DEFERIPRONE EVALUATION IN PAEDIATRICS

This project has received funding from the European Union's Seventh Framework Programme for research technological development and demonstration under Grant Agreement n°261483

DEEP

Deferiprone Evaluation in Paediatrics

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Deferiprone Evaluation in Paediatrics

4-years research project funded by the European Commission within the 7th Framework Program (Health 2010.4.2-1)

Why DEEP as a case study?

- DEEP trials are investigator-driven… but **registrative studies** which are **PIP compliant**
- The condition under treatment is a **rare condition**
- The concerned population is **paediatrics**
- The studies are **multicentre, multinational** and**…multicultural**
- Include **PK**, **efficacy** and (long-term) **safety** evaluations
- A **paediatric formulation** is to be tested
- The envisaged MA is a **PUMA**

…so DEEP includes many of the difficulties which hamper the development of paediatric medicines!

What is deferiprone?

- First oral iron chelator
- Very competitive on the market in comparison to more expensive (thus often unaccessible) oral iron chelator
- Authorised for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate
- Was associated with increased incidence of neutropenia and agranulocytosis which prevented its widespread use notwithstanding its distinct efficacy profile in preventing cardiac iron accumulation
- A PUMA will give to the product 10 years of data protection
- Obtaining a “first line” approval will open the door to a similar indication in adults

REGULATION (EC) No 1901/2006

In 2008 Deferiprone was included in the PDCO Priority List

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.

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

Project acronym: DEEP
Project full title: DEferiprone Evaluation in Paediatrics
Grant agreement no: 261483
Date of preparation of Annex I (latest version): 2010-11-22

From the Priority List to the project funding

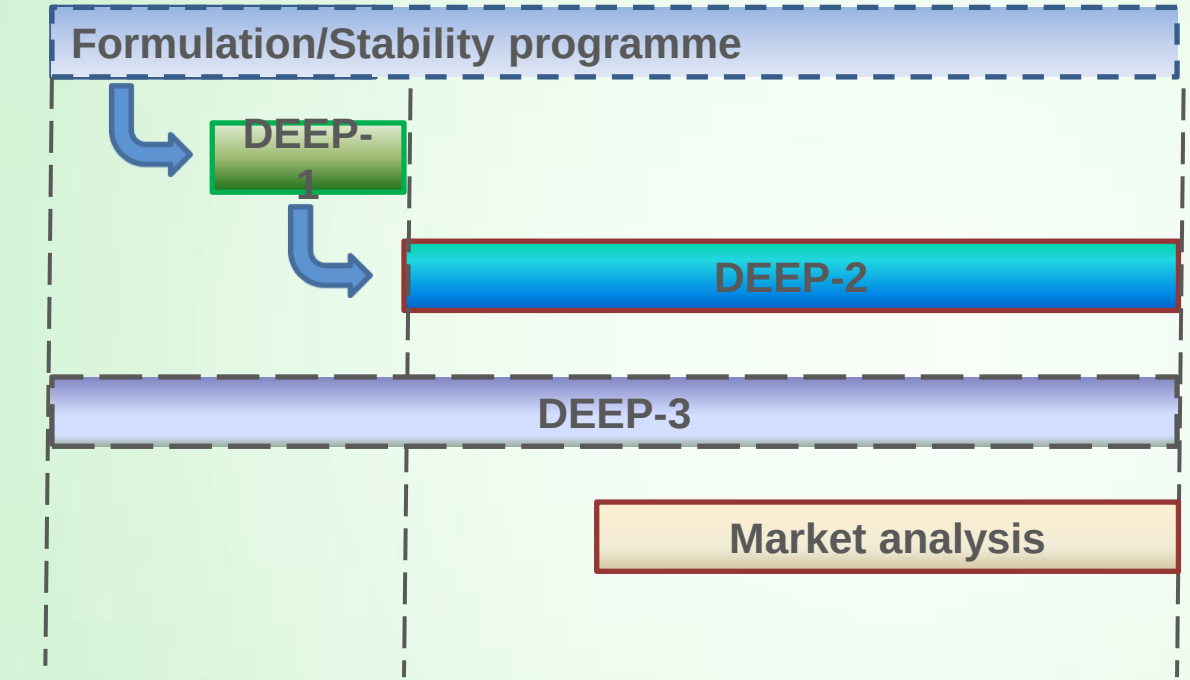
Need in the Priority list	**DEEP Project:**
Deferiprone: 1. condition Thalassemia 2. need: PK, efficacy and safety 3. age subsets: from 2 years to less than 10 years	**Deferiprone:** 1. condition Thalassemia 2. need: PK, efficacy and safety; 3. age subsets: from 2 years to less than 10 years Additional features: • a paediatric formulation • deferiprone to first line indication • long-term safety data • market analysis

How to respond to such need?

