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ORIGINAL ARTICLE *Infertility*

Evaluating risk, safety and efficacy of novel reproductive techniques and therapies through the EuroGTP II risk assessment tool

Esteve Trias[1,*], Martine Nijs[2], Ioana Adina Rugescu[3,4], Francesco Lombardo[5], Gueorgui Nikolov[5], Veerle Provoost[7], Annelies Tolpe[8], Nathalie Vermeulen[9], Zdravka Veleva[10], Rita Piteira[11], Ricardo Casaroli-Marano[11], and Kelly Tilleman[8]; on behalf of the EuroGTP II Study Group[†]

[1]Advanced Therapies Unit, Hospital Clinic Barcelona, Leitat Technological Center, Barcelona, Spain [2]Centre for Fertility Treatment, Netherlands [3]Embryolab Academy, Thessaloniki, Greece [4]Romanian Embryologists Association and Romanian Competent Authority, Romania [5]Laboratory of Seminology and Bank of Semen 'Loredana Gandini', Department of Experimental Medicine, University of Rome 'Sapienza', Rome, Italy [6]ReproBioMed MC, Sofia, Bulgaria [7]Department of Philosophy and Moral Science, Bioethics Institute Ghent (BIG), Ghent University, Ghent, Belgium [8]Department of Reproductive Medicine, Ghent University Hospital, Ghent, Belgium [9]European Society of Human Reproduction and Embryology, Grimbergen, Belgium [10]Department of Obstetrics and Gynecology, Helsinki University, Helsinki University Central Hospital, Helsinki, Finland [11]Banc de Sang i Teixits (BST) - Barcelona Tissue Bank, Barcelona, Spain

*Correspondence address. Advanced Therapies Unit, Hospital Clinic Barcelona, Villarroel 170, 08036 Barcelona, Spain.
E-mail: etrias@clinic.cat

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STUDY QUESTION: Can risks associated with novelties in assisted reproduction technologies (ARTs) be assessed in a systematic and structured way?

SUMMARY ANSWER: An ART-specific risk assessment tool has been developed to assess the risks associated with the development of novelties in ART (EuroGTP II-ART).

WHAT IS KNOWN ALREADY: How to implement new technologies in ART is well-described in the literature. The successive steps should include testing in animal models, executing pre-clinical studies using supernumerary gametes or embryos, prospective clinical trials and finally, short- and long-term follow-up studies on the health of the offspring. A framework categorizing treatments from experimental through innovative to established according to the extent of the studies conducted has been devised. However, a systematic and standardized methodology to facilitate risk evaluation before innovations are performed in a clinical setting is lacking.

STUDY DESIGN, SIZE, DURATION: The EuroGTP II-ART risk assessment tool was developed on the basis of a generic risk assessment algorithm developed for tissue and cell therapies and products (TCTPs) in the context of the project 'Good Practices for demonstrating safety and quality through recipient follow-up European Good Tissue and cells Practices II (EuroGTP II)'. For this purpose, a series of four meetings was held in which eight ART experts participated. In addition, several tests and simulations were undertaken to fine-tune the final tool.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The three steps comprising the EuroGTP II methodology were evaluated against its usefulness and applicability in ART. Ways to improve and adapt the methodology into ART risk assessment were agreed and implemented.

MAIN RESULTS AND THE ROLE OF CHANCE: Assessment of the novelty (Step 1), consisting of seven questions, is the same as for other TCTPs. Practical examples were included for better understanding. Identification of potential risks and consequences (Step 2), consisting of a series of risks and risk consequences to consider during risk assessment, was adapted from the generic methodology, adding more potential risks for processes involving gonadic tissues. The algorithm to score risks was also adapted, giving a specific range of highest

[†]The members of EuroGTP II Study Group are listed in the Appendix.

possible risk scores. A list of strategies for risk reduction and definition of extended studies required to ensure effectiveness and safety (Step 3) was also produced by the ART experts, based on generic EuroGTP II methodology. Several explanations and examples were provided for each of the steps for better understanding within this field.

LIMITATIONS, REASONS FOR CAUTION: A multidisciplinary team is needed to perform risk assessment, to interpret results and to determine risk mitigation strategies and/or next steps required to ensure the safety in the clinical use of novelties.

WIDER IMPLICATIONS OF THE FINDINGS: This is a dynamic tool whose value goes beyond assessment of risk before implementing a novel ART in clinical practice, to re-evaluate risks based on information collected during the process.

STUDY FUNDING / COMPETING INTEREST(S): This study was called EUROGTP II and was funded by the European Commission (Grant agreement number 709567). The authors declare no competing interests concerning the results of this study.

Key words: risk analysis / quality management / efficacy / novel techniques / safety / validation / assisted reproduction technologies / gamete / embryo / reproductive tissue

Introduction

Reproductive medicine is a highly dynamic field where novel technologies and treatment options rapidly develop and are quickly translated into clinical practice. This fast pace contrasts with the delay in obtaining solid clinical data on effectiveness and safety (Dondorp and de Wert, 2011; Vassena and the EBART Group, 2017). As a result, several innovations in assisted reproduction technologies (ARTs) have not been subjected to the necessary pre-clinical research and subsequent clinical trials, nor to short- and long-term follow-up studies (Dondorp and de Wert, 2011; Harper *et al.*, 2012; Wilkinson *et al.*, 2019). In particular, this affects the safety of ART, which has often been overshadowed by effectiveness.

In an effort to facilitate decision-making about the introduction of new technologies in clinical practice, Provoost *et al.* (2014) have proposed the distinction between experimental, innovative and established treatments, based on the level of evidence regarding efficacy, safety, procedure and effectiveness, each with different requirements regarding use and follow-up assessments. Among these criteria, safety assessment in ART—which goes beyond the mother to cover the long-term welfare of the child (Kennedy and Mortimer, 2007; Missmer, 2015)—has often been overshadowed by effectiveness. The lack of appropriate data is undoubtedly mostly due to limitations to conducting proper pre-clinical and clinical trials in this field (Evers, 2013). Waiting for the availability of these data gives rise to a delay in implementing ART, in a scenario where there is much pressure from women seeking to get pregnant (Scotland *et al.*, 2007; Bijlenga *et al.*, 2011). In addition, clinical trials on ART are usually underpowered to detect meaningful differences in the occurrence of adverse events (Dondorp and de Wert, 2011; Braakhekke *et al.*, 2015; Missmer, 2015).

Moreover, these studies have been shown to be at a risk of numerous study design and statistical pitfalls that affect interpretation of the results (Patounakis and Hill, 2018). Given the responsibility of the fertility specialist for the welfare of the offspring, it is expected that all 'presently known risk factors' will be considered before implementing novel ART technologies (Pennings *et al.*, 2007). There is a lack of homogeneous definition of safety in ART. It was probably best summarized by Braakhekke *et al.* (2015), who refer to it as 'the possible negative consequences of a treatment to the mother or her offspring, occurring either directly as a consequence of the treatment itself, as pregnancy complications or as the impact of the treatment on the long-term health of the mother or child'. In this scenario, a systematized way of assessing risk of novel technologies and treatments becomes fundamental, especially before they are used in humans for the first time, when strategies to reduce the likelihood of serious adverse reaction and events (SARE) have to be implemented (Kennedy and Mortimer, 2007). However, the methodology to perform such risk assessments is largely lacking in the scientific literature.

