Novel approaches to clinical trials: How smart design can improve yield

Saskia N. de Wildt, MD, PhD
Professor of Clinical Pharmacology
Pediatric intensivist
Nijmegen & Rotterdam, the Netherlands.

Erasmus MC
Universitair Medisch Centrum Rotterdam

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Presentation overview

- Microdosing
- Model-based dosing
- Sequential trial design
- Umbrella/basket design
- European Pediatric Trial Network
  - Innovation in Scientific Advice

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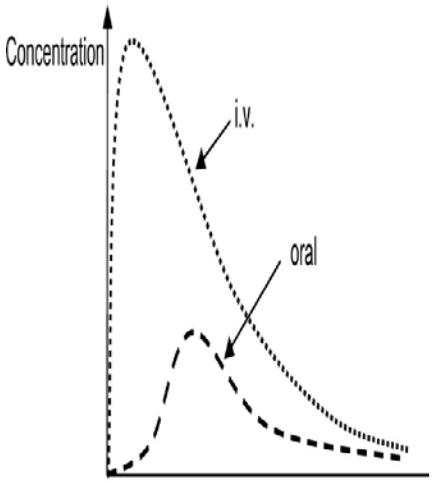
Oral bioavailability– information gap

- F = AUCoral/AUCiv
- Limitation cross-over design:
  - Drug 2 times, days apart
  - Non-therapeutic drug dosing
- **Unethical in children?**

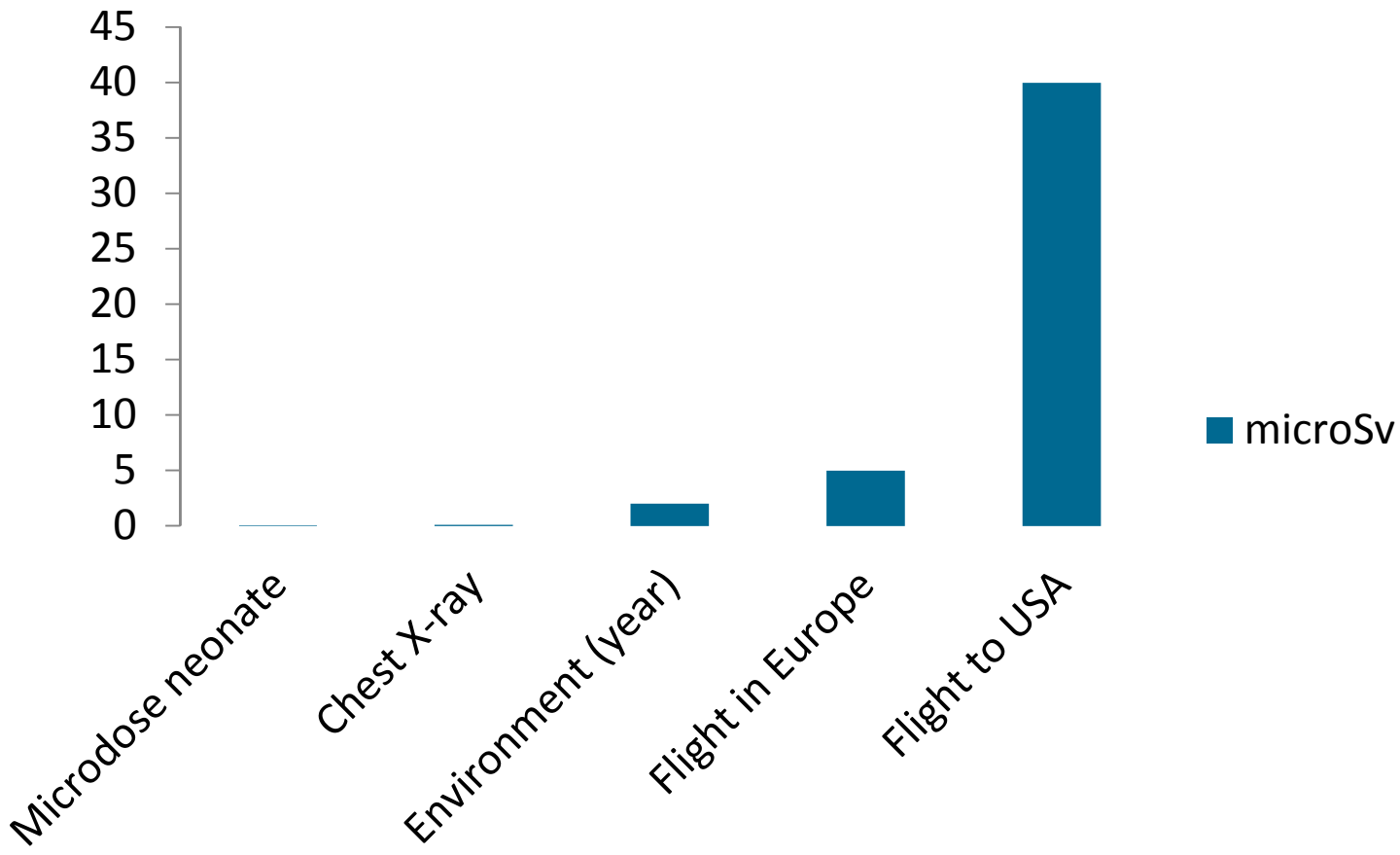


Microdosing - Definition

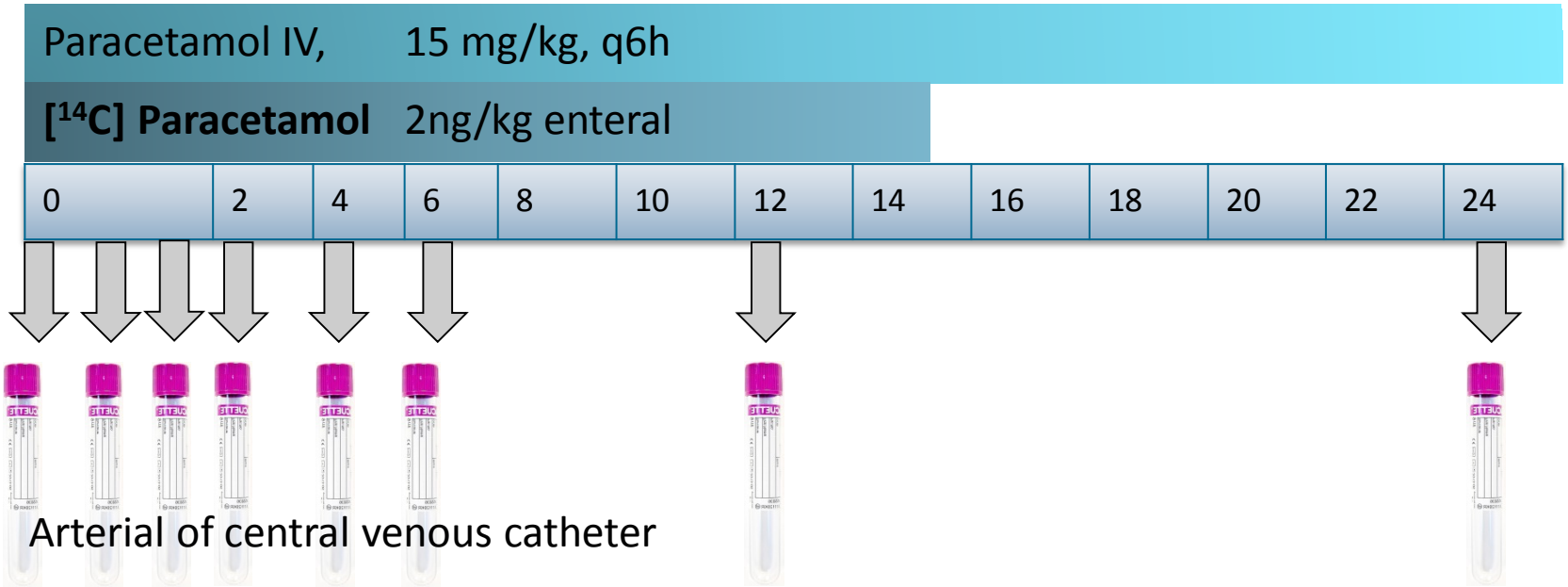
- Microdose
  - 1/100 of therapeutic dose
  - or max 100 µg
  - ± Radioactive label: ^{14}C
- Drug levels with LC-MS or AMS
- FDA/EMA supported

Radioactivity in kids?

