European Paediatric Clinical Trial Network

Mark Turner

Carlo Giaquinto

conect 4children

COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

Declaration of interests

- My employers have received funds for clinical studies from: Roche, Chiesi, Johnson & Johnson, Pfizer, EC FP7, NIHR, BLISS, MRC, AMR
- My employers receive funds for consultancy from Chiesi, BMS, Novartis, Shire, Janssen, Grunenthal, Ferring
- Lead for International Liaison, National Institute for Health Research, Children's Theme
- Co-Coordinator, Global Research in Paediatrics (GRiP)
- Chair, European Network for Paediatric Research at the European Medicines Agency
- Co-Director, International Neonatal Consortium

Critical Issues in paediatric trials

Medicines for Children and Young People need to be adapted with respect to:

- Formulation
- Dose
- Target
- Indication
- Safety

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Opportunities

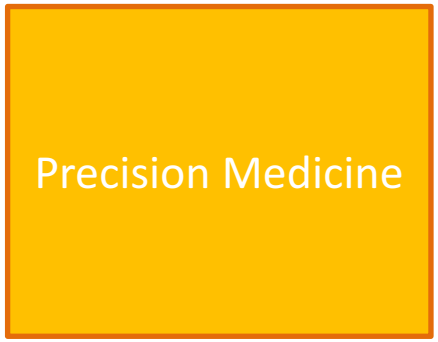
Challenges

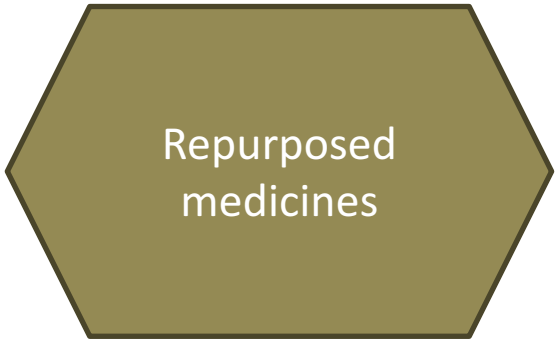
- Design
- Implementation

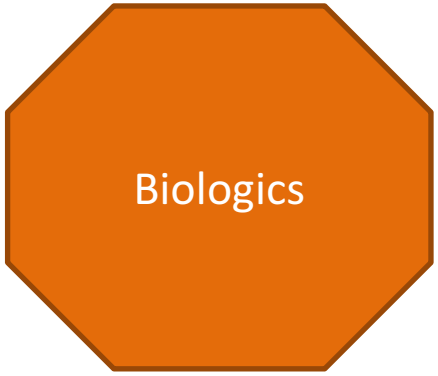
Solutions

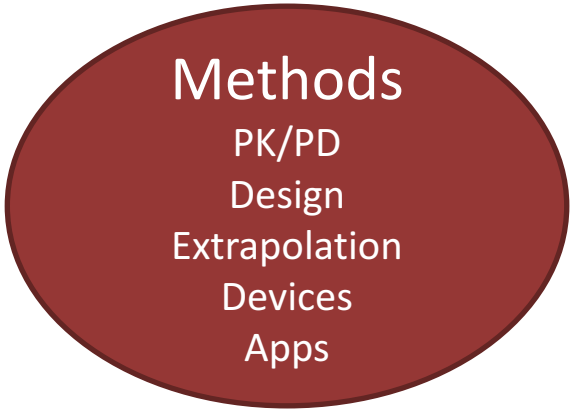
- Network

Opportunities









Number of children planned to be enrolled in clinical trials, by age by year of authorisation of the trial (or, if not available, by year of protocol upload into EudraCT).