The 'Good Practices for demonstrating safety and quality through recipient follow-up: European Good Tissue and Cell Practices II (EuroGTP II) Project' was started in 2016 with the aim of setting up good practices applied to tissue and cell preparation processes and patient follow-up procedures. This project is funded by the European Commission (Grant agreement number 709567). Within this umbrella project, an algorithm and an interactive tool that uses a systematic approach to assess the risks to the patient upon clinical application of novel tissue and cell therapies and products (TCTPs)—including human tissues, haematopoietic stem cells as well as reproductive tissue and cell products. This tool also helps to determine the extent of studies and/or follow-up needed to assure the safety and efficacy of TCTPs. In this paper, we describe the development of the EuroGTP II risk assessment methodology and tool addressing the need to identify, quantify and mitigate the risks to individuals undergoing ART treatments and the result of these treatments. Although the tool was constructed for the purpose of performing a risk assessment when novel treatments or technologies are developed, the tool can also be applied to assess risks when changes are made to already established ones. Examples on the use of the risk assessment tool in both scenarios and the interpretation of the results are provided.

Materials and methods

Development and description of the generic EuroGTP II tool

The EuroGTP II risk assessment methodology was developed by a consortium of 28 organizations from 15 countries comprising tissue establishments (TEs), Organizations Responsible for Human Application (ORHAs), National Competent Authorities, academics and European scientific societies. The rationale used in the development of the EuroGTP tool II tool was based on the International Conference on Harmonization of Technical Requirements for

Registration of Pharmaceuticals for Human Use (ICH E6 Good Clinical Practices (EMA, 2016) and ICH Q9 Quality Risk Management (EMA, 2014)) and tailored to the specificities of TCTPs (Trias *et al.*, 2020).

This tool consists of three steps that have been described elsewhere (Trias *et al.*, 2020). These are fully described in the EuroGTP II guidelines (EuroGTP II, 2019). As illustrated in Fig. 1, the process starts by identifying whether a new TCTP really represents a novelty and therefore is a candidate for risk assessment (Step 1). Once confirmed, the process continues by identifying potential risks and factors (Step 2). Based on the level of risk obtained for each of the identified risks, proposals are made for the risk-reduction strategies and extent studies required to ensure the safety and efficacy of the TCTP in terms of both pre-clinical (*in vitro* and/or *in vivo*) and clinical evaluation (Step 3).

Step 1 consists of seven questions. When the answer to all questions is 'Yes', the TCTP is not considered a novelty but a standard/established therapy. In this latter case, only regular, internal validations and follow-up procedures should be put in place or maintained, and risk assessment is not needed.

For the identification of potential risks and associated risk consequences (Step 2), the whole supply chain is considered. Five risk consequences are proposed, which have been categorized as unwanted immunogenicity, implant failure, disease transmission, toxicity/carcinogenicity and 'other'. The overall process requires that specific risks relating to the potential risk factors and risks consequences be first identified. This identification considers: (i) the probability (P) of the risk occurring (rare, unlikely, possible, likely, almost certain), (ii) the severity (S) of the consequences should the risk occur (non-serious, serious and life-threatening) and (iii) the detectability (D), i.e. probability of the risk consequence being detected, should it occur (very high, moderately high, low, very low and cannot be detected) (see Trias *et al.* (2020) for these definitions). Each of the risks identified must then be individually assessed to determine the residual risk of implementing the change.

An algorithm has been developed to estimate a risk score that integrates the scores obtained for the different risks and the number of risks assessed in the evaluation of the TCTP (Trias *et al.*, 2020). A combined risk value and a final risk score are generated (Fig. 2). A degree of risk reduction is considered in this calculation to include pre-existing data from peer-reviewed literature, internal validations, clinical outcomes and other relevant sources of data. The algorithm also includes a rule to guarantee that individual risks with a high score are not masked when several additional risks with low-risk scores are considered. The final risk score is proportional to the number of risks evaluated (in the form of a level of risk). This level of risk is classified as follows: negligible risk (0–2), low risk (>2–6), moderate risk (>6–22) and high risk (>22).

Step 3 proposed a series of risk-reduction strategies and extent studies required to ensure the safety and efficacy of the TCTP to be conducted according to the level of risk obtained. These are also proposed for each of the three TCTPs (Trias *et al.*, 2020). The value of this information is further discussed in the Results section.

Development of the ART-specific EuroGTP II tool

Based on the generic tool, an ART-specific EuroGTP II assessment tool was developed by a group of eight experts in ART (hereinafter 'ART Panel') (F.L., G.N., M.N., V.P., I.A.R., A.T., Z.V. and N.V.) led by K.T. Experts were selected on the basis of their expertise in quality, laboratory and clinical management and included medical doctors, embryologists and a bioethicist.

The specific contents for ART were developed over four meetings. During the first meeting, the generic EuroGTP II assessment tool was presented to the ART task force by the project co-ordinators and its applicability illustrated. The three steps of the procedure were discussed and their applicability to the human reproduction field assessed. Changes to shape the generic tool to the ART field and to optimize its usefulness were discussed and agreed in a consensus-based approach. With this purpose, examples of already implemented ART novelties were used, where the tool was applied. It was agreed that the extent of the studies needed to integrate a novel reproductive technique or therapy into clinical practice should be based on the information provided by the classification proposed by Provoost *et al.* (2014). This classification was to be used to define the extent of studies to specifically mitigate the risk (Step 3) in ART. The decision to include examples and to develop specific guidance on the use of this tool was taken during this meeting. Both examples and the explanatory guide were presented and agreed on in a second meeting.

A first draft of the EuroGTP II-ART tool was afterwards tested locally in small groups across all participant countries using the explanatory guide. These groups, gathering circa 200 individuals, included medical doctors, embryologists and quality managers from National professional committees or local hospitals and were led by the members of the ART Panel. Feedback on the user-friendliness of the interactive tool and comprehensibility of the explanatory guide was collected. Homogeneity of results across groups was also assessed. This was a sensitive point to ensure validity of the tool. However, it should be noted that this largely depends on subjectivity when scoring the risk and the sources of information available and used by each group. Rather than homogeneity on the results, their coherence was assessed. Feedback from these potential users was also collected. Changes to be made to the assessment tool on the basis of this information were agreed on a third meeting. The final version of the EuroGTP II-ART was agreed by the ART task force in a fourth meeting. The methodology was finally subjected to a public consultation. These remarks were taken into account to finalize the tool and the guidance document.

The EuroGTP II-ART tool is available at https://tool.goodtissuepractices.site since March 2019. More detailed information on the working groups and meetings is available at https://www.goodtissue practices.eu.

Examples

In order to show the applicability of the EuroGTP II-ART, five examples are provided and explanatory information for each step of the tool is presented. These examples are the following:

- Example 1. Assisted Reproductive Techniques—Gametes: Activation of sperm motility after thawing with a new compound based on methylxanthin and polyphenol present in the chemical matrix of guaraná (*Paullinia cupana*) in concentration 10 mg/ml.
- Example 2. Assisted Reproductive Techniques—Gametes: Sperm vitrification for severe oligoasthenoteratozoospermic patients.

