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Issues in conducting clinical trials in children and neonates: site PI perspective

Tuuli Metsvaht, MD, PhD;
University of Tartu, Dpt of Microbiology
Tartu Univeristy Hospital, Paediatric ICU

EMA workshop on development of antibacterial medicinal products for paediatric patients


OÜ AW2 Arhitektid

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International clinical trials in PNICU of Tartu University Hospital

Academic studies

- Running
  - Bed-side monitooring of beta lactams for the rpevention of resistance
  - PKPD of vancomycin in the treatment of late onset neonatal sepsis
- Starting in 2018
  - Allopurinol for prevention of HIE in asphyxiated neonates

Most recent industry sponsored studies

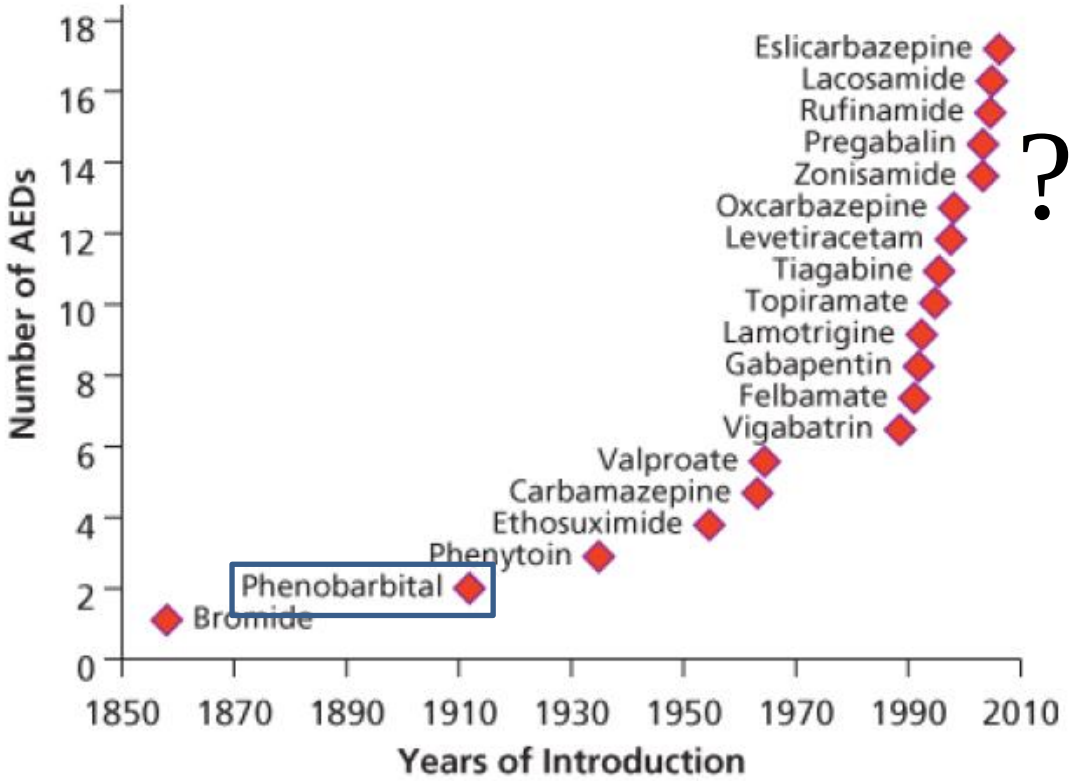
- Allopregnanolone in the treatment of superrefractory epileptic status
- Green laser facilitated peripheral vein cannulation in children and neonates

ELAV
Eesti Lasteuuringute Võrgustik

elav.ee

Issues with clinical trials in neonates: antiepileptic drugs

- Age dependent PK and mechanisms of disease, hence PD
- Logistical difficulties
  - Diagnosis and monitoring
  - Recruitment
  - Regulatory requirements (EMA/FDA, GCP)
  - Challenges of AE & AR Reporting
- Ethical predicament
  - Vulnerable age group
  - Acute, critical illness, co-morbidity
- Expensive, but low return



Modified from EMA Neonatology meeting March 2015; G Boylan & R Pressler

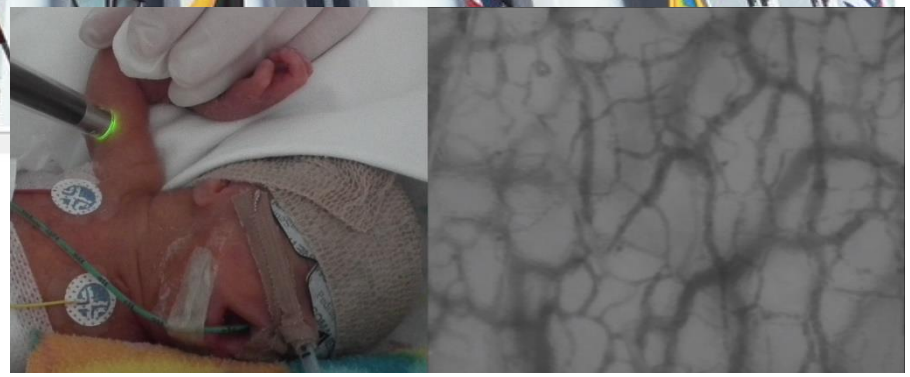
Study population related issues

– Vulnerability
  - Emotional/ physical distress
  - Ethics implications including IC

– Heterogeneity
  - Host – PK/PD (efficacy, toxicity)
  - Disease spectrum

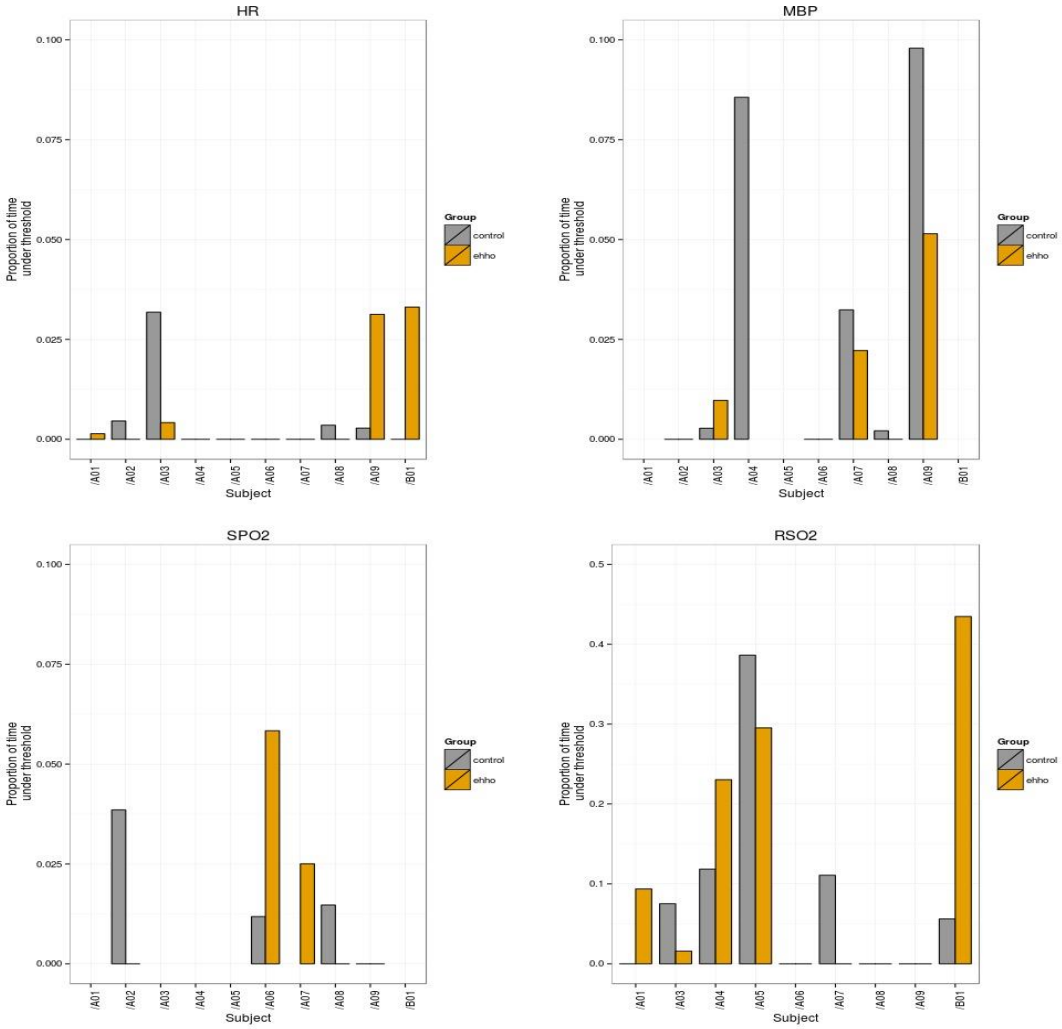
– (conflict of interests)

