



Thalassemia International Federation
World Congress

**13th International Conference on
Thalassaemia
Abu Dhabi, 20-23 October 2013**

**A multi-ethnic multi-national approach to ethical
approval of clinical trials involving Thalassaemia
patients:
the DEEP lesson**

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on behalf of the DEEP Project



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DEFERIPRONE
EVALUATION IN
PAEDIATRICS

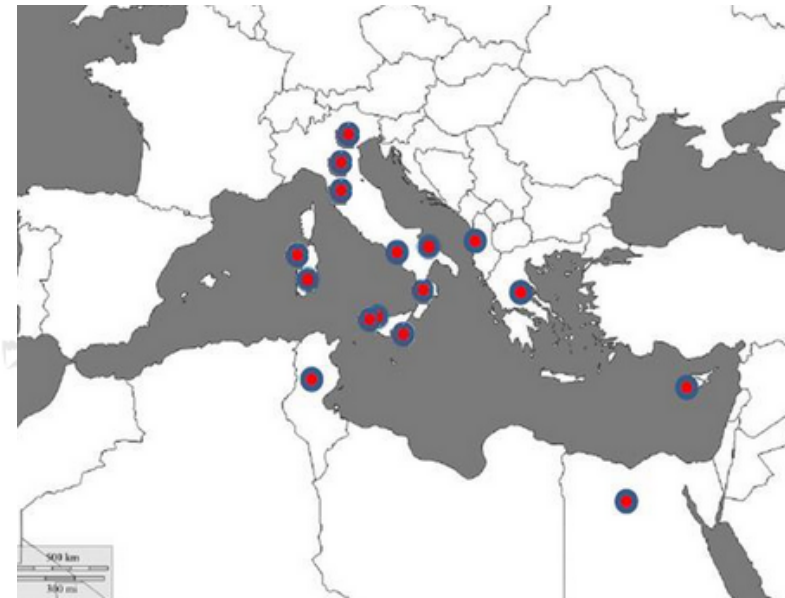
DEEP: a EU project planning paediatric trials

Two Clinical Trials

A long term safety Non Interventional Study

FP7 funded Project HEALTH-F4-2010-261483

- DEEP consortium is composed of 16 Partners
- 17 recruiting centres from 6 Countries:
 - EU Centres: Cyprus, Greece, Italy
 - non-EU Centres: Albania, Egypt, Tunisia



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Clinical Trials in DEEP: a challenging matter

P a e d i a t r i c
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
•Economic burden
•Ethical stringent
provisions
•GCP-ICH E11
obligations



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Multinational-multiethnic CT different cultures and laws

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

EU legislative 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)



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



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The legislative context: national provisions governing CTA in DEEP countries

- In EU Countries (Cyprus, Greece) the Competent Authority authorisation and the Ethics Committee approval are required according to Directive 2001/20/EC in terms of IMP documents, insurance, informed consent.



- In Albania specific rules and procedures are lacking; a special decision from the Ministry of Health is needed
- In Egypt CTA is largely similar to Europe, but informed consent procedures are different.
- In Turkey the Ministry of Health, the national and local authorities shall authorise 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



- To implement a unique procedure and a unique CTA 'package of documents'
- To organize a 'trials management plan and infrastructure' including SOPs preparation, data management, drug management, pharmacovigilance, monitoring, etc
- To develop a 'patients tailored approach' including children, families and association



PROGETTO GUARIGIONE



Partner representative. Loris Brunetta



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The DEEP strategy

STEP 1: THE 'PACKAGE OF DOCUMENTS'

- **Mandatory registration of CTs (EudraCT)**
- **Preparation for the concerned ECs of the common but multi-lingual 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 (different case by case)**



The EU legislative provisions have been assumed as DEEP Standard



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The timing of submission

in other countries

TRIAL SITE	From submission to EC approval	From EC approval to CA authorisation
Az. Osp. Ospedali Riuniti Villa		
Az. Ospedaliero Universitario		
Az. Osp. di Rilievo Nazionale		
Az. Osp. G. Di Cristina (Palestine)		
Clinica Pediatrica Univ. – ASL Pavia (Pavia)		
Clinica Pediatrica Univ. – ASL Pavia (Pavia)		
Policlinico di Modena , Clinica Pediatrica	5 months	2 months
Presidio Ospedaliero "Annunziata", Centro di Studi della Microcitemia (Cosenza)	< 4 months	< 8 months
Az. Osp. di Padova	7 months	Under evaluation
Ospedale Civile di Lentini, Centro di Talassemia, Lentini (SR)	6 months	Under evaluation
Az. Osp. Universitaria Meyer (Florence)	<i>Under evaluation</i>	<i>n.a.</i>
ARNAS Garibaldi (Catania)	1 month	Under evaluation
ASL Cagliari Ospedale Regionale per le Microcitemie	<i>Under submission</i>	<i>n.a.</i>

