conect 4children
COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS 4 CHILDREN

Paediatric Medicines Research: Urgent and Collaborative

Mark Turner
Reader / Consultant in Neonatology

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Message

Every prescription involves:

- Science
- Art
- Global Partnership

How can we make this happen?

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What is the problem?

What can go wrong with a prescription?

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Givin… …ong?

Medicines can do HARM

BMC Pediatrics (2001) 1:1 …www.biomedcentral.com/1471-2431/1/1

Meta-analysis

The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs

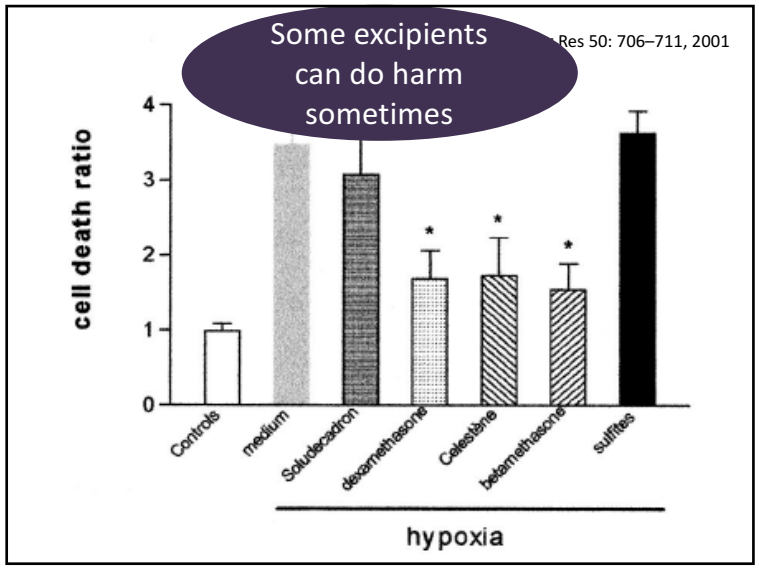
Keith J Barrington*

Study	Treatment n/N	Control n/N	RR (95%CI Fixed)	Weight %	RR (95%CI Fixed)
O'Shea	16 / 57	8 / 61		7.3	2.14[0.99,4.61]
Fitzhardinge	2 / 22	1 / 22		0.9	2.00[0.20,20.49]
Yeh	26 / 132	22 / 130		20.9	1.16[0.70,1.95]
Shinwell	44 / 132	23 / 116		23.0	1.68[1.08,2.61]
Jones	38 / 140	41 / 142		38.3	0.94[0.65,1.37]
Cummings	9 / 25	3 / 11		3.9	1.32[0.44,3.96]
Subhedar	1 / 21	4 / 21		3.8	0.25[0.03,2.05]
Vincer 1998	4 / 10	2 / 10		1.9	2.00[0.47,8.56]
Total(95%CI)	140 / 539	104 / 513		100.0	1.26[1.01,1.58]

Test for heterogeneity chi-square=8.74 df=7 p=0.27
Test for overall effect z=2.05 p=0.04

.1 .2 1 5 10
Favours treatment Favours control

Figure 2
Meta-analysis of the effects of postnatal steroids on neurodevelopmental impairment, among all randomized infants. Studies are displayed in order of the degree of known contamination of the randomization, Fitzhardinge and O'Shea known to have no contamination, Yeh, Shinwell, and Jones with progressively increasing degrees of contamination, and Cum- mings, Subhedar and Vincer unknown.



