Stakeholders survey providing comments on the EPTRI CDR

A questionnaire, focused on investigating the opinion of representatives of different stakeholders' groups on the EPTRI organisation, services, access rules and collaboration with the existing RIs and other paediatric research initiatives, has been administered to 516 Stakeholders.

Research organisations - Academia - Hospitals - Networks were more represented (82,17%) with Germany, Italy, Spain and UK with the higher number of Stakeholders.

Table 1. Invited stakeholders and rate by categories

(Pharma) companies - CROs	Patients' associations	Regulatory agencies - National authorities	Research organisations - Academia - Hospitals - Networks	**TOTAL INVITED**
45 (8,72%)	**20** (3,88%)	**27** (5,23%)	**424** (82,17%)	**516**

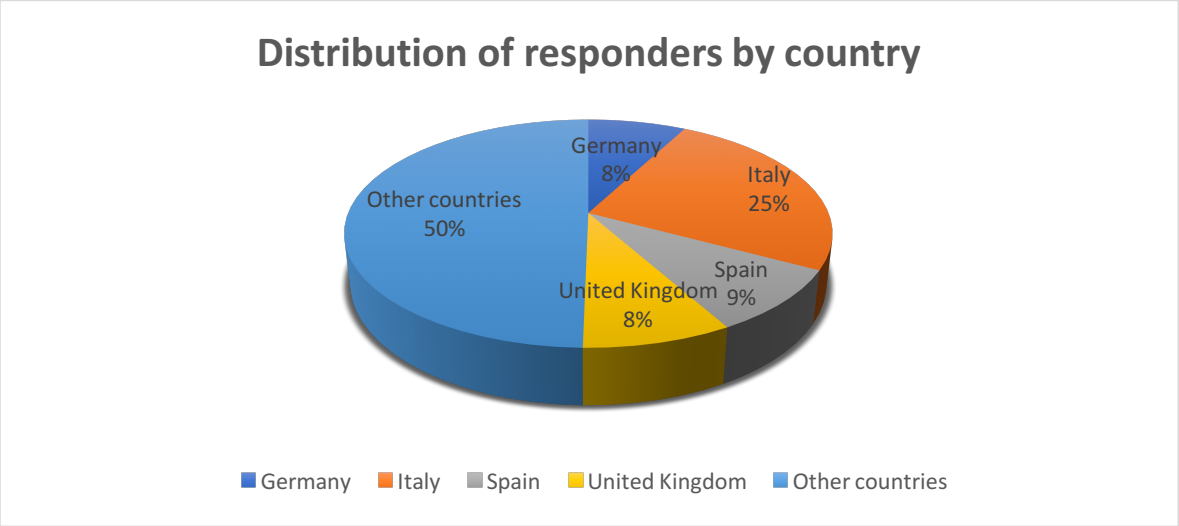
A total of 155 valid questionnaires from 31 countries were collected. Nine respondents were from non-EU countries (Canada, Israel, New Zealand, Russia and USA).

The distribution of the responses by category of stakeholders is shown in Table 2, and the distribution by country is shown in Table 3.

Table 2. Distribution of responders by category of stakeholders

(Pharma) companies - CROs	Patients' associations	Regulatory agencies - National authorities	Research organisations - Academia - Hospitals - Networks	**TOTAL RESPONDERS**
11 (7,1%)	**4** (2,6%)	**9** (5,8%)	**131** (84,5%)	**155**

Table 3. Distribution of responders by country



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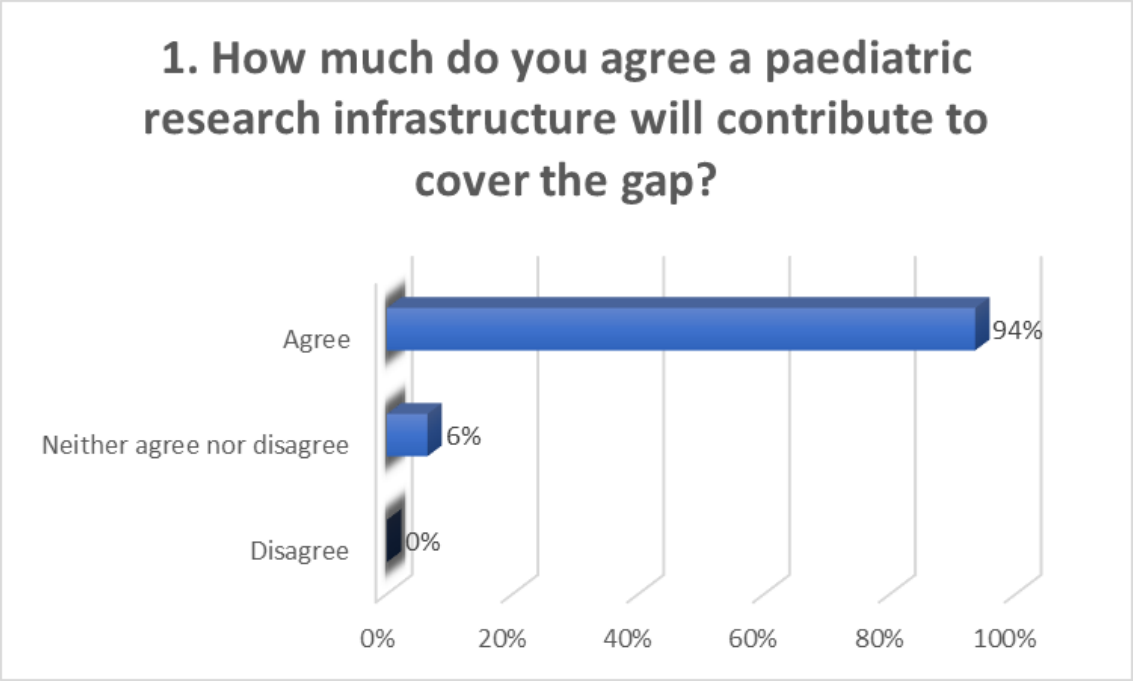
In the following of the document we report for each question the information provided to the participants, the table of results and a summary of the specific comments received.

