Short Version of the

EPTRI

Conceptual Design Report

1. Background

Evidence exists that children receive new and innovative therapies with huge delay respect to other populations or in many cases are excluded from any improved treatments. Moreover, the use of existing therapies that have not been studied in children results in off-label use in 30% to 80% of all cases, depending on children's age and therapeutic category of the drug. This situation exposes children to serious risks for their wellbeing and also creates discrimination against a vulnerable population, thus representing a social and ethical issue.

To close this gap babies, children and young people should be part of the research plans in order to meet their specific needs and also to address the needs of society.

A gap in basic science related to the human development mechanism is one of the reasons for a perceived high risk in developing novel drugs or therapies directly for children and for inducing pharmaceutical industries and regulatory authorities to extreme caution. In addition, the differences in organs size and maturation in the population lead to the need to stratify the paediatric population in at least five sub-populations: i.e. pre-term newborn infants, term newborn infants, infants and toddlers (from 28 days to 2 years), children (from 2 to 11 years) and adolescents (from to 12 to 17 years), reducing the size of each target sub-population and making complex both drugs development and medicinals administration.

EPTRI (European Paediatric Translational Research Infrastructure), the proposed new Research Infrastructure (RI) dedicated to support the research on human development, is aimed to enhance technology-driven paediatric research.

EPTRI can close the gap between innovative technologies and paediatric drug development processes, using an original scientific approach that is paediatric patients-centred and facilitate the researchers and increase the competitiveness of the European Research Area (ERA), allowing access to specialised resources and expertise.

This project has received funding from the European Union's Horizon 2020 research and innovation Programme under Grant Agreement n. 777554

ID-EPTRI – European Paediatric Translational Research Infrastructure
Coordinated by CVBF - Via N. Putignani, 178 – 70122 Bari (Italy)
Email: info@eptri.eu – Tel: +39 080 97 51 974 – www.eptri.eu

EPTRI has been funded by the European Union as a Design Study in the Horizon2020 Program under the INFRADEV-01-2017 call for proposals (Grant Agreement No. 777554).

The EPTRI Conceptual Design Report (CDR) has been prepared by the members of the Consortium, composed of research centres and universities from 16 EU Member States, 4 associated countries and Russia, consulting a wide group of scientists representing world-class expertise in paediatric basic pre-clinical and translational research. It can provide the decision makers in Europe and all the relevant stakeholders with relevant information for the establishment of such a highly innovative RI to support European science, industry and society.

2. EPTRI Concept

EPTRI is focused on paediatric medicines discovery and development to support the paediatric research community in the conduction of paediatric preclinical research activities and translation in paediatric clinical phases.

Support will be also provided in terms of access to key technologies (from biological, technological and data science advancements) specifically implemented for or adapted to the paediatric settings, either available in EPTRI or provided in collaboration with existing ESFRI-RIs.

EPTRI general objectives are:

- To extend the knowledge of the normal and pathological human development process in order to move from the current approach based on adult drugs that are administered off label to children to a new approach characterised by medicines studied and marketed for children, and consequently to reduce the existing gap on medicines availability for children.
- To involve multiple experts and competences to create multidisciplinary scientific and technology groups working to integrate basic science with key technologies (from biological, technological and data science advancements) to drive innovative medicines and health products discovery and development.
- To enhance clinical research and paediatric medicines availability contributing to creating a unique paediatric research framework.
- To accelerate the paediatric drug development processes from medicines discovery, biomarkers identification and preclinical research to developmental pharmacology, age tailored formulations and medical devices, with the final goal to facilitate the translation of the acquired new knowledge and scientific innovation into paediatric clinical studies phases and medical use.

The EPTRI concept has been designed and simulated during the three ID-EPTRI project phases to prove it being feasible, acceptable and long term sustainable.

