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Kliinilised uuringud kriitilises seisundis vastsündinutel – praktilisi probleeme

Tuuli Metsvaht

SA TÜK lasteintensiivravi osakond; TÜ Mikrobioloogia Instituut/ Anestesioloogia ja intensiivravi kliinik/ Lastekliinik

Juuni 2017

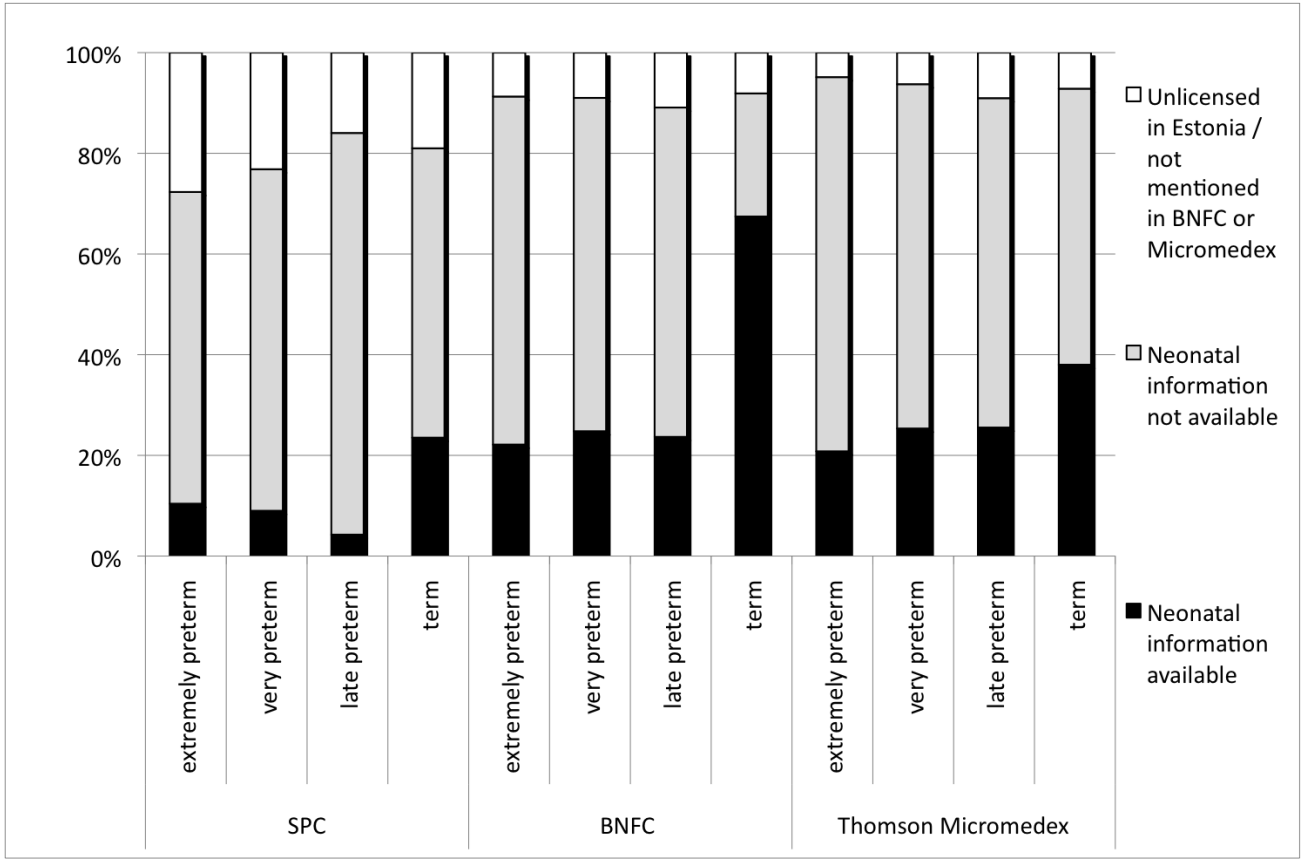
Millest tuleb juttu

- Kas/ miks meil on vaja kliinilisi uuringuid kriitilises seisundis vastsündinutel?
- Probleemide allikad praktikas
  - Heterogeenne populatsioon
    - Arenguline farmakoloogia – PK/ PD
    - Varieeruvad haigusmehhanismid – PD
  - Regulatoorsed ja eetika nõuded haavatavas populatsioonis
    - Riskide hindamine
    - Informeeritud nõusolek
    - Kõrvalnähud/ -toimed
  - Kuidas edasi?

Ravimid ja vastsündinud

Lastel kasutatavatest ravimitest

- 9-78,7% off-label
- 0.3-35% unlicensed

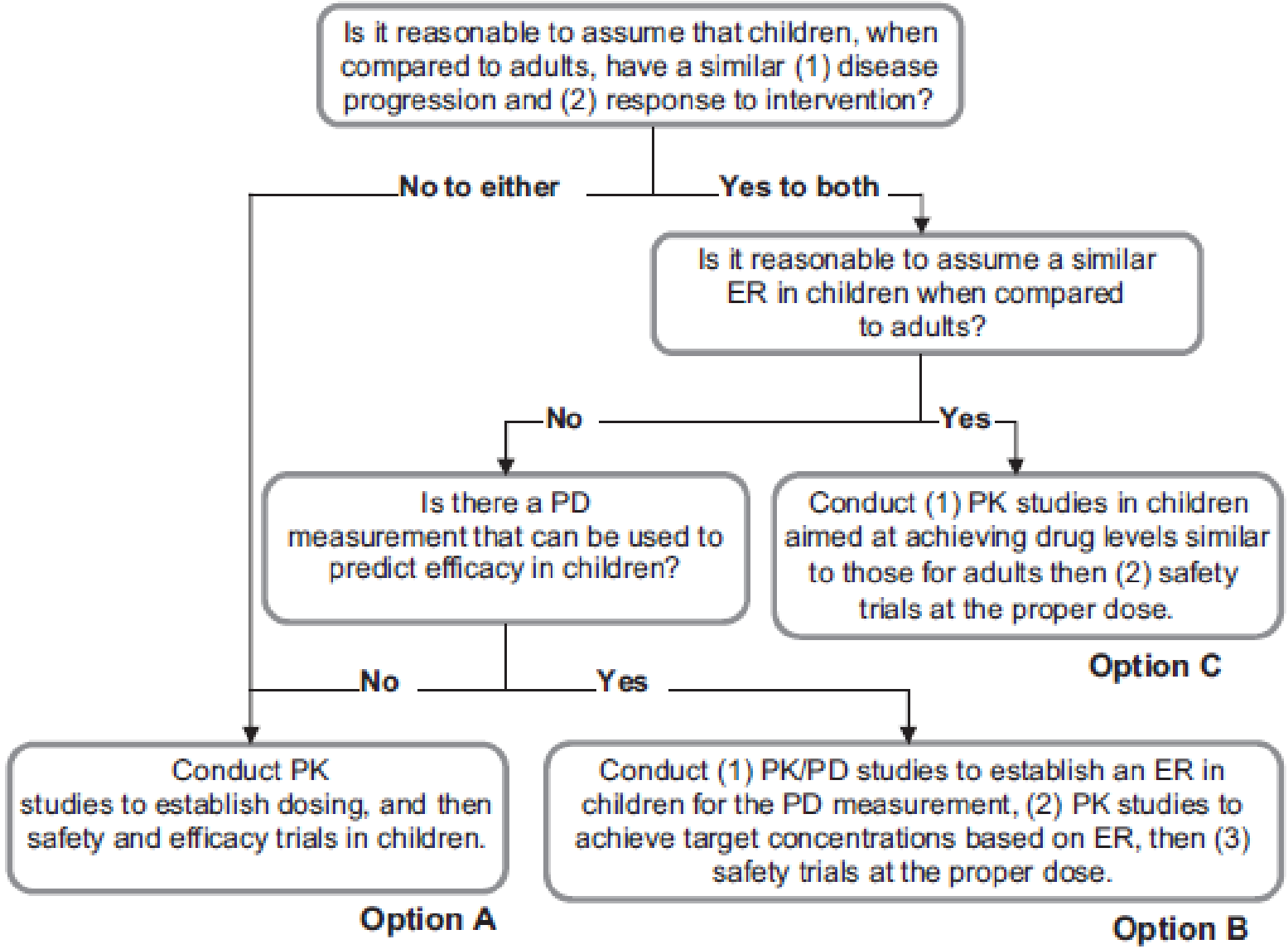


Extremely preterm: GA <28 wk; Very preterm: GA <32 wk;
Late preterm: GA 32-36 wk
SPC – summary product characteristics; BNFC – British National Formulary for Children

J Lass et al. Eur J Clin Pharmacol (2011) 67:1263–1271; Gore R[1], Chugh PK[1], Tripathi CD[1], Lhamo Y[1], Gautam S[1]. Curr Clin Pharmacol. 2017 Mar 17. doi: 10.2174/1574884712666170317161935

Kas meil on kliinilisi uuringuid lastel ja vastsündinutel vaja?