1. EPTRI relevance and need

Question presentation

The EPTRI survey has identified more than 300 Research Units in EU and non-EU countries involved in research activities aimed to develop new and innovative paediatric medicines or to repurpose existing medicines tailoring them for the paediatric population. A lot of capacities and resources are available covering all the phases of medicines development (from discovery to clinical studies and post-marketing use) but the survey also confirmed that these capacities are often dispersed and lacking structural and collaborative support. In particular, while in the field of paediatric clinical research many efforts have been done in the last years allowing to consolidated Paediatric Networks and structured paediatric initiatives, in the preclinical and translational research a structural gap still exists and EPTRI will contribute to cover this gap by creating a Distributed Paediatric RI in which all the available resources could be grouped and able to provide their services.

Fig. 1 – Question 1 answers distribution chart



Discussion. A very high percentage of the respondents (145 on 155 = 94%) agreed that a paediatric research infrastructure will contribute to cover the gap.

For this question several comments have been collected:

- 20 comments included positive general judgements.
- 2 comments were suggesting collaboration with **BBMRI** for biobanking and **EMA.**

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- Some of the most interesting comments were aimed to suggest both EPTRI geographical enlargement (to less developed countries, **to cover geographical dispersion**, to include non-EU countries, etc) **or scientific enlargement** (to specific disease area, or new field such as medical devices).
- Finally, integration with the pre-existing Research Infrastructures and Networks was also suggested.

2. EPTRI organisation

Question presentation

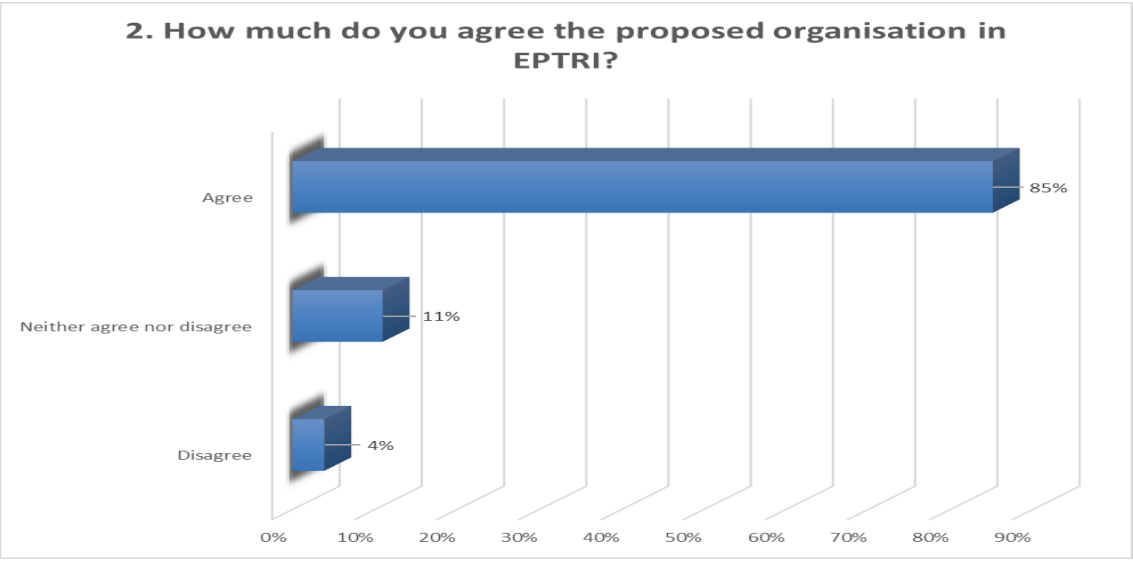
The C-Hub is the core of EPTRI. It will host the government Body and the Central management office. The C-Hub operations are supported by an IT infrastructure, web-based and cloud-enabled, able to empower the interactions between the actors of the processes and to support the execution of each service request, integrating the Single Access Point (based on a public facing website which will collect the requests) and a portal to make accessible all the EPTRI IT tools to the users.

