

# Networking in Paediatric Clinical Research in France

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## Current challenges and future perspectives

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# What happened in the past 50 years ?

Identification of the lack of studies evaluating drugs in children

70% of drugs used in paediatrics had

- No dosing information
- No safety and/or efficacy data
- Restrictions based on age

Lobbying by pharmacologists and paediatricians

FDA initiative



EU initiative



EU Regulation

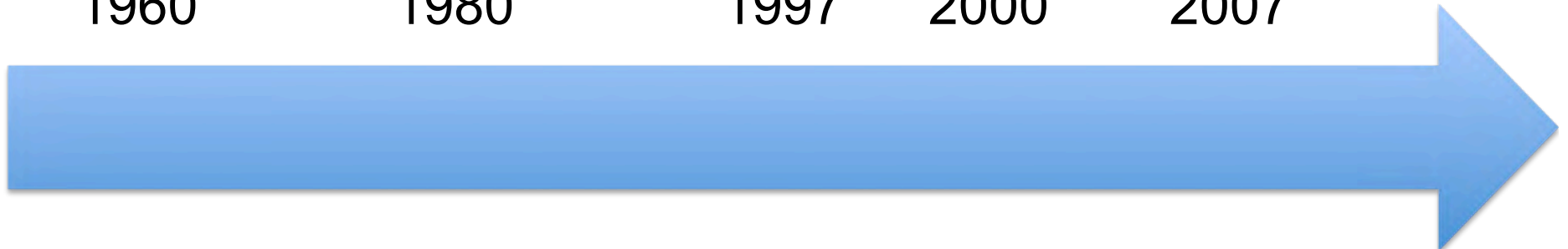
1960

1980

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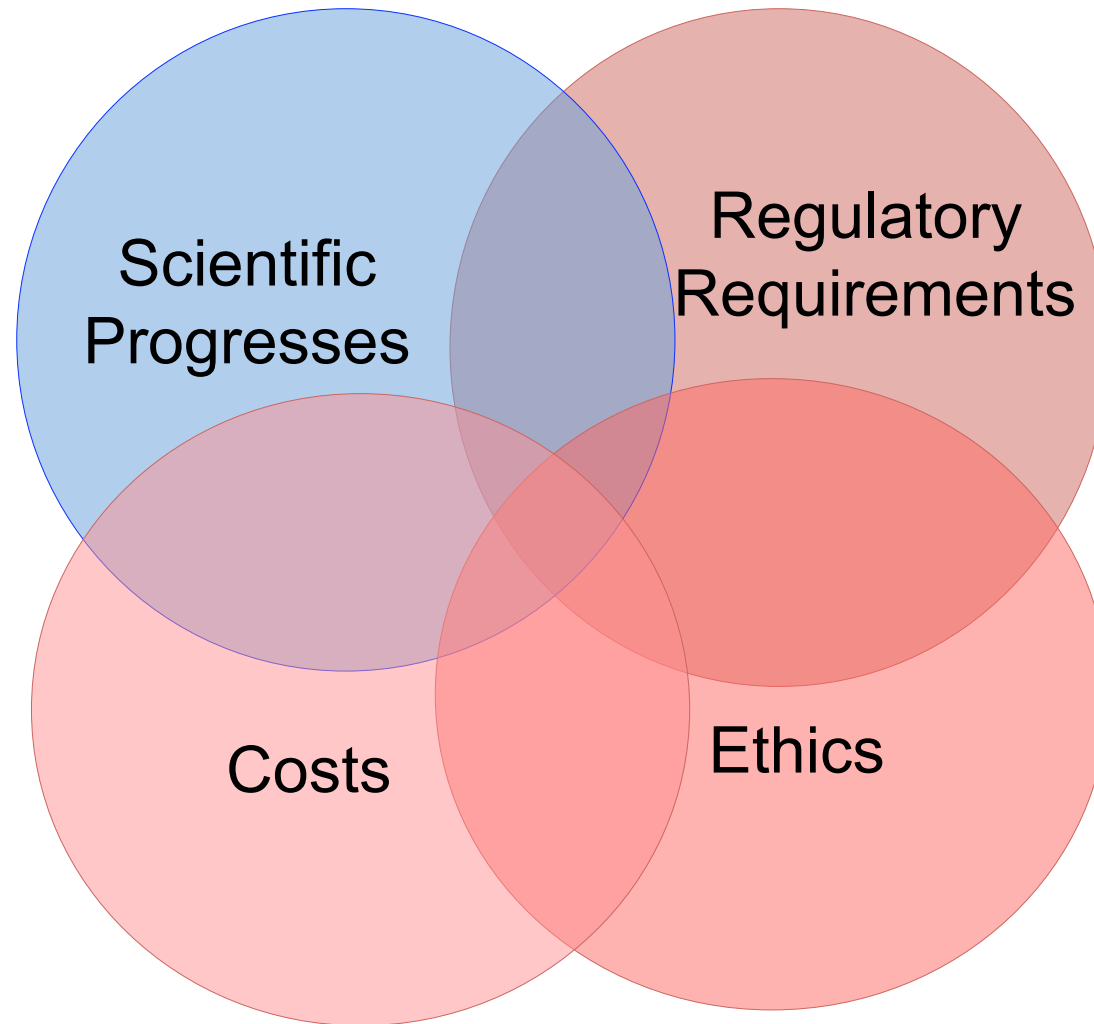


# The EU regulation



How to increase the availability of drugs for children ?

**Concile different objectives**



# The EU Regulation

- Among all objectives .....

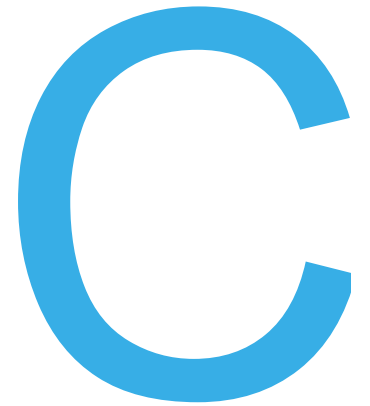
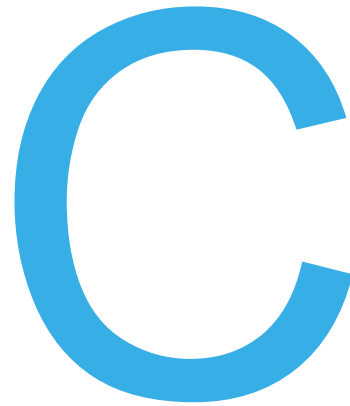
Network of paediatric research  
ENPREMA