- Formulation development of a paediatric oral solution
- Pharmacokinetic study in children 2-6 yrs (DEEP-1)
- Efficacy and safety study in children 2-10 yrs (DEEP-2)
- Long term safety study in children < 18yrs (DEEP-3)
- Market analysis

DEEP started on January 1st, 2011

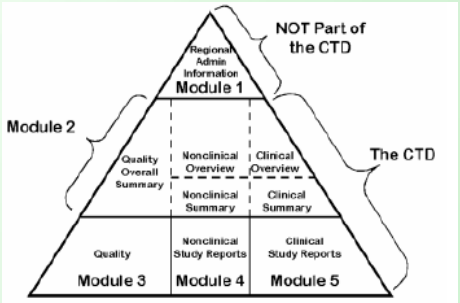
Project plan and timelines



study reports

PIP compliance check

PUMA



The steep path:

from funding to first patient's recruitment

Studies' protocol IMPLEMENTATION!

Studies' protocol approval by ECs and CAs

Development plan approved by EMA-PDCO

Project approved by EC

What's next? Deferiprone PIP application!

In compliance with the Paediatric Regulation (EC) 1901/2006 and within the remit of the call "FP7 Cooperation Work Programme "Health-2010-4.2-1"

on **February 14th 2011 a PIP** (Paediatric Investigation Plan) was submitted to the Paediatric Committee (EMA-PDCO)

Paediatric Investigation Plan Application for

Deferiprone

EMEA procedure number: EMEA-001126

Scientific documentation

(Parts B-F)

Applicant:

Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) - Coordinator for DEEP (DEferiprone Evaluation in Paediatrics) Project (HEALTH-F4-2010-261483)

DEFERIPRONE EVALUATION IN PAEDIATRICS

FP7 Project - SP1 – Cooperation
HEALTH-F4-2010-261483

Impact of PDCO requests on trials: the DEEP-2 case study

Efficacy-Safety	PIP APPLICATION	APPROVED PIP
CONDITION	Beta-Thalassemia	Haemoglobinopathies requiring transfusion
AGE GROUPS	2-10 yrs	Up to 18 yrs
TOTAL PATIENTS	254	310
STUDY AIMS AND DESIGN	To assess the non-inferiority of DFP in reducing serum ferritin levels compared to DFO	To assess the non-inferiority of DFP compared to DFX in terms of changes in ferritin levels and cardiac iron concentration

Revised DEEP-2 trial: the overall impact

- Enlargement of the condition
  - Increase heterogeneicity of the population
- Enlargement of the concerned age subsets
  - Need for stratification in the study design
- Change of study aim
  - Comparator, with associated substantial increase of costs
  - Composite endpoint:
    - Significant increase of sample size
    - Introduction of complex and expensive assessment (cardiac MRI)
- Inclusion of patients < 6yrs of age possible only after completion of DEEP-1 PK study
  - Delay of recruitment closure

DEEP-2 final protocol

Multicentre, **randomised**, **open label**, non-inferiority **active-controlled** trial to evaluate the efficacy and safety of deferiprone compared to deferasirox in paediatric patients aged from **1 month to less than 18 years** of age affected by transfusion-dependent **haemoglobinopathies**

Pts eligible for **randomisation**
(n = 344)

Pts allocated to **DFP** liquid formulation NEW STRENGHT 80 mg/ml
(n = 172)

- 1 year of treatment
- 16 hospital visits
- several observational and instrumental assessments

Pts allocated to **DFX**
(n = 172)

