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Innovative methods to facilitate paediatric medicine development: the EPTRI experience

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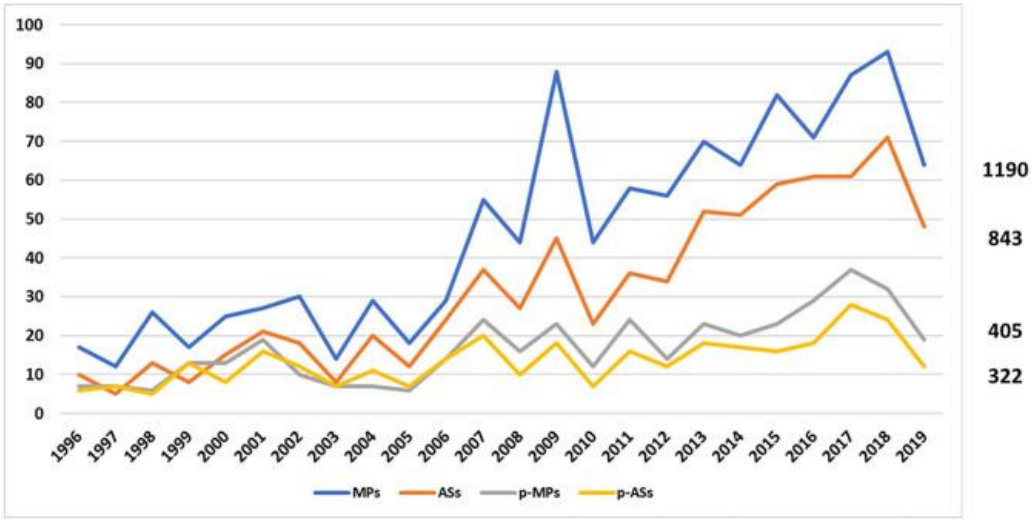
20th International Conference on Pharmaceutical Medicine – Athens, 20/10/2022

CVBF

Consorzio per Valutazioni Biologiche e Farmacologiche

Lights and shadows after the Paediatric Regulation



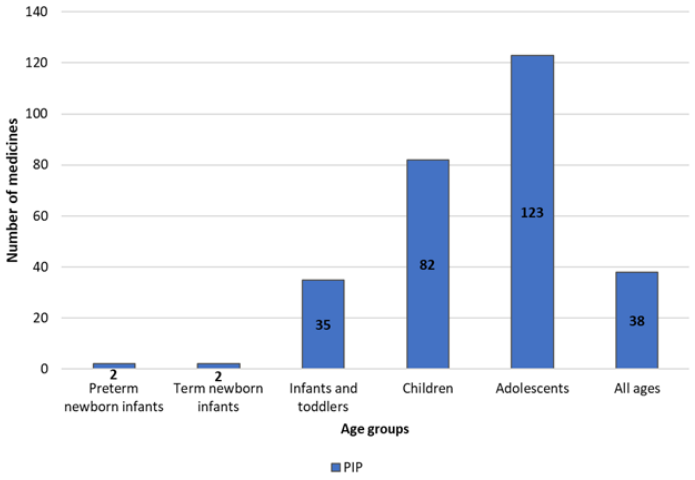
The blue line represents the medicinal products, the orange the active substances, the grey the paediatric medicinal products, and the yellow the paediatric active substances.

EMA medicines approved from Jan.1996 to Dec. 2019 include 322 new paediatric medicines (38% of the total new medicines). However:

- a limited number of products (16 %) cover all the paediatric age groups
- a significantly lower number of products available for neonates and preterm (22 %) than in adolescent
- No uniform distribution across therapeutic areas (+ antiinfectives, - nervous system, oncology).

Improvements

- **New biological drugs and ATMPs** also approved in paediatrics.
- About **50%** of approved paediatric medicines are intended for the treatment of a rare disease.