- To date, a total of **33 networks and centres** have submitted self-assessment reports.
- **Category 1** includes the 18 networks and centres that are now **members of Enpr-EMA**

**One of them is the French Paediatric Network of Clinical Investigation Centers**

French Network of  
Paediatric  
Clinical Investigation  
Centers



Infrastructure network

## Objectifs des CIC Pédiatriques en France

- **Stimulate clinical research in paediatrics** (physiopathology, pharmacology and therapeutics)
- **Help paediatricians to performe research**
- **Optimize the conduct** of trials (including methodological and technical aspects...)
- **Participate to training** of all health professionals
- **At both the local and the French national levels**

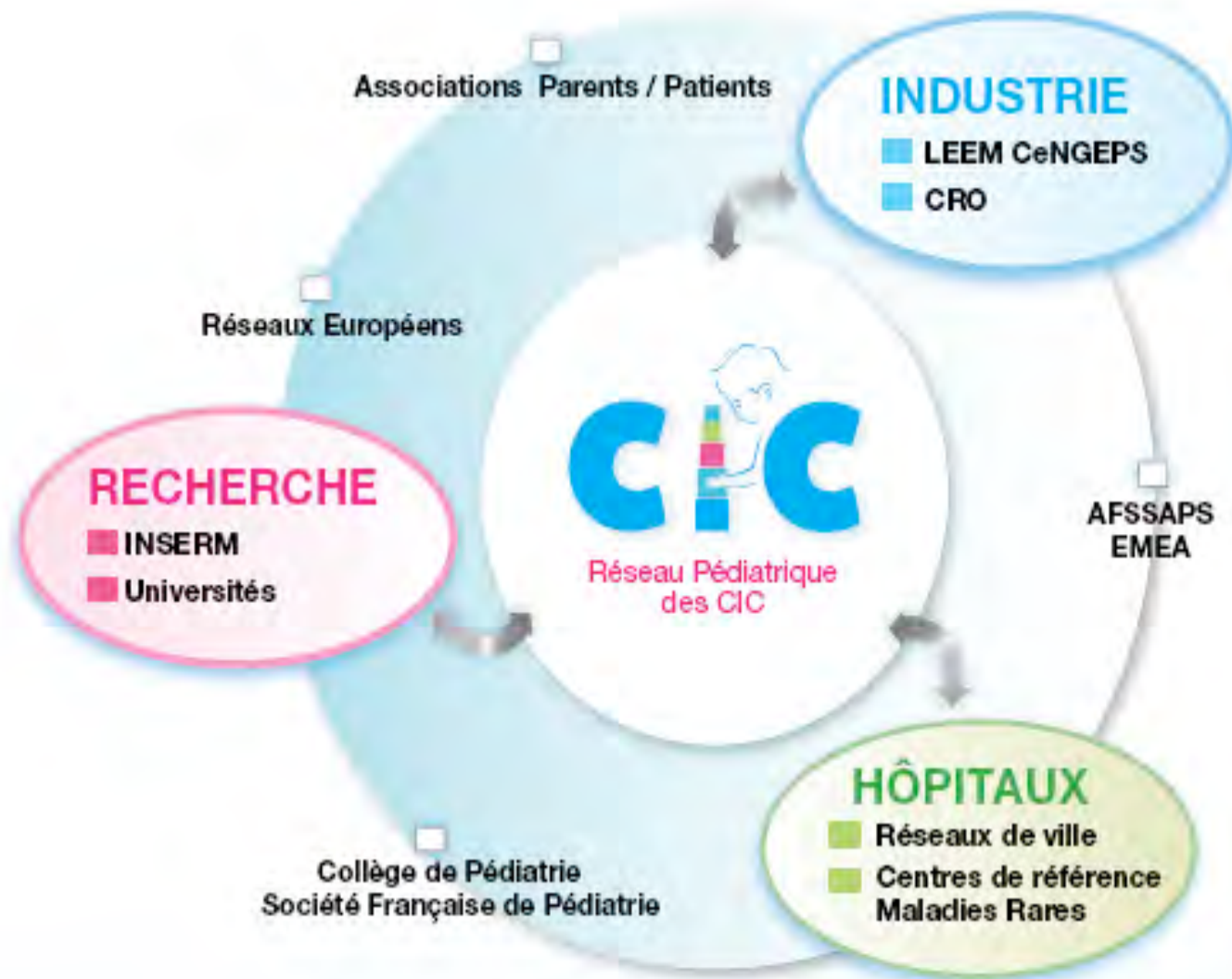


# Partenaires du réseau

14 CIC ayant une activité pédiatrique (et adulte)



# Réseau pédiatrique des CIC



# Paediatric CIC Network

- Paediatricians of the different centers are subspecialists (gastroenterology, endocrinology...) are experts for the network
- Methodologists and statisticians
- TC each month
- Face to face meeting every 6 months