Ekstrapoleerimine täiskasvanutelt on võimalik vaid teatud piirides



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

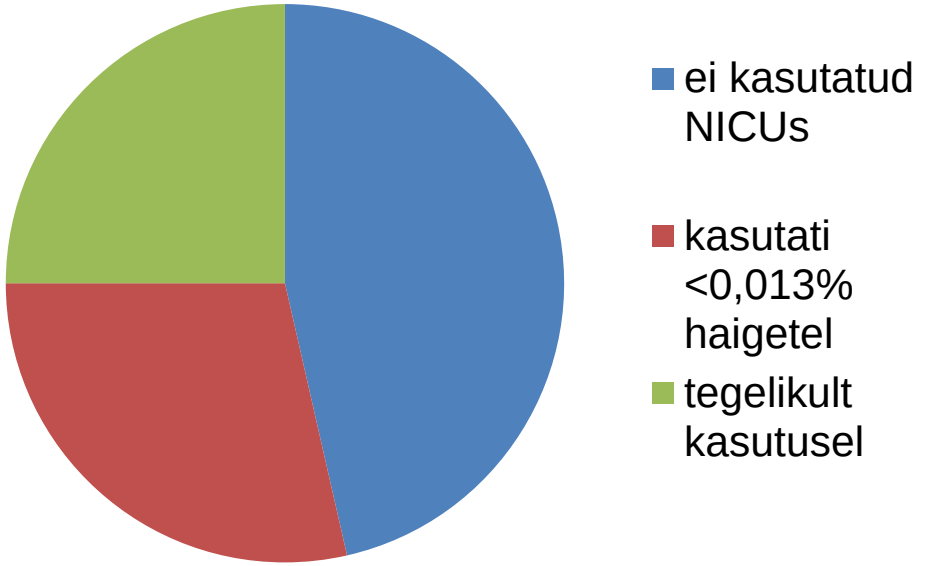
J Dunn et al. Pediatrics 2011; 128:e1242-e1249

Newborns, One of the Last Therapeutic Orphans to Be Adopted

Justin L. Stiers, MD; Robert M. Ward, MD
JAMA Pediatrics February 2014 Volume 168, Number 2

- 290 vastsündinute osakonda, 446 335 vastsündinut
- Kasutusel 406 ravimit
  - 28 (7%) uuringutes vastsündinutel

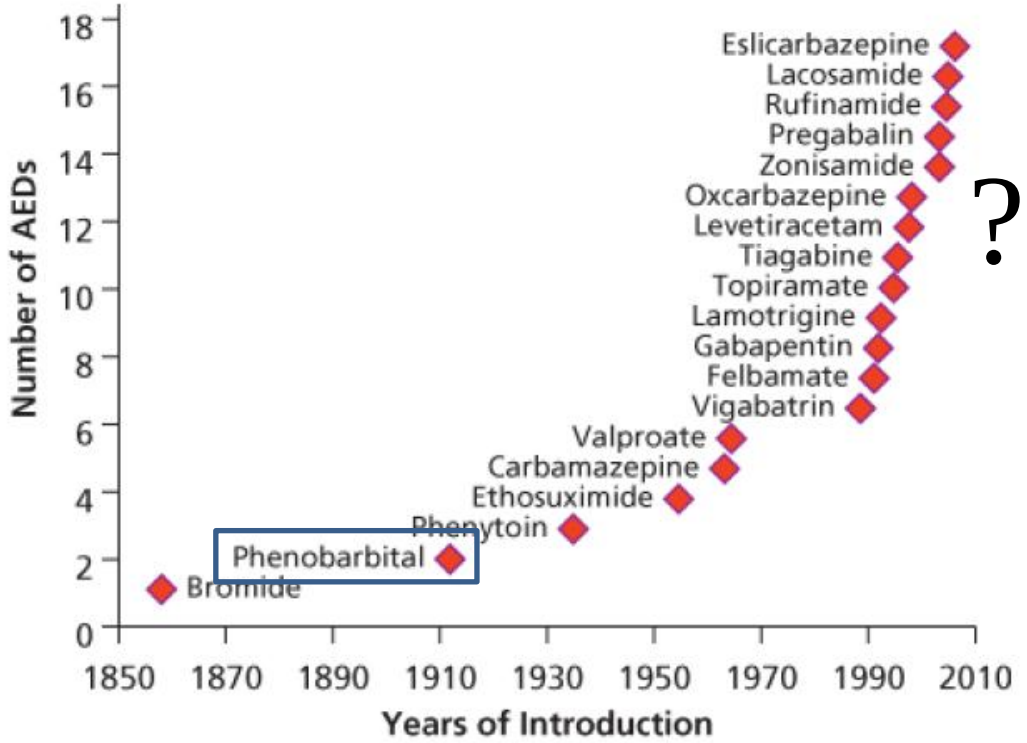
28 uuringutes olevat ravimit



EU Paediatric regulation – neonatoloogias 2% 2007-2011 algatatud uuringutest (PIP)

Probleemid uuringutega vastsündinutel – antiepileptilised ravimid

- 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; Geraldine Boylan & Ronit Pressler

Vanusest sõltuv PKPD ja haigusmehhanismid: uuringu metoodilised probleemid

- Heterogeenne patsientide grupp
- Piirangud tulemusnäitajate valikul
- Väike „signaali/müra“ koefitsient
- (Huvide konflikt)

→ Uuringu teaduslik väärtus

Dobutamiini annusest sõltuv toime (vaheanalüüs)

20 vastsündinut

- mediaan (min-max) gestatsioonivanus 31,5 (22–41) nädalat
- sünnikaal 1668 (465–4380) g

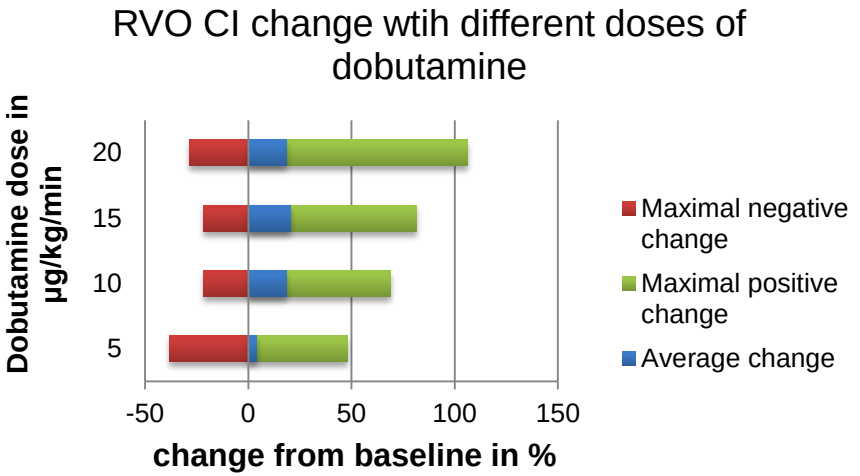
Vajasid dobutamiini kliinilisel näidustusel esimese 2 elupäeva jooksul

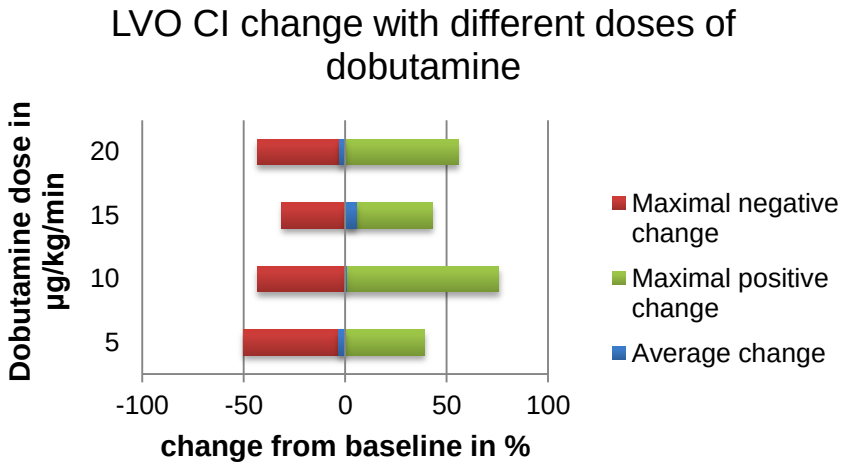
annus 5→10→15→20 µg/kg/min

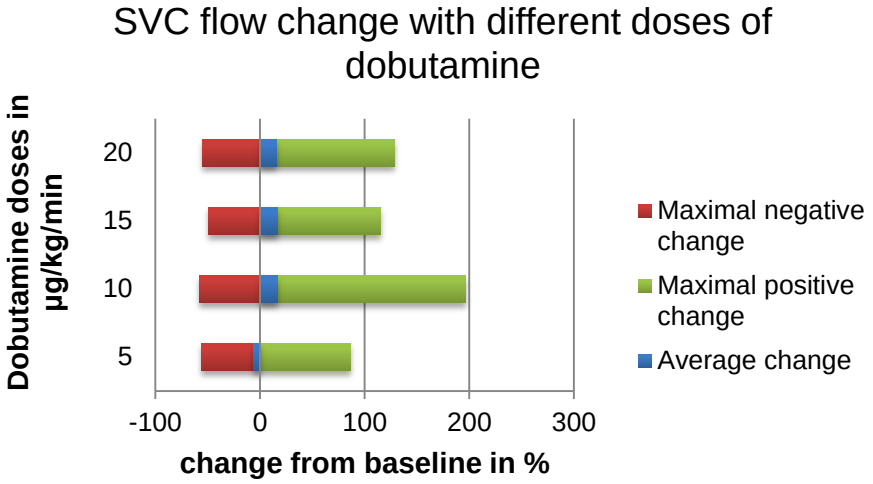
- Max annus 10 ühel, 15 neljateistkümnel ja 20 viiel haigel