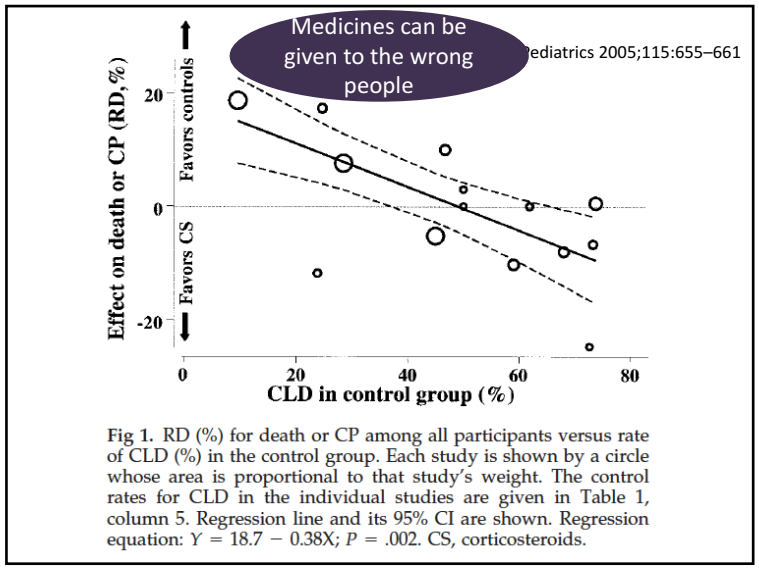


Fig 1. RD (%) for death or CP among all participants versus rate of CLD (%) in the control group. Each study is shown by a circle whose area is proportional to that study's weight. The control rates for CLD in the individual studies are given in Table 1, column 5. Regression line and its 95% CI are shown. Regression equation: $Y = 18.7 - 0.38X$; $P = .002$. CS, corticosteroids.

Richey et al. BMC Pediatrics 2013, 13:81
http://www.biomedcentral.com/1471-2431/13/81

BMC Pediatrics

Drug dosage form	Manipulation for dose accuracy includes
Tablet	• split/broken/cut and a segment given
	• crushed and a proportion of the powder given
	• dispersed in liquid and a portion of the liquid given
Capsule	• opened, dispersed in liquid and a proportion of the liquid given
	• opened and a portion of the powder given
Sachet (powder)	• opened, dispersed in liquid and a portion of the liquid given
	• opened and a proportion of the powder given

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Richey et al. BMC Pediatrics 2013, 13:81
http://www.biomedcentral.com/1471-2431/13/81

BMC Pediatrics

RESEARCH ARTICLE Open Access

Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence

Conclusion: Manipulations to achieve the required dose occur throughout paediatric in-patient settings. The impact of manipulations on the efficacy of the drugs, the accuracy of the dose and any adverse effects on patients is not known. There is a need to develop evidence-based guidance for manipulations of medicines in children.

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Richey *et al. BMC Pediatrics* 2013, **13**:81
http://www.biomedcentral.com/1471-2431/13/81

Medicines can be given at the wrong dose

BMC Pediatrics

RESEARCH ARTICLE Open Access

Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence

Conclusion: Manipulations to achieve the required dose occur throughout paediatric in-patient settings. The impact of manipulations on the efficacy of the drugs, the accuracy of the dose and any adverse effects on patients is not known. There is a need to develop evidence-based guidance for manipulations of medicines in children.

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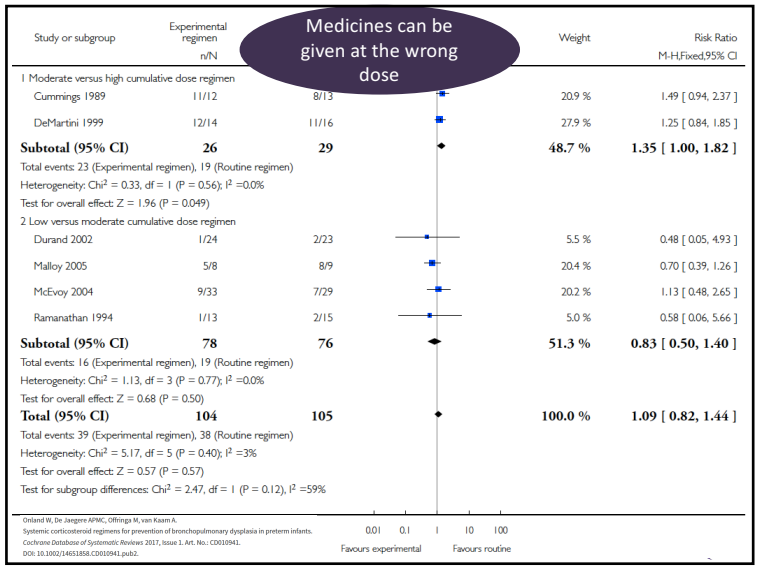


Are you sure?