# Paediatricians, research nurses and research technicians







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Network of CIC

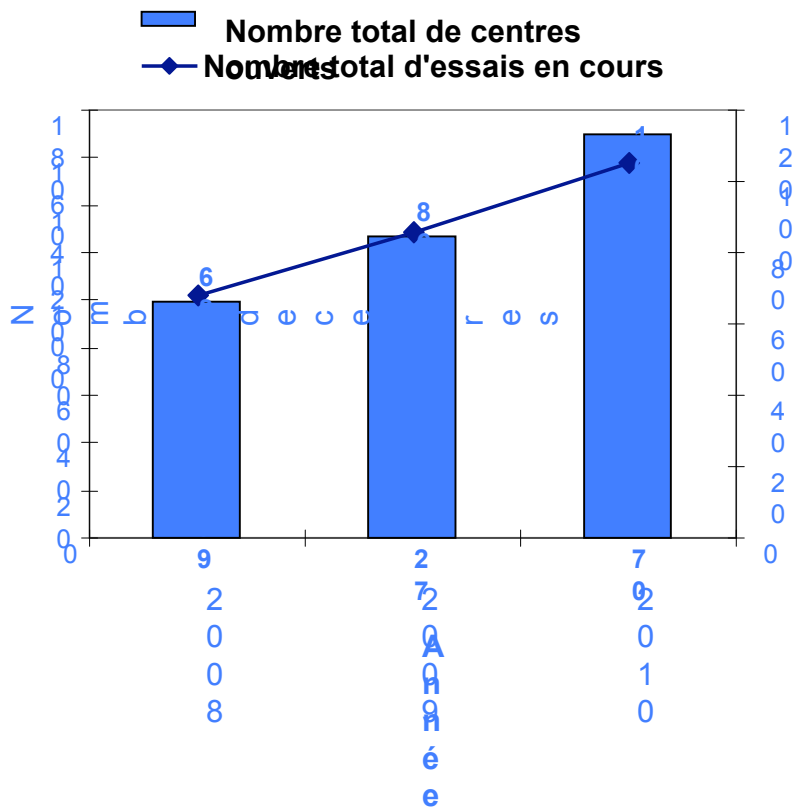
# Industry sponsored trials





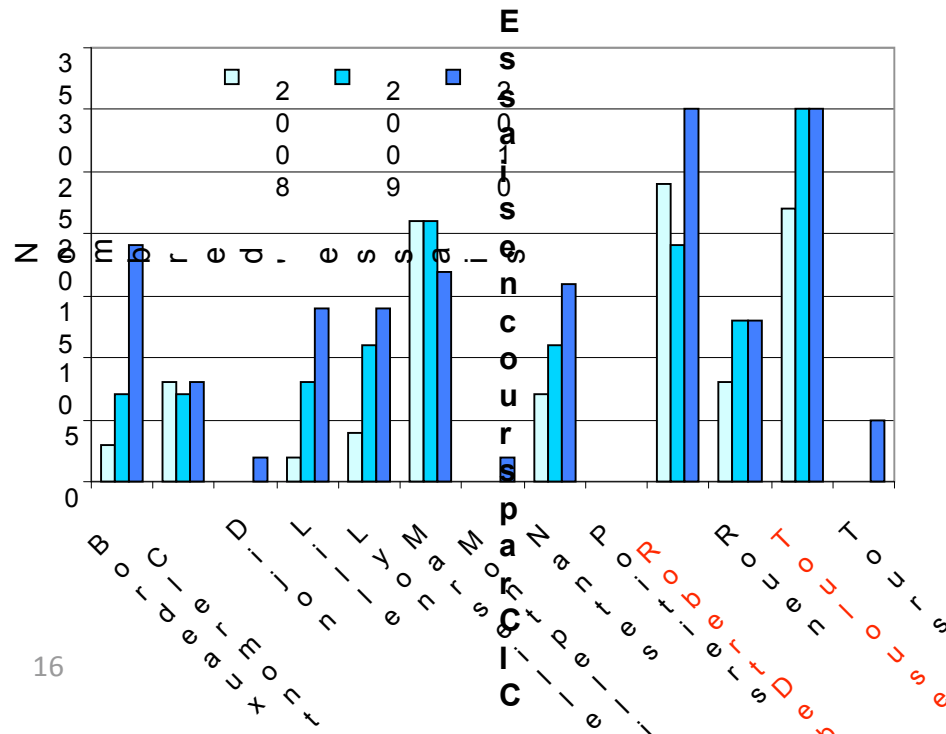
# Ongoing Industry trials

Nombre d'essais



2008 - 2010

➤ Augmentation nette du nombre d'essais



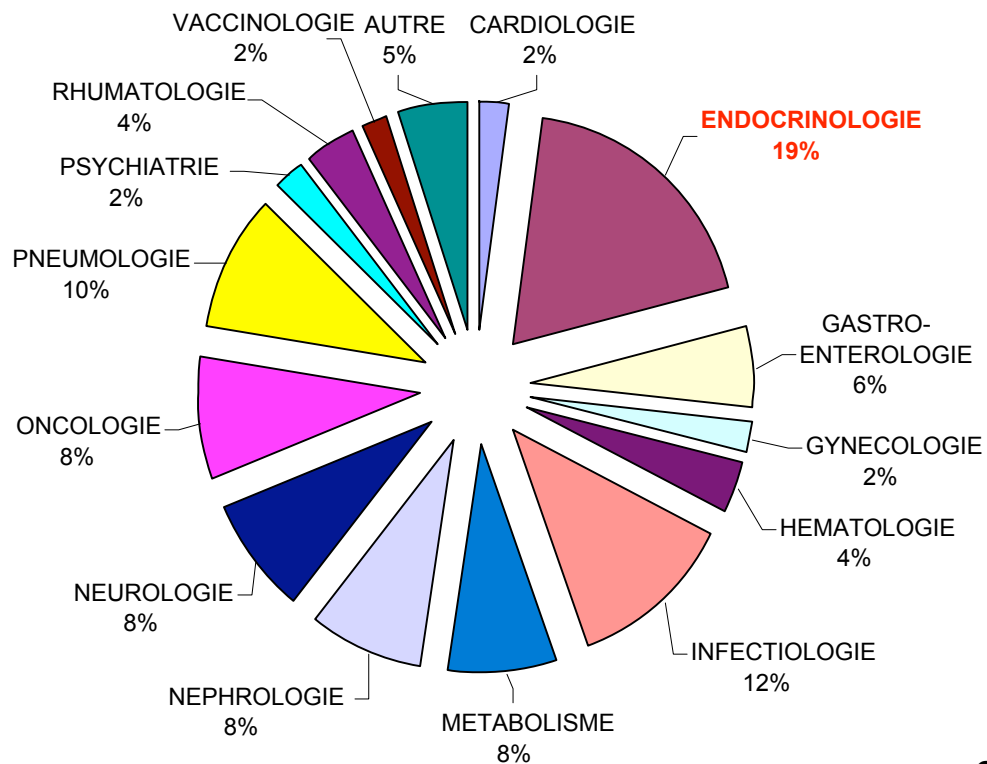




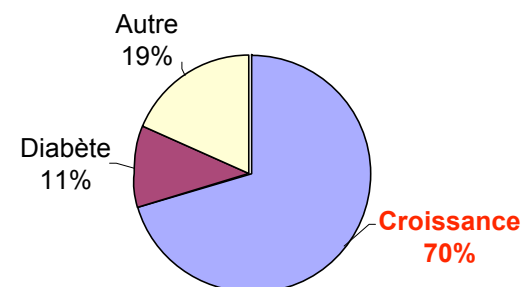
# Thématiques

## Répartition des Essais (142) par Discipline

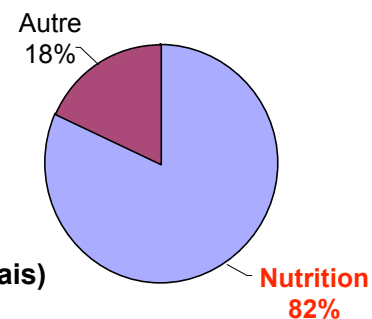
142 essais recensés



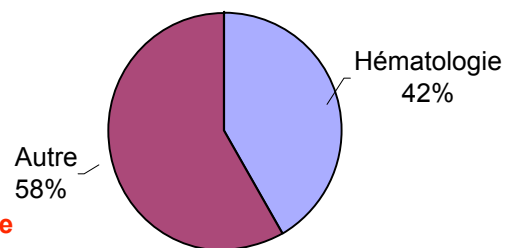
### Endocrinologie (27 essais)