M. Hallik et al. 2017 avaldamata andmed

PD parameetri valik



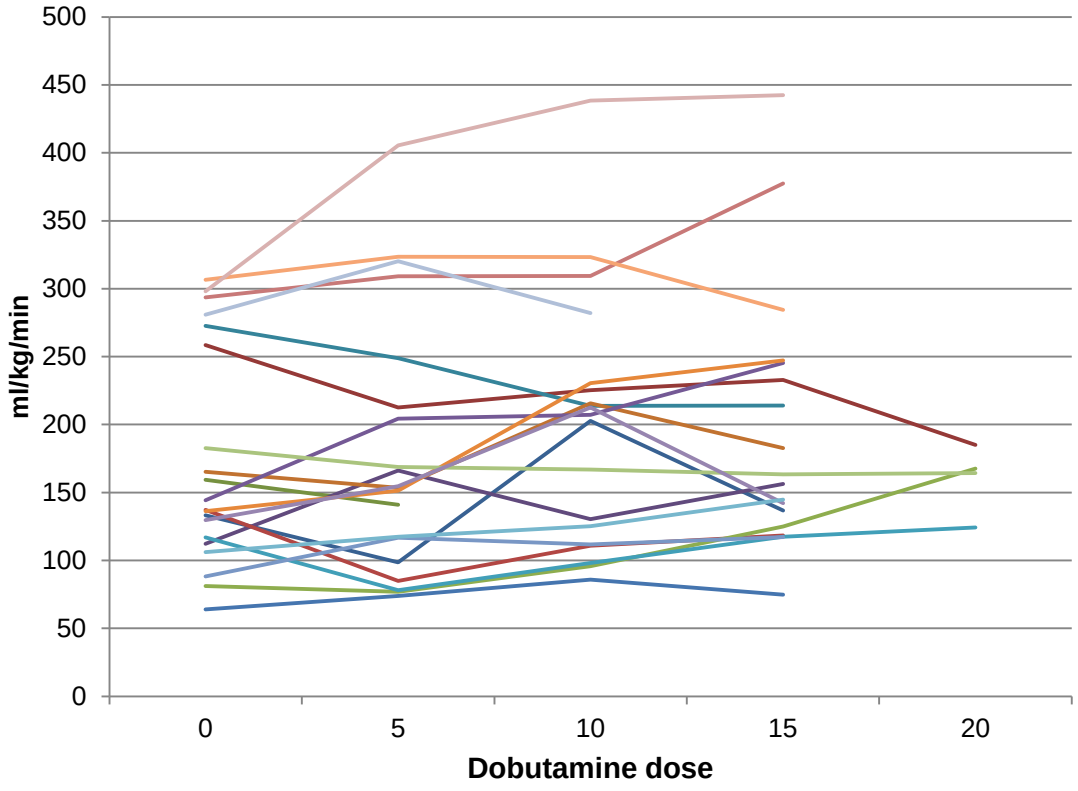




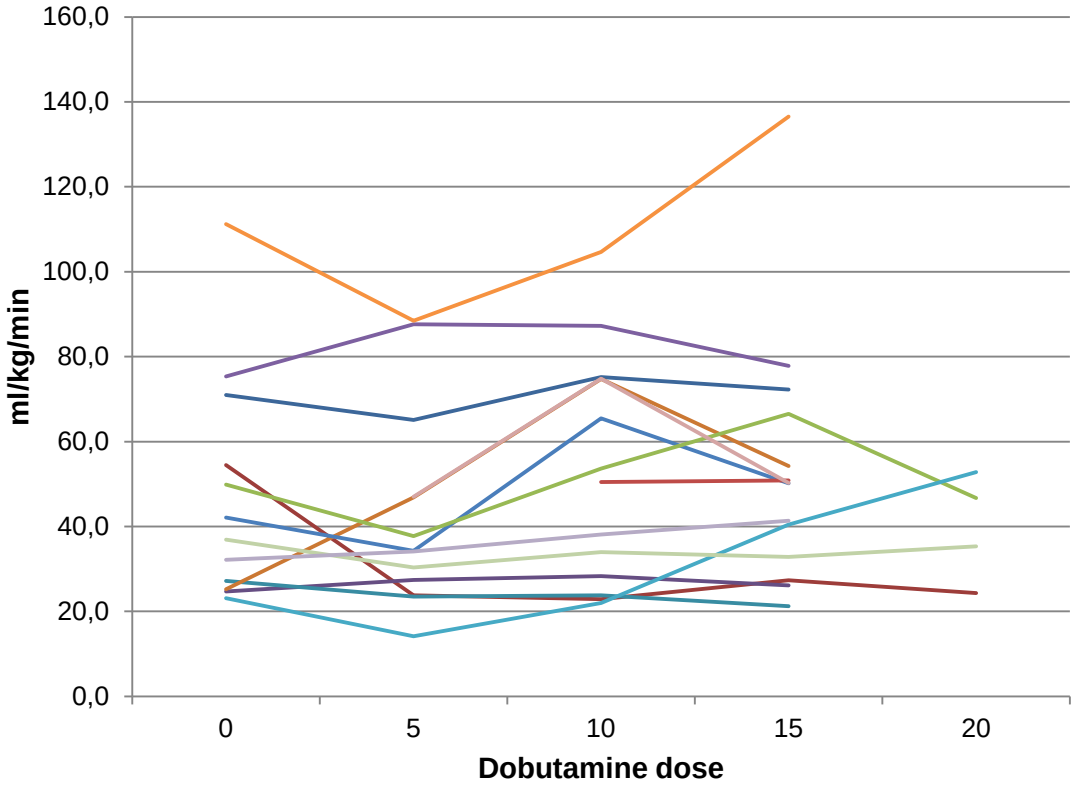
M. Hallik et al. 2017 avaldamata andmed

Dobutamiini annusest sõltuv toime: individuaalne efekt

Individuaalne RVOT CI



Individuaalne SVC CI



Aga mikrotsirkulatsioon? Tsentraalse ja perifeerse HD koherents?

Uuringu disain, mis kasutab maksimaalselt ära olemasolevad teadmised ja võimalused

- Populatsiooni valik
  - Uuringusse arvamise ja välja arvamise kriteeriumid
  - Potentsiaalne haigete arv
- Olemasolev informatsioon
  - Modelleerimine ja simulatsioon
- Disain
  - Minimaalne interventsioon, s.h. proovide/ uuringute maht, tagamaks mõtestatud tulemuse
  - Tulemusparameetrid!

Neonatology

Short Communication

Neonatology 2017;111:8–11
DOI: 10.1159/000447049

Received: January 5, 2016
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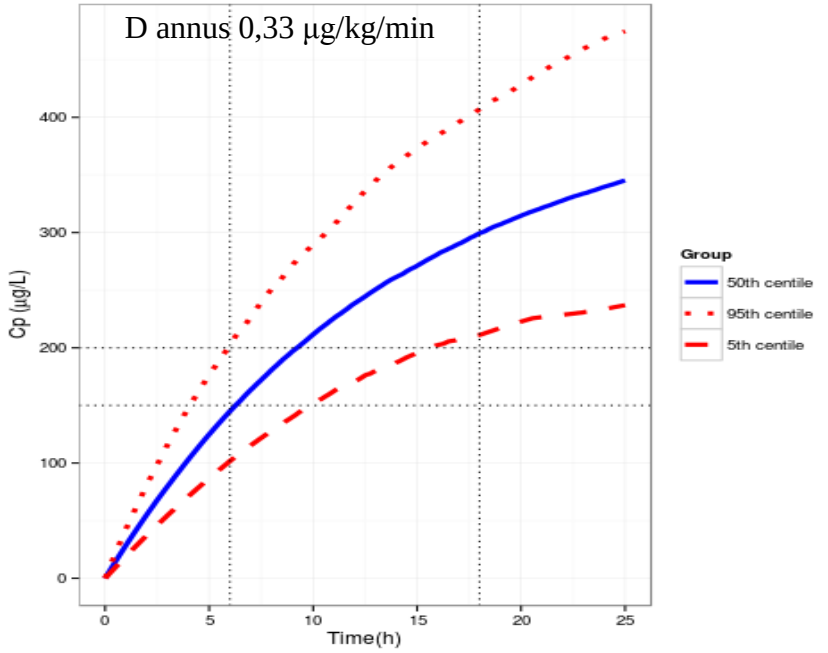
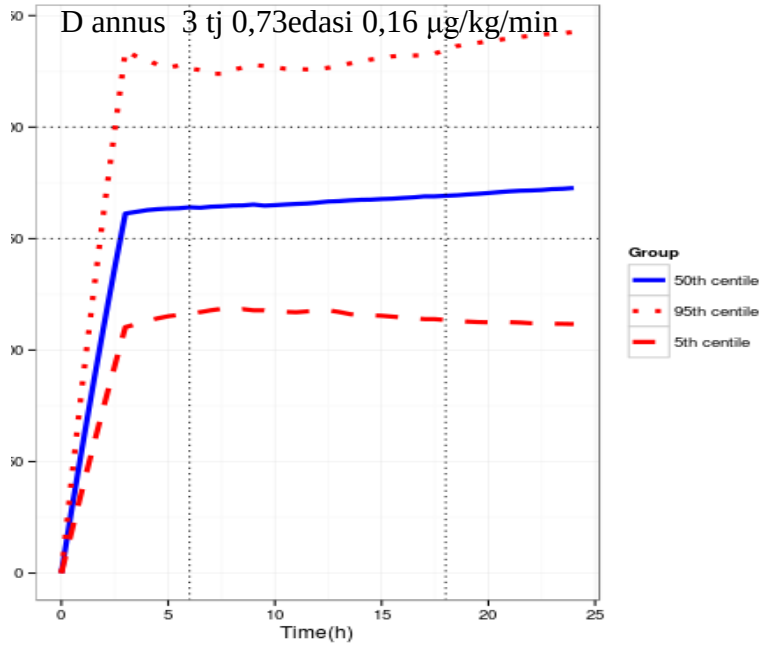
Published online: August 5, 2016