During the **Context Analysis phase**, the Paediatric Scientific Community have been enquiring on the perceived values and the possible gaps to be covered by the proposed RI. A total of 259 Institutions, often grouping more than one research group, distributed across 29 countries in the European area and encompassing a total of 330 research units **operating in the field of paediatric medicine reserach**, answered to the EPTRI questionnaire and described their specific field of activities, scientific competences, human resources, tools, facilities, services available, as well as the perceived gaps and obstacles to paediatric research (Figure 1).

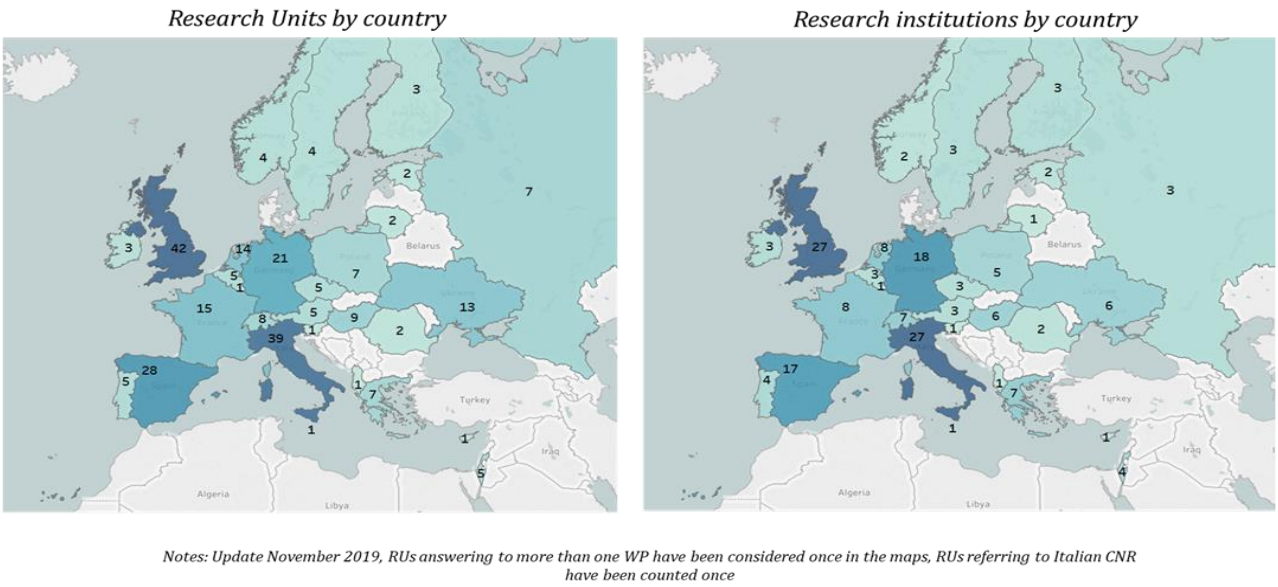

Figure 1. Map of Research Institutions and Units in EPTRI

Moreover, potential users of EPTRI have been identified and an online survey of users has been delivered with the aim to identify the nature and extent of the needs for integrated approaches to paediatric drug development. This users' survey has been crucial to acquire preliminary ideas and feelings from 337 users, as well as information on their interests and needs in terms of access, costs, barriers and integration between preclinical and clinical paediatric research sector. The survey has also investigated the willingness of some users to be engaged in running pilot activities intended to test EPTRI's feasibility, and has highlighted the strong recommendation to develop new and complementary areas of research, such as age-tailored paediatric medical devices, advanced therapies and artificial intelligence for children health.

In the **Operational phas**e the results from the context analysis have been used to draft the EPTRI Technical Design and the Conceptual Design Report (CDR), describing aims and scientific goals, organisation, operation, governance, the IT-architecture model, services to be provided and business plan as preliminary elements.