→ Scientific value of the study



Vulnerability: diagnosis and monitoring

Pilot study
10 preterm neonates median (min-max) GA 26 (22-27) wk, PNA 5 (2-17) h
HD: invasive blood pressure (BP), heart rate (HR), saturation (SpO_2), brain regional saturation ($rScO_2$)
Heart US x 2 48 tj, including right and left ventricular output (RVO, LVO), superior vena cava flow (SVCF)
Microcirculation (**videocapillaroscopy**)



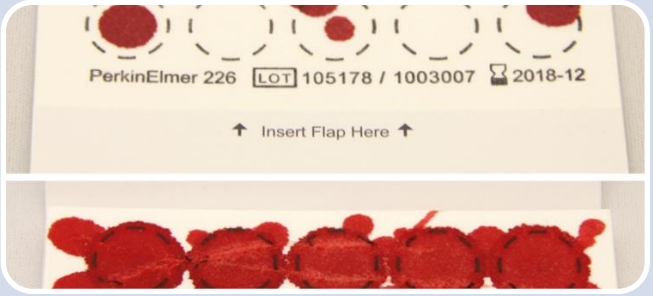
% time below clinically relevant threshold (HR < 100 bpm, SpO2 < 85%, MBP< 30 mmHg, rScO2 <50%) during heart ultrasound and capillaroscopy (yellow) and previous 30 min (grey)

M Hallik et al. ESPNIC 2015

Blood sampling: timed vs scavange vs dried blood spots

- Extra blood loss
+ Well predicted (personnel availability)
+ quality
+ Controlled distribution over dosing interval

+ No extra blood loss
- Quality depends on lab routines
- unstable analytes?
- Time distribution?



+ Limited volume
+/- Quality: study-specific procedure
- Stability
• Volatile agents??

Semi-rich sampling PK study: blood loss

500g birth weight: CBV ca 50 ml!
3% of CBV = 1,5 ml

Retrospective cohort analysis
VLBW neonates:
Birth weight <1200g; GA <28 weeks
PK study
7 blood samples, total volume ≤ 2.3 ml over 12 h
Study group: 18 neonates
Control group: 35 neonates matched by GA, birth weight and PNA

Figure 1. The effect of participation in PK study to HGB values

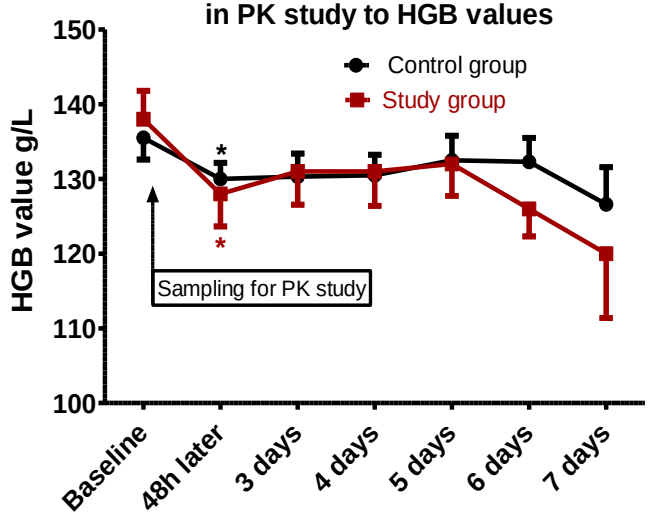
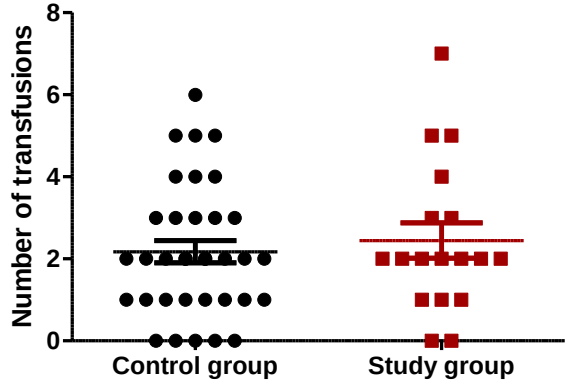


Figure 3. Number of transfusions during follow-up period



Observed characteristic	Study group (n=18)	Control group (n=35)	P-value
Daily fluid requirements (ml)*	123.6 (22)	125.5 (21.3)	0.773
Diuresis 12h (ml)*	41.5 (15.2) n=16	54.0 (15.2) n=7	0.09
Blood sampling for clinical indications (n per day)*	4.8 (1.0)	5.6 (1.8)	0.127
Need for vasoactive treatment (n=)	3 (17%)	7 (20%)	1
IVH I-III (nr. of patients)	4 (22%)	11 (31%)	0.539

L-T Heidmets et al. Neonatology 2010

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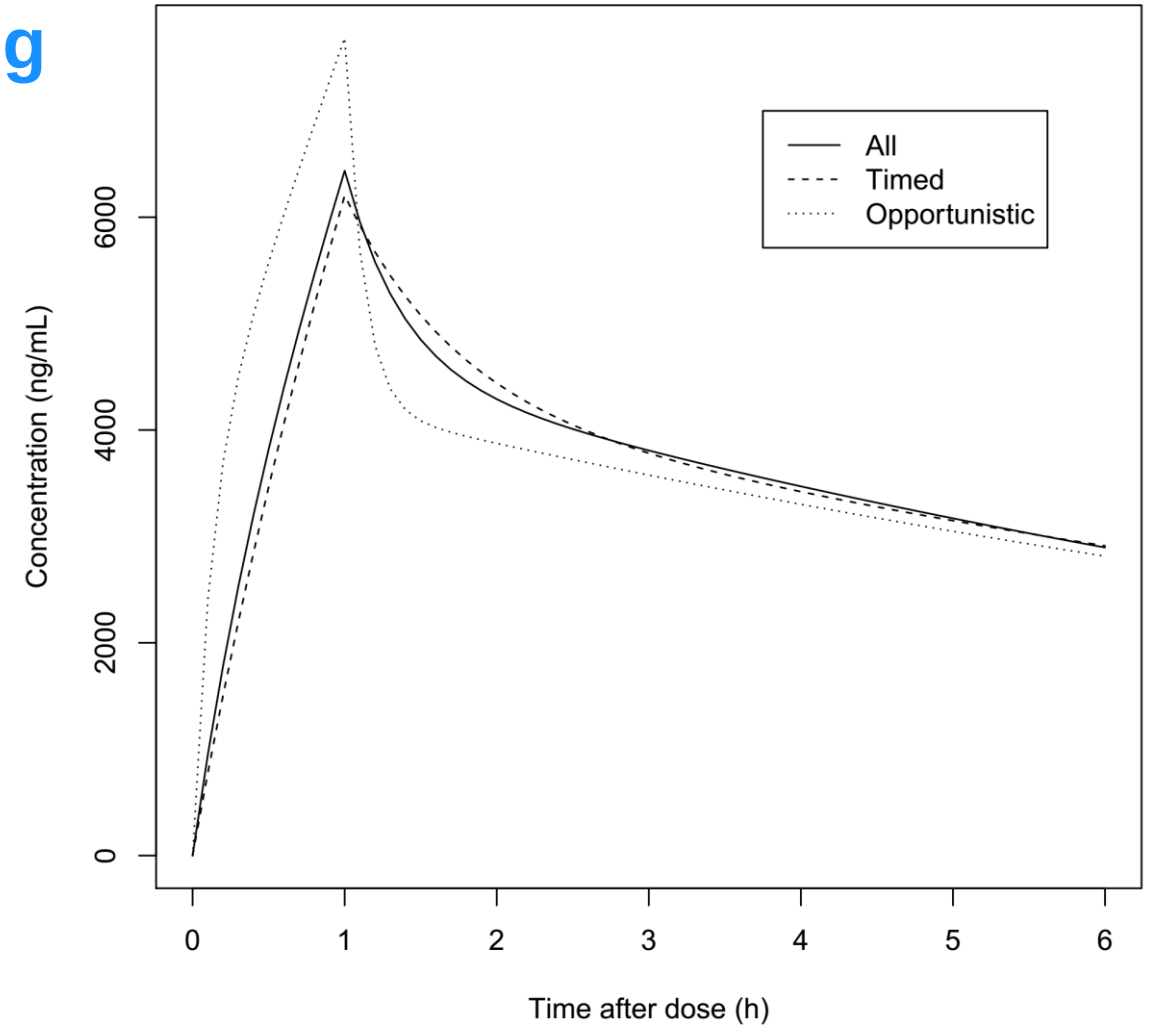
Opportunistic vs timed PK sampling

Clin Pharmacokinet
DOI 10.1007/s40262-015-0291-1

ORIGINAL RESEARCH ARTICLE

Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design

Stéphanie Leroux[1,2,3,4] · Mark A. Turner[5,6] · Chantal Barin-Le Guellec[7] · Helen Hill[5,6] · Johannes N. van den Anker[8,9,10,11] · Gregory L. Kearns[12,13] · Evelyne Jacqz-Aigrain[1,2,3,14] · Wei Zhao[1,2,3,14,15] · On behalf of the TINN (Treat Infections in NeoNates) and GRiP (Global Research in Paediatrics) Consortiums

