Donato Bonifazi – Adriana Ceci

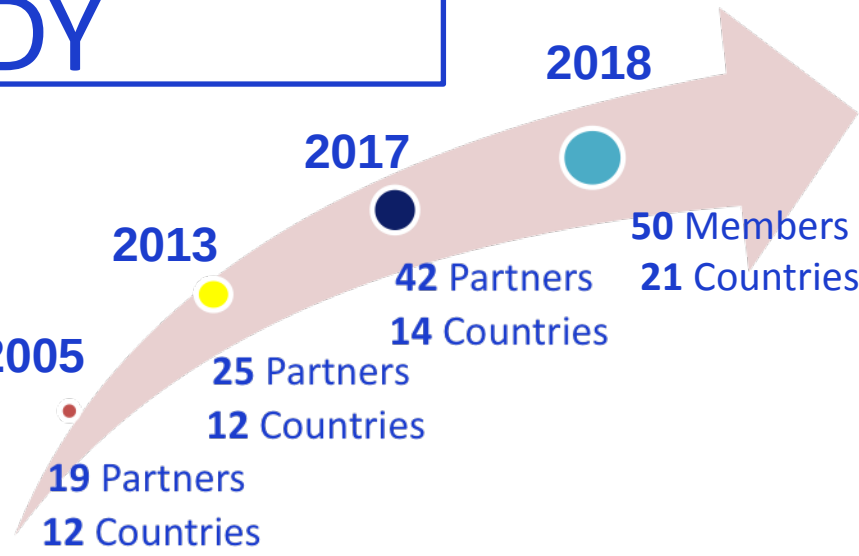
TEDDY Network

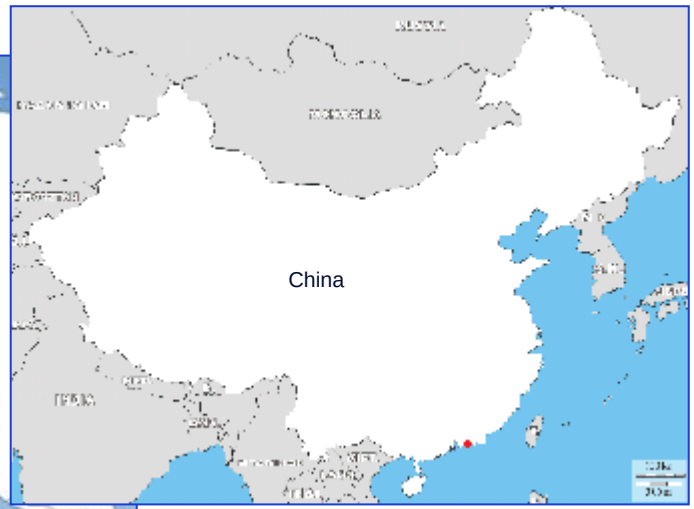
European Network of Excellence for Paediatric Clinical Research

What is TEDDY

...is **an independent multidisciplinary Network** aimed at facilitating the performance of good quality paediatric studies and research

...encompasses **50 partners** from **21** EU and non-EU **countries**





TEDDY demonstrated **networking capacities** involving European and non-European research centers

TEDDY members

INSTYTUT
"POMNIK - CENTRUM ZDROWIA DZIECKA"

THE UNIVERSITY
of LIVERPOOL

Universitätsklinikum
Erlangen

Cairo University

Institute of Physiology
Academy of Sciences
of the Czech Republic

REPUBLIC OF CYPRUS
MINISTRY OF HEALTH
OF THE REPUBLIC OF CYPRUS

HELLENIC REPUBLIC
National and Kapodistrian
University of Athens

University Medical Center
Utrecht

TEDDY is now 13 years old

2005-2010

XTH FRAMEWOR ROGRAMME

1°in Europe Network of Excellence to promote Paediatric Research and Paediatric Medicines development