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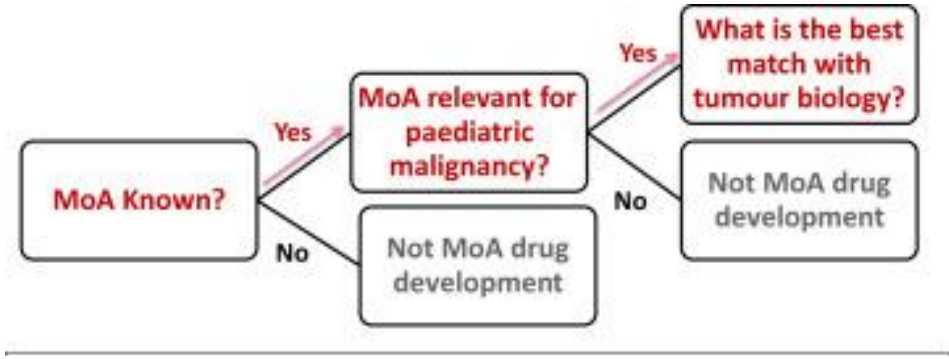
Toma M et al 2021 Front.Med 8:593281

Target-based approach in paediatric cancers

Still today, relatively few children with cancer are treated with targeted agents as standard of care

Nishiwaki S, Ando Y. Sci Rep 10, 17145 (2020). doi.org/10.1038/s41598-020-73028-w

By appling MoA scheme an higher number of drug will be developed.



As example: an EPTRI ongoing study

- More than 100 molecules have been identified as potential target agents for Neuroblastoma
- About **20 products** addressing a relevant target for NBL have been approved in EU for adult cancer with a waiver for paediatric studies

- How it will be possible to predict succesful development based **on biology and preclinical data**?

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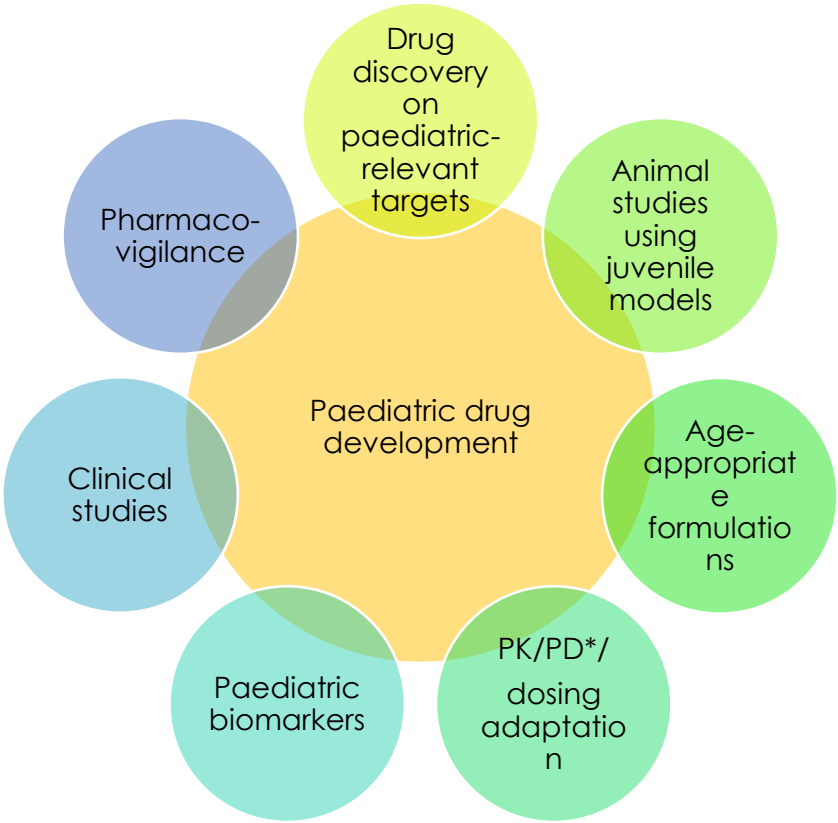
Adults studies cannot work for children

Growth and maturation progress by age
Ontogeny influences drugs response

Due to many paediatric specificities the current drug development process needs to be adapted

Paediatric drugs must be developed in children using ad hoc methods and technologies

All the drug developmental phases are involved:
From the basic, to translational to clinical



