Akadeemilised kliinilised uuringud – kellele ja milleks?

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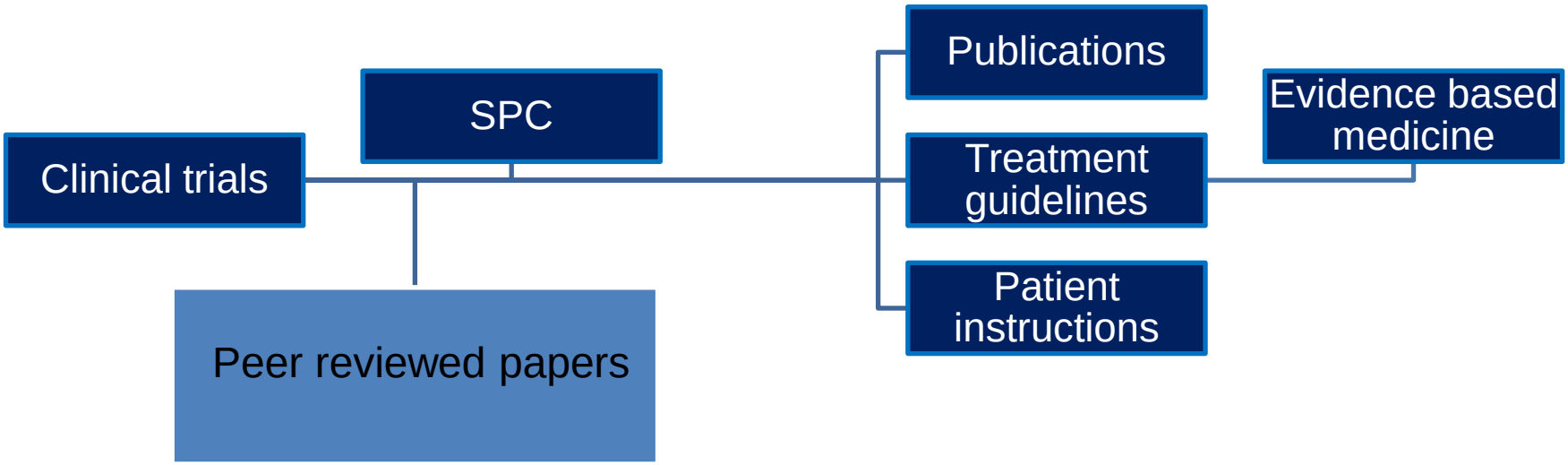
Tartu, 14. 06. 2017

Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing (Voltaire; 1694-1778)

Clinical trials form basis of evidence based medicine



Definitions

Clinical trials are prospective biomedical or behavioral research studies on human participants designed to answer specific questions about biomedical or behavioral interventions, including new treatments and known interventions that warrant further study and comparison.

An **academic clinical trial** is a clinical trial not funded by pharmaceutical or biotechnology company for commercial ends but by public-good agencies (usually universities or medical trusts) to advance medicines

wikipaedia

Registration vs academic trials

- **Registration trials (industry trials)**
  - Aim to bring new medicinal products into market
  - Phase 1 to Phase 3 studies
  - Performed by the pharmaceutical industry
  - Sponsored by the pharmaceutical industry

- **Academic clinical trials**
  - Aim to describe PK, efficacy of safety of marketed medicines (incl. off patent medicines) in special populations
  - Strategic trials
    - what is the best method for treatment
  - Endpoint validation
  - Initiated and conducted by the universities, hospitals, private consortia etc.
  - Sponsored by the government, charities, research grants, pharmaceutical industry

Outstanding issues of registration trials

- What will happen in everyday practice?
- Is the new method effective around the globe
- What will happen over time?
- Can every patient or health insurance programm afford new treatment?
- If the result is negative does this mean that new treatment cannot be used?
- What is the most appropriate patient group for a new treatment?
- Head to head comparison of a new treatment
- How to combine new treatment with existing one?

Doribax (doripenem): SPC

- The data of using Doribax in **immunocompromised patients** or in those **receiving immunosuppressive therapy** are limited because this population has been excluded from phase 3 trials
- Doribax is not recommended for patients **below 18 years** due to lack of efficacy and safety data in this population
- The data on using Doribax in patients **receiving haemodialysis** are limited to provide adequate dosing recommendations

Populations/situations excluded from registration trials

- Critically ill patients with end stage organ failure(s)
  - Renal failure requiring RRT
  - Liver failure requiring transplantation
  - Patients requiring resuscitation
- Children and adolescents, including neonates
- Patients with extreme obesity
- Patients with congenital and acquired immunodeficiency (HIV, chemotherapy etc.)
- Effectiveness and safety in real-life situations

All groups likely have different PK properties of those included to trials

Akadeemilised kliinilised uuringud – milleks?

- Ravijuhiste koostamiseks
- Missugune ravimeetod on parim?
- Missugune ravimite kombinatsioon on parim?
- Ravimi mõju ja kõrvalmõju väljaspool tavapopulatsioone
  - Immuunsuse häiretega haiged
  - Multimorbiidsusega ja polüfarmaatsiga haiged
  - Väga paksud ja väga kõhnad

Mai Blöndal's PhD thesis

(defended 18. January 2013)

Higher-risk patients are less likely to receive guideline recommended therapies ….

…

Another reason for this "risk-management paradox" is probably the fact that clinicians are concerned about applying evidence from clinical trials to their **everyday practice because trials tend to exclude older higher-risk patients**

Type of academic studies

- Observational studies
- Endpoint and biomarker validation studies
- PK/PD studies
- Interferences studies
  - Comparative efficacy/safety studies
    - Comparing different drugs or doses
  - Comparative management studies
    - Comparing one methods to the other

