European Neonatal Networks: Platforms for Clinical Research

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Bilbao, Spain

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Porto, Portugal
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Outline

1. Networking for Research

2. Neonatal Networks

3. European Neonatal Networks
   - EuroNeoNet (DG SANCO)
   - GRIP, NeoCirculation (7th RFWP EC)
   - EnPrEMA (EMA)

4. Spanish Research Network (Red SAMID)
**Networking**

- **Network**: Group of people/organizations closely connected and that work with each other, **toward a common aim**

- **Networking**: Exchange of information/services among individuals/groups/institutions

- *More than a word, is a concept!*

- **Specifically for research**: cultivation of productive relationships for a common **scientific goal**
Neonatal Research Networks

- **In general**: Individual initiatives: academic, neonatal societies, *ad hoc*
  . Networks Neo: VON, NICHD-NN, CNN, JNRN, ANZNN…
  . National & European funding agencies

- **In a few countries**: Structured public funded initiatives
  . **USA**: Stable research networks
    . VON: numerous no pharmacological RCT
    . NICHD: Neonatal Research Network: many RCT
    . Pediatric Trials Network
  
  . **UK**: MCRN: Medicines for Children Research Network (England)
    . Specialized Pediatric Network: >150 RCT (60% public)

  . Similar structures in: The Netherlands, Finland…
US Neonatal Clinical Research Network

✓ In 1986 “Eunice Kennedy Shriver National Institute of Child Health & Human Development” (part of NIH) established it

- Neonatal Research Network to develop multicentric RCT. Great record pharmacological, non-pharmacological RCT

- Pediatric Clinical Trial Network
## Networking

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<td>“European neonatal clinical research network”</td>
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Aims: 1) Quality-assessment of perinatal care VLBWI in Europe

3) Quality improvement initiatives

2) Safety initiative ("EuroNeoSafe" project)

4) RCT Network

Methods: A common perinatal data-set, based VON (Copyright)

. Virtual environment by up-to-date technology

Participation: >200 NICU´s from 18 countries

. > 5.000 datasets/year (50,000)

EuroNeoNet Coverage

National/Regional Networks

1) Integrated:
   - Belgium
   - Portugal
   - Spain
   - Sweden
   - N Ireland
   - Lazio
   - Switzerland

2) Pending:
   - Estonia
   - Norway
   - Austria
   - Denmark
   - Hungary
   - Ireland
   - France
Follow-up data

- **ENS I: 2 Years Corrected Age Follow – Up**

- **Leader:** Michael Weindling, Univer. of Liverpool
  Adolf Valls i Soler, Cruces University Hospital

- **Objectives:** To develop & validate a minimal follow-up dataset of indicators to assess quality of life of VLBWI at 24 months CA

- **Achievements:** A minimum number of items were selected, discussed & agreed to asses follow-up at 2 years of CA. It is used routinely in ENN to collect data
• **ENS II: 4 Years Corrected Age Follow-up**

• **Leader**: Javier de la Cruz, FIBH12 Octubre, Madrid

• **Objetives**: Expansion of the Information System, by a consensus process among EURONEOSTAT partners. The process included a literature review, 2 rounds of web based questionnaires & a nominal group

• **Achievements**: A proposal of indicators framed in the WHO International Classification of Health & Disability. A list of domains of assessment was agreed. For each domain the assessment tools most used in the scientific literature is described. Data not routinely collected yet
Euro-NEOKISS
Quality Improvement initiative

- **Designed**: Step-by-step wedge cluster RCT
- **Intervention**: Structured multimedia QI package
- **Primary outcome**: Evaluate effectiveness evidence-based structured educational intervention to reduce the incidence of NS in VLBW
- **Measuring instrument**: EuroNeoKiss systematic integrated epidemiological surveillance system
- **Sample size**: 2,800 VLBWI (1,400 per arm)
  - 56 clusters NICUs (28 per arm)
  - estimating mean 50 VLBWI per NICU
“Medicines for Children” program
EC Funding schemes

1. **Specific drug development**
   (EMA annual pediatric drug list)

2. **Networks of excellence**
   - Life Health Priorities 6th RFWP
     - TEDDY project (financed: 2005-2010)
   - Life Health priorities 7\(^{th}\) RFWP
     - GRIP project (financed: 2011-2015)
Global Research in Paediatrics

GRIP

"Network of Excellence"

EC, 7th RFWP. HEALTH-2010.4.2-2:

International Paediatric Initiative
1. Ospedaliera Padova, Italy: Carlo Giaquinto (PENTA)
2. NICHD-NIH; US: Steven Hirschfeld, Washington, DC
3. EMA, London, UK: Agnes Saint-Raymond
5. Univer. Liverpool, MCRN-LIV, UK: Rosalind Smyth
6. Ospedale Pediatrico Bambino Gesú, Italy: Paolo Rossi
7. INSERM, Paris, France: Evelyne Jacqz Aigrain
8. NCCH, Japan: Hidefumi Nakamura
9. St. George’s Hospital Med. School, UK: Mike Sharland
10. Teddy
13. BIOEF; Bilbao, Spain: Adolf Valls-i-Soler
13BIS- Osakidetza
16. WHO, Switzerland: Suzanne Hill
17. School Pharmacy, Univer. London, UK: Ian Wong
19. Brighton Collaboration Fund; Switzerland: Jan Bonhoeffer
20. PENTA
21. Hospital for Sick Children, Toronto, Canada
22. Parent´s organisation & Pharmaceutical Co. (small)
EU Paediatric data

- 75 M children (20% population)
- 45,000 paediatricians (1/1,666 children)
- Only 12 Pediatric Clinical Pharmacologists

- Few pediatric RCT
- Few pediatric preparations
- Most drugs used “off. label”
GRIP Project. Objectives

1. **Training Program on Pediatric Clinical Pharmacology**

2. Identify key block for drug development for children/neonates

3. Propose how to overcome those blocks

4. Harmonise / Validate specific research tools

5. International cooperation for drug development (EU, US, Japan, others)
NeoCirculation

Development of a Dobutamine formulation for newborns. Finding biomarkers for neonatal shock

Collaborative project
Project leader. Heike Rabe

EC, 7th RFWP. HEALTH-2010.4.2-2

Medicines for Children
# Proposal

**Proposal full title:** Dobutamine for NEOnatal CIRCulatory failure defined by novel biomarkers

**Proposal acronym:** NEO-CIRC

**Type of funding scheme:** Collaborative Project (CP) - Small or medium-scale focused research project (STREP)

**Work programme topics addressed:** Investigator-driven clinical trials on off-patent medicines for children, FP7-HEALTH-2011-single-stage.

**List of participants:**

<table>
<thead>
<tr>
<th>Participant no.</th>
<th>Participant organisation name</th>
<th>Participant short name</th>
<th>Country</th>
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<tr>
<td>1 (CO)</td>
<td>BRIGHTON AND SUSSEX UNIVERSITY HOSPITALS</td>
<td>BSUH</td>
<td>UK</td>
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<td>2</td>
<td>NATIONAL INSTITUTE OF HEALTH AND MEDICAL RESEARCH</td>
<td>INSELM</td>
<td>France</td>
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<td>3</td>
<td>HANNOVER MEDICAL SCHOOL</td>
<td>MHH</td>
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<td>4</td>
<td>BID EUSKO FOUNDATION</td>
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<td>Spain</td>
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<td>5</td>
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<td>Germany</td>
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<td>VEST CHILDREN'S HOSPITAL DATTEN UNIVERSITY</td>
<td>WJK</td>
<td>Germany</td>
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<td>8</td>
<td>LA PAZ UNIVERSITY HOSPITAL SPANISH CLINICAL RESEARCH NETWORK (CAIBER)</td>
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<td>12</td>
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<td>18</td>
<td>TUFTS MEDICAL CENTER</td>
<td>TMC</td>
<td>USA</td>
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**Name of the coordinating person:** Heike Rabe

**Coordinator email:** Heike.Rabe@bsuh.nhs.uk

**Coordinator fax:** 44 121 73 65 4435
Spanish Maternal, Child Health & Human Development Research Network
## Consortium

<table>
<thead>
<tr>
<th>Group Name</th>
<th>Coordinator</th>
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<tbody>
<tr>
<td>Hospital Universitario Cruces</td>
<td>Adolf Valls i Soler</td>
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<tr>
<td>Hospital Universitario Cruces</td>
<td>Pablo Sanjurjo Crespo</td>
</tr>
<tr>
<td>Universidad de Zaragoza</td>
<td>Luis Alberto Moreno Aznar</td>
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<tr>
<td>Hospital Sant Joan de Deu</td>
<td>José Maria Lailla Vicens</td>
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<tr>
<td>Hospital La Paz</td>
<td>Fernando Cabañas González</td>
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<tr>
<td>Hospital La Paz</td>
<td>Juan Antonio Tovar Larrucea</td>
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<tr>
<td>Hospital 12 de Octubre</td>
<td>Carmen R Pallás Alonso</td>
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<tr>
<td>Hospital La Fe</td>
<td>Máximo Vento Torres</td>
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<td>Hospital Marques de Valdecilla</td>
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<td>Jesús López-Hérce Cíd</td>
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<tr>
<td>Universidad de Granada</td>
<td>Angel Gíl Hernández</td>
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Red SAMID 2009-16: Some data