* Pharmacokinetic/Pharmacodynamic – PK/PD

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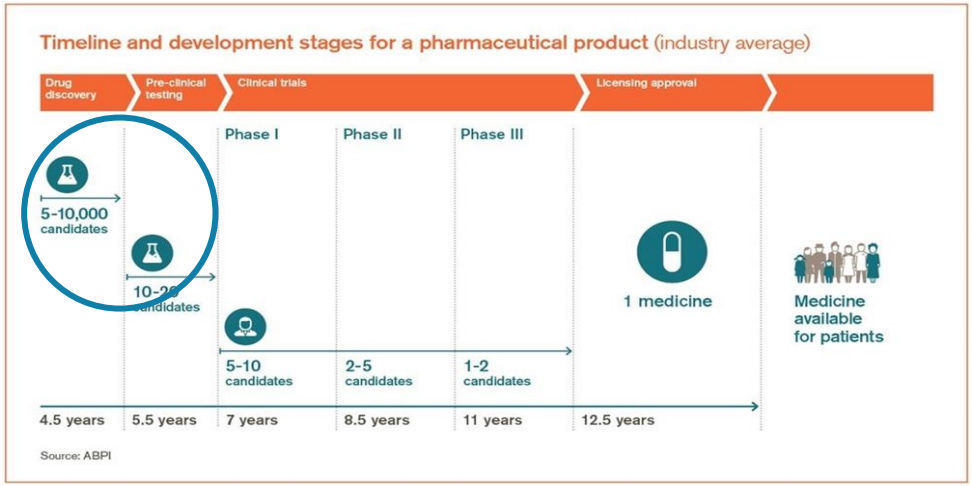
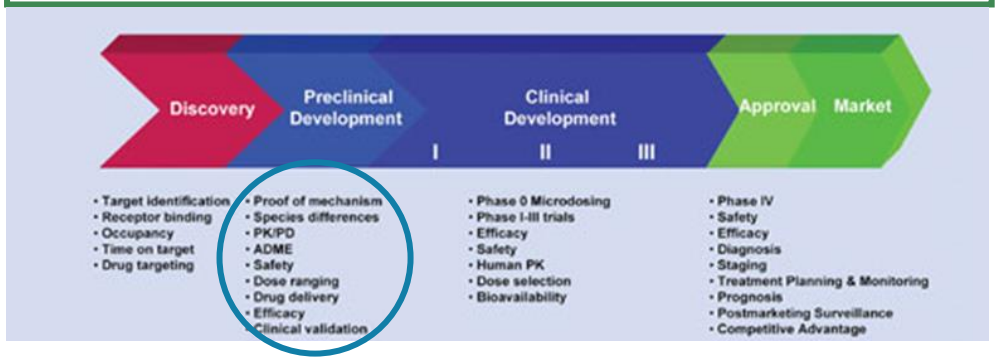
The advancement of paediatric research



Medicines development is a complex process involving **specific disciplines and competences** in different stages

Each stage needs information from previous stages



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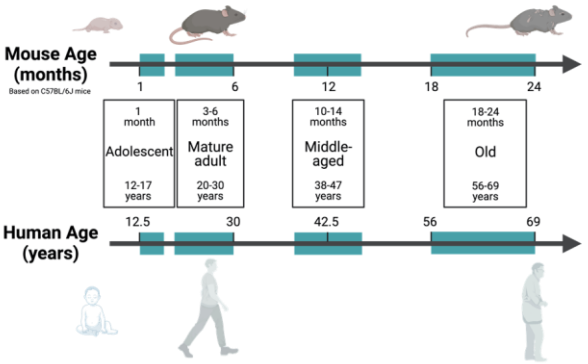
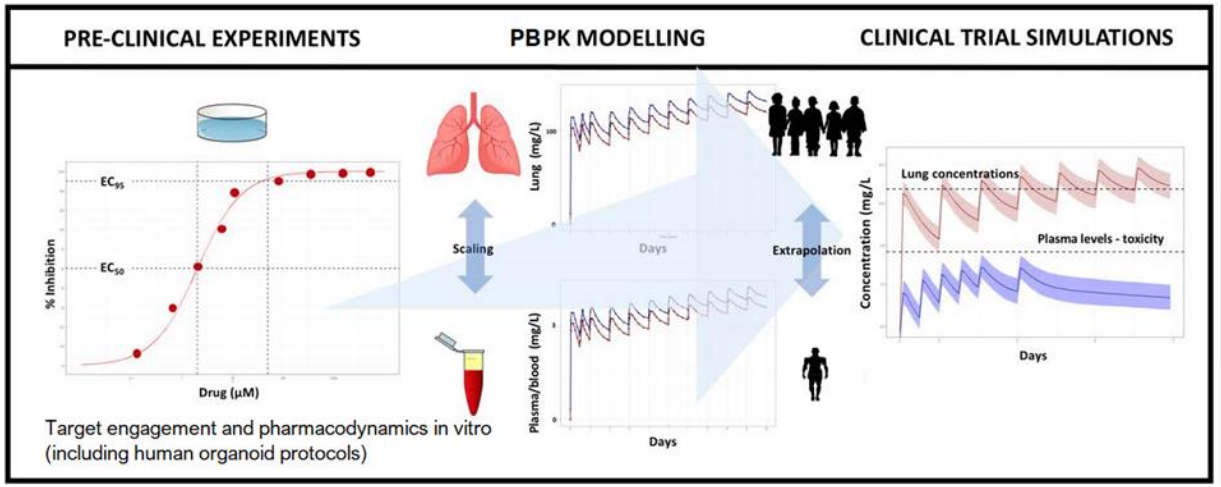
new approaches for preclinical assessment - from in vivo studies to organoids