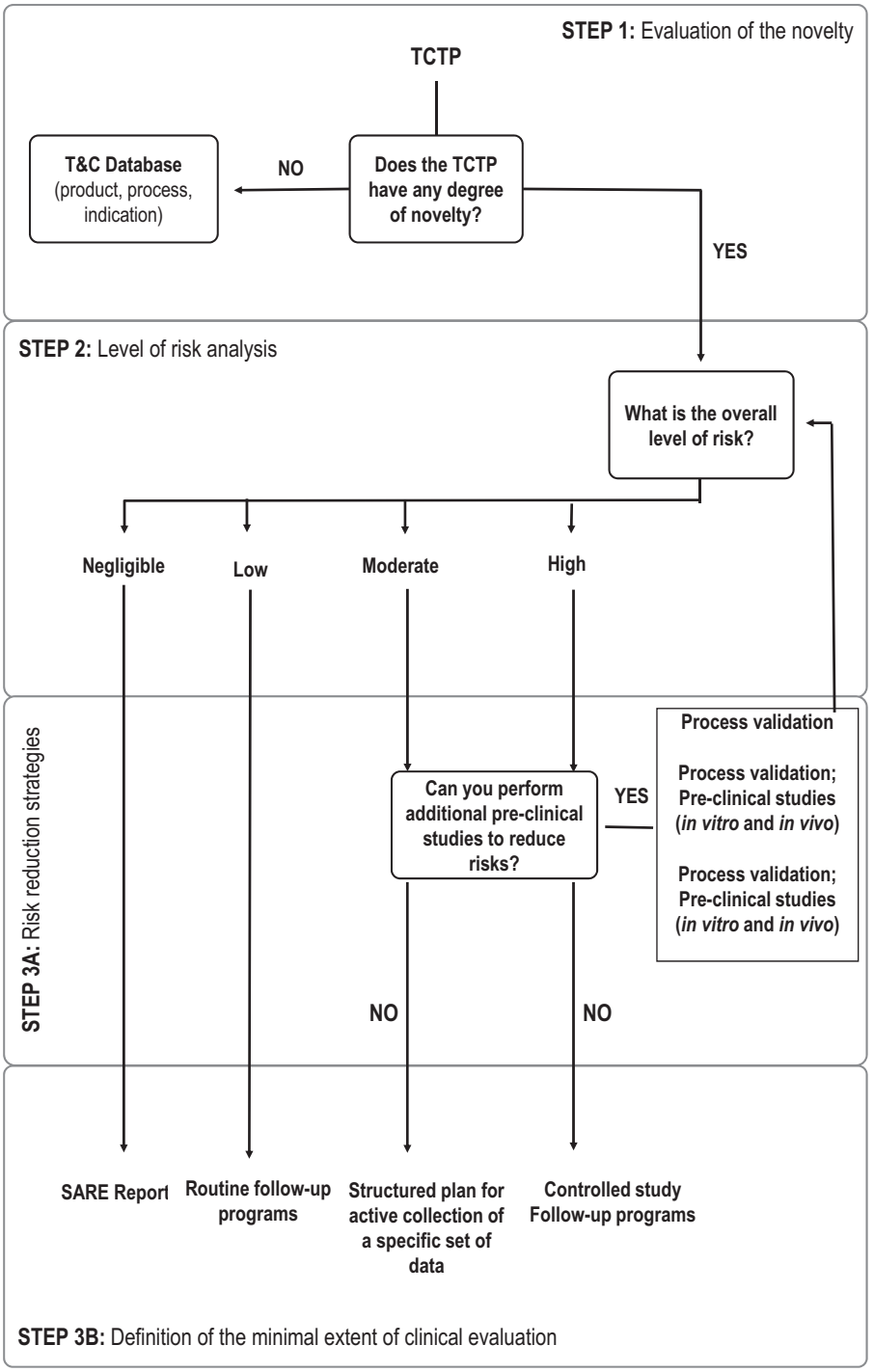

Figure 1 EuroGTP II flowchart. EuroGTP II approach showing evaluation of the novelty (Step 1), the analysis of the level of risk (Step 2), risk-reduction strategies (Step 3A) and definition of the extent of the clinical studies (Step 3B) (EuroGTP II, 2019; Trias *et al.*, 2020). Reproduced with the permission from Trias *et al.*, 2020. TCTP, tissue and cell therapies and products; T&C, tissue and cell; SARE, serious adverse reaction and events.

- Example 3. Assisted Reproductive Techniques—Embryos: Human biopsied blastocyst—Day 5-vitrified—with failed genetic test in biopsied trophectoderm cells. Blastocyst will need to be warmed, cultured, re-biopsied and re-vitrified.
- Example 4. Assisted Reproductive Techniques—Gametes: Changing a manual oocyte aspiration protocol into an aspiration using a pump.
- Example 5. Assisted Reproductive Techniques—Gametes: Changing from a long GnRH agonist protocol to a GnRH antagonist protocol.

Risk value = Σ risks = Σ ([S x P x D] - [S x P x D x % RR])

Where:
P = Probability (1 – 5)
S = Severity (1 – 4)
D = Detectability (1 – 5)
RR = Risk reduction (0 – 95)

Combined risk value =

$$\frac{\text{Risk value x highest possible score}}{P_{max} \text{ x } S_{max} \text{ x } D_{max} \text{ x number of applicable risk consequences*}}$$

Where:
Highest possible risk score = P_{max} x S_{max} x D_{max} x maximum number of risks consequences x maximum number of risk factors

- P_{max} = 5
- S_{max} = 4
- D_{max} = 5
- Maximum number of risk consequences = 4 for gametes/embryos and 5 for gonadic tissue*
- Maximum number of risk factors = 8 for gametes/embryos and 10 for gonadic tissue*

Range of applicable risk consequences = 1 – 32 for gametes/embryos and 1 – 50 for gonadic tissue.

Final risk score = $\frac{\text{Combined risk value x 100}}{\text{Highest possible score}}$

Figure 2 The EuroGTP II algorithm used for scoring the risks inherent to novelties (EuroGTP II, 2019; Trias *et al.*, 2020). *See Table II. Please, refer to reference (EuroGTP II, 2019) for P, S, D and RR assessment. Reproduced with the permission from Trias *et al.*, 2020.

Results

Assessment of novelty (Step 1)

New ARTs may be major innovations or adaptations of existing ones, which nevertheless include significant changes that may involve a risk for the recipients. Therefore, the assessment of the novelty is a crucial step before considering whether a given ART is innovative enough to be the subject of research, as stated by ethical principles and guidelines on human research (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979; Declaration of Helsinki, 2013). When developing the EuroGTP II-ART, the ART Panel decided to keep the same seven questions as in the generic tool (Table I). For more information on this assessment, please see the explanation provided for the generic tool in the Materials and methods section. Novelty assessment of the five examples provided, together with the justification for each answer, is shown in Table I. All are considered to be novel as the answers to the seven questions included at least one NO.

Risks identification and assessment (Step 2)

The ART Panel assessed the applicability and value of the list of possible risk factors and risk consequences—as displayed in the generic version (Trias *et al.*, 2020)—which would be applicable to a novel ART. The eight risk factors displayed in the generic tool were deemed adequate for processes concerning gametes and embryos (Table II). However, for processes involving gonadic tissues, two extra risks were included (i.e. the reliability of microbiological testing and the presence of unwanted cellular material and/or graft vascularity) (Table II). Besides the explanation on how to assess each possible risk—provided in the generic tool—as for Step 1, the ART Panel decided to include ART-specific examples on risk assessment for better understanding.

Risk consequences for each of the risk factors followed the categorization of the generic tool, i.e. unexpected immunogenicity (except for gametes or embryos), implant failure/pregnancy loss, disease transmission (including infection) and toxicity/carcinogenicity. The ART Panel provided a series of comments and other explanations about these factors to improve identification, some of which are only applicable to processes involving gonadic tissues.

When identifying the risk, it is important to consider the potential harm to the recipients and/or the offspring, as well as the impact on the availability and accessibility of treatment. It is important to note that the risks may also refer to the viability of the embryo. For example, if the viability of a blastocyst could be harmed because of a novel

Table I Assessment of novelty (Step 1).