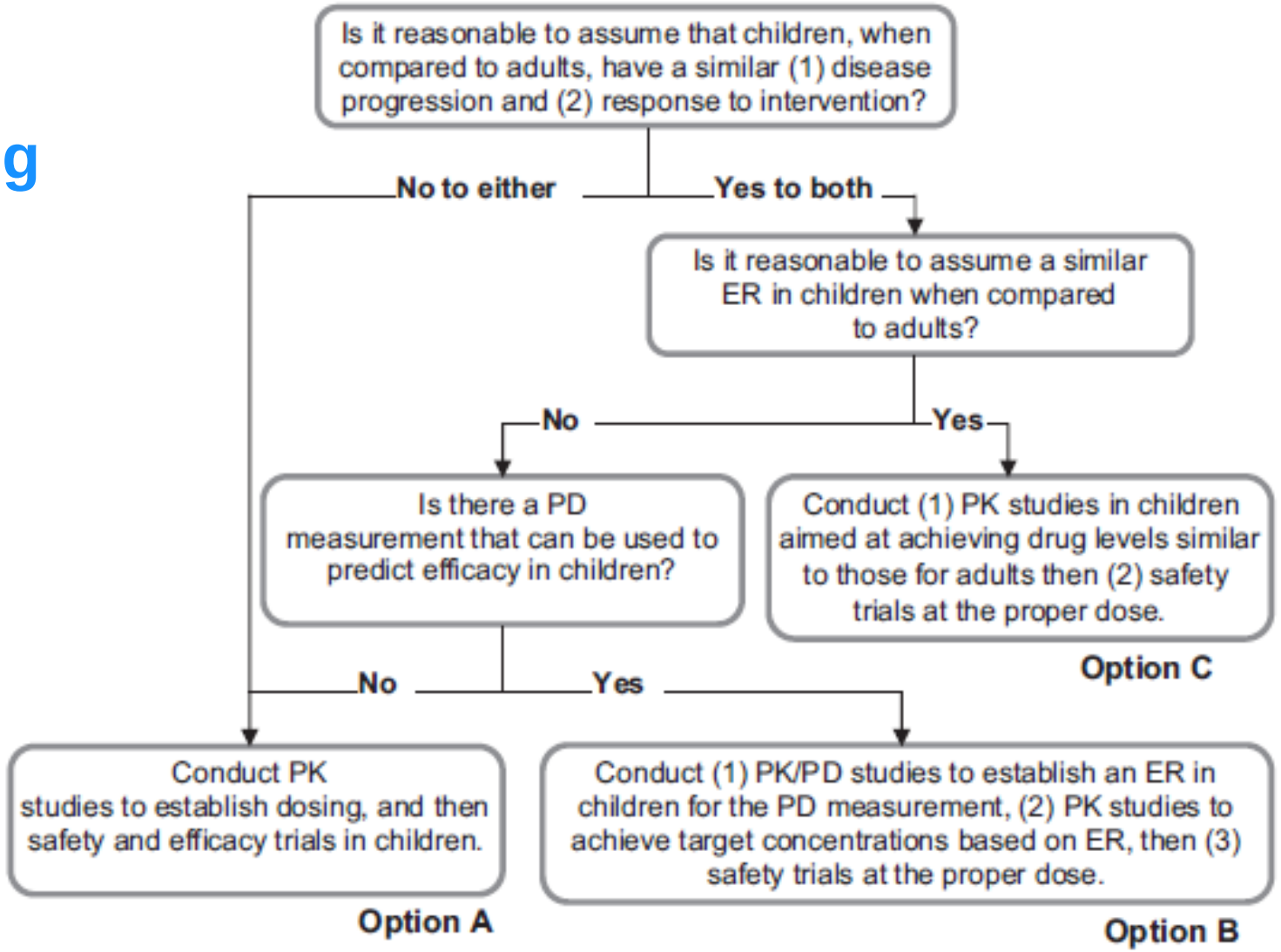


Clin Pharmacokinet. 2015 Dec;54(12):1287-8. doi: 10.1007/s40262-015-0344-5. Comment on Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design. Standing JF[1], Anderson BJ[2], Holford NH[3], Lutsar I[4], Metsvaht T[5].

Extrapolation and modelling

+ maximum use of existing data
+ limiting No of study participants

- Clinicians' trust
- „all models are wrong, some are useful"



ER – exposure response; PD – pharmacodynamic; PK – pharmacokinetic

J Dunn et al. Pediatrics 2011; 128:e1242-e1249

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Data repositories; „next generation“ modelling with pooled data? Data quality assurance?

LARGE BODY OF PK DATA AVAILABLE; LIMITED EXTERNAL VALIDATION (3/12); VARIABLE PERFORMANCE

Study population selection: relevance to results/ conclusions

NeoMero: EMA Expert Meeting on Neonatal and Paediatric Sepsis criteria for sepsis

Clinical parameters
1. hyper- or hypothermia or temperature instability;
2. reduced urinary output or hypotension or mottled skin or impaired peripheral perfusion;
3. apnea or increased oxygen requirement or need for ventilatory support;
4. bradycardia spells or tachycardia or rhythm instability;
5. feeding intolerance or abdominal distension;
6. lethargy or hypotonia or irritability;
7. skin and subcutaneous lesions (such as petechial rash or sclerema)
Laboratory parameters
1. white blood cell count < 4 or > 20 x 10^9 cells/L;
2. immature to total neutrophil ratio > 0.2;
3. platelet count < 100 x 10^9/L;
4. C-reactive protein > 15 mg/L or procalcitonin ≥ 2 ng/mL;
5. glucose intolerance when receiving normal glucose amounts (8-15 g/kg/day) as expressed by blood glucose values > 180 mg/dL or hypoglycemia (<40 mg/dL) confirmed on at least two occasions;
6. acidosis with base excess (BE) < -10 mmol/L or lactate above 2 mmol/L

Ampicillin vs penicillin for the treatment of neoates at risk of EOS

Inclusion criteria

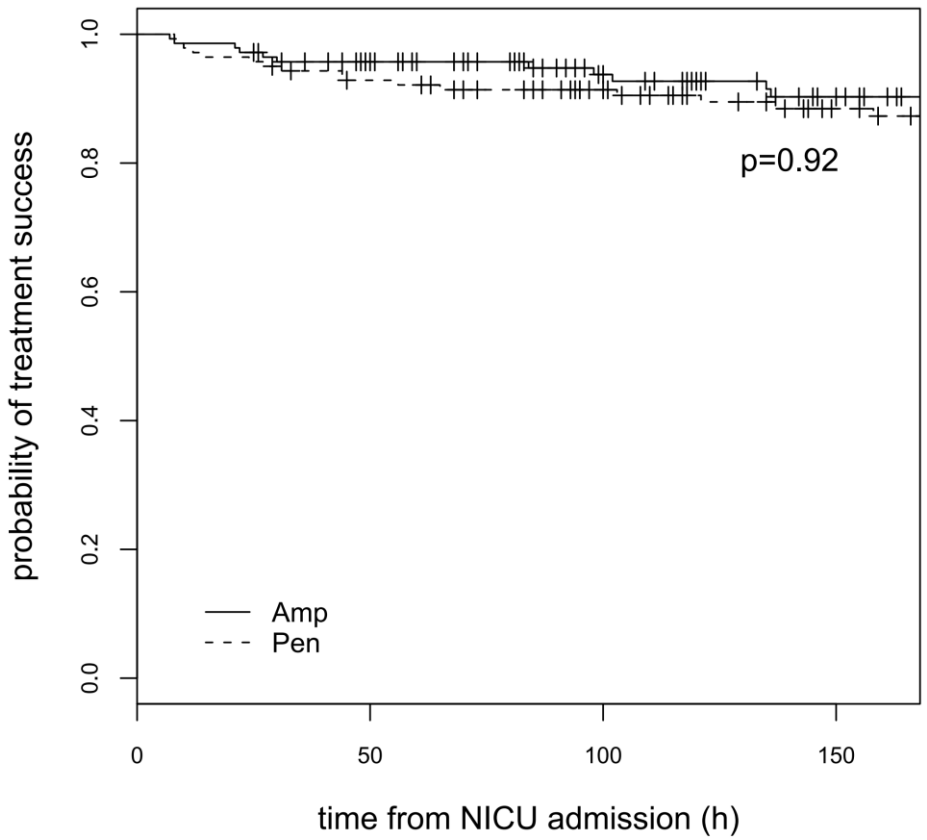
(1) admitted to NICU within 72 hours of life