Radiation comparison

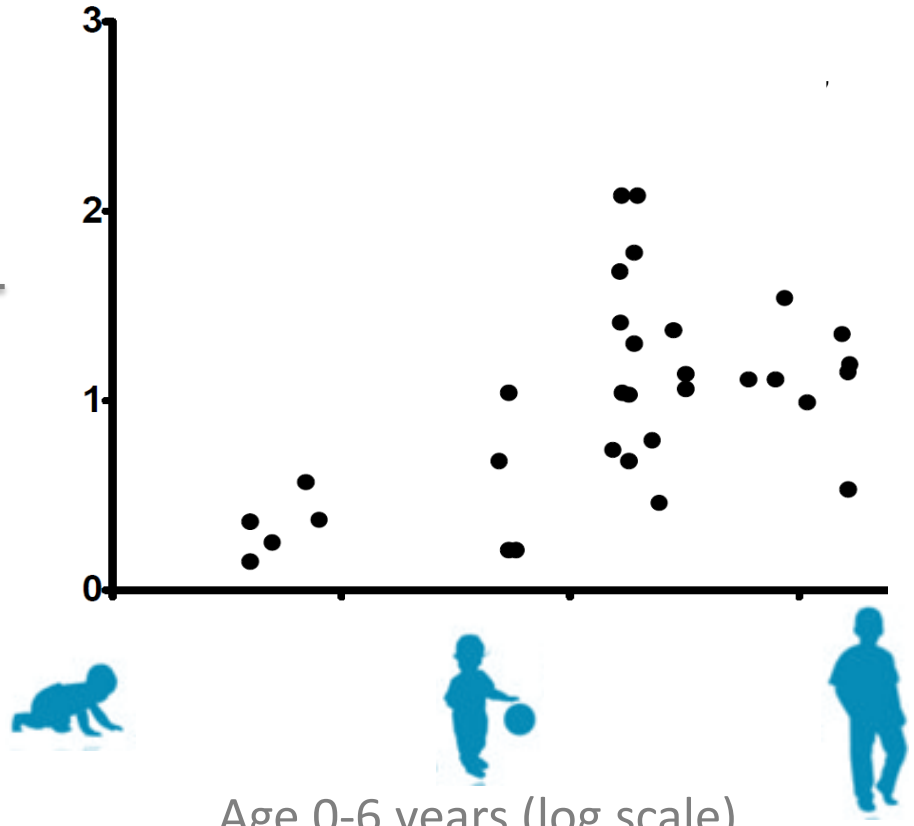


Paracetamol oral bioavailability study



Age affects paracetamol metabolism

$AUC_{0\text{-}inf}$ $\frac{AAP\text{- }Glu}{AAP\text{- }Sul}$



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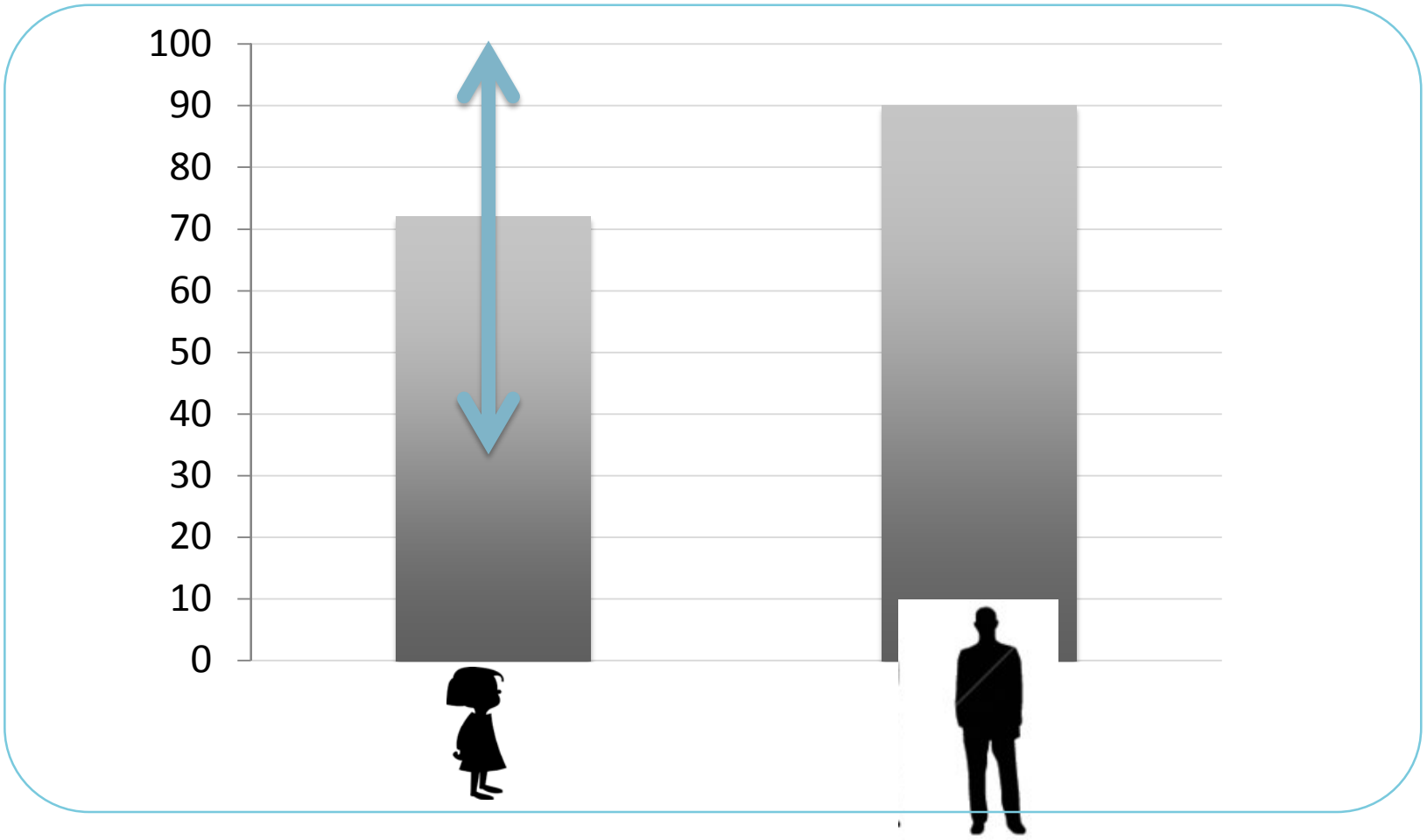
Mooij et al, Clin Pharmacokinet 2017

Paracetamol oral bioavailability



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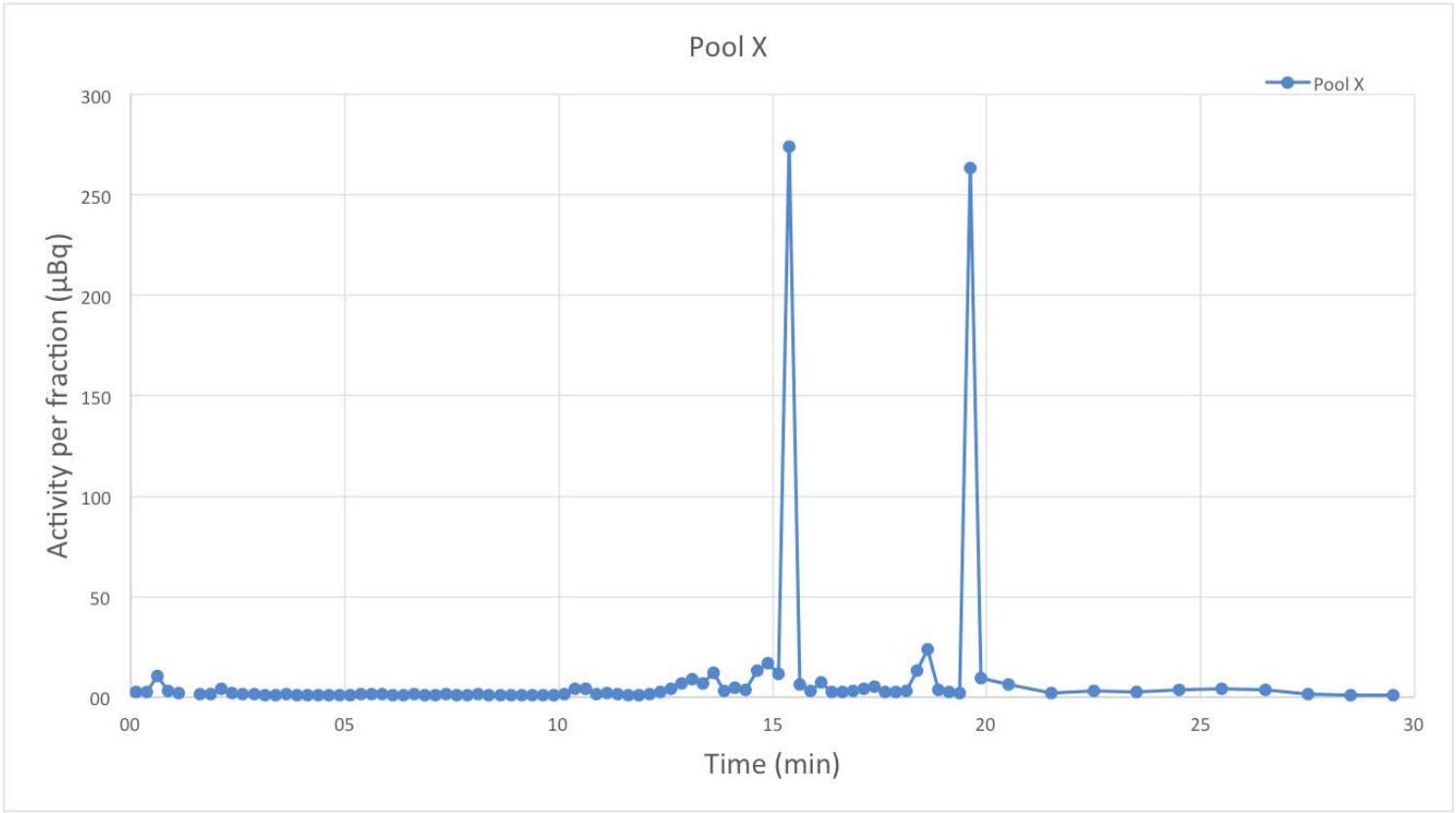
Kleiber, Mooij et al , manuscript in preparation

Metabolite in Safety Testing: Midazolam



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Paracetamol for major surgery

CARING FOR THE CRITICALLY ILL PATIENT

Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery

A Randomized Controlled Trial

Ilse Ceelie, MD, PhD
Saskia N. de Wildt, MD, PhD
Monique van Dijk, MSc, PhD
Margreeth M. J. van den Berg, MD
Gerbrich E. van den Bosch, MD
Hugo J. Duivenvoorden, PhD
Tom G. de Leeuw, MD
Ron Mathôt, PharmD, PhD
Catherijne A. J. Knibbe, PharmD, PhD
Dick Tibboel, MD, PhD

Importance Continuous morphine infusion as standard postoperative analges in young infants is associated with unwanted adverse effects such as respiratory de

Objective To determine whether intravenous paracetamol (acetaminophe significantly (>30%) reduce morphine requirements in neonates and infants jor surgery.