This project has received funding from the European Union's Horizon 2020 research and innovation Programme under Grant Agreement n. 777554

Finally, several **Feasibility Studies (FSs)** have been developed, as case-studies that would provide information about services/technologies that EPTRI could offer to support the researchers in the translational phase, and aimed to test at different level the acceptability, feasibility and sustainability of the future EPTRI.

3. EPTRI Structure

EPTRI will be a Distributed Research Infrastructure, to connect many different resources dislocated across Europe and presenting their services through a Single Access Point (SAP).

It will have based on a **HUB and SPOKE** model, with a Central Hub and several Spokes. The Research Units, identified during the ID-EPTRI context analysis phase, will be aggregated according to both geographical distribution in National Nodes (***National EPTRI Infrastructures***) and in scientific fields of activities (***Thematic Research Platforms***), as shown in the figure 2.

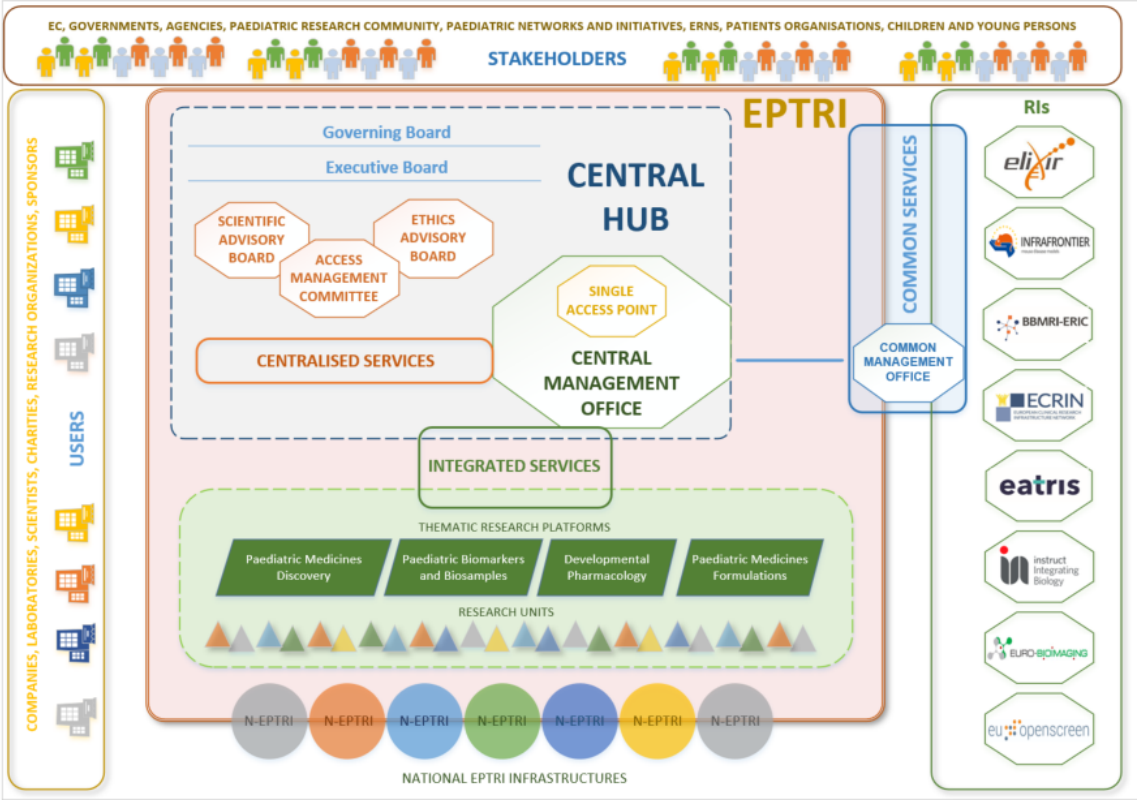

Figure 2. EPTRI organisation

A strong IT infrastructure will serve as support to the different EPTRI activities and to provide access to EPTRI services. The IT platform will also act as a direct channel of communication to ensure internal and external connections among the EPTRI operational levels, stakeholders and users.