Within EPTRI about 300 Research Units (RUs), identified and selected in the context of a large survey, will be grouped in the following Thematic Research Platforms - TRPs that we consider strategic in order to cover the area of competence in the paediatric drug developmental process:

- *Paediatric Medicines Discovery*
- *Paediatric Biomarkers and Biosamples*
- *Developmental Pharmacology*
- *Paediatric Medicines Formulations*

However, the Research Units will be also organised in National EPTRI Infrastructures (N-EPTRIs) under the responsibility of each Member State participating in EPTRI.

Fig. 2 – Question 2 answers distribution chart



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Discussion: A high percentage of the respondents (132 on 155 = 85%) agreed with the proposed organisation in EPTRI with 9% less respect to the previous question and 15% expressing some doubts or clearly disagreement.

A total of 48 respondents provided specific comments of whom:

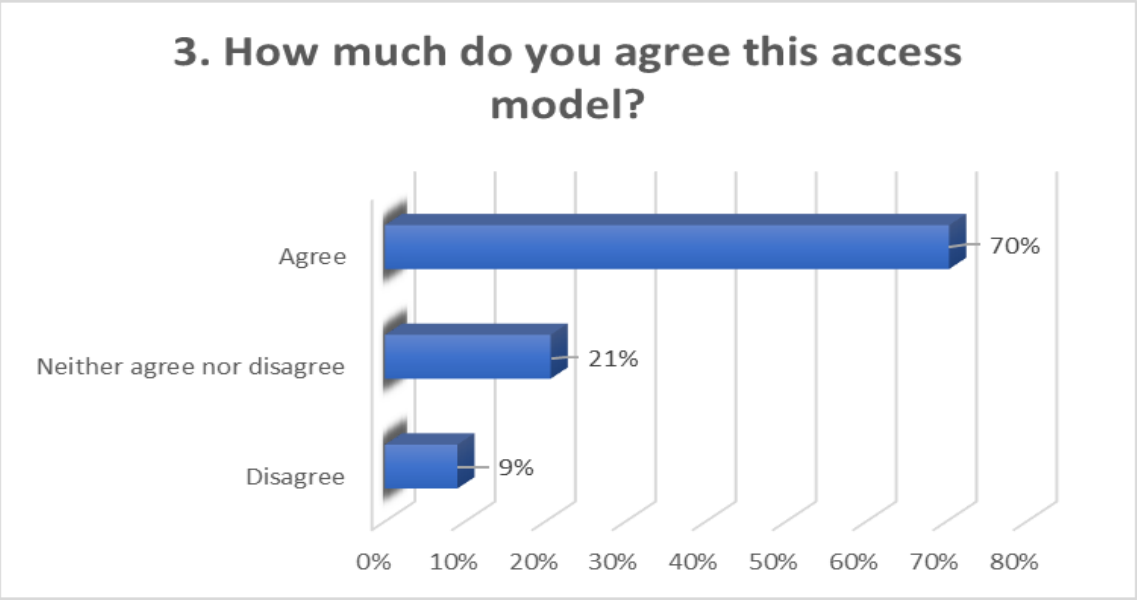
- 8 comments included positive general judgements
- 4 comments expressed criticism on the Platforms (Biosample/Biomarkers (2 comments), Developmental Pharmacology (1 comment) and on Drug Discovery (1 comment))
- The majority of comments (11= 23%) were focused on issues related on the **National Nodes** (N-EPTRI), of which 6 were negative about their adoption (risk of redundancies).
- Suggestion on enlargement or collaboration were:
    - Need of additional Thematic Research Platforms **(Paediatric Medical Devices (4), Paediatric Translational Neuroscience, Modelling and simulation or extrapolation techniques)**
    - Suggestion of collaboration with EOSC
    - Try to **cover also the network of HTA bodies and Payers**.

3. Access Model

Question presentation

'The access rules to EPTRI services will be aligned with the provisions of the European Charter for Access to Research Infrastructures. Access mode is planned to be 'excellence driven' and to enable collaborative research and technological development efforts across geographical and disciplinary boundaries. A fee will be the condition for the access, based on an agreement (that will also include confidentiality) between each User and EPTRI CMO (Central Management Office)'.