Dosing of Milrinone in Preterm Neonates to Prevent Postligation Cardiac Syndrome: Simulation Study Suggests Need for Bolus Infusion

Maarja Hallik[a, e] Tõnis Tasa[c] Joel Starkopf[a, d] Tuuli Metsvaht[b, d]

[a]Department of Anaesthesiology and Intensive Care, [b]Department of Paediatrics, and [c]Institute of Mathematics and Statistics, University of Tartu, and [d]Clinic of Anaesthesiology and Intensive Care, Tartu University Hospital, Tartu, and [e]Department of Anaesthesiology and Intensive Care, Tallinn Children's Hospital, Tallinn, Estonia





Eesmärgid

Simuleerida doosiga 0,33 µg/kg/min milrinooni aja-kontsentratsioonikõverad enneaegsetel vastsündinutel PDA ligeerimise järgselt

Leida optimaalne milrinooni annus enneaegsetele vastsündinutele südamepuudulikkuse ärahoidmiseks PDA ligeerimise järgselt

Meetodid

Simuleeritud milrinooni aja-kontsentratsiooni kõverad 1000 subjektile kasutades Paradisise kirjeldatud ühekambrilise populatsiooni farmakokineetika (FK) mudeli parameetreid (jaotusruumala, kliirens)[3] ja retrospektiivselt kogutud 2012.-2014. aastal PDA ligeerimise operatsiooni läbi teinud Eesti patsientide demograafilisi andmeid.

Soovitud kontsentratsioonivahemik 150-200 µg/L

Tulemused

31 vastsündinut

mediaan (min-max) GV 26 (23-35) nädalat, SK 760 (500-2351)g, vanus 13 (3-29) p

0,33 µg/kg/min – terapeutilises kontsentratsioonivahemikus 3 tunniga 0% ja 6 tunniga 36% subjektidest; 18 tunni pärast milrinooni plasmakontsentratsioon 99% subjektidest > soovitud vahemiku

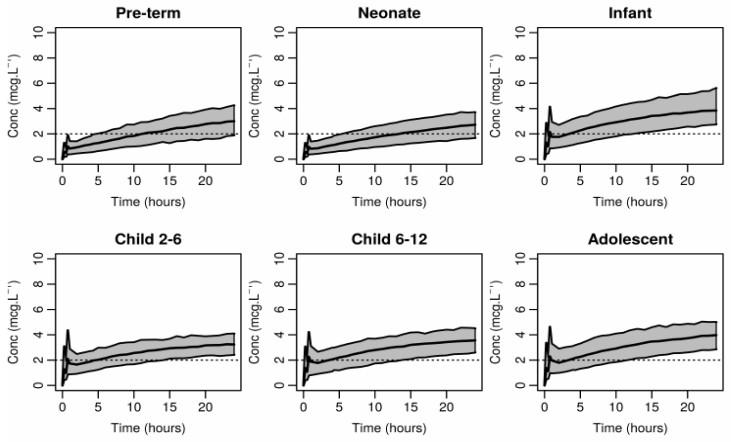
Eesmärk tagatud enim: 3 tunnine boolusinfusioon 0,73 + säilitusinfusioon 0,16 µg/kg/min.

Kokkuvõte

Olemasolevate FKFD andmete alusel tuleks optimaalsema aja-kontsentratsiooni profiili saavutamiseks enneaegsetel vastsündinutel PDA kirurgilise sulgemise järgselt kasutada milrinooni doseerimisskeemi aeglase boolusinfusiooni ja väikeses doosis säilitusinfusiooniga. Soovitatud annustamisskeem vajab valideerimist prospektiivses kliinilises uuringus.

CloSed: A double blind, randomised, multicentre, active controlled, parallel-group, phase III trial to evaluate the efficacy, safety and pharmacokinetics of intravenous clonidine (hydrochloride) compared to midazolam for sedation in children from birth to less than 18 years of age.

Clonidine: $t_{1/2}$ 7.4-16.9h



Midazolam: $t_{1/2}$ 1.5-12h

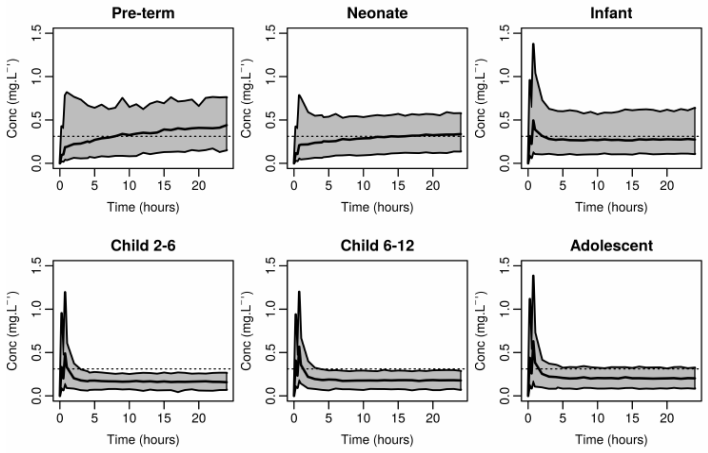
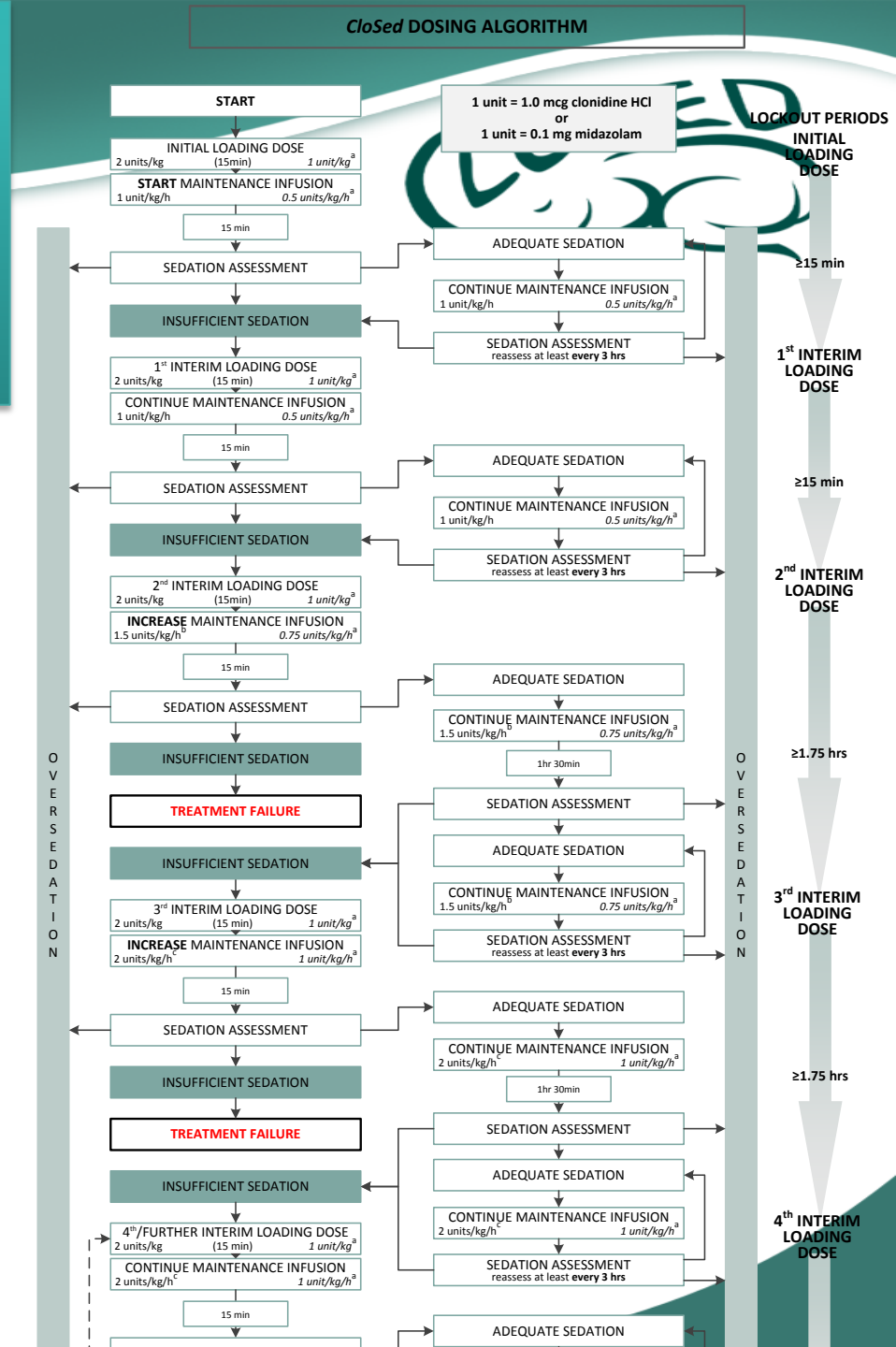


