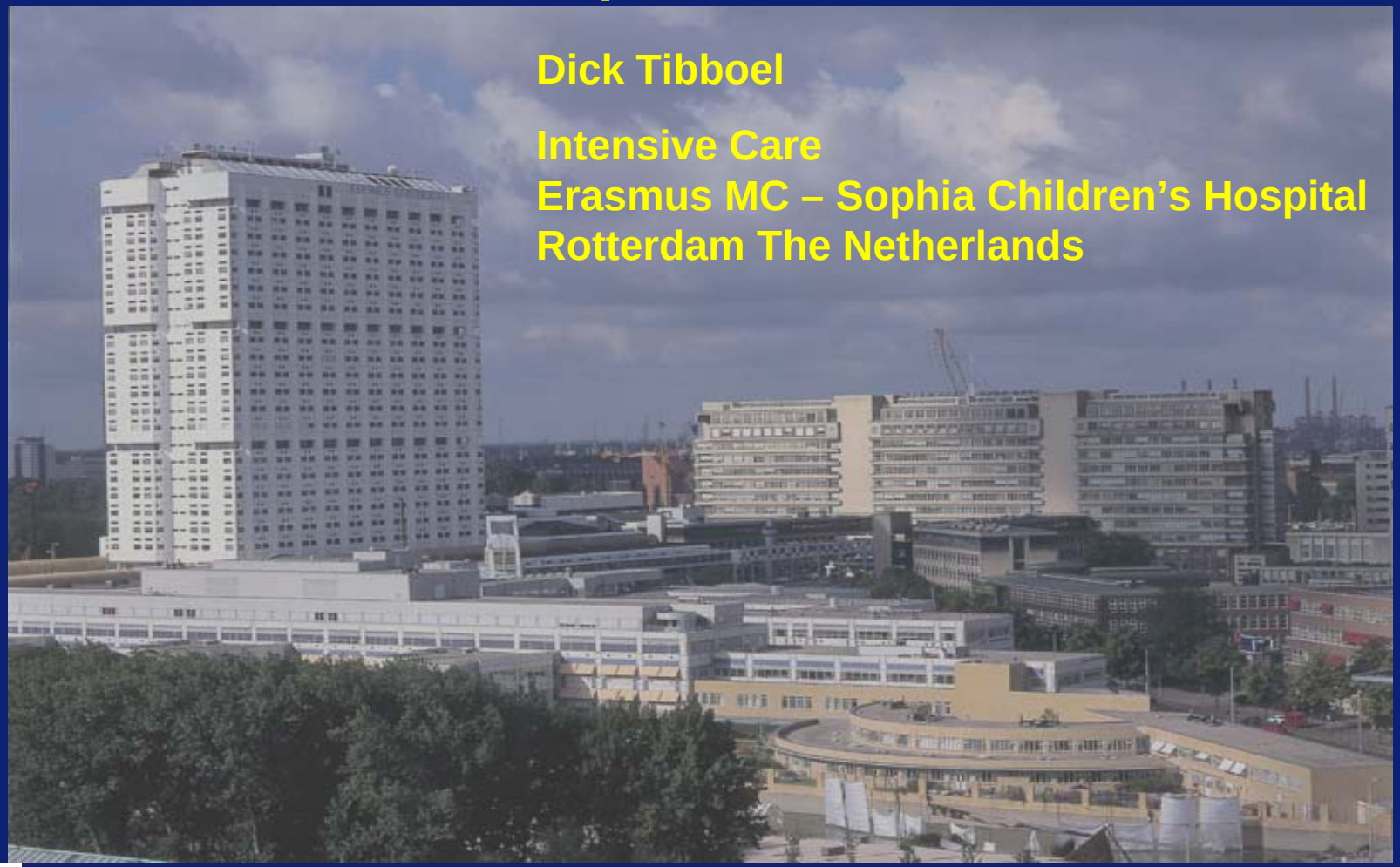
Trials with neonates: desirable scientific approaches, their ethical issues and potential solutions



Dick Tibboel

Intensive Care
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Pharma-Child Rotterdam

Erasmus MC

Children in the intensive care:

- Are generally acutely ill

- Are treated with a curative intention

- Often with drugs used off-label

- Majority under the age of three

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Table 4. PPV of Research Findings for Various Combinations of Power (1 – β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

1 – β	*R*	*u*	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17
0.80	1:10	0.30	Adequately powered exploratory epidemiological study	0.20
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12
0.20	1:1,000	0.80	Discovery-oriented exploratory research with massive testing	0.0010
0.20	1:1,000	0.20	As in previous example, but with more limited bias (more standardized)	0.0015

The estimated PPVs (positive predictive values) are derived assuming $\alpha = 0.05$ for a single study.
RCT, randomized controlled trial.

HYPOTHESIS

It is more unethical not to perform trials in children than to continue prescribing off-label and unlicensed drugs in children.

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Critical Care Trials

Critical care trial design and interpretation: A primer

Jonathan E. Sevransky, MD, MHS; William Checkley, MD, PhD; Greg S. Martin, MD, MSc, FCCM

- Trial design
- Selection of experimental subjects and controls
- Outcome measures
- Bias
- Sample size calculation
- Interpretation of results

Crit Care Med 2010;38:1882-1889

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Critical Care Trials

Table 1. Comparison between observational and controlled studies

	Observational Studies	Controlled Studies
Strengths	Easier to conduct More efficient recruitment Lower cost Lower threshold for investigator participation More real-world representation (external validity) Limited study subject risk	Minimization of confounding Permits intervention testing Stronger causal inference; superior resulting clinical evidence Greater publication impact
Weakness(es)	Weaker evidence for cause–effect relationship	More difficult to conduct Less external validity ("generalizability") Inherent study subject risk

Crit Care Med 2010;38:1882-1889

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Safety and Transparency of Pediatric Drug Trials

Daniel K. Benjamin Jr, MD, PhD, MPH; P. Brian Smith, MD, MHS; M. Jessica M. Sun, MD; M. Dianne Murphy, MD; Debbie Avant, RPh; Lisa Mathis, MD; William Rodriguez, MD; Robert M. Califf, MD; Jennifer S. Li, MD, MHS

Objectives: To quantify the frequency and type of new safety information arising from studies performed under the auspices of the Pediatric Exclusivity Program, to describe the dissemination of these findings in the peer-reviewed literature and compare this with the US Food and Drug Administration (FDA) review, and to describe their effect on pediatric labeling.

