DEFERIPRONE EVALUATION IN PAEDIATRICS

SEVENTH FRAMEWORK PROGRAMME

FP7 Projects in Rare Anaemias: DEEP - Deferiprone Evaluation in Paediatrics

Adriana Ceci
DEEP Scientific Coordinator,
on behalf of DEEP Consortium

DEFERIPRONE EVALUATION IN PAEDIATRICS - FP7 PROJECT - SP1 - COOPERATION HEALTH-F4-2010-261483

OUTLINE

1- Project Specificities:

2- The Regulatory steps:

PIP

Clinical Trials in the project

3- The DEEP CT facilitating strategy

4- Status of the projects and preliminary results

PROJECT SPECIFICITY: RESPONDING TO EU POLICY NEEDS (FP7-HEALTH-2010. 4.2.)

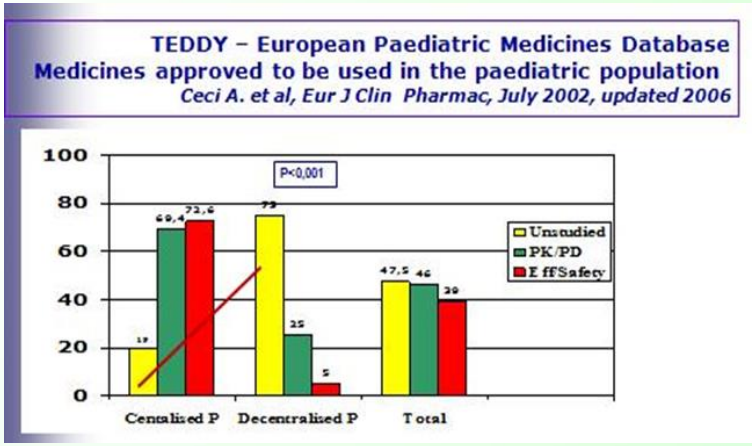
- only ~ 30% of marketed drugs are paediatric in Europe

- a large Paediatric 'off-label' use occurs as:
  - Unapproved formulations
  - Drugs for adults not tailored for children

- Less than 50% of Paediatric Medicines have been studied in children

Age	UK(%)	It(%)	NL(%)
< 2	33.0	20.0	32.1
2-11	0.4	1.6	26.4
12-17	2.0	2.0	42.5
Total	4.7	7.6	32.4

Neubert and al, on behalf of TEDDY NoE, Pharmacol Res. 2008 Nov-Dec;58(5-6):316



Increase drugs and Trials in children

Grant a Paediatric Investigational Plan before the trials will start

Identify therapeutic needs and Priority for funding

REGULATION (EC) No 1901/2006

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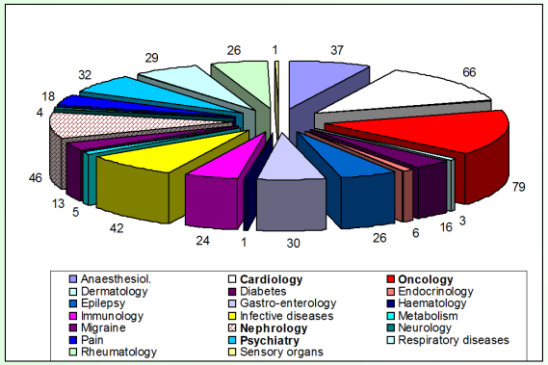
PROJECT SPECIFICITY: RESPONDING TO EU POLICY NEEDS (HEALTH-2010-4.2-1 : OFF-PATENT MEDICINES FOR CHILDREN)

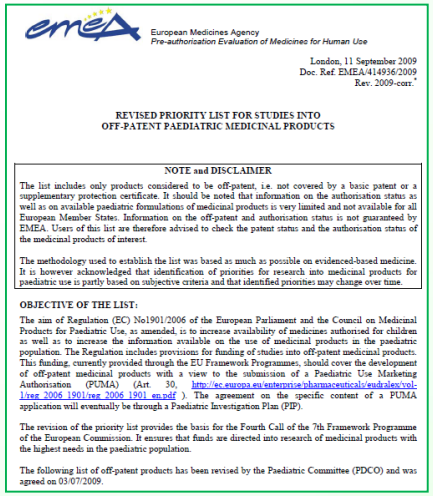
Measures in the Paediatric Regulation

- ensuring that **new products (or variations)** will be developed to meet paediatric needs according to PIPs agreed by the Paediatric Committee (art.7- art.8)
- Give a new MA (PUMA) to the **existing** medicines (OFF-PATENT) willing to developing at least one paediatric study (art.30). **PIP is needed**