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Preterm neonates	0	0	0	327	82	2,527	1,552	3,634	4,997	1,979
Term neonates	0	98	5	184	169	1,353	2,283	1,488	2,168	1,749
Infants and toddlers	530	119	20	54,715	2,224	13,318	62,226	17,772	39,095	122,295
Children	2,683	706	270	5783	2,771	21,665	30,831	27,994	65,824	48,358
Adolesecents	435	36,458	285	5801	4,869	20,206	22,680	17,628	45,717	36,921
Total	3,648	37,381	580	66,810	10,115	59,069	119,516	68,516	157,261	211,302

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Clinical + Regulated

Therapeutic Development: Clinical

Starting point: Clinical question.

Goal: Answer that question for publication and guidelines

- Refine clinical experience
- Develop hypotheses
- Recruit as many participants as possible
- Is the result true (internal validity)?
- Is the result useful (external validity / generalisability)?

I can review the results in the patients I treat subsequently

Risk-based monitoring: Sponsor needs – GCP compliant

Therapeutic Development: Regulated

Starting point: Identify condition and indication

Goal: Satisfy an independent body of the efficacy, safety and quality of the intervention before people can sell the product

- What is known already?
- What do I need to gather to meet the standards of efficacy, safety and quality?
- Can the regulator trust my results?
- Can I justify the steps I taken (given that all research involves judgments and compromises, can the regulator accept my judgments and compromises)?

Risk-based monitoring: Sponsor needs + FDA/EMA compliant

Reforming Clinical Trials in Drug Development: Impact of Targeted Therapies

Janet Woodcock, M.D.

Director, CDER, FDA

Extracted from a slide set from November 16, 2016

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm074833.htm

Common Problems in Rare Disease and Disease Subsets

- Natural history of the disease or disease subset not clear
  - For disease subset, includes prognosis compared to overall disease
- Biomarker measurements, their discriminatory performance, cutoffs, etc. not well worked out
- Outcome measures for disease have never, or rarely, been tested
- Overall development plan not a whole
- Murphy's law operates

Natural History of Disease: Critical to Planning a Development Program

- Burden of disease
  - What are the symptoms?
  - What would patients most like to have relieved?
  - Are there instruments to measure these?
  - Tradeoffs: how much risk is acceptable for benefits?
- Rate of progression of symptoms
  - Over what time period does measurable change occur?
  - What symptoms progress faster and is this true for everyone?
  - Don’t just rely on experts, they are usually wrong, due to sampling bias

Natural History

- Disease heterogeneity
  - Often, rare diseases are heterogeneous in their expression; rare subsets may or may not be
  - Introduces more variability, which is the bane of finding signal within noise
  - With highly variable disease, self-controlled trials may be best
- Many natural history studies are done by academia through registries, etc. May lack documentation, may not be representative sample

Improving the quality of advice

	What we offer: (Business proposition)		We will use a number of tools: (Value Creation)			
Function	Based on information about:	We will provide	Level 1	Level 2 Tool	Level 3 Tool	Level 4 Tool

Improving the quality of advice

	What we offer: (Business proposition)		We will use a number of tools: (Value Creation)			
Function	Based on information about:	We will provide	Level 1	Level 2 Tool	Level 3 Tool	Level 4 Tool
Natural history	Incidence, progression, outcomes, etc. AND extent of variation AND delineation of important subtypes	Interpretation of natural history data that identifies relevant information gaps	Expert group +/- selected case series	Cumulative registry of patients	Full –omic characterisation (genomics, proteomicsmetabolomics,)	Harmonisation of definitions Interoperability