Design, Setting, and Patients Single-center, randomized, double-blind st ducted in a level 3 pediatric intensive care unit in Rotterdam, the Netherlands. Pati 71 neonates or infants younger than 1 year undergoing major thoracic (noncardi dominal surgery between March 2008 and July 2010, with follow-up of 48 ho

Interventions All patients received a loading dose of morphine 30 minut the end of surgery, followed by continuous morphine or intermittent int paracetamol up to 48 hours postsurgery. Infants in both study groups recei phine (boluses and/or continuous infusion) as rescue medication on the gu

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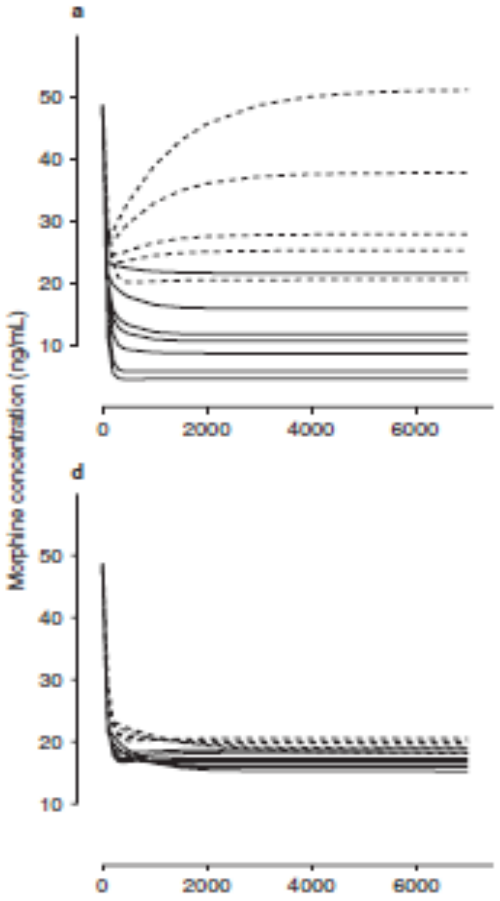
Ceelie et al. JAMA 2013

Morphine pharmacokinetics infants

Traditional dosing:
100 mcg/kg followed by
10mcg/kg/u

Model-based dosing
100 mcg/kg followed by :
>10 dagen: 10 mcg/kg$^{1.5}$/h
<10 dagen: ½(10mcg/kg$^{1.5}$/h)

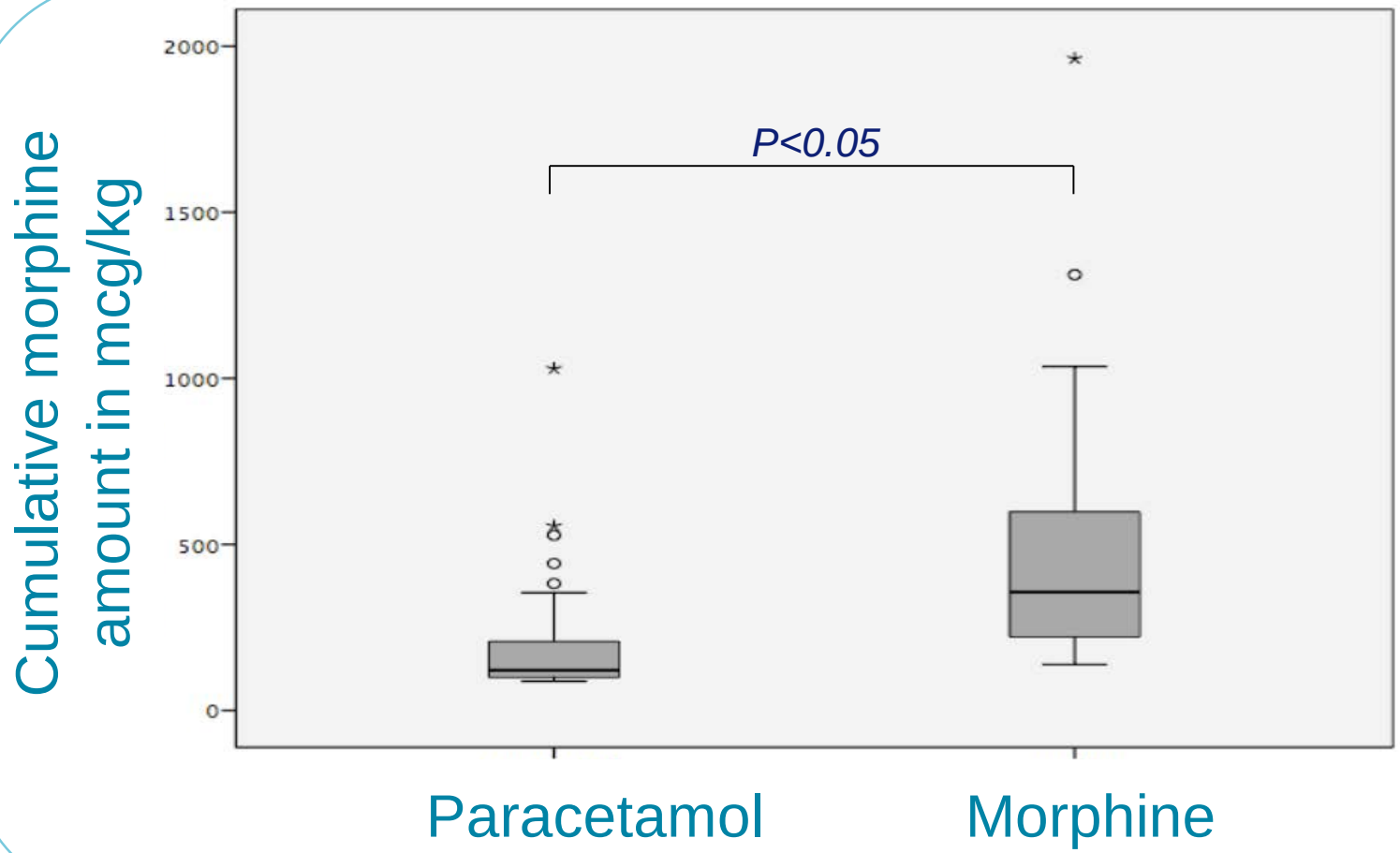


---- <10 days
___>10 days

10 kg =31 mcg/kg/u
5 kg = 22 mcg/kg/u
3 kg = 17 mcg/kg/u
3 kg<10d=8 mcg/kg/u

Knibbe et al 2009, clin pharmacokinet

Paracetamol group 66% less morphine



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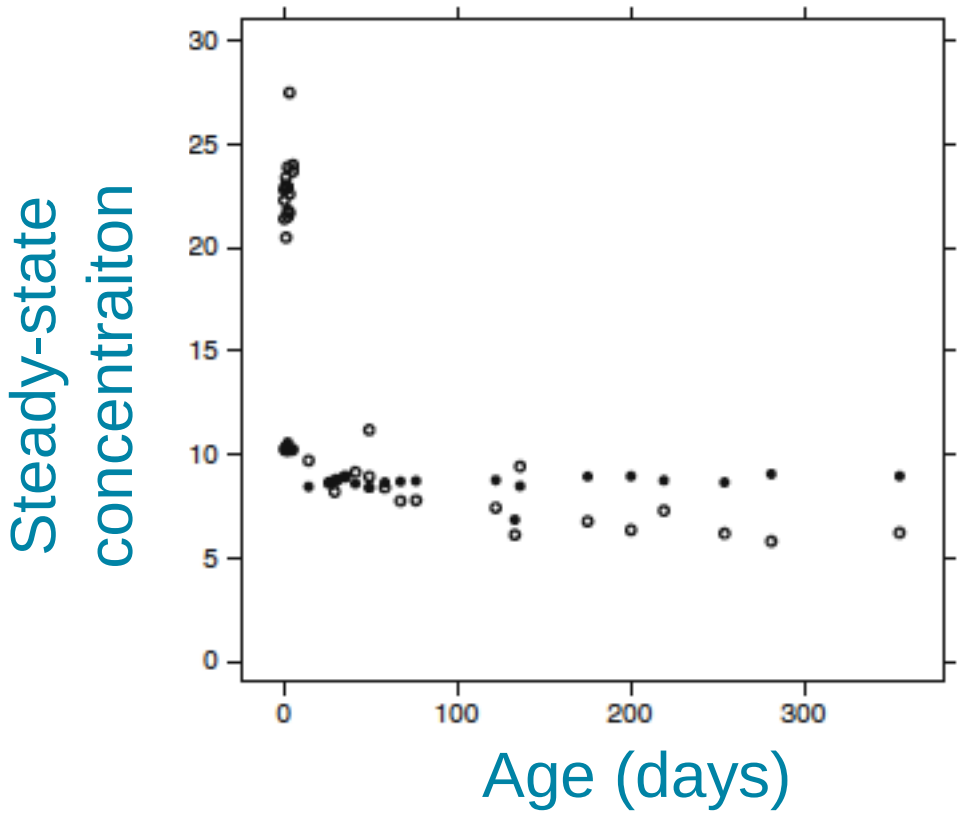
Ceelie et al. JAMA 2013