- Preclinical findings in animal species remain few predictive and still represent one of the main obstacles in the evaluation of paediatric medicines especially for neonates and very young children, since **these studies do not allow direct extrapolation to children**.
- It may be preferable **to study the effects of age specific developmental process directly on human cells/tissues** including organoids



Mouse development stages don't correspond to human developmental studies.

Integration of human organoids studies into PBPK modelling and in silico clinical trials



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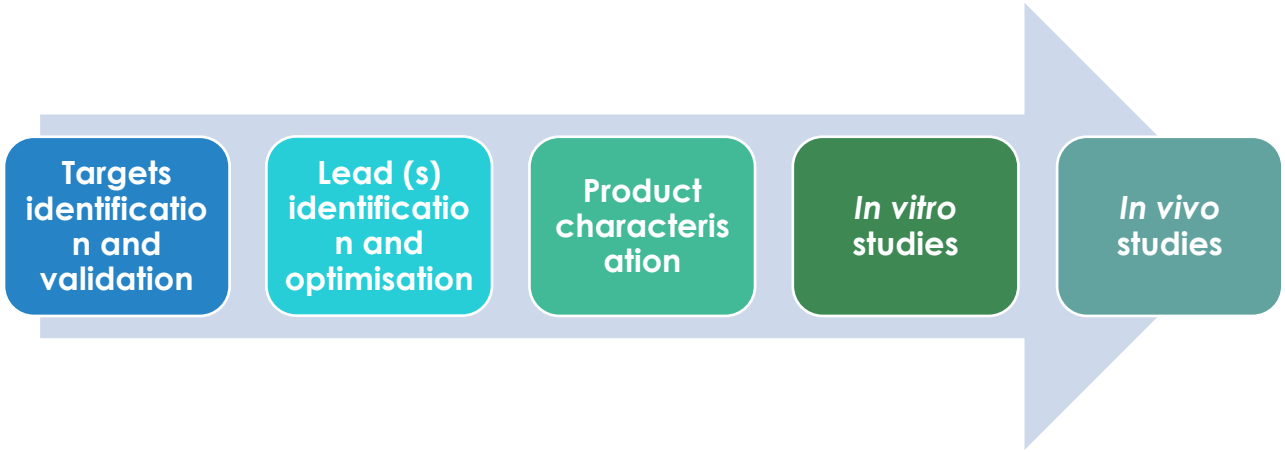
Preclinical & translational research

Pre-clinical research needs to account for how the results will be applied to design best clinical studies.

Clinical phases should integrate preclinical results



Preclinical package:
Target biological effects
Dosage prediction
Anticipated target toxicity
Main safety information
Preformulation studies

Accelerated clinical evaluation
Dose ranging
Efficacy/safety
Formulation studies
Post –marketing studies, etc

The EPTRI focus

- Paediatric-oriented preclinical research, especially to cover **drug discovery** and **preclinical studies**
- **Translation of the results** into good **clinical phase**

