EPTRI

EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH INFRASTRUCTURE

STAKEHOLDERS ROUNDTABLE
27 March 2019, Madrid
EPTRI 3rd General Assembly Meeting

SUMMARY REPORT

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Representatives from Paediatric Networks, Research Infrastructures (RIs), European Reference Networks (ERNs), Charities, Patients' Associations, Young Persons Advisory Groups (YPAGs), Companies' Federations, Regulatory Agencies, Governments, Authorities had a very productive discussion during the Stakeholders Roundtable held in the framework of the 3rd General Assembly of the EPTRI (European Paediatric Translational Research Infrastructure) project, on March 27th, 2019, in Madrid at the Ministry of Health, Consumption and Social Welfare.

Seventeen Stakeholders were asked to provide their views on how to aggregate the huge paediatric research capacities existing in the EU to produce enhanced results through collaboration. To this aim, they briefly presented their Institutions and answered to the following three questions:

1. *Do you think that EPTRI survey has provided reliable information to identify the 4 thematic platforms foreseen in the project in term of composition and organization? Which Platform do you consider more strategic for your country/scientific domain? (Please include consideration on the perceived needs and wants, barriers and facilitators to allow paediatric research units to form research platforms, knowledge and funding gaps).*
2. *Do you agree with this vision of EPTRI and the attributed relevance to the issues of paediatric medicines development? (please include consideration on priorities and the relevance for stakeholders, what is the role you can act in this scenario).*
3. *How do you consider the importance/potential impact of EPTRI on the communities and on the European scenario? Are you willing to support the scientific community of reference to reinforce their action and influence through EPTRI? How do you suggest to achieve it? What is the contribution that you can bring?*

A one hour debate followed the presentations and was conducted by the EPTRI Coordinator, Donato Bonifazi.

The feedback received from the Stakeholders is crucial to confirm the strategic relevance of the scientific domains identified by EPTRI through its thematic platforms and to define the strategy to design the new paediatric Research Infrastructure. Important advices were provided on how EPTRI can represent the scientific community that is still "underwater" in terms of organisation, governance and funding and not yet represented in any of the existing Research Infrastructures in the Biomedical field.

EPTRI will be a space where dispersed and disaggregated paediatric research expertise can be linked and integrated through increased collaboration and sharing of facilities, resources and related services and to propose solutions for the benefit of knowledge, economic development and ultimately patients' health.

PARTICIPANTS

Anna Ambrosini, Head of the Neuromuscular Research Programs, Research & Development of Telethon Foundation; Scientific Director of the Italian Research Foundation for Amyotrophic Lateral Sclerosis (AriSLA), Italy

Fondazione Telethon is an Italian non-profit organisation founded in 1990 as a response to the appeals of people with rare diseases. The mission of Telethon is fostering research that leads to cures for rare genetic diseases.

Toni Andreu, Scientific Director of the European Advanced Translational Research Infrastructure in Medicine (EATRIS-ERIC), the Netherlands

EATRIS is a non-profit European Research Infrastructure Consortium (ERIC) that plays a fundamental role in the advancement of knowledge and technology in translational research and drug development and seeks solutions to the many problems faced in the development of new therapies.

Dimitrios Athanasiou, Patients Representative at the PDCO EMA, EPAC/TAG EURORDIS, UPPMD, MDA Hellas, Greece

EURORDIS-Rare Diseases Europe is a unique, non-profit alliance of 851 rare diseases patient organisations from 70 countries that work together to improve the lives of the 30 million people living with a rare disease in Europe.

Eva Bermejo-Sánchez, Chief of Area at the Research Institute for Rare Diseases (IIER), ECEMC's Scientific Coordinator, the Research Center on Congenital Anomalies (CIAC), Instituto de Salud Carlos III, Spain
The **ECEMC** (Spanish Collaborative Study of Congenital Malformations) is a clinical network composed by more than 300 paediatricians working at paediatric units in hospitals with delivery units. ECEMC has been working since year 1976, using a common methodology for the registration and diagnosis of infants born with congenital anomalies.

Joana Claverol Torres, Member of the Coordination team of the European Young Persons' Advisory Group network (eYPAGnet), Spain

The European Young Person's Advocacy Group (**eYPAGnet**) is a virtual consortium of existing YPAG's in Europe, established to support the development of new YPAG's within Europe, and to provide the necessary infrastructure to support meaningful and valued involvement of children and young people (CYP) in clinical trial design and health research.