Figure 2: Simulated **clonidine (C) and midazolam (M)** concentration (90% prediction intervall) for patients with **lowest expected clearance – 2 loading doses**. Dose was C2/M200 mcg/kg loading dose (C1/M100 mcg/kg neonatal groups) followed by C1/M100 mcg/kg/h (C0.5/M50 mcg/kg/h neonates) for 15 minutes and second loading dose of C2/M200 mcg/kg (C1/M100 mcg/kg neonates) followed by C1/M100 mcg/kg/h (C0.5/M50 mcg/kg/h neonates)



Logistilised probleemid

- Diagnostika ja monitooring
- Uuringusse kaasamine
- Regulatoorsed nõuded (EMA/FDA, GCP)
  - Erinevused EU riikide regulatsioonides
  - Kõrvaltoimete ja –nähtude raporteerimine

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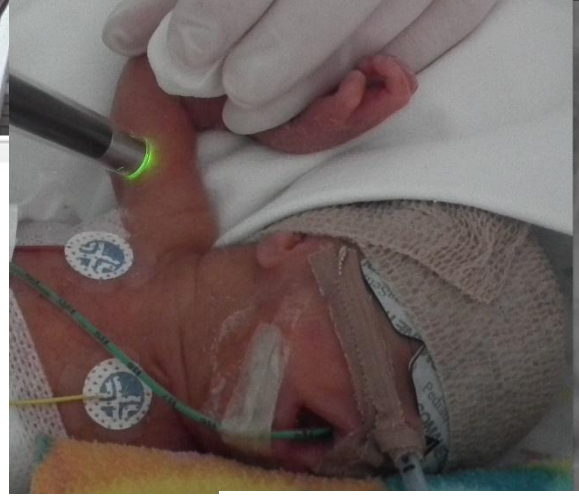
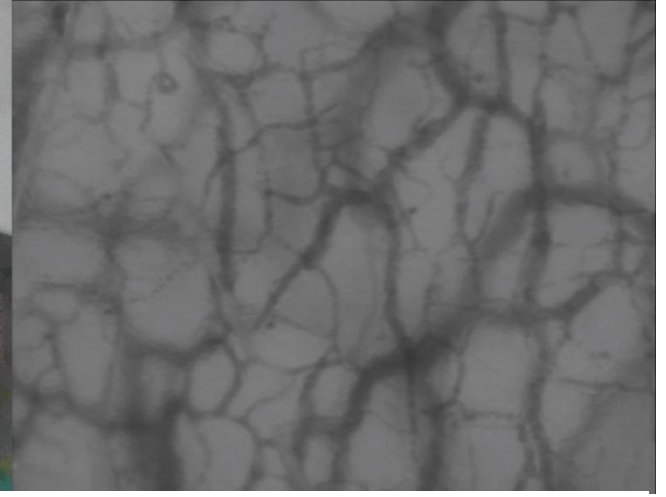
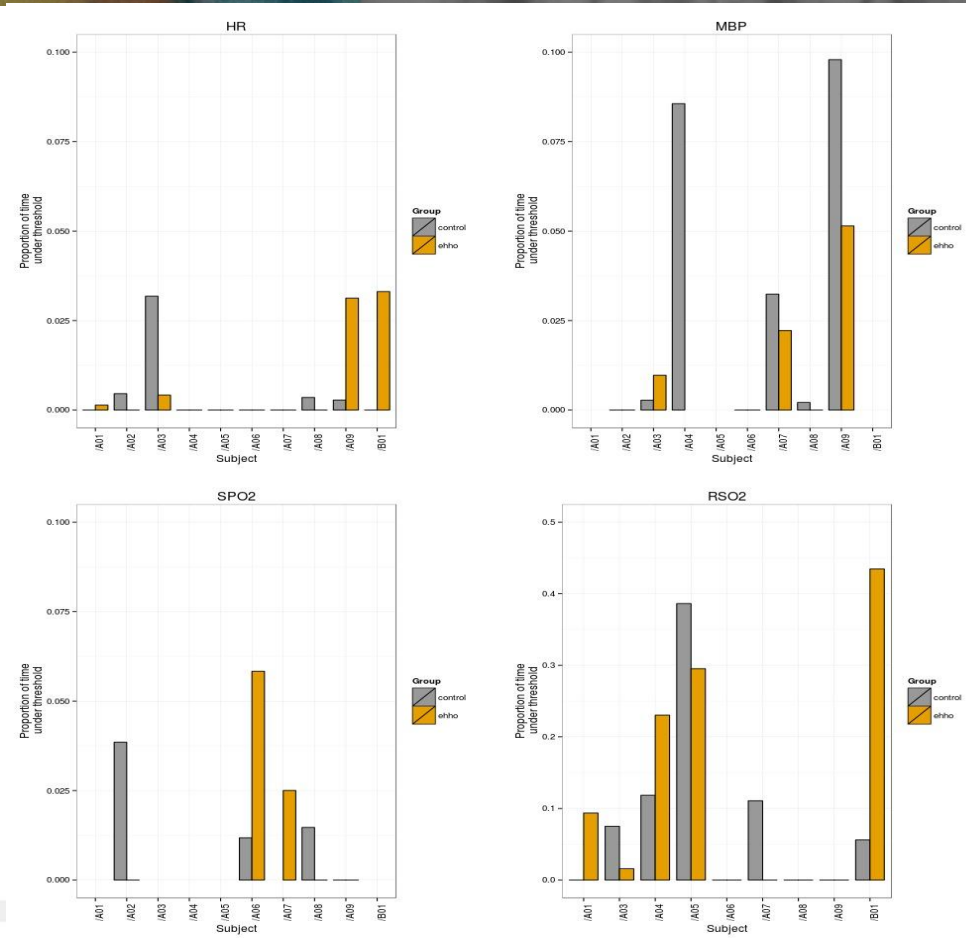




Diagnostika ja monitooring

Pilootuuring
10 EA vastsündinut mediaan (min-max) GV 26 (22-27), vanus 5 (2-17) t
HD: invasiivne vererõhk (BP), südame löögisagedus (HR), saturatsioon (SpO_2), aju regionaalne saturatsioon ($rScO_2$)
Südame UH x 2 48 tj, s.h. parema ja vasaku vatsakese väljutus (RVO, LVO), ülemise õõnesveeni vool (SVCF)
Mikrotsirkulatsioon (**videokapillaroskoopia**)



% aega väärtustega <kliiniliselt olulise lävendi (HR < 100 bpm, SpO2 < 85%, MBP< 30 mmHg, rScO2 <50%) UH ja kapillaroskoopia (kollane) vs eelenva 30 min jooksul (hall) oli sarnane