Arch Pediatr Adolesc Med. 2009;163(12):1080-1086

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Medication	% exposed	FDA labeling for premature infants
Ampicillin	74	None
Gentamicin	68	None
Cefotaxime	36	None
Caffeine citrate	19	None < 29 weeks
Furosemide	19	None
Vancomycin	17	None
Beractant	14	Yes
Metoclopramide	11	None
Aminophylline	11	None
Dopamine	10	None

Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. Pediatrics 2006;117(6):1979-87

Neonatal pain studies as a model system

It’s an important research area due to:

- High incidence of pain in critically ill children around the world
- Most drugs are used off label and/or unlicensed
- Clinical effects are unpredictable even of classical drugs as paracetamol and opioids
- Major concern about cell biological effects of the developing central nervous system
- Lack of properly designed studies on long term effects

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Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants

Conclusions. Neonates have a narrower therapeutic window for postoperative morphine analgesia than older age groups, with no difference in the safety or effectiveness of intermittent doses compared with continuous infusions in any of these age groups. In infants >1 month of age, analgesia is achieved after morphine infusions ranging from 10.9 to 12.3 $\mu g\ kg^{-1}\ h^{-1}$ at plasma concentrations of <15 $ng\ ml^{-1}$.

Br J Anaesth 2003; **90**: 642–52

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Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants

Table 7 Overview of morphine requirements and plasma concentrations of morphine in term neonates and infants after non-cardiac surgery in earlier studies and the present study

Age	*n*	Loading dose or single dose (S) (μg kg^{-1})	Dosage M infusion (μg kg^{-1} h^{-1})	Plasma concentration morphine (ng ml^{-1})	Comments	References
Earlier studies:						
1–7 days	4	50	7–11	18.9 (15.0–29.0) median (range)	At steady state	Lynn *et al.* [24]
31–90 days	6	50	13–19	9.1 (6.5–14.5) median (range)		Lynn *et al.* [24]
91–180 days	6	50	17–25	10.5 (7.0–22.0) median (range)		Lynn *et al.* [24]
180–380 days	10	50	25–35	10.0 (6.0–17.0) median (range)		Lynn *et al.* [24]
1–18 days	20	50	15	39.0 (23.0) mean (SD)	At steady state	Farrington *et al.* [25]
0–6 months	5	mean 150 (S)		26.2 (22.5) mean (SD)	129 min after M dose	Olkkola *et al.* [26]
2–4 years	5	150 (S)		3.8 (2.3) mean (SD)	189 min after M dose	Olkkola *et al.* [26]
Present study (CM group only)						
0–4 weeks	31	100	10.8 (mean)	22.0 (15.1–29.5) median (IQR)	At 24 h after start of M	Present study
⩾1–6 months	32	100	15.7 (mean)	7.4 (5.3–13.4) median (IQR)		
⩾6–12 months	16	100	16.7 (mean)	6.4 (4.2–9.0) median (IQR)		
⩾1–3 years	18	100	12.1 (mean)	4.8 (3.7–56) median (IQR)		

M=morphine, *n*=number of patients, IQR=interquartile range.

Table I. Overview of the internal datasets (Int. 1 and 2) used to develop the original morphine model and external datasets (Ext. 1–6) used in the current external validation of the original morphine model

Dataset	Patient population	Research centre	Patients (n)	Samples (n)	Postnatal age (d)[a]	Bodyweight (g)[a]	Administered morphine salt
Int. 1[12]	Postoperative term neonates, infants and children	Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands)	185	Morphine: 618 M3G: 512 M6G: 594	97 [0.1–1070]	4700 [1900–16 800]	Morphine hydrochloride
Int. 2[13]	Preterm and term neonates on artificial ventilation	Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands); Isala Clinics (Zwolle, the Netherlands)	63	Morphine: 110 M3G: 132 M6G: 128	0.4 [0.1–6.7]	1180 [565–3875]	Morphine hydrochloride
Ext. 1[5]	Preterm neonates on artificial ventilation	Isala Clinics (Zwolle, the Netherlands)	41	Morphine: 88 M3G: 111 M6G: 65	1 [0.1–13]	1035 [640–3550]	Morphine hydrochloride
Ext. 2[6]	Postoperative term neonates and infants	Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands)	28	Morphine: 98 M3G: 122 M6G: 115	14 [0.1–294]	3100 [1700–9300]	Morphine hydrochloride
Ext. 3[7]	Postoperative term neonates and infants	Children's Hospital and Regional Medical Center, (Seattle, WA, USA)	9	Morphine: 16	10.5 [1–271]	3800 [2640–8100]	Morphine sulphate
Ext. 4[8]	Term neonates and infants on artificial ventilation	Alder Hey Children's Hospital (Liverpool, UK)	12	Morphine: 8 M3G: 12 M6G: 10	13 [3–354]	3050 [2200–8700]	Morphine sulphate
Ext. 5[9,10]	Term neonates on ECMO treatment without CVVH	Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands)	14	Morphine: 328 M3G: 326 M6G: 296	1.1 [0.1–26.1]	3220 [2150–4520]	Morphine hydrochloride
Ext. 6[11]	Term neonates on ECMO treatment with CVVH	Erasmus MC-Sophia Children's Hospital (Rotterdam, the Netherlands)	16	Morphine: 167 M3G: 197 M6G: 195	0.5 [0–7]	3250 [2700–4000]	Morphine hydrochloride

a Values are expressed as median [range].

CVVH = continuous venovenous haemofiltration; **ECMO** = extracorporeal membrane oxygenation; **M3G** = morphine-3-glucuronide; **M6G** = morphine-6-glucuronide.

Predictive Performance of a Recently Developed Population Pharmacokinetic Model for Morphine and its Metabolites in New Datasets of (Preterm) Neonates, Infants and Children

Conclusion: The predictive value of the original morphine pharmacokinetic model is demonstrated in new datasets by the use of six different validation and evaluation tools. It is herewith justified to undertake a proof-of-principle approach in the development of rational dosing recommendations – namely, performing a prospective clinical trial in which the model-based dosing algorithm is clinically evaluated.