Martine Dehlinger Kremer, President of the European Clinical Research Organization Federation (EUCROF), Germany

EUCROF is a non-profit organisation founded in 2005. Its mission is representing the interests of CROs towards: regulatory bodies, pharmaceutical, biotech, medical device industry, healthcare related industry within the field of clinical research, patients associations. EUCROF goal is to promote Clinical Research by improving the knowledge, competence and skills of CROs.

Ruben Diaz Naderi, General Secretary of the European Children's Hospitals Organisation (ECHO), Spain

European Children's Hospitals Organisation (**ECHO**) advocates for children's health and their access to the best quality care through the collaborative work of children's hospitals. ECHO's vision is to be a united voice of children's hospitals promoting children's rights, holistic care for children, professional excellence and friendship among people of different countries.

Krisztian András Fodor, Head of the Department of Strategy, Development and Methodology of the National Institute of Pharmacy and Nutrition (OGYÉI), Hungary

The National Institute of Pharmacy and Nutrition (**OGYÉI**) is the licensing authority for pharmaceutical matters. The main activity of OGYÉI is to provide the public with safe, effective and quality medicines in accordance with the regulations. OGYÉI is the national organisation of official drug controlling tasks and it is also a research methodology Institute of Hungary.

Moshe Gavish, Senior Scientist at the Technion-Israel Institute of Technology, Israel

Technion-Israel Institute of Technology is a science and technology research university, among the world's top ten, dedicated to the creation of knowledge and the development of human capital. Technion-Israel Institute of Technology has the technical facilities to support translational research for the development of medicines for Child's Diseases.

César Hernández Garsía, Head of Department of Medicines for Human Use of the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Spain

The Spanish Agency of Medicines and Medical Devices (**AEMPS**) is a regulatory agency that acts as the highest sanitary authority in terms of medical safety on medicines. The Agency is responsible for the regulation and authorization of clinical trials; the authorization of clinical laboratories; the development of the specific rules to ensure the quality of the medical products and inspect all sanitary products.

Victor Kazantsev, Vice Rector National Research Lobachevsky State University of Nizhny Novgorod (UNN), Russia

National Research Lobachevsky State University (**UNN**) is a large research multidisciplinary university. It is proud of its international reputation and centennial history. One of the advantages of the University is the capacity to conduct interdisciplinary research and produce innovations on the intersection of different fields of science.

Panos Macheras, Head of the PharmaInformatics Unit at ATHENA Research and Innovation Center in Information Communication & Knowledge Technologies, Greece

Athena Research and Innovation Centre (**ARC**) is a scientific research and technological organisation, functioning under the auspices of the General Secretariat for Research and Technology (Ministry of Education). It comprises 3 research Institutes: Institute for Language and Speech Processing (ILSP), Institute for the Management of Information Systems (IMIS), and Industrial Systems Institute (ISI).

Graziano Pesole, Italian National Research Council (CNR), Director of the Institute of Biomembranes, Bioenergetics and Molecular Biotechnologies, Head of the Italian Node of ELIXIR, European Bio-Informatics Infrastructure, Italy

ELIXIR, the distributed infrastructure for life-science information, is an intergovernmental organisation that brings together life science resources from across Europe. These resources include databases, software tools, training materials, cloud storage and supercomputers. This infrastructure makes it easier for scientists to find and share data, exchange expertise, and agree on best practices.

Nicola Ruperto, Coordinator of the Paediatric Rheumatology INternational Trials Organisation (PRINTO), Italy

PRINTO is a not for profit, non-governmental, international research network founded in 1996. PRINTO includes 90 countries, 653 centres worldwide with 1374 members, with the goal to foster, facilitate and co-ordinate the development, conduct, analysis, and reporting of multi-centres, international clinical trials and/or outcome standardisation studies in children with paediatric rheumatic diseases (PRD).

Franz Schaefer, Coordinator of the European Reference Network for Rare Kidney Diseases (ERKNet), Germany

ERKNet is the European Reference Network for Rare Kidney Diseases, a consortium of 38 expert pediatric and adult nephrology centers in 12 European countries providing healthcare to more than 40,000 patients with rare disorders of the kidneys.

Mark Turner, Conect4Children (c4c) Scientific Coordinator, University of Liverpool, UK

c4c (conect4children) is a large collaborative European network that aims to facilitate the development of new drugs and other therapies for the entire paediatric population. It is a pioneering opportunity to build capacity for the implementation of multinational paediatric clinical trials whilst ensuring the needs of babies, children, young people and their families are met.