Fig. 3 – Question 3 answers distribution chart



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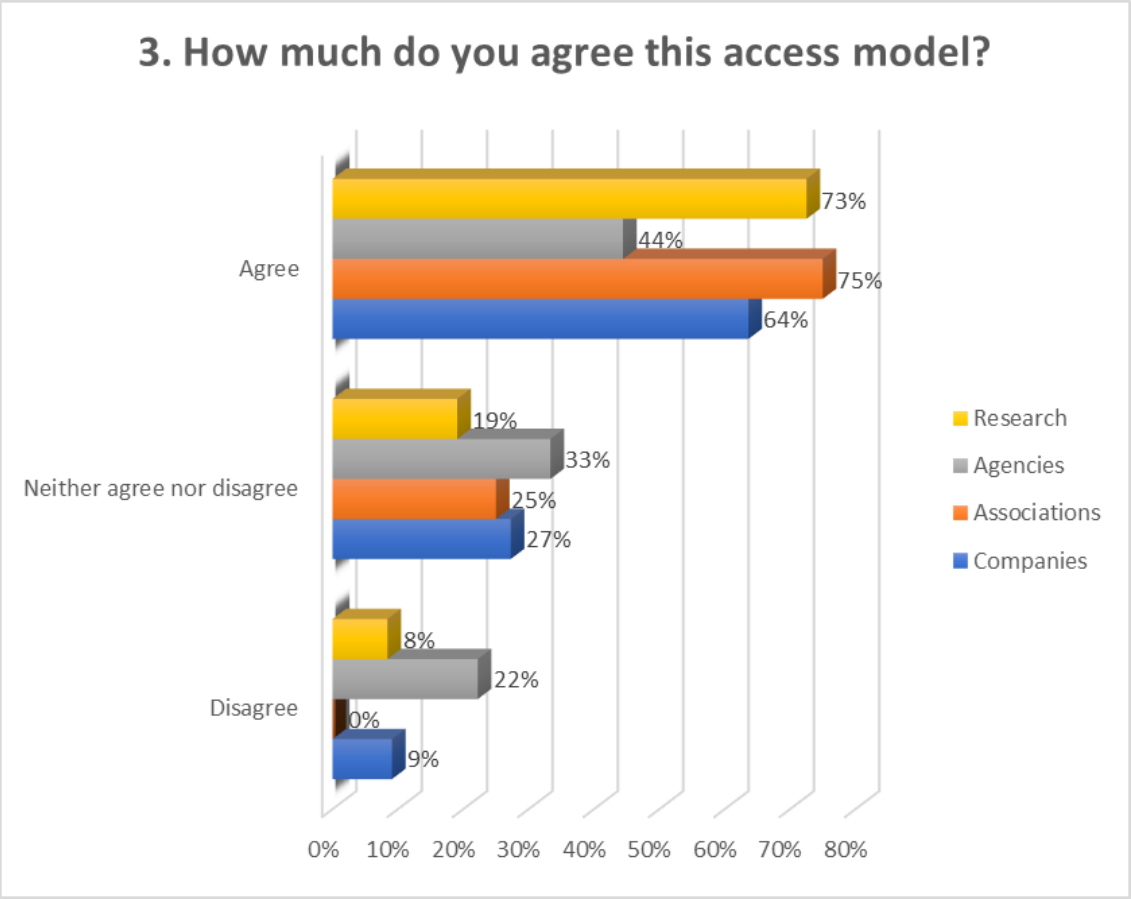
Discussion. The 70% of the respondents (109 on 155) agreed the access model adopted in EPTRI while a total of 30% is uncertain or disagrees. Moreover, the category related to "Regulatory agencies and National authorities" has a percentage of "uncertain" or "disagrees" particularly high (55%), as shown in the following chart (Fig.4).

Fig. 4 – Question 3 answers distribution chart (by stakeholders' category)



More information can be obtained from the 44 comments that have been collected of whom:

- **35** comments (79,5%) were focused on issues related on "**Access and Fees**", which is a clear indication of how much this issue is relevant for the stakeholder community. It confirms that the amount of the fee is an important issue to be faced. Positively some proposal on how to manage the payment of the fees have been provided.

4. Single Access Point

Question presentation

The EPTRI Single Access Point (SAP) will be a way to put Users in contact with RUs and facilities to perform high technology research, to receive Integrated, Centralised or Common services, and to be in contact with relevant scientific partners in different areas of interest. Ad hoc procedures will be identified to link scientists