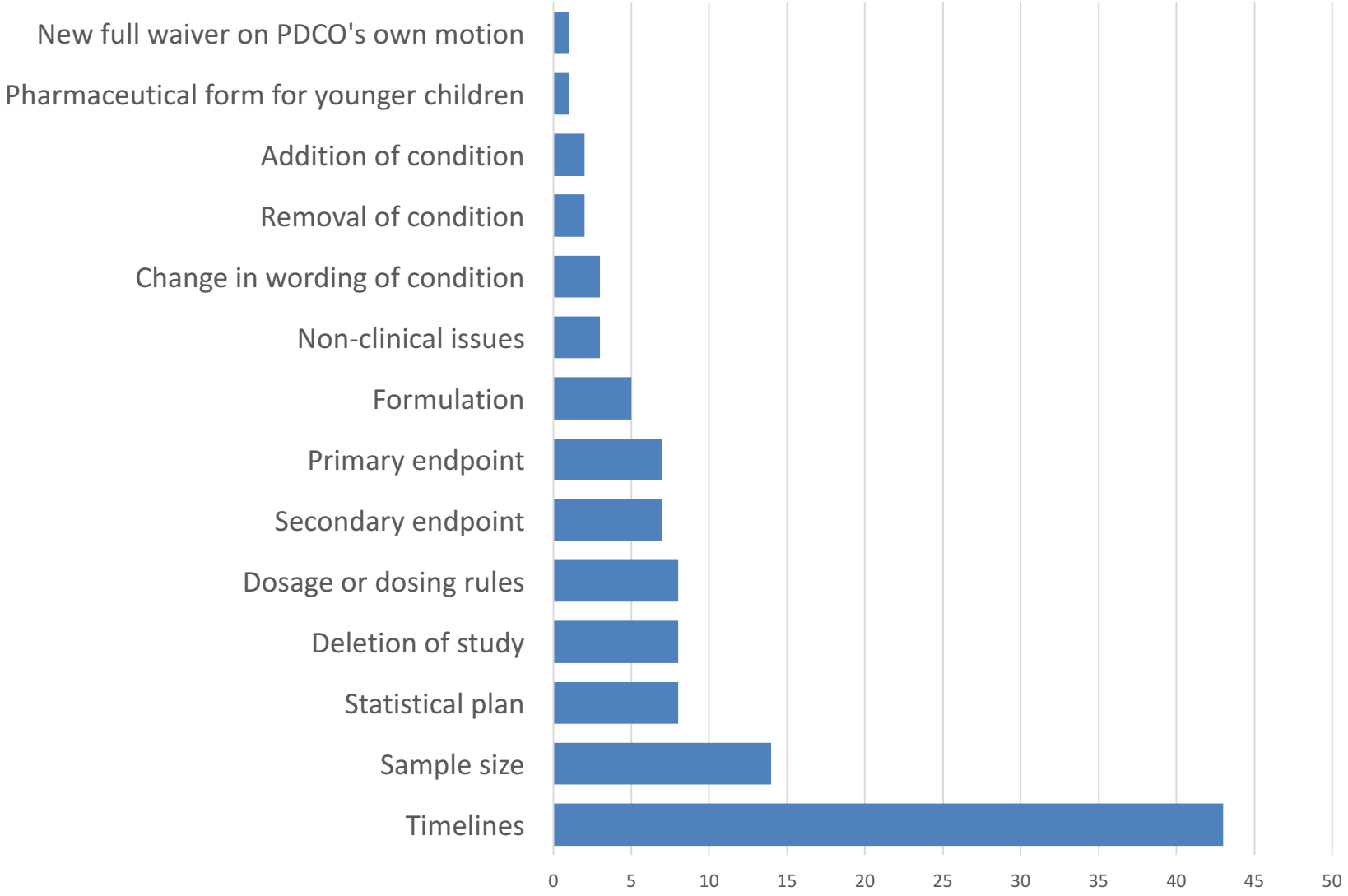
Improving the quality of advice

	What we offer: (Business proposition)		We will use a number of tools: (Value Creation)			
Function	Based on information about:	We will provide	Level 1	Level 2 Tool	Level 3 Tool	Level 4 Tool
Evidence-based feasibility	Aggregated information about Demographics, Diagnosis, Current condition and treatment	Factors that promote or hinder recruitment of patients who appear to be eligible	Expert group +/- selected case series	Cumulative registry of patients	Integrated data from all of Europe that is compatible with global sources	Harmonisation of definitions Interoperability

Quality and Value

We could charge: (Value Capture)
For Access to: Data Data systems Underlying elements: e.g. harmonised definitions Experts
Payment by results: charge if clinical input is used in a PIP