Amelia Martín Uranga, Responsible of the Innovative Drugs Platform of Farmaindustria, Spain

Farmaindustria is the National Trade Association of the Spanish based pharmaceutical industry. It gathers most of the R&D based pharmaceutical companies established in Spain, representing nearly 100% of prescription medicines sales in Spain. Farmaindustria main role is to support different actions regarding pharmaceutical R&D through several initiatives in pediatric field.

DISCUSSION

In this Summary Report we have argued that **EPTRI will be focused on building a Research Infrastructure where meaningful and relevant pre-clinical and other technology-driven research fields that underpins clinical research is performed, making sure that the goal of the research is to answer patient unmet needs.**

This is a societal challenge that will require a coordinated effort of existing capacities not only within the academic community but also the synchronization with other stakeholders relevant in the translational medicine process, industry, clinical networks, patient community, policy-makers and regulators.

Wide collaboration

The importance of promoting coordinated joint actions to raise awareness on EPTRI and put together the disaggregated paediatric expertise was highlighted by several stakeholders:

- "*Important will be to widely promote the outcome of the EPTRI achievements. A European organisation such as EUCROF would be in a position to support dissemination of information*", M. Dehlinger Kremer (EUCROF);

- "*ERN WG Research could efficiently disseminate standards and concepts across pediatric ERN units*", F. Schaefer (ERKNet);

- "*ECHO and its membership can support advocacy efforts to highlight EPTRI's mission*", R. Diaz Naderi (ECHO);

- "*It is Important to enhance the EPTRI National systems and nodes. We will invite the Russian Academy of Sciences to contribute to this aim*", V. Kazantsev (UNN);

- "*Technion can contribute to EPTRI by identifying facilities and involve experts in directions that match the goals of EPTRI. Our services are comprehensive, reliable, and attentive to the needs of the researchers and their projects and can be of great value for EPTRI.*" M. Gavish (TECHNION).

Without an equivalent initiative in the EU and with a growing demand from the scientific and industry communities for a mechanism bringing together the fragmented paediatric research to promote innovative medicines in this sensitive and neglected population, EPTRI can offer a meaningful answer given that it will also develop a mechanism that will bring ROE (Return on Engagement) for the Paediatric Patient Community. **Paediatric research has its specificities and is moving forward to have an entity of reference that will allow harmonization, and faster progress. This entity is EPTRI.**

Strategic will also be the collaboration with some existing Research Infrastructures. "*EATRIS and other Biomedical RIs can provide assets and capacities to energize the process of developing new drugs for diseases that affect children and together with the EPTRI community create an effective and efficient problem-solving approach*" pointed out T. Andreu from EATRIS.

In this same way, "*The European Infrastructure for biological data can provide support and links on many fronts in EPTRI: best practices, IT infrastructure, -omics data processing and managemet expertise, training, knowledge in relevant topics as human data and rare diseases*" suggested G. Pesole from ELIXIR.

Public and Private Partnership

EPTRI is particularly needed considering the largely recognised principle that in research children cannot be addressed with adult instruments. Research in children needs to account for growth, development, and with the ethical imperative to minimise the impact of research in children and young people.

EPTRI innovative approach is expected to maintain paediatrics at the forefront of the advancement of research as well as to be translated in increased knowledge and competitiveness at European Industry level.

In this sense, A. Martín Uranga, representative from FARMAINDUSTRIA, recognised the relevance of EPTRI to improve the paediatric research and pointed that "*Industry is happy to work with EPTRI in increasing European capabilities and expertise in the field of Paediatric research, most important would be a clear mapping of available capabilities and to increase reach of that expertise. Industry might also be willing to support capability building through specific initiatives and public-private partnership models*".

The four EPTRI thematic platforms i) Human Development and Paediatric Medicines Discovery, ii) Paediatric Biomarkers and Biosamples, iii) Developmental Pharmacology, iv) Paediatric Medicines Formulations and Medical Devices, that will address the EPTRI services with specific paediatric expertise and capability, are those strategically necessary to set up the new research infrastructure and at the end meet the needs of the community of paediatric patients.

The future of EPTRI will be strongly dependent on the final design of the RI and the architectural process that will lead to the development of solutions for the needs of the paediatric patient community. In a transition period towards a new research agenda centred on tackling societal challenges through an alignment of the current capacities of the ERA (European Research Area), degranulating the current ecosystems of scientific and technological capacities, EPTRI has an outstanding opportunity to provide proof of concept that a solving challenge-oriented strategy can, indeed, synchronize what is already existing to maximize the impact of the outcomes for creating novel solutions in the process of developing new drugs for diseases that affect children. As Mark Turner from c4c pointed out "*the c4c experience in the paediatric clinical trials performance leads to suggest to look at the process map first. Then look at the gaps and the capabilities, have a huge discussion and design the organisation governance around a shared vision of what is needed*".

