



DEFERIPRONE EVALUATION IN PAEDIATRICS



FP7 Health Program supporting paediatric initiative: the **DEEP multinational and multicultural experience**

*Adriana Ceci
DEEP Scientific Coordinator,
and member of PDCO-EMA*



DEEP -DEFERIPRONE EVALUATION IN PAEDIATRICS

DEEP is a 4-year multinational project aimed to make available reliable treatments to children with

beta-thalassaemia, sickle cell disease and other congenital haemoglobinopathies

which represent the most severe forms of anaemia in the world with specific reference to the

Mediterranean Area

A large research-driven network covering the
'area' to which the disease belongs to



- 16 Partners
- 18 recruiting centres from 7 Countries:
 - EU: Cyprus, Greece, Italy, (UK)
 - non-EU: Albania, Egypt, Tunisia



The DEEP project: what's new

Starting from an **old drug**, the project aims to perform paediatric studies in order to develop a new liquid formulation specific for the paediatric population and a new paediatric indication

The Project develops

around a full drug developmental Plan (PIP) approved by the European Agency-PDCO that includes:

- **Liquid Formulation preparation**
- **2 Clinical Trials:**
 - PK trial providing appropriate dose definition (DEEP-1)
 - efficacy-safety multicentre, comparator controlled trial (DEEP-2)
 - long-term safety non-interventional study (DEEP-3)
- **1 post-marketing study**
 - pharmacoeconomic study



A new Marketing Authorisation (PUMA)



The DEEP project: what's Innovative

- Innovative approaches in CTs: **DEEP-1 PK modeling/simulation** study to define drug exposure and appropriate dosage of deferiprone for children aged < 6yrs
- Inclusion criteria based only on number on **transfusional Fe** intake without **any age threshold**
- First time comparison between the **two oral available comparators**: deferiprone vs deferasirox
- **DEEP-2**: the **larger RCT** in *paediatric patients*
- **New, more reliable endpoint based on magnetic resonance:**

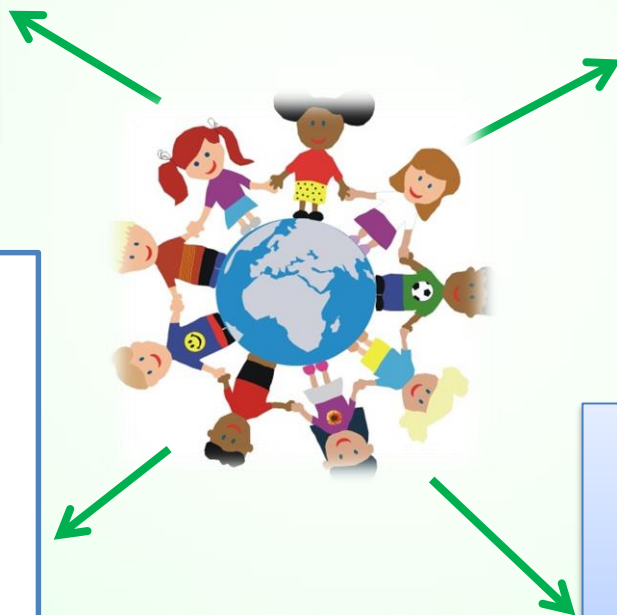
Cardiac **MRI T2*** included as **co-primary endpoint** for children above 10 year and liver **MRI-R2** included to measure **LIC instead of liver biopsy** in all patients not requiring sedation.



The DEEP Project: what's Challenging

Paediatric
population
(involves children
of different ages)