New MA



All the needs: ~ 20 therapeutic classes
~ 400 active substances



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 11 September 2009
Doc. Ref. EMEA/414936/2009
Rev. 2009-corr.*

REVISED PRIORITY LIST FOR STUDIES INTO OFF-PATENT PAEDIATRIC MEDICINAL PRODUCTS

NOTE and DISCLAIMER

The list includes only products considered to be off-patent, i.e. not covered by a basic patent or a supplementary protection certificate. It should be noted that information on the authorisation status as well as on available paediatric formulations of medicinal products is very limited and not available for all European Member States. Information on the off-patent and authorisation status is not guaranteed by EMEA. Users of this list are therefore advised to check the patent status and the authorisation status of the medicinal products of interest.

The methodology used to establish the list was based as much as possible on evidenced-based medicine. It is however acknowledged that identification of priorities for research into medicinal products for paediatric use is partly based on subjective criteria and that identified priorities may change over time.

OBJECTIVE OF THE LIST:

The aim of Regulation (EC) No1901/2006 of the European Parliament and the Council on Medicinal Products for Paediatric Use, as amended, is to increase availability of medicines authorised for children as well as to increase the information available on the use of medicinal products in the paediatric population. The Regulation includes provisions for funding of studies into off-patent medicinal products. This funding, currently provided through the EU Framework Programmes, should cover the development of off-patent medicinal products with a view to the submission of a Paediatric Use Marketing Authorisation (PUMA) (Art. 30, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf). The agreement on the specific content of a PUMA application will eventually be through a Paediatric Investigation Plan (PIP).

The revision of the priority list provides the basis for the Fourth Call of the 7th Framework Programme of the European Commission. It ensures that funds are directed into research of medicinal products with the highest needs in the paediatric population.

The following list of off-patent products has been revised by the Paediatric Committee (PDCO) and was agreed on 03/07/2009.

Products into the Priority List
~ 13 therapeutic classes,
~100 active substances

Funding of studies into off-patent medicinal products should be provided through the EU FRPs (art. 40) with the aim to develop a PUMA

Why Ferriprox was included in the Priority List

The legal status	Ferriprox obtained the EU MA under exceptional circumstances in Oct. 1999 'Off-patent drug'
The relevance of the therapeutic Area	To be used in **rare and more severe** forms of anaemia in the world
The scarsity of approved chelators in some paediatric ages: **Therapeutic Need**	***Age: >2 and < 6y SmPCs information:*** *the only approved drug in this group of age is DFO. Oral chelators can be used if DFO is refused, inadequate or contraindicated*
The scarsity of clinical evidence	**Few data** in children **<10 years** No controlled comparative trials
The expected **therapeutic benefits:** Optimal doses of SC DFO or PO DFX are less effective than DFP in reducing cardiac iron and improving cardiac function	**Reduced cardiac mortality and morbility** if the drug used as first line Possible preventive effect if used in younger children before iron accumulation

DEEP

DEferiprone Evaluation in Paediatrics

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THEME [HEALTH.2010.4.2-1]
[Off-Patent Medicines for Children. FP7-HEALTH-2010-single-stage]
Grant agreement for: Collaborative project*

Annex I - "Description of Work“

Project acronym: DEEP
Project full title: DEferiprone Evaluation in Paediatrics
Grant agreement no: 261483
Start date : 2011-01-01

The DEEP consortium

A large research-driven network including:

- 15 Partners
- 17 recruiting centres from 6 Countries:
  - EU Centres: Cyprus, Greece, Italy
  - non-EU Centres: Albania, Egypt, Tunisia
- industrial partners: to guarantee the future commercial development of the drug (Apopharma-Apotex)

The DEEP project

Objective to perform paediatric studies on ***deferiprone*** and to develop a new liquid formulation specific for the paediatric population

Project contents:

New Liquid Formulation

2 Clinical Trails:

-PK trial providing dose definition (DEEP-1)

-efficacy-safety multicentre, controlled, active comparator trial (DEEP-2)

2 post marketing studies

long-term safety non-interventional study (DEEP-3)

pharmacoeconomic study

A new Marketing Authorisation (PUMA)