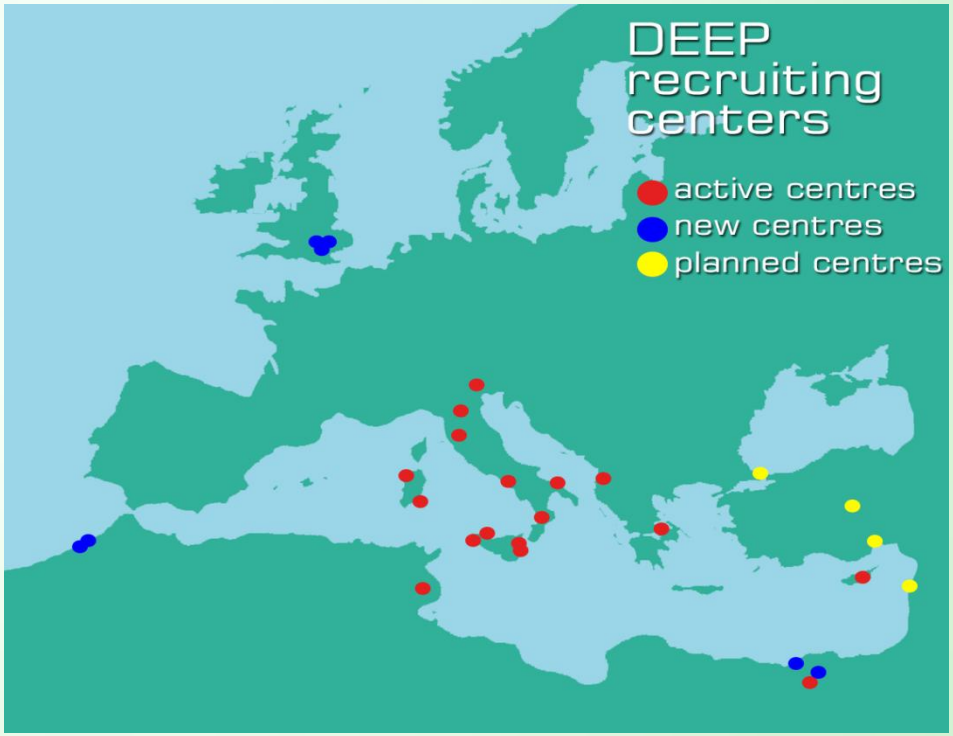
Data collection and analysis

First obstacle: large patient population (…and PAEDIATRIC!)

The answer: a large research network

A large researchers-driven Network including centres from :

- EU: Albania (1), Cyprus (1), Greece (1), Italy (12), UK (3, new)
- non-EU: Egypt (3), Tunisia (1), Morocco (2, new)
- probably new centres will be activated in Lebanon (1) and Turkey (3)



Next steps:

study approval by ECs and Cas in Italy

1. Study registration in EudraCT portal
2. Study registration in the "Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (OsSC)"
3. Study submission to the Ethics Committee of the Coordinator Centre
4. Study submission to the ECs of the other Italian Centers
5. Formal approval by each Competent Authority of each involved recruiting centres

→ Centres opened

→ **Recruitment starts!**

Next steps:

study approval by ECs and CAs (2)

Despite EMA-PDCO and coordinating centre approval… each EC may put forward specific request for changes:

- integrations to the text of the Informed Consent and Informed Assent documents in relation to blood volumes and contraceptive measures
- specification on use and storage of biological samples
- provision of additional administrative information
- clarifications requested on study design, study funding

Next steps:

study approval by ECs and CAs (3)

Additional hurdles have to be faced in other Countries:

- Egypt ⇨ the approval from National Security granted with restriction for sending samples abroad
- Greece ⇨ insurance must cover foetus damages even though contraceptive measures are indicated in the informed consent form
- Tunisia ⇨ a ‘special’ authorization from the Ministry of Health is necessary for paediatric trials before EC submission
- Albania ⇨ specific rules on CTs were lacking until 07/14; DEEP-2 approval set the path

Learned lesson :

study approval by ECs and CAs is

a lengthy and wearying procedure!

Reflection paper on ethical and GCP aspects of CTs outside EU/EEA (EMA/121340/2011)