A **rare and disperse**
population involving
different
Rare Congenital
Anaemia



'Registrative' CTs with

- Economic burden
- Ethical stringent provisions
- GCP-ICH E11 obligations

**Multi-ethnic
population**

with different cultures
and laws



The DEEP strategy deals with COMPLEXITY

THE DEEP MULTISTEPS APPROACH



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

2. To implement a unique procedure and a unique CTA 'trial submission package'



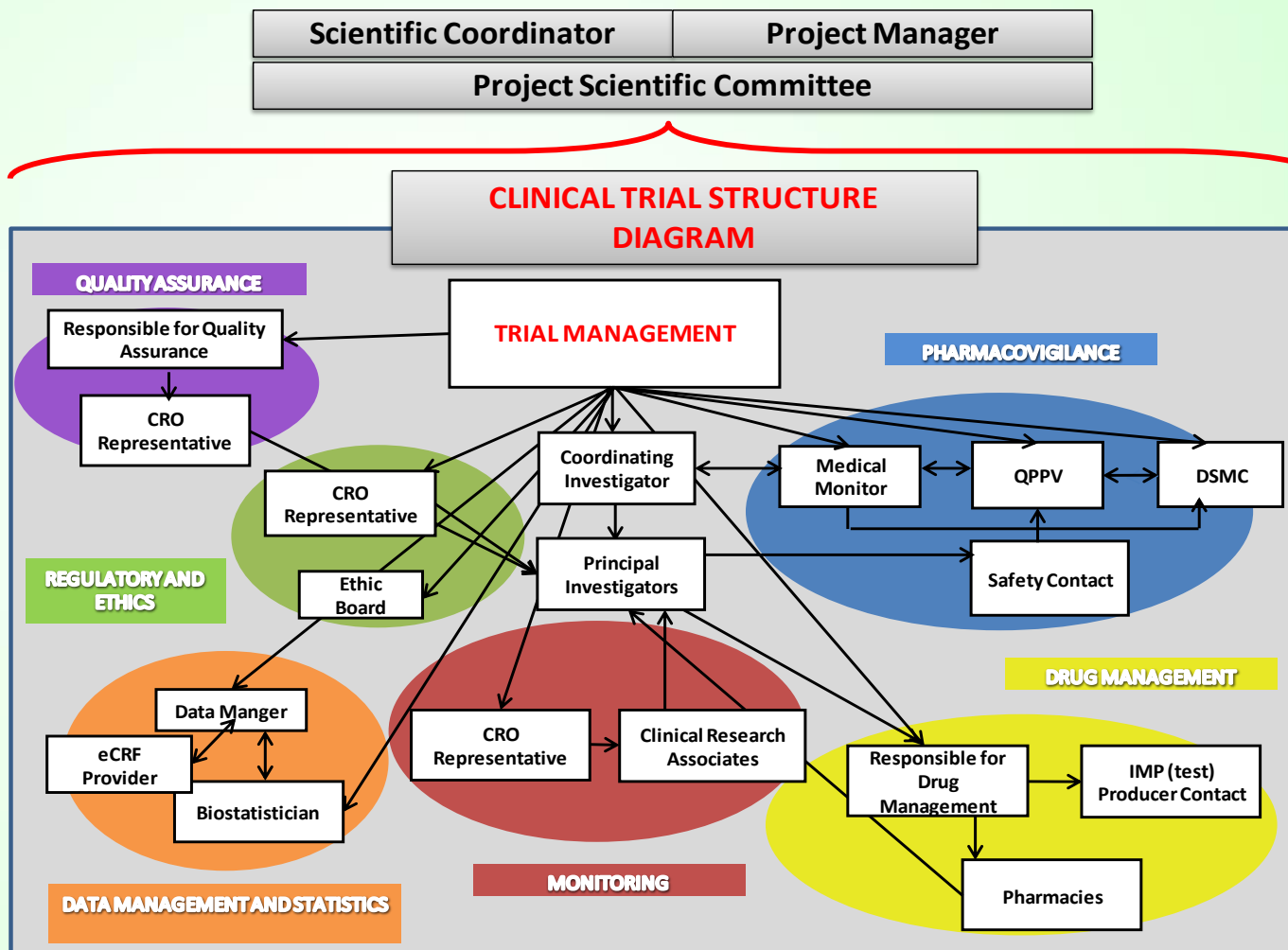
3. To develop a 'patients tailored approach' involving children, families and association





The DEEP strategy deals with DIVERSITY

STEP 1:
A COMPLEX (AND
EXPENSIVE)
ORGANISATIONAL
INFRASTRUCTURE
HAS BEEN SET UP





The legislative context: national rules in DEEP countries

- In **EU Countries (Italy, Cyprus and Greece)** the Competent Authority authorisation and the Ethics Committee approval is ruled by the **Directive 2001/20/EC** in terms of CTA form, IMP documents, insurance, informed consent Specific rules for the paediatric population PIP, EMA 2008 recommendations, ICH-E11, etc)