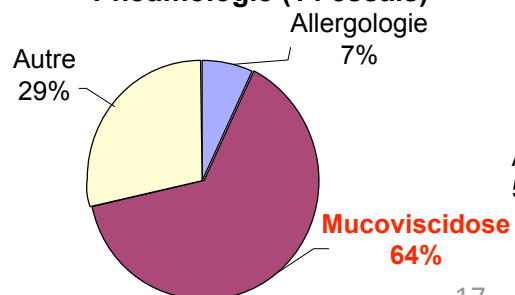
### Métabolisme (11 essais)



### Oncologie (12 essais)



### Pneumologie (14 essais)





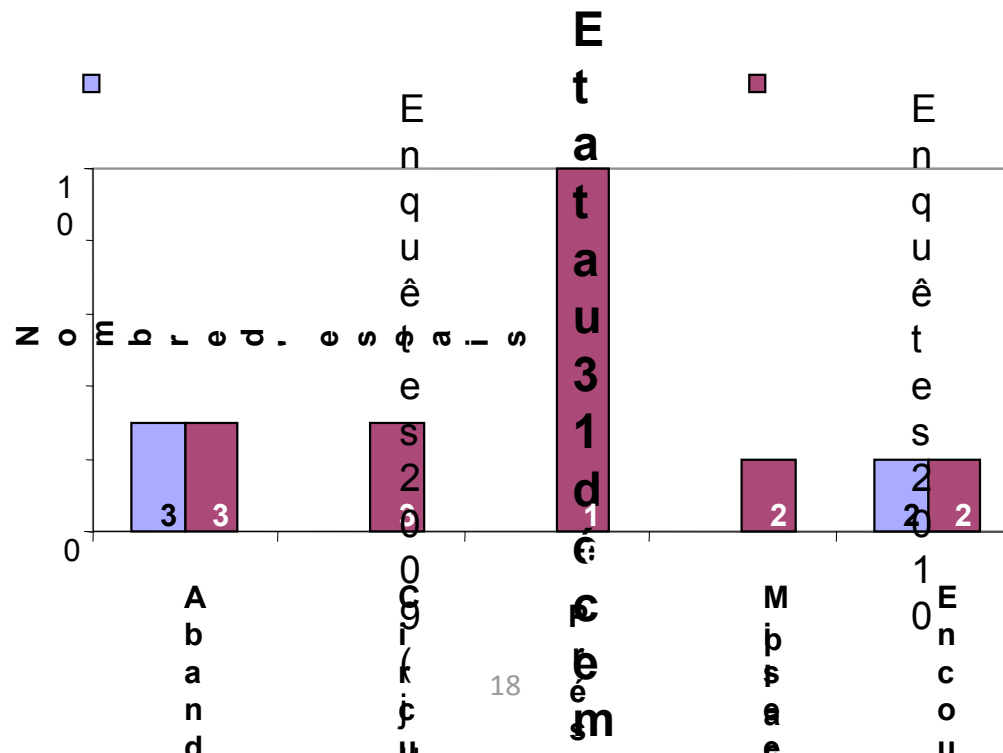
# Coordination (juillet 2009 - décembre 2010)