	Yes	No	N/A
A. Has this type of tissue and cell therapies and product (TCTP) previously been prepared and issued for clinical use by your establishment?			
Explanation: Consider whether or not your tissue establishment (TE) has previous experience working with the TCTP.			
• Example 1. Sperm has been prepared and issued for clinical use before, so the answer is 'yes' to this question.	X		
• Example 2. Though this is an attempt to implement a new cryopreservation technique, our centre is a Sperm Bank and we regularly prepare spermatozoa for cryopreservation and for clinical use in ART.	X		
• Example 3. Human blastocysts are biopsied for pre-implantation genetic testing.	X		
• Example 4. Oocyte pick-up has been practised before and the clinic is licensed to do this.	X		
• Example 5. Your clinic has performed ovarian stimulation for IVF/ICSI.	X		
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?			
Explanation: Consider whether or not the starting material is from the same donor population.			
• Example 1. The novel procedure does not imply a change in donor population.	X		
• Example 2. The implementation of the vitrification procedure does not assume any change in the donor population of the Sperm Bank composed of men who are going to undertake antineoplastic gonadotoxic treatments. Sperm vitrification can be also applied to these subjects with the same indications of the 'standard' freezing procedure.	X		
• Example 3. Same patient population.	X		
• Example 4.Starting material and donor population refer to the patients from whom oocytes are aspirated. Patient groups are not changing.	X		
• Example 5. Patient population is not going to change.	X		
C. Will the starting material for this TCTP be procured using a procedure used previously by your establishment for this type of TCTP?			
Explanation: Consider the starting material and how it is procured or collected and if this changes in the novel protocol or therapy.			
• Example 1. The change in procedure does not imply a change in collecting of the sperm.	X		
• Example 2. The new vitrification procedure does not require different methods for sperm retrieval than standard cryopreservation.	X		
• Example 3. Warming and re-vitrification are similar to standard vitrification methods, culturing of blastocyst is standard method.	X		
• Example 4. Even though your clinic has performed oocyte pick-up before, the procedure is about to change by substituting the type of oocyte aspiration pump.		X	
• Example 5. The procedure in question is the stimulation protocol, and this is changing.		X	
D. Will this TCTP be prepared by a procedure (processing, decontamination and preservation) used previously in your establishment for this type of TCTP?			
Explanation: Consider the complete processing procedure of the product. If changes occur in the new protocol or therapy, answer the question accordingly.			
• Example 1. The post-thawing procedure will include activation of sperm motility with a 10 mg/ml CCMP solution.		X	
• Example 2. The vitrification will require entirely different processing than the standard protocol.		X	
• Example 3. The re-biopsy method could be more complex.		X	
• Example 4. Preparation procedure will remain the same.	X		
• Example 5. Screening the patient for infectious diseases and other conditions will remain the same.	X		

(continued)

Table I Continued

	Yes	No	N/A
E. Will this TCTP be packaged and stored using a protocol and materials used previously in your establishment for this type of TCTP?			
Explanation: Consider whether changes will occur in the packaging and storage and whether you have experience with these items in your TE for the specific cell or tissue product where the novelty is to be introduced.			
• Example 1. There is no change in the packaging or storing of the sperm.	X		
• Example 2. Also packaging of vitrified sperm and materials required for the vitrification will be slightly different.		X	
• Example 3. Identical vitrification method and carrier.	X		
• Example 4. Culture media and dishes will not be affected by the introduction of the new pump.	X		
• Example 5. No packaging, storing and distribution are used in this case.			X
F. Will this type of TCTP provided by your establishment be applied clinically using an implantation method used previously?			
Explanation: Consider whether the product or therapy has been clinically applied previously and answer accordingly.			
• Example 1. Although the processing of the sperm has changed, the clinical application will be the same.	X		
• Example 2. Although the cryopreservation procedure is different, the following clinical indication and use (ART) are the same of the 'standard' cryopreserved semen.	X		
• Example 3. No difference in clinical application—pre-implantation genetic testing.	X		
• Example 4. The clinical application of oocytes will remain the same.	X		
• Example 5. The monitoring of the stimulation protocol is not going to use any novel methods.	X		
G. Has your establishment provided this type of TCTP for transplantation into the intended anatomical site before? (this question will only appear if gonadic tissue is chosen)			
Explanation: Consider the experience with the clinical application of the product in your TE and answer the question concerning the intended anatomical site.			
• Example 1. The intended use of the sperm will not change.	X		
• Example 2. As stated before, the following intended use for vitrified sperm is ART. As such, no variation in the post-cryopreservation procedure is expected.	X		
• Example 3. Healthy blastocyst will transferred after warming as in standard blastocyst transfer protocol.	X		
• Example 4. Oocytes will be still transferred into the uterus.	X		
• Example 5. Ovarian stimulation is already performed using two other protocols.	X		

Application of adapted EuroGTP II Guidelines (2019) to five ART scenarios: Example 1: Gametes: Activation of sperm motility after thawing with a new compound based on methylxanthin and polyphenol present in the chemical matrix of guaraná (*P. cupana*) in concentration 10 mg/ml. Example 2: Gametes: Sperm vitrification for severe oligoasthenoteratozoospermic patients. Example 3: Embryos: Human biopsied blastocyst—Day 5-vitrified—with failed genetic test in biopsied Trophectoderm cells. Blastocyst will need to be warmed, cultured, re-biopsied and re-vitrified. Example 4: Gametes: Changing a manual oocyte aspiration protocol into an aspiration using a pump. Example 5: Gametes: Changing from a long GnRH agonist protocol to a GnRH antagonist protocol. Please, refer to the text for more information about these examples.
NA, not applicable.

biopsy procedure, then the risk factor loss of viability and/or functionality should be chosen.

Based on the number of risk consequences and factors considered, when the algorithm for estimating the final risk score (Fig. 2) is applied, a range of 1–45 encompasses the possible risk scores for gonadic tissues and of 1–32 for gametes and embryos.

Risks identified for each of the five examples provided and their scoring is shown in Table III. Final risk score was 8 (Moderate risk) for Example 1, 16 for Example 2 (Moderate risk), 5 (Low risk) for Example 3, 1 (Negligible risk) for Example 4 and 0 (Negligible risk) for Example 5.

Risk-reduction strategy and extended studies (Step 3)

Table IV shows the strategies for risk reduction for each of the four possible risk levels obtained (negligible, low, moderate and high, see Materials and methods section). As proposed by the ART Panel, this table also provides specific recommendations on extended studies needed to safely introduce ART novelties into clinical practice, following the classification of evidence proposed by Provoost *et al.* (2014). Please refer to this table to check the risk-reduction strategy and the extent of studies needed for each of the examples provided according to their level of risk.

Table II Combined table of the identification of the risk factors and the associated risks (Step 2).