Cochrane Library

Cochrane Database of Sy

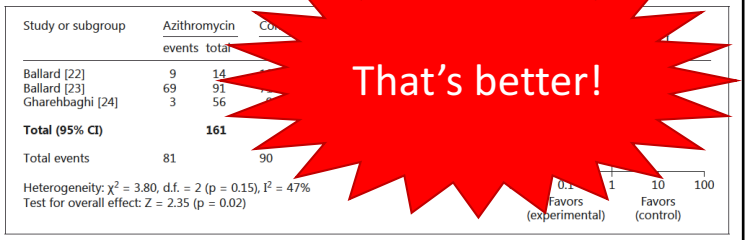
Authors' conclusions

"A well-designed large RCT is urgently needed to establish the optimal systemic postnatal corticosteroid dosage regimen"

Systemic corticosteroid regimens for prevention of bronchopulmonary dysplasia in preterm infants (Review)

Can Azithromycin ...?

That's better!



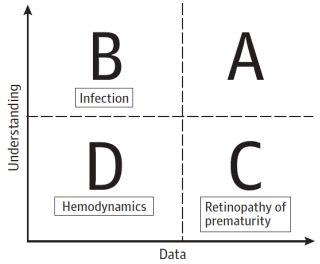
CONCLUSION:
This meta-analysis demonstrates prophylactic azithromycin therapy was associated with statistically significant reduction in BPD and the composite outcome of BPD/death in preterm infants. However, given the limited information on pharmacokinetics and potential harmful effects, further studies should be done before routine use of azithromycin in the neonatal population.

Neonatology 2014;106:337–347

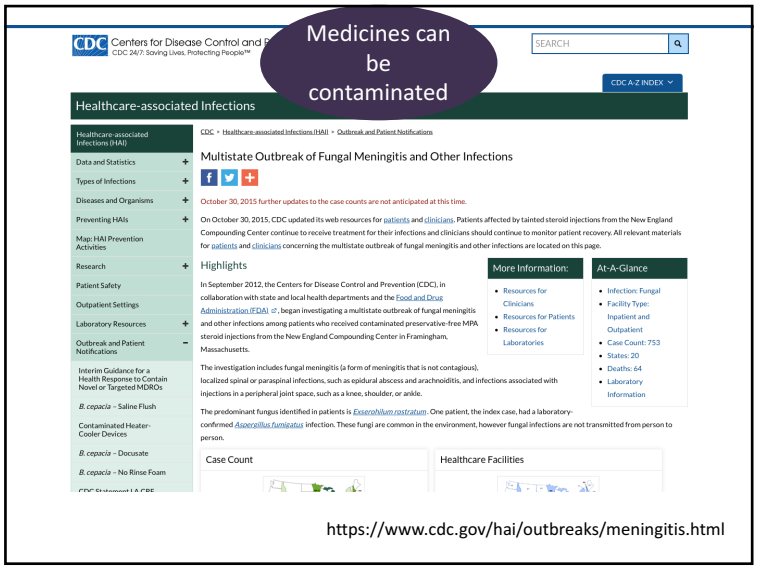
VIEWPOINT

Regulatory Science in Neonates
A Framework That Supports Evidence-Based Drug Therapy

Figure. Scheme for Regulatory Science



Turner MA et al. JAMA Pediatr. 171:721



https://www.cdc.gov/hai/outbreaks/meningitis.html

Prescriptions need information

- Baby, child, young person
- Condition
- Formulation
  - Made well
  - Appropriate
- Dose
- When does the medicine work?
- When does the medicine do harm?