Enquêtes de faisabilité

Industry contacts

2009 : 5

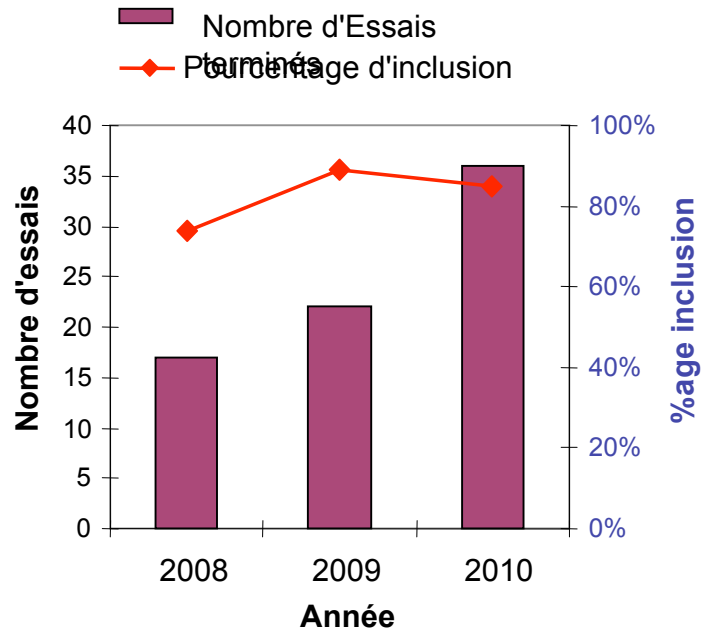
2010 : 20



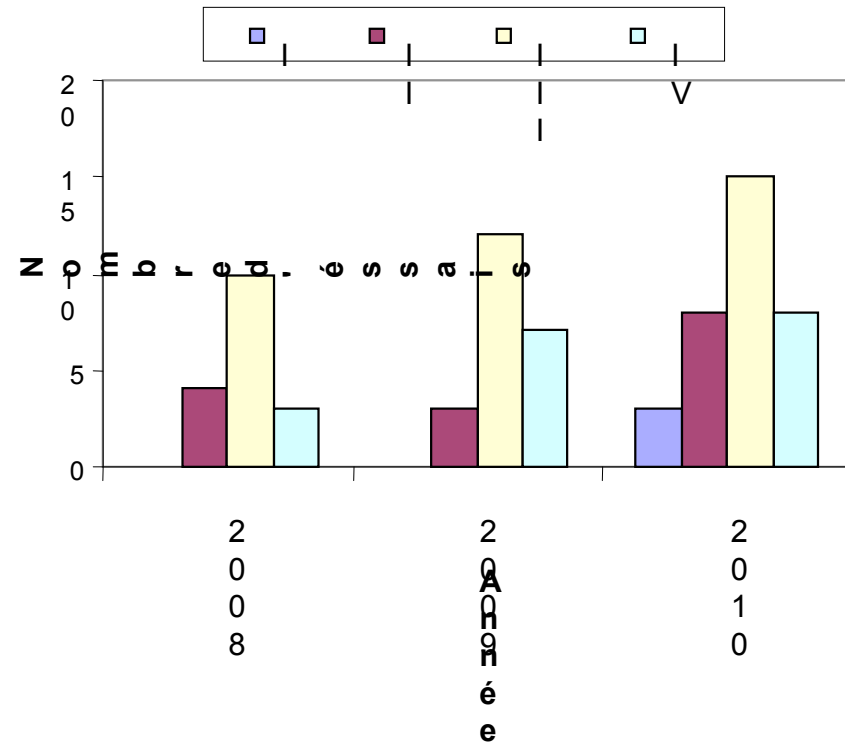


# Essais terminés 2008 - 2010

## Nombre d'essais

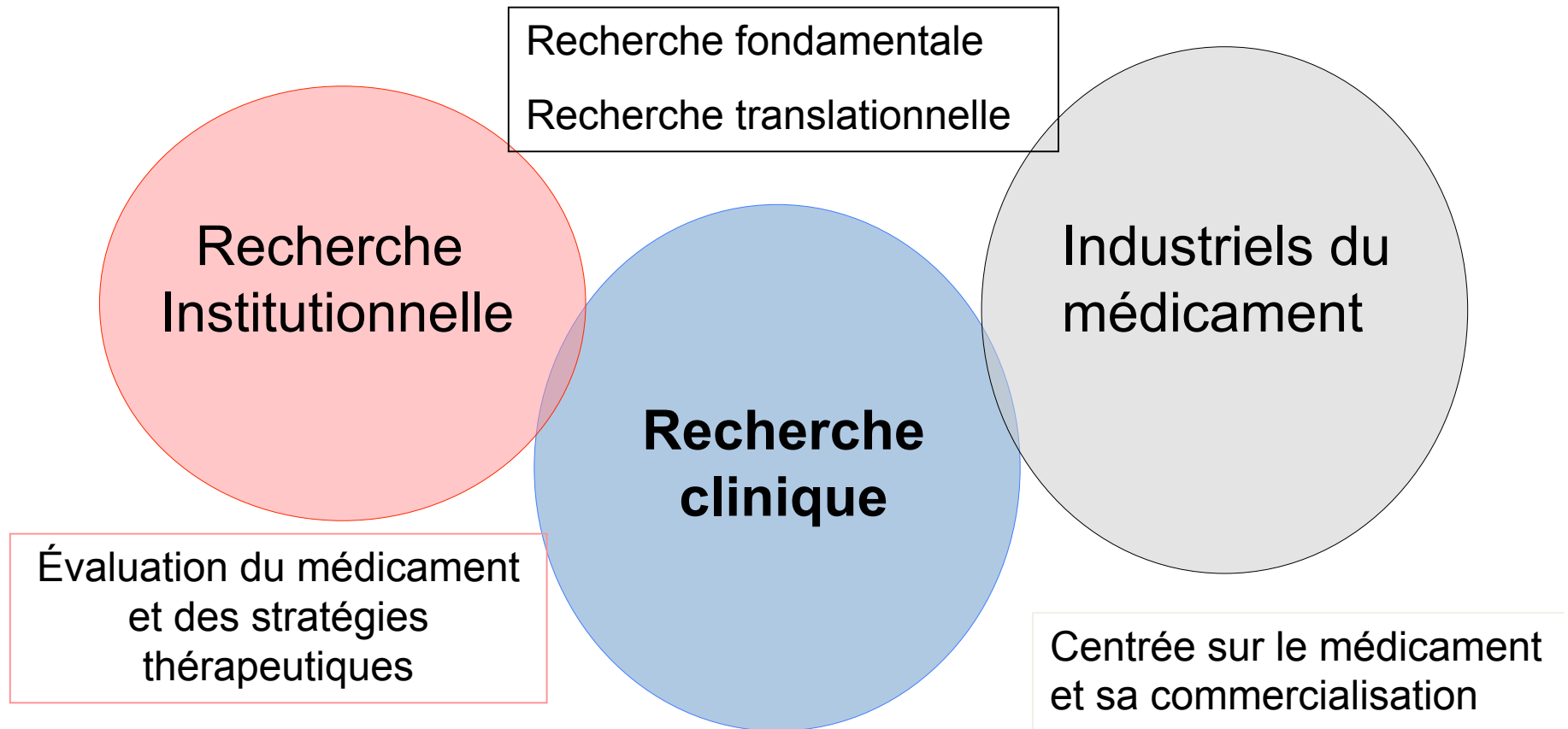


## Répartition par phase



- Augmentation du nombre d'essais terminés
- Maintien du %age d'inclusion en 2009 et 2010

# Challenges and difficulties of clinical research in children

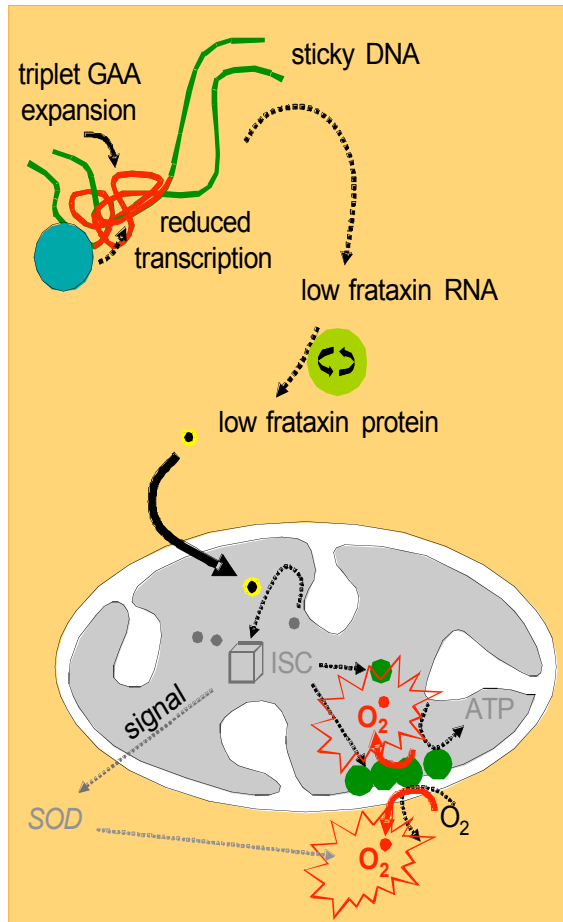


Perform Drug evaluation studies  
Maintain Translational researches  
Maintain Evaluation of therapeutic strategies.....