2014-2016

European Network of Excellence for Paediatric Clinical Research

Cat.1 (ex cat.4) Member of Enpr-EMA

Partners Agreement

2017-2018

Legal Status

A Network with a legal status to be fully represented in the European paediatric research framework

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TEDDY from the past to the future

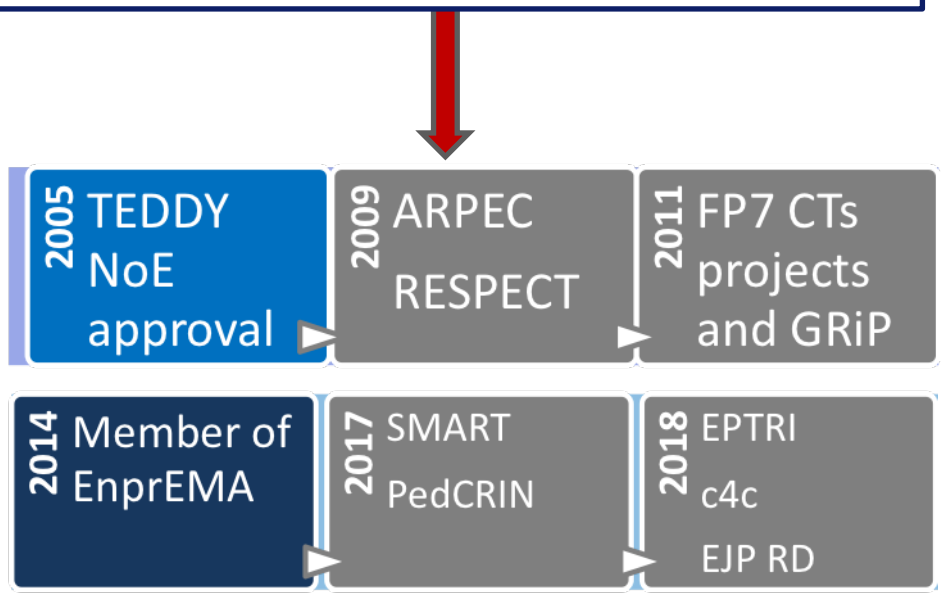
MAIN TOPICS

- *Life Science and Innovation*
- *Clinical Research*
- *Ethics and Regulatory*
- *Drug uses in children and Pharmacovigilance*
- *Education and Knowledge dissemination*

… and AMBITION

Be aligned with the PAEDIATRIC INITIATIVE(S) in EU

Be part of the European Paediatric Research Community



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TEDDY Network BODIES

The Scientific Coordination Committee (SCC)

- ***Annagrazia Altavilla –*** Espace Ethique Mediterranée- Marseille
- ***Adriana Ceci*** – G. Benzi Pharmacologic Research Foundation – Valenzano
- ***Giovanni Migliaccio –*** Consorzio Val. Biologiche e Farmacologiche – Bari
- ***Oscar della Pasqua –*** University College London
- ***Francesca Rocchi –*** Ospedale Pediatrico Bambino Gesù – Roma
- ***Saskia de Wildt –*** Radboud University

The Strategic Planning Board (SPB)

- ***Carlo Giaquinto*** – Penta Foundation – Padova
- ***Maria Mellado*** – Universidad Autónoma de Madrid
- ***Marek Migdal –*** Children's Memorial Health Institute – Warsaw
- ***M. Sturkenboom*** – University Medical Center Utrecht
- ***Mark Turner*** – University of Liverpool
- ***Ian Wong*** – University College London

Scientific Secretariat
Lucia Ruggieri/Annalisa Landi

Networking Management
Mariangela Lupo

Coordination and Administration
Donato Bonifazi

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TEDDY Network WGs

TEDDY Network Working Groups are:

- A practical way to exchange expertise within the Network and to engage interested stakeholders
- An instrument to react and interface with relevant actors in the arena (EnprEMA, EMA, EC, Paediatric Networks/Initiatives, etc.)