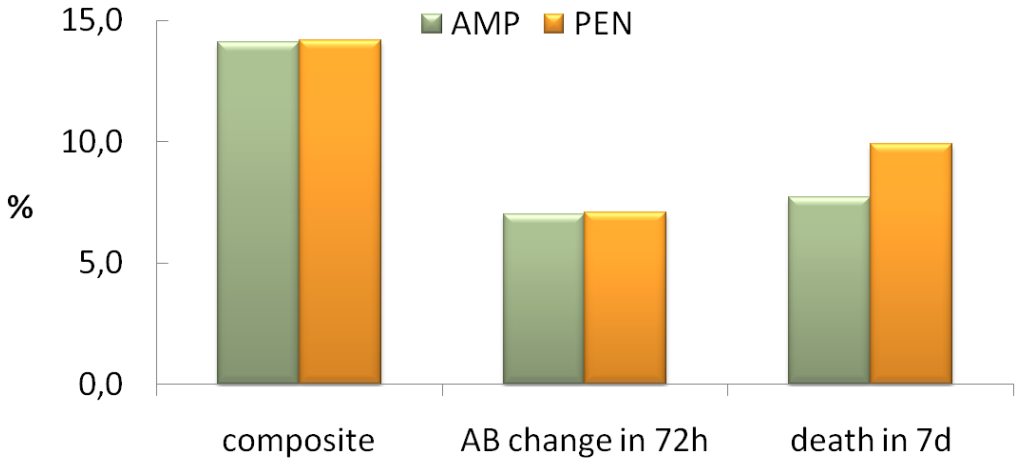
(2) Need for antibiotic treatment for EOS or risk factors of EOS (Schrag *et al.* 2002)

(3) Not transferred within 24 h

Diagnosis of sepsis	98% vs 20%
Culture proven sepsis	52% vs 5%

Ampicillin vs penicillin G combined with gentamicin for the treatment of neonates at risk of EOS (RCT, n=283)





Outcome measure	Treatment difference % (95% CI)
Composite	0.1 (-8.1; 8.3)
AB change	0.05 (-6.3; 6.4)
Death in 7d	2.2 (-4.7; 9.1)

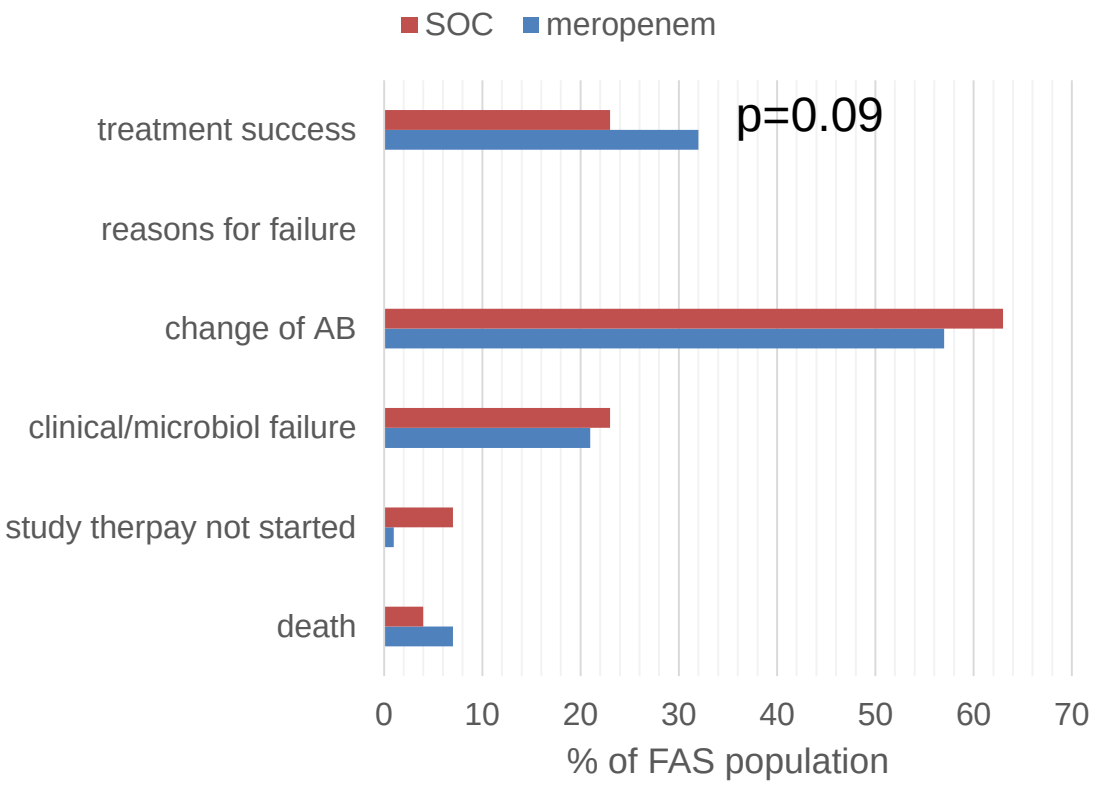
(T. Metsvaht et al. Acta Paediatr 2010;99:665-672)

Conclusion:

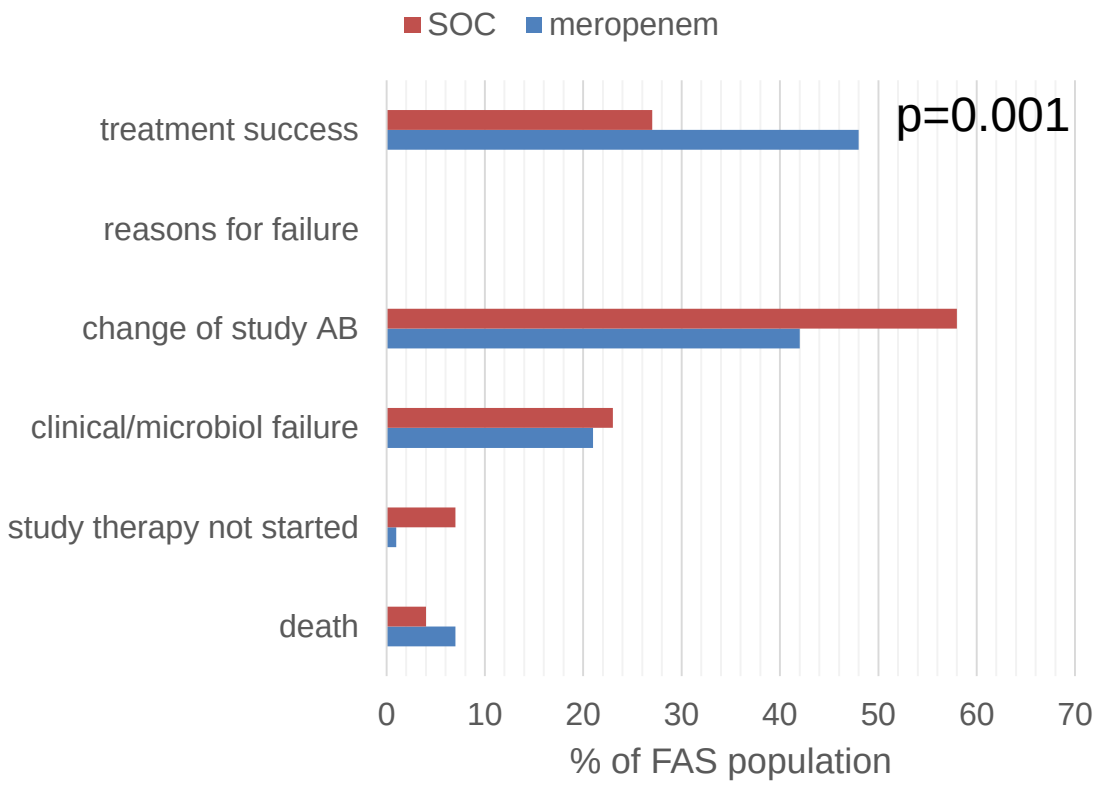
AS LONG AS WE TREAT THOSE WHO DO NOT NEED TREATMENT, EFFICACY IS NOT A PROBLEM …

Outcome parameters: NeoMero experience

Treatment success – study AB for 8-14 d



Treatment success – study AB for 7-14 d



I. Lutsar et al. 2018 submitted

Clinical problem (i.e. neonatal sepsis) vs heterogenous population/ multiple reasons (variable bacterial aetiology, host characteristics, disease mechanisms)

LACK OF VALIDATED WELL DEFINED OBJECTIVE DIAGNOSTIC CRITERIA/ OUTCOME PARAMETERS

Lack of data leads to wide variation in practice:

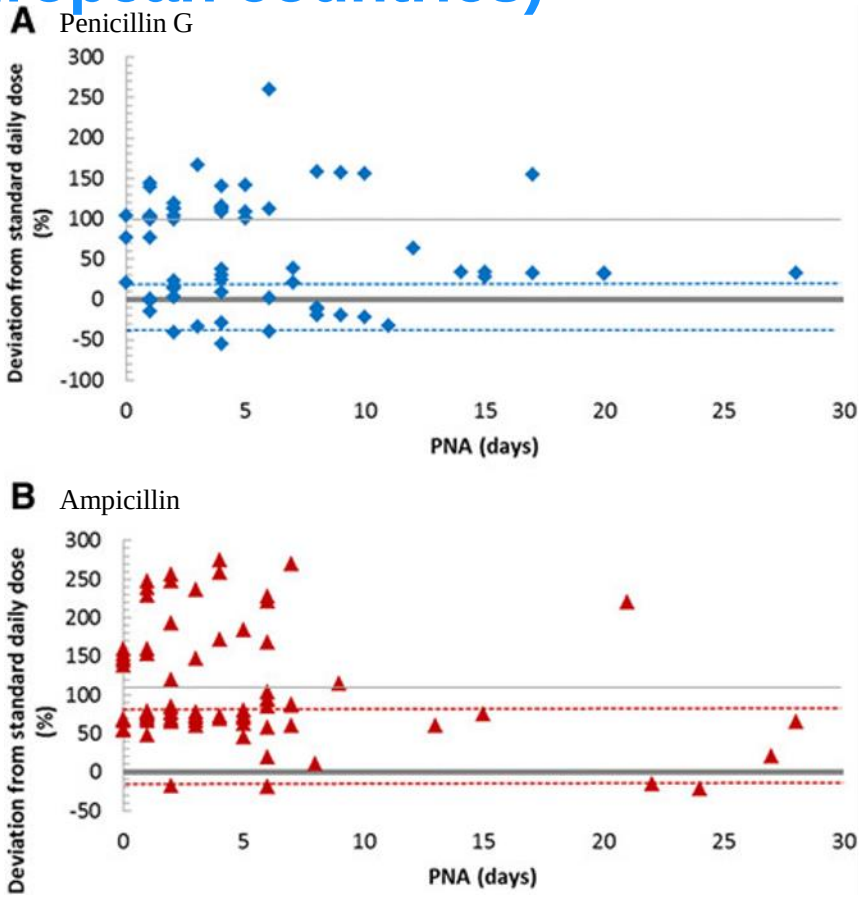
43 Ab regimens in 113 neonates with late onset sepsis

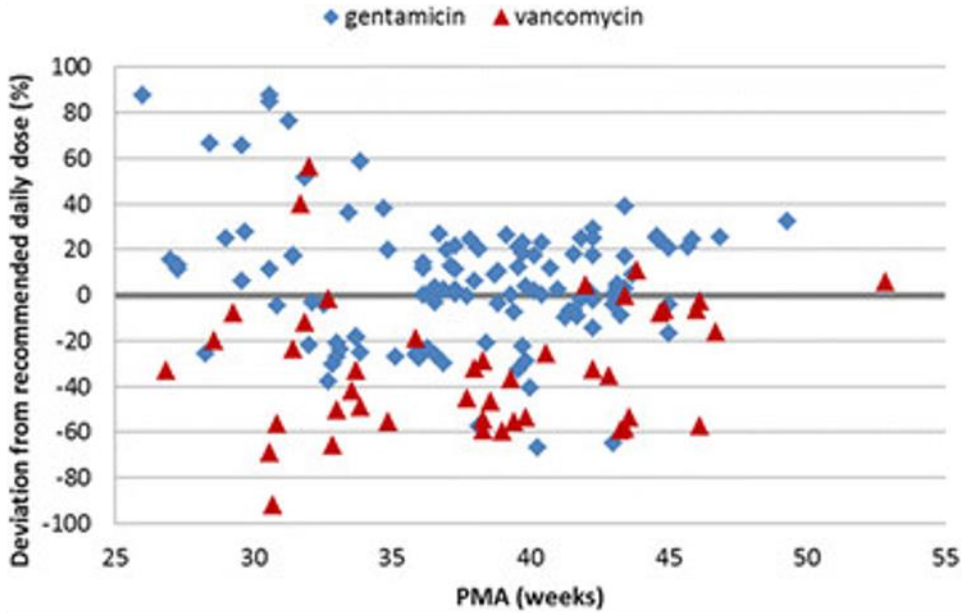
First line of ATB (i)	Total N=113
AMPICILLIN	1 (1%)
AMPICILLIN\Gentamicin	**7 (6%)**
AMPICILLIN\NETILMICIN	1 (1%)
Amikacin	2 (2%)
Amikacin\Cefotaxime	2 (2%)
Amikacin\Colistin	1 (1%)
Amikacin\Meropenem	2 (2%)
Amikacin\PenicillinG	1 (1%)
Amikacin\Teicoplanin	1 (1%)
Amikacin\Vancomycin	10 (9%)
Amikacin\Vancomycin\Meropenem	1 (1%)
AmpicillinSulbactam	1 (1%)
AmpicillinSulbactam\NETILMICIN	1 (1%)
CEFEPIME	4 (4%)
CEFEPIME\Teicoplanin	1 (1%)
CEFEPIME\Vancomycin	1 (1%)
Cefotaxime	4 (4%)
Cefotaxime\Gentamicin	**1 (1%)**
Cefotaxime\Gentamicin\PenicillinG	2 (2%)
Ceftazidime	1 (1%)
Ceftazidime\Teicoplanin	2 (2%)
Ceftazidime\Vancomycin	8 (7%)
Cefuroxime	2 (2%)
Cefuroxime\Meropenem\Vancomycin	1 (1%)
Colistin	1 (1%)
Gentamicin	3 (3%)
Gentamicin\Meropenem\Vancomycin	1 (1%)
Gentamicin\PIPERACILLINTazobact	2 (2%)
Gentamicin\PIPERACILLINTazobact\PenicillinG	1 (1%)

First line of ATB (ii)	Total N=113
Gentamicin\PenicillinG	2 (2%)
Gentamicin\Vancomycin	2 (2%)
IMIPENEM\Metronidazole\NETILMICIN\Colistin	1 (1%)
Meropenem	**10 (9%)**
Meropenem\Teicoplanin	1 (1%)
Meropenem\Vancomycin	13 (12%)
Metronidazole	1 (1%)
NETILMICIN\Vancomycin	1 (1%)
PIPERACILLINTazobact\Gentamicin\Meropenem	1 (1%)
Teicoplanin	1 (1%)
Teicoplanin\CEFEPIME	1 (1%)
Vancomycin	9 (8%)
Vancomycin\CIPROFLOXACIN	1 (1%)
Vancomycin\NETILMICIN	2 (2%)
Vancomycin\PIPERACILLINTazobact	1 (1%)

Variations in the dosing of antibiotics in neonates (89 units in 21 European countries)

ESNEE
ERA-NET PRIOMEDCHILD





Problems related to limited prior information and large variations in existing practice

- Defining study population
- Defining standard of care/ comparator(s)
- Clinicians „trust“ in the light of missing efficacy and safety data
  - Selection bias
  - Biased subjective outcome measures (i.e. change of antibiotic regimen)

Ways to improve – better targeting?

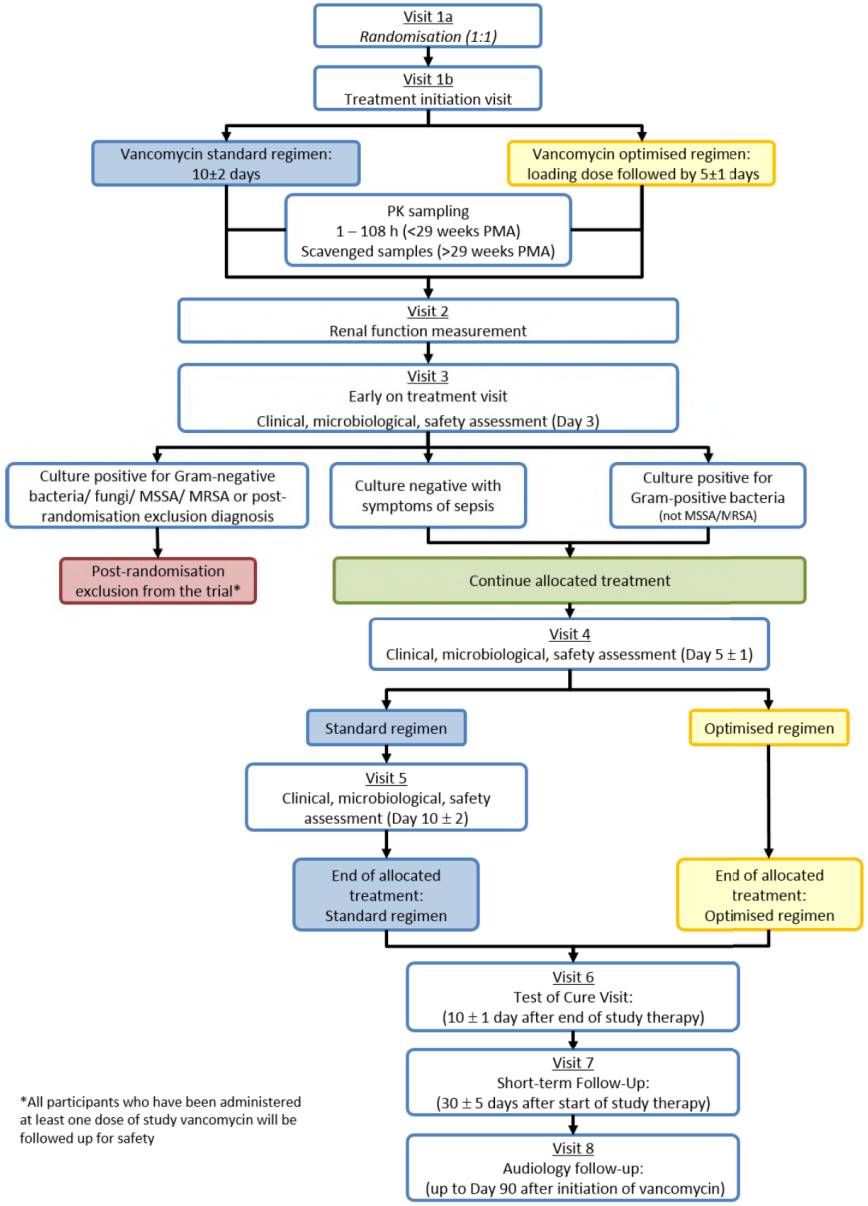
- Rapid and reliable identification of bacterial aetiology
  - PCR, microarray, proteomics
- Criteria to define those failing on (study) therapy
  - Clinical characteristics
  - Biomarkers?
  - Novel statistical approaches: CART, neural networks
- Individualised PK/PD approach
  - Developing appropriate PD characteristics??

