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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DEEP: a EU project planning paediatric trials

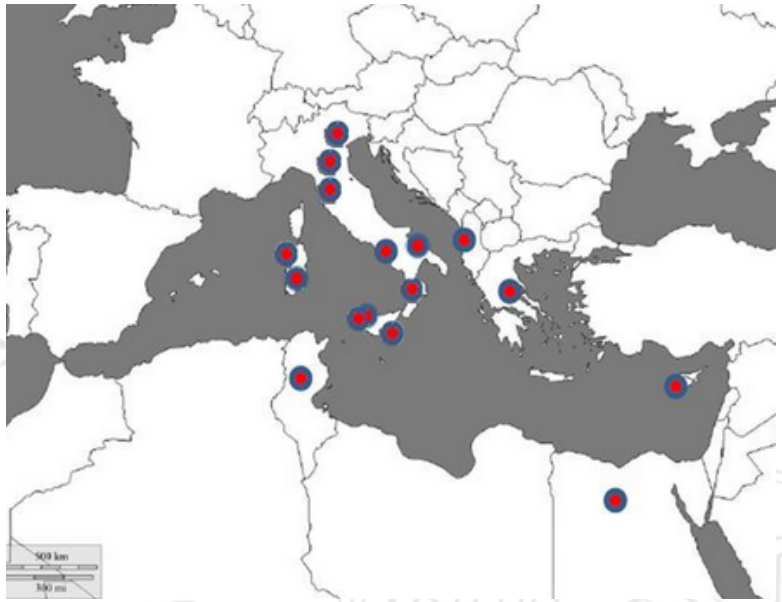
DEFERIPRONE EVALUATION IN PAEDIATRICS

FP7 funded Project HEALTH-F4-2010-261483

Two Clinical Trials

A long term safety Non Interventional Study

- 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

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

- Economic burden
- Ethical stringent provisions
- GCP-ICHE11 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

The legislative context: national provisions governing CTA in DEEP countries

Thalassemi… …ternational Federation
World C…

- In EU Countrie… …ly, Cyprus … Greece) the Competent Autho… …thorisat… …and the Ethics Committee approval … …ed a… …ding to Directive 2001/20/EC in terms o… …, IMP documents, insurance, informed conse…

- In Albania spe… …rules … …are lacking; a special decision fro… …Ministry o… …th is needed
- In Egypt … …CTA is largely si… …to Europe, but informe… …nsent procedures are d… …t.
- In Tu… …the Ministry of Health, the … …onal and loc… …s 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

THALASSEMIA PROGETTO GUARIGIONE

THALASSEMIA INTERNATIONAL FEDERATION MEMBER

Partner representative. Loris Brunetta

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 Vil		
Az. Ospedaliero Universitari		
Az. Osp. di Rilievo Nazionale		
Az. Osp. G. Di Cristina (**Pale**		
Clinica Pediatrica Univ. – AS Pediatria (**Sassari**)		
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**)	*Under evaluation*	*n.a.*
ARNAS Garibaldi (**Catania)**	1 month	Under evaluation
ASL **Cagliari** Ospedale Regionale per le Microcitemie	*Under submission*	*n.a.*