This 'gold standard' is to be applied in all centers modified according to the national rules



- In Albania specific rules on CTs are lacking; a special decision from the Ministry of Health is needed
- In Egypt the CTA is largely similar to Europe, but informed consent procedures are different (i.e. consent from only one parent is accepted- sending samples abroad is regulated)
- In Tunisia the Ministry of Health, the National and local ECs shall authorise a paediatric trial



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, Albanian, 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 RULES FOR OUR TRIAL:

- 344 children and young people under the age of 18
- 14 months of trial
- 6 days without any medicine
- 12 months with the syrup or soluble tablets

At the beginning of the trial, doctors will pick the children's names out of a hat and divide them into two groups. The first group will take the syrup and the second group will take the tablets.

Jump onto the track to find out what you will be doing each month!

GO!

mission Iron Buster

DEEP - Deferiprone Evaluation in Paediatrics

During the trial, some children will do more tests on their heart and liver. But no worries: these tests are very simple!

DEEP - Deferiprone Evaluation in Paediatrics

DEEP-2 Clinical Trial
EudraCT Number: 2012-000353-31

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

تقييم عقار ديفيريبرون لدى الأطفال نموذج موافقة

التجربة السريرية DEEP-2
EudraCT number: 2012-000353-31

دراسة متعددة المراكز، عشوائية، مفتوحة العيون، باستخدام مواد فعالة معروفة لتقييم فعالية وإمان الـديفيريبرون (deferiprone) مقارنة بالـديفيريبرون (deferasirox) عند المصابين بأمراض الدم الوراثية المعتمدة على خلايا الدم والذين تتراوح أعمارهم بين الشهر الواحد إلى أقل من 18 عام.

2.0.0
تاريخ الإصدار: 30/09/2012

نموذج الموافقة

مرحباً! هل يمكنك الإجابة عن بعض الأسئلة قبل أن نبدأ؟
فنحن نرغب في التأكد من وضوح جميع الأمور لديك.
بمستوى السهولة، ضع علامة إلى جوار الإجابات التي تختارها!

هل فهمت ما شرحه الطبيب والغرض من التجربة؟

هل تترك أنك ستتناول شراباً أو أقراصاً قابلة للذوبان في الماء لتقليل الحديد في دمك؟

هل تترك أنك ستأتي إلى المستشفى لأخذ عينة من دمك وفحصك في الأيام التي يحددها الطبيب المتابع لحالتك؟

هل تعلم أن بإمكانك أن تستأجر الطبيب مع تشاء إذا كانت لديك أي استفسارات أو مخاوف؟

هل تعلم أنه بإمكانك للشرب أو الأكل، قد تشعر ببعض الإضطرابات؟

هل تعلم أنه إذا شعرت بهذه الإضطرابات، ينبغي عليك أن تخبر والدك أو طبيبك؟

هل تعلم أنه في حالة لم ترغب في الإستمرار في التجربة، فإنه بإمكانك تغيير رأيك متى شئت، والطبيب سوف يتم بالإعتناء بك كما في السابق؟

هل ترغب في المشاركة بهذه التجربة؟

توقيع الطفل
الاسم الشخصي والاسم العائلي (بحروف واضحة)
التاريخ

توقيع الطبيب
الاسم الشخصي والاسم العائلي (بحروف واضحة)
التاريخ

PROJECT - SP1 - COO

SEVENTH FRAMEWORK PROGRAMME

DEFERIPRONE EVALUATION IN PAEDIATRICS

DEFERIPRONE EVALUATION IN PAEDIATRICS



The DEEP strategy to deal with diversity

STEP 3: PATIENTS EMPOWERMENT IN DEEP

BOOKLET and ASSENT FORM for 11-17 years old adolescents





Recruitment and approval: the state of the art

- *New formulation* is available to the investigational sites and used in the trials
- *DEEP-1* is concluding recruitment with success
- *DEEP-2* approved by the 80% of the Ethics Committees and Competent Authorities and the recruitment is now starting
- *DEEP-3* observational study is on-going