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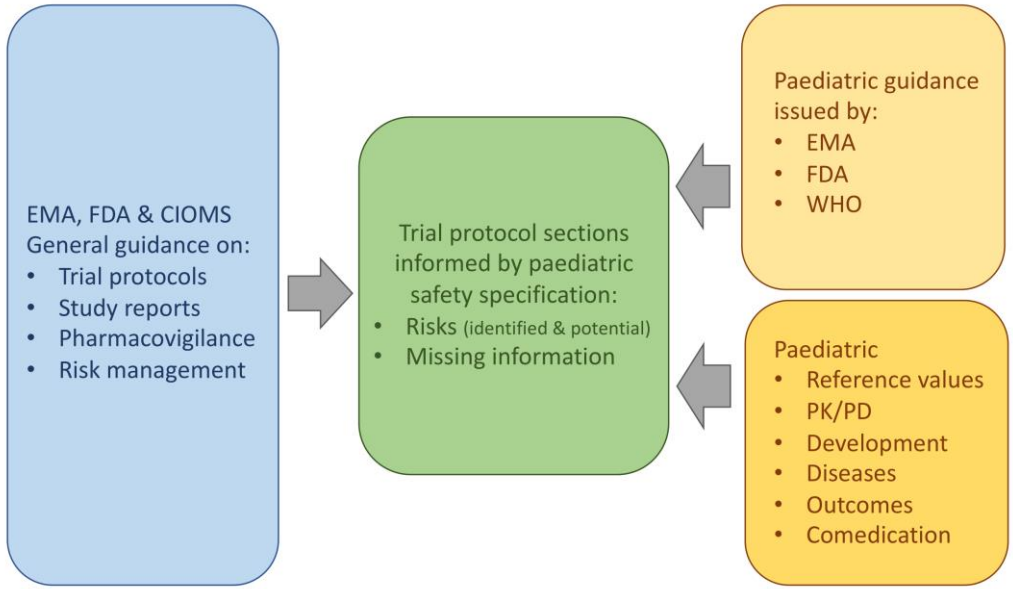
The value of Preclinical Studies for paediatric medicines development

Pharmaceutics **2021**, *13*(5), 695; 11 May 2021

Beate Aurich and Evelyne Jacqz-Aigrain

Drug Safety in Translationa Paediatric Research: Practica Points to Consider for Paediatric Safety Profiling and Protoco Development: A Scoping Review



No article was identified providing **practical guidance** on how to establish a paediatric safety specification and its integration into a paediatric protocol. Proposal for a checklist for the development of a paediatric safety specification

Special Issue Scientific Highlights in the First European Paediatric Translational Research Infrastructure

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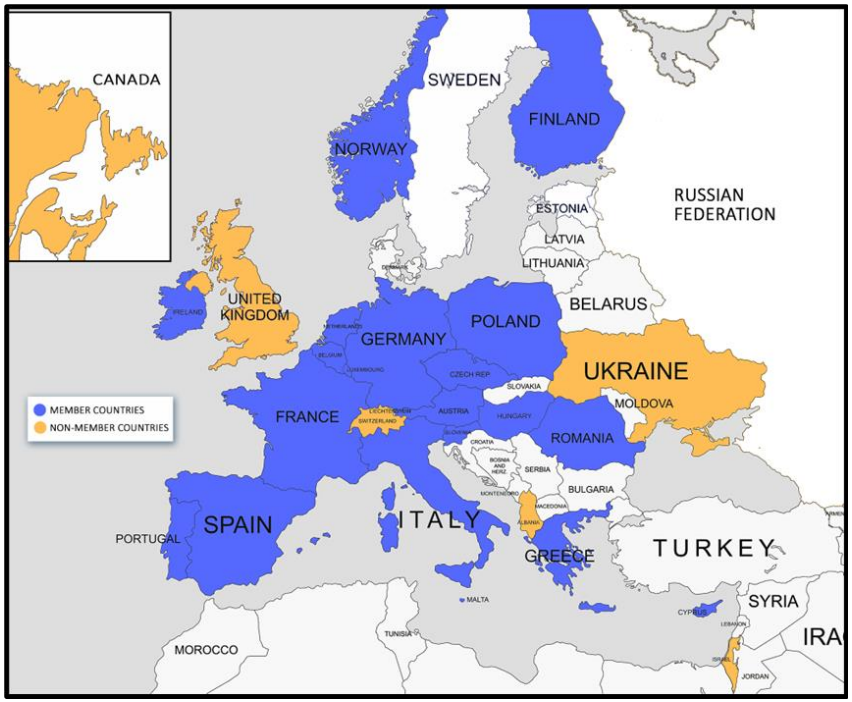
What is EPTRI