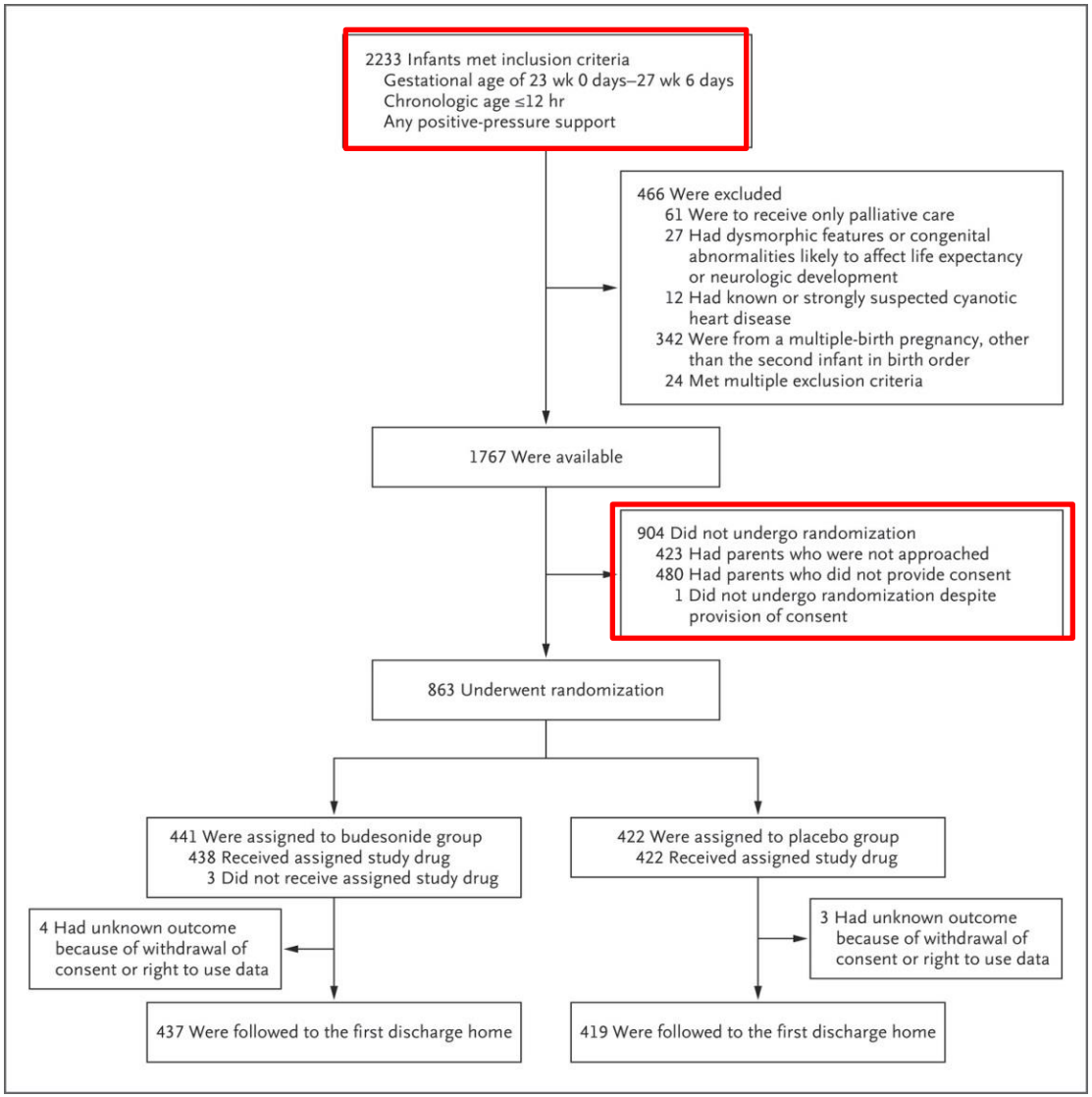
Akadeemilised uuringud ei pruugi anda lõplikke vastuseid

Neurosis study

- **Hypothesis**: Systemic glucocorticoids reduce the incidence of BPD among extremely preterm infants
- **Aim**: to define effects of inhaled glucocorticoids on outcomes in extremely preterm infants
- **Study design**: placebo controlled RCT (1:1), multicenter, multinational

Bassler D et al. N Engl J Med 2015;373:1497-1506.

Neurosis study flow



Bassler D et al. N Engl J Med 2015;373:1497-1506

Neurosis study main outcomes

Table 3. Primary Outcome.*

Outcome	Budesonide Group	Placebo Group	Unstratified Relative Risk (95% CI)	Stratified Relative Risk (95% CI)†	P Value	Odds Ratio (95% CI)‡
	no./total no. (%)					
Composite primary outcome	175/437 (40.0)	194/419 (46.3)	0.86 (0.74–1.00)	0.86 (0.75–1.00)	0.05	0.71 (0.53–0.97)
Components of primary outcome						
Death	74/437 (16.9)	57/419 (13.6)	1.24 (0.90–1.71)	1.24 (0.91–1.69)	0.17	1.39 (0.89–2.18)
Survival with bronchopulmonary dysplasia§	101/363 (27.8)	138/363 (38.0)	0.73 (0.59–0.90)	0.74 (0.60–0.91)	0.004	0.61 (0.44–0.85)
Primary outcome in subgroups						
Intubated at randomization						
No	29/136 (21.3)	48/132 (36.4)	0.59 (0.40–0.87)	0.61 (0.42–0.90)	0.01	0.48 (0.27–0.86)
Yes	146/301 (48.5)	146/287 (50.9)	0.95 (0.81–1.12)	0.94 (0.80–1.10)	0.45	0.84 (0.59–1.20)
Gestational age — wk						
23 wk 0 days to 25 wk 6 days	104/183 (56.8)	109/175 (62.3)	0.91 (0.77–1.08)			0.74 (0.48–1.15)
26 wk 0 days to 27 wk 6 days	71/254 (28.0)	85/244 (34.8)	0.80 (0.62–1.04)			0.72 (0.49–1.08)
Histologic chorioamnionitis¶						
No	55/137 (40.1)	66/143 (46.2)	0.87 (0.66–1.14)	0.89 (0.68–1.16)	0.40	0.75 (0.44–1.26)
Yes	33/90 (36.7)	32/76 (42.1)	0.87 (0.60–1.27)	0.86 (0.60–1.23)	0.42	0.63 (0.31–1.28)