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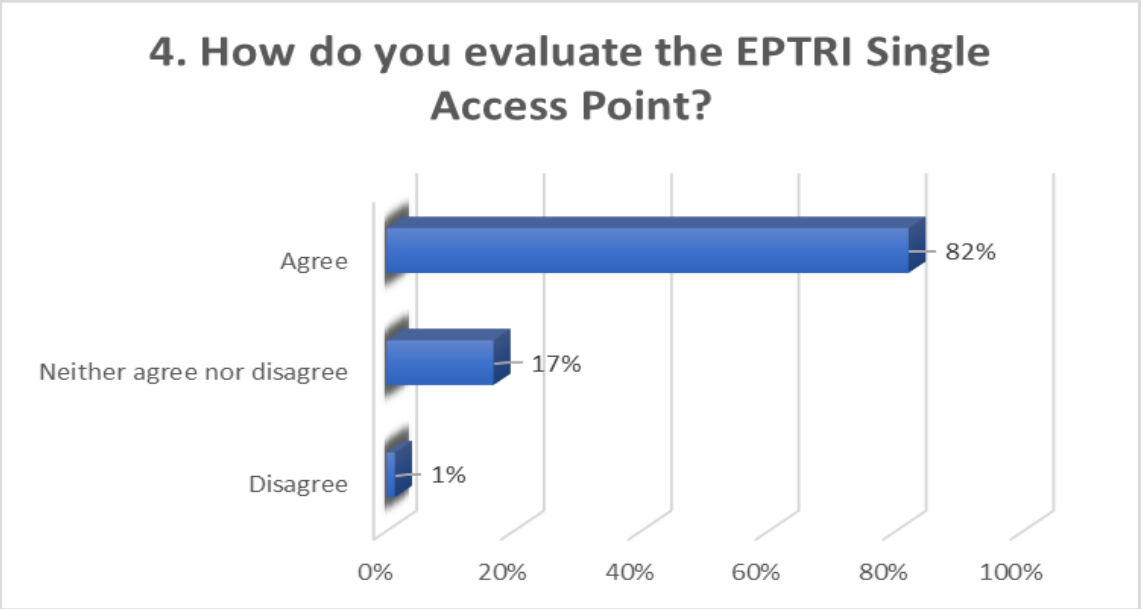
and interested people, including patients, company, regulatory bodies, etc., in order to implement an integrated supporting action in favour of developing medicines for children.

Fig. 5 – Question 4 answers distribution chart



Discussion. A high percentage of the respondents (127 on 155 = 82%) positively evaluated the EPTRI Single Access Point model.

Of a total of 30 comments received to this question:

- 8 comments included positive general judgements
- 5 comments focused on the procedures to be applied for SAP functioning
- 3 comments showed a certain scepticism
- Suggestions were made with regard to a wider access (to National nodes, to patients, to low income setting).

5. Integration with paediatric clinical setting

Question presentation

Paediatric research about medicines in Europe should have a single identity representing and integrating all the components of drug development (competences, facilities and initiatives).

The development of medicines to be administered to babies, children and young people is a complex process where preclinical work is aimed to underpin clinical work. A strategy for an integrated approach between the work of EPTRI and relevant paediatric clinical trial networks and initiatives to better deal with all the phases needed to develop new paediatric medicines or to adapt old medicines to the paediatric specificities, is being agreed between relevant actors. Following a common strategy for an integrated system it will be strengthened the capacity to provide expertise, experienced facilities and practical support for pre-clinical and clinical research.

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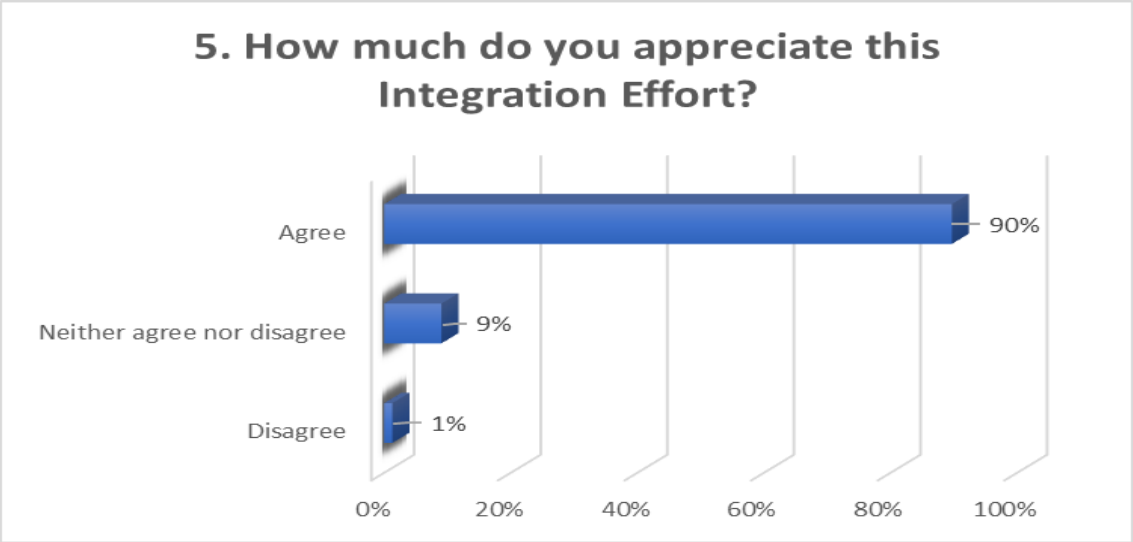
Fig. 6 – Question 5 answers distribution chart



Discussion. A very high percentage of the respondents (139 on 155 = 90%) positively evaluated the integration effort promoted by EPTRI.