1. Paediatric Clinical Studies Methodologies and Procedures
2. Ethical Issues in paediatric research
3. Off-label use in Paediatrics
4. Regulatory procedures for paediatric clinical trials and Pharmacovigilance
5. Active engagement of children and adolescents in the themes of clinical research
6. Health data
7. Advanced Therapies in paediatrics

TEDDY participates in the EnprEMA WGs:

- WG on Ethics
- WG on Training
- WG on Young Patients Advisory Groups
- WG on Trial Readiness and Preparedness
- WG on public-private partnership

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Paediatric Clinical Studies Methodologies and Procedures Working Group

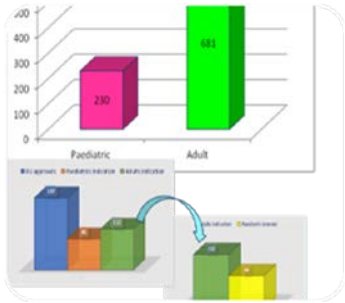
Paediatric Trials and Studies analysis (data available in TEDDY-EPMD)

FP7 Paediatric Trials and Studies results monitoring (still ongoing)

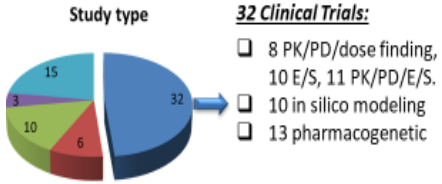
GRiP WP4 methodological recommendations published papers

Methodological expertise contribution in PIPs/PUMA preparation

European Paediatric Medicines Database, October 2017



Paediatric studies and trials in FP7



Ceci A, Medicines for children licensed by the EMEA. Eur J Clin Pharm,2006

Baiardi P, Innovative study design for paediatric CT. Eur J Clin Pharmacol. 2011

Ruggieri L, Successful private-public funding of paediatric medicines research Eur J Pediatr. 2015 174(4

Della Pasqua O. *Age-Related Factors on the Pharmacokinetics of Lamotrigine, Cl. Pharmacokinetics · January 2018*

Bonifazi D., Challenges in Paediatric CTs: How to Make It Feasible, InTech, O. Vallisuta Ed., June 2018

DEFERIPRONE EVALUATION IN PAEDIATRICS

CLOSED — Clonidine for Sedation of Paediatric Patients in the Intensive Care unit

GAPP — GAbapentin in Paediatric Pain

NeoMero

neoVanc

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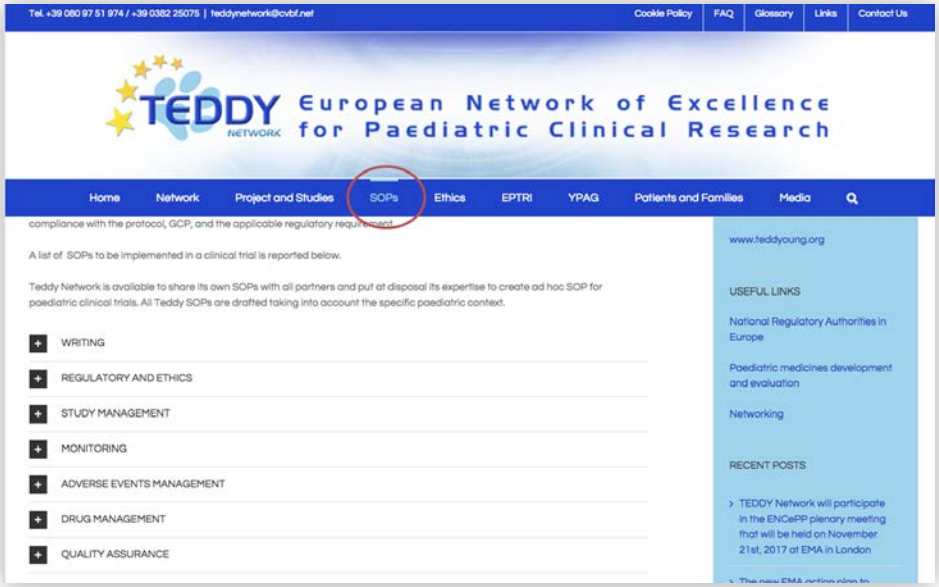
Participation to the Enpr-EMA WGs 3 + 5: Network consultation process & guideline

