nature of the risk is not related to the process itself, the requirement for validation may not apply, for example where the novelty is in the method of clinical application. Pre-clinical *in vitro* evaluation, specific to the identified risks, should be performed if not already done Pre-clinical *in vivo* evaluation, specific to the identified risks, using an animal model should be done if applicable (and if not already completed).
	Step 3B: Extent of clinical evaluation A structured plan for active collection of a specific set of data relating to the safety and efficacy of the TCTP should be put in place, in addition to routine clinical follow up. Ethical approval may be required and the principles of Good Clinical Practices (GCP) adhered to. Consideration should be given to restricting provision of the TCTP to a limited number of patients and/or centres until the risks have been adequately mitigated.

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Risk Reduction Strategies

Mitigation

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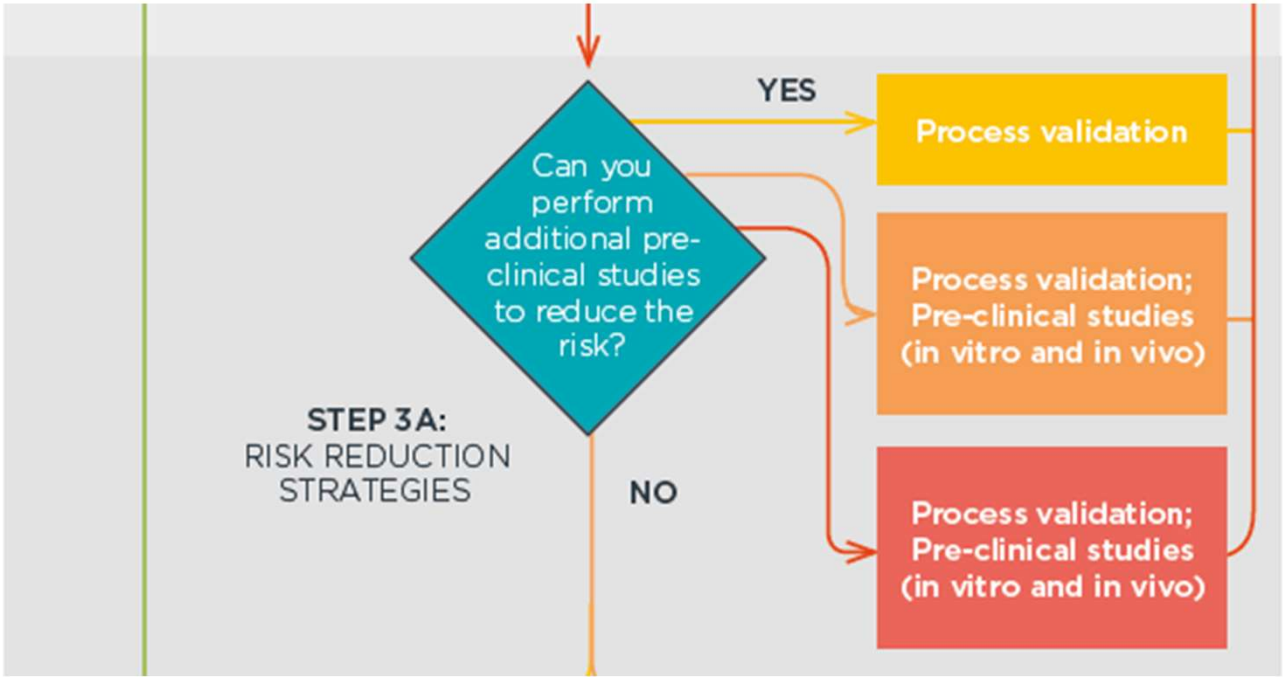

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Cardiovascular Tissues – Heart Valves and Vascular Grafts

STEP 3A: RISK REDUCTION STRATEGIES

Pre-clinical evaluation – Examples of ***in vitro*** tests to assist in potentially reducing the risk consequences identified (**blue** cells represent the tests that might be used to address the respective risk consequences) - Tissues: Cardiovascular Tissues