Clin Pharmacokinet 2011; 50 (1)

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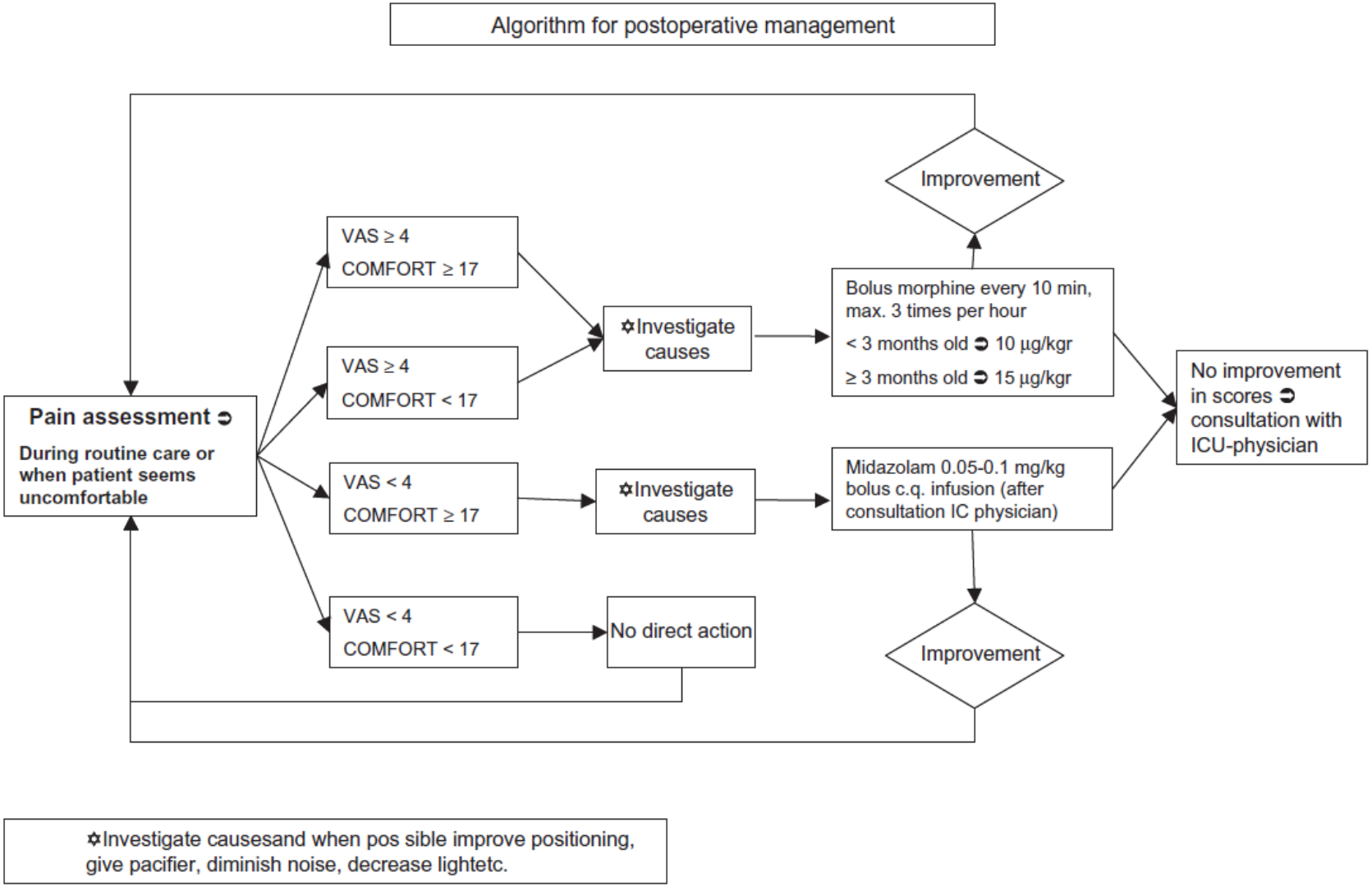
Does minimal access major surgery in the newborn hurt less? An evaluation of cumulative opioid doses

European Journal of Pain (2010)



Does minimal access major surgery in the newborn hurt less? An evaluation of cumulative opioid doses

European Journal of Pain (2010)

Table 1
Patient characteristics.

	EA			CDH		
	MAS	Conventional surgery	*p*-value	MAS	Conventional surgery	*p*-value
	n = 14	*n* = 28		*n* = 10	*n* = 20	
Male/female	7/7	14/14	–	5/5	10/10	–
Weight at surgery (in kg) mean (SD)	2.62 (0.52)	2.79 (0.75)	*0.45*	3.36 (0.73)	3.25 (0.67)	*.69*
Initial length of stay at ICU (in days) median (IQR)	10.5 (7–13.3)	18.5 (12.3–32.0)	*0.10*	23 (10.3–28.8)	21 (13.3–34.3)	*.57*
Duration surgery (in min) mean (SD)	260 (39)	204 (59)	***0.002***	219 (53)	171 (47)	***.02***
Age at surgery (in days) median (IQR)	2.0 (1.8–2.0)	1.0 (1.0–2.0)	***0.001***	4.0 (2.0–5.0)	3.5 (3.0–6.0)	*.45*
Time from ICU admission to surgery (in hours) median (IQR)	29.5 (20–38.3)	18.0 (12.0–25.8)	***0.01***	76.4 (44.5–103.8)	83.5 (58–120.5)	*.36*
Duration initial ventilation after surgery (in hours) median (IQR)	19.5 (16.3–41.8)	32.5 (17.5–46.8)	*0.22*	141.0 (48.3–217.5)	135.0 (49.8–253.3)	*.86*
No. (%) of pts not on ventilatory support postoperative	1 (7.1%)	1 (3.6%)	*1.00*	0 (0%)	0 (0%)	–
No. (%) of pts still on ventilatory support 48 h postoperative	2 (14.3%)	6 (21.4%)	*0.70*	8 (80%)	15 (75%)	*1.00*
No. (%) of pts re-intubated in the first week after surgery	0 (0%)	2 (7.1%)	*0.55*	0 (0%)	3 (15%)	*.53*
PELOD score in						
No. of pts (%) with PELOD score 0–1	6 (42.9%)	10 (35.7%)	*0.83*	0 (0%)	1 (5%)	*1.00*
No. of pts (%) with PELOD score 10–11	8 (57.1%)	18 (64.3%)		10 (100%)	19 (95%)	
No. of pts receiving additional sedatives and analgesics:	7 (50%)	7 (25%)	*.17*	8 (80%)	14 (70%)	*1.00*
Paracetamol	5 (35.7%)	6 (21.4%)	*.46*	6 (60%)	8 (40%)	*.44*
Midazolam						