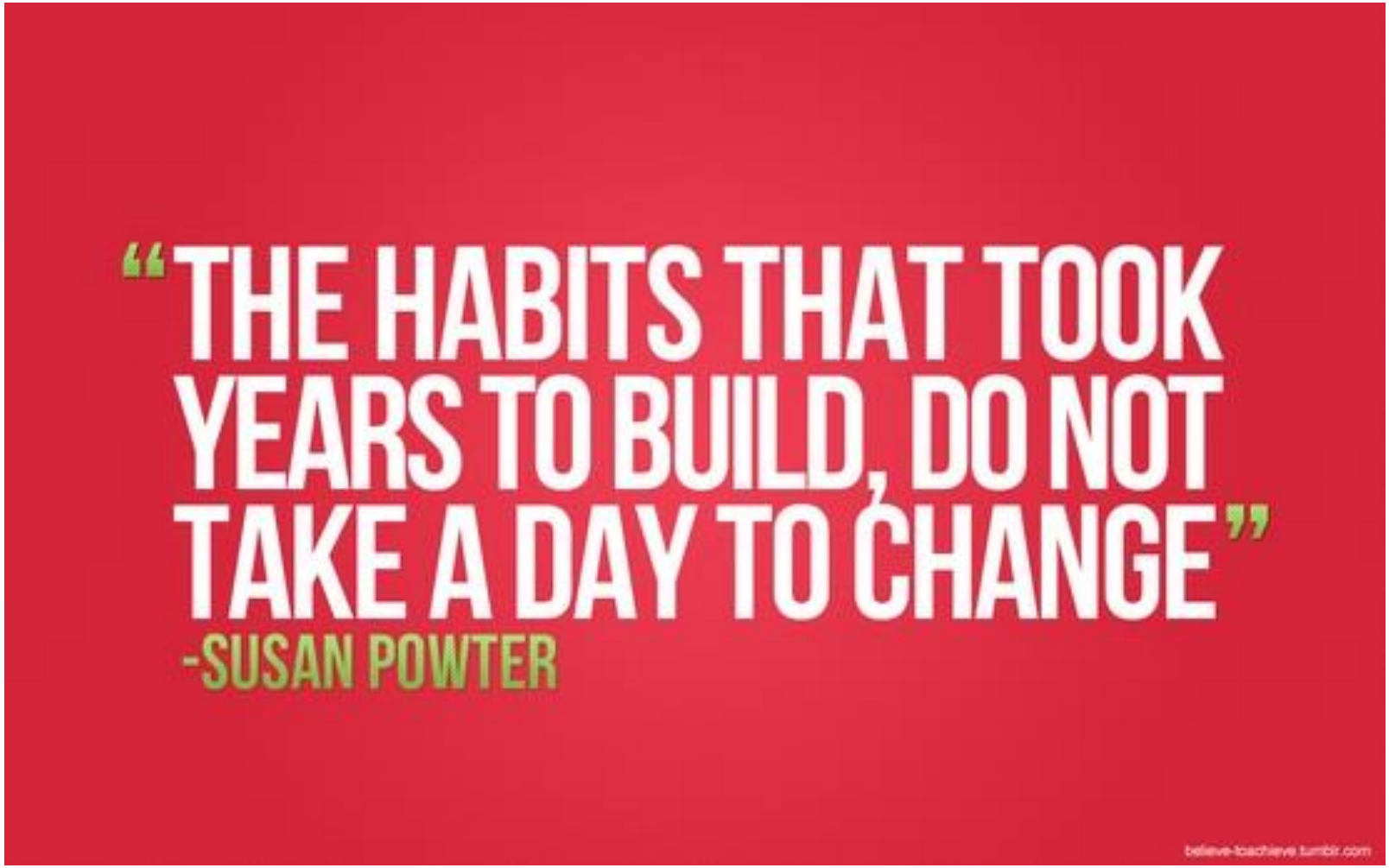
* The primary outcome was a composite of death or bronchopulmonary dysplasia at 36 weeks of postmenstrual age. CI denotes confidence interval.
† Stratification was performed for gestational age.
‡ Odds ratios were adjusted for the covariates of gestational age, intubation status, birth weight (<750 g vs. ≥750 g), and caffeine use with the use of logistic-regression analysis; details are provided in Table S5 in the Supplementary Appendix.
§ The component of bronchopulmonary dysplasia was assessed in 363 infants in each group who were alive at a postmenstrual age of 36 weeks. One infant in the placebo group died 1 day after bronchopulmonary dysplasia was diagnosed.
¶ Histologic examination was performed in 446 infants (227 in the budesonide group and 219 in the placebo group).

Bassler D et al. N Engl J Med 2015;373:1497-1506

Neurosis study conclusion

- Among extremely preterm infants, the incidence of BPD was lower among those who received early inhaled budesonide vs placebo, but the advantage may have been gained at the expense of increased mortality
- PK samples not collected
- **NEJM editorial** - *No End to Uncertainty about Inhaled Glucocorticoids in Preterm Infants*
- No change in clinical practice – business as usual