# Public sponsored trials



# Effet de la Pioglitazone dans l'ataxie de Friedrich



**Maladie neurodégénérative** autosomique récessive aboutissant à une perte d'autonomie avant l'âge adulte

## Mutations dans le gène de la frataxine (9q13))

- mauvaise transcription du gène
- perte de fonction de la frataxine
- modifications biochimiques, en particulier défaut de mise en place des défenses antioxydantes

## Pioglitazone ACTOS® : candidat à la neuroprotection dans l'ataxie de Friedreich

### Essai monocentrique ouvert – PHRC 2007

Unité INSERM (Pr Gressens / P. Rustin)  
Neurologie, CIC / Pharmacologie

**50 patients – 4 séjours de 4 jours**

Multiples explorations cardiaque, marche,...

Robert Debré

**DIRC**  
**Sud-Ouest**  
**Outre Mer**

**PHARM-A**



**Pharmacocinétique de population des anti-infectieux  
(Ceftazidime, Ciprofloxacine et Voriconazole) chez  
l'enfant agé de 1 mois à 5 ans**

Réseau des CIC pédiatriques  
CRCM, Onco-hématologie, réanimation, Pédiatrie générale

# Essai Guard Control /Medical device

## Le Guardian®RT (Medtronic-Minimed)

- CAPTEUR
- TRANSMETTEUR (sans cable)
- MONITEUR
- Mesure de glucose en temps réel / 5 min (RT)
- Alarmes hyper- et hypo
- Calibration (au moins 2/jours)
- Téléchargement des profils (21 derniers jours)



Multicentrique inter CIC



# Challenge 1 : Ethical issues

## Protecting children in research

- Measures to minimise pain, distress and fear
- Advocating sparse sampling where possible
- Modelling and simulation where possible
- Innovative (non conventional) methodology for design and analysis, if this allows limiting the number of children while maximising information....

## Challenge 2 : Scientific issues in drug evaluation in children

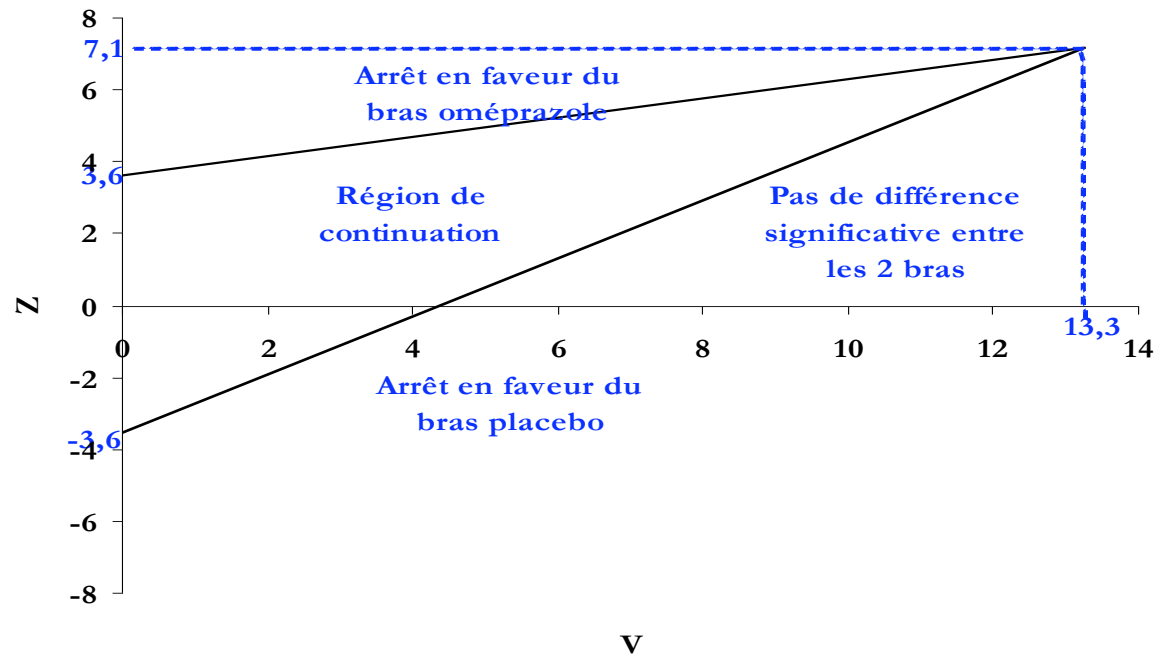
- Difficulties in assessing feasibility of trials, especially in neonates
- Lack of (validated) endpoints
- Maturation effects on PK and PD
- Modelling and Simulation
- Extrapolation (decision tree of ICH E11 issues: what is similar disease progression, expected response to treatment)
- Theoretical development versus reality
- Excipients in paediatric formulations
- Long term efficacy and SAFETY

# Challenge 3 : Perform efficient trials

## Study design / Avoid trial failures

- Small clinical trials (limited number of patients)
- RCT versus observational studies
- Use of placebo
- Evaluation of disease modifying effects

Triangular test used to evaluate omeprazole in preterm and term neonates



## Challenge 4 : DELIVER...

- Faisability : methodology, recrutement....
- Selection of protocols according to paediatric needs :
  - Industry protocols and diabetes
  - Evaluation of a drug versus therapeutic strategy
- Quality : inclusions, monitoring...
- Evaluation (number of studies ? patients publications ?)
- International collaborations (EU)



## WHY FP7 EU PROJECTS IN PAEDIATRICS ?

The examples of FP7 projects in neonates : TINN, TINN 2,

GRIP

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More studies are required in neonates as up to 90% of drugs are used unlabelled). There are many major scientific, practical and ethical issues in relation to studying paediatric patients

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The need for :

- ✓ adapted formulations
- ✓ suitable methodological approaches for PK, PK PD studies, clinical trials...
- ✓ sufficient number of trained investigators with expertise in neonatal clinical trials (inadequate critical mass of investigators in any single European country)
- ✓ harmonized definitions
- ✓ adequate pharmacoepidemiology and drug monitoring programs
- ✓ to consider major ethical issues

All these issues are examined in two neonatal FP7 EU programmes

The TINN project aims at validate PIPs for two anti-infective drugs in the « EMEA priority list » and apply for a PUMA  
Coordinator : Evelyne Jacqz-Aigrain

