European Reference Network
for rare or low prevalence complex diseases

Network Transplantation in Children (ERN TRANSPLANT-CHILD)

PAEDIATRIC TRANSPLANTATION EUROPEAN REGISTRY

peter

PaEdiatric European Transplant Registry
PETER

PETER registry protocol

Co-funded by the European Union, by the project GA 947629

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HISTORY OF DOCUMENTS

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02.11.2023	2.0	Protocol Update
14.06.2024	2.1	Change of Principal Investigator

DOCUMENT SIGNED

Drafted by:	Approved by:
Position: Executive Committee	Position: Network Coordinator on behalf of PETER & Network Board
Date: 13.06.2024	Francisco Hernández Oliveros Date: 14.06.2024

LEVEL OF DISSEMINATION

PU	Public	✓
EN	Internal use only	☐
CO	Confidential, only for consortium members (including Commission services)	☐

INFORMATION IN THE DOCUMENT

PETER REGISTRATION PROTOCOL

Type of ERN document: Protocol

Taxonomic**reference:** Reporting of ERN activities

ERN: TransplantChild

See the SOP00 Standard Operating Procedure (SOP) for managing TransplantChild documentation for more information on this classification.

CONTENT TABLE

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1. BACKGROUND AND JUSTIFICATION

The establishment in 2017 by the European Commission of European Reference Networks (ERNs) for rare diseases or complex conditions requiring highly specialised treatment, expertise and resources was an important milestone in ensuring access and specialised care for these patients. This initiative enabled the mobilisation of the best multidisciplinary teams and the exchange of expertise across Europe. ERN-TransplantChild is one of the 24 networks launched in 2017, in accordance with Article 12 of 2011 of the "Directive on patients' rights in cross-border healthcare" in the field of rare, complex or low prevalence diseases or conditions.

The ERN TransplantChild is the only network that focuses on a complex procedure such as pediatric transplantation, which is a complex and low-prevalence condition that requires highly specialized knowledge and resources. Current approaches are insufficient to fully address long-term graft and patient survival, while providing the best possible quality of life.

At present, the ERN TransplantChild has 40 European hospitals from 21 EU Member States (MS), in which 33 full members (FM) and 7 affiliated partners (AP) participate. The aim of the ERN TransplantChild is to empower and improve the hope and quality of life of paediatric patients requiring transplantation in the EU, as well as their families, by: (1) Ensure their access through the network to the best possible care practices and support procedures related to a cross-cutting and multidisciplinary approach to paediatric transplantation; (2) develop and bring together efforts within the network for better, inclusive and innovative procedures, information, training, knowledge and experience; (3) integrate stakeholders into the transplantation process and make knowledge and information available to them. This view is especially necessary in pediatric transplantation compared to adult transplantation, where the number of patients per transplanted organ is higher.

Patient registries and databases are key tools for developing clinical research in the field of rare diseases, improving patient care and healthcare planning. They are the best way to pool data to achieve sufficient sample size for epidemiological or clinical investigation. The registries serve as a recruitment tool for launching studies focused on the etiology of the disease, pathogenesis, diagnosis or therapy. On 8 June 2009, the Council of the European Union recommended that, in the area of rare diseases or complex conditions, Member States considered supporting all appropriate levels, including the EU, for epidemiological purposes, registries and databases, while being aware of independent governance. In order to support this process and in particular the interoperability of data in rare disease registries, the Commission decided to set up a European platform on rare disease registries and to develop specific standards for the interoperability of rare disease registries ("JRC standards" developed by the *Commission's Joint Research Centre*).

Pediatric transplant.

Pediatric transplantation, both solid organ transplantation (TOS) and hematopoietic progenitor transplantation (HTP), have dramatically changed the life expectancy of many children by providing treatment for complex diseases or conditions that would not have survived otherwise. Worldwide, about 150,000 TOS and 80,000 TPH are performed annually. Pediatric

transplantation accounts for approximately 10% of all TOS and 20% of all TPH. Between 2012 and 2016, approximately 7,741 paediatric TOS and 14,717 paediatric TPHs were performed in the European Union, data that continue to increase paediatric age.

Both TOS and TPH offer the possibility of a cure, but at the same time increase the risk of treatment-related mortality and long-term side effects. That is, transplantation would replace end-stage disease with a more sustainable chronic disease state and, as such, with profound clinical and psychosocial consequences. Transplant care is however a medical challenge, as effective transplantation requires an interdisciplinary team approach, supporting the transplant procedure in common processes for TOS and TPH, such as: immunosuppressive treatment, immune reconstitution, rejection, tolerance, risk of infection, transition to adult care and psychosocial well-being.