DEEP Project: Regulatory Steps

FP7 project approval

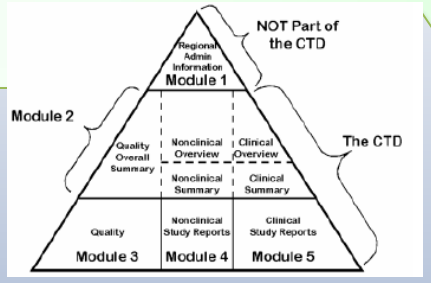
March 2010

November 2011

PIP granted

CTs Application and conduct

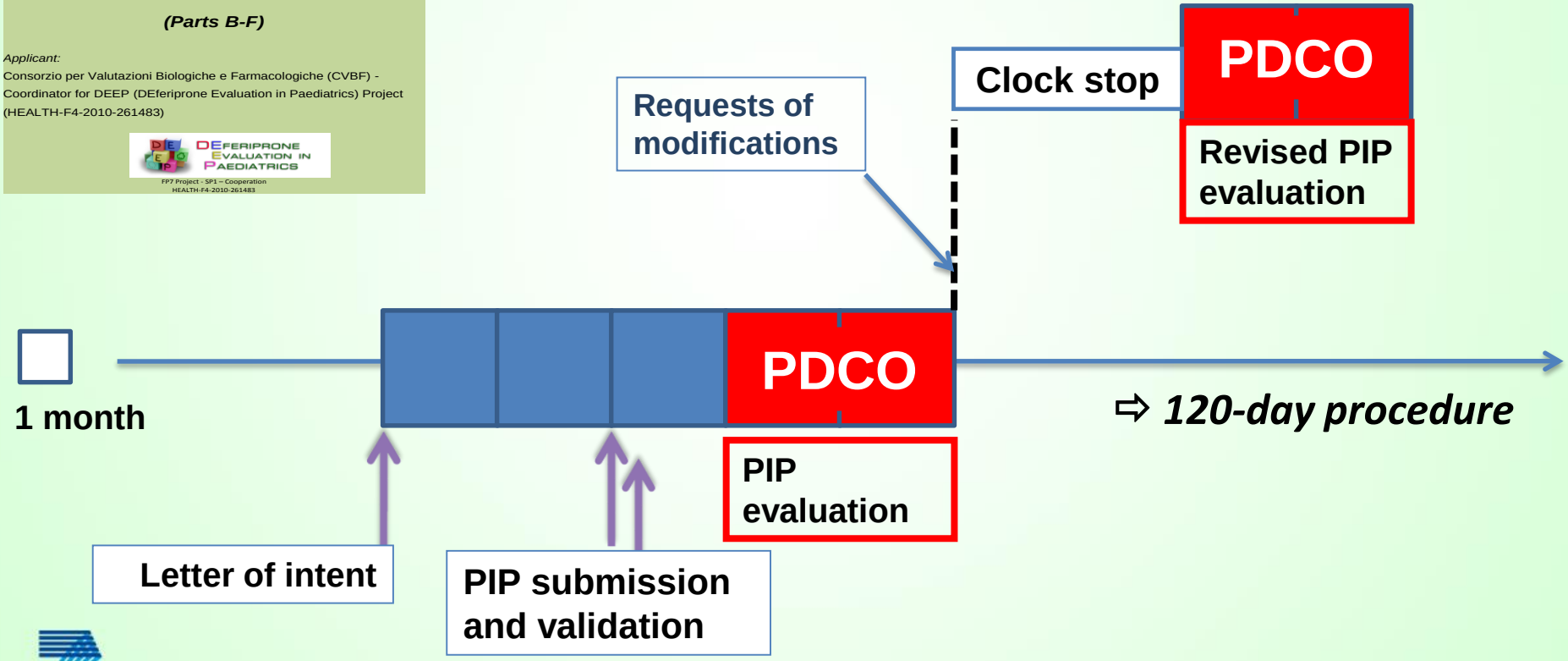
May 2012 - ongoing



PUMA Application

REGULATORY REQUIREMENTS IN DEEP: PUMA AND PIP

PIP: a document aimed at ensuring that the necessary data are generated for the **conditions** in which a MP can be authorised to treat the paediatric population (all ages)