Morphine concentrations versus age



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Krekels et al Clin Pharmacokinet 2014

Age-related PK changes and use modeling & simulation for pediatric dose selection

- 2 clinical trials gabapentin for neuropathic pain
- **Which dose to use?**
- PK data in children (Ouellet et al):
  On a weight basis, **33% larger doses** would be required **in younger children** (<5 years) to achieve the same exposure as older children

GAPP GAbapentin in Paediatric Pain

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement n° 602962

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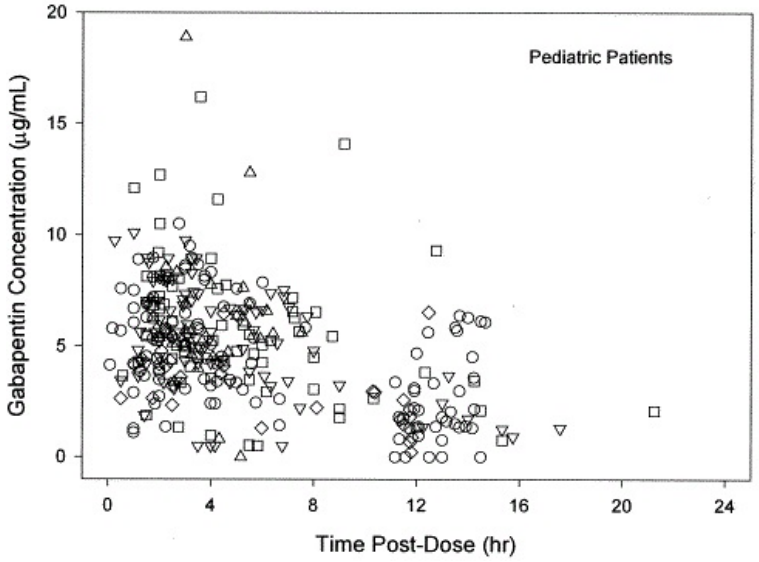
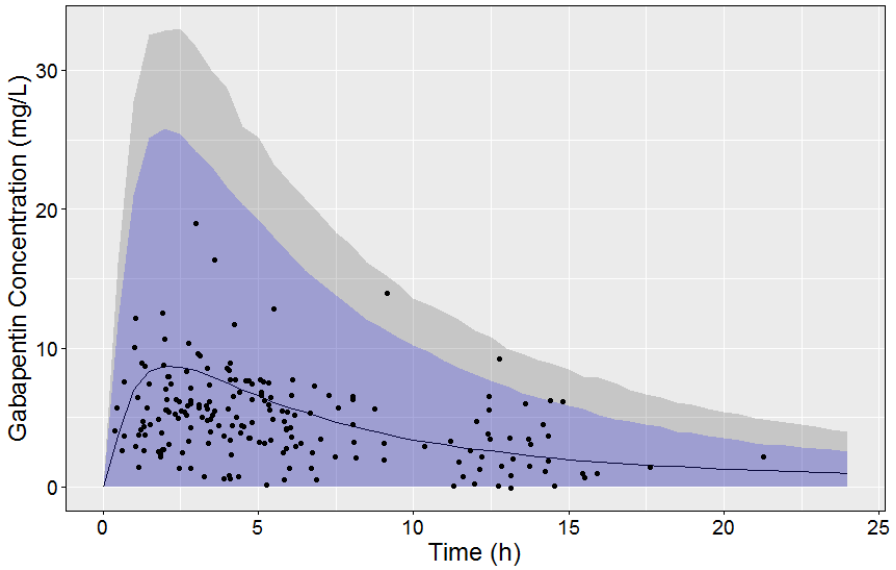
Gabapentin PK Modelling

Observed PK data



Visual predictive check



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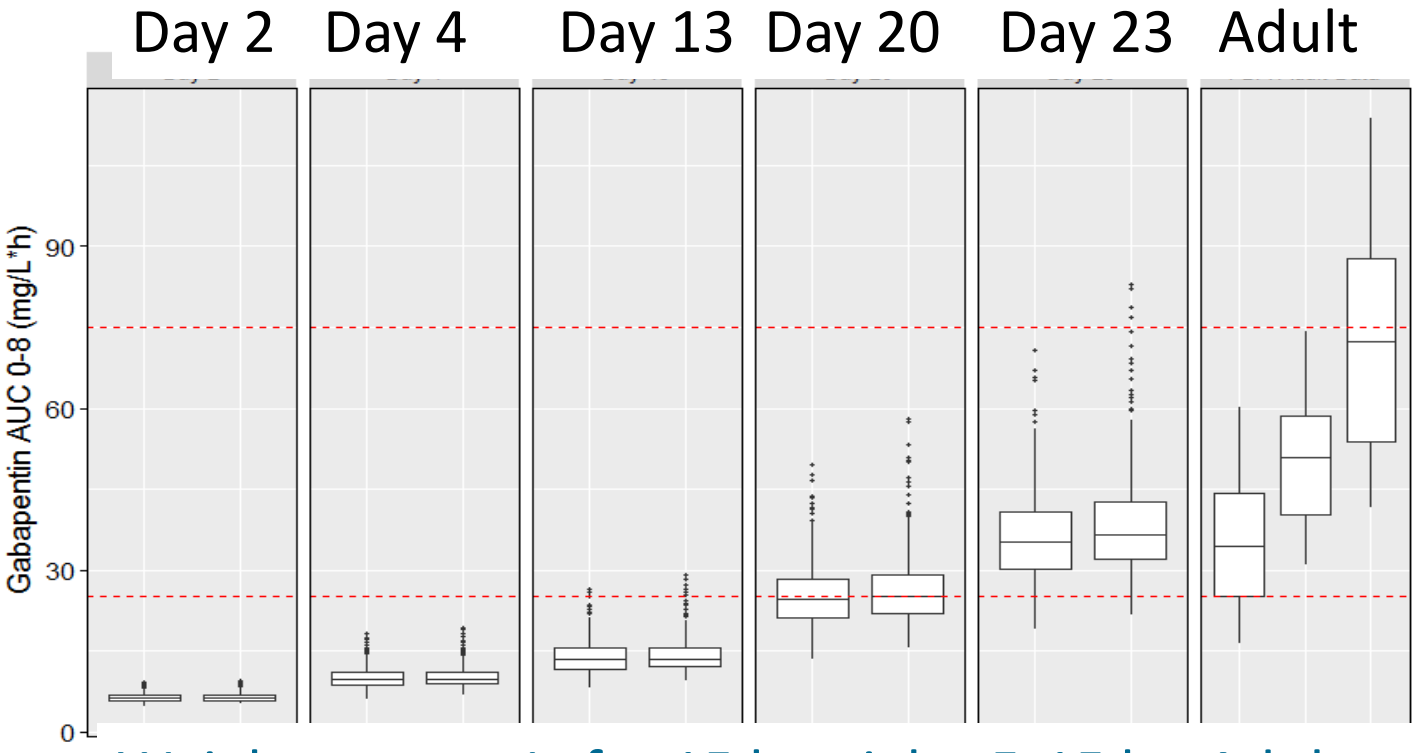
Predicted gabapentin exposure



Weight groups: Left >15 kg, right 5-15 kg Adults

3 doses

GAbapentin in Paediatric Pain

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Proposed gabapentin dosing

2 weight groups and titration

Day 1 starting dose in mg/kg/day;
Day 3 2 times the starting dose;
Day 5 3 times the starting dose;
Day 14 2 times the dose of Day 5;
Day 21 3 times the dose of Day 5.

Doses in mg/kg/day

Weight group	Day 1	Day 3	Day 5	Day 14	Day 21
5-15 kg	7	14	21	42	63
>15 kg	5	10	15	30	45

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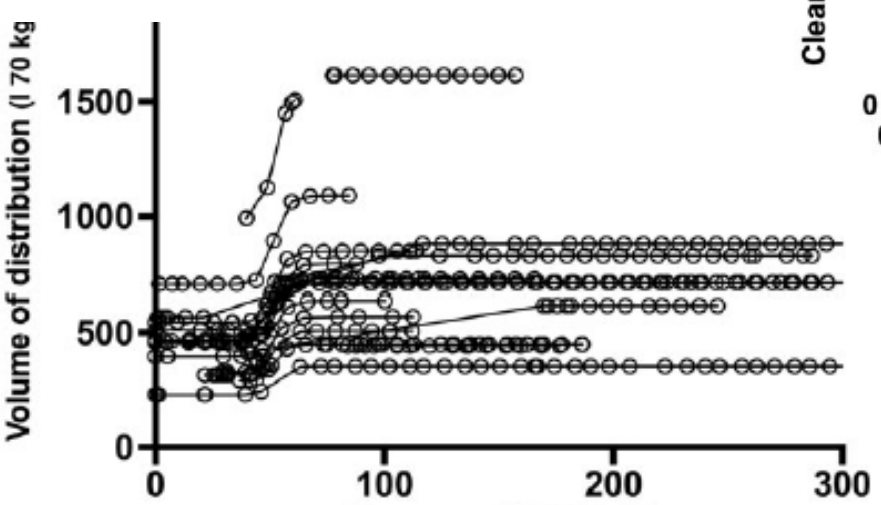
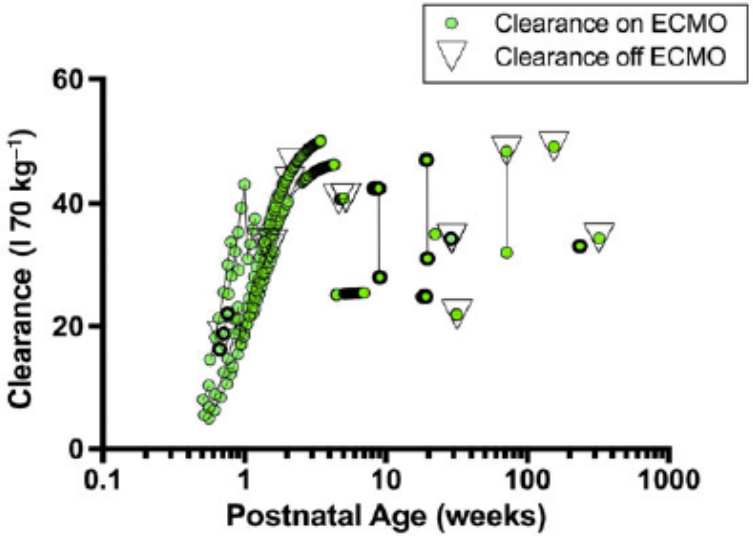
Population PK of clonidine in pediatric ECMO