M Hallik et al. ESPNIC 2015

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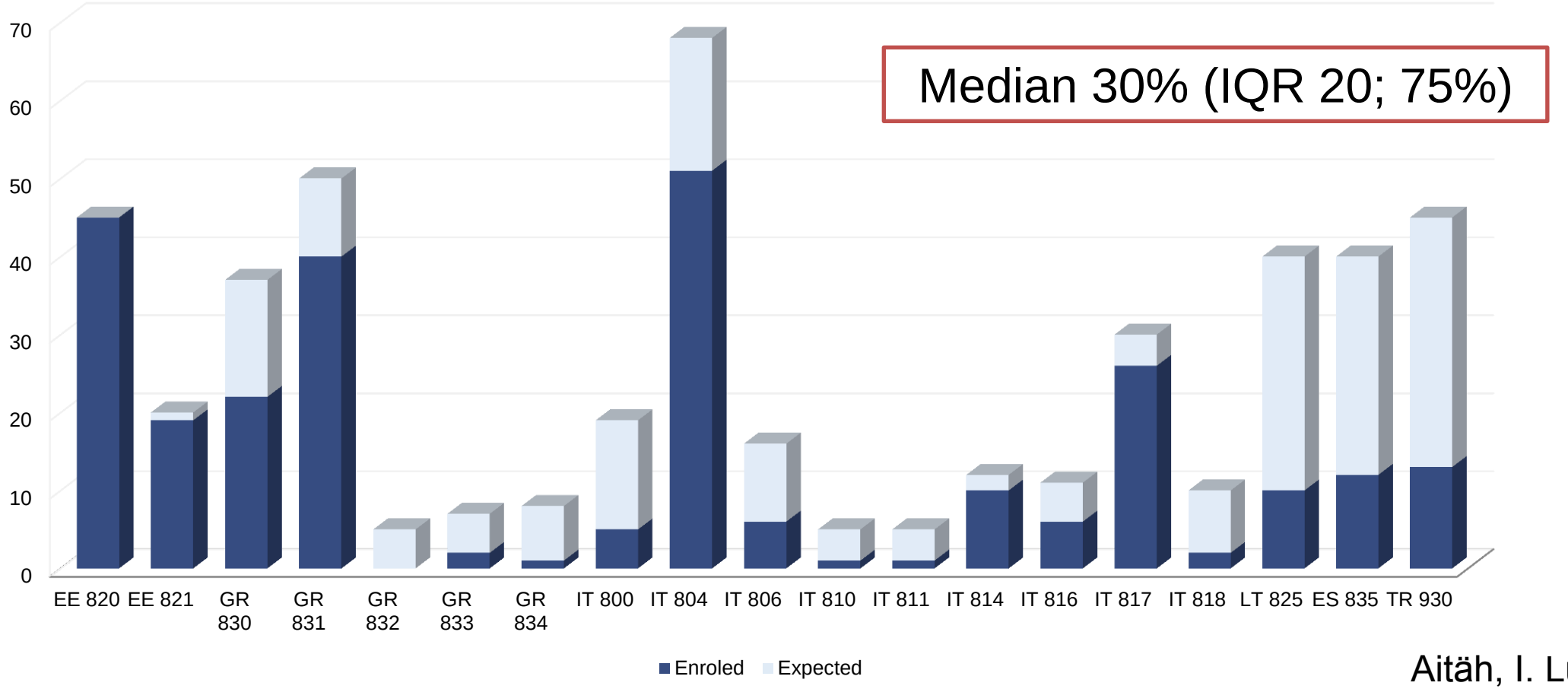
Recruitment: patients enrolled vs forecasted

NeoMero

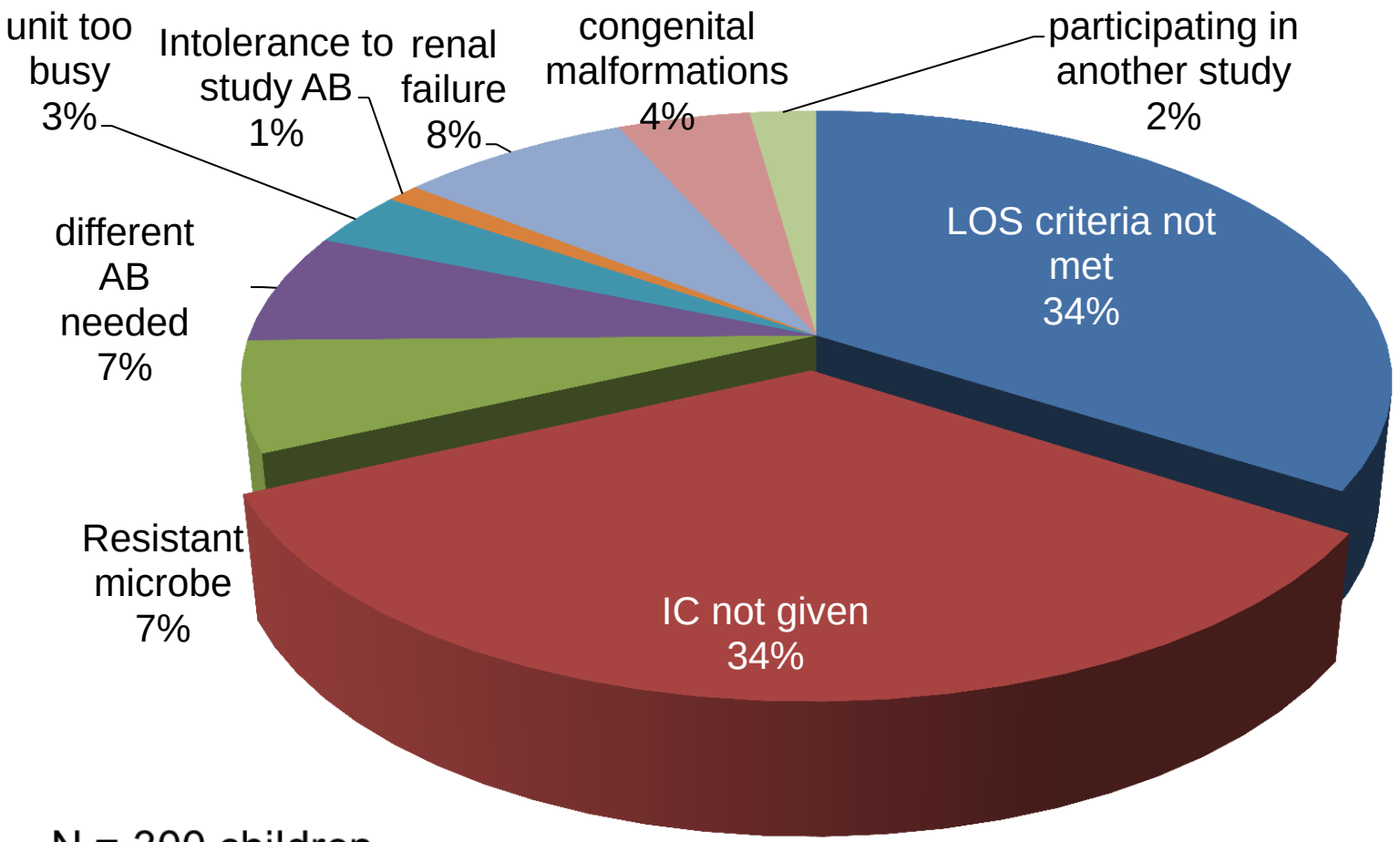
SEVENTH FRAMEWORK PROGRAMME



Median 30% (IQR 20; 75%)

Aitäh, I. Lutsar

Reasons for non-inclusion of patients



N = 300 children

Aitäh, I. Lutsar

CloSed protocol amendment 2.0 due to recruitment issues: exclusion criteria at Screening (Visit 1)

Removed

- Subjects who have already received clonidine as a sedative agent within the last 7 days prior to admission to PICU
- Subjects currently being treated with continuous positive airway pressure (CPAP)
- Subjects with acute asthma
- Subjects with paralytic ileus

Exclusion criteria at Screening (Visit 1)

Change of definition "Circulatory failure"

Despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 hr:

- Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age (see table 2 below)

OR

- ~~Need for vasoactive drug to maintain BP in normal range (dopamine >5 mcg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)~~

OR

- Two of the following:
  - Unexplained metabolic acidosis: BE <-5 mmol/L
  - Increased arterial lactate > twice the upper limit of normal
  - Oliguria: urine output <0.5 mL/kg/hr
  - Capillary refill > 5 secs
  - Core-to-peripheral temperature gap > 3 °C

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Regulatoorsed nõuded: kõrvaltoimete ja –nähtude raporteerimine

neoVanc

Multi-centre randomised open label phase IIb study to compare the efficacy, safety and pharmacokinetics (PK) of an optimised dosing to a standard dosing regimen of vancomycin in neonates and infants aged ≤ 90 days with late onset bacterial sepsis known or suspected to be caused by Gram-positive microorganisms

Anticipated serious adverse events defined in the table below will be recorded and reported in the e-CRF, but are exempt from expedited reporting to the Sponsor and regulatory bodies as they are anticipated in this high risk population[63].
If an Investigator believes that one of these events is causally related to vancomycin then would be a SUSAR and requires expedited reporting.

SERIOUS ADVERSE EVENT	ESTIMATED INCIDENCE
Necrotising enterocolitis (diagnostic radiological/surgical changes)	15%
Intracranial abnormality on cranial ultrasound scan (parenchymal haemorrhage or focal white matter injury)	15%
Ventilator dependency (28 days) and/or oxygen dependency (36 weeks CGA)	65%
Patent ductus arteriosus medical or surgical management	25%
Retinal surgery for retinopathy of prematurity	5%
Pulmonary haemorrhage	5%
Infection (positive blood culture with clinical signs)*	65%
Persistent derangement of liver function tests (36 weeks CGA)	10%
Serious extravasation injury (permanent scarring and/or/joint deformity)	< 5%

* Both infections other than condition for inclusion in trial and, in case of infections linked to the sepsis episode that is the reason of the participant's inclusion in the trial, worsening (e.g. septic shock) and relapse.