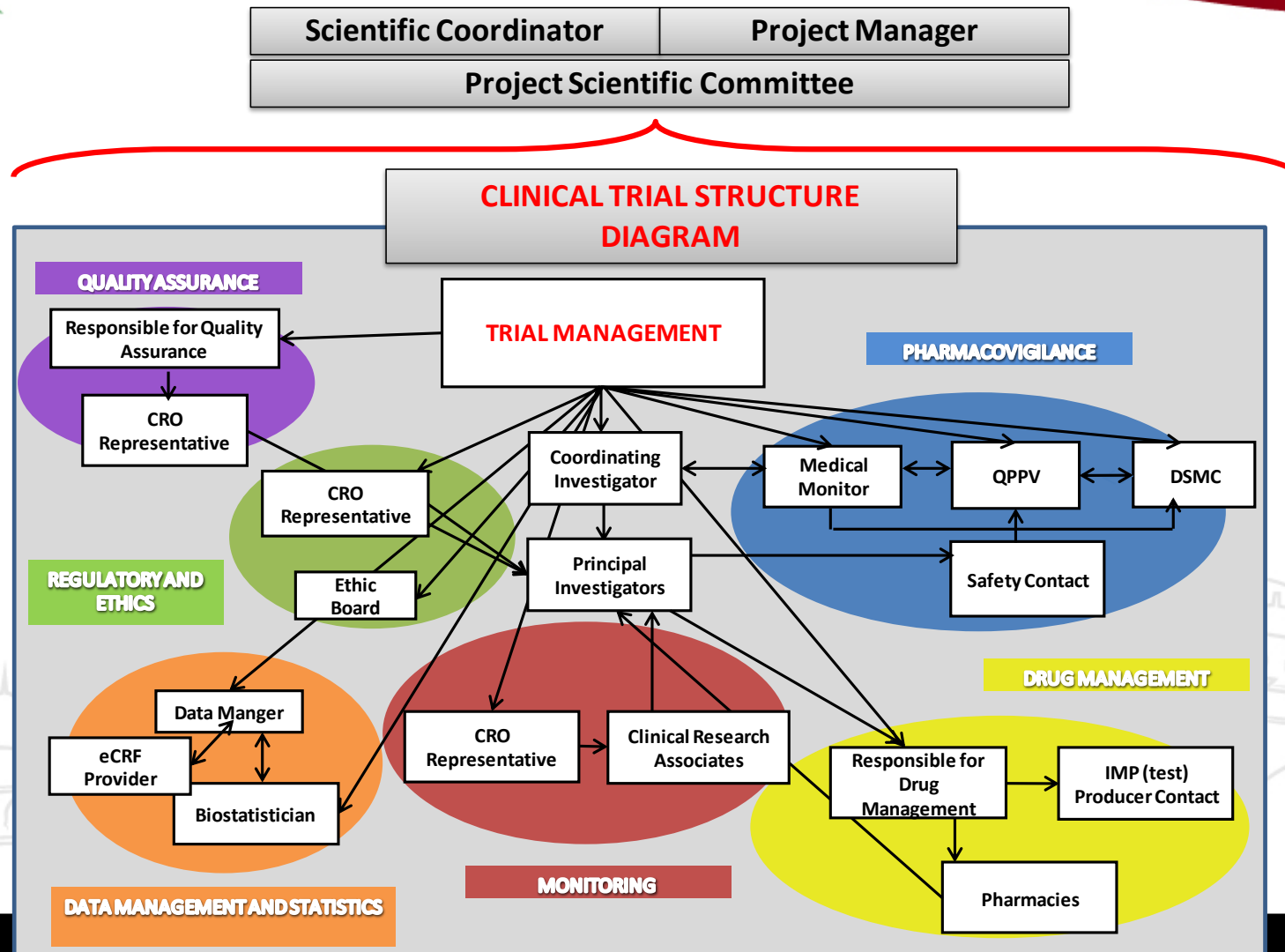
- EC approval expected in October 2013
- CA authorisation expected in December 2013