The C-Hub composition will include two Decisional Boards, the Governing Board (GovB) and the Executive Board (ExeB), two consultancy Boards, the Scientific Advisory Board (SAB) and the Ethics

This project has received funding from the European Union's Horizon 2020 research and innovation Programme under Grant Agreement n. 777554

Advisory Board (EAB), and an operational Central Management Office (CMO). The CMO will manage interaction with the EPTRI Spokes composed by the many Research Units (aggregated in Thematic Research Platforms and National Nodes) that, thanks to their proper organization, expertise and resources, will make consistent the functioning of the research infrastructure providing services.

4. EPTRI Services

Through the SAP, users will have access to ***three types of services***:

a) Centralised services, located at Central Hub level;
b) Integrated services, provided by the RUs organised in TRPs;
c) Common services, performed in collaboration with other Research Infrastructures.

Centralised Services

Centralised services are provided by CMO and experts from EPTRI partner Institutions covering transversal relevant users' needs. They are services which for their own nature are best supplied in a centralised manner and are described in the table 1 below.

Table 1. Centralised Services

Centralised Services
• Document Repository and e-Library • Access to e-learning and training • Support in scouting and application to funding opportunities • Advice on the design and requirements of not clinical specific studies/experiments and on the innovation pathway for specific products • Advice on translation to clinical phases

Integrated Services

Integrated Services will be provided through the Thematic Research Platforms in which the RUs providing key enabling technologies and expertise are grouped and operate under a specific framework agreement, using their own scientific competencies, facilities and equipment.

The main research areas and related integrated services that will be offered by the Thematic Research Platforms are summarized in the following table.

This project has received funding from the European Union's Horizon 2020 research and innovation Programme under Grant Agreement n. 777554

Table 2. Integrated Services

Paediatric Medicines Discovery TRP	**Paediatric Biomarkers and Biosamples TRP**
• In vitro screening of novel drugs using paediatric cellular targets • In vitro pre-clinical studies (effect, efficacy, biomarkers, etc.) in paediatric cell models • Access to the neonatal and juvenile animal models to screen novel drug for a paediatric specific target • Access to the neonatal and juvenile animal models to perform preclinical studies • In silico screening of novel drugs for specific paediatric targets • In silico prediction of ADME properties & toxicity for new molecular entity of paediatric interest	• Access to/deposit of annotated paediatric biological samples • RNA transcripts and DNA variants biomarker identification and characterisation in paediatric samples • Protein biomarker identification and characterisation in paediatric samples • Metabolite candidate biomarker identification and characterisation in paediatric samples • Bioinformatics for the analysis of the data generated by omics platforms • Verification in paediatric samples of the presence and levels of biomarkers (metabolites, proteins, RNA transcripts, DNA variants)
Developmental Pharmacology TRP	**Paediatric Medicines Formulations TRP**
• Microdosing to establish the "in vivo" PK profile of the new drug • In vitro models to study ontogeny of drug disposition • Placental studies • In vivo toxicity juvenile animal studies • Paediatric ADME, modelling and simulation • Sensitive analytical methods adapted to paediatrics	• Pre-formulation advice and Pre-formulation studies • Formulation of drug for paediatric use for enteral and non-enteral routes of administration • Assessment and design of drug delivery systems for enteral and non-enteral routes of administration • Paediatric in vitro and in vivo palatability assessment

<u>Common Services</u>

EPTRI aims to develop 'common services' in collaboration with other RIs dealing with biomedical and transnational research and other international and national infrastructures to harness efficiency and delivery of paediatric research activities and services and to strengthen collaboration within the scientific community. Common services for which a collaborative framework has been already considered are:

- ELSI paediatric service
- Paediatric data interoperability service

This project has received funding from the European Union's Horizon 2020 research and innovation Programme under Grant Agreement n. 777554