	Risk factors	Explanation	Risk consequences	Comments
Donation	Donor Characteristics / Source of material	Consider whether the novelty in your process or procedures changes donor characteristics and if these changes could pose a risk to the recipient. Examples: • When collecting sperm from peripubertal boys (12-14y) in comparison to the previous protocol where only pubertal boys (>14y) were included in the donor population. • When there is a change in donor population from autologous to allogenic donors: If the TCTP is sourced from an allogenic donor, there may be immunogenicity-related risks that could impact on the clinical performance of the TCTP, and there could be increased risks of disease transmission.	Unwanted immunogenicity	Only applicable for gonadic tissue.
			Implant failure/ pregnancy loss	Consider and quantify the risk that sperm collected from peripubertal boys might lead to pregnancy loss when used in assisted reproduction.
			Disease transmission	Although highly unlikely, consider and quantify the risk that sperm collected from peripubertal boys might lead to disease transmission in the recipient. If these boys in this population were from a specific area known to have a high incidence of certain viral diseases, then this might impact on the risk for disease transmission.
			Toxicity/Carcinogenicity	It is highly unlikely that the change in donor characteristics would entail a risk for toxicity in the recipient. In the case of gonadic tissue originating from a donor with an oncological disease, the carcinogenic should be taken into account when an autologous transplantation is planned.
			Other	Consider other risks if applicable.
Procurement	Recovery/Procurement process and environment	Consider where and how the TCTP is collected, procured or recovered, and if this process could have an influence on the TCTP. How long does the process take, how complex is it and what is quality of the environment where the processing takes place. What is the probability that the TCTP may become contaminated or damaged during recovery. Example: • When a new semen collection container is used, this could have an effect on the recovery process.	Unwanted immunogenicity	Only applicable for gonadic tissue.
			Implant failure/ pregnancy loss	It would be highly unlikely that the use of a new semen container during collection would impact on implant failure.
			Disease transmission	It could be possible that if this new container were non-sterile, that this might influence disease transmission, although the risk would be rare.
			Toxicity/Carcinogenicity	Consider the risk that using a new semen container could have on the toxicity or carcinogenicity in the recipient.
			Other	Consider other risks if applicable.
Processing/ storing / transport	Preparation process and environment	Consider where and how the TCTP is prepared. How long does the preparation process take and how complex is it—this may impact on the risk of contamination or it may not be prepared to consistent specifications and quality. Also consider the quality of the preparation environment, which may also affect the risk of contamination. Examples: • When changing from laser assisted hatching on day 3 to day 5 for trophectoderm biopsy. This change may potentially have an effect on several risks during the preparation process. • Changes from performing ICSI outside a laminar flow hood, compared to performing ICSI enclosed in a laminar airflow cabinet.	Unwanted immunogenicity	Only applicable for gonadic tissue.
			Implant failure/ pregnancy loss	This change in preparation will rarely affect pregnancy loss.
			Disease transmission	If this procedure were to take place in a different environment where the risk for environmental contamination is higher that may have an impact on the risk for disease transmission in the recipient.
			Toxicity/Carcinogenicity	It is highly unlikely that the change from Day 3 to Day 5 laser-assisted hatching would introduce toxic compounds in the recipient.
			Other	Consider other risks if applicable.
	Reagents	Consider any reagents used during recovery, preparation, decontamination and storage of the TCTP. Could they damage the TCTP in any way, or could residual traces of reagents remain in the TCTP that could cause toxic or immunogenic effects in recipients? Example: • When changing a cryopreservation medium: this could result in a potential risk. • When using a new anaesthetic during oocyte collection.	Unwanted immunogenicity	Only applicable for gonadic tissue.
			Implant failure/ pregnancy loss	It is unlikely that The change in reagents would impact on the risk of pregnancy loss.
			Disease transmission	If this new reagent contains for example albumin from a source that is doubtful, then there is a risk for disease transmission to the recipient.
			Toxicity/Carcinogenicity	If this medium contains different types of antibiotics, then this might have an impact on toxicity reactions in the recipient.
			Other	Consider other risks if applicable.
	Storage Conditions	Consider any potential risks arising from how the starting material and TCTP are stored, not only after processing and before clinical application, but also in intermediate steps: e.g. between procurement and processing, during processing, and between processing steps. Examples: • When stimulation medication is now stored at room temperature instead of refrigerated. • When sperm is being stored in liquid nitrogen and the novel storage facility only has vapour phase tanks.	Unwanted immunogenicity	Only applicable for gonadic tissue.
			Implant failure/ pregnancy loss	The change in storage conditions might have a direct impact on implant failure when this preserved sperm is used for insemination.
			Disease transmission	The change in storage might theoretically have an impact on disease transmission, even though the risk would be very rare.
			Toxicity/Carcinogenicity	The impact of the novel storage conditions will, in this example, have very little or even no impact on the introduction of toxic compounds.
			Other	Consider other risks if applicable.

(continued)

Table II Continued

	Risk factors	Explanation	Risk consequences	Comments
	Transport Conditions	Consider any potential risks arising from how the starting material and TCTP is transported for example between the procurement and processing sites and between the storage and clinical application sites. Examples: • When a new type of dryshipper is used to transport frozen sperm to clinical sites. • When an ART centre starts to provide transport or satellite IVF where oocytes are collected in another clinic.	Unwanted immunogenicity	Only applicable for gonadic tissue.
			Implant failure/ pregnancy loss	New transport conditions might have an impact on pregnancy loss if not adequately controlled.
			Disease transmission	Disease transmission is rarely impacted if only transport conditions are changed.
			Toxicity/Carcinogenicity	Toxicity could be impacted if not only transport conditions are changed, but there are also medium differences present between the satellite centre and the current TE.
			Other	Consider other risks if applicable.
	Reliability of Microbiology Testing(in case of gonadic tissue)	Consider the risk that the testing methodology and /or presence of residual processing reagents such as antibiotics in the finished TCTP may impact the accuracy of any microbiology/ mycology testing of the TCTP. This risk factor is not about blood tests on the donor.Example: • When a change in the processing medium of ovarian tissue may mask the current microbiology testing because of the presence of antibiotics in the new protocol in comparison to the previous one.	Unwanted immunogenicity	This change could have an impact on unwanted immunogenicity when this tissue is transplanted in the recipient.
			Implant failure/ pregnancy loss	This change could lead to implant failure due to residual microbiological load that has an impact on the graft viability.
			Disease transmission	If this change is solely in the processing medium, but it is still for autologous use of the tissue, then the risk of disease transmission will probably not change in comparison to the former procedure.
			Toxicity/Carcinogenicity	There might be a risk for introducing toxic compounds.
			Other	Consider other risks if applicable.
Product	Loss of viability and or functionality	Consider the risk that the changes in procedures of processes can have on the viability or functionality of the TCTP. Example: • Change in a cryopreservation processing step could result in loss of viability after thawing or when trophectoderm biopsy is implemented, harm to the blastocyst needs to be taken into consideration.	Unwanted immunogenicity	Only applicable for gonadic tissue.
			Implant failure/ pregnancy loss	This novelty can have a direct impact on implant failure and pregnancy loss.
			Disease transmission	The impact on disease transmission due to harming of the embryo because of the new biopsy technique is highly unlikely.
			Toxicity/Carcinogenicity	The impact of loss of viability on the introduction of toxicity or carcinogenicity in the recipient is likely to be very rare..
			Other	Consider other risks if applicable.
	Presence of unwanted cellular material and/or graft vascularity (in case of gonadic tissue)	This risk must be considered from the perspective that for some TCTPs, the presence of intact vital cells is desirable, although it may also increase risks of, for example, immunogenicity or disease transmission. This presence might affect tumour formation, immunogenicity and disease transmission risks. Vascular tissues may be more at risk to infiltration by pathogens or malignant cells than avascular tissues. Example: • When ovarian tissue autologous transplantation is performed in patients with a history of haematological cancer at the moment of tissue procurement. The risk of transmission of malignant cells should be considered.	Unwanted immunogenicity	Consider the risk that presence of cellular material/graft vascularity could have on unwanted immunogenicity in the recipient.
			Implant failure/ pregnancy loss	There could be a risk for implant failure when malignant cells are present in the graft.
			Disease transmission	If malignant cells are transplanted together with the graft, then there is a risk for the transmission of oncological disease.
			Toxicity/Carcinogenicity	Presence of cells might impact on the risk of carcinogenicity.
			Other	Consider other risks if applicable.
Clinical application procedure	Complexity of the preparation/ application method	Consider how complex the method of clinical application will be for this TCTP. How long will it take, and could this introduce risks? What is the scope for errors to be made, and what could the consequences of these errors be?Low feasibility of application standardization might at the very least have an influence on the risks of implant failure and disease transmission. Example: • When a new transfer catheter is going to be used, is there a risk for re-transfer and how would this affect the outcome?	Unwanted immunogenicity	Not applicable it this example, only for gonadic tissue.
			Implant failure/ pregnancy loss	There might be an impact on the risk of implant failure when a new transfer catheter is introduced.
			Disease transmission	It is highly unlikely that the risk for disease transmission would be impacted when only a new transfer catheter is implemented.
			Toxicity/Carcinogenicity	A new transfer catheter could, although it is unlikely, introduce toxicity to the recipient.
			Other	Consider other risks if applicable