DEEP is a
success story in
the EUROMED
perspective

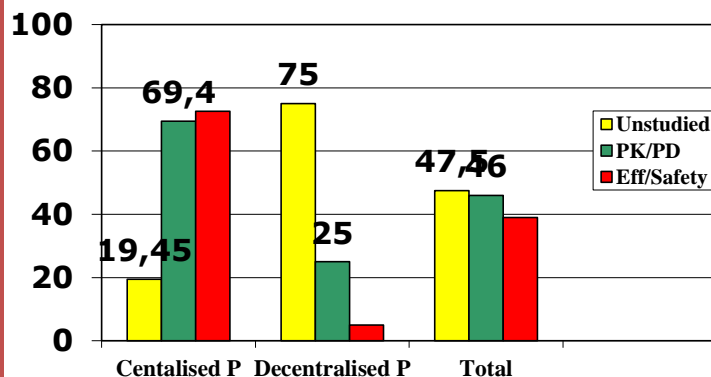
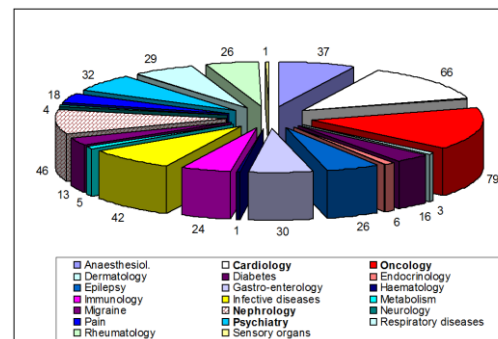


What makes DEEP project so special in the contest of FP7 Projects Framework?

*DEEP is aimed to **respond to a specific need** from the European Union Policies and rules on **Paediatric Medicines as stated in the Paediatric Regulation***

Less than 30% of Medicines on the market are approved for children. Unapproved drugs are used 'off-label' because uncovered therapeutic needs.

*Ref. EMA: All the needs: ~ 20 therapeutic classes
~ 400 active substances*



DEEP is responding to a real therapeutic need.

This need is a common need in european and no-european MEDITERRANEA REGIONS



The DEEP project: based on scientist excellence located to European/no-European countries

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DEEP demonstrate to be able



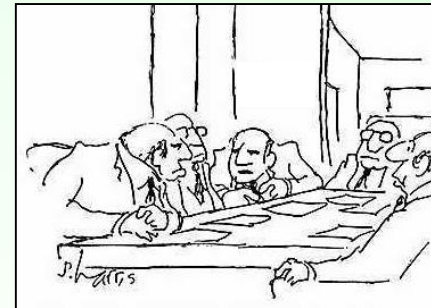
FP7 application

- Project considered on the basis of scientific excellence (no paediatric needs)
- No mention to the **trials conduct**
- Very few preclinical studies funded



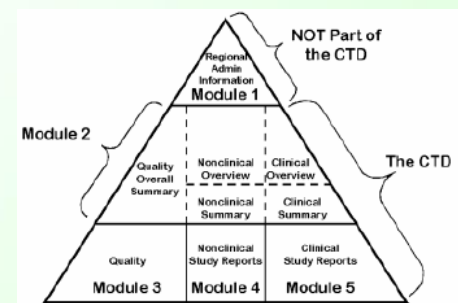
PIP application

- Research Consortia having no experiences in regulatory process
- A whole **research & development plan requested.**
- All paed. subsets should be covered
- Details of timing & measures including preclinical, formulation
- Efficacy, Safety



PUMA Applications

- **Commercial Sponsor**
- **Intellectual Property**





The lesson learnt from these projects

☐ ***In response to the EC Research policies***

- ☐ ***Networking action:*** a very large scientific community is sharing competencies and skills.
- ☐ **Public-private** integration and support to **SMEs**

☐ ***In response to the specific topic (Paediatric Medicines:***

- ☐ ***Development of Paediatric Plans (PIPs available*** for 15 Active Substances)
- ☐ ***Consistent number of paediatric patients, also neonates,*** in the trials
- ☐ An appropriate drug for treating **iron overload in children**

☐ ***In response to the Scientific Community expectations***

- ☐ ***Innovative elements*** included in the trials: pharmacogenetic studies
- ☐ **New competencies** acquired (Regulatory, trials managements, Ethics, Communication with parents/patients, etc)



Conclusions

Is DEEP Research CONSORZIUM qualified to apply for?



Health, demographic change and wellbeing

- Excellent Science
- Industrial Leadership
- Societal Concerns