DEEP ADVANCEMENT FROM THE APPROVED PIP

	PROJECT	APPROVED PIP
CONDITION	Beta-thalassemia	Haemoglobinopathies requiring transfusion and chelation
AGE GROUPS	2-10 years	Up to 18 years
STUDIES and PATIENTS	PK study: 18 pt Efficacy-Safety: 254 Longterm Safety: 400	18 pt → 344 400
STUDY AIMS AND DESIGN	•To study PK in a trial with patients receiving multiple oral doses of DFP •To assess the non-inferiority of DFP in reducing serum ferritin levels compared to DFO	• To study PK through an experimental phase and a modelling phase • To assess the non-inferiority of DFP compared to DFX in terms of changes in ferritin levels and cardiac iron concentration

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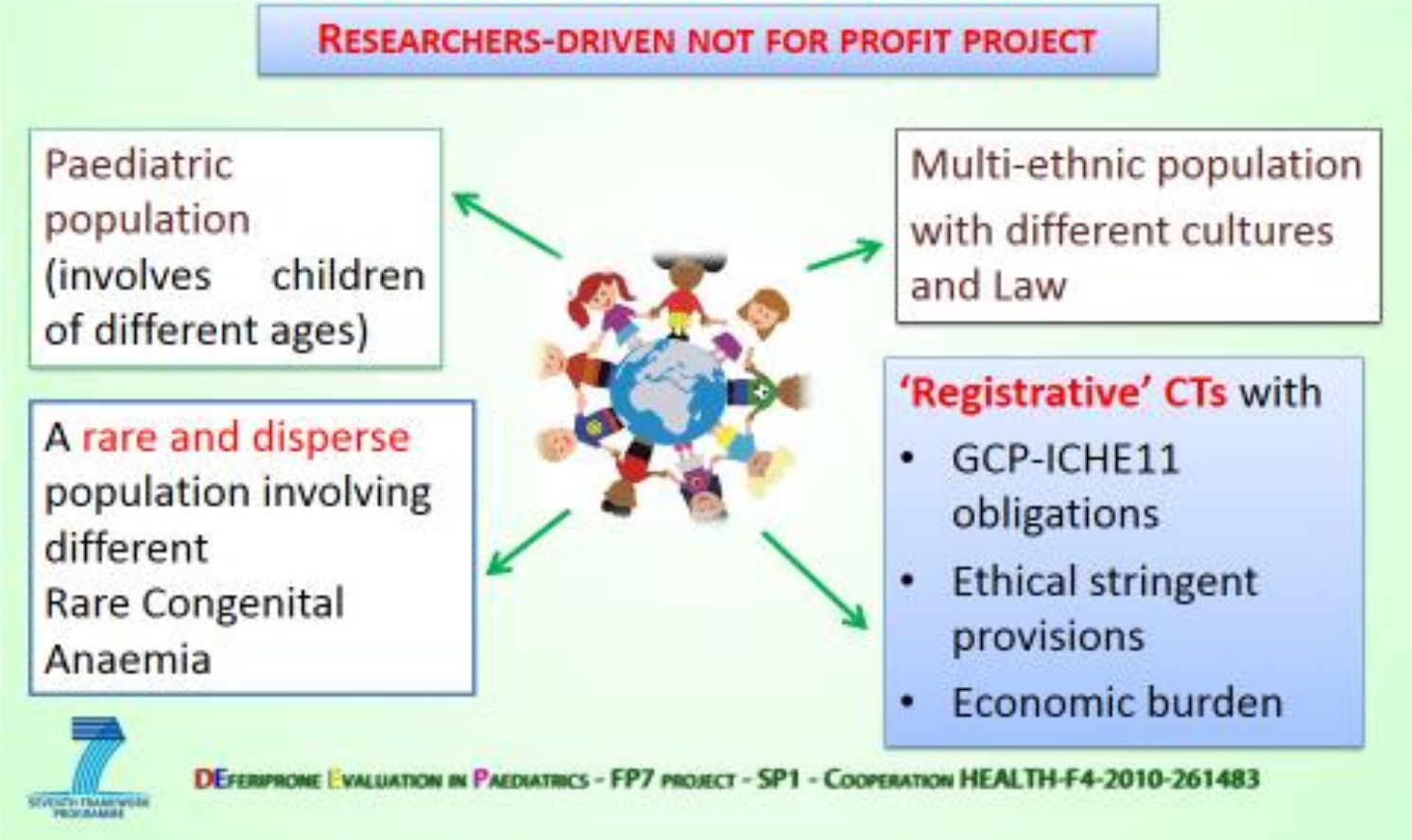
DEEP ADVANCEMENT FROM THE APPROVED PIP