- A pan-European initiative involving more than one hundred research units gathered together to boost the **paediatric research ecosystem** and provide services for the development of medicines for children.
- It acts as is a distributed Research Infrastructure organised according to a **Hub and Spoke** model with a **Central Hub** and **several Spokes**, represented by several research units grouped both within **Thematic Research Platforms** – TRPs (according to their field of expertise) and **National Nodes** (according to their location).

Centralised services
managed and delivered directly at *Central Management Office* level

Integrated services
provided through the five *TRPs* according to their specific research area of expertise



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EPTRI Centralised Services

Centralised services are managed and delivered directly at *Central Management Office (CMO)* level involving Experts from EPTRI AISBL

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EPTRI Thematic Research Platforms (TRPs)

Integrated services are provided through the *five TRPs* according to their specific research area of expertise

Paediatric Medicines Discovery

Developmental Pharmacology

Paediatric Biomarkers and Biosamples

Paediatric Medicines Formulations

Paediatric Medical Devices

EPTRI Integrated services - 1

PAEDIATRIC MEDICINES DISCOVERY TRP

- In vitro screening of novel drugs for paediatric use
- Pre-clinical studies of novel drug in paediatric cell/tissue/organoid models
- Access to paediatric tailored animal models to screen novel drug for a paediatric specific target
- In silico screening of novel drugs for paediatric use

PAEDIATRIC BIOMARKERS AND BIOSAMPLES TRP

- 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 platform
- Verification and monitoring in paediatric samples of the presence and levels of biomarkers already identified

DEVELOPMENTAL PHARMACOLOGY

- Microdosing to establish first-in-human dose
- In vitro models to study drug disposition
- Placental studies
- In vivo toxicity studies including juvenile animal studies
- Preclinical Paediatric ADME and Modelling & simulations

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EPTRI Integrated services - 2

PAEDIATRIC MEDICINES FORMULATIONS TRP

- Pre-formulation advice and studies
- Formulation of drug for paediatric use for enteral/non-enteral routes of administration
- Assessment and design of drug delivery systems for enteral and non-enteral routes of administration
- Paediatric in vivo/in vitro palatability assessment

PAEDIATRIC MEDICAL DEVICES TRP

- Prototype analysis and design of the medical device
- In vitro and in vivo pre-clinical test
- Analysis of the safety risk related to the medical device
- Physico-chemical characterisation
- Microbiological testing
- Biocompatibility testing
- Mechanical, electrical, electronic or non-clinical toxicological testing
- Performance studies
- Medical device validation
- Administration Devices end user/usability assessment

287 Research Units (RUs) update

29 COUNTRIES

THEMATIC RESEARCH PLATFORM	PARTICIPATING RESEARCH UNITS	UPDATED RESEARCH UNITS
PAEDIATRIC MEDICINES DISCOVERY TRP	89	25
PAEDIATRIC BIOMARKERS AND BIOSAMPLES TRP	92	28
DEVELOPMENTAL PHARMACOLOGY TRP	42	14
PAEDIATRIC MEDICINES FORMULATIONS TRP	35	12
PAEDIATRIC MEDICAL DEVICES TRP	29	9
TOTAL	287	88

A **new EPTRI survey** is ongoing since August 2022

updated on 14.10.2022

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Services requests to EPTRI

Since 2019, **28 project proposals** for both centralized and integrated services have been managed by EPTRI CMO. One or more services have been requested for each project proposal received.

Paediatric Medicines Discovery

14 service requests

Paediatric Biomarkers and Biosamples

5 service requests

Developmental Pharmacology

8 service requests

Paediatric Medicines Formulations

4 service requests

Paediatric Medical Devices

-

36 request for centralised services:

- *Design of not clinical specific studies/experiments (1)*
- *Design of paediatric clinical studies based on preclinical results (3)*
- *Regulatory and ethical procedures (10)*
- Support in application to (public and private) funding opportunities (17)
- IT service (data integration) (2)
- Provide access to paediatric patients' cohort/samples (3)

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Thank you for the attention!

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