For this question 24 comments have been collected of which:

- 10 comments included positive general judgements;
- 2 comments related to the risk of Duplication / Redundancy;
- 4 comments showed a certain **scepticism on feasibility** of this approach;
- 2 comments were focused on supporting the collaboration with other specific entities involved in paediatric clinical trials (e.g. c4c and MICYRN[1]).

6. EPTRI Integrated Services

Question presentation

Integrated services *will be provided to the users corresponding to the area of interest in the specific thematic research platforms. Only services tailored for paediatric research will be offered.*

Some considerations to adopt paediatric specific medicine research methodologies are:

- *More specific target identification processes should be considered for paediatric and/or genetic diseases especially where Mechanism of Action (MoA) and/or protein targets are unknown;*
- *Specific biomarkers should be identified, since predicted genotype-phenotype relationships based on adult experience are not applicable until the gene product is fully expressed during childhood;*
- *Juvenile animal studies should be as much as possible reduced in favour of in vitro non animal studies. However, when necessary animal studies should refer to animals corresponding to the specific paediatric ages for which the drug is intended*
- *Pharmacotoxicological tests should cover all the paediatric ages from preterm- birth to adolescence and be based on implemented knowledge related to the mechanism for body changes during the human development process, influence the tests;*
- *Variability from pharmacogenetic developmental changes is to be considered for the reasons that pharmacogenetic characteristics are affected by maturation variations;*

[1] Maternal Infant Child Youth Research Network (https://www.micyrn.ca/)

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- *To predict drug disposition in the maternofoetal compartments, placental platform facilities can provide information from in - vivo human placental perfusion parameters using specific methods of evaluations;*
- *Collection of adapted biological samples is a specific issue in paediatrics where the lack of biological materials and associated data deals to a low number of established in vitro and in vivo models for paediatric diseases; procedures and collaboration for clinical setting are also paediatric specific;*
- *Biosimulation and other methods and technologies developed in the context of computer science (system biology, system pharmacology, sharing data and big data use,) have huge relevance in the paediatric field contributing to alternative models to provide clinical evidence thus reducing clinical trials burden and time to new medicinal products in the market.*

Respondents were invited to assign a score value ranging from 1 (very low) to 5 (very high) to the integrated services proposed in EPTRI. Table 4 shows the average score for each service ordered by score level.

Table 4 – Integrated services scoring table

Integrated Services (ordered by score level)	Average score
Biomarkers targeted on paediatric disease identification and validation	4,3
Biomarker validation plan design and execution	4,1
Paediatric and neonatal Biobanking and Biosamples repositories organisation	4,0
In vitro/in vivo preclinical study	3,9
Omics technology applicable to paediatric drug development	3,9
Analytic methods adapted to low volume samples	3,8
PK/PD modelling and simulations in the different age groups	3,8
Formulation of drug for paediatric use	3,8
Drug administration Devices for paediatric use	3,7
First in child PK/PD studies and dosage extrapolation	3,7
Pharmacogenetics biomarkers analysis and developmental interaction	3,7
Cellular/Animal models suitable for new drug target identification/developing	3,7
Drug micro dosage adjustment	3,5
Paediatric Pre-Formulation studies	3,4
Palatability testing of novel paediatric formulation	3,4
In-vitro modelling of foetal/neonatal tissue maturation	3,3
Foetal/neonatal cell line with a stable phenotype for validation of the in vitro model against normal foetal/neonatal parameters.	3,2
Juvenile animal studies for toxicity-safety studies	3,1
In vivo/ex vivo Placental transfer studies to predict drug disposition in the materno-fetal compartments	3,0

Discussion. The average level of interest for the proposed integrated services is generally greater than 3; biomarkers and paediatric pharmacology services have the highest scores.

No remarkable differences appear in the two groups for each service in the list. Only the Placental transfer studies has obtained a score lower than 3 (2.9).

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7. Centralised Services

Question presentation

In addition to the integrated services offered through its Thematic Research Platforms (TRPs), EPTRI will be organised to overcome the many barriers specific to paediatric drug development. Those barriers have been identified and described in EPTRI with reference to:

-Support to matters of general interest in paediatric research (regulatory issues; ethical issues covering preclinical and translational research; quality, monitoring and guidelines in performing research with children).