- Innovative approaches in CTs: ***DEEP-1*** **PK modeling/simulation** study to define the drug exposure and appropriate dosage of deferiprone for children aged < 6yr
- Deletion of the age-cut off. Inclusion criteria based only on number on **transfusional Fe** intake
- First time comparison between the **two oral available comparators**: ***DEEP-2****:* the **larger RCT** in *paediatric patients* comparing deferiprone vs deferasirox
- **Cardiac MRI-T2* as primary endpoint**

- Multiple serum ferritin levels evaluated in all patients throughout the study
- Cardiac MRI T2* included as **co-primary endpoint** for children above 10 year and liver MRI-R2 included to measure **LIC as a secondary endpoint** in all patients not requiring sedation.

Clinical Trials in DEEP

FP7-HEALTH-2010	HEALTH-2010-4.2-1 Off-patent medicines for children
For clinical trials, EC contribution will be limited **to phases I and II** and only exceptionally to further studies	Consideration may be given to studies including up to **Phase III clinical trials**



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3- challenging matters in CTs

RESEARCHERS-DRIVEN NOT FOR PROFIT PROJECT

Paediatric population (involves children of different ages)

Multi-ethnic population with different cultures and Law

A rare and disperse population involving different Rare Congenital Anaemia

'Registrative' CTs with

- GCP-ICHE11 obligations
- Ethical stringent provisions
- Economic burden

The ethical and legal framework of CTs in DEEP

Specific approach to be adopted taking into account the cultural characteristics and the possible diversities in human subject protection regulations

EU framework

- Directives 2001/20/EC and 2005/28/EC implementing GCP
- Directive 95/46
- EudraLex Vol. 10 Detailed guidance on CTA (EC, 2006, 2010)
- Reflection paper on ethical and GCP aspects of CTs outside EU/EEA (EMA/121340/2011)
- Paediatric Ethical Recommendations (EC, 2008)

Extra Europe

The legal approach is different among Countries: each of them has its own rules governing the submission of CTs

The legislative context: national provisions governing CTA in DEEP countries

- In EU Countri[illegible]ly, Cyprus and Greec[illegible]e Competent Authority authoris[illegible]and the Ethics C[illegible]ttee approval is ruled according to D[illegible]e 2001/20/EC[illegible]erms of CTA form, IMP documents, insura[illegible]formed [illegible]nt Specific rules for the paediatric population [illegible]A 2[illegible]ecommendations, ICH-E11, etc)

- In Albania specifi[illegible]s on [illegible]e lacking; a special decision from the Minist[illegible]Health is [illegible]
- In Egypt the [illegible]s largely simila[illegible]urope, but informed consent pr[illegible]res are different.
- In Tunisi[illegible]Ministry of Health, the Na[illegible]and local ECs shall a[illegible]se a paediatric trial

How to deal with existing differences?

Without compromise the trials coherence?

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The DEEP strategy to deal with diversity

THE DEEP MULTISTEPS APPROACH

1. To implement a unique procedure and a unique CTA 'package of documents'

2. To organize a 'trials management plan and infrastructure' including SOPs preparation, data management, drug management, pharmacovigilance, monitoring, etc

3. To develop a 'patients tailored approach' including children, families and association

THALASSEMIA PROGETTO GUARIGIONE

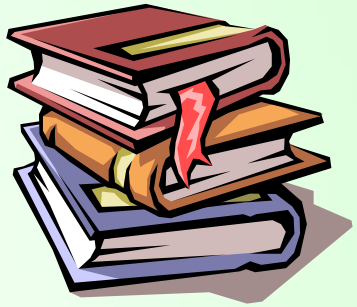
THALASSEMIA INTERNATIONAL FEDERATION MEMBER

Partner representative. Loris Brunetta

The DEEP strategy to deal with diversity

STEP 1: THE 'PACKAGE OF DOCUMENTS'

- **Mandatory registration of CTs (EudraCT)**
- **Preparation for the concerned ECs of the common package including**
  - Protocol (according to **GCP and ICH Topic E11**)
  - IMPs (drugs) information
  - Insurance (*not limiting the liability period*)
  - Privacy and confidentiality
  - Trial facilities at each recruiting center
  - Locally-requested documents
- **Administrative authorisation**