Paediatric Clinical Studies Methodologies and Procedures Working Group

Standard Operative Procedures

The TEDDY Network has provided methodological support in the context of the FP7 trials producing CTs management procedures



A plan for providing support to its members in the SOPs preparation is ongoing

- REGULATORY AND ETHICS
  - Information leaflet, consent and assent forms
  - Clinical Trial Application
- STUDY MANAGEMENT
  - Trial Master File and Investigator Folder
  - Contracts and agreements
- MONITORING
  - Site Initiation Visit
  - Monitoring Visit
  - Close-Out Visit
- ADVERSE EVENTS MANAGEMENT
  - SAE Reporting
  - SAE Processing
  - SAE Archiving
  - SAE Reconciliation
- DRUG MANAGEMENT
  - Set-up of Clinical Trials Supply and Drug Management Activities
- QUALITY ASSURANCE
  - Preparation, review, approval and distribution of SOPs

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www.teddynetwork.net

Ethical and Regulatory Issues in paediatric research Working Groups

2 Surveys on the involvement of Ethics Committees in paediatric research in EU

-an overview about ethical issues in paediatric clinical research at European level

-an inventory of European Ethics Committees, with full contact details

Participation to the EnprEMA WG on Ethics:
Cristina Manfredi (cmanfredi@cvbf.net)
Viviana Giannuzzi (vg@benzifoundation.org)

Current field of interest:

Paediatric research under the new EU regulation on clinical trials: old issues new challenges (Gennet, Altavilla, EJHL 2016)

Clinical Trial Application in Europe: What will change with the new regulation? (Giannuzzi, Ethics, 2015)

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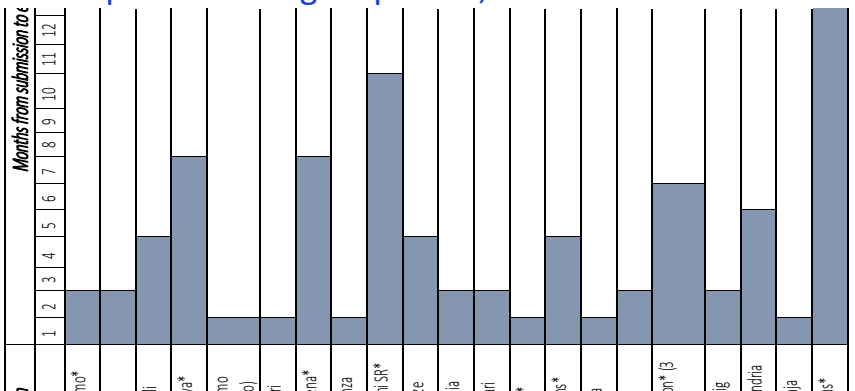
Months from submission to ethical approval

The special case of DEEP a Multinational Multiethnic project involving EU- non EU:

- In **Albania** specific rules on CTs was lacking; a special decision from the Ministry of Health was needed
- In **Egypt** the CTA is largely similar to Europe, but informed consent procedures are different; samples cannot be sent abroad. Details on contraception in the consent and assent documentation should be avoided, since this information is not considered tailored for girls.
- In **Tunisia** the Ministry of Health, the National and local ECs shall authorise a paediatric trial

- **Greece** ⇨ the insurance must cover phoetus damages even though contraceptive measures are explicitly mentioned in the informed consent form
- **Italy** satellite ECs provided 'opinion' instead of 'acceptance of single opinion';



Off Label use in paediatrics Working Group

1- create a framework for using off patent drugs more safely

A TEDDY 'Off-Label' WG was held June 30, 2016 aimed to prepare an '*European consensus statement on off-label use in children*'

Program, achievements and future plans was presented by S. de Wildt during the 2017 TEDDY GA