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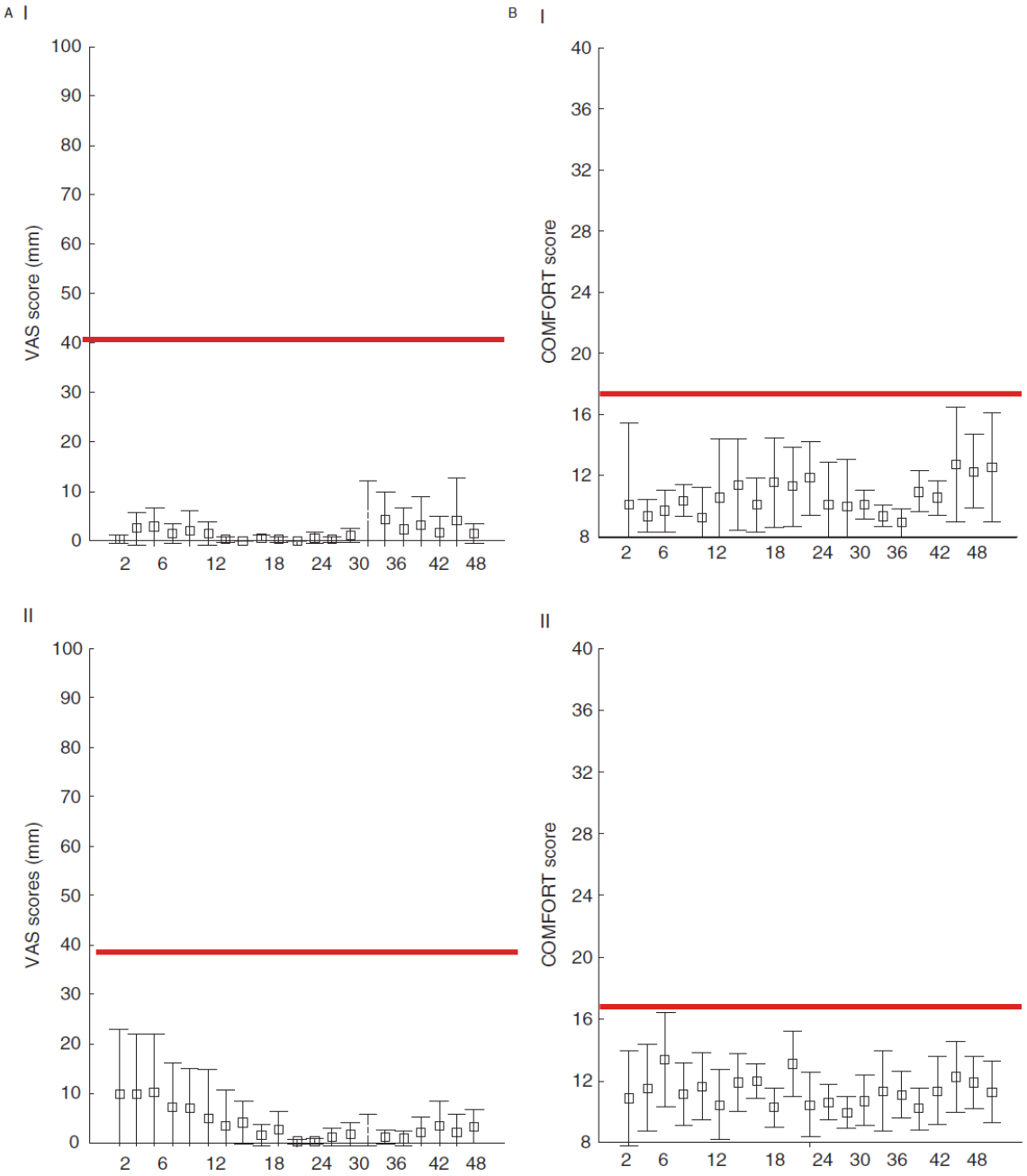

Fig 2 (A) VAS scores: I, acetaminophen group and II, placebo group. (B) COMFORT scores: I, acetaminophen group and II, placebo group.

Routine Morphine Infusion in Preterm Newborns Who Received Ventilatory Support

A Randomized Controlled Trial

Methods

The parents of eligible patients were asked to give written informed consent within 8 hours after endotracheal intubation. If possible, parents were informed about the study before the birth of their child. If consent was refused, information about morphine use of the patient involved was collected retrospectively and compared with information on the participants. Data from nonenrolled patients were not incorporated into other outcome analyses or pooled with that from any other patients.

JAMA. 2003;290:2419-2427

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Routine Morphine Infusion in Preterm Newborns Who Received Ventilatory Support

A Randomized Controlled Trial

Table 2. Pain Scores for the Morphine- and Placebo-Treated Infants*

	Median (IQR)					
	NIPS		PIPP†		VAS	
	Morphine Group	Placebo Group	Morphine Group	Placebo Group	Morphine Group	Placebo Group
Baseline	0.0 (0.0-0.0)	0.0 (0.0-0.8)			0.6 (0.3-2.2)	0.7 (0.3-1.5)
30 min after start of infusion	0.0 (0.0-0.0)	0.0 (0.0-1.0)			0.6 (0.3-1.6)	0.6 (0.2-1.4)
Before suctioning	0.5 (0.0-1.0)	1.0 (0.0-1.0)			0.8 (0.5-1.3)	0.9 (0.6-1.6)
During suctioning	4.8 (3.7-6.0)	4.8 (3.2-6.0)	10.1 (8.2-11.6)	10.0 (8.2-12.0)	2.8 (2.0-3.9)	2.6 (1.8-4.3)
30 min after suctioning	0.0 (0.0-1.0)	0.0 (0.0-1.0)			0.9 (0.6-1.4)	0.9 (0.6-1.4)

Abbreviations: IQR, interquartile range; NIPS, Neonatal Infant Pain Scale (scale range, 0-7); PIPP, Premature Infant Pain Profile (scale range, 0-21); VAS, visual analog scale (scale range, 0-10).
*Pain scores were not significantly different between the 2 groups. Pain scores were averaged in the case of repeated measures. For all scales, the higher the number, the more severe the pain.
†The PIPP was assessed only during suctioning.