Directive 2001/20/EC

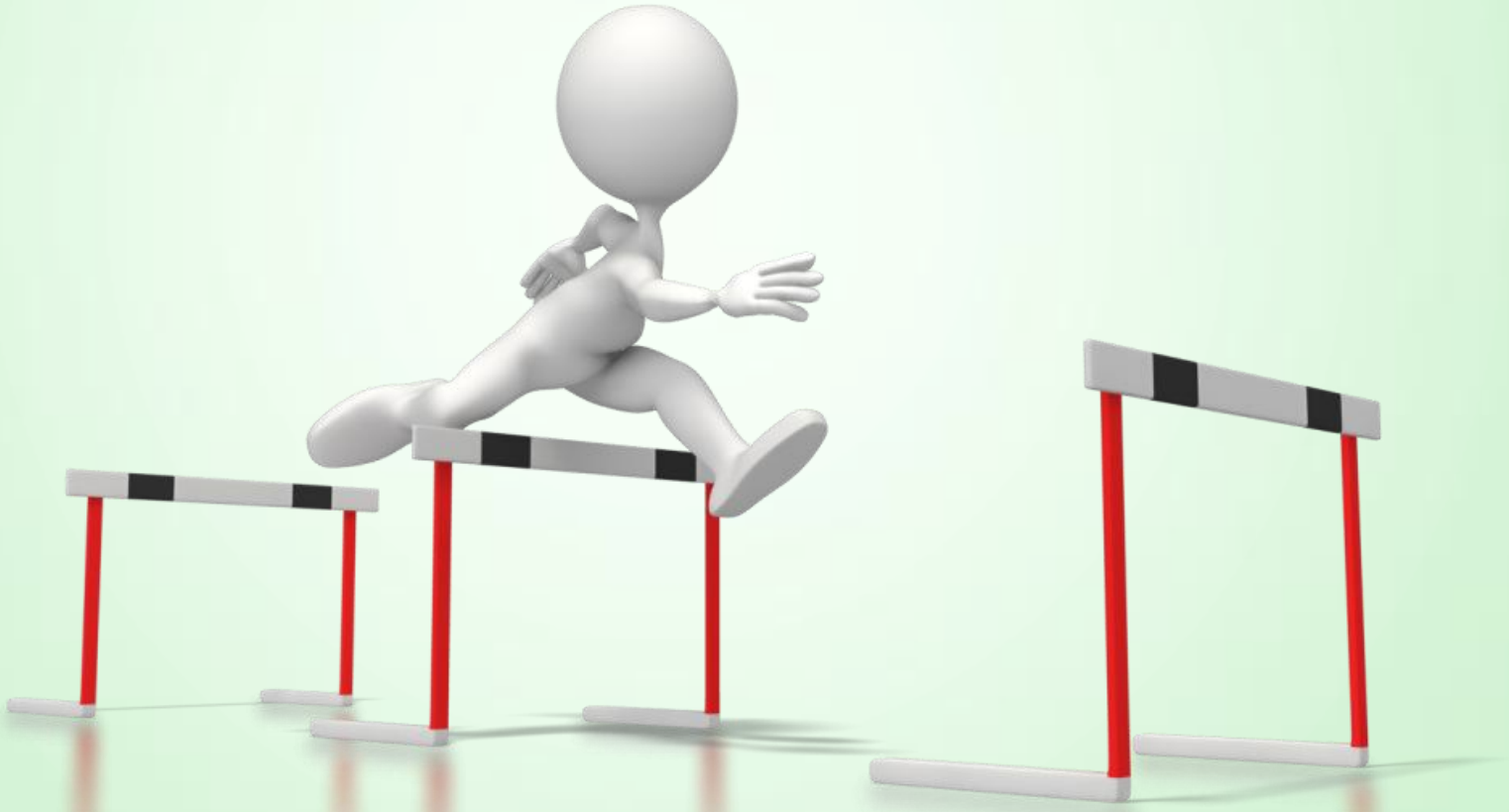
EudraLex Vol. 10

Directive 2005/28/EC

Paediatric Ethical Recommendations (EC, 2008)

Next steps: protocol implementation

Most of the hurdles around the conduct of a paediatric clinical trial are embedded in the DEEP-2 protocol…



Problem: delivery of transparent information to a wide audience

Solution: respect of diversity and patient's empowerment

- Not only parents and legal guardian were properly informed of the aim and procedures of the study, but significant efforts were devoted to build suitable communication tools for children
- Informative materials were produced adopting a patient-tailored approach by stratifying the population (< 6yrs; 6-11 yrs; > 12 yrs)
- Any tool delivered to patients and family was translated into native language: Albanian, Arabic, English, French, Greek, Italian

Problem: delivery of transparent information to a wide audience (2)

Solution: respect of diversity and patient's empowerment

DEEP – تقييم عقار ديفيريبرون لدى الأطفال نموذج موافقة

التجربة السريرية DEEP-2

EudraCT number: 2012-000353-31

دراسة متعددة المراكز، عشوائية ومفتوحة العنونة باستخدام مواد فعالية معروفة، لتقييم فعالية وأمان الديفيريبرون (deferiprone) مقارنة بالديفيراسيروكس (deferasirox) عند المصابين باعتلالات الهيموغلوبين المعتمدة على عمليات نقل الدم، والذين تتراوح أعمارهم مابين الشهر الواحد الى اقل من 18 عام

الإصدار 2.0

تاريخ الاصدار 30/09/2012

نموذج الموافقة

مرحباً! هل يمكنك الإجابة عن بعض الأسئلة قبل أن نبدأ؟ فنحن نرغب في التأكد من وضوح جميع الأمور لديك.