Starting from recent literature data and documents (especially **the FIP–WHO technical guidelines**) and considering recent initiatives (the **GOLUP Declaration as an example),** on the basis of a large consultation approach (Delphi or similar).

a consensus statement/policy statements will be prepared, formalised within the TEDDY Network and shared with regulatories, scientific societies and other stakeholders

Off-Label WG Participants: *S. de Wildt (chair), T. van der Zanden and L. Ruggeri (scientific secretariat), D. Bonifazi, M. Turner, M. Mellado, R. Piñeiro.A. Neubert, E. Jacqz-Aigrain, H. Sammons, F. Lagler, T. Sainz Costa,*

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Off Label use in paediatrics Working Group

2- support niche off-patented medications and drug repurposing

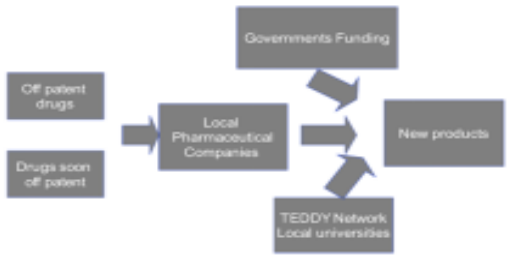
Re-purposing of off-patent drugs for children -TEDDY to create a bridge between Europe and Asia

(action proposed by Ian Wong-UCL, TEDDY GA, 2018)

Background. New drug development is expensive and high risk.
Asian countries (except Japan) is less well developed in biopharmaceutical industry. Mainly generic company to produce local pharmaceutical products
In EU some interesting experiences are developed: EG. **Buccolam** developed by Therakind having a worldwide sale over US$ 45million

- Thailand - Chulalongkorn University and University of Hong Kong are in the positions to work to develop repurposed medicines for children.
- TEDDY can support the initiative by following the example developed in EU. Discussion is still on-going

Model for the collaboration →



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Active engagement of children and adolescents in the themes of clinical research

Working Group

Informative documents and YPAG

The GAPP (GAbapentin in Paediatric Pain) project intends to improve the therapeutic perspectives of children who suffer from chronic pain, providing them with the drug " Gabapentin"

➢ 3 different BOOKLETS for each study (GABA-1 e GABA-2) for different age groups

➢ 2 different ASSENT FORMS for patients from 7 to 11 and from 12 to 17 years of age

Available in the 7 languages of the project (Albanian, French, Greek, English, Italian, Dutch and German)

Patient diary for each study (GABA-1 and GABA-2)

The objective of the DEEP project is the marketing of a new formulation of deferiprone for the treatment of iron overload in paediatric patients affected by congenital anaemias

- 3 different BOOKLETS explaining CTs aims and procedures and what they are going to experience
- 2 different ASSENT FORMS

Available in the 6 project languages (Albanian, Arabic, English, French, Greek, Italian)

Two animated videos have been developed:

- presenting general information on clinical trials for young children
- presenting general information on clinical trials for teenagers

Active engagement of children and adolescents in the themes of clinical research

Working Group

Informative documents and YPAG

YPAG (Young Persons Advisory Group)

A Young Persons Advisory Group, or YPAG, is an organization composed of youths, patients, carers and people interested in a health condition or in research, actively participating as partners, advising researchers and their teams in a full range of activities in various research projects and initiatives.

KIDS Bari

TEDDY in collaboration with Consorzio per Valutazioni Biologiche e Farmacologiche and the paediatric University Hospital Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari – Ospedale Pediatrico "Giovanni XXIII" promoted the first italian YPAG in Bari corresponding to a new chapter of iCAN, named "KIDS Bari".

KIDS BARI

Launch event on 7th June 2017 in Bari

KIDS Objectives:
Peer support for young patients;
advocacy for children, patients and participants in clinical trials;
advise young people on research;
raising public awareness;
fundraising.