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When can we trust the information?

- Clear questions
- Studies that answer the questions
- Good conduct of studies
- Independent review
- Quality of the medicine
- Appropriate balance between benefits and harms

} Regulation

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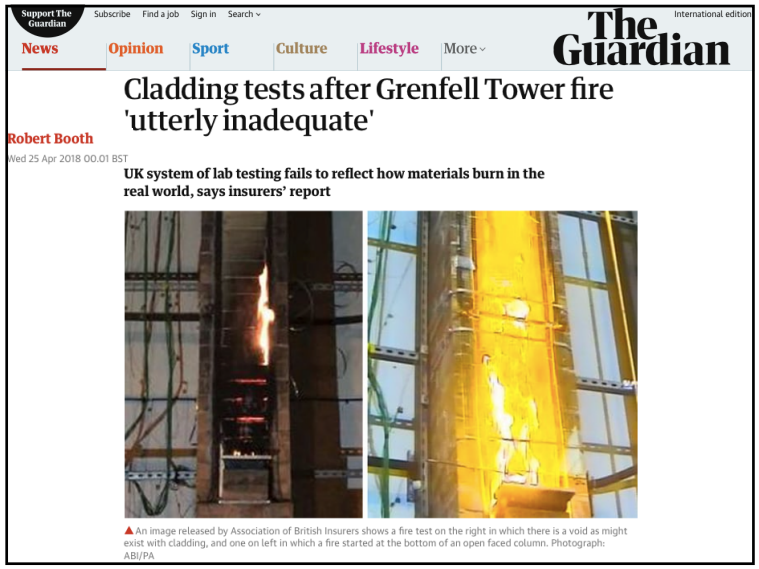

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Cladding tests after Grenfell Tower fire 'utterly inadequate'

Robert Booth

Wed 25 Apr 2018 00.01 BST

UK system of lab testing fails to reflect how materials burn in the real world, says insurers' report

▲ An image released by Association of British Insurers shows a fire test on the right in which there is a void as might exist with cladding, and one on left in which a fire started at the bottom of an open faced column. Photograph: ABI/PA

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Cladding tests after Grenfell Tower fire 'utterly inadequate'

Robert Booth

Wed 25 Apr 2018 00.01 BST

UK system of lab testing fails to reflect how materials burn in the real world, says insurers' report

The British system for fire testing building materials is utterly inadequate and underestimates the ferocity and spread of real blazes, a study commissioned after the Grenfell Tower disaster has claimed.

Full-scale laboratory tests of the combustibility of walls have been essential in assessing whether cladding on hundreds of highrises meet fire regulations after the blaze in west London that killed 71 people.

But they fail to reflect how materials burn in the real world, according to a highly critical report published on Wednesday by the Association of British Insurers (ABI).

It also alleges some manufacturers have been gaming the tests by reinforcing their systems in the laboratory in a way that would not happen in reality, for example using rivets to stop flaming panels falling off as happened at Grenfell.

Where can we find the information?

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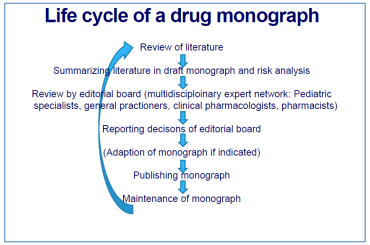
The Dutch Pediatric Formulary

(www.kinderformularium.nl)

How a drug monograph is created:

- **Aim:** risk- benefit assessment on use in children, based on available scientific literature
- Using a SOP on search, selection, appraisal and documentation of literature