Eetilised küsimused vastsündinute kaasamisel kliinilistesse uuringutessse

- Haavatav grupp – riski hindamine
  - Uuritavast vahendist/ravimist
  - Uuringu protseduuridest
- Ägedad seisundid – kiire sekkumise vajadus
  - Informeeritud nõusolek

Inimõiguste ja biomeditsiini konventsioon: inimõiguste ja inimväärikuse kaitse bioloogia ja arstiteaduse rakendamisel

V peatükk TEADUSUURING; **Artikkel 17. Nõusoleku andmiseks võimetu isiku kaitse**

1. Isikut, kes ei ole võimeline andma artiklis 5 ettenähtud nõusolekut, võib uurida üksnes siis, kui:
   - [teadusuuringu üldnõuded] on täidetud;
   - on tõenäoline, et uuringu tulemused **toovad tema tervisele otsest ja tuntavat kasu;**
   - võrdväärselt tulemuslikku **uuringut ei ole võimalik teha isikule, kes on võimeline andma uuringuks nõusoleku**;
   - [isiku esindaja või seadusega ettenähtud isiku või asutuse või muu instantsi] **luba on antud kirjalikult ja kindla juhtumi kohta; ja asjaomane isik ei ole uuringu vastu**

https://www.riigiteataja.ee/akt/78570

Inimõiguste ja biomeditsiini konventsioon: inimõiguste ja inimväärikuse kaitse bioloogia ja arstiteaduse rakendamisel

2. Kui on tõenäoline, et uuringu tulemused ei too asjaomase isiku tervisele otsest kasu, võib erandkorras lubada uuringu teha juhul, kui rakendatakse seaduses ettenähtud kaitseabinõusid ning kui on täidetud lõikes 1 (…) loetletud nõuded ning järgmised lisatingimused:
   - uuringu eesmärk on isiku **seisundi, haiguse või puude** senisest märksa põhjalikuma **teadusliku käsitluse** kaudu **aidata kaasa tulemuste saavutamisele**, mis oleksid **kasutatavad** nii **asjaosalise enda** kui ka **teiste** samasse vanuserühma kuuluvate või sama haiguse või tervisehäire all kannatavate või samasuguses seisundis olevate isikute **huvides**
   - uuring on asjaosalisele isikule ainult **minimaalselt ohtlik ega koorma** teda liigselt

https://www.riigiteataja.ee/akt/78570

Levels of risk accepted in paediatric population

I. Minimal risk with benefit for the individual or benefit for the group.

II. Minor increase over minimal risk, with benefit to the individual or benefit to the group, and with the benefit to risk balance being at least as favourable as that of available alternative approaches.

III. Greater than minor increase over minimal risk with benefit for the individual that is especially favourable in relation to any available alternative approaches for the individual's condition.

Mitmekeskuseline topeltpime III faasi uuring: klonidiini vs midasolaami laste sedatsiooniks LIROS

Risk assessment: CloSed (Clonidine for Sedation of Paediatric Patients in the Intensive Care Unit *FP7-HEALTH-2013-INNOVATION-1)*

Novel treatment modality in very vulnerable paediatric patients

- Minor increase over minimal risk
  - Study drug – off-label use in PICU; included in paed sedation guidelines
  - Blood sampling
- Prospect of direct benefit or monitoring procedure(s) likely to contribute to the subject's well-being
  - Reduced doses of sedatives and analgesivs
  - Assumed favourable side effect profile

Limiting procedural risks

- Minimal amount of distress and discomfort
  - Indwelling lines in place
  - Non-medicamentous analgesia
  - Local anaesthetics
  - Venepuncture vs heel lancing [2]
  - Align with clinical samples
- Trial related blood loss must not exceed 3% of the total blood volume during a period of 4 weeks and 1% at any single time [1]
  - Analysis method development for minimum sample volumes (50 mkl)
  - Optimal design for most informative sampling times

Adequate volume to allow meaningful analysis

[1] Ethical considerations for clinical trials on medicinal products conducted with the paediatric population, EMA, June 2008; [2] Larsson BA et al. Venipuncture in more effective and less painful than heel lancing …. in neonates. *Pediatrics*. 1998;101(5):882–886.

Protseduuri riskid: verekaotus

500-grammine vs: RVM ca 50 ml!
3% RVM = 1,5 ml

Retrospektiivne kohort-analüüs
VLBW vastsündinud:
sünnikaal <1200g; GA <28 weeks

PK uuring
7 vereproovi kokku max 2,3 ml 12 tj
uuringugrupp: 18 neonates
kontrollgrupp: 35 neonates

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

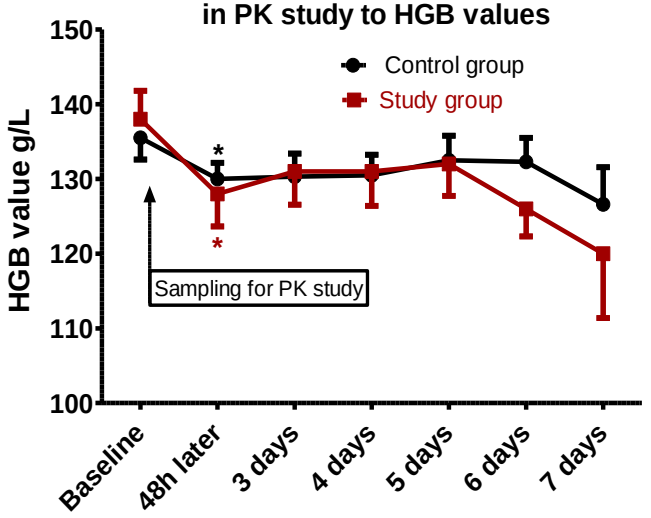
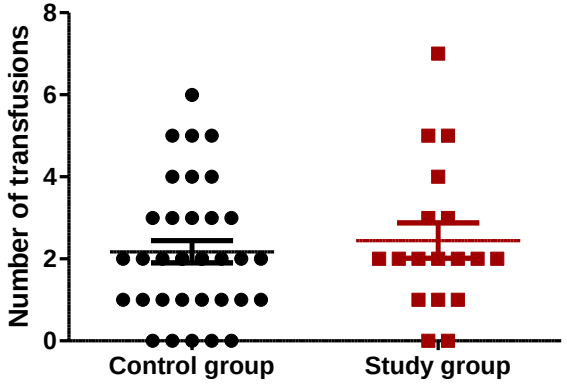


Figure 3. Number of transfusions during follow-up period



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

Informeeritud nõusolek – spetsiifilised probleemid

- Kriitiline seisund, kohene interventsiooni vajadus
  - Emotsionaalne stress vs ajaline surve
  - Vanema(te) kättesaadavus
  - Kompleksne informatsioon
- Erinevused EU riikide regulatsioonis

Informed consent – practical approach

- parental/legal guardian's consent prior to procedure/surgery likely requiring PICU admission and sedation.
- deferred and ongoing consent/assent of the patient together with informed consent of the parents / legal guardian.

ALBINO

DECLARATION OF INTENT

(to attach to the maternal health passport)

We

Name Mother (surname, first name)

Name Father (surname, first name)

have taken note of the above mentioned study and

[_] we deny participation of our child

[_] we can imagine to agree to the participation of our child in the unlikely emergency of oxygen deficiency during birth.

We have understood that in case of such an emergency, detailed information can only be given after administration of the first dose of study medication. Thereafter, we will have enough time to discuss and think about whether to agree to let our child further participate in this study. We have taken note that we can find more information on the study on www.albino-study.eu

Date

Signature (Mother & Father)

TRIAL SUPPORTED BY

Hypothermienetzwerkes Dresden

Headed by:
Prof. Dr. med. M. Rüdiger
Fetscherstraße 74, 01307 Dresden, Germany

IN CLOSE COOPERATION WITH

Center for Pediatric Clinical Studies (CPCS)

CPCS Kinderklinik Tübingen

Headed by:
Dr. biol. hum. C. Engel
PD Dr. med. J. Riethmüller
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Frondsbergstraße 23, 72070 Tübingen, Germany

CONTACT:
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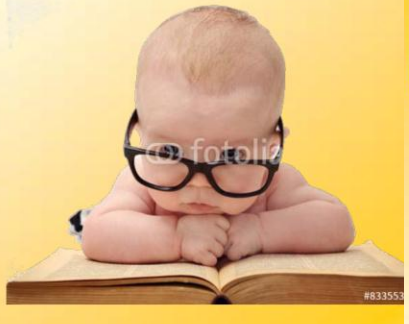
ALBINO

Effect of Allopurinol in addition to hypothermia for hypoxic-ischemic brain injury on neurocognitive outcome

FOR THE RARE CASE OF EMERGENY…
Please inform yourself now!

A European Trial to detect a possible reduction of brain damage by Allopurinol in children with oxygen deficiency during birth



Dear parents to be!
Despite best prenatal care and monitoring during delivery, 1-4 per 1000 births are complicated by insufficient oxygen supply to the newborn's brain.

At this hospital, a well-known drug used for adults is currently being tested in these emergency cases in newborns because it may reduce brain damage.

ALBINO

FOR THE RARE CASE OF EMERGENY …
Please inform yourself now!!