Complexity of protocols: answering all questions at the same time

Substudies

- PCR for pathogens
- Biomarkers
- Colonisation

- Pharmacogenetics
- Imaging (US, CT, MRT)
- …..



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Sample collection: SSPs

Primary Specification: Specimen C

**Ensure that consent for the l

**Ensure

- Wash hands and put on gloves
- Collect a **minimum** of 200 – 2
- Immediately after collecting th
- Place the label on the outside
- Complete the NeoVanc Pharm
- If specimen cannot be centri however, this should be avoid the requisition form

- Do not collect in BC PPT (plasr
- Do not collect in tubes that co

Storage Container(s)

Screw cap microcentrif
University of London

Centrifugation & Processing

Sample: "

- Centrifuge the lithium heparir (ambient temperature)
- The total available plasma vo careful not to disturb the cell l
- Prepare the appropriate label
- Complete the date and time o provided "**Plasma for PK Study**
- Wipe the tube and stick the ap
- Complete the **NeoVanc Pharm**

Personnel using this method / protocol are responsible for ens understood the contents, and the procedure is followed. They must b as documented in their training records. It is the duty of the Principa are aware of this responsibility.

Collection Containers

Sterile universal specimen container provided by

(appearance may vary between hospit

Primary Specification: Collection & Handling

Only collect the tip for the NeoVanc study if line removal is indicated is not being sent to the local laboratory for routine culture either beca all tips are routinely processed by the local laboratory

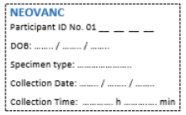
Specimen Collection

Umbilical catheter/central venous line

**Ensure that consent for the NeoVanc study has been obtained

**Ensure that consent has not been withdr

- Wash hands and put on gloves
- Remove umbilical catheter/central venous line as per local
- Cut the catheter 1.5 cm proximally from the tip and transf into the sterile tube, whilst taking care not to contaminate t
- Cap lid and avoid touching the inside of the lid or container
- Place the **label for primary specimen containers** on the out



- Complete the NeoVanc Laboratory Requisition Form

Specific Information

⚠ Cryovial prefilled with cyropreservative must be stored between +4°C/+8°C until its use

Key Summary Points of this SSP

Please refer to the appropriate section of this SSP for more detailed instructions

- Ensure that consent for the NeoVanc study has been obtained from the parent/guardian
- Ensure that consent has not been withdrawn
- This technique is used for the collection of **Neonatal Whole Blood** samples into Blood RNA tubes pre-filled with PAXgene RNA reagent
- Biomarker samples can be collected from *umbilical artery catheters, umbilical venous catheters, peripherally inserted central catheters, peripheral venous catheters, through venepuncture or through capillary blood sampling*
- Always ensure that:
  - ✓ NeoVanc specific label is completed
  - ✓ The specimen is stored as outlined after collection
  - ✓ The NeoVanc Biomarker Requisition Form is completed

Related documentation

Appendix: Material Data Safety Sheet, PAXgene Blood RNA tube.

Materials

Please refer to the appropriate section of this SSP for more detailed instructions

Blood RNA tube

Pierceable rubber membrane

Screw cap lid

PAXgene Blood RNA Stabilisation reagent

50 µl Minivette

[Rubber membrane has been pre-pierced with a 16G needle to allow the Minivette to pierce]

Key Summary Points of this SS

Please refer to the appropriate

- Ensure that consent for th
- Ensure that consent has n
- Specimen to be collected: (If the baby has a stoma,
  - Stool is preferred, if if this is not possible
- Please do not clean the p
- Please moisten the swab the sample
- Always ensure that:
  - ✓ NeoVanc specific lab
  - ✓ The NeoVanc sample

Collection Containers

Stool specimen collect

Sterile universal specimen cont

⚠ If there is NO stool sam then please collect a rectal sw

Primary Specification: Collect

Collect the sample at the appr
At each allocated time a stoo (colonisation) swabs should be

- Collect specimens on:
  - **Visit 1a** – Screening and r
  - **Visit 4** – Day 5±1/EOAT(opt) visit (only participants in optimised arm)
  - **Visit 5** – Day 10±2/EOAT(std) visit (only participants in the standard arm)
  - **[EVT** visit (only in participants who undergo an EVT visit)]
  - **Visit 7** – Short term Follow up visit

Key Summary Points of this SS

Please refer to the appropriate

- Ensure that consent for th
- Ensure that consent has no
- Bacterial DNA specimens s
- Specimen to be collected:
- Specimen can be collec *peripherally inserted centr* **cannot** be collected throug
- Always ensure that:
  - ✓ NeoVanc specific labe
  - ✓ The NeoVanc Laborat

Collection Container(s)

Sterile

Specific Information

- Do not collect specimen ir
- Do not collect in tubes tha

Responsibilities

Personnel using this method understood the contents, and th as documented in their training are aware of this responsibility.

Primary Specification: Specime

- Collect the sample at the a
- At each allocated time a w
- Collect specimens on:
  - **Visit 1a** – Screening an
  - **Visit 3** – Early on treatr
  - **Visit 7** – Short term Follow up visit

Key Summary Points of this SS

Please refer to the appropria

- Ensure that consent for
- Ensure that consent has
- Fresh Pharmacokinetic s age (PMA)
- Specimen to be collecte
- PK specimens can be *peripherally inserted ce* Fresh PK specimens **cann** through the same line adequate flushing of the
- Always ensure that:
  - ✓ NeoVanc specific la
  - ✓ The NeoVanc Pharn

Responsibilities

Personnel using this metho understood the contents, and as documented in their traini to ensure that staff are aware

Collection Container(s)