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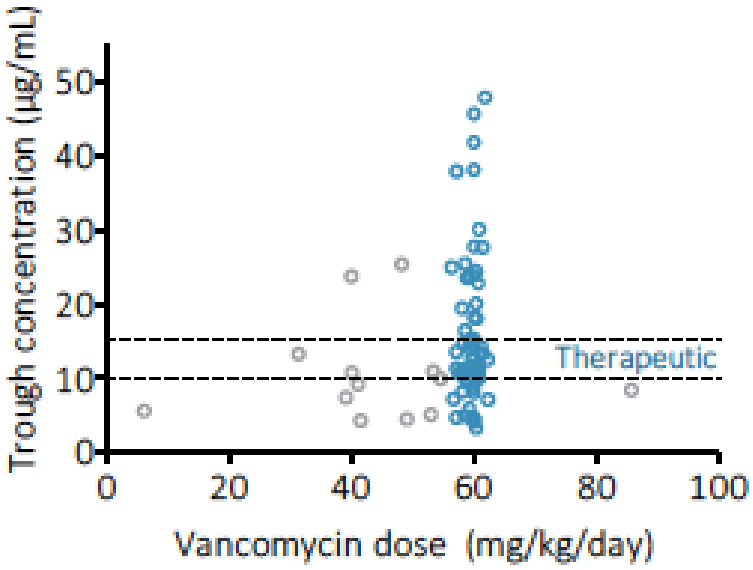
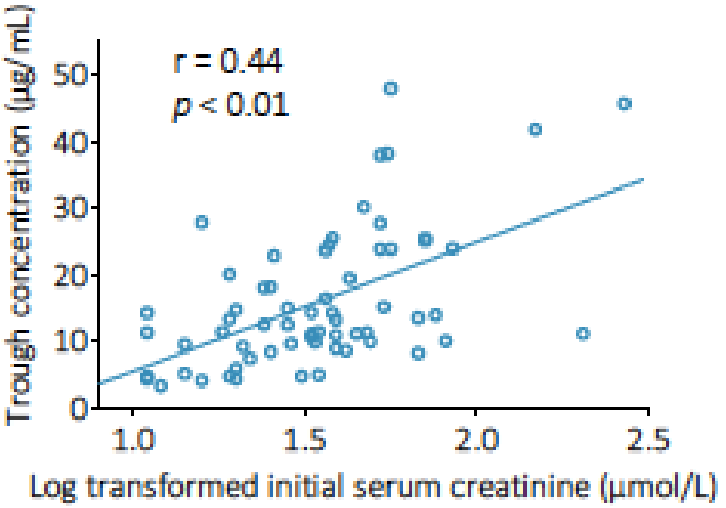
Kleiber N Br J Clin Pharmacol 2017

Target attainment with model-based vancomycin dosing guidelines?

Aim 1. Assess incidence of target attainment with new dosing guideline

Aim 2. Identify risk factors for non-therapeutic concentrations





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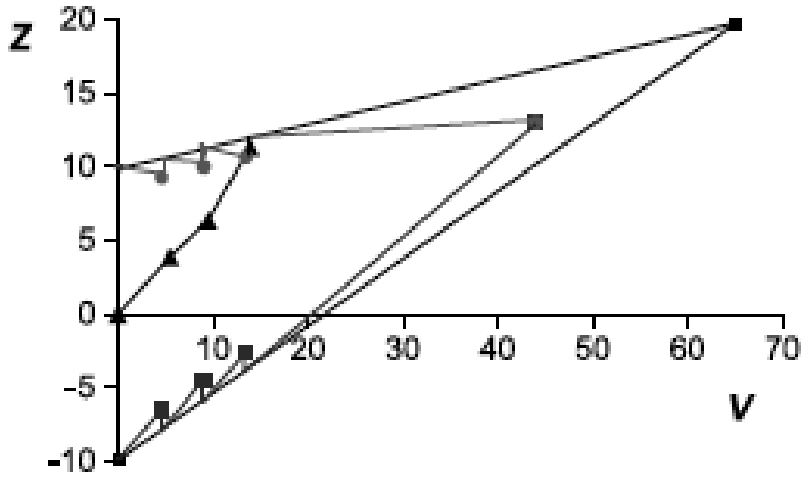
RCT with sequential analysis

Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial

Olivier Baud, Laure Maury, Florence Lebail, Duksha Ramful, Fatima El Moussawi, Claire Nicaise, Véronique Zupan-Simunek, Anne Coursol, Alain Bauchet, Pascal Bolot, Pierre Andrini, Damir Mohamed, Corinne Alberti, for the PREMILOC trial study group*

- Sequential analytical design, based on intention to treat
- Planned sample size n= 786, analyses at every 100 included patients
- Stopped prematurily for financial and technical support limitations
- Final sample size N=523
- OR 1.48 (CI 1.02-2.16, p=0.04) for BPD-free survival treatment vs control

Sequential analysis example



- Accrued difference in outcome between groups at each interim data inspection
- Upper boundary stopping rule (significant difference)
- Lower boundary stopping rule (no significant difference)

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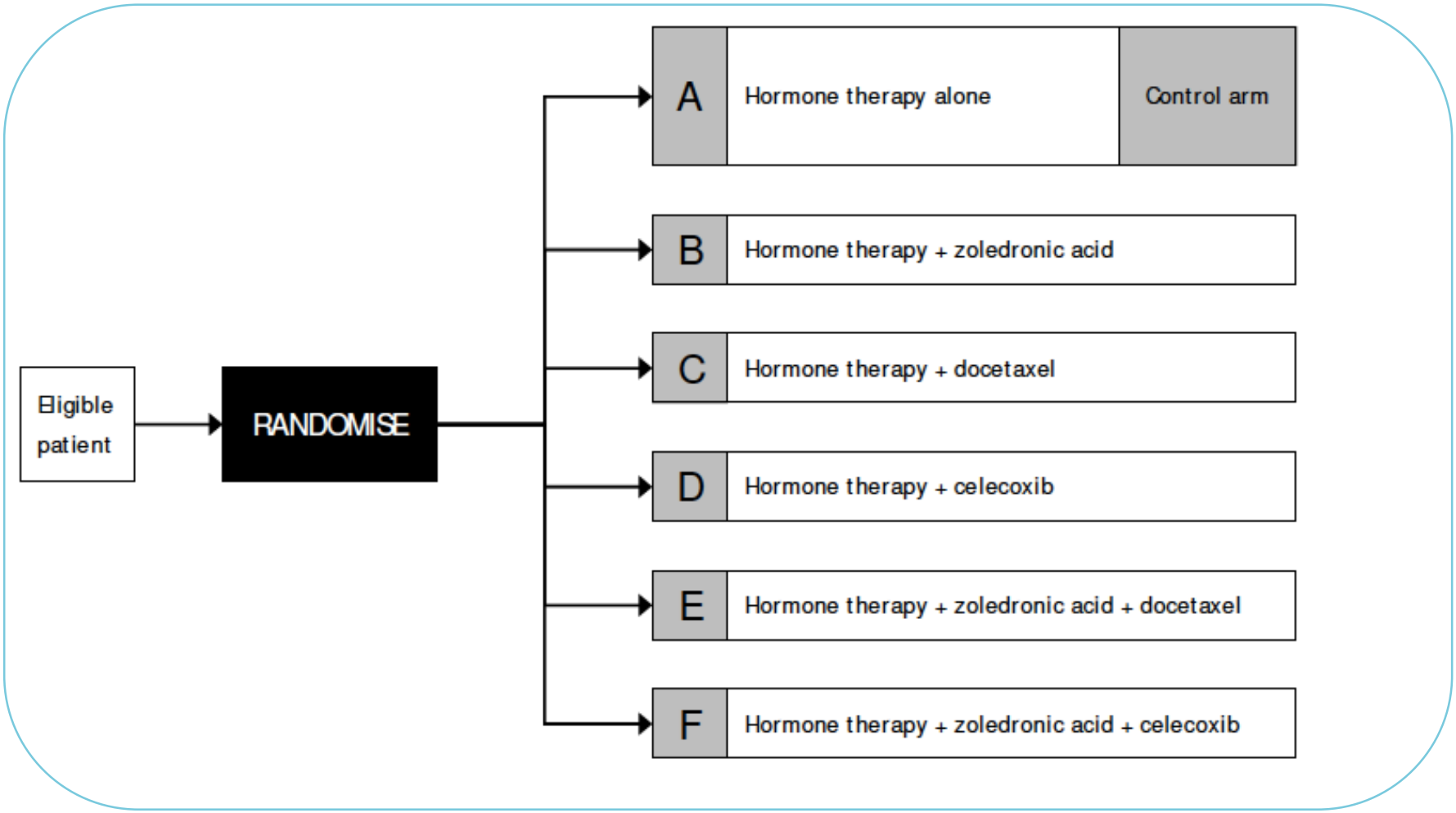
MAMS: multi-arm, multi-stage design