Adapted from the EuroGTP II guideline (EuroGTP II, 2019).
TCTP, tissue and cell therapies and products; TE, tissue establishment.

Table III Risk identification and assessment.*

Example 1. Activation of sperm motility after thawing with a new compound based on methylxanthin and polyphenol present in the chemical matrix of guaraná (*P. cupana*) in concentration 10 mg/ml.

	Risk factors	Does it apply?	Comments	Risk consequences	P	S	D	PR	RR (%)	Risk
Donation	**Donor Characteristics / Source of material**	No	The procedure will be applied to the same population of subjects							
Procurement	**Recovery/Procurement process and environment**	No	The procedure will be applied to the same population of subjects through the same procurement methods and within the same environment.							
Processing/ storing /transport	**Preparation process and environment**	Yes	The processing of thawed semen will include exposition to 10 mg/ml CCMP solution in thawing medium (sperm preparation medium.	Implant failure/ pregnancy loss	3	2	2	12	25	9
				Toxicity/ Carcinogenicity	1	1	2	2	25	1.5
	Reagents	Yes	New reagent will be used during preparation—CCMP in concentration 10 mg /ml.	Implant failure/ pregnancy loss	3	2	2	12	25	9
				Toxicity/ Carcinogenicity	1	1	2	2	25	1.5
	Storage Conditions	No	The same storage conditions will apply as in non-treated samples. Treatment is after thawing and not before cryopreservation.							
	Transport Conditions	No	Transport conditions are the same.							
Product	**Loss of viability and or functionality**	Yes	The new preparation method with 10 mg/ml CCMP after thawing might have a detrimental role on functionality, especially on fertilization ability of sperm, although motility is expected to be improved.	Implant failure/ pregnancy loss	3	2	2	12	25	9
				Mutagenicity	2	2	4	16	0	16
Clinical application procedure	**Complexity of the preparation/ application method**	No	The method is simple and does not introduce any additional risk.							
										Total risk score = 8

Table III Continued

Example 2. Sperm vitrification for severe oligoasthenoteratozoospermic patients.

	Risk factors	Does it apply?	Comments	Risk consequences	P	S	D	PR	RR (%)	Risk
Donation	**Donor Characteristics / Source of material**	No	The novel vitrification protocol uses sperm form the same donor population of the standard freezing procedure; thus, no additional risks are expected from the donor population.							
Procurement	**Recovery/Procurement process and environment**	No								
Processing/ storing / transport	**Preparation process and environment**	Yes	The vitrification protocol will necessarily require a different freezing procedure and specific material which has not yet been routinely used in our Institution. Thus, we will expect theoretical risk of implant failure due to damage to spermatozoa during freezing, which can hardly be detected before its clinical use.Furthermore, problems may arise from processing materials with a theoretical of disease transmission and toxicity/carcinogenicity due to the novel and yet untested material/procedure which might expose sperm to unknown toxicants.	Implant failure/ pregnancy loss	2	2	5	20	25	15
				Disease transmission	2	2	5	16	0	20
				Toxicity/ Carcinogenicity	2	2	5	20	0	20
	Reagents	No	No novel risk is anticipated from the culture media/reagents used in vitrification.							
	Storage Conditions	No	Vitrification does not require different storage conditions than standard cryopreservation							
	Transport Conditions	No	Also, once required for clinical use, transportation of vitrified sperm to an ART centre will not require different conditions than standard cryopreserved sperm							
Product	**Loss of viability and or functionality**	Yes	We estimate a theoretical risk of unfeasibility of vitrified sperm for ART. Although unlikely, this could lead to failure of the artificial reproduction technique (ICSI) which to our knowledge cannot be anticipated and/or mitigated in any way.	Implant failure/ pregnancy loss	2	2	5	20	0	20
Clinical application procedure	**Complexity of the preparation/application method**	No	No changes in the pre-implantation and in the ART procedure is expected.							-
									Total risk score = 16	

Table III Continued

Example 3. Human biopsied blastocyst—Day 5-vitrified—with failed genetic test in biopsied Trophectoderm cells (TE). Blastocyst will need to be warmed, cultured, re-biopsied and re-vitrified.

	Risk factors	Does it apply?	Comments	Risk consequences	P	S	D	PR	RR (%)	Risk
Donation	**Donor Characteristics / Source of material**	Yes	No changes in patient population for PGT	Implant failure/ pregnancy loss	2	2	1	4	0	4
Procurement	**Recovery/Procurement process and environment**	Yes	Standard warming of vitrified blastocystRe-biopsying is more complex	Implant failure/ pregnancy loss	1	1	1	1	50	0.5
Processing/ storing / transport	**Preparation process and environment**	Yes	Re-biopsy can damage the embryo. Re-vitrification and warming can damage the embryo	Implant failure/ pregnancy loss	3	2	2	12	50	6
	Reagents	No	Similar culture conditions—similar vitrification and warming media—similar biopsy pipettes.							
	Storage Conditions	No	Identical culture conditions and carrier storage conditions.							
	Transport Conditions	No	Not applicable.							
Product	**Loss of viability and or functionality**	Yes	Change to re-biopsy programme.	Implant failure/ pregnancy loss	3	2	2	12	50	6
				Toxicity/ Carcinogenicity	2	2	2	8	25	6
Clinical application procedure	**Complexity of the preparation/application method**	Yes	Extra culture time (sometimes to Day 6) and double vitrification and warming exposure.	Implant failure/ pregnancy loss	2	2	2	8	25	6
										Total risk score = 5

Table III Continued

Example 4. Changing a manual oocyte aspiration protocol into an aspiration using a pump.

	Risk factors	Does it apply?	Comments	Risk consequences	P	S	D	PR	RR (%)	Risk
Donation	**Donor Characteristics / Source of material**	No	No patient characteristics will be affected by the introduction of the new oocyte aspiration pump.							
Procurement	**Recovery/Procurement process and environment**	Yes	Recovery time, i.e. the length of oocyte pick-up will remain the same. However, the complexity quality of the environment, i.e. the new appliance that will be used for oocyte aspiration, is going to change.	Implant failure/ pregnancy loss	1	2	2	4	75	1
				Toxicity/ Carcinogenicity	1	1	1	1	75	0.25
Processing/ storing / transport	**Preparation process and environment**	No	Oocyte preparation, i.e. denudation, will not be affected by the new aspiration pump.							
	Reagents	No	Flushing and culture mediums are not going to change.							
	Storage Conditions	No	Storage of oocytes, i.e. incubation, is not going to change.							
	Transport Conditions	No	Transportation of the oocytes from the pick-up room to the embryo lab is not going to change.							
Product	**Loss of viability and or functionality**	Yes	Use of the new aspiration pump might result in oocyte damage, however, the risk is lower, compared with manual oocyte aspiration. Oocyte damage caused by the new pump is likely to be detected very soon if the damage issubstantial. However, it might be subtle, and in this case it would take some time to find out.	Implant failure/ pregnancy loss	1	2	2	4	75	1
Clinical application procedure	**Complexity of the preparation/application method**	No	The clinical use of oocytes is not going to change. The methods of pre-implantation preparation are culture and embryo diagnosis method, they are not changing. The application method is embryo transfer, this is not changingeither.							
									Total risk score = 1	

Table III Continued

Example 5. Changing from a long GnRH agonist protocol to a GnRH antagonist protocol.