JAMA. 2003;290:2419-2427

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Routine Morphine Infusion in Preterm Newborns Who Received Ventilatory Support

A Randomized Controlled Trial

Table 4. Clinical Outcomes

	Morphine Group (n = 73)	Placebo Group (n = 77)	*P* Value*
Poor neurologic outcome			
28-Day mortality, No. (%)	4 (5)	7 (9)	NA
Periventricular leukomalacia, No. (%)	2 (3)	2 (3)	NA
Intraventricular hemorrhage, No. (%)			
Severe†	3 (4)	7 (9)	NA
Overall	17 (23)	31 (40)	NA
Comorbidities, No. (%)			
Chronic lung disease	17 (23)	18 (23)	.95
Secondary infection or sepsis	29 (40)	35 (45)	.47
Necrotizing enterocolitis	7 (10)	7 (9)	>.99
Patent ductus arteriosus	26 (36)	28 (36)	.92
Infusion of study medication, median (IQR), h	55 (23-96)	42 (18-96)	.35
Artificial ventilation, median (IQR), h			
First period	73 (35-172)	72 (27-154)	.72
Total	77 (36-184)	82 (32-221)	.81
NICU stay, median (IQR), h	336 (156-804)	312 (144-1068)	.92

Abbreviations: IQR, interquartile range; NA, not applicable; NICU, neonatal intensive care unit.
*Outcomes reported as NA were analyzed using logistic regression analyses (see Table 5). *P* values were calculated using the Mann-Whitney *U* test, asymptotic significance (2-sided), except for necrotizing enterocolitis, which was calculated with the Fisher exact test, exact significance (2-sided).
†Grade III intraventricular hemorrhage or intraventricular hemorrhage plus apparent periventricular hemorrhagic infarction.

JAMA. 2003;290:2419-2427

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Routine Morphine Infusion in Preterm Newborns Who Received Ventilatory Support

A Randomized Controlled Trial

Conclusions Lack of a measurable analgesic effect and absence of a beneficial effect on poor neurologic outcome do not support the routine use of morphine infusions as a standard of care in preterm newborns who have received ventilatory support. Follow-up is needed to evaluate the long-term effects of morphine infusions on the neurobehavioral outcomes of prematurity.

JAMA. 2003;290:2419-2427

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Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial

Interpretation Pre-emptive morphine infusions did not reduce the frequency of severe IVH, PVL, or death in ventilated preterm neonates, but intermittent boluses of open-label morphine were associated with an increased rate of the composite outcome. The morphine doses used in this study decrease clinical signs of pain but can cause significant adverse effects in ventilated preterm neonates.

Lancet 2004; **363:** 1673–82

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Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial

Methods Ventilated preterm neonates (n=898) from 16 centres were randomly assigned masked placebo (n=449) or morphine (n=449) infusions. After a loading dose (100 μg/kg), morphine infusions (23–26 weeks of gestation 10 μg kg^{-1} h^{-1}; 27–29 weeks 20 μg kg^{-1} h^{-1}; 30–32 weeks 30 μg kg^{-1} h^{-1}) were continued as long as clinically justified (maximum 14 days). Open-label morphine could be given on clinical judgment (placebo group 242/443 [54·6%], morphine group 202/446 [45·3%]). Analyses were by intention to treat.

Analgesia with bolus doses of the study drug or increases in the infusion rate were not permitted, but the infusion rate was increased if the baby grew to a higher gestational stratum.

Ethical concerns related to a masked placebo group[26] necessitated the option to use open-label morphine for both groups, indicated by defined criteria in the protocol.