2. OBJECTIVE

This document aims to comprehensively cover the key aspects that define the PETER register and its functioning. Understands its characteristics, legal aspects, patients' rights, data protection, governance related to its operation and funding considerations.

3. SCOPE

This document is applicable to **each hospital (HCP) involved in the PETER registry. The responsible researchers shall ensure that the PETER registry is implemented in accordance with this protocol, following the instructions and procedures described in this document.**

4. PETER'S RECORD CONCEPT AND OBJECTIVES

The European Paediatric Transplant Registry (PETER) arises from the need to integrate the cross-sectional approach to paediatric transplantation and quality of life reports of patient-reported outcome measures (PROMs) (fig.1). PETER enables rational, efficient and interoperable access to information on all types of paediatric transplantation. PETER is based on a transversal approach regardless of the type of transplant, integrating variables from the different phases of the transplant process. In addition, it will increase knowledge about the transplant procedure in children, with the aim of detecting the determinants of the effectiveness of the transplant, which will allow the development of lines of research to improve the survival and quality of life of pediatric patients and their families.

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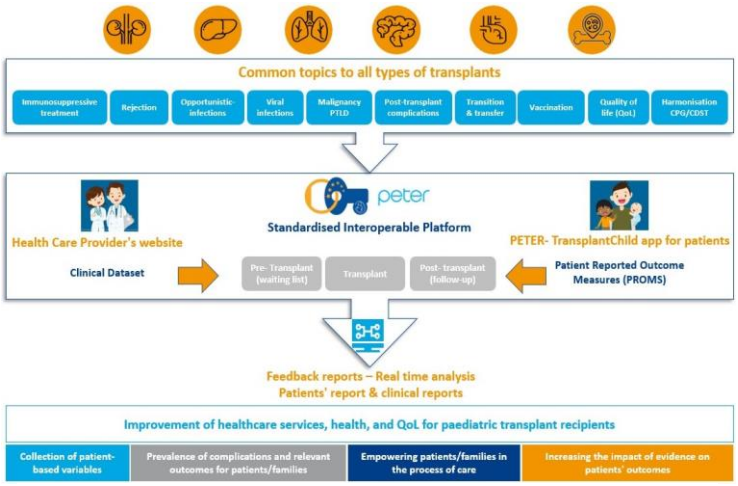

Figure 1: Peter's registration approach

The general objective is to describe the state of health of transplant patients of pediatric age, from their inclusion in the waiting list and during post-transplant follow-up, both from the clinical point of view and from their own (quality of life). Comply with the European standards of the *FAIR* principles by improving their searchability, accessibility, interoperability and reuse, and in full respect of current data protection policies.

The specific objectives are:

- Assess the long-term efficacy and safety of the transplant.
- Evaluate clinical outcomes, including graft survival, complications, and patient survival.
- Assess the quality of life of pediatric transplant recipients.
- Correlate changes during the transplant process with patients' quality of life.
- Identify areas of quality improvement and harmonization of clinical practice.
- Support the generation of knowledge about the pediatric transplant process and the promotion of research.

By meeting these goals, PETER aims to improve the care and outcomes of pediatric transplant recipients.

5. CHARACTERISTICS OF THE REGISTER

PETER is designed to prospectively collect clinical data from the pediatric transplant process, as part of patient management.

Data collection for PETER will not require additional hospital examinations, admissions or visits beyond the standard care provided. The interventions will be to collect health status data, already present in the clinical record, and the quality of life reported by the patient/parents.

5.1. Patient inclusion criteria.

Patients under 18 years of age who have received or will receive a solid organ or haematopoietic progenitor transplant may be included in the PETER registry from their inclusion in the transplant waiting list.

5.2. Patient exclusion criteria.

- Transplant recipients after age 18.
- Regular monitoring of transplantation outside the EU.
- Non-acceptance of informed consent.

5.3. Hospitals included in the register

The purpose of the PETER registry is to collect data from patients who meet the specified inclusion criteria.

These data are collected from hospitals belonging to the ERN-TransplantChild, as well as from expert hospitals not included in TransplantChild and through national and/or regional clinical networks in European countries.

As of August 2023, there are 40 ERN-TransplantChild HCPs located in 21 EU MS.

5.4. Data collection

The data collected shall not include demographic data or patient identifiers.

Each patient will receive a pseudonymized internal code according to the Xolomon platform system. PETER is working on the implementation of the EC-recommended ERDRI.spider (Secure*Privacy-preserving Identity management in Distributed Environments for Research)*pseudonymisation tool.

An online platform (Xolomon) with protocols ensuring the security of data entry shall be used for the collection of clinical data. Only users registered and authorised by the principal investigator as participants in the study may enter data on the platform.

