GOOD PRACTICES FOR DEMONSTRATING SAFETY AND QUALITY THROUGH RECIPIENT FOLLOW-UP
COORDINATOR

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SPAIN: Organización Nacional de Trasplantes (ONT)

THE NETHERLANDS: TRIP Foundation, Netherlands Office for Hemo- and Biovigilance (TRIP)

UNITED KINGDOM: National Health Service Blood and Transplant (NHSBT)
GOOD PRACTICES FOR EVALUATING QUALITY, SAFETY AND EFFICACY OF NOVEL TISSUE AND CELLULAR THERAPIES AND PRODUCTS

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

KBC – Gruppo Italiano per il Trapianto di Midollo Osseo, cellule staminali emopoietiche e terapia cellulare
BISLIFE Multi Tissue Centre
Sanquin Blood Supply Foundation
Instituto Português do Sangue e da Transfusão

EBMT – European Society of Human Reproduction and Embryology

OTHER COLLABORATIONS

VISTART
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ECCTRI
ARTHIQS
NOTIFY LIBRARY

Department of Experimental Medicine Medical Fisiopathology Division of the Rome La Sapienza University
Grupo Italiano per il Trapianto di Midollo Osseo cellule staminali emopoietiche e terapia cellulare

Sanquin
Fondazione Banca degli Occhi del Veneto Onlus
WHY DO WE NEED TOOLS AND METHODOLOGIES TO ASSESS AND VERIFY QUALITY, SAFETY AND EFFICACY OF NOVEL TISSUE AND CELLULAR THERAPIES AND PRODUCTS (TCTP)?

Advances in basic science, technology and medicine continually create opportunities for new and improved TCTP. These may be wholly new types, or improved methodologies for the preparation of existing TCTPs. While the objective of these changes and novelties is to prepare TCTPs that are safer, clinically more effective and meet the needs of clinicians and patients, there is always a risk that any change in the processing method can result in harm in the recipient. It is therefore vital that an evaluation of the potential risk of a process is systematically evaluated whenever a significant change is made.

The European Commission, being conscious of the necessity to strengthen standards for quality, safety and efficacy of TCTPs, especially those related to innovative TCTPs, funded the EuroGTP II project (European Good Tissue and cells Practices II) – "Good Practices for demonstrating safety and quality through recipient follow up", to provide practical tools which assist TEs and ORHAs, in the assessment and verification of the quality, safety and efficacy of novel TCTPs.

The main objective was to set up good practices with regard to pre-clinical and clinical evaluation of human Tissues, HSC and ART and reproductive tissues and cells products.

EuroGTP II gives continuity to the first EuroGTP project, which has developed European Good Tissue Practices for the activities carried out in TEs.

Achieving a systematic and standardized approach

The project developed good practices, principles and reference tools applicable to TCTPs and how to conduct adequate clinical evaluations. The methodologies proposed aim to be systematic and consistent, in order to promote a standard approach to practices and recognition amongst the stakeholders.

There are three key outputs from the EuroGTP II Project:

A. Systematic, risk-based mechanism and IAT
B. T&C database of tissues/cells products, preparation processes, applications and therapies - structure defined to publish data related to the products and therapies available, and support end users in the evaluation of TCTPs for safe and efficacious use.
C. GTP’s Management Model assures the continuity and sustainability of the outcomes of the EuroGTP II Project, and the future update, promotion and harmonization of standards.

While all outcomes were developed to assist professionals in their daily activities, an effort was done to produce guidance and tools in accordance with the regulatory principles, legislation and good practices. This tool will be also available to National Competent Authorities, hence may support facilitating the evaluation and the authorisation procedures.
ACRONYMS:

ART – Assisted Reproductive Technologies

EBMT – European Society for Blood and Marrow Transplantation

ESHRE – European Society of Human Reproduction and Embryology

GTP – Good Tissues and Cells Practices

HSC – Haematopoietic Stem Cells

IAT – Interactive Assessment Tool

ORHA – Organization Responsible for Human Application

T&C – Tissue and Cells

TCTP – Tissue and Cellular Therapy/Product

TE – Tissues Establishment

WP – Work Package
EuroGTP II methodology for assessment of novelty and risk evaluation

WP5 | PRODUCING GENERIC GOOD PRACTICES FOR DEMONSTRATING SAFETY AND QUALITY THROUGH RECIPIENT FOLLOW UP

WP leader: Istituto Superiore Di Sanita – Centro Nazionale Trapianti (ISS-CNT), Italy

This WP had the task to pave the basis for the specific WPs of the EuroGTP II methodologies and the work developed by the specific WPs (WP 6, 7, and 8).