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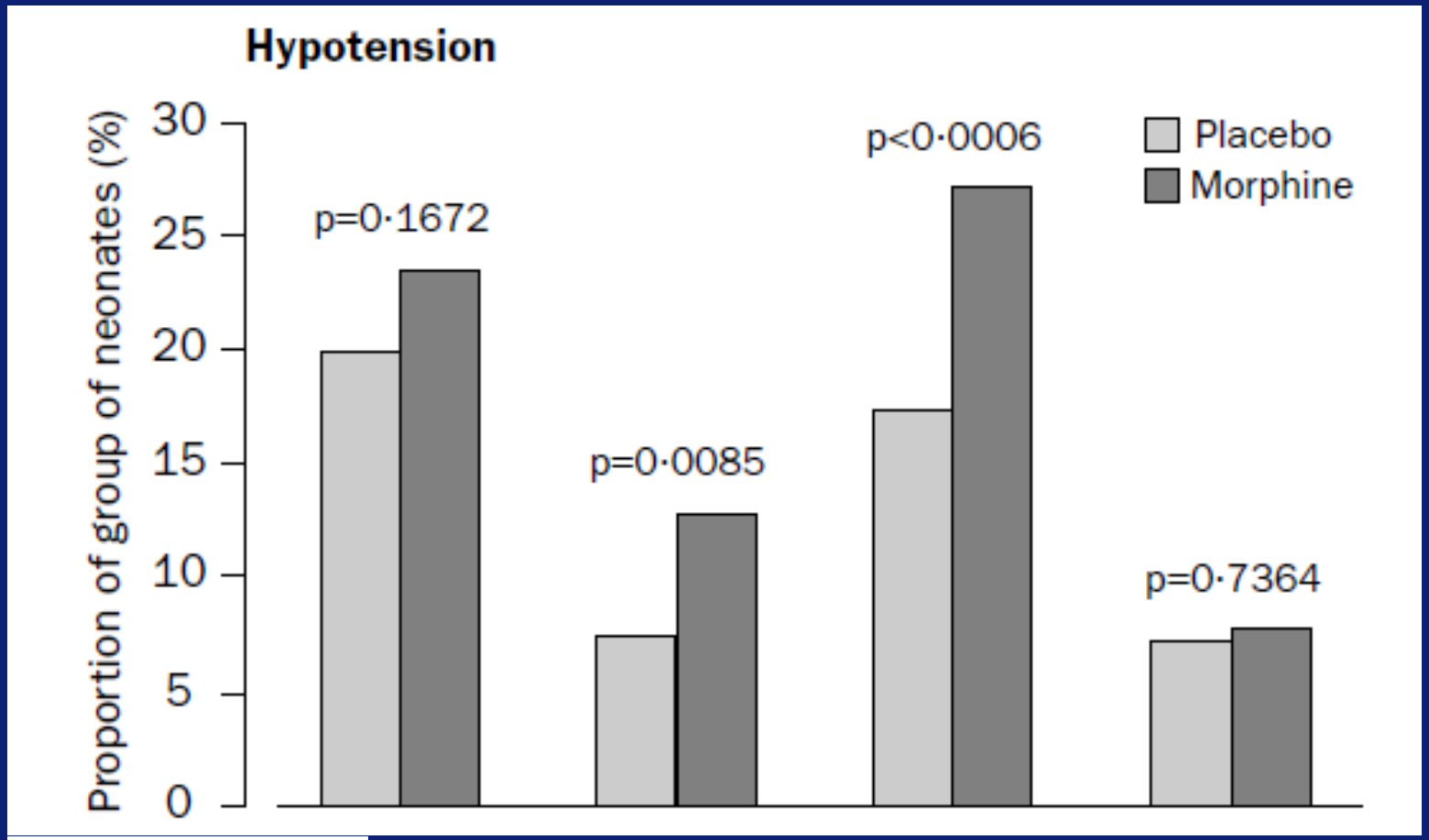
Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial



Lancet 2004; **363:** 1673–82

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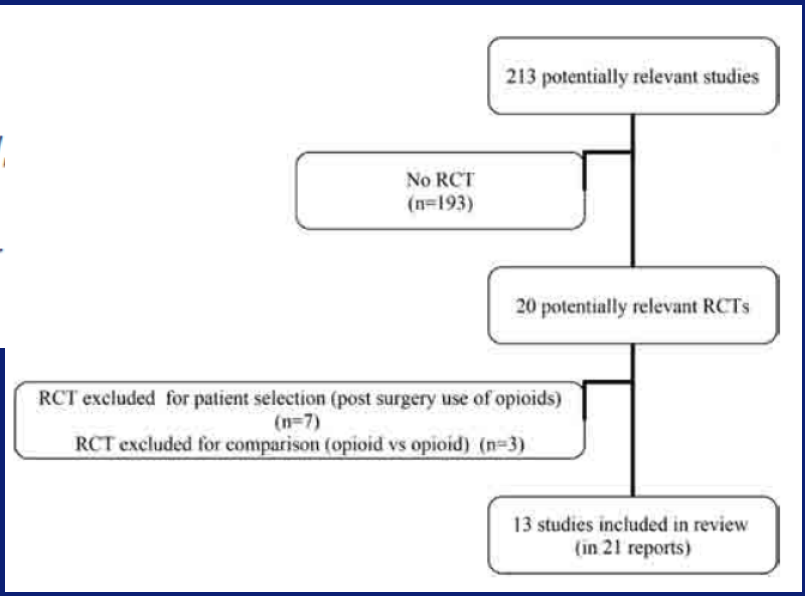
Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis

R Bellù,[1] Koert de Waal,[2] R Zanini[1]

Conclusions There is insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns. Opioids should be used selectively when indicated by clinical judgment and evaluation of pain indicators. If sedation is required, morphine is safer than midazolam.



Arch Dis Child Fetal Neonatal Ed 2010;**95**:F241–F251

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Innovative clinical trial design for pediatric therapeutics

Performing clinical trials in children is challenging and is limited by:

1) low study consent rates for parents of vulnerable infants;

2) limited blood volume available to conduct PK studies;

3) lack of pediatric population PK/PD analysis expertise;

4) difficulties associated with blood sampling timing; and

5) the relative absence of microanalytical techniques sufficiently sensitive so as to enable accurate determination of drug concentration from very small volume specimens.

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Innovative clinical trial design for pediatric therapeutics

Improving the field of PK trials in children:

- **multiple-drug assays**
- **dried blood spot sampling (DBS)**

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Innovative clinical trial design for pediatric therapeutics

Potential advantages of blood spot sampling

- **-low sample volume**
- **-minimal personnel training**
- **-no sample processing (sample is collected as is at the patient bedside)**
- **-room temperature storage**
- **-simple bioanalytical analysis.**

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Innovative clinical trial design for pediatric therapeutics

An opportunistic study is one where a child is receiving an off-patent or understudied therapeutic as part of standard of care and, after informed consent, investigators collect PK samples

- at the time of routine laboratory draws

- use scavenged samples

- collect a low number (sparse sampling)

- low volume samples

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Innovative clinical trial design for pediatric therapeutics

Other advantages of opportunistic studies include enrollment of:

- the population of interest
- intensive care patients with comorbid conditions
- children with many concomitant medications that might affect PK parameters
- subtypes of pediatric populations
- pediatric patients presenting during “disaster” situations.