Several agents or combinations of agents versus a single control group in a randomised controlled trial (RCT)

Arm with insufficient promise:	discontinue
Promising arms:	continue
Control arm:	continue

UNTIL: sufficient patients to assess impact related to primary outcome

Randomisation arms: example



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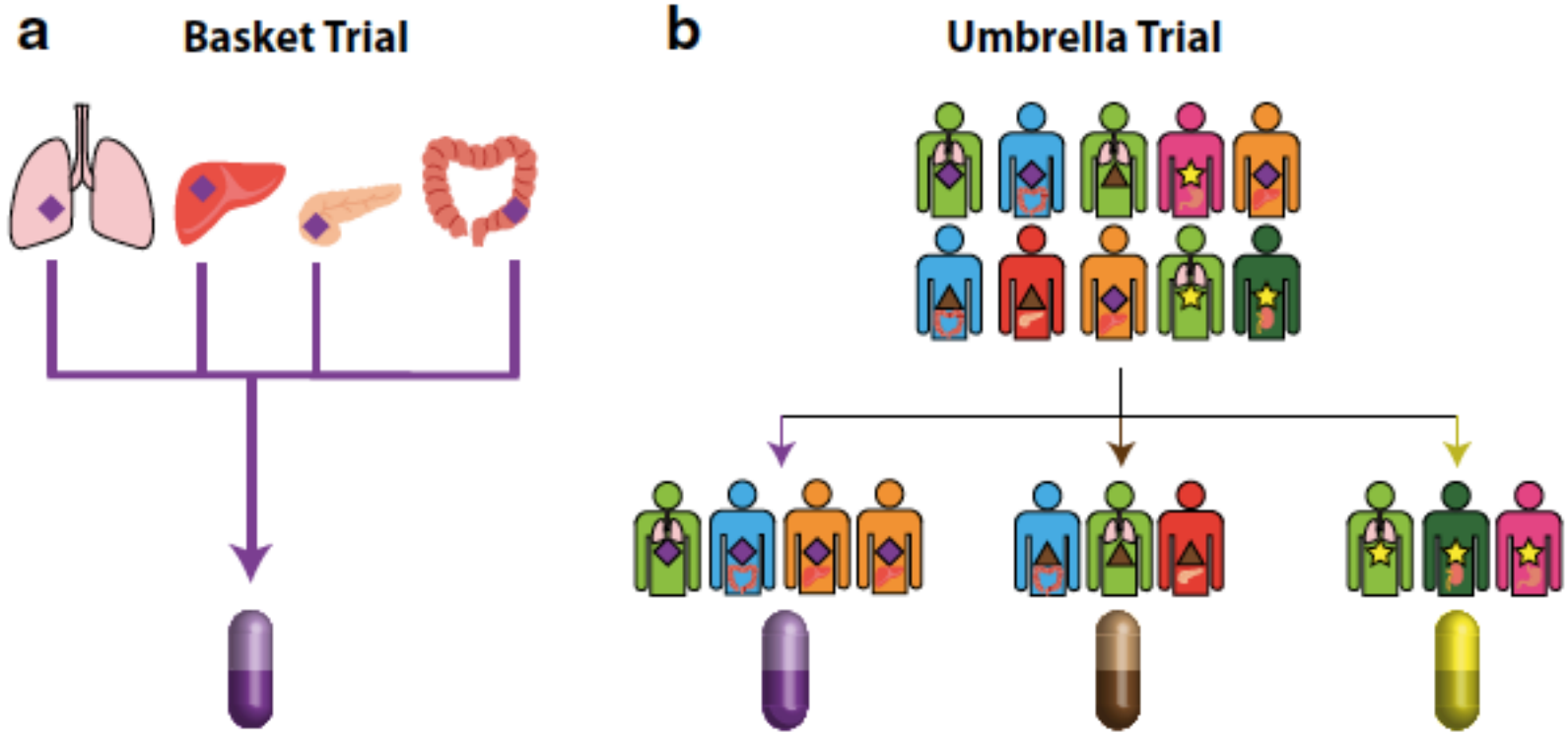
Sydes et al Trials 2009 10:39

Genomic/biomarker trial design



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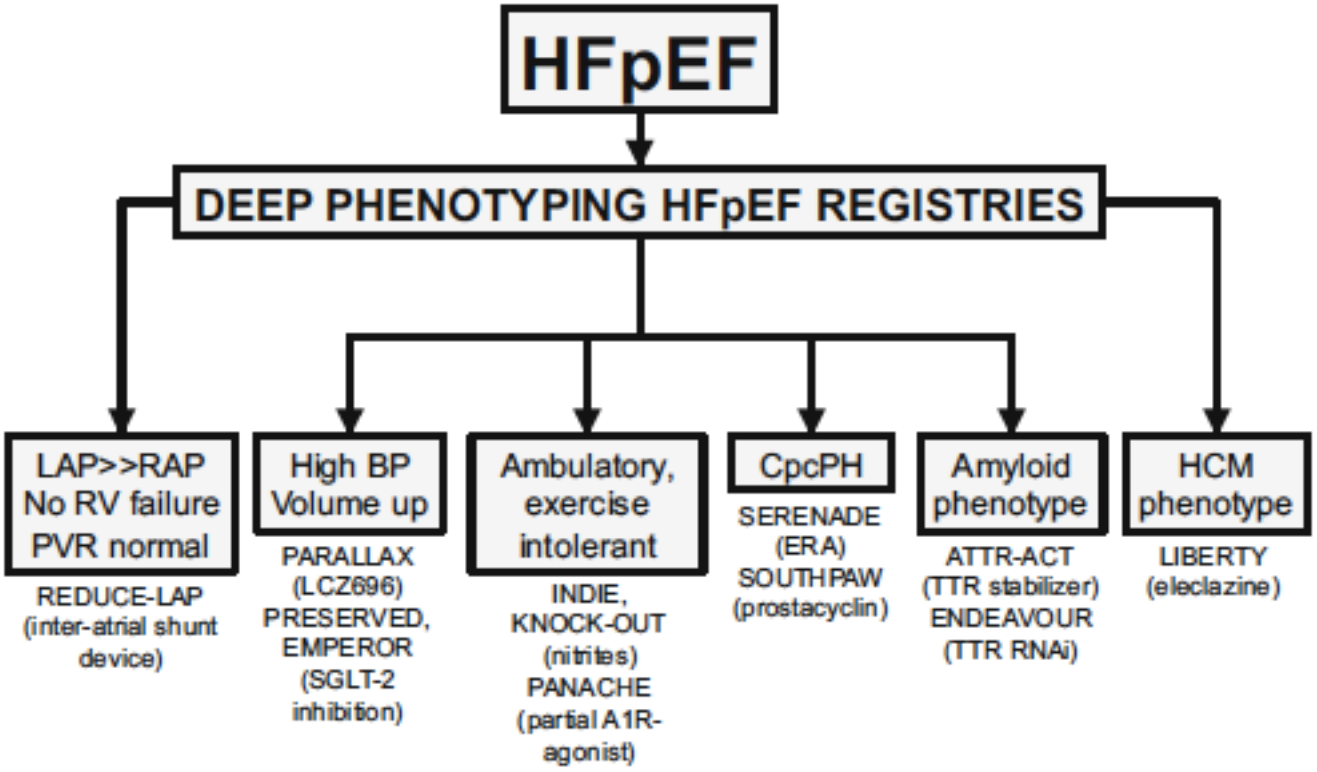
Bul N Q et al. J Mol Med 2018 31-38

Example of umbrella trials

Heart Failure with preserved ejection fraction



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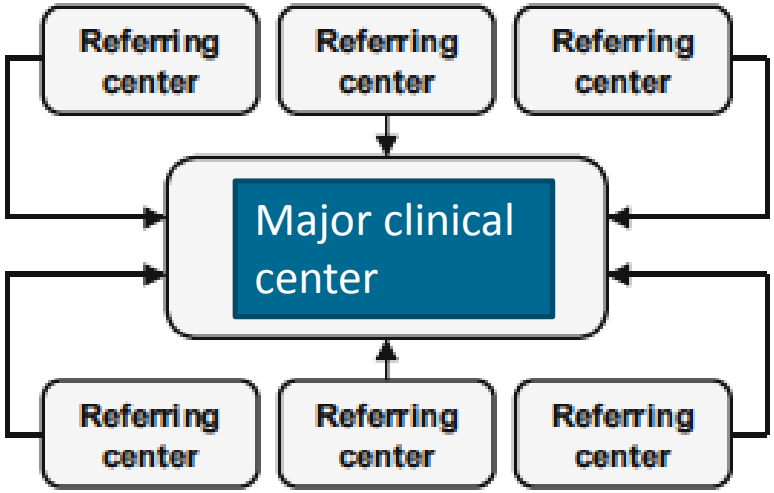
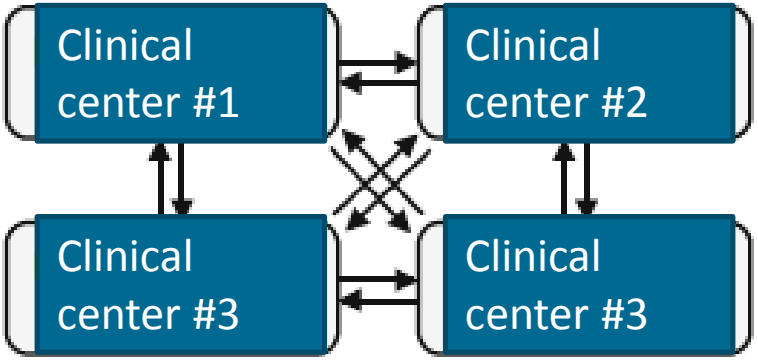
Sjah, SJ J of Cardiovasc Trans Res 2017 322-236

Models for umbrella trials



Hub-and-spoke model



Distributive model

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Pediatric Drug Development: EU outlook

3. Pediatric label /more data for off-label use

2.