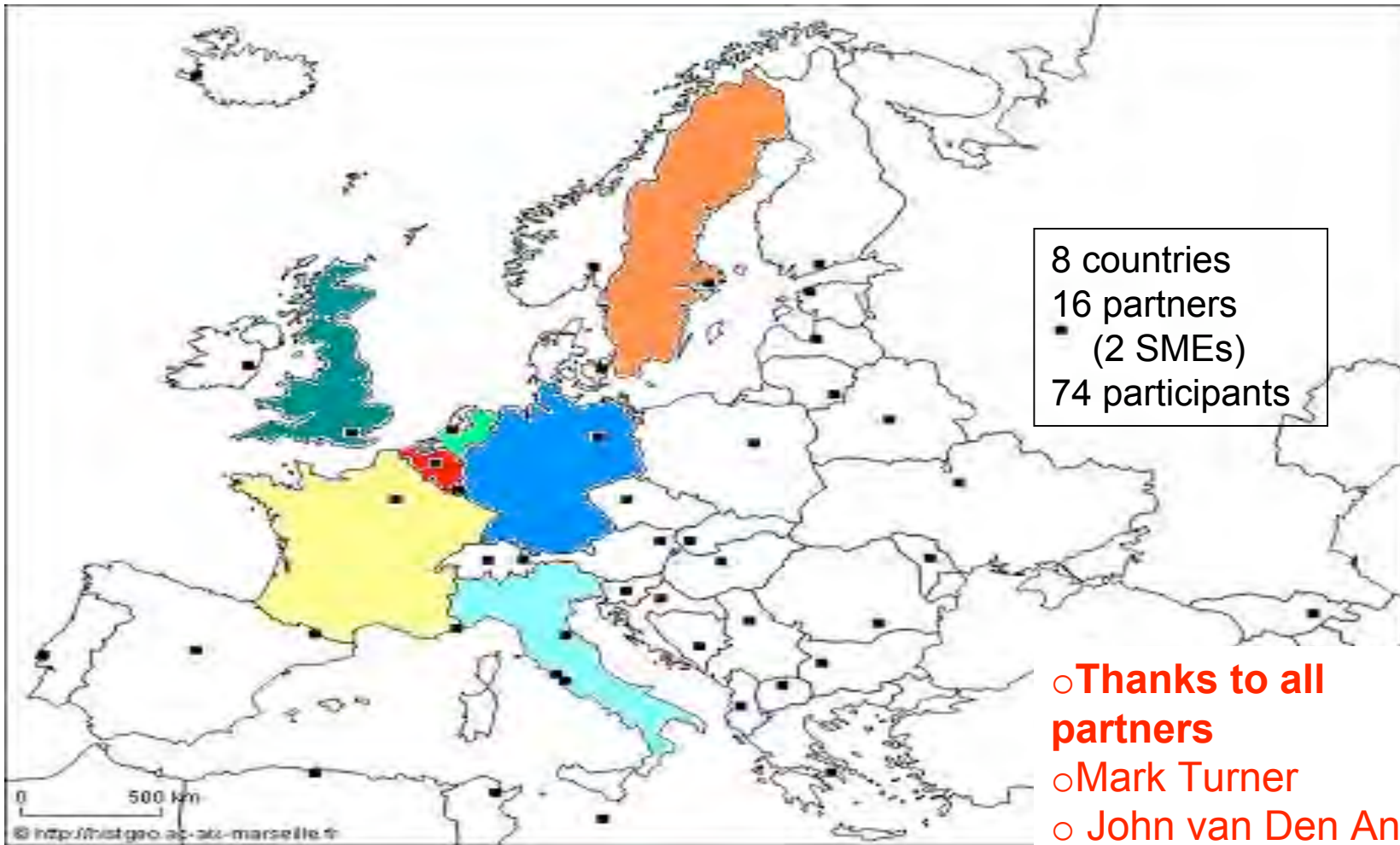
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## Evaluation of the pharmacokinetics, efficacy and safety :

- Ciprofloxacin administered to treat neonates with sepsis caused by multiple resistant organisms, against which only ciprofloxacin is effective
- Fluconazole administered to prevent and or treat neonates with invasive candidiasis
- Treat Infections in NeoNates