Quality of life data will be collected through a mobile application designed by Xolomon. Patients will be provided with a username and password for the mobile app, which they will need to change at the first login. The information for the patient (QRs, username and password) will be generated from the web application by the researcher who has enrolled the patient.

5.5. Data to be collected

The core data elements shall include the set of common data elements for rare disease registration, developed by the JRC (https://eu-rd-platform.jrc.ec.europa.eu/set-of-common-data-elements) to address the specificities of paediatric transplantation, a complex condition, compared to rare diseases.

Following the objectives of the PETER registry, prospective data on patient characteristics, transplant data and outcomes will be collected. Post-transplant data will be recorded 3 months after transplantation and annually, until the transition to adult medical care is completed (fig.2).

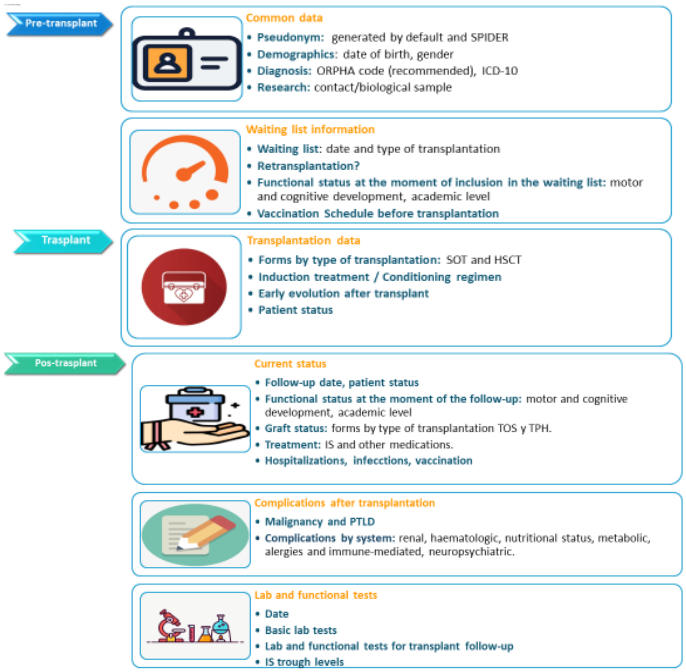

Figure 2: Data Required During All Phases of Transplantation

5.6. Data storage

PETER is a centralised register. All data is transferred to the central PETER database using the Xolomon Software. The Software, developed by Xolomon Tree S.L (info@xolomon.com), is the electronic data capture (EDC) and transfer software chosen to develop the PETER. Xolomon is a SaaS (Software*as a Service)*EDC (Electronic*Data Capture)*software, and is a*multi-tenant web application.* The software infrastructure is hosted on Microsoft Azure. The study data will be stored on a secure Microsoft Azure server with an appropriate level of encryption based on the Azure 'Western Europe' region. Although Microsoft does not disclose the public location of its servers, the data centers that support and host the Western European region are located in Ireland (Dublin area).

5.7. Data analysis

The statistical analyses will be carried out on the basis of a study protocol. Consultations will be carried out, in collaboration with clinical experts, to consult the PETER database, in order to generate the descriptive statistics and relevant information necessary to plan the statistical analyses provided for in the study protocol. The registry data shall support observational studies based on secondary use of available data, in accordance with applicable EU and national legislation, and in the context of the European Health Data Space and JRC/EU RD guidelines and guidance.

5.8. Data management and quality

The PETER registry has a Quality*Data Assurance Plan (QDAP)* that comprises governance structures, policies, procedures and protocols for managing data and information quality, as well as ethical, legal, security and privacy considerations.

The QDAP includes the controls established in the platform itself to guarantee the quality of the data, as well as the Audit and Quality Assurance plan to evaluate and monitor the measures established in the QDAP.

5.9. Registry integration and interoperability

The PETER registry is registered on the EU Rare Diseases Platform (EU RD), ERDRI.dor – European Registry Directory (https://eu-rd-platform.jrc.ec.europa.eu/erdridor/register/list/place/ES). Synergies with other ERN registers will be fostered through the ERN Registers Working Group and the ERICA project.

The PETER register shall be interoperable with the European platforms.

6. REQUIREMENTS FOR THE INTEGRATION OF PATIENT DATA INTO THE REGISTRY

6.1. Prior approval by local Hospital Ethics Committees

The registration protocol will be submitted to the Ethics Committees (EC) of the hospitals involved. In addition, the EC will pre-authorise any research carried out using the PETER data.

6.2. Informed consent

The prior acquisition of the informed consent of the patient/guardian prior to their inclusion in the registry is the legal basis of the registry.