Has this drug already been used for newborns?
Tests performed on animals and preliminary studies involving a total of 196 newborns **suggest remarkable benefit and no severe side effects.**

Who is financing this study?
This study is financed by the **European Commission** and supported by **your pediatricians**.

Where can I get further information?
Visit us at the following page:
www.albino-study.eu

If in case of emergency your child shall not participate in this study, please IMMEDIATELY INFORM your midwife or physician! and fulfill the 'DECLARATION OF INTENT' on the back of this flyer!

Why is informed consent immediately after birth not possible?
The drug must be administered immediately after birth which is why **in case of emergency there is no time for detailed informed consent discussions** or for the parents to take a well-considered decision. Therefore and because of the expected benefit and the low risk, the ethics committees and the National Regulatory Authority approved that **in babies concerned the first dose of the medication is administered immediately after birth – before the parents could have given written consent as usual.**

Best wishes for you and your baby!

CONTACT:
Info.Albino@med.uni-tuebingen.de

OR
VISIT OUR HOMEPAGE
under

www.albino-study.eu

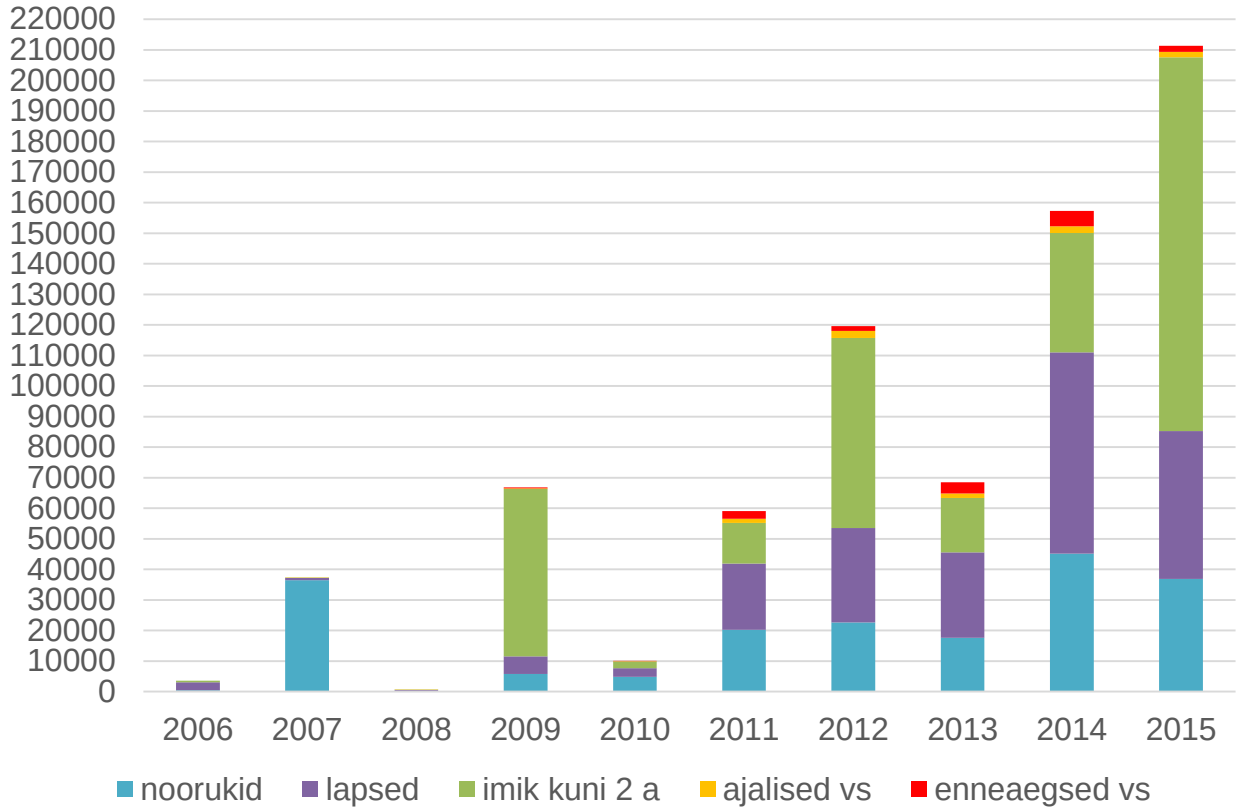
Veel võimalusi:

- Lühike suuline nõusolek
- „broadcasting“ + opt-out võimalus

Vastsündinuid kaasatakse uuringutesse vähe

2006-2015 laste kliinilised uuringud moodustavad kõikidest kliinilistest uuringutest 7-18% (2015)

Number of children planned to be enrolled in clinical trials, by age by year of authorisation (or, if not available, by year of protocol upload into EudraCT).

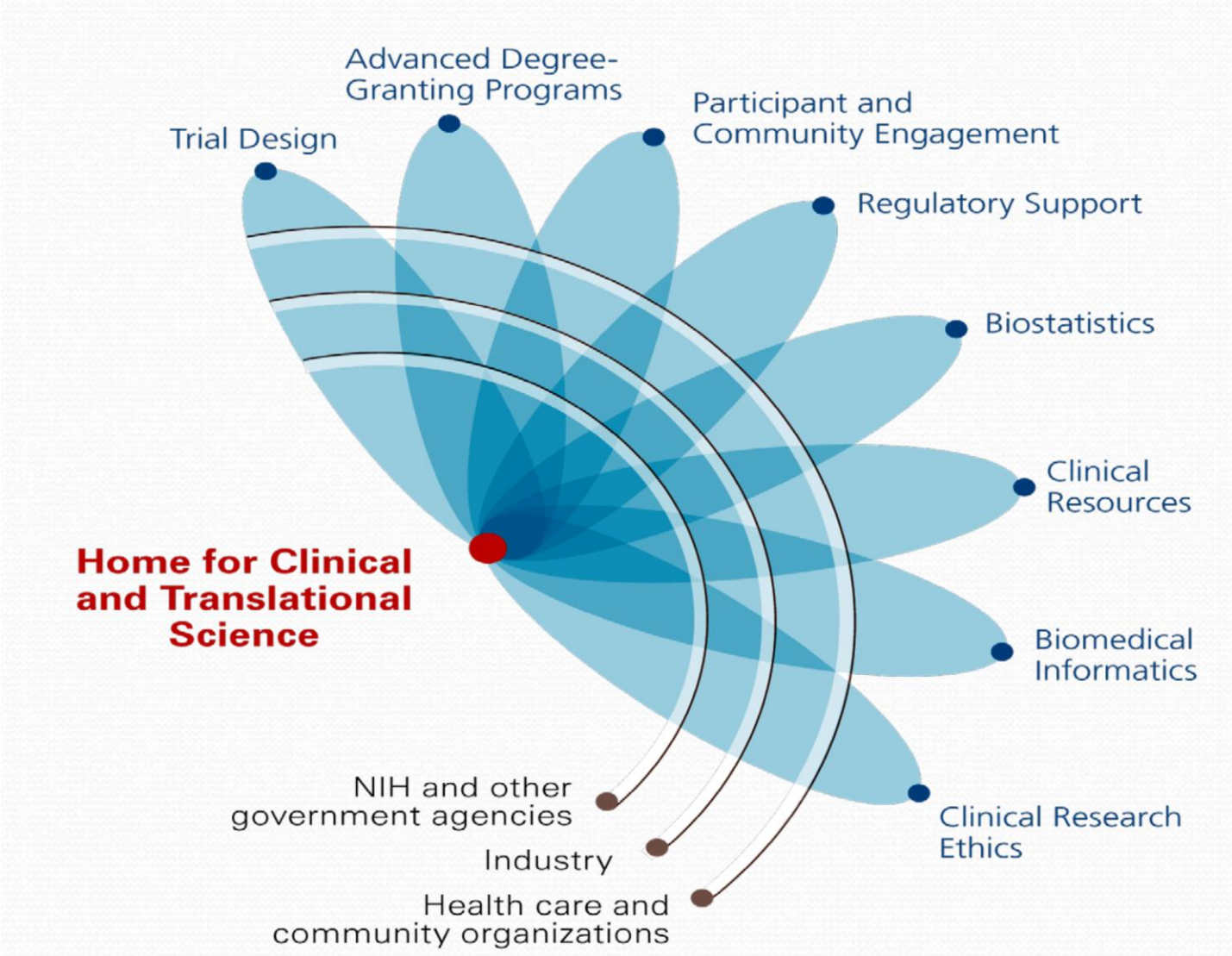


https://ec.europa.eu/health/sites/health/files/files/paediatrics/2015_annual_report.pdf

Kuidas edasi?

Kõik osapooled peavad mõistma ja toetama vastsündinute uurimise vajalikkust

- Regulatoorne raamistik
  - Lihtsustatud nõuded kasutuses olevatele ravimitele
  - Osalejate ja avalikkuse kaasamine
- Kompetentne ja motiveeritud meeskond
  - Akadeemilised CROd
  - võrgustumine
- Ressursid



Ootame lootusrikkalt uut regulatsiooni! Aitäh!