PEDCRIN

Paediatric Clinical Research Infrastructure

IMI2

European Pediatric Clinical Trial Network

PEDMED-NL

1. EPTRI

European Paediatric Translational Research Infrastructure

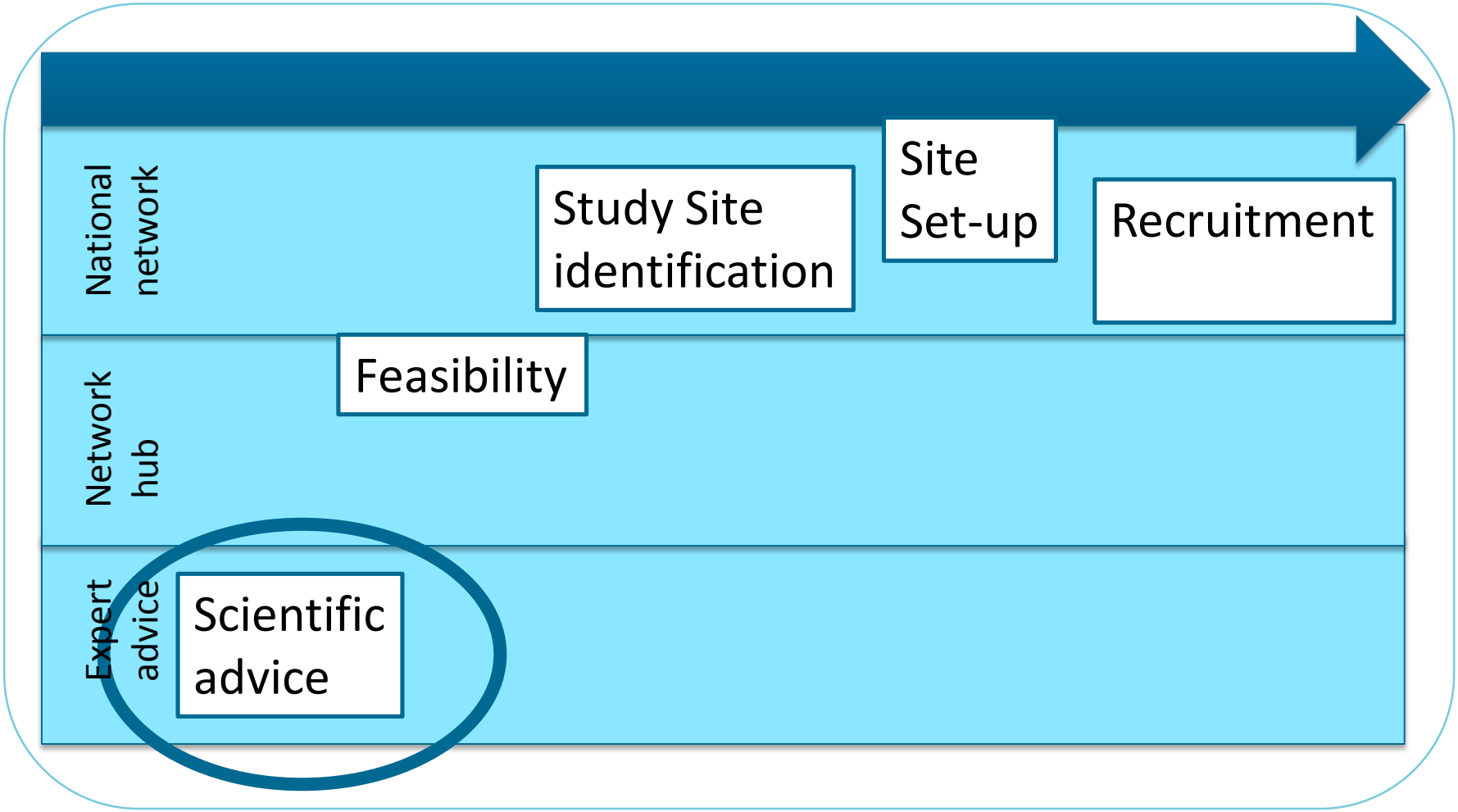
Innovative Medicines Initiative

- IMI2 funding
  - 50% European Commission
  - 50% EFPIA European Federation of Pharmaceutical Industry Association
- Call 2017: European Pediatric Clinical Trial Network
- 130 million euros
- 6 years

Network Mission

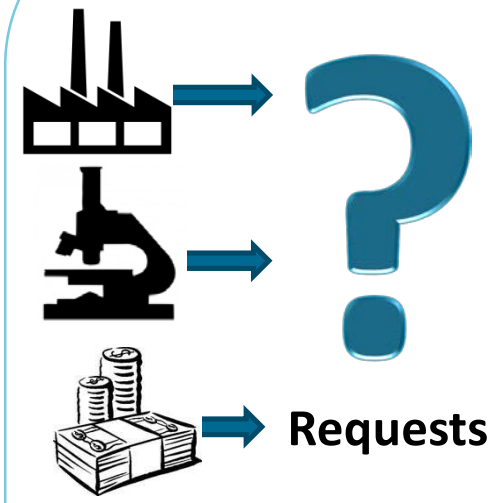
- Improve availability of information about medicines used by children
- Promote the delivery of high quality trials of medicines for children by supporting:
  - Trial implementation using resources shared between studies
  - **Trial design through a combination of information about natural history, feasibility and expert opinion**
  - Public- and industry-funded studies