بمنتهى السهولة: ضع علامة إلى جوار الإجابات التي تختارها!

1) هل فهمت ما شرحه الطبيب والغرض من التجربة؟ نعم لا

2) هل تدرك أنك ستتناول شراباً أو أقراصاً قابلة للذوبان في الماء، لتقليل الحديد في دمك نعم لا

3) هل تدرك أنك ستأتي إلى المستشفى لأخذ عينة من دمك وفحصك في الأيام التي يحددها الطبيب المتابع لحالتك؟ نعم لا

4) هل تعلم أن بإمكانك أن تسأل الطبيب عمَّا تشاء إذا كانت لديك أي استفسارات أو مخاوف؟ نعم لا

5) هل تعلم أنه بأخذك للشراب أو الأقراص، قد تشعر ببعض الإضطرابات؟ نعم لا

6) هل تعلم أنه إذا شعرت بهذه الإضطرابات، ينبغي عليك أن تخبر والديك أو طبيبك؟ نعم لا

7) هل تعلم أنه في حالة لم ترغب في الإستمرار في التجربة، فإنه بإمكانك تغيير رأيك متى شئت، و الطبيب سوف يتم بالإعتناء بك كما في السابق؟ نعم لا

8) هل ترغب في المشاركة بهذه التجربة؟ نعم لا

توقيع الطفل .....

الاسم الشخصي و الاسم العائلي (بحروف واضحة) .....

التاريخ .....

توقيع الطبيب .....

الاسم الشخصي و الاسم العائلي (بحروف واضحة) .....

التاريخ .....

DEferiprone Evaluation in Paediatrics

Consorzio per Valutazioni Biologiche e Farmacologiche

Problem: delivery of transparent information to a wide audience (3)

Solution: respect of diversity and patient's empowerment…

…not only at start, but also when they finish the study, to increase their motivation and to recognise the value of the collaboration and the potential additional burden to their day-to-day life

Problem: comparator drug supply

Solution: comparator provided as standard of care

- As PDCO considers deferasirox the only other suitable comparator to deferiprone in paediatrics to its oral formulation, this has to be considered standard of care and be supplied by the national Health System:

  - This is acceptable in some countries (Italy, Albania, Tunisia)
  - In those countries where this is not acceptable (because of high cost) the comparator is supplied with project funding with additional and significant economic burden

Problem: conduct of laboratory assessments in several local settings

Solution: centralisation of analysis key for primary endpoints and harmonisation and quality assurance of local laboratories

A complex clinical operations infrastructure had to be in place to manage:

- Local and central medical procedures
- Pharmacovigilance
- Drug supply
- Sample shipments and logistics
- Regulatory and Ethics
- Data management and statistics

Problem: conduct of laboratory assessments in several local settings (2)

Solution: centralisation of ferritin

Ferritin is assessed in duplicate:

- for patient's management and dose adjustments ⇨ local laboratories
- for the evaluation of the primary endpoint ⇨ centralised laboratory
  - Respect of maximum volume of blood allowed in compliance with the Paediatric Ethical Recommendations (EC, 2008)
  - Shipment of biological sample to a central laboratory
  - Obtain consent, when applicable to export samples form the given Country
  - Disposal of any remaining sample
  - Associated costs

Problem: conduct of laboratory assessments in several local settings (3)

Solution: centralisation of cardiac MRI

Cardiac MRI is conducted on every child >10 yrs of age provided sedation is not needed, using a unique MRI protocol sequence:

- locally, if a suitable MRI equipment is present

or alternatively…

- patients are referred to one of the trial references centres for MRI

All the scan analyses are centralised in ONE unique analytical centre to ensure consistency of results

Learned lesson:

conduct of laboratory assessments in multicentre trial requires harmonisation and/or centralisation