	Criteria	Process Validation tests								*In vitro* cytotoxicity		Donor cell viability		Physical / morphological properties	
	Specific test	Validation of the e efficacy of the decontamination process	Validation of the efficacy of the decellularisation process (if the graft has been decellularised)	Validation of the reliability of microbiology analytical methods	Aseptic handling (Media fill) validation	Validation of packaging integrity following simulated use (including sealing tests)	Validation of the transport methodologies	Validation of the stability of the TCTP during storage ("shelf life")	Extract cytotoxicity[ii]	Contact cytotoxicity[i]	Microculture viability assays (e.g. MTT, fibroblast culture)	Expression of cell surface markers	Evaluation of the morphology/anatomy of processed tissue (leaflet morphology, fenestrations, coaptation of leaflets, calcification, atheromatosis)	Hydrodynamic properties: competency test under pressure and pulsatile flow testing
Immunogenicity	Systemic Immune response	■	■	■	■	■	■						■		
	Localised Immune response	■	■	■	■	■	■						■		
	Anaphylaxis	■	■	■	■	■	■						■		
Graft failure	Failure to integrate with host tissue	■	■	■	■	■	■	■	■	■					
	Gradual mechanical failure	■	■	■	■	■	■	■	■	■					
	Sudden mechanical failure	■	■	■	■	■	■	■							■
Toxicity/ Carcinogenicity	Localised cytotoxicity									■					
	Systemic cytotoxicity								■						
	Carcinogenicity										■				
	Teratogenicity										■				
Disease transmission	Presence of Donor Derived Infectious Agents	■	■												
	Infections acquired during procurement or processing	■		■	■	■	■							■	

Criteria	Specific test	Biocompatibility				Functionality in vivo (stenosis or regurgitation)								Health						Valves functionality/ integrity				
		IHC staining (Post explantation: cell infiltration)	HLA matching	Calcification	Echodoppler / Echocardiography/ computed tomography (CT) Scan / Magnetic resonance imaging (MRI)	Echocardiography for regurgitation and stenosis evaluation; bleeding, thrombosis, infection	Regurgitation grade	Tissue regeneration	Bleeding events	Rupture of the graft	Thrombosis / Thromboembolic event	General condition/wellbeing after implantation (alive and well, sick, dead)	Infection/endocarditis	Growth/weight increase	Unexplained fever (due to immune induced reaction and/or toxicity)	Thrombogenicity	Post explantation histological analysis	Radiograph analysis	Morphological evaluation post explantation: structual integrity, fibrosis, calcification	Thrombogenicity	Post explantation histological analysis
Immunogenicity	Systemic Immune response		■		■			■				■	■	■	■	■	■					
	Localised immune response	■		■				■				■	■	■		■	■					
	Anaphylaxis											■	■	■	■	■	■					
Graft failure	Failure to integrate with host tissue	■		■				■			■	■	■	■	■	■	■					
	Gradual mechanical failure			■	■	■	■	■				■	■	■	■	■	■	■	■	■	■	■
	Sudden mechanical failure			■	■	■	■	■	■	■		■	■	■	■	■	■	■		■	■	■
Toxicity/Carcinogenicity	Localised cytotoxicity	■						■				■	■	■	■	■	■					
	Systemic cytotoxicity		■					■				■	■	■	■	■	■					
	Carcinogenicity											■	■	■	■	■	■					
	Teratogenicity											■	■	■	■							
Disease transmission	Presence of Donor Derived Infectious Agents											■	■	■	■	■	■					
	Infections acquired during procurement or processing											■	■	■	■	■	■					