Akadeemiline uuringu tulemus võib olla üldarusaamade vastu

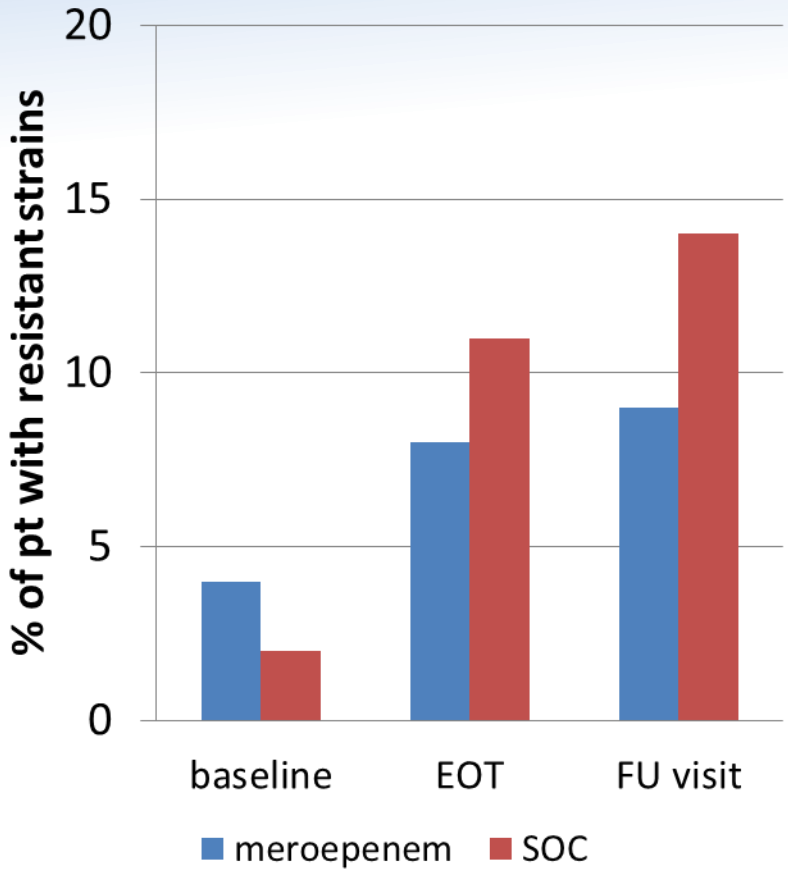


Neomero meropenem resistance story

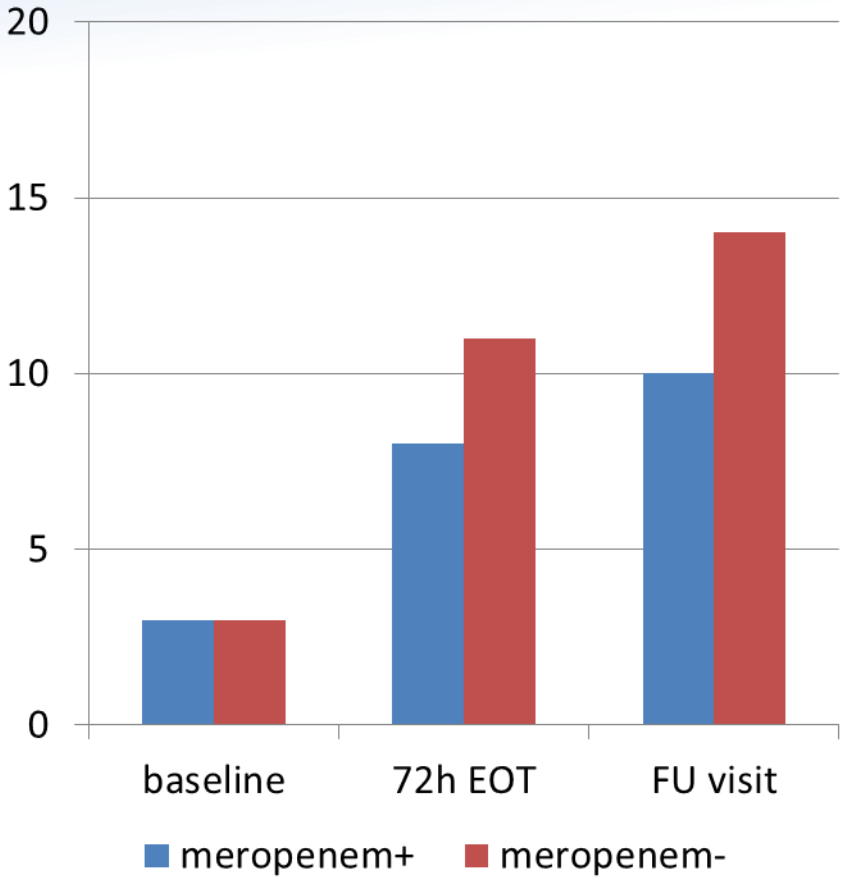
- Meropenem is a broad spectrum antibiotic
- Meropenem outselects meropenem/carbapenem resistant strains

Cumulative percentage of patients with CRGNO in rectal swab

Meropenem vs SOC



Meropenem yes vs no



CRGNO – carbapenem resistant Gram-negative organisms

NeoMero

SEVENTH FRAMEWORK PROGRAMME

Modern approach to academic clinical trials (1)

- Integrating academic clinical trials into everyday practice
  - Avoid double-reporting and transcribing
  - Coordinate clinical and study related sampling
  - Use electronic health records – from clinical database to study database (X-tee)
  - Accommodate study to clinical guidelines
  - Use of patient registries
  - Distance monitoring

NEJM

Clinical and Applied
Thrombosis/Hemostasis
1-6
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Safety and Efficacy of Bridging With Low-Molecular-Weight Heparin During Temporary Interruptions of Warfarin: A Register-Based Cohort Study

Vilhelm Sjögren, MD[1], Bartosz Grzymala-Lubanski, MD[1], Henrik Renlund, PhD[2], Peter J. Svensson, MD[3], and Anders Själander, MD[1]

In this large cohort of almost 15 000 bridging maneuvers, we found no benefit from LMWH bridging. About 1% of temporary interruptions of warfarin resulted in a complication requiring specialist care within 30 days. This might seem like a low

Modern approach to academic clinical trials (2)

- Use of modern technology
  - Apps for monitoring patients at home or from distance
  - Direct data entry from lab-databases and patients monitors
  - Electronic and distant analysis of clinical findings
  - ID-cards for signing ICF

Modern approach to academic clinical trials (3)

- Optimal study design
  - Adaptive design
  - Withdrawal/discontinuation design
  - SMART (Sequential multiple assignment randomized trial)
  - Patient preselection based on genes or biomarkers
  - Patient oriented „soft“ or surrogate endpoints
  - Optimal sampling
  - Modelling and simulations

SMART: each participant is randomised twice

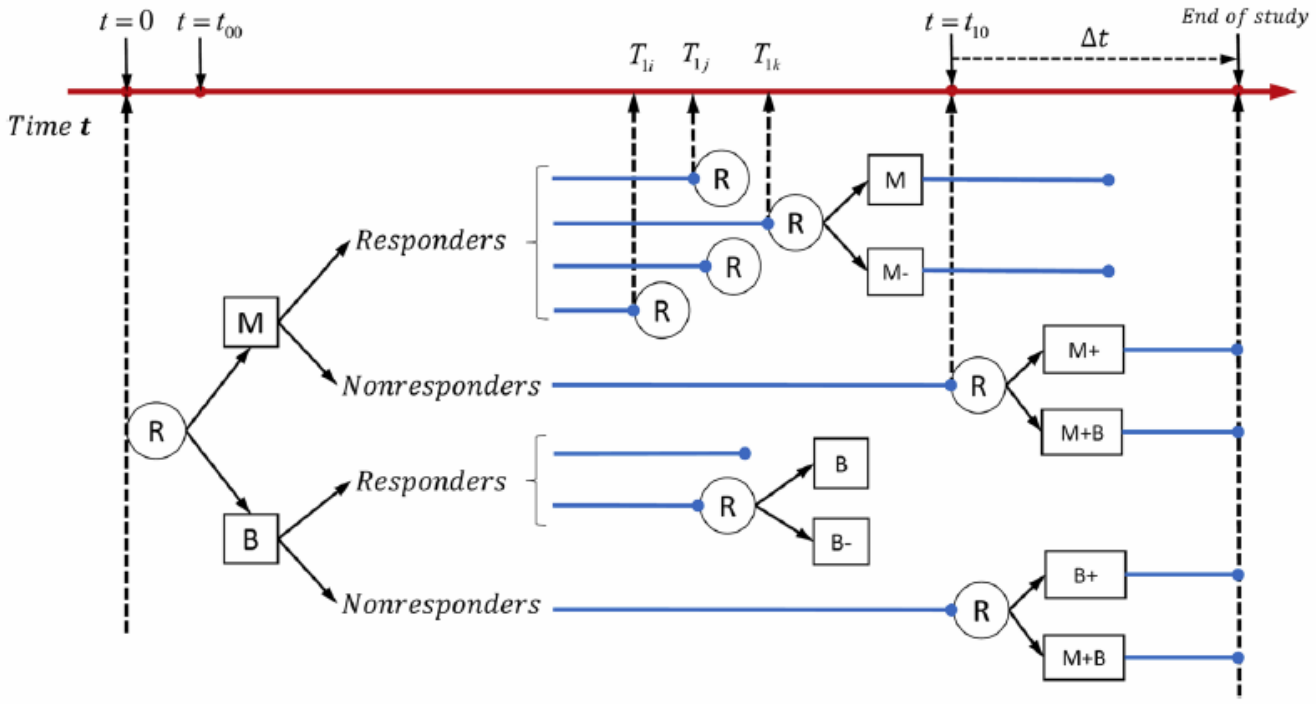


Fig. 1 Example of time-varying two-stage SMART design with equal probability allocation: each participant is randomized twice