- **Approved**: Red SAMID II: 2013-2016
- **Established**: February 2009, Bilbao: 12 research G.
- **Funding**: € 2.0 m
- **Basic funding**: 11 researchers, 1 manager
## Indicators. I. Publications & Research Projects

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<td>1:4.5</td>
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<td>Mobility</td>
<td>1</td>
<td>19</td>
<td>&gt;100</td>
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</table>
1. Low-molecular-weight *heparin* in Preeclampsia  
   PI: LL. Cabero, Barcelona

2. *PresOX*. High vs. low FiO$_2$ for resuscitation of VLBW infants  
   PI: Max Vento, València (leads international collaboration)

3. *NeoCirculation*: Dobutamine vs placebo on low SVC flow state on systemic hemodynamic instability in VLBWI  
   PI: Adelina Pellicer, Madrid (Spanish branch)
Funded RCT

**Perinatal – Neonatal trials (n=6)**

4. **Topiramate** on HI-encephalopathy with seizures  
   PI: Max Vento, València

5. **Safe-Boot**: Effect of monitoring cerebral-O$_2$ in short-term outcome  
   PI: Fernando Cabañas, Madrid (Spanish branch)

6. **EuroNeoKiss**: Prevention of HAI in VLBWI  
   PI: Adolf Valls-i-Soler, Bilbao
Funded RCT Pediatrics (n=3)

7. Effect of steroids post-intubation in children
   PI: Jesus Lopez-Herce, Madrid

8. Nutritional intervention on prevention of Metabolic Synd. in pre-adolescents
   PI: Luis Moreno-Aznar, Zaragoza

9. Metformin for prevention of type II Diabetes in obese preadolescents
   PI: Luis Moreno-Aznar, Zaragoza
Red SAMID: Coordinator Group

- Coordinator
- Manager / Administrator

- **Platforms**: Methodological support
  - Pediatric academic clinical trials center

1. **Epidemiology**: Epidemiologist
   - Biostatistician
   - Pharmacologist, Microbiologists
   - Data manager, admin, support

2. **Preclinical pharmacology**: 3 biologists
A European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)

Nicolino Ruperto, Irmgard Eichler, Ralf Herold, Gilles Vassal, Carlo Giaquinto, Lars Hjorth, Adolf Valls-i-Soler, Christina Peters, Peter J Helms, Agnès Saint Raymond

Arch Dis Child 2012, 97 (3): 185-8
European Network of Paediatric Research Networks

- foster high-quality, ethical research on medicines for children
- enable collaboration between networks & stakeholders
- co-ordinate studies relating to paediatric medicines & avoid unnecessary testing
- build up scientific & administrative competence at EU level
- help recruitment of patients for RCT
- promote EC framework programme applications

Enpr-EMA does not perform RCT or fund studies, research or decide on areas for pediatric research. This is responsibility of MS and each individual paediatric network
EnprEMA Accreditation

- **EnprEMA**: Coordinator: Mark Turner, Liverpool
  - Three NN networks:
    - German & Italian NN, NeoCirculation, EuroNeoNet, Red SAMID

- **Red SAMID**:
  - 2012: Class 3
  - 2013: promoted to Class 2, Class 1

- **EuroNeoNet**
  - From 2012: Class 3
    (Upgrading awaiting a RCT)
Strategic decision

• To build a Platform to promote & perform RCT in pregnant women, neonates, children and pre-adolescents

• Collaborate with the Spanish RCT Platform (funds end-2013)

• Workshop on Paediatric RCT: Madrid, February 28th, 2014
A European Clinical Research Network for Clinical Trials ???
EuroNeoNet RCT Platform

- **EuroNeoNet** branch lead by interested partners

- **Aims**: To developed / conduct pharmacological & non-pharma RCT in neonates at European level

- Collaboration with GRIP partners: + other interested partners

- **Recognition**: European level: EMA, ECRIN ...

- Establish working relationships with other NR networks & groups around the world (NICHD-NRN, CNN, ANZNN ....)
EuroNeoNet RCT Platform - 1

• Is it a good idea?
• Is it needed?
• Is it feasible?
• Is it the right time?
• What is the best strategy to set it up?
  - Start by developing 1-2 RCT as “prove-of-concept?”

Anyone interested ????
EuroNeoNet RCT Platform
A proposal

Interested persons contact:

administrator.euroneonet@euskalnet.net

Initial Plans:

1. Set up a e-Discusion Forum at: www.euroneonet.org
2. Develop a Working Group
3. Set-up several TCF
4. Select a Coordinator
5. Outline a developing plan
6. Search for funds and RCT proposals
Research Groups

Neonatal Epidemiology

Preclinical Pharmacology