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StaR Child Health: Developing Evidence-Based Guidance for the Design, Conduct, and Reporting of Pediatric Trials

L Hartling[1], KDM Wittmeier[2], PH Caldwell[3], JH van der Lee[4], TP Klassen[5], JC Craig[3] and M Offringa[4] for the StaR Child Health group (http://www.starchildhealth.org)

CPT 2011; 90; 727-731

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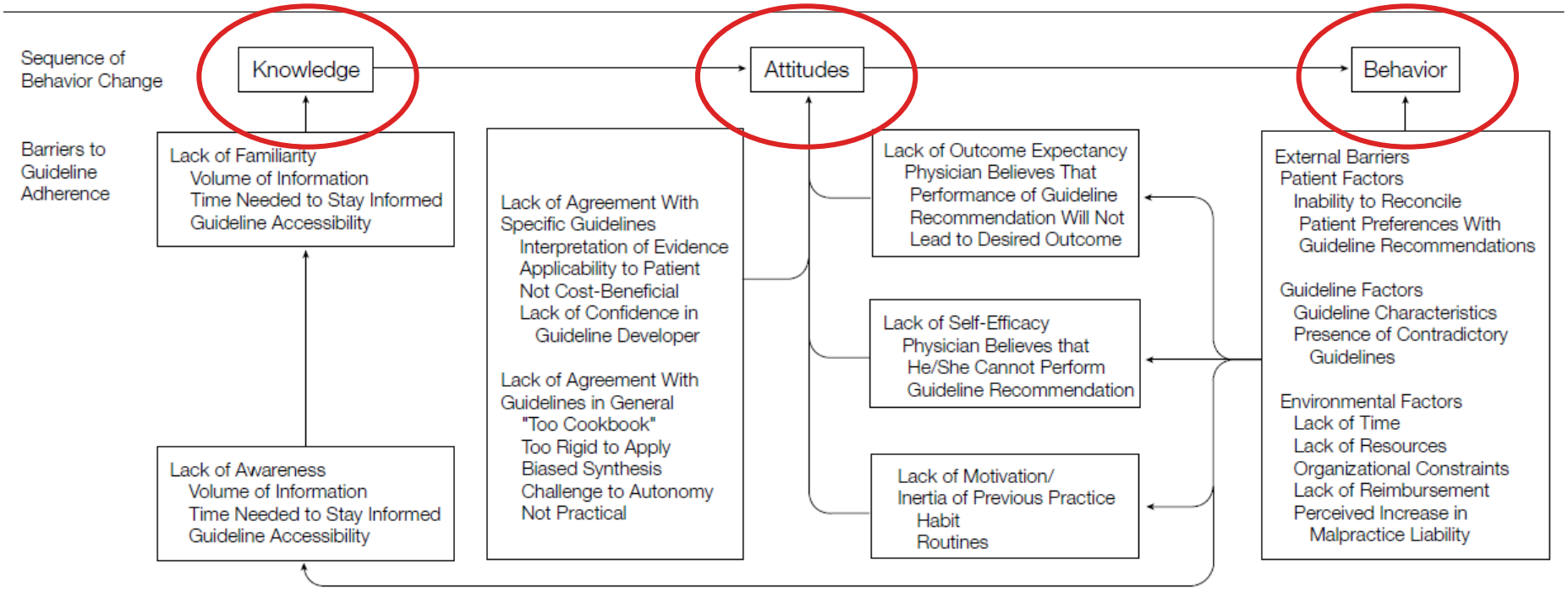
Why Don't Physicians Follow Clinical Practice Guidelines?

A Framework for Improvement

Figure. Barriers to Physician Adherence to Practice Guidelines in Relation to Behavior Change



Cabana MD et al. JAMA 1999;282:1458-1465

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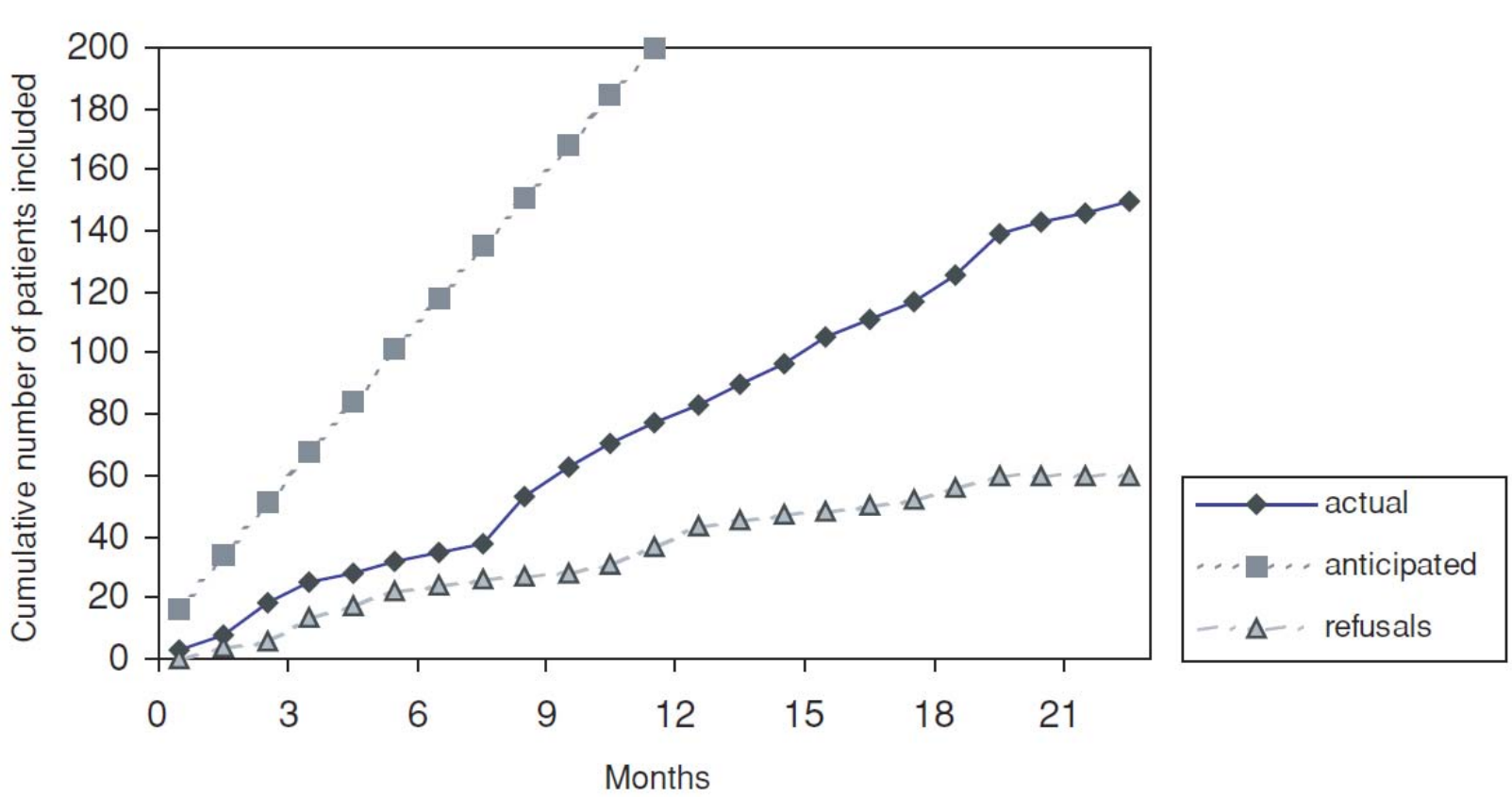
Lies in speed of recruitment



Comparison of actual and planned inclusion of patients in NICU pain study.