The aim was to elaborate practical recommendations on how to deal with a novel TCTP. Although it is difficult to find a common approach for defining the adequate technical and scientific information needed to support the quality and safety of a novelty, this group of work defined a systematic methodology and a practical tool to guide the user through a standardized way of thinking. (Fig. 1).

Novelties or innovative changes can arise from any phase of the cycle “donation – procurement – processing – storage – distribution – clinical use” and in principle it would be possible to correlate the different novelties according to the degree of risk (negligible, low, moderate, high), as has been initially described in the VISTART project (Deliverable 5.4 “Principles for Competent Authorities for the Evaluation and Approval of Clinical Follow Up Protocols for Blood, T&C Prepared with Newly Developed and Validated Processing Methodologies”).

Experts from the three fields (T&C, HSC and ART) coming from tissue establishments, ART centres, universities, hospitals, scientific societies and Competent Authorities gave their input in developing the tool and determining the extent of studies required to demonstrate safety and efficacy of the new TCTPs.

The first Step for applying the IAT consists in verifying if the novelty can be classified as such. To that purpose the user has to answer the seven questions in the checklist about the evaluation of novelty (Step 1). If the status of “novelty” is recognized, the user has to identify and quantify the potential risks of that given innovation (Step 2).

With the Step 2 the user is lead through the process of establishing the potential risks. Users can consider the possible risk factors for each phase of the donation-clinical application chain, in order to determine if those risks fit with, or are applicable to, a given innovative product.

Since the issue of novelty degree linked to the entity of risk represents the focal point of the whole exercise, the IAT process also helps you to:

- Characterize the potential risk consequences of the identified risks like: unexpected immunogenicity, implant failure, toxicity, carcinogenicity etc. -
- Assess probability, severity and detectability levels
- Consider possible means to reduce the risk according to the type of innovation.

At this point the user has a rather precise outline of the novelty and needs to be assisted for the last part of the IAT: planning the extent of studies needed on the basis of the risks quantified (Step 3).

The studies comprehend preclinical in vitro and in vivo tests and clinical evaluation protocols. Design and typology of the studies were defined by WP 5 and are better described in the WPs dedicated to the specific sectors (T&C, HSC and ART).
The goal of this group was to transpose the generic methodologies developed by the WP 5 into practical tools, for the safe implementation of novel tissues.

The WP 6 worked in close collaboration with the other technical WPs and consulted with a large number of experts (associative partners, collaborative partners and invited experts), to determine the risk factors and risk consequences to be considered for the implementation of novel tissue products and/or therapies.

In addition to the technical meetings with the partners, several ad-hoc meetings were held with end users (musculoskeletal tissues (United Kingdom), skin, acellular dermis (Belgium), ocular tissues and amniotic membrane (Italy), cardiovascular tissues and fresh cartilage (Spain)), to define a list of suggested clinical evaluation protocols.

The criteria for the correct assessment of novel tissues, definitions and examples are included as part of the methodologies proposed by the EuroGTP project, and detailed in the Tissues Specific Chapter – Specific guidance for the use of EuroGTP II methodologies and tool (chapter 4) - of the EuroGTP II Guide.

Additionally, risk reduction strategies (in vitro and in vivo tests) and suggested clinical evaluation/follow-up protocols, are defined for the different tissues – Cornea, Sclera, Amniotic Membrane, Skin, Acellular Dermis, Heart Valves, Vascular grafts, Bone, Tendons, Meniscus and Fresh Cartilage – and included as annex VI of the EuroGTP II Guide. The risk reduction strategies are presented as a set of matrices and tables which suggest a number of different test criteria, which are specific for different types of tissues, and could be applied to address specific risk consequences.

Partners involved in this WP had also an important role for the definition of the structure and data entries of the T&C Database, and the validation of its future use. These contributions helped to determine the contents of the database, ensured its consistency, harmonized the criteria for the characterization of TCTPs, and facilitate possible future collaborations of TE at European level.
The group focused on the evaluation of HSC novelties (other than Advanced Therapy Medicinal Products) that can be introduced in each step of the process, starting from donor selection to clinical application.

The aim of this WP was to adapt the methodologies and IAT developed by the generic WPs for HSC products and therapies. Experts in the field of stem cells, with laboratory and clinical background, participated by sharing their expertise and giving advice.

Some methods were applied to design and validate the adapted version of the methodologies, such as performing literature review and using some examples or describing novelties developed in the preparation and application of human HSC.

Novelty or not?