Challenge: Implementation Modification to PIPs (%)



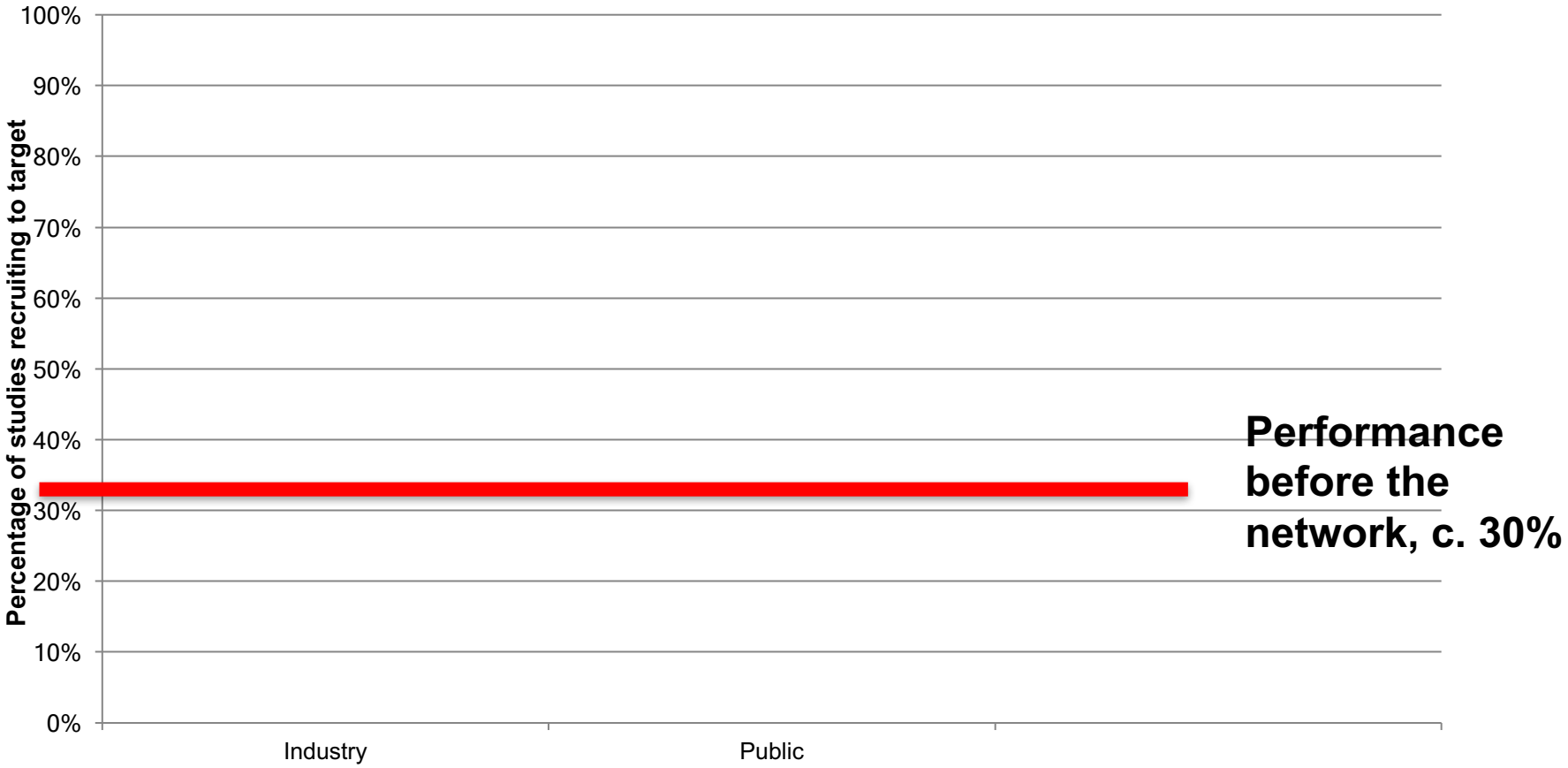
Delivery of paediatric trials

Need to overcome

- Fragmentation
- Inefficiency

Recruitment to target (2013/14)