Harmonisation and/or centralisation of procedures and assessments…

…ensure consistency and robustness of data

…but…

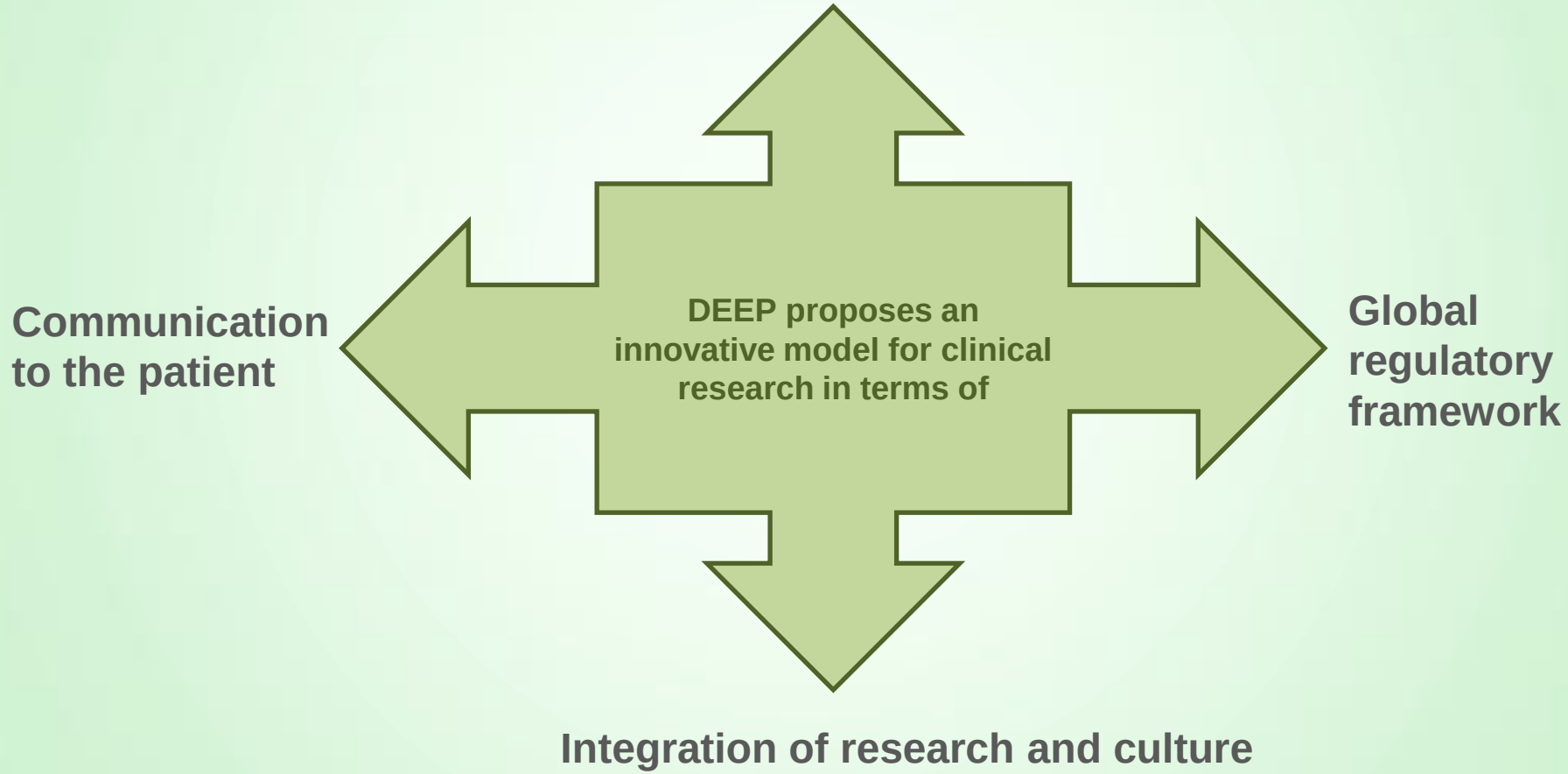
…is very expensive!

Careful budget management is critical to the success of any trial!

DEEP responds to several open questions

- *EC Research policies*
  - ***Networking action:*** a very large scientific community is sharing competencies and skills.
  - **Public-private** integration and support to **SMEs**
- *Specific medical needs (Paediatric Medicines)*
  - ***Development of Paediatric Plans***
  - ***Consistent representation of paediatric patients***
  - An appropriate drug for treating **iron overload in children**
- *Scientific community expectations*
  - ***Innovative elements*** included in the trials: modelling studies
  - **New competencies** acquired and disseminated (regulatory, trial management, ethics, communication)0

FOCUS ON THERAPEUTIC NEEDS IN PAEDIATRICS



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