KIDS ALBANIA

TEDDY in collaboration with Consorzio per Valutazioni Biologiche e Farmacologiche – Dege e shoqerise se huaj, Albanian Branch Office and University Hospital Center Tirana "Mother Teresa", Service of Paediatrics), promoted the first YPAGin Albania, named KIDS Albania.

Launch event on 15th September 2017 in Tirana

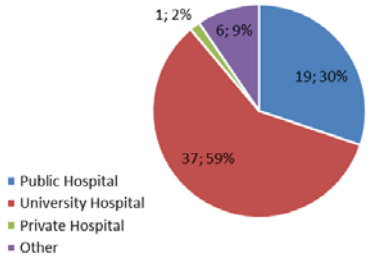
Inventory of paediatric clinical sites and facilities to evaluate Paediatric Trials feasibility

TEDDY Sites Inventory - questionnaire in collaboration with EnprEMA

Expertise of centres performing paediatric clinical trials, available services, equipment and the centralised services supporting clinical trials in each site

Answers from **63 centres belonging to 11 EU and non-EU countries** (Ireland, UK, Italy, Albania, Finland, Sweden, Norway, Iceland, Denmark, Austria, Switzerland)

Sites identification provided by TEDDY and validated by National Nodes and Networks.



Studies were research-driven (n=2016) and industry funded trials (n=1878), while globally, centres were involved in 432 trials (both research-driven (n=2016) and industry funded trials (n=1878))

From 50 to 65% of centers declared:

*- to have a dedicated **clinical trial centre** or unit*

- at least 1 Medical Doctor, 1 Nurse, 1 pharmacist, 1 study manager and 1 data manager

*- dedicated **pharmacy services** and personnel,*

*- GCP-compliant **technical facilities** and electronic electronic Case Report Forms*

*38 centres declared the use of **performance metrics** for individual studies*

Item (n. total 60)	*Proposed indicator(s)*	*Number of centres responding to the item*
Centres readiness to perform trials	Existence of a specific clinical trial centre or unit acting as single contact point for study entry	26
	Presence of study manager(s) dedicated to paediatric clinical trials and studies within the site	
	Presence of an internal agreement, regulation or standard contract for the definition of clinical trial agreements	
Clinical competences	Number of beds for hospitalization > 20	44
	Coverage of > 70% of therapeutic areas in the management of paediatric subjects aged 0-<18 yrs	
	Coverage of at least two complex therapeutic areas (neonatology, oncology, rheumatology, cardiology, neonatal/paediatric intensive care units)	
Capability to perform GCP clinical trials	Conduct of paediatric trials contributing to drug registration with a national regulatory agency, European Medicines Agency or others	8
	Availability of a dedicated unit for PK evaluation (phase I-II studies)	
	Managing paediatric clinical trial data (collection, integration and validation of clinical trial data)	
	Managing paediatric clinical trial technical aspects (e.g. shipping agent, operative instructions, laboratory procedures, etc.)	
	Managing Investigational Medicinal Products for paediatric clinical trials	
	Performing Pharmacovigilance activities in paediatric clinical trials	
	Performing Quality Assurance activities for paediatric clinical trials	
	Performing monitoring activities for paediatric clinical trials	
Ethics and patients interactions	Assist the preparation of a Paediatric Investigation Plan or a Paediatric Study Plan	30
	Design protocols for paediatric clinical trials/other paediatric studies	
	Design Case Report Forms for paediatric studies	
	Performing submission of documents to Ethics Committees/Competent Authorities for the approval/authorisation of paediatric clinical trials	
	Establishment of structured collaboration with Patients Associations and Young Patients Advisory Groups	

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Inventory of paediatric clinical sites and facilities to evaluate Paediatric Trials feasibility

Current status of TEDDY contribution in the field

- *A valuable Pilot experience demonstrating that a large number of centers could be engaged in a very complex survey*
- *The involvement of many National Contact Points has increased noticeably the possibility to reach many centers in all EU countries*
- *Results could be usefully implemented in the ongoing Networks experience (National Network as INCiPiT has adopted the TEDDY survey; TEDDY survey has been also cited in the framework of c4c, etc.)*

TEDDY contribution to Enpr-EMA Working Group on clinical trial preparedness

Action group 1

Published guidance and literature was searched for documents discussing trial preparedness.