NHS
National Institute for Health Research
Clinical Research Network Children



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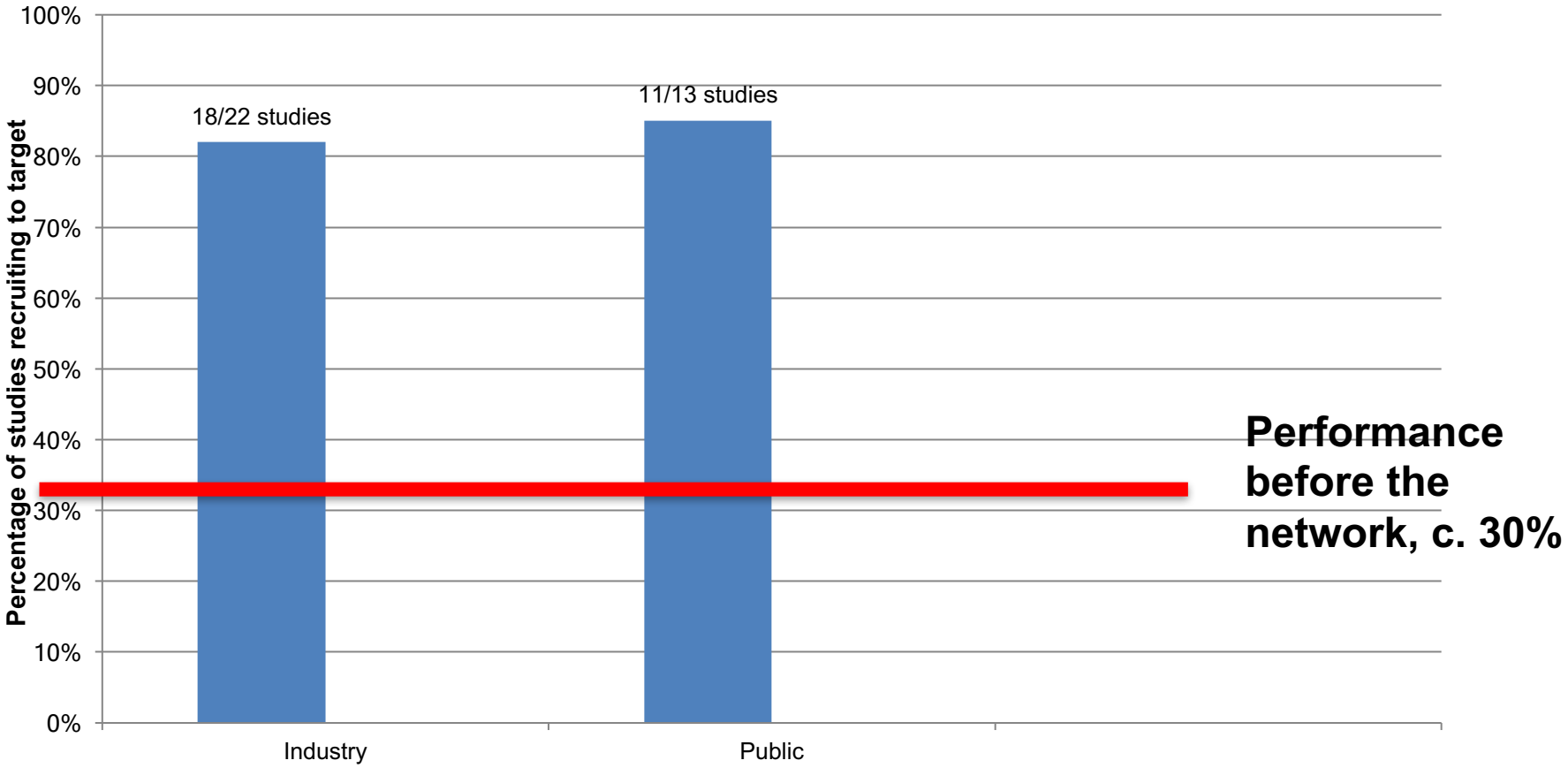