Primary Specification: Specir

- Collect the specimen at
- A total of 3 pre-defined

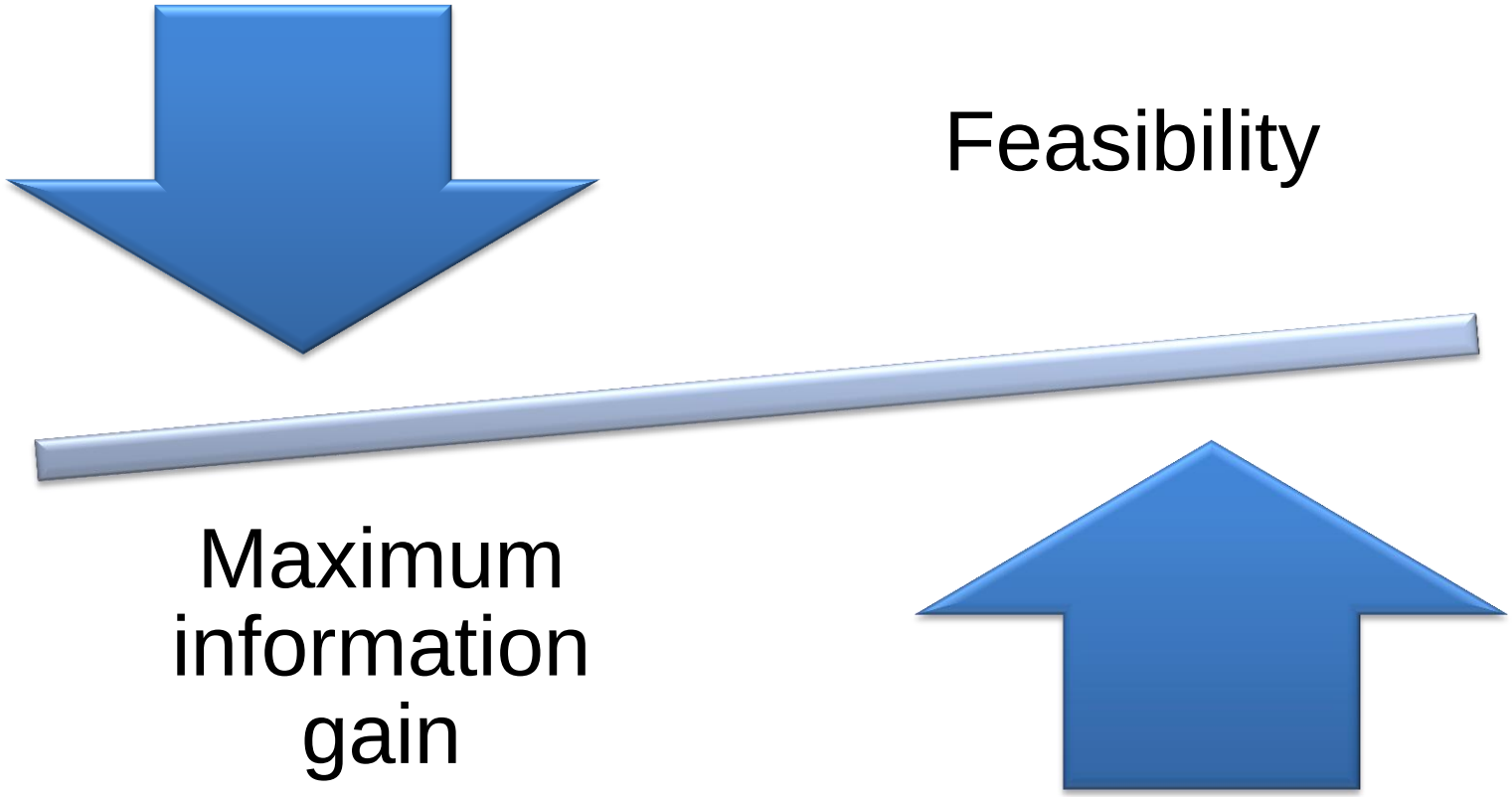
First infusion:

- 1st – 5 – 1
- 2nd – 8 – 1

Fourth or fifth infusio

- 3rd – 4 to 12h from the start of fourth or fifth infusion (PK3)

Balancing



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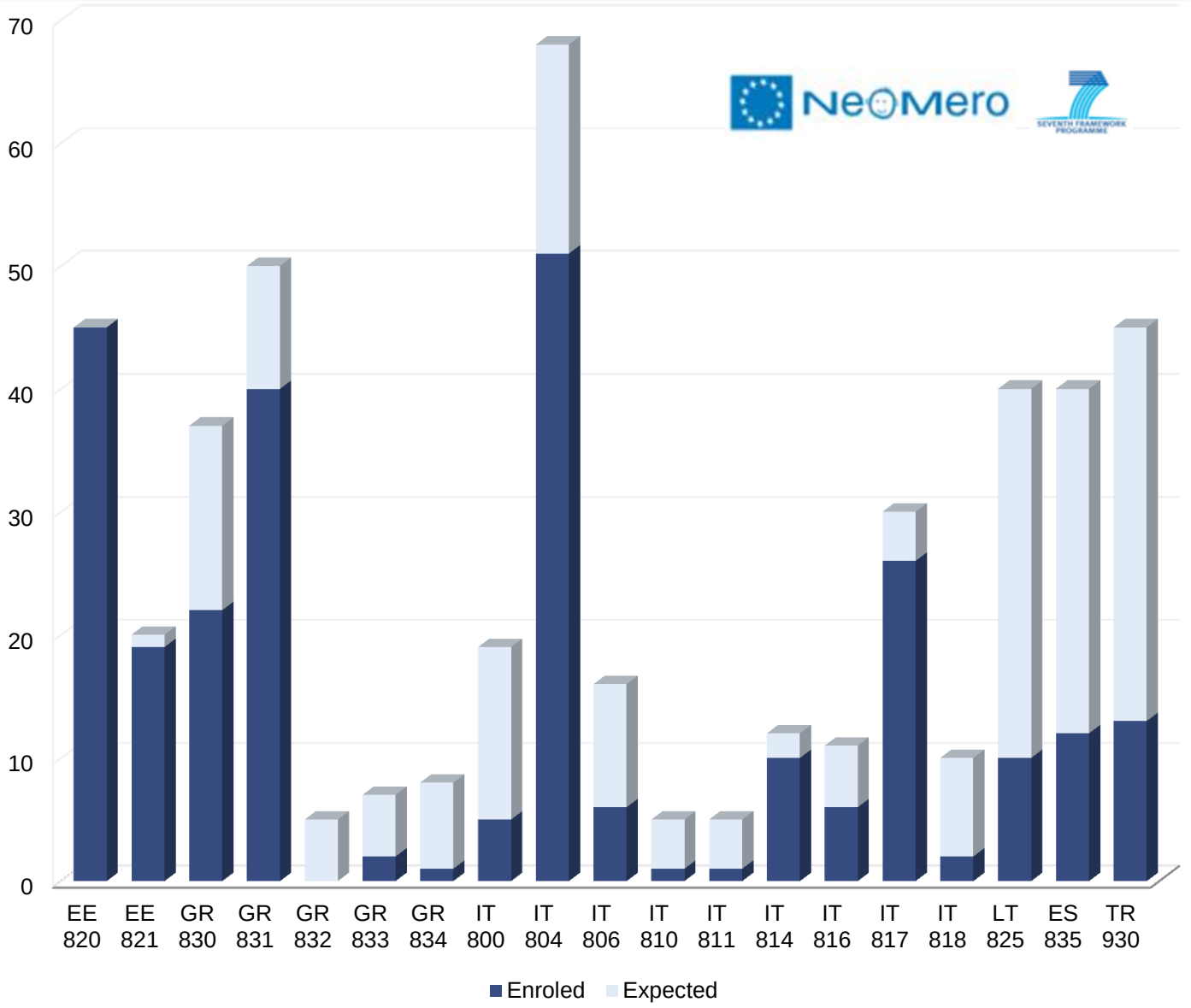
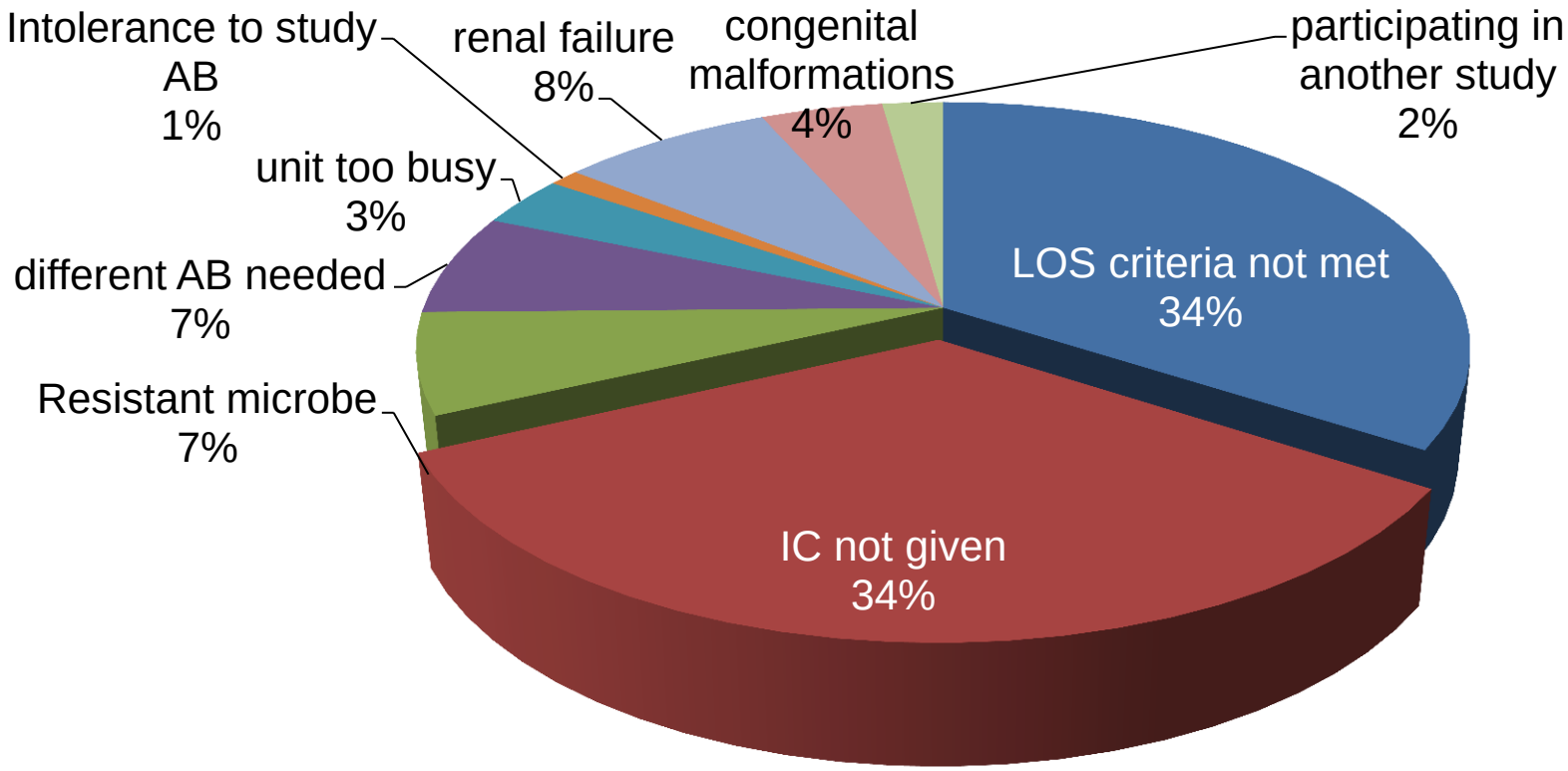
Recruitment