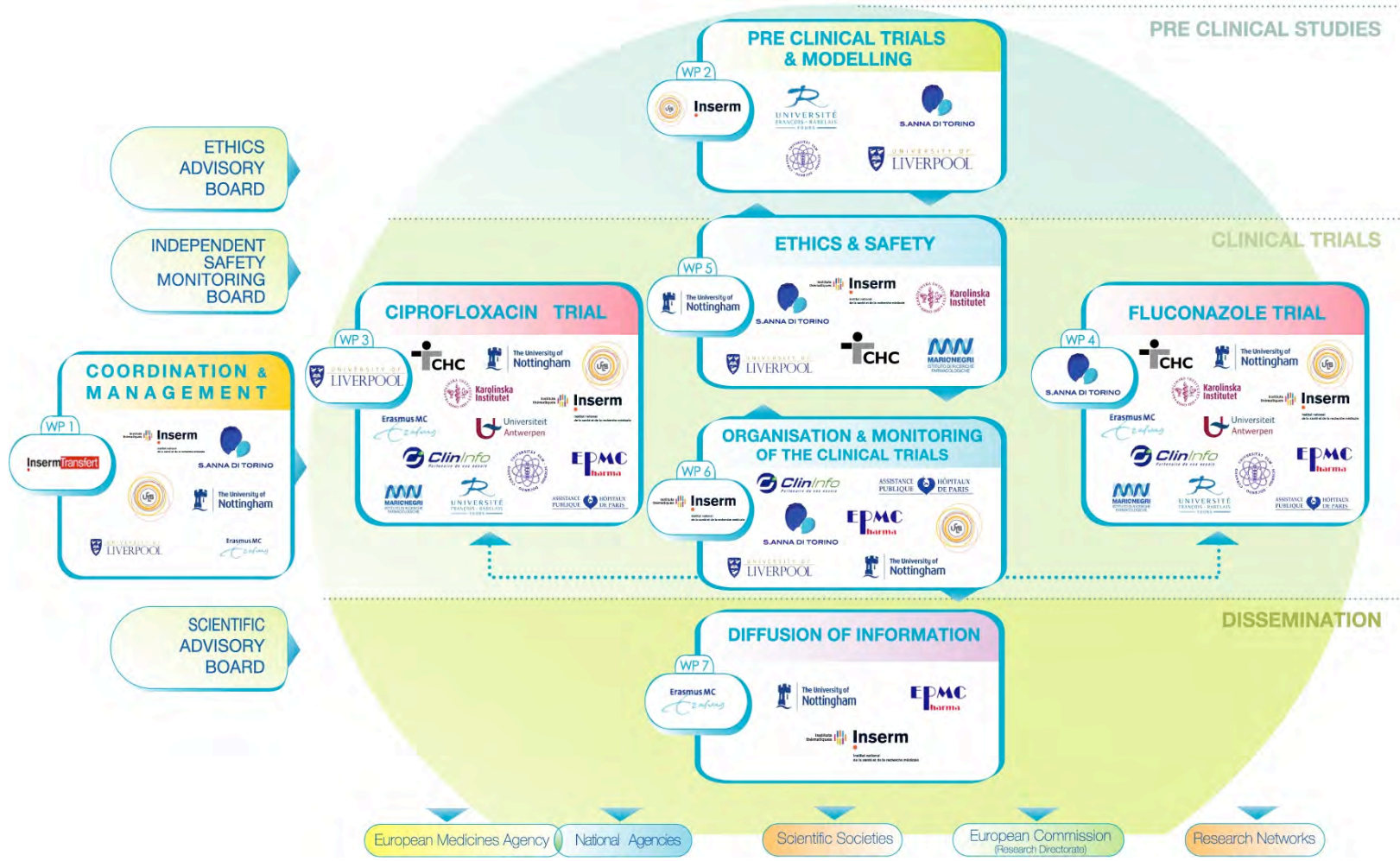


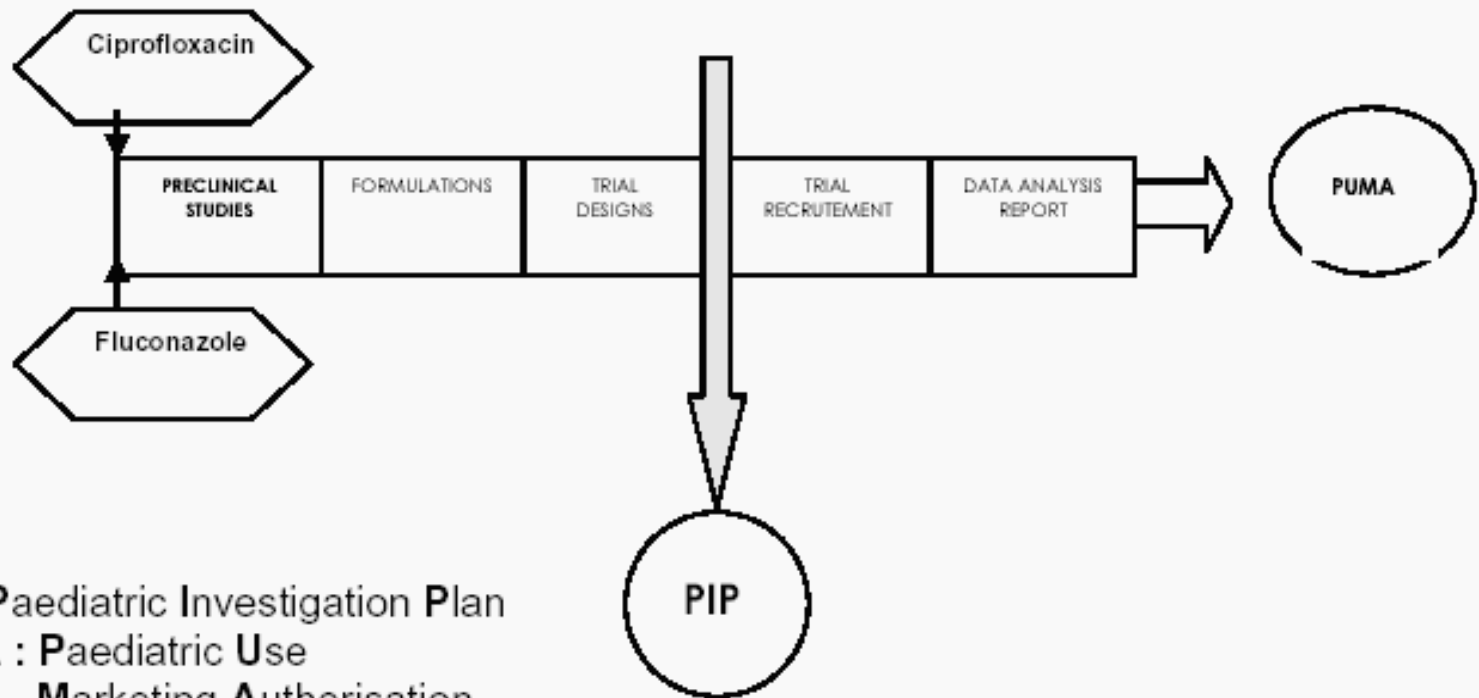


- **Thanks to all partners**
- Mark Turner
- John van Den Anker,
- Imti Choonara
- Paolo Mansoni
- Mauriio Bonati, etc...

**Tinn**







**PIP** : Paediatric Investigation Plan  
**PUMA** : Paediatric Use Marketing Authorisation

# Azithromycin in preterm neonates

Coordinator Evelyne Jacqz-Aigrain

Azithromycin is a macrolid antibiotic with anti-inflammatory properties active against Ureaplasma that might be effective in reducing the severity of bronhopulmonary disease in which Ureaplasma infection and inflammation play a role.

Aims : evaluate its pharmacokinetics, efficacy and safety in preterm neonates at high risk of pulmonary bronchodysplasia



# GRIP : Global Research in Paediatrics

Coordinator : Carlo Giaquinto, Padua, Italy -

Aim of GRIP will be to implement an infrastructure matrix to stimulate the development and safe use of medicine in children, focussing on

- development of a Paediatric Clinical Pharmacology Training Program;
- Validation of research tools specific for paediatrics;
- sharing of strategies and plans;
- use of ongoing/planned research studies to evaluate the feasibility of proposed research tools and strategies.

Partners in Europe, the US and Asia with integration of the WHO, EMEA and the NICHD associated networks, including the FDA and partnership with families

# Challenges ?

(among many others...)

- ◆ Selection of protocols according to paediatric needs (...design, ethics...)
- ◆ Evaluation of strategies as well as drugs
- ◆ Organisation of training
- ◆ Maintain infrastructure funding
- ◆ Collaboration .....at the EU and international level





Thank you