Dai and Shete BMC Medical Research Methodology (2016) 16:112

SMART: Non-responders are re-randomised

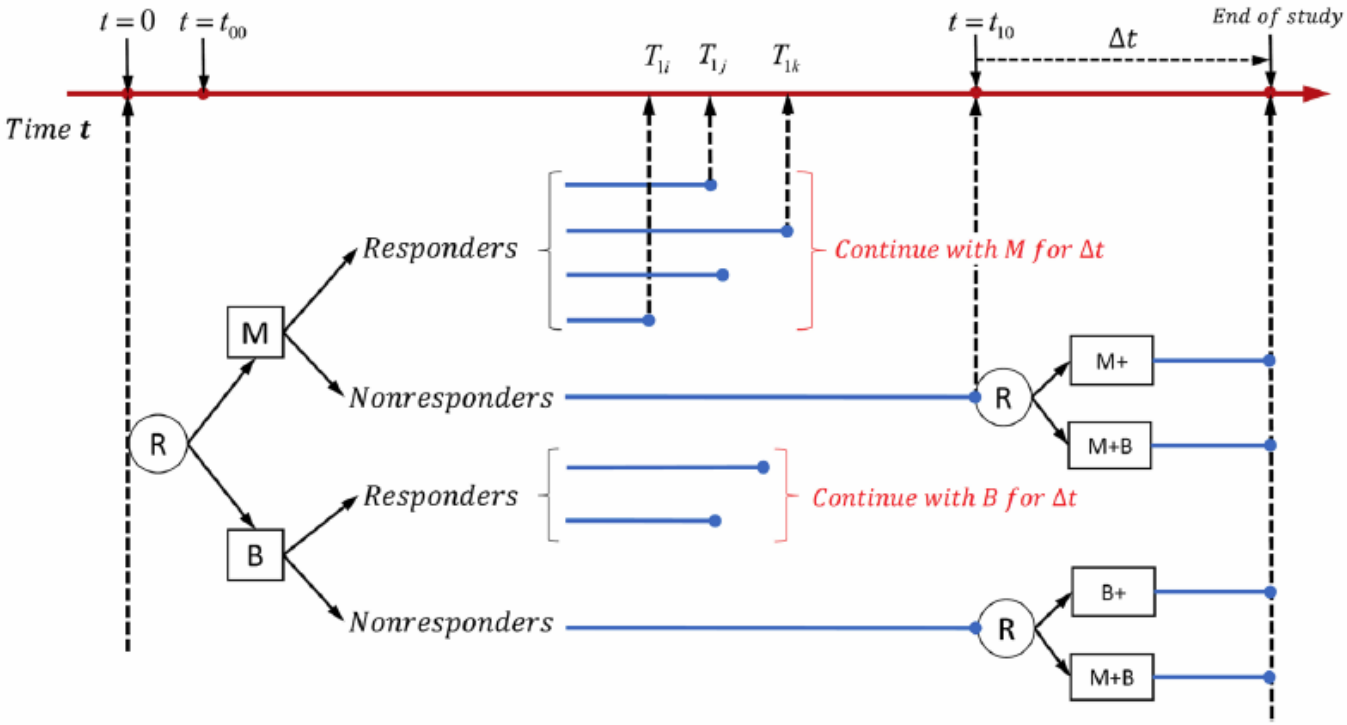


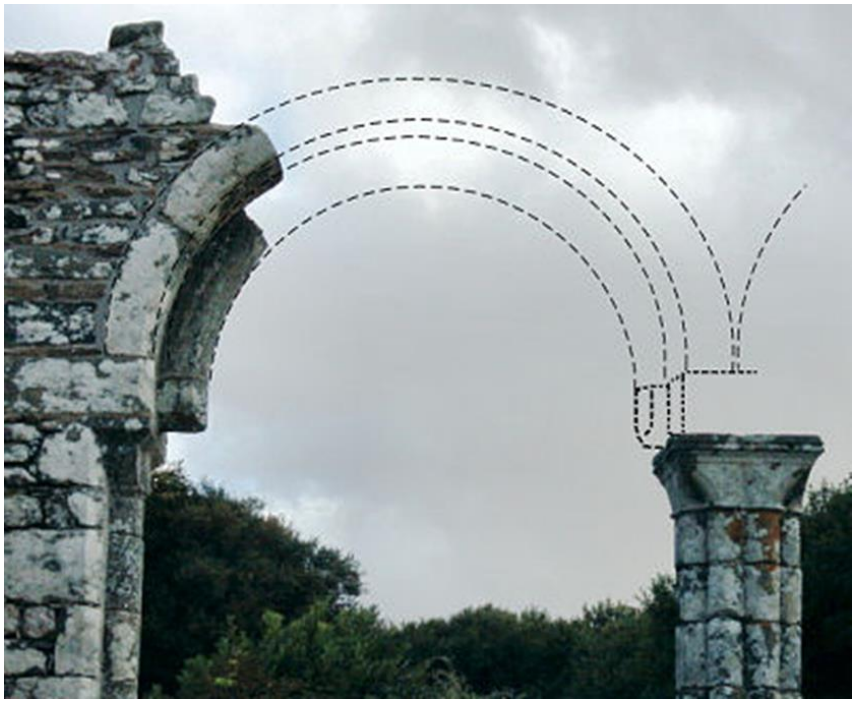
Fig. 2 Example of time-varying two-stage SMART design with unequal probability allocation: only non-responders are re-randomized in the second stage

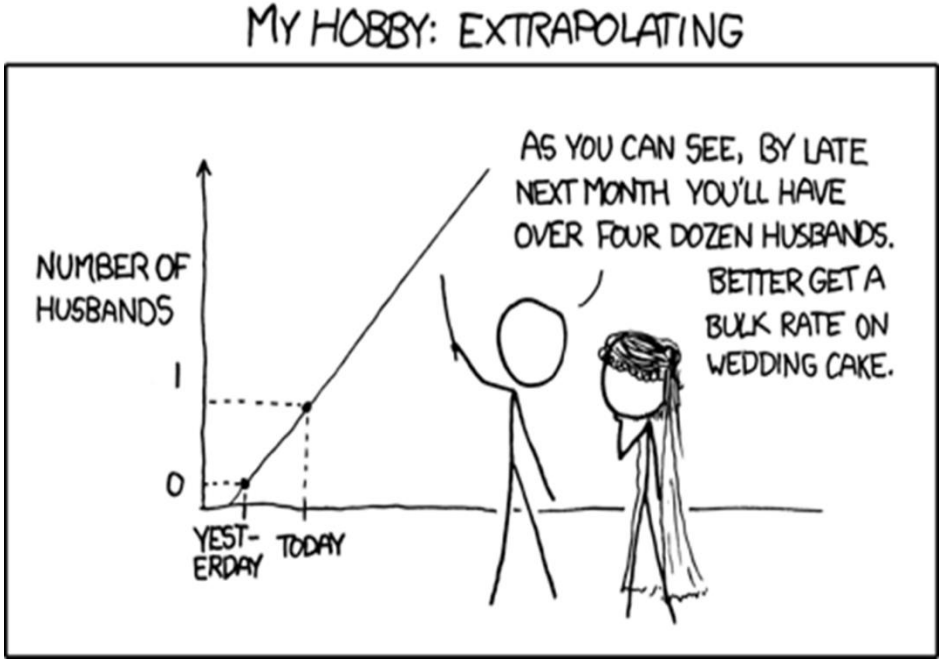
Dai and Shete BMC Medical Research Methodology (2016) 16:112