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

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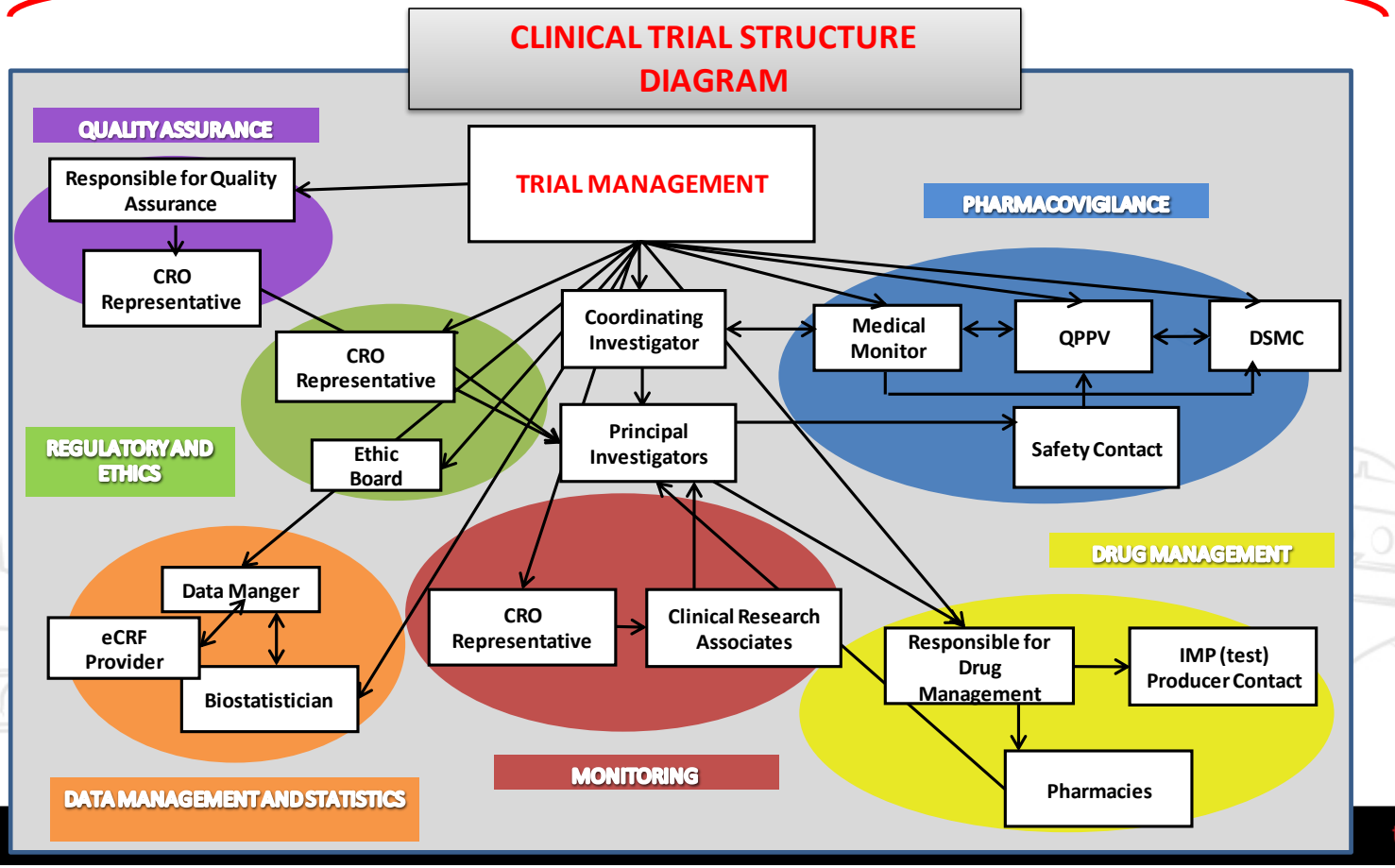
STEP 2: THE INFRASCTRUCTURE

Scientific Coordinator	Project Manager
Project Scientific Committee	



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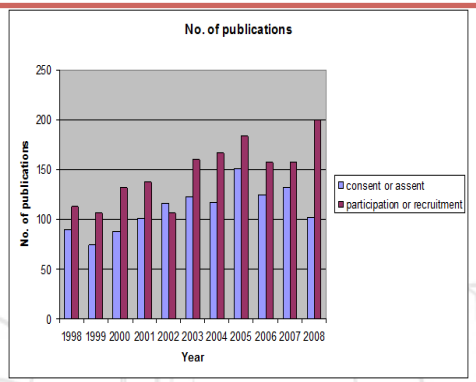
STEP 3: THE PATIENTS AND FAMILIES

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 QUESTIONAIRES

Case study, interviews with children & parents

- Diabetes (*Sweden*)
- HIV (*Italy*)
- Thalassemia(*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

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Informed consent process for children

BOOKLET and ASSENT FORM for 11-17 years old adolescents

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