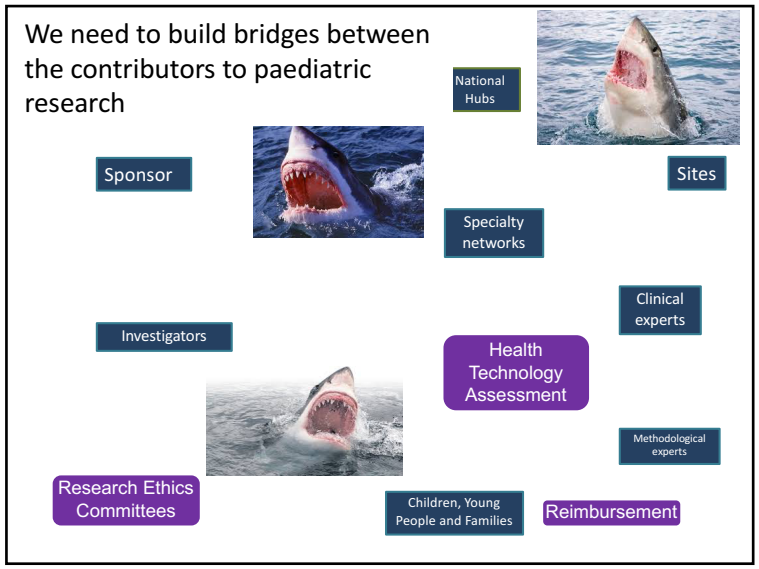
- **Best-evidence dosing guideline**
- **Webbased, unrestricted access, free of charge**
- **Unbiased, up to date, referenced, drug specific, paediatric, information**

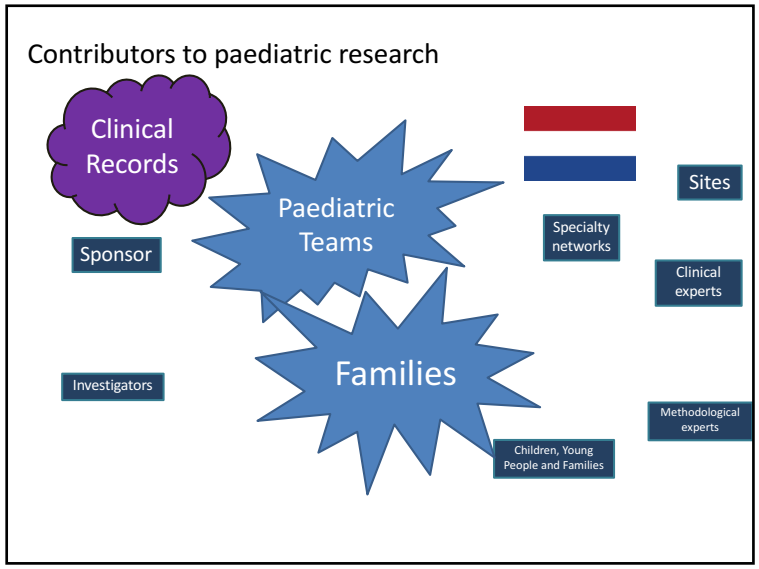
Aandacht voor kinderdoseringen

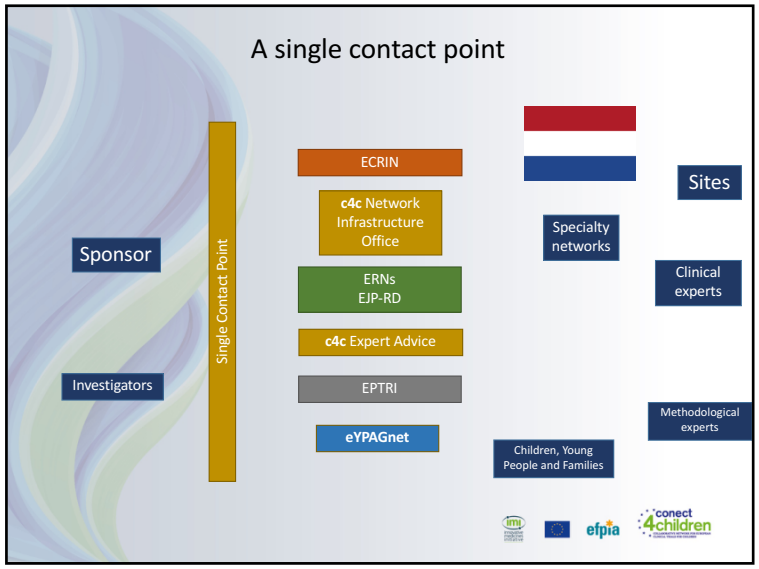
van der Zanden et al. **Developing a paediatric drug formulary for the Netherlands.** Arch Dis Child. 2017 Apr;102(4):357-361