Modelling ja simulation ja extrapolation

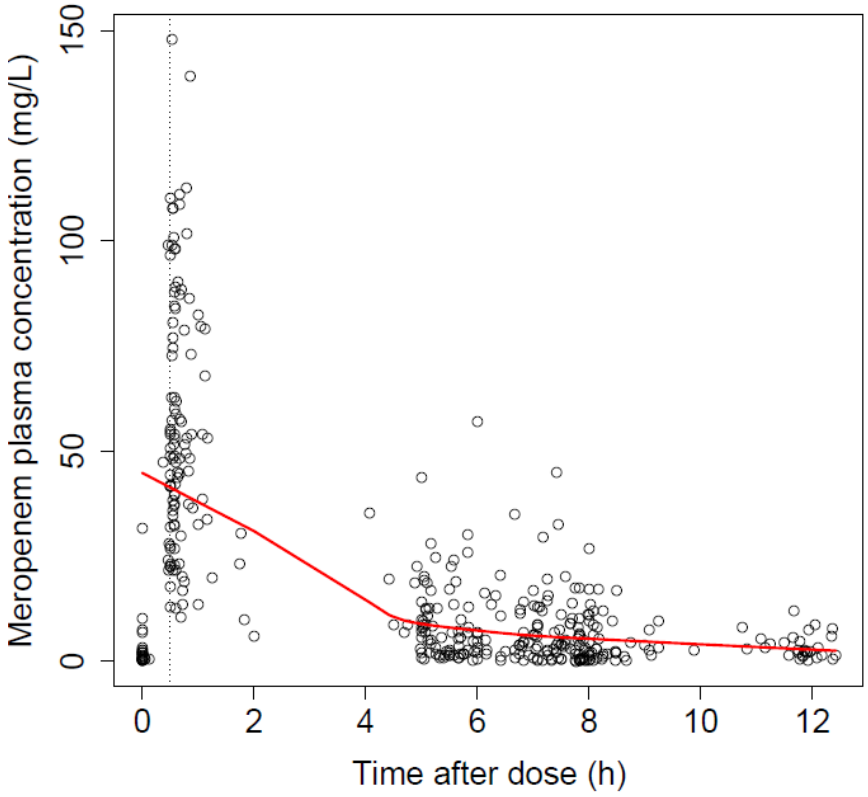
Jheronimus Bosch
Ennustaja

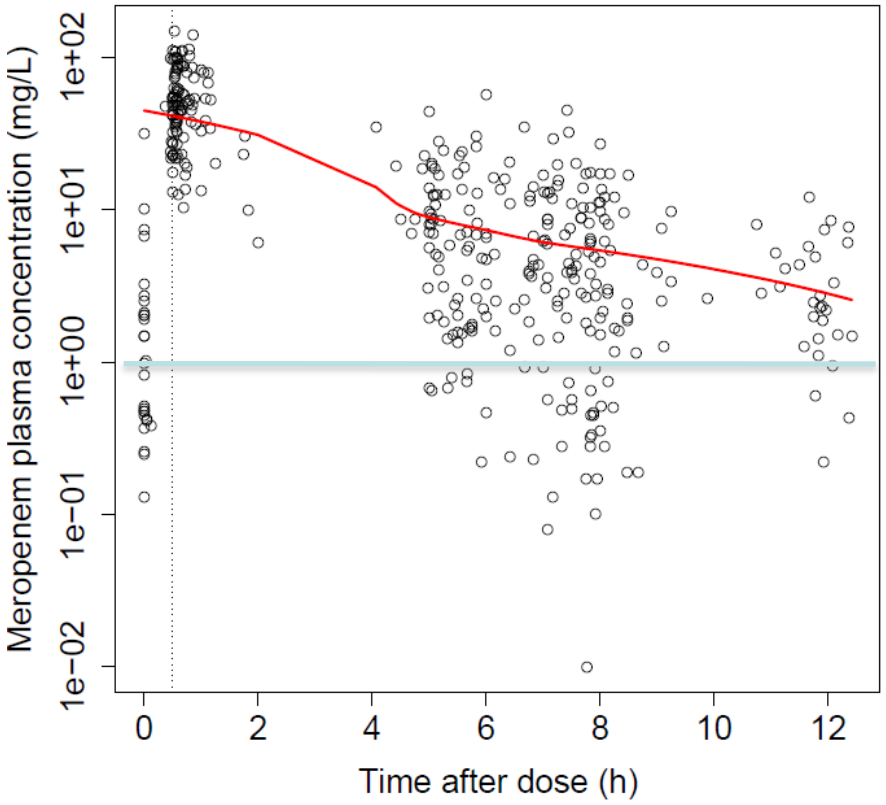
Extrapolation
all models are bad but might be useful



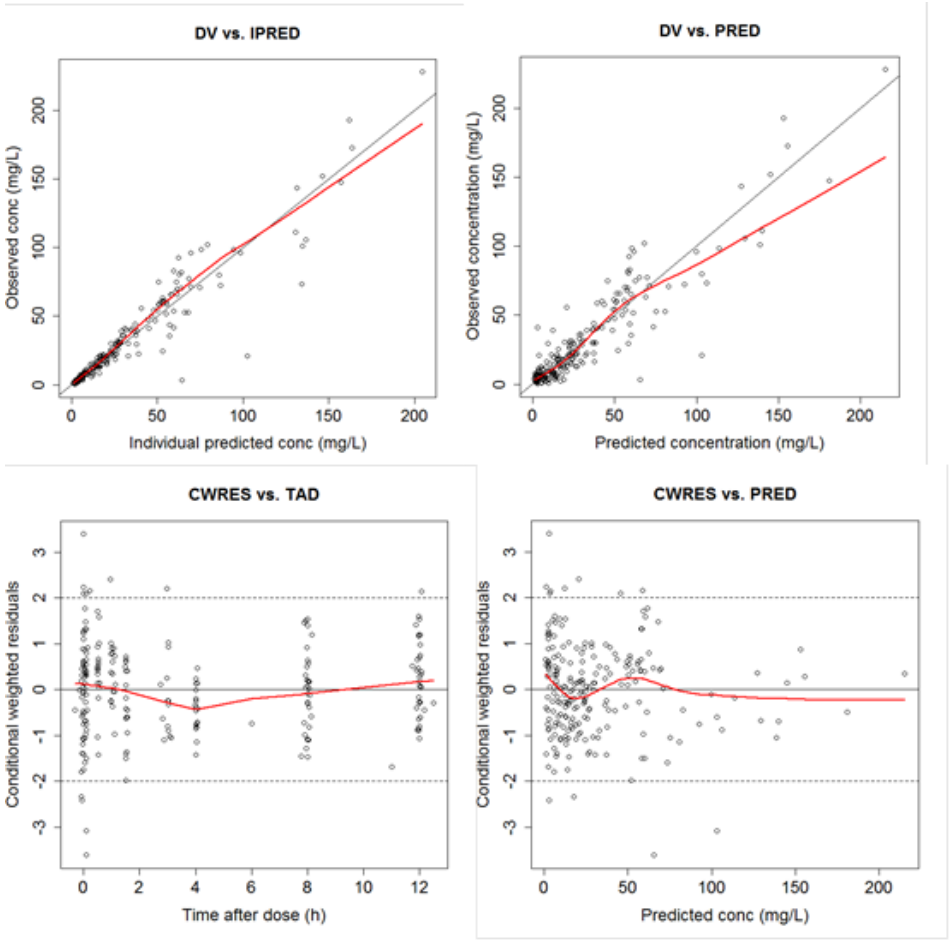


Meropenem levels: plasma (n = 401 samples and 167 patients)