PIP
Protocols
ECs Submission

The EU legislative provisions have been assumed as DEEP Standard

State of art of submission

in Italy

TRIAL SITE	From submission to EC approval	From EC approval to CA authorisation
Az. Osp. Ospedali Riuniti Villa Sofia – Cervello (**Palermo**)	< 2 months	4 months
Az. Ospedaliero Universitaria Consorziale Policlinico di **Bari**	< 2 months	< 6 months
Az. Osp. di Rilievo Nazionale "Antonio Cardarelli" (**Napoli**)	3 months	< 1 month
Az. Osp. G. Di Cristina (**Palermo**)	1 month	2 months
Cli Pe	< 1 month	3 months
Pol	5 months	2 months
Pre Mi	< 4 months	< 8 months
Az.	7 months	Under evaluation
Osp	6 months	Under evaluation
Az.	*nder evaluation*	*n.a.*
ARNAS Garibaldi (**Catania**)	1 month	Under evaluation
ASL **Cagliari** Ospedale Regionale per le Microcitemie	*Under submission*	*n.a.*

In other countries

- EC approval and CA authorisation expected in October-December 2013
- EC approval granted

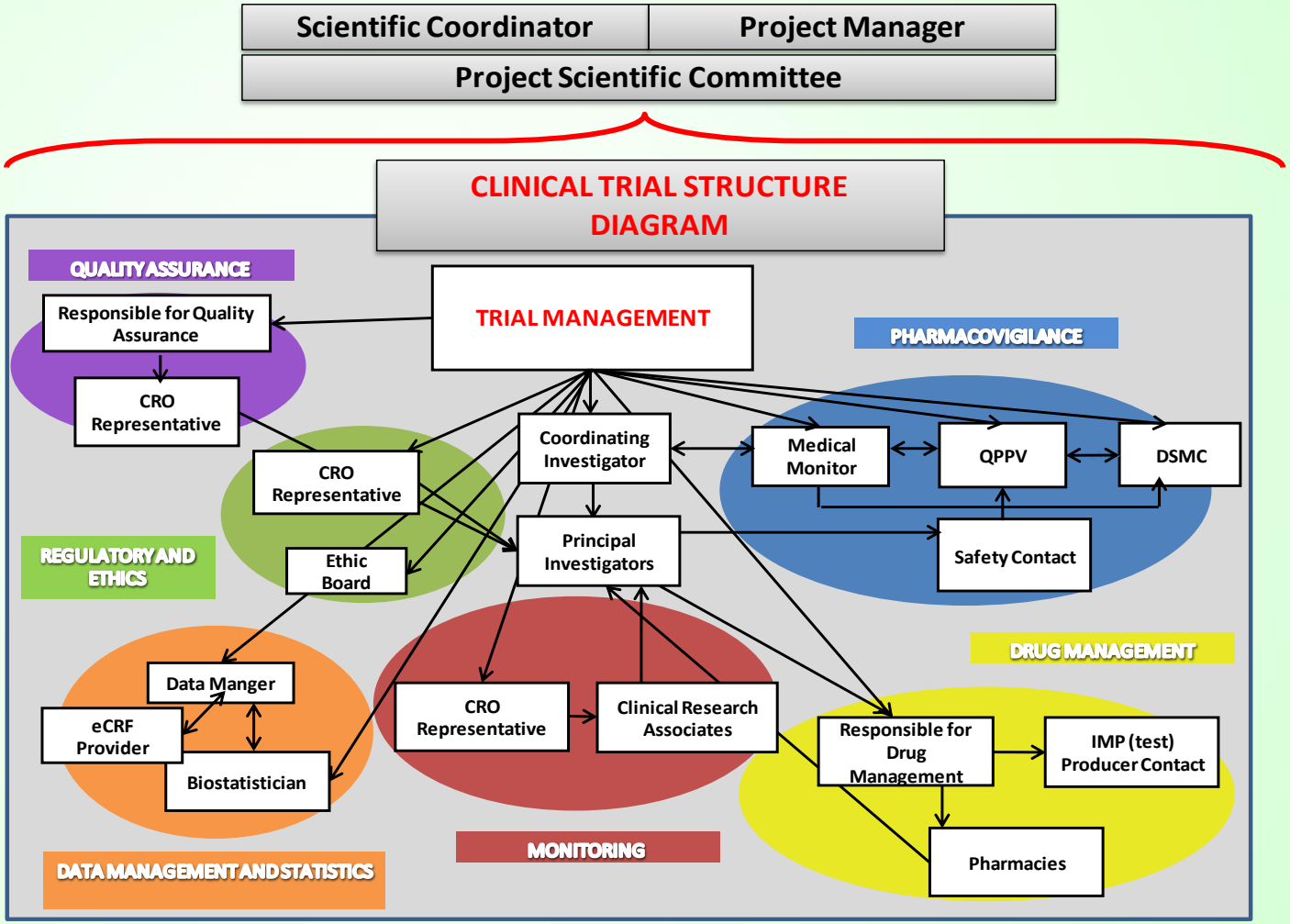
Recruitment and approval: the state of the art