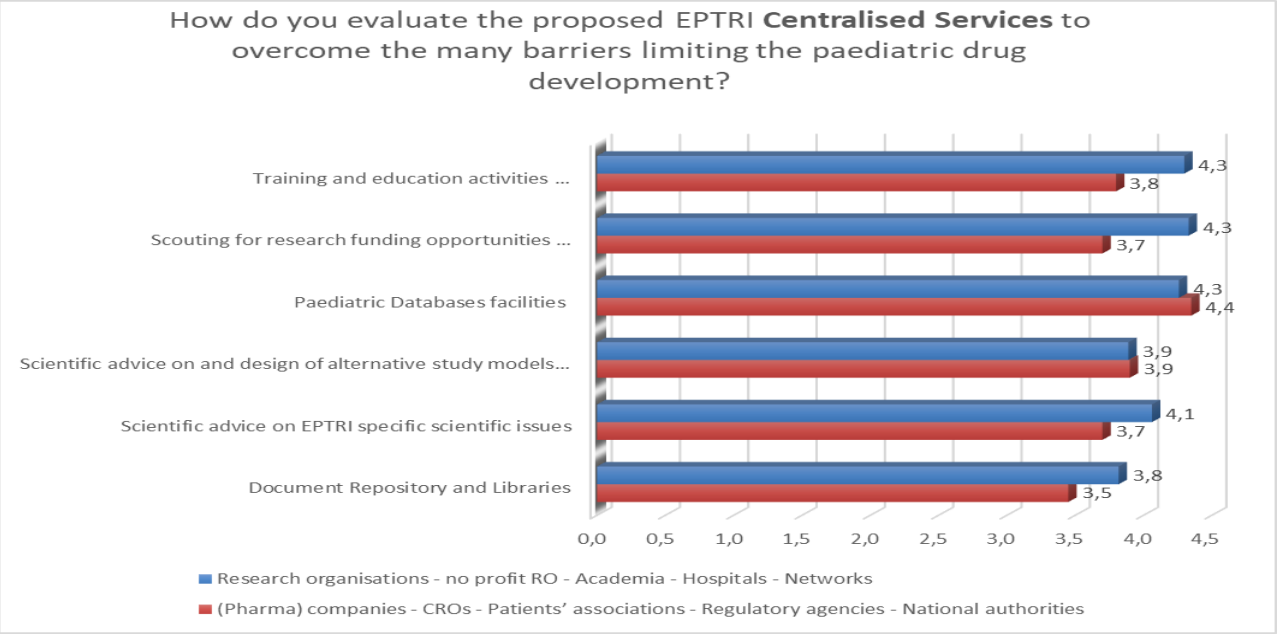
-Knowledge translation and dissemination (on human developmental mechanisms relevant for paediatric diseases; scientific, regulatory and technological issues with impact on paediatric drug development procedures and methods) using e-learning, virtual laboratories, notebooks, training.

-Support to use new technologies including imaging and data and new models and assessment methods to generate evidence to be translated in innovative clinical study design.

-Problems with funding (identification of funding sources, funds applications, research project management).

Respondents were invited to respond the following question: How do you evaluate the proposed EPTRI centralised services to overcome the many barriers limiting the paediatric drug development? and to assign a score value ranging from 1 (very low) to 5 (very high) to the centralised services proposed in EPTRI. As for integrated services we compared for each of the proposed centralised services, the levels of interest showed by the category "Research organisations - no profit RO - Academia - Hospitals - Networks" vs. the other stakeholders' categories ((Pharma) companies - CROs - Patients' associations - Regulatory agencies - National authorities). Next Fig.8 shows the average score for each centralised service grouped by subgroups.

Fig. 7 - Level of interest in EPTRI Centralised Services by subgroups



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Discussion. The average level of interest for these services is generally greater than 3,5 (in a scale from 1 to 5 where 5 is the highest level of interest) and for some services is very high. For most of the proposed centralised services, the average level of agreement is greater for the category "Research organisations - no profit RO - Academia - Hospitals - Networks".