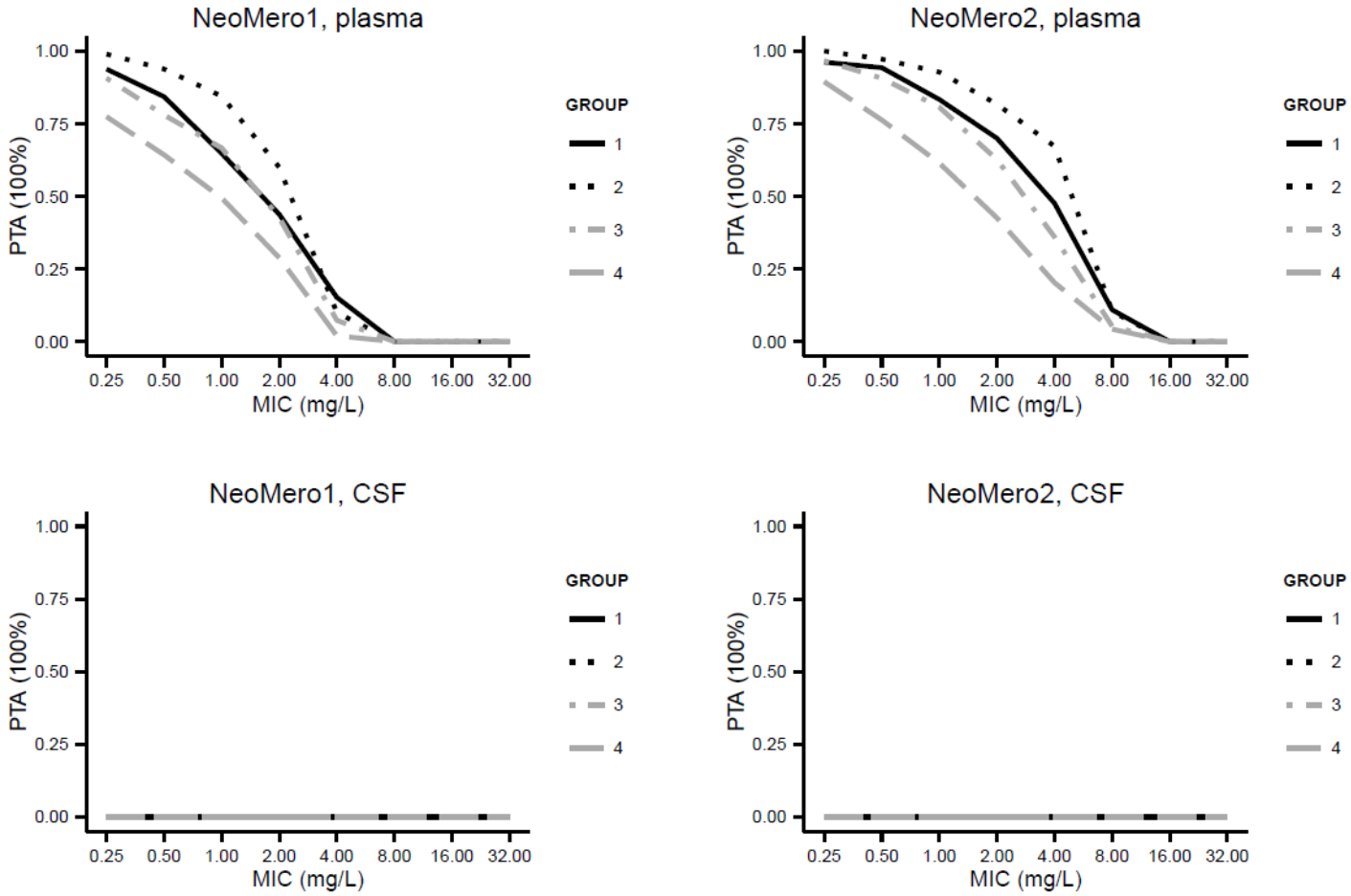


Basic goodness-of-fit plots from the final popPK model of penicillin G in neonates



DV: dependent variable; PRED: population prediction; IPRED: individual prediction; CWRES: conditional weighted residuals; TAD: time after dose

Probability of target attainment: 20/40, 0.5h #2



Group 4 q12h, other groups q8h

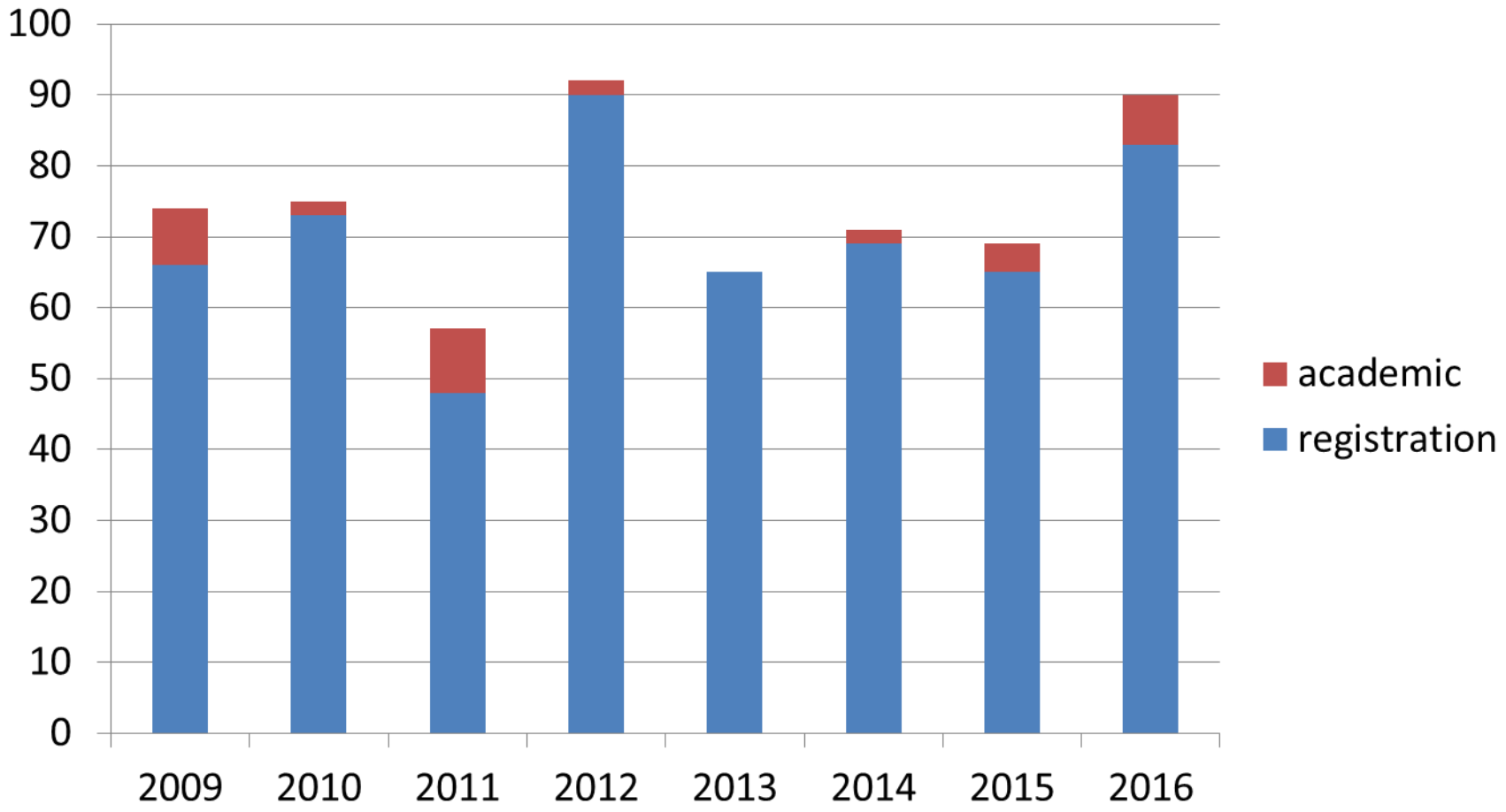
Stakeholders of academic clinical trials