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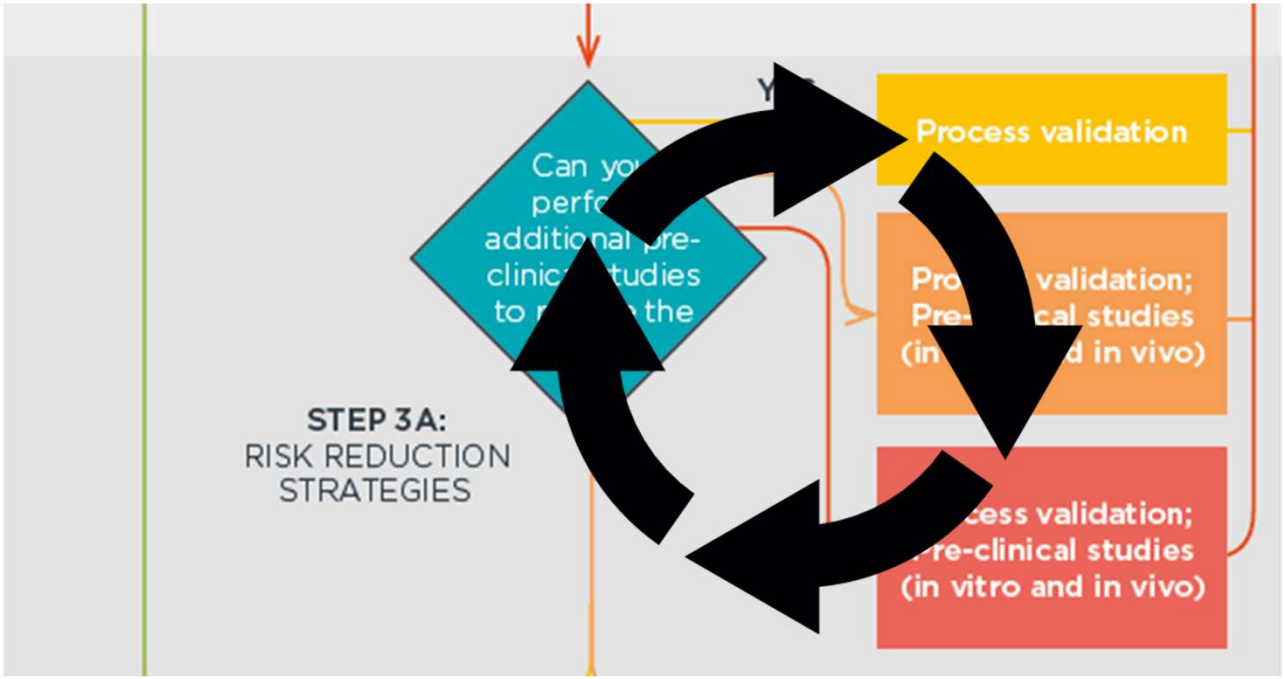