To ascertain that a HSC donor product is actually developed into a novelty, firstly the stem cell laboratory or ORHA has to define which specific source (bone marrow, peripheral blood, cord blood or other) is involved. Then a novelty assessment step (step 1 of EuroGTP II methodologies) can be performed for each source, to determine to what extend the change in the product is posing a risk for the recipients.

The WP 7 defined explanations and examples on how to answer those questions, which were included in the Chapter 5 of the EuroGTP II Guide and the IAT.

How to identify risks?

Every modification in the process associated with the donor selection, donation, procurement, testing, processing, storage or distribution may affect the quality of the final product and the safety of the recipient.

Some questions are included as part of the assessment to help users to identify the type of risk factors that can be associated with the novelty, and to determine which are the specific risk consequences of the clinical application of the TCTP.

Follow up after clinical application of a novelty

To determine suitable follow-ups according to the level of risk, the WP 7 aligned as much as possible with the registries and definitions of the EBMT, which is already the standard for the majority of European transplant centres of HSC.

Thus, to determine safety and efficacy in the clinical application of novel TCTP, EuroGTP II strongly recommends the use of the EBMT MED-A form. Although these forms are intended for advanced cellular therapies, the different elements of the MED-A Cell Therapy form also give guidance to establish the appropriate steps to be taken to safeguard safety and efficacy of HSC novelities.

When dealing with novelties in stem cell therapy, often life-saving product innovations are involved. It is for the best of the patients, that the process of setting conditions under which clinical use can be considered, proceeds seamlessly, not only to safeguard the quality and safety of these novel therapies, but also to facilitate the approval process for clinical use.

The Euro GTP II risk assessment tool can demonstrate that an adequate processing and clinical follow-up program is designed for these innovative treatments, and thus compliantly bridges the gap between science and clinical practice.
Determining ART specific risk factors, risk consequences and finding the pre-clinical evaluation tests and studies in novelties in ART

In order to clearly define the correct interpretation and scope of the individual risk factors and risk consequences defined for ART, examples are fully explained in writing and included in the guide and IAT.

The criteria and parameters considered essential for the implementation and follow-up of the different ART’s novelties are also described, and incorporated as part of the ART Specific Chapter—Specific guidance for the use of EuroGTP II methodologies and tools (Chapter 6 of the EuroGTP II Guide).

The ART team used the paper of Provoost et al. (2014) as a basis where the concepts of validation and evaluation studies in ART were already summarized. Additionally, ART has a long tradition of publishing papers on performance indicators which can be used to find out the level of experience needed in order to introduce a novel procedure in the ART laboratories (e.g. the Alpha consensus paper (on cryopreservation indicators (Alpha scientists, 2012)) and the Vienna consensus (on ART laboratory performance indicators (ESHRE SIG embryology and Alpha scientists, 2017).

Validation of Tools
At a first stage, the usability of the IAT, as well as the validation of methodologies, were tested in smaller groups, promoted at national level. This aimed to determine if the guidance document for the ART Specific Chapter would suffice to execute the assessments of novel ART TCTPs. The results of these exercises determined the tool as very user friendly and the results of the risk assessments were as to be expected. These exercises allowed also identifying minor technical aspects which were addressed to complete the ART specific chapter of the guide.

Expected impact for professionals
Risk-based thinking is something that is quite natural in ART. Changes in the lab are closely monitored through outcomes in the clinic. In ART, the laboratories mostly work in close collaboration with their clinical partners, and the outcome most favourable of all ART technologies is a healthy live birth. The EuroGTP II gives the possibility to professionals of this particular sector to organize their risk assessments in a consistent manner and are thus able to facilitate exchanges in novel therapies and treatments. The interactive tool takes care of the entire process of risk-based thinking and will result in uniform and in-depth risk analyses concerning novelties in ART.

Adapting the methodologies to ART
The group analysed the tools and methodologies proposed by the generic WP 5, to have a feel of its user-friendliness and to shape it according to ART specific criteria.

WP leader: Universitair Ziekenhuis Gent (UZGent), Belgium

It is clear from scientific literature that follow-up and outcome registries are common practice in ART. There is follow-up in national registries, and the ESHRE collects data at European level. Experts working in ART are aware of the wobbly evidence basis of certain novel treatments and techniques that are used, and there are several reports in literature that addresses exactly these issues.

In 2014, Provoost et al. presented a conceptual framework for distinguishing experimental, innovative and established ART treatments. This paper was specifically chosen as the basis for EuroGTP II and thus, the awareness for the need of good risk assessment tools in case of ART novelties was already present in the ART community.