	Risk factors	Does it apply?	Comments	Risk consequences	P	S	D	PR	RR (%)	Risk
Donation	**Donor Characteristics / Source of material**	No	The new stimulation protocol will not change the patient characteristics.							
Procurement	**Recovery/Procurement process and environment**	No	No significant change in stimulation time or complexity of treatment is expected.							
Processing/ storing / transport	**Preparation process and environment**	Yes	Because of the use of lower gonadotropin doses, the new protocol might be associated with lower carcinogenicity, even though the overall carcinogenicity of ovarian stimulation is very low. The carcinogenicity of ovarian stimulation has been researched quite extensively.	Toxicity/ Carcinogenicity	2	3	1	6	95	0.3
	Reagents	No	No new medicines are used in the new protocol.		-					
	Storage Conditions	No	The new protocol is already in use in many clinics. There will be no changes in oocyte storage conditions.							
	Transport Conditions	No	There will be no changes in oocyte transport conditions.							
Product	**Loss of viability and or functionality**	Yes	The new protocol has been shown to be safe for the patient population but there is always a potential for loss of viability of the oocytes.	Implant failure/ pregnancy loss	1	1	1	1	75	0.25
Clinical application procedure	**Complexity of the preparation/application method**	Yes	Ovarian stimulation is a complex procedure. The new protocol is associated with a possibility for malignant tumours, but the overall risk is very small. The detectability of ovarian malignant tumour is very high. There have been no publications on the incidence of malignant tumours after stimulation with mild ovarian protocol.	Toxicity/ Carcinogenicity	2	3	1	6	95	0.3
									Total risk score = 0	

*Only risks consequences identified among those exposed in Table II are shown.
P, probability; S, severity; D, detectability; PR, potential risk; RR, risk reduction (see Fig. 2).

Table IV Risk-reduction strategy and the extent of studies needed in order to implement novelties in clinical practice based on risk score (Step 3) (EuroGTP II, 2019; Trias *et al.*, 2020).

Risk score	Risk level	Risk-reduction strategy and guidance on the extent of studies needed
0–2	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 as established or standard. In this case multi-centred studies (ideally RCT) are published in a peer-reviewed journal and the procedures are performed according to a validated and standard protocol. **Minimal process validation** is needed. The technical performance of staff should be monitored and comparable with other TE or published studies; therefore, standard KPIs should be monitored on the technical quality of the staff performing the procedures. Dropping KPIs can result in protocol drift and must lead to investigation of both the procedural steps and/or the need to re-train staff. **Step 3B: Definition of clinical studies** **A routine/safety follow-up programme** is enough as the good practices state. 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. Long-term (ideally trans-generational) health effects, including aspects such as fertility, oncology and mental health should be monitored.
>2–6	Low	**Step 3A: Risk-reduction strategies** Implementing a standard procedure or treatment in an ART centre that has never performed this procedure requires an **intensive validation.** Training of staff is necessary in order to reach the outcomes published in scientific literature. Having a mentor/mentee relationship with an ART centre having experience is highly recommended. Specifications on performance should be determined and when these limits are met by training on spare tissues and cells, staff can be authorized to perform the procedure. A learning curve is to be expected and should be part of the validation report. When implementing the procedure, additional quality controls must be performed to **monitor CPPs and CQAs**. For example, when a TE is switching from IVF to ICSI (which they never performed before), fertilization rates, and damage rates etc. of embryos should be carefully monitored in relation to the staff performing the procedure. **Step 3B: Definition of clinical studies**Step 3B: Definition of clinical studies **A safety follow-up programme** is necessary. 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 and in relation to the results published in scientific literature. As the procedure or treatment encompasses an established or standard technique, the expected learning curve should be kept as short as possible and be related to the follow-up programme. Likewise, established techniques should be subject to long-term (ideally trans-generational) follow-up of the health effects. ART centres implementing an established technique should perform long-term follow-up and could keep track of their follow-up items at the mentor facility. This way of working could provide periodic performance evaluations of the mentor/mentee relationship.
>6–22	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 are reassuring data in literature in terms of both safety and effectiveness, at least in animal studies, and preclinical data show normal embryology development. The studies that have published this data should have a sound methodology and be published in peer-reviewed journals. In order to implement an innovative treatment, **enhanced validation** is necessary, including performance of a range of **additional quality controls** to monitor CPPs, CQAs and the impact of the implemented changes on gametes, embryos and gonadic tissue, which should be carefully monitored. Since reassuring data of this innovative treatment are already available, more specific monitoring of the published critical parameters can be performed instead of a registration of all critical parameters. **Step 3B: Definition of clinical studies** **Clinical evaluation and follow-up programmes** should be implemented to provide reassurance on mid-term safety (3 months up to 5 years post-delivery including data on psychological well-being) and these studies should refer to patients undergoing the procedure as well as the children born from it.
>22	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. **An extensive validation** including a range of **additional quality controls** performed to monitor CPPs, CQAs and the impact of the implemented changes is required. This extensive validation should include: **Non-clinical studies**: preferably there should be studies showing the experimental procedure is safe in animals. **Pre-clinical Studies:** when experimental treatments encompass a laboratory IVF phase, then at least the structural integrity of the gametes, embryos or gonadic tissue should be looked at in detail, monitored and registered. Clinical embryology data should indicate normal cleavage embryo morphology and blastocyst formation. **Step 3B: Definition of clinical studies** At first 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 (the lack of knowledge about) possible risks, alternative treatments, etc. ART centres should only offer experimental treatments or treatments based on experimental procedures after approval by a medical ethics committee.

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CPP; critical process parameter; CQA, critical quality attribute; KPI, key performance indicator; RCT, randomized controlled trial; TE, tissue establishment.

This is a dynamic step to be followed and interpreted by a multidisciplinary team. Studies needed for a given identified risk may have been published and should be properly identified. These in turn may give rise to new questions, as illustrated in Fig. 1.

Discussion

A systematized way of assessing risk of novel ART is fundamental before they are used in humans for the first time, when strategies to reduce the likelihood of SARE have to be implemented. The EuroGTP II-ART provides a unique procedure for performing risk assessment of novel ART and reproductive tissue and cell products in a systematic manner that ensures uniform and in-depth risk analyses of these TCTPs. The availability of the EuroGTP II interactive tool, together with the explanatory guides and examples provided to improve its comprehensibility, is likely to foster its application to the validation procedures prior to inclusion of ARTs in the clinical practice. Risk assessment may be performed not only before the implementation of the ART but at different stages of the development and implementation processes in order to re-evaluate risks on the basis of information collected (studies conducted or relevant publications).