Therefore, **a dedicated paediatric infrastructure integrating the different research facilities and expertise addressed to paediatric medicines development will help in the process to reduce time and increase the outcomes, towards a faster translation into the clinical phase and the therapeutic use.**

Patient centered approach

EPTRI takes care of the voice of the patients and their families with dedicated tasks to facilitate the consultation and involvement of children and young patients and to ensure that the design of the future Research Infrastructure (EPTRI) is patient centered. Meaningful and early involvement of patients is, indeed, the facilitator that can help identify the real needs, connect and advocate for the importance of EPTRI on national and international levels, build awareness and contribute to the attractiveness of the Project to the stakeholders. The importance of involving paediatric patients was supported by eYPAGnet - "*We can bring the availability of patient groups that are already contributing the development of pediatric research projects to ensure that the patients' needs are always considered including in the pre-clinical setting.*" (J. Claverol Torres) and EURORDIS - "*Provide our patient networks and advocacy groups resources to ensure and strengthen the immediate development of the key priorities and promote sustainability.*" (D. Athanasiou).

EPTRI will be an Infrastructure where the research data is Findable, Accessible, Interoperable and Reusable (FAIR) to be used for the benefit of the community. This will bring trust to EPTRI but will also provide access to the vast resources of various types that the patient community can offer. In this sense, EPTRI will bring benefits on children's health establishing an efficient framework to speed-up the drug development process in paediatrics and including top-level innovations in research for children's health. This will end in an increased offer of appropriate efficacious and safe medicines for children of all ages (from neonates to adolescents).

"*We can assist European industry for the development of paediatric formulations via our expertise in pharmacometrics while we can assist the scientific paediatric community in drug dosage regimen design. We can collaborate for the development of novel milk based formulations for paediatric use e.g. antiretrovirals.*" P. Macheras (ARC).

Regulatory standards

Another key aspect arisen from the discussion is the need for EPTRI to promote and work with a solid scientific paediatric community that would provide a robust environment for developing innovative medicines and support broad portfolios. Connections between EPTRI and clinical networks would need to be established and maintained throughout the time. All these collaborations would need to be supported by Regulatory Authorities and other Government Agencies.

Indeed, having a robust preclinical mapping will allow to create partnerships with sponsors and specialised networks to develop clinical trials. Sponsors work on both internal and external innovation, so we consider them key to reinforce and promote the specialization through these kinds of networks. "*I would like to highlight the importance of having any of the EPTRI four thematic platforms oriented to produce results that may really impact clinical practice by providing evidences that might be used for regulatory purposes. From our regulatory perspective, it is much easier to tackle stakeholders' needs from a general perspective (and then go to the particulars of research groups)*" highlighted C. Hernández García from AEMPS. In Europe nearly 20% of the population is represented by minors and their care is one of the most important priorities and challenges for Europe. It's essential the development of evidence-based paediatric medicines and treatment strategies. Nowadays around the 50% of the medicines addressed to children and young patients have not been tested specifically for them. For this reason, it's strategic the development of the research infrastructures that can reduce this problem, developing paediatric research from the early phases to the paediatric formulations. Moreover, innovative medicines will have a lifelong effect and a cost-efficient benefit for the whole community. **Advancement of innovative medicines will also require thorough knowledge of regulatory issues**, which often is considered a major obstacle. Many regulatory agencies in Europe now offer various types of scientific advices to various stakeholders, including academic research groups.

"*Hungary can provide regulatory support for any development project, as paediatric experts are well represented among the assessors. One specific suggestion is to launch EU supported nationwide paediatric oncology projects to understand the biology underlying the cancer genome and the function of unexplored noncoding regions and structural variation in the human genome*" pointed out K. András Fodor (OGYÉI).

Some coordination, or at least some participation or input, should be sought from the European Medicines Agency (EMA), since it created and operates the Paediatric Committee to provide objective scientific opinions on paediatric investigation plans (PIPs) for medicines to be used in children. Moreover, the interaction with EMA might have an impact on the regulatory aspects.

Harmonization is essential especially for complex research and development programs, where standardized methodologies should be used. In this respect regulators also have a key role in EPTRI as they can advise developers to use the best possible approaches.