Background to the IMI2 call

Widespread agreement that the current approach is not working

- Companies
- Regulators
- Investigators

Companies and EC want a coordinated system and will pay to set one up

IF it is well-run and delivers clinical trials reliably

Project Concept

1. Use resources from the IMI2 project to setup the network and its processes
   - National
   - International
2. Demonstrate the value of the network approach with selected
   - Studies
   - Sites
3. Generalise from the demonstration projects to the broader network

Sustainability

"Generalise from the demonstration projects to the broader network"

This involves:

- Persuading funders to invest in sites, national networks and international networks (including expert advisory groups)
- Demonstrating financial, economic and social value of the network
  - Capturing value that sites and networks create
- Proof-of-viability: inclusion or exclusion in the demonstration projects does not affect involvement in the definitive network

Consortium Members

National networks		Emerging networks
UK	Finland	*Poland*
Spain	Norway	*Portugal*
France	Estonia	*Sweden*
Italy	Austria	*Denmark*
Switzerland	Ireland	*Greece*
Belgium	Hungary	*Serbia*
Netherlands		*Croatia*
Germany	*Czech Republic*	*Slovenia*

Consortium Members

Specialty	ERNs	Others
PENTA-ID	MetabERN	European Young People's Advisory Group Network
PRINTO	Renal	
CF	Rare epilepsies	EURORDIS
SIOPE	Paediatric Oncology	ECRIN
Treat-NMD		EUREC
ENCP		*INNODIA*
		Other IMI2 projects

Benefits of the network

This initiative will benefit individual clinical study sites and specialty networks through:

- harmonized, streamlined procedures across the trial lifecycle,
- access to a wide range of study sponsors through a transparent, evidence-based, network-wide vetting procedure
- input from national networks (sites, standardisation, training)

Early and clearly coordinated communication between investigators and sponsors, regulators, and experts will streamline and facilitate the process of generating and applying much needed information on medicines for children.

WP1

Project Management and Oversight of IMI project

a) project design and charters with clear accountabilities;

b) set-up of joint governance structure;

c) provide coordination and support to work package teams;

d) define work expectations of different work streams, deliverables, dates and activities and review progress regarding adherence to budget, timelines and quality;

e) ensure that key cross-functional partners are engaged;

f) define project interdependencies, stakeholders and risks;

WP2

Organisation and Governance of the pan European Paediatric Clinical Trials Network

a) establish the structure and governance of the network;

b) build a lean central coordinating organisation to steer the network;

c) establish a single point of contact for entering the network for all kind of sponsors;

d) develop a transparent process and criteria for selection of studies to be performed by the network. A process needs to be installed that ensures proper selection and allocation of all kinds of studies (industry and non-industry studies) to the network:

- this process is to be applied to all new studies brought to the attention of the network after successful conduct of all planned proof of viability studies (three to four from industry and at least one non-industry study);
- in the initial period, a separate process will be needed to allow allocation and selection of at least one non-industry sponsored study (including budgeting) to test the network;
- the project will also need to ensure that network's own scientific advisory groups (to be implemented under work package 4 are adequately involved in this process.

WP2

Organisation and Governance of the pan European Paediatric Clinical Trials Network

e) build network-wide processes for contracting and invoicing of respective activities (studies, scientific advice etc.);

f) build governance processes ensuring close management of budgetary, quality and data protection/privacy related processes and activities, including coordination of scientific advisory and feasibility groups;

g) build quality management processes to ensure all network activities are in compliance with common research standards and (inter-) national regulations for the conduct of clinical trials;

h) build external stakeholder management process to:

- establish liaison with governments of participating countries, and with identified national hub sites and other participating sites;
- leverage synergies with other IMI2 projects, existing research consortia, existing national and disease specialty networks, and patient advocacy groups;
- collaborate with other emerging paediatric clinical trial networks (in North America and beyond) to assure international interoperability.