- Hospitals, universities, researchers and institutions who view trials as **a source of income and prestige**, and receive private, charitable and governmental funding
- Pharmaceutical or biotech companies who view the **development and commercialization of treatments** as their business
- Regulators who wish to **ensure treatments are safe and work effectively**
- Patients and patients' organizations and associations who want **faster access to advanced treatments**
- Health insurance companies **who wish to get evidence based data**

Estonia as place of academic clinical research

- **Pro's**
  - A small country with well developed medical and patient tracking system
  - Hospitals are highly equipped
  - IT services should be available
- **Problems**
  - Low number of patients
  - Lack of supporting systems
  - Lack of training and qualified researchers
  - Moderate interest in clinical research

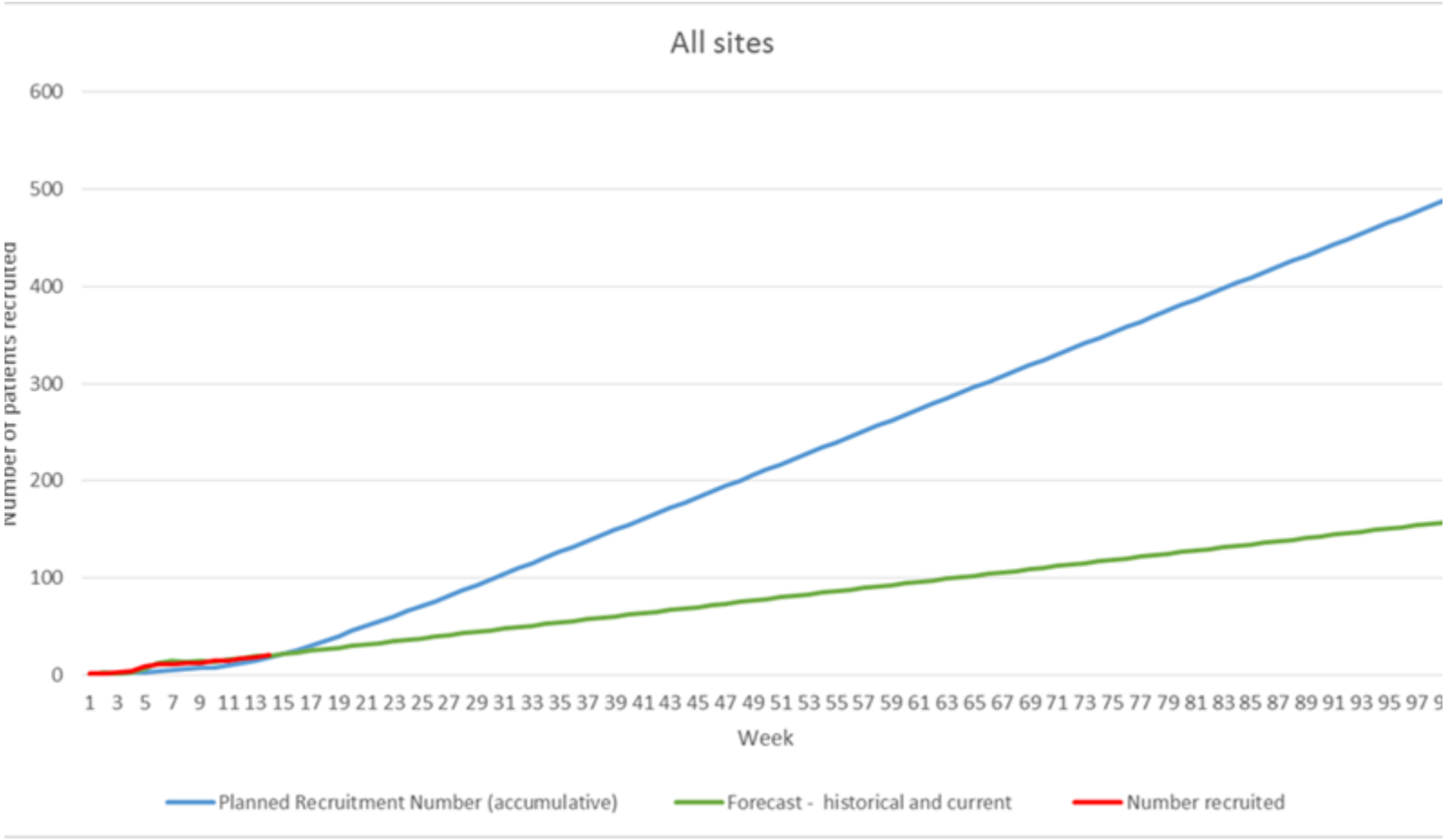
Academic vs registration trials in Estonia



Key points to consider

- Appropriate study population (disease definition)
  - Disease poorly defined
- Adequately powered
  - Too small trials do not have power
  - Too large trials – long-lasting, too many centres, too biased
- Appropriate endpoints and effect size
- Comparative rather than single arm studies
- Blinding and randomisation rather than single arm
- Modelling and simulations rather than large trials
- Modern world offers new opportunities rather than we always have done like this

Planning is a key



The End

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