8. Common Services

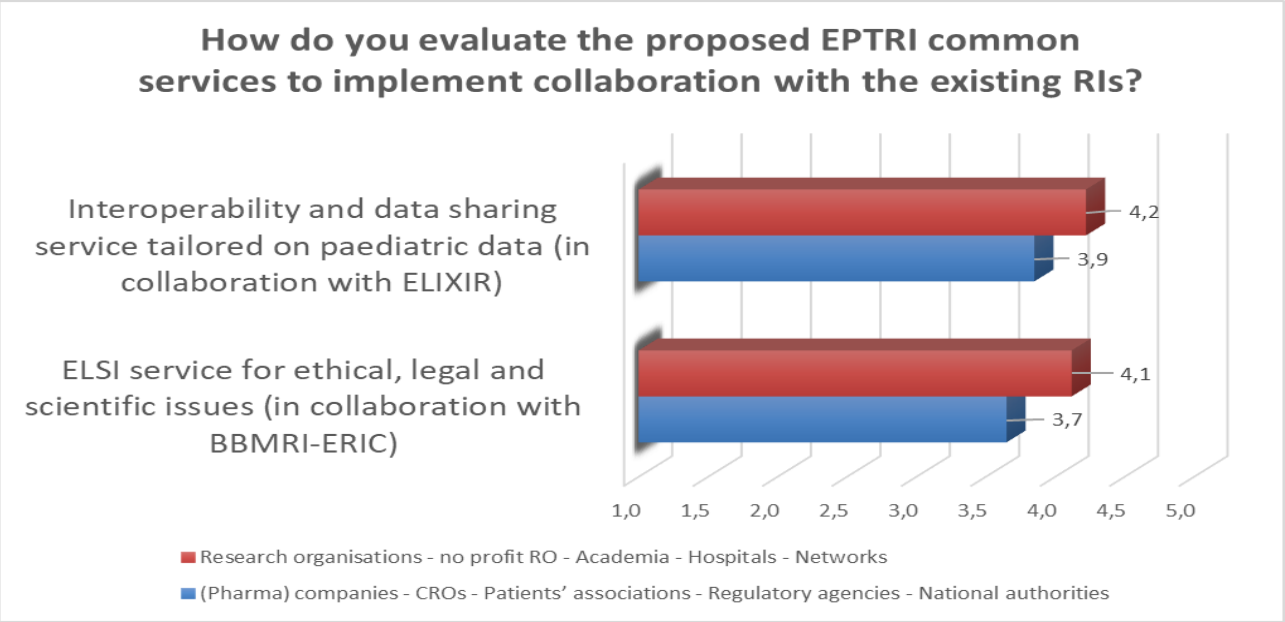
Question presentation

Common Services will be offered in cooperation with other Research Infrastructures in order to avoid duplication of services and to optimise the use of the available resources. To be offered efficiently they need to have a single point of distribution of the service requests balancing the need of the users with the offer and capacity of the providers. They will be based on agreements between RIs.

Provisionally, two Common Services have already been identified by the ID-EPTRI consortium. The first in the field of legal, ethic and social issues linked to sample collection and use. It will be developed in collaboration with BBMRI. The second relates to the data sharing and interoperability issues to make available to the paediatric community a large amount of data on basic, preclinical and clinical research already available by identified common model suitable in children research.

Interoperability will be managed in collaboration with ELIXIR.

Fig. 8 - Level of interest in EPTRI Common Services by subgroups



Discussion: Fig. 9 shows the total score for each Common Service grouped by subgroups.

The average level of interest for these proposed services is generally greater than 3,7 (in a scale from 1 to 5 where 5 is the highest level of interest). For both the services, the average level of agreement is greater, but not significantly, for the category "Research organisations - no profit RO - Academia - Hospitals - Networks".

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9. Discussion and conclusion

The stakeholders survey has been based on a large range of questions covering most of the main EPTRI design components and has provided many relevant contributions useful to finalise the CDR before the submission and to plan the next EPTRI preparatory phase.

General agreement

First of all, we underline that a high percentage (30%) of invited people accepted to fill in the survey' questionnaires, demonstrating general interest in collaborating with EPTRI and in supporting its further development.

Of particular interest are the suggestions:

1) to address EU (non-EU) area in which EPTRI is less present
2) to include in a clear manner the Medical Devices sector as an integrated part of EPTRI
3) to strengthen collaboration with relevant initiative (EMA, BBMRI and IMI2 c4c were specifically cited).

Specific comments on EPTRI organisations, services, access, integration

We have summarised in the table below (Table 5) the most relevant results and considerations in the different topics objects of the survey, also in order to better understand feeling and concerns from stakeholders.

Table 5 – Summary of main comments and suggestions

QUESTION	MAIN COMMENTS AND SUGGESTIONS
EPTRI organisation	- General agreement 85% - Proposals for including Medical Devices in EPTRI - Some concerns on National Nodes organisation
Access Model	- General agreement 70% - 30%, is uncertain or disagrees on fees (amount, payment requirements...). - Proposals were: no fees or fees differentiated by public and private users
Single Access Point	- General agreement 82% - Clarification on the procedures to be applied. - Proposal for a wider access (for PPI, for low income settings)and for local access points (at NNs level)
Integration with clinical setting	- General agreement very high (90%) - The collaboration with IMI2 c4c (and other Networks such as MICYRN) strongly supported
EPTRI Integrated Services	- -All the proposed services were agreed (grading 3 or more) - Additional services and implementation of scientific area are proposed especially in the Medical Devices field by many responders
Centralised Services	- -All the proposed services were agreed (grading 3 - 4.4) - These Services are mainly appreciated by Research Organisations - Paediatric Medicines Database service had the higher appreciation also by companies and other stakeholders
Common Services	- -All the proposed services were agreed (grading 3 - 4.2) - The average level of agreement has been greater for the category "Research organisations"

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