WP3

Business Plan Development, Expansion of the Network, and Sustainability of the Network Sources of Funding post IMI2 support

Work with stakeholders

Can't use ethical arguments alone

** Need data to support the business case **

WP3

a) development of a business model to ensure sustainability and sufficient funding of the network after the end of the IMI project;

b) development of a fee structure for participating sites, networks, and other organisations that are part of the network, and for sponsors submitting studies to the network for consideration and execution;

c) development of a procedure to recruit and integrate new sites into the network, and to allow new, additional industry and non-industry sponsors to use the network;

d) engagement with national entities (ministries of health, national government research organisations) to support the clinical trial infrastructure that has been developed for the network in their country;

e) investigation of other sources of continued funding.

WP4: Scientific advice, feasibility and innovation

a) implement expert panels evaluating the rationale for a clinical development plan, the requirements for data generation/integration, and whether a certain study proposal can be implemented and successfully conducted by the network (feasibility groups);

b) set-up and maintain groups of scientific experts to trigger innovation (develop and implement innovative methods, including dose selection, biomarkers, endpoints and/or study designs);

c) implement standing disease or condition-focused network clinical advisory groups (made up of non-industry medical experts) who consult with all sponsors on scientific and clinical questions for specific paediatric drug development programs and protocols within the field of their expertise;

d) set-up process to allow patients/parent representatives to give input to new innovative study designs and to participate in evaluation of feasibility, design, meaningful endpoints, and risk-benefit of given paediatric study protocols;

e) creation of the charter, definitions of operations, and selection of members of the different scientific bodies.

WP5: Data coordinating centre and data quality standards

a) establish procedures and systems/tools to monitor performance metrics in all network trials at the sites, national hubs, and in the central network organisation;

b) promote shared definitions of terminology enabling uniform process for collection and storage of clinical data;

c) contribute to common eCRF definitions (e.g. common paediatric data dictionary);

d) contribute to common program/process to allow electronic storage and archiving of study related documentation.

WP6

Network Research Personnel Education and Training

Educational palette

- Parents and Young People
- Clinical staff
- Investigators
- Dedicated researchers

GRIP Masters / Road Show

WP7: Planning and execution of clinical trials

a) develop and implement uniform standards and processes for clinical project management (subject to country variations), including processes for study planning and budgeting, contracting, clinical monitoring, data management, regulatory interactions, CRO interactions;

b) develop network-wide standardised study procedures and documents, including but not limited to confidentiality agreements (CDAs), master contracts, budget templates;

c) network-wide unique procedures/templates for ethics committee (ICFs, assents) liaisons, and regulatory reporting and procedures (at least uniform and centralised at member state level), in accordance with EU clinical trial regulations;

d) define and utilise all available tools for a robust assessment for trial readiness and feasibility at each site;

e) develop an operational implementation plan to execute the study of a new drug, including execution of three to four industry and at least one non-industry study to be conducted to test the viability of the network;

f) organise a procedure for applying performance metrics to measure site and network performance in the execution of clinical trials, and institute measures to improve efficiency, including but not limited to requirements for site accreditation, performance metrics, and quality control;

g) after finalisation of the 'proof of viability studies', evaluate the performance of the network based on performance metrics created under f) above and feedback results to network governance, the full consortium management board and IMI.

WP7

Planning and Execution of Clinical Trials

3 – 4 industry trials

3 – 4 non-industry trials (€5 – 10 million)

- Open selection
- Trials are autonomous
- Network joins TSC

WP7

Planning and Execution of Clinical Trials

Infrastructure to keep track of process in order to address issues that arise with:

- Motivation
- Resources
- Performance

Summary

We have the opportunity to develop a lasting solution to many of the problems in paediatric drug development

The solution includes expert groups, common procedures and standards for sites that will benefit all of paediatrics.

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