The majority of paediatric trials have enrollment problems

- pre-calculated sample size not reached



Reasons for non-inclusion of patients



N = 300 children

Informed consent: specific issues

- Complexity of information
- Variations between EU countries
- Emotional stress vs time-lines
  - Studies in critical conditions
- Availability of parent/ legal guardian

Informed consent: practical approach

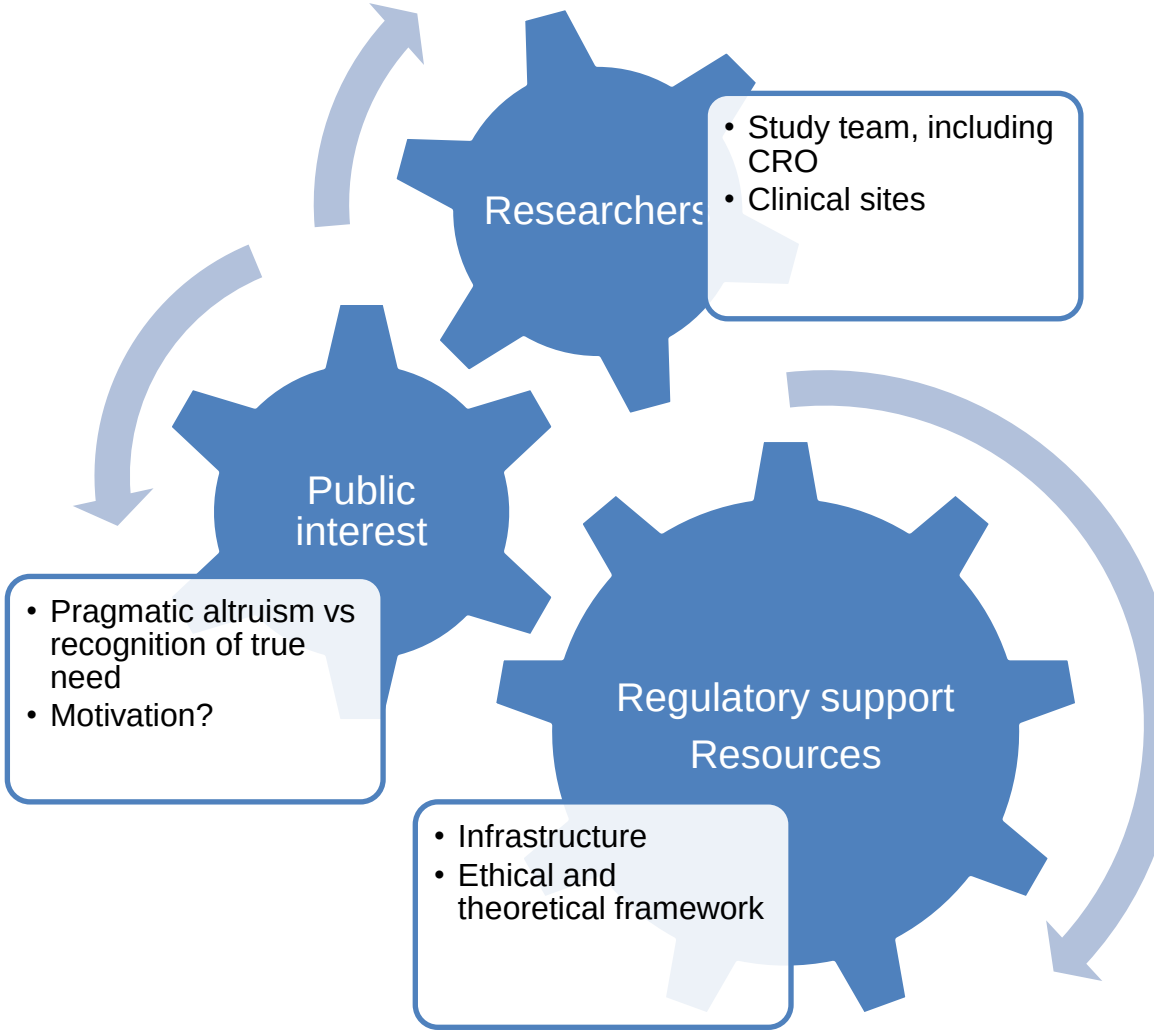
- Pre-consent
  - prior parental/legal guardian's consent in those likely requiring studied intervention
- Deferred and ongoing consent/assent of the patient together with informed consent of the parents/legal guardian
  - If participation declined, clear regulations on management of already collected data
- Electronic signature
- Multimedia approach to provide information?

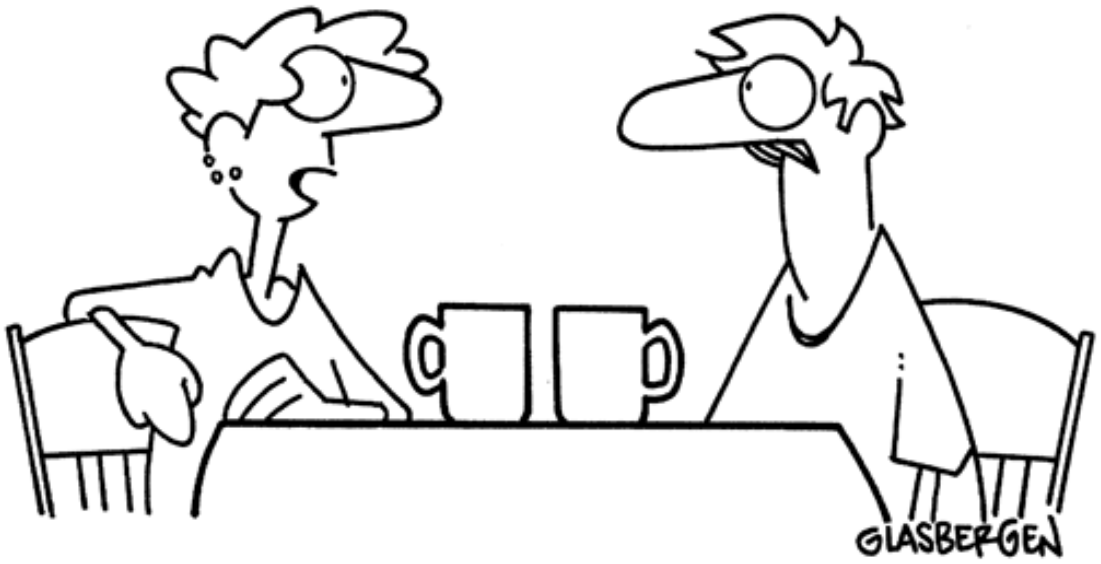
How to improve recruitment?

- Study design and management
  - Pragmatic clinical trials; adaptive study designs
  - CRO/ sponsor support
- Selecting study centres
  - motivation?
- Valid screening logs
- Informed consent procedure
- Adequate resources
  - High level of expertise required
  - Large fluctuations in actual time consumption

Using limited resource in best possible way …

- Limiting studies to relevant problems/ conditions/ interventions
  - Maximum use of existing data
  - Prioritising (bewteen and within studies and centres)
- Networking
  - Centres of excellence; external consultation
  - Resource allocation
  - Academic CROs
- Feasible study design and protocol
  - No more but also no less than necessary





"Let's compromise. You do everything I say and I'll say everything you do."

http://elav.ee

Professor Irja Lutsar
Institute of Microbiology

MD, PhD student
Dpt of Paediatrics

Karin Kipper
PhD, researcher;
Institute of Chemistry

Tuuli Metsvaht MD, PhD
Ass. Professor
Dpt of Paediatrics

Dr. Mari-Liis Ilmoja
MD, Head of Paediatric ICU;
Tallinn Children's Hospital;
researcher, Institute of Microbiology

Heili Varendi MD, PhD
Ass. professor
Dpt of Paediatrics

Koit Herodes
PhD; Ass. Professor
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Jana Lass
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When you do nothing you feel overwhelmed and powerless. But when you get involved, you feel the sense of hope and accomplishment that comes from knowing you are working to make things better.

Albert Einstein

Thank you!