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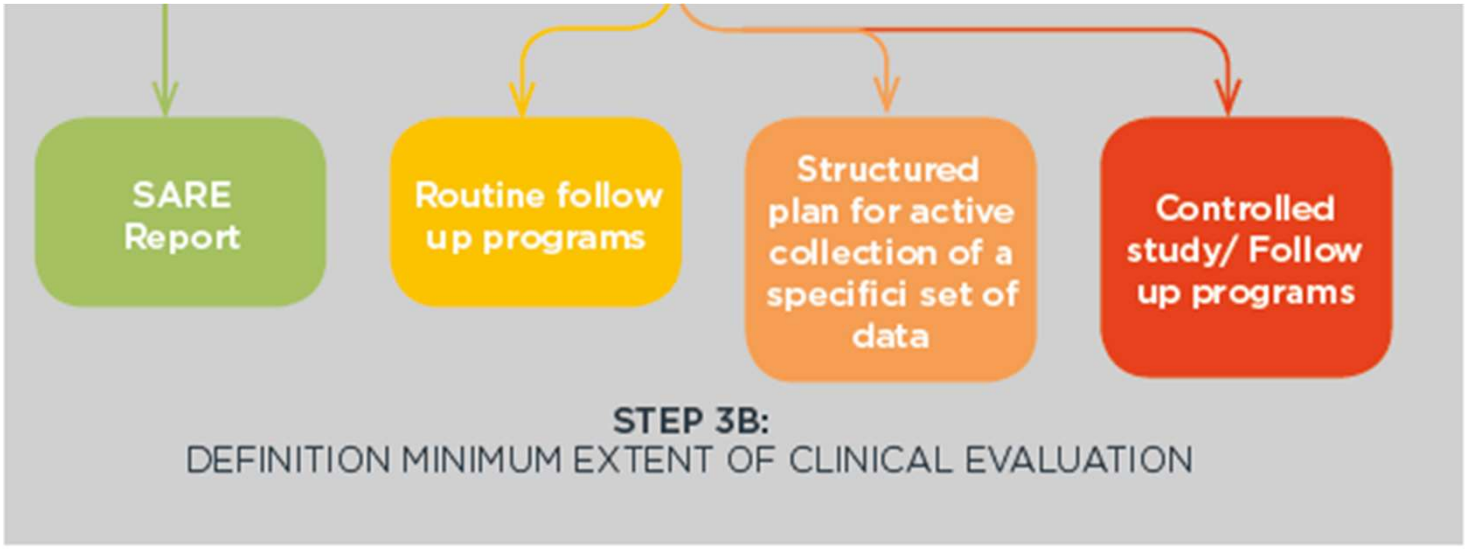

STEP 3B:
DEFINITION MINIMUM EXTENT OF CLINICAL EVALUATION

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	Clinical Indication	
	Heart Valves	Vascular Grafts
Test category	Detailed investigational options	
Graft failure (during procedure / immediately after implantation)	1. Perioperative (surgical) graft Failure (transoesofageal echocardiography)	1. Perioperative (surgical) graft Failure(Doppler echo)
Post operative complications	1. Unexplained fever (due to immune induced reaction and/or toxicity) 2. Bleeding events 3. Rupture of the graft; 4. Thrombosis / Thromboembolic event 5. Infection/endocarditis	1. Unexplained fever (due to immune induced reaction and/or toxicity) 2. Bleeding events 3. Rupture of the graft; 4. Thrombosis / Thromboembolic event 5. Infection/endocarditis
Patient Reported symptoms and outcome	1. Fatigue 2. Loss of physical capacity 3. Dyspnoea	1. Pain in the operated limb 2. Colour and temperature changes in the skin distal of the graft 3. Decreased functional capacity of the operated limb
Physical investigation (discrete outcome measures with quantifiable results) And Overall Clinical outcome measures	1. Graft related mortality 2. Graft normal function (Auscultation / echocardiogram/ MRI) 3. Abnormal function (increase peak pressure gradient) due to mismatch, calcific degeneration with/ without stenosis – (Auscultation / Echocardiogram and CT scan) 4. Abnormal function - Annular dilation (by echocardiogram or CT scan) 5. Regurgitation (by echocardiogram or MRI) 6. Graft related re-operation (due to graft survival)	1. Lack of pulsation 2. Graft related mortality 3. Graft normal function (pulse palpation / Auscultation / Doppler echo) 4. Abnormal function (increase pressure gradient) due to mismatch, calcific degeneration with/without stenosis – (Auscultation / Doppler echo / CT Scanner) 5. Abnormal function - graft dilation (Aneurism formation) by Doppler echo, angiography or CT scan) 6. Graft related re-operation (due to graft survival)

Key principles for effective use of the EuroGTP II methodologies

- The process should be **integrated** into the product/process development pathway
- It is important that the **rationale for decisions is recorded and documented**
- **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 IAT may be used at any point in the process/product development cycle**
- There must be a clear **understanding of the critical parameters of the TCTP which will contribute to its safety and efficacy,** to enable the risk assessment to be performed accurately

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Thank you!

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