A total of 47 documents were identified and considered relevant.

TEDDY analysed **14 documents** indicating all trial preparedness factors and proposed solutions from the reviewed documents.

Action group 2
Now started

Action group 4

15 potential stakeholders identified for surveys and interviews. TEDDY contributed in the following:

Stakeholders groups	Survey completed	Interviews
CRO representatives	7	
Patient associations	7	1
Study Coordinators	3	
ERNs	5	
ENPREMA networks	7	

Tot Working Group: 56 completed surveys and 13 personal interviews

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TEDDY future plans and ambition

Through an **autonomous representativeness we aim to:**

Favouring cooperation between the different stakeholders to **accelerate the availability of safe and efficacious medicines for children all over the world**

Have a **consolidated role** in the European paediatric research community framework **actively taking part in new EU projects**

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EPTRI

EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH INFRASTRUCTURE

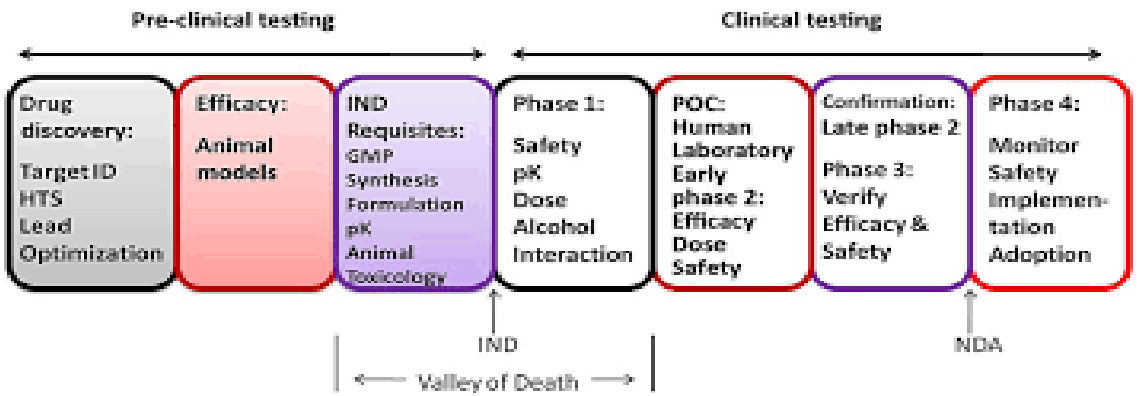
EPTRI: the European Paediatric Traslational Research Infrastructure

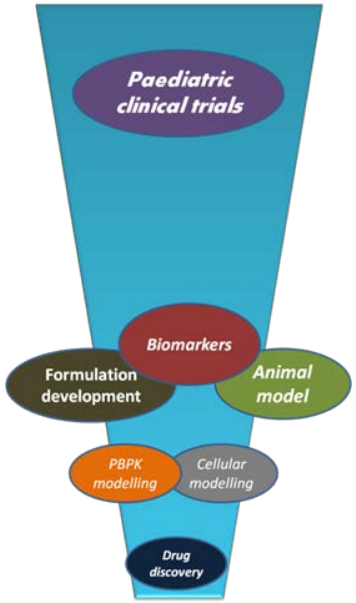
Adriana Ceci – Donato Bonifazi

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 777554

EPTRI: Why a new RI

Paediatric Research to be complemented with structural support
On a total of 13 RIs in EU, none deal with paediatric specificities





Children are not little adults: physiologic characteristics are different from the adults and extremely variable. All phases need an ad hoc paediatric approach

Traslational approach is particularly needed in paediatric where structural and research support are very limited

Paediatric Research should be better integrated in order to become more efficient in providing useful results