A team of ART experts was chosen to tackle the ART WP of this project and these people were invited because of their expertise in quality management, guideline development methodology, competence in data management and data collection and know-how on bioethics.

Meeting in Barcelona @ESHRE annual meeting (3rd July 2018)
WP9 | T&C DATABASE AND INTERACTIVE ASSESSMENT TOOL (IAT)

WP leader: Barcelona Tissue Bank - Banc de Sang i Teixits (BST), Spain

The WP 9 had the aim of producing and validating the dynamic tools that incorporate the methodologies and technical information developed by the EuroGTP II project.

Working in collaboration with other technical WPs, this group was responsible for the implementation and validation of the EuroGTP II algorithm, and the development of functionalities specific to the different areas of Substances of Human Origin – Tissues, HSC and ART.

Tools available

The IAT (http://tool.goodtissuepractices.site) has been developed to facilitate the use of the EuroGTP II methodologies. It addresses the first two steps of the EuroGTP II methodology: evaluation of novelty and analysis of risk.

This tool generates the **Final Risk Score** and the consequent **level of risk** based on the algorithm defined by the WP 5. The output from the analysis of risk is used to determine whether or not the TCTP can be made generally available for clinical application on request, or if further pre-clinical and/or clinical evaluations are required.

WP 9 also developed the **T&C Database** (http://db.goodtissuepractices.site), according to the structure determined by the other technical WPs. The purpose of this database is to promote the safe and effective use of TCTPs, by the provision of data related to the products and therapies available, and references relating to their efficacy.

The T&C Database provides structured and systematic information regarding TCTPs implemented by the TEs, information on clinical application and references and evidence related to available efficacy and safety data.

The information contained in the T&C Database intends to:

- Encourage stakeholders and Competent Authorities to accept the validity of data generated for products in other countries (harmonization of practices);
- Advocate the collaboration amongst TEs, boosting multicenter collaborations for the development of novel TCTPs;
- Promote the accessibility for patients, by developing knowledge amongst clinicians regarding the availability of TCTPs.

The data included in the T&C Database will be voluntarily shared by TEs, with the intention of contributing to the knowledge base associated with novel and well-established TCTPs within Europe.

Structure of the T&C Database
ASSOCIATED PARTNERS

Banc de Sang i Teixits – BST (Spain, Coordinator, WP1, WP9 Leader and WP4 Co-leader); Organización Nacional de Trasplantes – ONT (Spain, WP2 Leader); Ministry of Health of the Republic of Croatia – MZRH, Institute for Transplantations and Biomedicine (Croatia, WP3 Leader); National Health Service Blood and Transplant – NHSBT (United Kingdom, WP4 Co-leader); Istituto Superiore di Sanità - ISS/CNT Italy, WP5 Leader); Krajowe Centrum Bankowania Tkanek i Komórek, National Centre for Tissue and Cell Banking – KCBT/K/NCTCB (Poland, WP6 Leader); TRIP Foundation, Netherlands Office for Hemopoiesis and Biovigilance – TRIP (Netherlands, WP7 Leader); Ghent University Hospital, Department of Reproductive Medicine – UZGent (Belgium, WP8 Leader); Bulgarian Executive Agency of Transplantation – BEAT (Bulgaria); Semmelweis University, Health Services Management Training Center, SU – (Hungary); German Society for Tissue Transplantation gGmbH – DFGF (Germany); Saint Jean Clinic, European Homograft Bank – CSJ/EHB (Belgium); Regea Cell and Tissue Center, University of Tampere – Regea/UTA (Finland); École Royale Militaire, Koninklijke Militaire School – ERM/KMS (Belgium).

COLLABORATING PARTNERS

European Association of Tissue Banks – EATB; European Society for Blood and Marrow Transplantation – EBMT; European Society of Human Reproduction and Embryology – ESHRE; European Eye Bank Association – EEBEA; European Directorate for the Quality of Medicines & HealthCare, Council of Europe – EDQM/CoE; Klinički Bolnički Centar Zagreb; Banca dei Tessuti della Regione Veneto; Fondazione Banca degli Occhi del Veneto Onlus; Department of Experimental Medicine - Medical Physiopathology Division of the Rome La Sapienza University; Gruppo Italiano per il Trapianto di Midollo Psoeo, Cellule Stamminali Emopoietiche e Terapia Cellulare - GITMO; European Tissue Bank; Multi Tissue Centre - BISLIFE; Sanquin Blood Supply Foundation; Instituto Português do Sangue e da Transplantação.

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