Researchers should explain to each patient (or legal representative) the nature of the PETER record, its purpose, the type of data collected, the expected duration, and the potential risks and benefits involved. Each patient should be informed that consent to have their data in the PETER register is voluntary, that it can be withdrawn from the register at any time, and that the withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician. Informed consent shall be given by means of a standard written statement, using non-technical language.

The patient/guardian must read and consider the statement before signing and dating it, and must receive a copy of the signed document to keep it. If the subject is unable to read or sign the document, it may be presented orally or signed by the subject's legally designated representative, if witnessed by a person not involved in the record, indicating that the patient was unable to read or sign documents. Information about a patient cannot be entered in the PETER register before informed consent has been obtained. Informed consent is part of the protocol and must be submitted by the researcher to the local EC.

7. DATA PROTECTION

Since personal data will be recorded and stored in pseudonymised format in the central PETER database using Xolomon software, all parties involved in the development of the registry will

maintain strict confidentiality to ensure that the personal privacy and privacy of the families of patients participating in the registries is not violated.

The data will be processed exclusively by authorised personnel involved in the development of the PETER register. Access to computer systems and the premises where they are stored will be controlled by appropriate security measures that comply with the requirements of privacy regulation.

The processing of personal data of patients participating in the PETER registry, and specifically in relation to data related to consent, will comply with local privacy legislation and the General Data Protection Regulation 2016/679 (GDPR) of the European Union.

8. GOVERNANCE

According to the QDAP, governing bodies are described in the PETER mandate (ToR), which defines the PETER Board as the highest governing body (included in the highest governing body of the ERN TransplantChild), **led by the PETER registry coordinator (Dr. Francisco Hernández. Hospital Universitario La Paz)**. In addition, other governing bodies, such as the Executive Committee and the Data Access Committee, have been established to oversee the development of the registry and data access requests. The governance structures of PETER are shown in the figure below (fig.3).

The PETER Board is supported by a Technical Secretariat of TransplantChild, located at Paseo de la Castellana 261, 28046, Madrid, Spain (contact: Telephone number: +34 917.27.75.76; e-mail; coordination@transplantchild.eu).

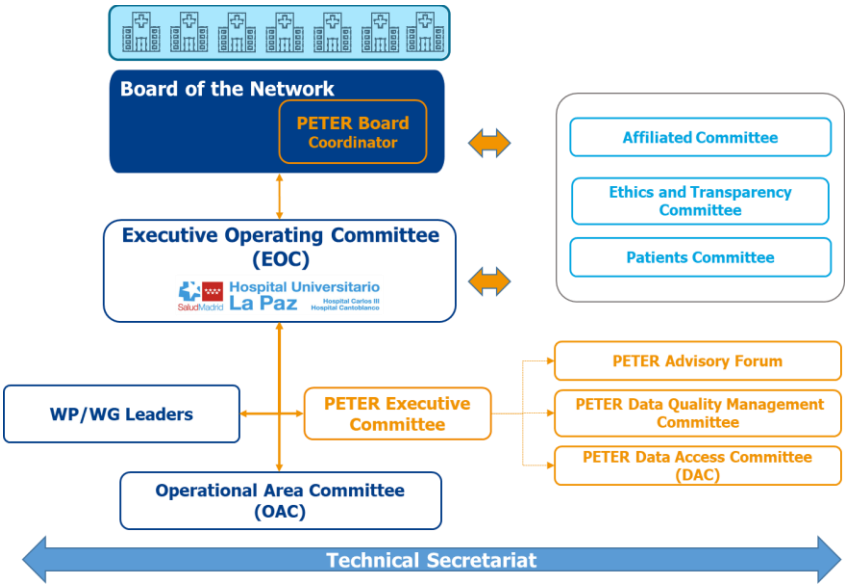

Figure 3: Governance structures of the PETER registry in the framework of the ERN TransplantChild.

9. FUNDING

The registry created was co-funded by the European Union Health Programme (2014-2020). Consumers, Health, Agriculture and Food Executive Agency (CHAFEA). Grant agreement number: 947629 – PETER – HP-PJ-2019. Grant of EUR 199 981.42.

10. ENTRY INTO FORCE, REVISION AND AMENDMENTS

This protocol will enter into force once approved by the PETER Board.

This protocol shall be reviewed and updated, if necessary, annually.

However, any member of the PETER Board may propose amendments to this protocol for justified reasons.

In this regard, any proposal shall be accompanied by an explanatory report on the causes and scope of the proposed amendment. Proposals will be submitted by the PETER registry coordinator at the regular meetings of the PETER Board and decisions and agreements will be recorded in the minutes of the meeting.

Any amendment to the protocol shall be communicated to the members of the network and uploaded and disseminated by the coordination centre.

Each member of the network shall comply with the rules and principles set forth in this protocol.