What information do we need to evaluate medicines?

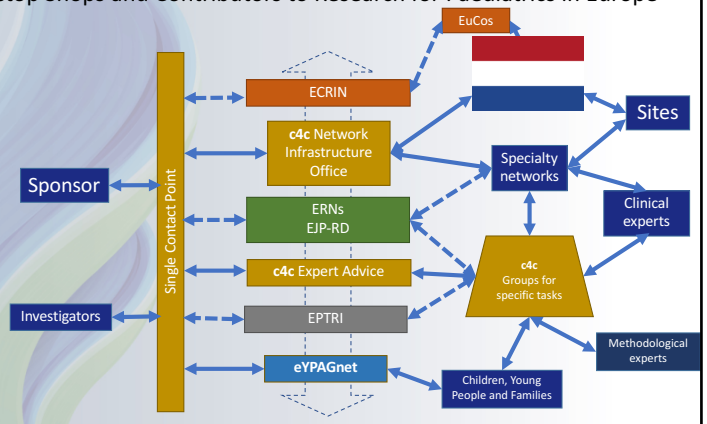
Step in medicines development	Data	Source
What do children need?	Diagnostic codes	Clinical teams
How many sick children are there?	Codes and text	Clinical teams
Where are the children?	Codes and text and discussions	Clinical teams
	Research	
Who has side effects?	Codes and text and reports	Clinical teams
How many people	Prescribing data	Clinical teams







Full Information flow between Sponsors, Single Contact Point, One-stop Shops and Contributors to Research for Paediatrics in Europe



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COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

c4c: a pan-European paediatric clinical trials network

Mark Turner (ULIV)
Carlo Giaquinto (PENTA)
Heidrun Hildebrand (Bayer)
Katharine Cheng (Janssen)

Arnhem 15° June 12° 2018

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777389.
The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Conect4Children

Vision: Better medicines for babies, children and young people through a pan-European clinical trial network.

Arnhem June 15th 2018

Conect4Children

c4c Mission

- Europe will use a coordinated approach to deliver high quality "regulatory grade" clinical trials in
  - Multiple countries
  - Multiple sites
  - All paediatric age groups
- By supporting
  - Trial implementation using resources shared between studies
  - Trial design through a combination of information about natural history, feasibility, appropriate innovation, and expert opinion
  - Education and awareness within and beyond the network

Arnhem June 15th 2018

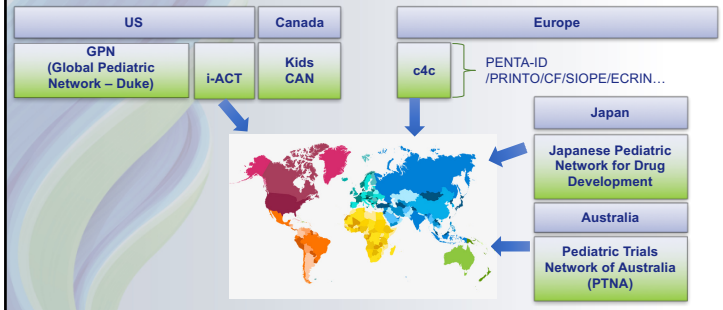
Planning, set-up & conduct of a Paediatric Development Program