FP7/H2020 paediatric projects addressing paediatric themes as core topic (analysis of projects from http://cordis.europa.eu/search/simple_en).

ePTRI
European Paediatric Translational Research Infrastructure

ID-EPTRI: the contents

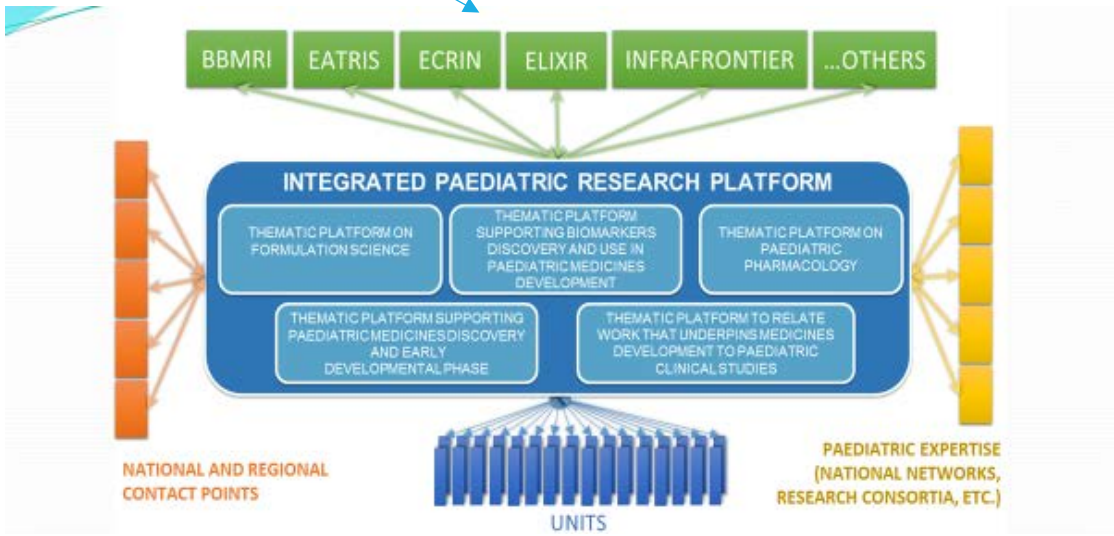
WHAT WE HAVE IN MIND:

- Keep the paediatric specificity at the core of the RI
- Integrate the available enabling technologies in paediatric research to advance the development of medicines in children
- Identify and populate 4/5 thematic research Platforms

All Contacts (n=~900)

- specific targets for paediatric indications
- in vitro models to quantify the impact of ontogeny on the ADME
- validation of genetic biomarkers relevant in paediatric diseases
- emphasis on paediatric and neonatal specificities
- pro-active pre-clinical investigations based on preclinical and adult data
- contribution of the systematic use of "placental platforms" to quantify placental drug transfer (in vitro, ex-vivo studies) and fetal / neonatal / potential long-term risks
- systematic bio-banking of small biological samples (gut, liver, kidney and brain)
- integration of IT technologies in the drug development process (data exchange, integration and reuse)
- planning extrapolation, modelling and simulation

-etc



ID-EPTRI project: What is it

EPTRI project: a framework for a new translational paediatric research Infrastructure conceptual design

European Commission

TOPIC : Design Studies

Topic identifier:	INFRADEV-01-2017
Publication date:	14 October 2015
Types of action:	RIA Research and Innovation action
DeadlineModel:	single-stage
Opening date:	08 December 2016

26 partners, 19 countries (EU-non EU)

EPTRI
European Paediatric Translational Research Infrastructure

Conclusion

- EPTRI is just at the beginning
- Key words in the project are ‘integration, complementarity’
- EPTRI will be a Research Infrastructure for basic research and innovative tools to be integrated into clinical trials
- We aim to come back to EnprEMA in a next future to:
  - Show and discuss the results of the survey
  - Identify windows for useful collaboration

ePTRI
European Paediatric Translational Research Infrastructure