Time-line of studies



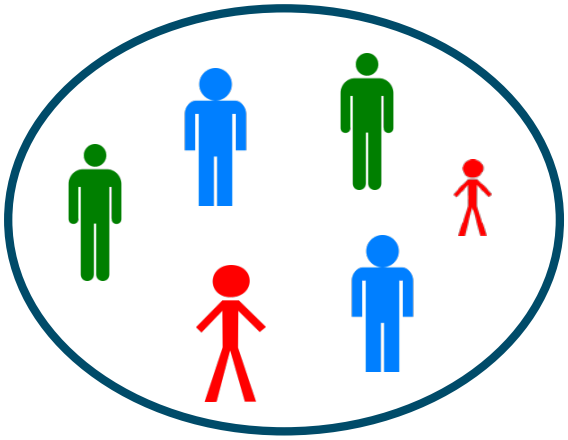
innovative medicines initiative

Scientific innovative advice



Requests

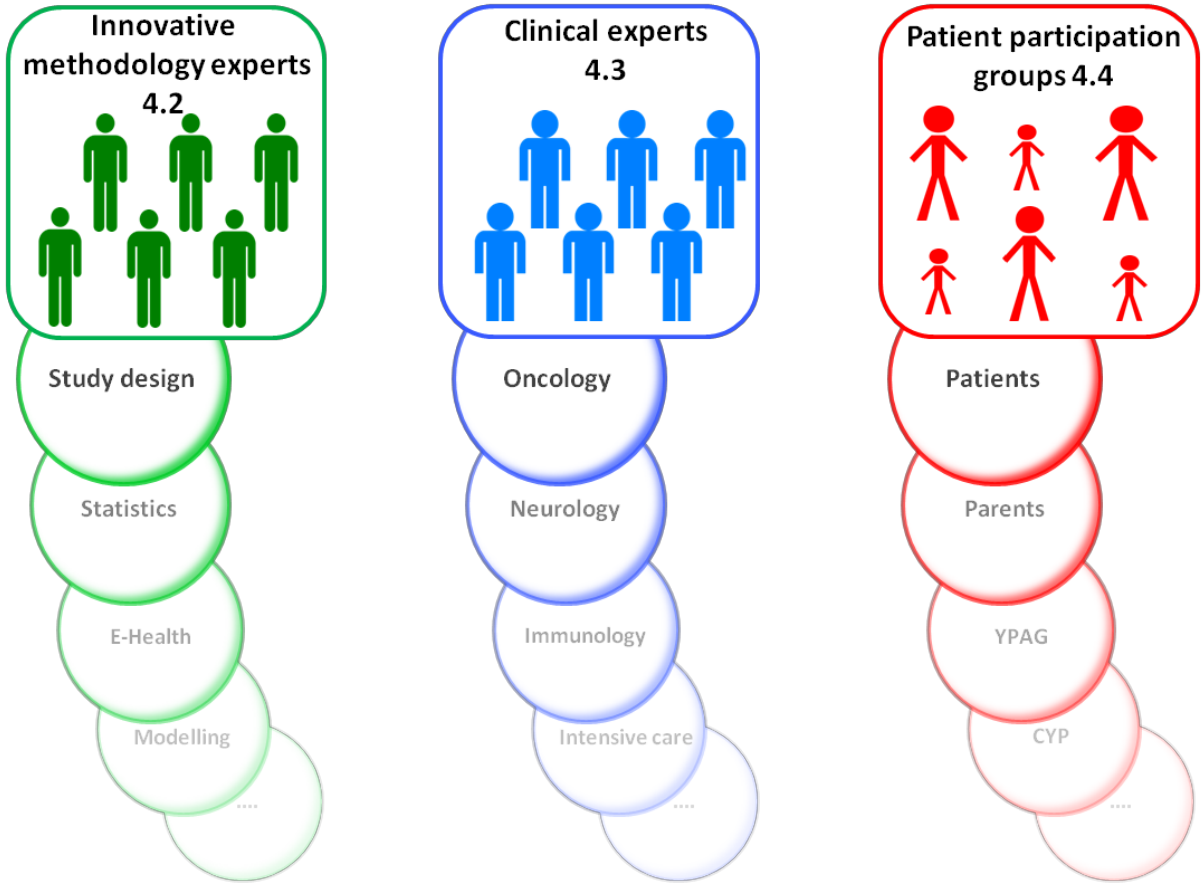
Strategic feasibility groups



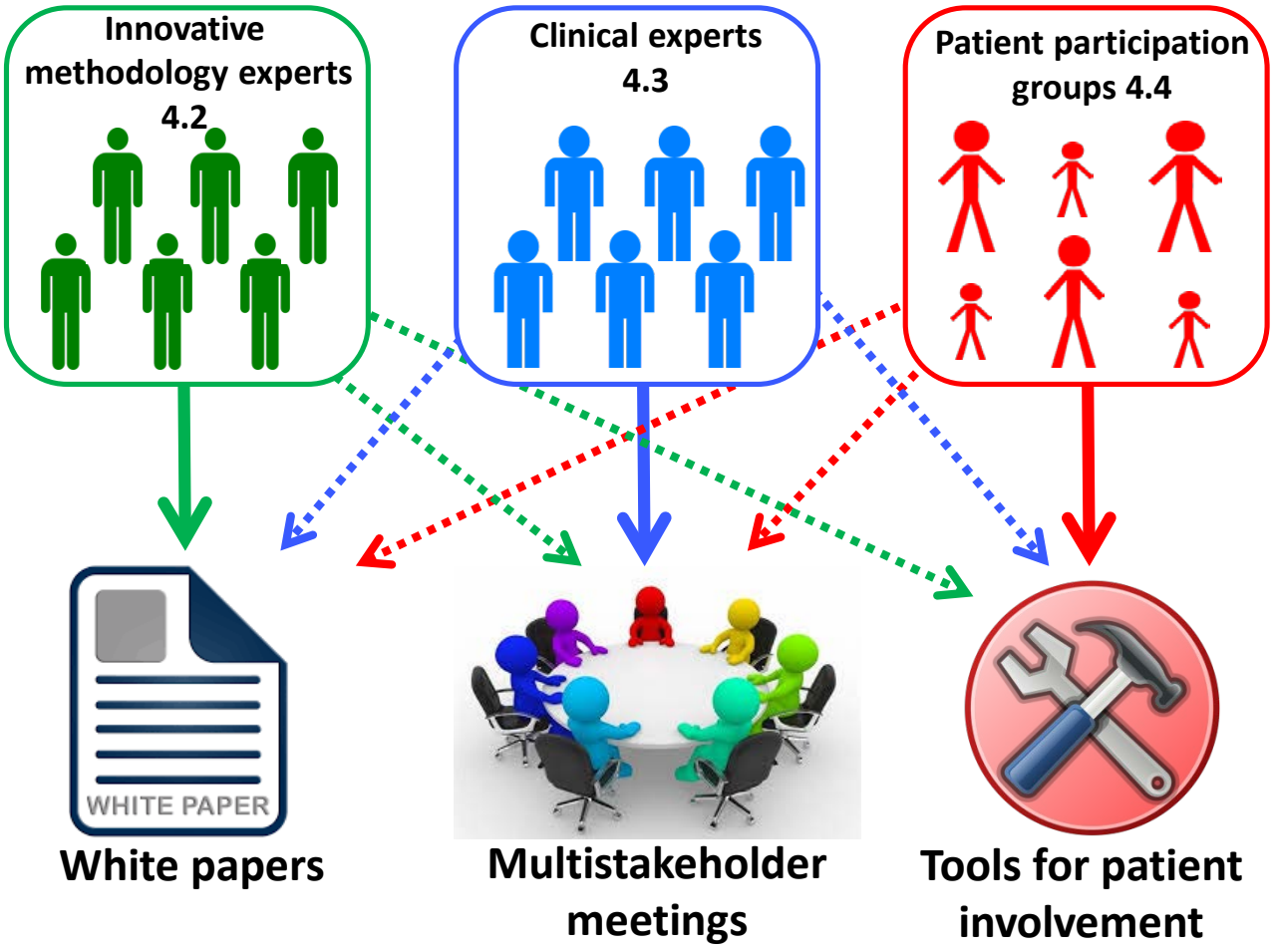
Advice

Single drug
Single/multiple PIP development
Clinical
Methodology
Feasibility assessment

Strategic feasibility groups



Added value for network goals



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PEDCRIN

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IMI2

European Pediatric Clinical Trial Network

PEDMED-NL

1. EPTRI

European Paediatric Translational Research Infrastructure

Acknowledgements

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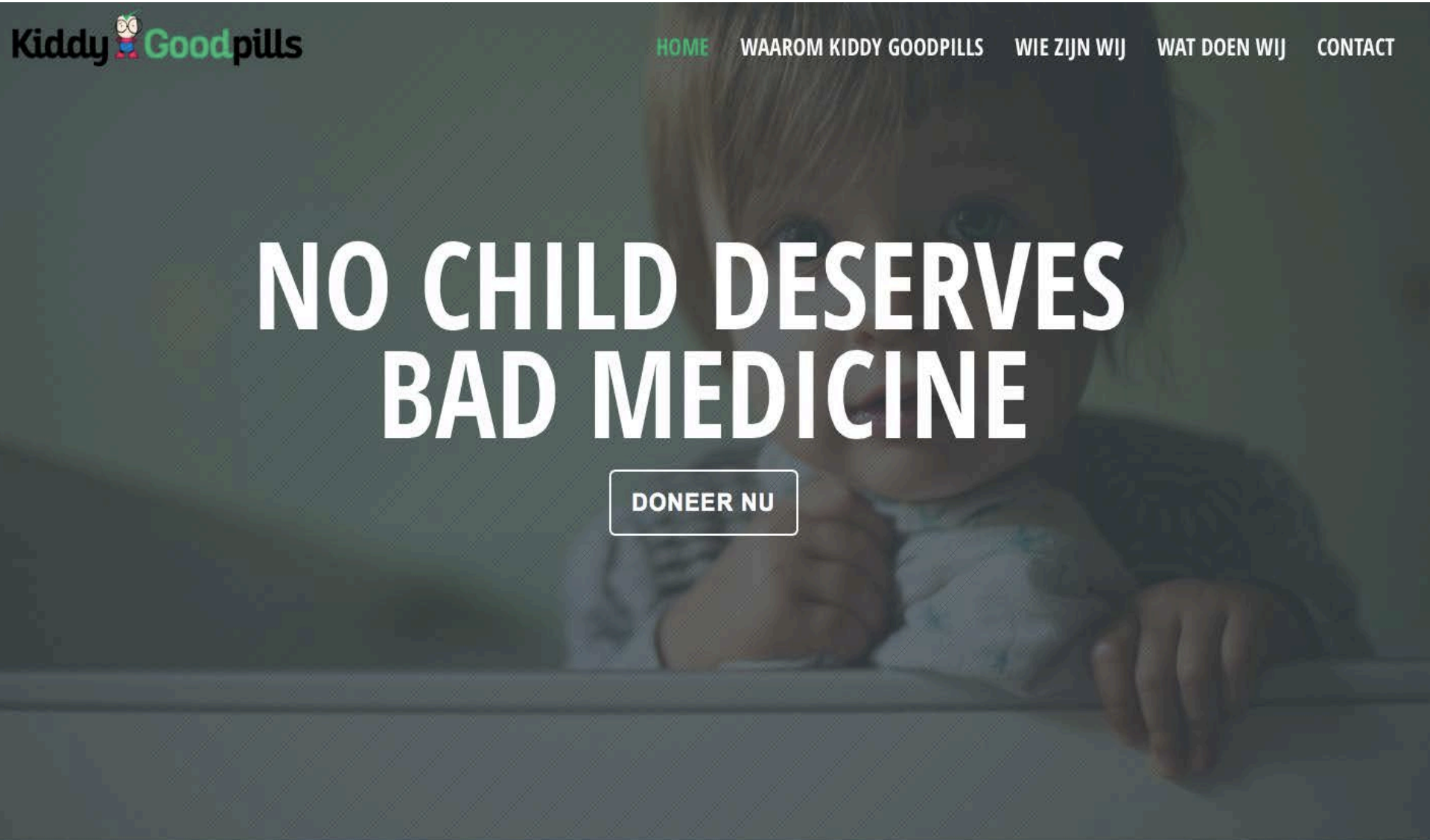
Questions?


Kiddy Goodpills
HOME
WAAROM KIDDY GOODPILLS
WIE ZIJN WIJ
WAT DOEN WIJ
CONTACT
NO CHILD DESERVES
BAD MEDICINE
DONEER NU

Pediatrics: enough room for innovation

Phase 0/1 **Phase 2** **Phase 3** **Phase 4**

Microdosing

Model-based dosing
Bayesian dose-finding

MAMS multi-arm
multi-stage

Sequential analysis

Pragmatic trials
Real-world data