- *DEEP-1* is concluding recruitment with success
- *DEEP-2* approved by the 80% of the Ethics Committees and Competent Authorities and the recruitment in Italy and Tunisia is now starting
- *DEEP-3* observational study has recruited a total of 34 patients

The DEEP strategy to deal with diversity

STEP 2:

A COMPLEX (AND EXPENSIVE) ORGANISATIVE INFRASTRUCTURE HAS BEEN SET UP



.. Some critical points to be faced…

The language and habits barriers is preventing an easy and free communication with children and parents

- Participation of Fondazione Giambrone/TIF in the PIP and Protocols design
- Involvement of patients, parents or their organisations in creating the protocol information package
  - Active role in preparing documents for children
  - Contribution in dissemination strategy
- Evaluation of appropriateness of documents in different countries (impact of cultures, languages, social status on readability and acceptability)

The DEEP strategy to deal with diversity

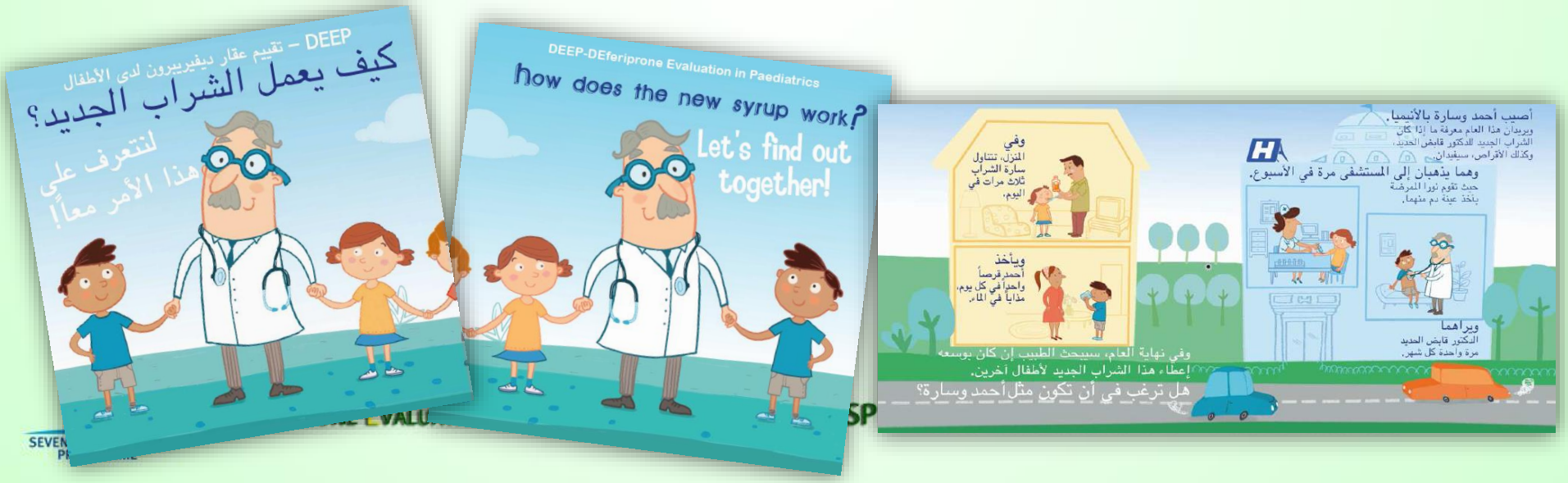
STEP 3: PATIENTS EMPOWERMENT IN DEEP

Patient-tailored communication model:

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

Translated in the national language: available in Arabic, French, English, Italian, Greek

BOOKLET for the younger ones (under 6 years old)