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The DEEP strategy

STEP 2: THE INFRASTRUCTURE





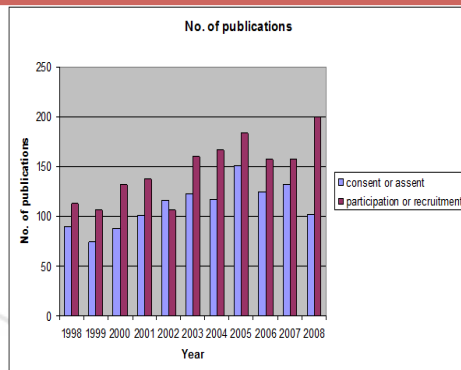
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The DEEP strategy

STEP 3: THE PATIENTS AND FAMILIES

RESPECT - Relating Expectations and needs to the Empowerment of Children in CTs

*...conducting 'gold standard' paediatric trials depends not only on appropriate legislations and guidelines, but also on the **decision of patients and families** to participate or not, and then on acting upon this decision...*



Determinants of Patient Participation in Paediatric Clinical Trials: A literature review

Wulf F, Krasuska M, Chaplin J, Sanna L, Wool PS, Altavilla A, Neubauer D, Crawley FP, Chaplin C, **Ceci A**, Mackensen S & Bullinger M

CHILDREN QUESTIONNAIRES

Case study, interviews with children & parents

- Diabetes (Sweden)
- HIV (Italy)
- Thalassaemia (Italy)
- Epilepsy (Slovenia)
- Mitochon. disorders (Slovenia)

- More often the child does not have much say in the **decision**
- *Children require pain and distress reduction Less involved in decision*
- For adolescents, **altruism** was a stronger motivation than personal benefit
- *They require more information on trial*



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STEP 3: PATIENTS AND PARENTS

Parents have been described

to feel dependent on clinicians
to experience considerable unease
in making decisions
to feel deserved of any influence on
the treatment decision



In the **decision-making process** parents
potentially fail to grasp the distinction between
the imperatives of clinical research and of ordinary
treatment

“therapeutic misconception”

In the **current evidence from literature** parents
and children are not involved in study design,
duration and alternative

new approaches are under discussion based on:

- appropriate information
- active programs for empowerment



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 September 2012
EMA/PDCO/388684/2012
Paediatric Committee (PDCO)

Concept paper on the involvement of children and young
people at the Paediatric Committee (PDCO)





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STEP 3: PATIENTS AND PARENTS

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)





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Informed consent process for children

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!

UN mese dopo ARRIVO!

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

mission Iron Buster

DEEP - Deferiprone Evaluation in Paediatrics

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.

2.0.0
30/09/2012

نموذج الموافقة

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

نعم لا

1) هل فهمت ما شرحه الطبيب والغرض من التجربة؟

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

3) هل تترك أنك ستتلقى إلى المستشفى لأخذ عينة من دمك وفحصها في الأيام التي يحددها الطبيب المتابع لحالتك؟

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

5) هل تعلم أنه إذا شعرت بهذه الأعراض: قد تشعر ببعض الإضطرابات؟

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

7) 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؟

8) هل ترغب في المشاركة بهذه التجربة؟

توقيع الطفل
الاسم الشخصي والاسم العائلي (بحروف واضحة)
التاريخ

توقيع الطبيب
الاسم الشخصي والاسم العائلي (بحروف واضحة)
التاريخ

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Informed consent process for children

BOOKLET and ASSENT FORM for 11-17 years old adolescents





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Conclusions

- DEEP is a researchers-driven Consortium that acts as sponsor to bring a new deferiprone form on the market
- DEEP is an EU-nonEU International Research Consortium dealing with
 - a paediatric condition
 - a rare condition
 - the derived regulatory and ethical burdens
- At the starting of the studies DEEP Consortium is willing to implement a stronger participation of patients and families
- This could help to overcome the challenges of the studies and could represent a good example of an innovative **patient-driven CTs model**