A multifaceted challenge…

Defining the medical need	Right indication and population	Preparing and agreeing a Paediatric Development Plan	Small patient populations – competing developments
Use/acceptance of innovative study designs	Insufficient trial infrastructure	Divergent view of Ethic Committees	Contradictory local regulations
Diverse standard of care across Europe	Impact on daily lives of patients and families	Dose, route of administration, application device	Acceptance of Paediatric research in society

Global Paediatric clinical trial networks

- The **c4c** network will collaborate with other existing networks
- Make the most of information from families and clinical teams



Project Concept

1. Use resources and funding of the IMI project to setup the network and its processes
   1. National
   2. International
2. Demonstrate the value of the network approach with selected
   1. Studies
   2. Sites
3. Generalise from the demonstration projects to the broader network

Project Concept

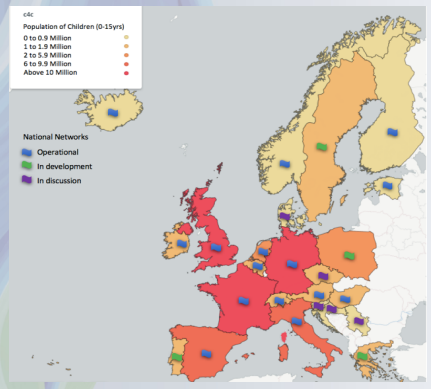
1. Use resources and funding of the IMI project to set
   1. Nat
   2. Inte
2. Demo appro
   1. Stu
   2. Site
3. Gene jects to the broader network

From
- **Specific**
- **Selected**

To
- **Generalised**
- **Sustainable**

2019 → 2024

c4c consortium members



- 10 EFPIA companies
- 18 pediatric national networks
- 2 large patient advocacy groups
- 8 EU Multinational sub-specialty Networks,
- 2 large children's hospitals

Arnhem June 15th 2018

New consortium – experienced partners

Internationally recognized public partners such as:

PRINTO
Paediatric Rheumatology INternational Trials Organisation (PRINTO)

PENTA-ID Network

The European Society for Paediatric Oncology

The European Cystic Fibrosis Society

EURORDIS RARE DISEASES EUROPE
European Organisation for Rare Diseases Association

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Where does the time come from?

Collaboration with colleagues and hospitals

Year	Change	My Research	Infrastructure work
2001	*Steroids: SR and excipients*	Placental cytokines	Nil
2005	*Steroids: balance between lung and brain* Consultant post	Where is my desk?	Nil
2007	Which dose?	PK studies Excipients Trials (x15)	National network
2011			European network
2015	Why do the same thing 15 times?	Less and less	European and global networks; regulators and industry

University of Liverpool | Department of Women's and Children's Health

Liverpool Women's

The secret of happiness:
Find something more important than you are
and
dedicate your life to it.

Daniel C. Dennett

Scope of c4c (by 2024)

Type of study	Industry/non-industry
Intervention	Drug, biologics, devices; non-interventional
Geography	Europe
Phase of study	Ph 1- 4; observational, registry studies
Endpoints	PK/PD, efficacy, safety
Responsibilities	The c4c network will provide some central services for trials, for example, trial feasibility, pharmacovigilance activities and commissioning of trial supplies. c4c is not a CRO

Expected long term impact of c4c

- **Access to new experimental therapies** for children in well-designed clinical trials
- **Better training** for research personnel and **improved trial**

"Better medicines for babies, children and young people through a pan-European clinical trial network"

- **Enhanced role** of **clinicians and patient/parent advocacy groups** in planning and designing studies
- **Broadening the access of centers** across Europe to new experimental therapies

Conclusion

Every prescription involves:

- Science
- Art
- Global Partnership
  - Clear procedures
  - Equity of access
  - Transparent governance

Roles and Benefits for Everyone