Integrating paediatric research

EPTRI will bring a positive impact on the scientific community, as it is expected that, following the rising integration of several isolated research units, the scientific relevance of the paediatric research at specific and global level will increase. EPTRI is also expected to positively impact on the social and ethical aspects, since it will address the theme of research for a vulnerable and neglected population.

Reduced fragmentation through harmonized procedures will deliver in the medium/long term benefits for the public. Infrastructure elements should be focused on specific paediatric areas to avoid redundancy and duplication of services provided by other research infrastructures.

It is important to harmonise and build synergies between EPTRI and other existing efforts, which may not be dedicated exclusively to paediatric research, but have already mapped relevant resources (es. INFRAFRONTIER, EATRIS, BBMRI, EJP-RD, etc.). One relevant field is the rare diseases where networking and sharing of facilities is essential.

Perceived needs identified for research on rare diseases that can be addressed by EPTRI are: i) preclinical confirmation of results obtained in Proof of Concept (POC) studies (preclinical trials, data reproducibility in animal models confirmed by GLP laboratories); ii) drug delivery (preclinical and clinical); iii) PK and toxicology studies (going translational from preclinical into clinical steps, or repurposing from adult to pediatric use); iv) drug manufacturing and formulation.

A. Ambrosini (Telethon) supported this vision underling that "*We operate in the rare diseases field. Rare diseases have often pediatric onset and can be very severe and neglected. Addressing them to increase knowledge and seeking a cure is a relevant ethical issue.*". Also E. Bermejo-Sánchez (ECEMC) offered support from her Network to "*reinforce actions that deserve further developing, especially in the field of birth defects and rare congenital anomalies, as well as foetal medicine. Also, members of ECEMC´s Clinical Network, of which I am Scientific Coordinator from IIER-ISCIII in Spain, could be interested in collaborating in some specific initiatives, since most of them are paediatricians (also with the participation of some obstetricians).*"

Paediatric cancer medicines discovery is also considered very relevant for EPTRI. Research performed over the last several decades has led to an increased understanding of the genetics of cancer. The clinical application of this knowledge for paediatric cancer has lagged behind studies performed for adults.

To truly achieve personalized medicine in paediatric oncology, it is necessary to be able to determine if a child is genetically predisposed to develop cancer. In addition to tumour testing, germline testing that uses a sample of a patient's blood, is critical for identifying those children who have a genetic risk for developing cancer in the future. Besides benefiting the patient, this information has implications for the entire family, since an abnormality that is passed down from parent to child can also raise the risk of developing cancer in siblings.

As a result, nationwide, large-scale pan-cancer sequencing studies have to be launched to delineate additional mechanisms that appear to be uniquely important in the development of paediatric cancers.

CONCLUSIONS

Is the need of the paediatric research community better covered by a platform-oriented structure or by a program-oriented organization? This is a key question for creating a paediatric patient-oriented process, particularly considering that many services and capacities identified in the EPTRI survey are relevant also for other RIs.

The sheer complexity and specialisation of science today means that attitudes of openness and collaboration are not a nice complement, but rather a critical factor for success. As a matter of fact, EPTRI will be complementary to the other existing Biomedical Research Infrastructures and will act as a 'Paediatric Common Service' in the ESFRI (European Strategy Forum on Research Infrastructures) scenario. **EPTRI will represent the system resulting from the existing competences developed at pan-European level which have not been integrated yet in a structured paediatric research plan and system and are currently disaggregated and disperse in different contexts.**

EPTRI final aim is to realise an integrated system in order to bring together all these paediatric activities and technologies with a big impact on preparing clinical research in so producing a huge acceleration and qualification of procedures for the development of new medicines for children.

From the debate, we can conclude that:

- it is possible to close the gap between innovative technologies and paediatric drug development process;
- the advancement of innovative technologies in the paediatric pharmacology and preclinical phases will contribute to speed up the paediatric clinical phases and the availability of new medicines for children;
- the collaboration with other RIs having relevant technologies is key to identify which gaps require to be covered with specific paediatric competencies;
- focus on the scientific domains identified by the EPTRI thematic platforms can effectively meet the needs of patients and their families, public authorities, academia, clinical networks and industrial companies, in order to speed up the paediatric drug development process;
- standardization of methods and approach resulting in high quality data will facilitate the regulatory controlled pathway to the clinical stage and ultimately to the patients care. EPTRI is committed to ensure high quality and standardization from the earliest stage of paediatric research.

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