The DEEP strategy to deal with diversity

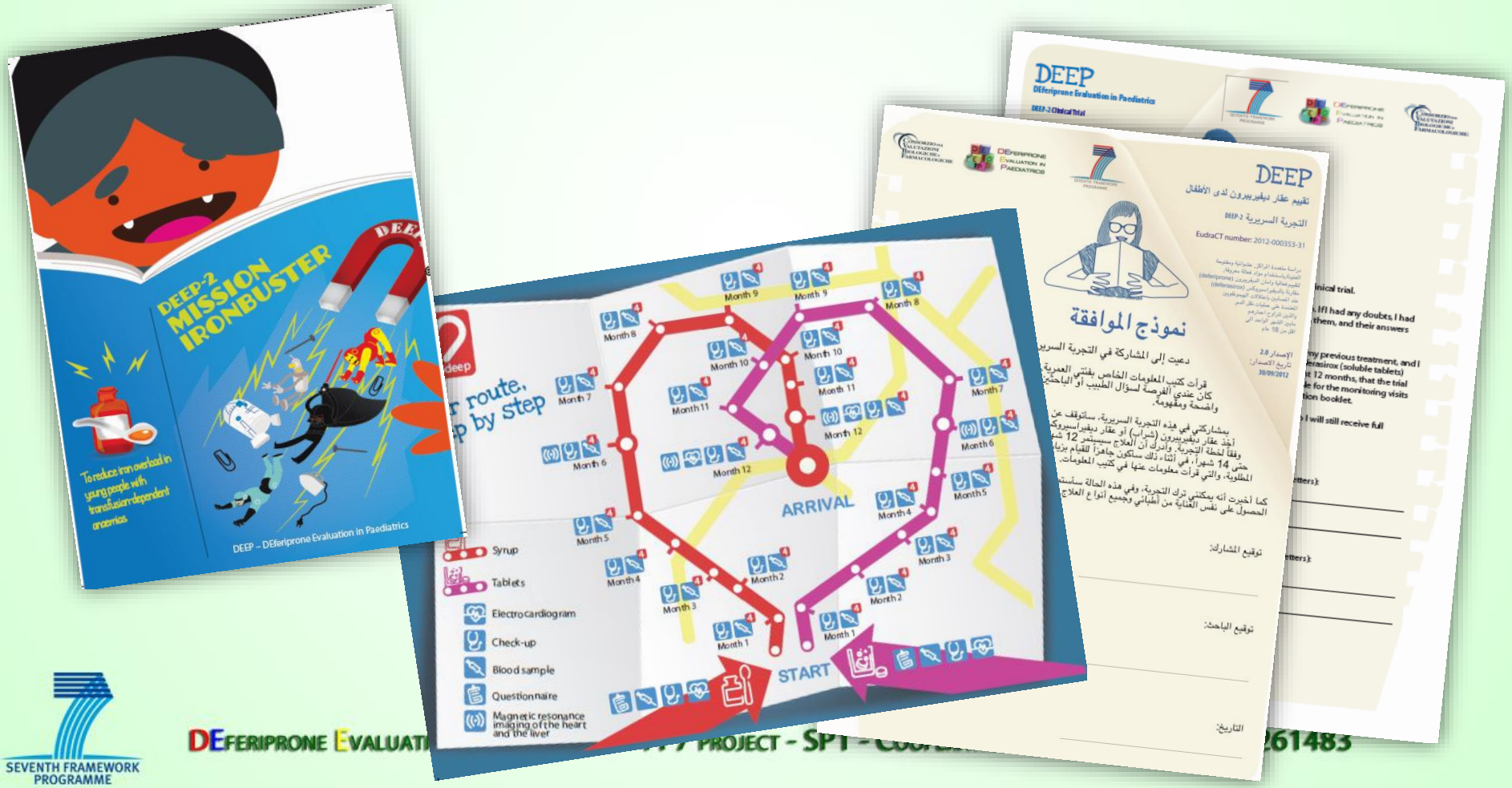
STEP 3: PATIENTS EMPOWERMENT IN DEEP

BOOKLET and ASSENT FORM for 6-10 years old children

The DEEP strategy to deal with diversity

STEP 3: PATIENTS EMPOWERMENT IN DEEP

BOOKLET and ASSENT FORM for 11-17 years old adolescents



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Conclusions

- The projects funded by EC and aimed to develop a PUMA represent the only one tool specifically aimed to translate paediatric research into a new paediatric drug
- The feasibility of the research-driven trials aimed to develop PUMA still presents critical problems in the context of the Paediatric Regulation implementation
- Nevertheless, the FP7-funded projects are keeping their promises and deserve to be refinanced in the next EC plan "Horizon 2020"