Regardless of the risk score and the result of the risk assessment exercise, it is important to state that ART centres should be prepared to invalidate treatment when it proves problematic, even when a novelty of negligible risk is implemented. Outcome and follow-up data should be recorded in a systematic way and made available to the scientific community regardless of the success of the novel treatment. Additionally, regardless of the level of risk, SARE should always be recorded and analysed.

Despite its usefulness, it is important to remark that adherence to this guidance does not guarantee a successful or specific outcome, nor does it establish a standard of care. EuroGTP II outcomes do not override the healthcare professional's clinical judgement and treatment of patients. Ultimately, healthcare professionals must make their own clinical decisions on a case-by-case basis, using their clinical judgement, knowledge and expertise, taking into account the patient's condition and circumstances and after consultation with the Competent Authorities. EuroGTP II makes no warranty, express or implied, regarding the guidance and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. EuroGTP II authors shall not be liable for direct, indirect, special, incidental or consequential damages related to the use of the information contained herein. While EuroGTP II has made every effort to compile accurate information, it cannot, however, guarantee the correctness, completeness and accuracy of the guideline in every respect. The information provided in this document/tool does not constitute business, medical or other professional advice, and is subject to change.

The EuroGTP II interactive tool is available since March 2019. Part of this content has already been published in the guideline on Good Practices for evaluating quality, safety and efficacy of novel tissue and cellular therapies and products (http://www.goodtissuepractices.site/docs/EuroGTP_II_Guide.pdf).

Conclusion

EuroGTP II-ART provides a unique procedure for performing risk assessment of novel ART and reproductive tissue and cell products in a systematic manner that ensures uniform and in-depth risk analyses of these TCTPs. Its value goes beyond assessment of risk before implementing a novel ART in clinical practice, as it allows re-evaluating risks based on information collected during the process.

Authors' roles

All authors made substantial contributions to the conception, drafting and critical revision for intellectual content of this article. All authors gave final approval of the final version.

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Conflict of interest

None.

Appendix

EuroGTP II Study Group

Associated Partners (Banc Sang i Teixits—Barcelona Tissue Bank (BST/BTB): Anna Vilarrodona, A. Rita Piteira, Elba Agustí, Elisabet Tahull, Esteve Trias, Eva Maria Martinez, Ivan Miranda, Jaime Tabera, Maria Luisa Perez, Marta Torrabadella, Nausica Otero, Oscar Fariñas, Patricia López-Chicón, Sergi Querol and Ricardo Casaroli; National Health Service—Blood and Transplant (NHSBT): Akila Chandrasekar, Kyle Bennett, Paul Rooney, Richard Lomas; Organización Nacional de Trasplantes (ONT): Mar Carmona, Esteban Molano, Myriam Ormeño; Ministry of Health of the Republic of Croatia (MZRH)—Institute for Transplantations and Biomedicine In collaboration with Klinički Bolnički Centar Zagreb (KBCZ): Branka Golubić Cepulić, Ivan Rozman, Marijana Dragović; Italian National Transplant Centre (ISS-CNT): Cristina Pintus, Eliana Porta, Fiorenza Bariani, Letizia Lombardini, Liliam Santilli, Mariapia Mariani, Paola Di Ciaccio, Silvia Pisanu; Krajowe Centrum Bankowania Tkanek i Komórek (KCBTiK): Artur Kamiński,

Izabela Uhrynowska-Tyszkiewicz, Ewa Olender; TRIP Foundation, Netherlands office for hemo- and biovigilance (TRIP): Anne Marie van Walraven, Arlinke Bokhorst, Ingrid van Veen; Ghent University Hospital—Department of Reproductive Medicine: Kelly Tilleman, Tolpe Annelies, Veerle Provoost, Lieve Nuytinck; Bulgarian Executive Agency for Transplantation (BEAT):Maryana Simeonova, Daniela Staneva-Petkova, Dessislava Tzoneva, Tsvetelina kircheva-Nikolova, Violetta Marinkova, Valery Georgiev, Yoran Peev, Elizabeth Manova; Semmelweis University, Health Services Management Training Center, SU (HSMTC): Cecilia Surján, Éva Belicza, Gábor Szarvas, Judit Lám, László Bencze; German Society for Tissue Transplantation GmbH (DGFG): Martin Börgel, Mareike Derks, Sibylla Schwarz; Saint Jean Clinic, European Homograft Bank (CSJ/EHB): Ramadan Jashari, Richard N. Noumanje; Rosario Daiz Rodriguez; Regea Cell and Tissue Center, University of Tampere: Tiia Tallinen, Hanna Kankkonen, Toni-Karri Pakarinen; Ecole Royale Militaire—Koninklijke Militaire School (ERM/KMS): Gilbert Verbeken, Jean-Paul Pirnay, Thomas Rose, Jean-Pierre Draye. Collaborative Partners and Invited Experts: European Association of Tissue Banks (EATB): Simone Hennerbichler; Jill Davies; Jacinto Ibañez; European Society of Human Reproduction and Embryology (ESHRE): Cristina Magli, Nathalie Vermeulen, Monserrat Boada; The European Society for Blood and Marrow Transplantation (EBMT): Eoin McGrath; European Eye Bank Association (EEBA): John Armitage, Gary Jones; EDQM, CoE—European Directorate for the Quality of Medicines & HealthCare, Council of Europe: Marta Fraga; Instituto Portugues do Sangue e da Transplantaçao (IPST,IP): Dulce Roldao, Josefina Oliveira; Fondazione Banca dei Tessuti di Treviso Onlus (FBTV): Adolfo Paolin, Diletta Trojan, Giulia Montagner; Fondazione Banca degli Occhi del Veneto Onlus (FBOV): Diego Ponzin, Stefano Ferrari; Rome La Sapienza University: Francesco Lombardo; Sanquin Blood Supply Foundation: Carlijn Voermans; ETB-BISLIFE Foundation: Nelleke Richters; AER Embryologists Association, Romania: Ioana Adina Rugescu; Big burns Unit, University Padova Hospital: Gianpaolo Azzena; Cardio surgery Unit, University Padova Hospital: Assunta Fabozzo; Ghent University Hospital (UZGent): Helene Schoenmans; Hospital Clinic Barcelona: Jose Luis Pomar; Hospital de la Santa Creu i Sant Pau: Pablo Gelber; Hungarian Stem Cell Donor Registry at the National Hungarian Blood Transfusion Service: Katalin Rajczy; Institut Paoli Calmettes Cell Therapy Facility: Boris Calmels; Karolinksi Instituut Stockholm: Stephan Mielke; Leiden University Hospital: Tanja Netelenbos; Maxillofacial Surgery Unit, Treviso Hospital: Mirko Ragazzo; MC ReproBioMEd: Gueorgui Nikolov; Neurosurgery Unit Treviso Hospital: Elisabetta Marton; Nij Geertgen, Centre for Fertility: Martine Nijs; Ophthalmology Department—SS. Giovanni e Paolo Hospital, ULSS3 Serenissima, Venice: Antonella Franch; Orthopaedic and Traumatology Unit, Sacro Cuore Don Calabria Hospital, Verona: Gianluca Piovan; Plastic Surgery Unit, Treviso Hospital: Francesco Dell'Antonia; Royal Orthopaedic Hospital, Birmingham: Martyn Snow; University Hospital Center Zagreb: Ines Bojanic; University of Oulu: Zdravka Veleva; University of Warsaw: Grezgorz Basak; Centro Hospitalar do Porto: Margarida Amil; Irish Blood Transfusion Service: Sandra Shaw; Notify Project: Aurora Navarro; European Society for Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA): Tim Spalding, Peter Verdonk.

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