Van Dijk M et al. 2005;6:203-210

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Ethical Issues in drug trials in children

- What information is provided

- What is the role of trust, dependency, altruism, therapeutic misconception, hope, understanding and loyalty

- How should researchers deal with seemingly intuitive dissent

- Is stimulation of motivated consent ethically acceptable.

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The informed consent process and understanding information

- Randomization

- Information overload

- Difficulties in remembering information

- Emotional constraint

- Motivation to participate in research

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Motivations of minors and their parents in clinical trials is related to:

- Their personal interests in research participation

- Practical issues in the informed consent process

- Personal characteristics such as age and nature of illness.

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Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

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Pharma-Child Rotterdam

Erasmus MC

Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants

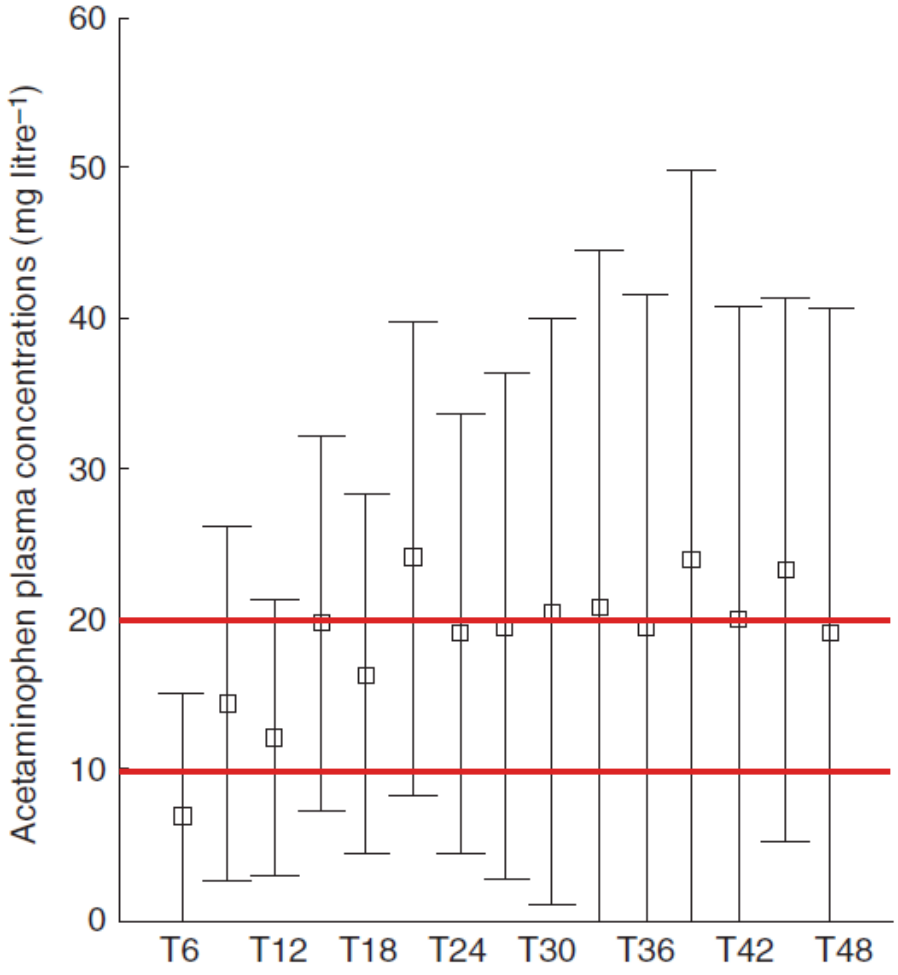

Fig 3 Acetaminophen plasma concentrations and confidence interval of mean.

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Routine Morphine Infusion in Preterm Newborns Who Received Ventilatory Support

A Randomized Controlled Trial

Table 3. Results of Multiple Regression Analyses of Pain Scores Measured During Suctioning*

	PIPP		NIPS		VAS	
Outcome Variable	B (95% CI)	*P* Value	B (95% CI)	*P* Value	B (95% CI)	*P* Value
Treatment group	0.038 (–0.97 to 1.04)	.94	–0.16 (–0.74 to 0.41)	.58	–0.43 (–1.00 to 0.15)	.14
Amount of extra morphine, per 1 µg/kg/h	–0.066 (–0.25 to 0.12)	.48	0.011 (–0.096 to 0.12)	.83	0.030 (–0.078 to 0.14)	.59
Center	0.56 (–0.51 to 1.62)	.30	0.31 (–0.29 to 0.91)	.31	–1.40 (–2.00 to –0.80)	<.001
Sex	–0.11 (–1.12 to 0.89)	.82	0.29 (–0.29 to 0.86)	.32	0.30 (–0.28 to 0.87)	.31
Total length of study	–0.0022 (–0.013 to 0.009)	.69	–0.0070 (–0.013 to –0.001)	.03	–0.0067 (–0.013 to 0.00)	.04
Correlation coefficient (adjusted R^2)	0.14 (0.026)		0.22 (0.012)		0.46 (0.19)	

Abbreviations: CI, confidence interval; NIPS, Neonatal Infant Pain Scale; PIPP, Premature Infant Pain Profile; VAS, visual analog scale.
*P values show the significance of the predictive value of each independent variable on the different outcome variables. B values are unstandardized regression coefficients.

JAMA. 2003;290:2419-2427

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Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial

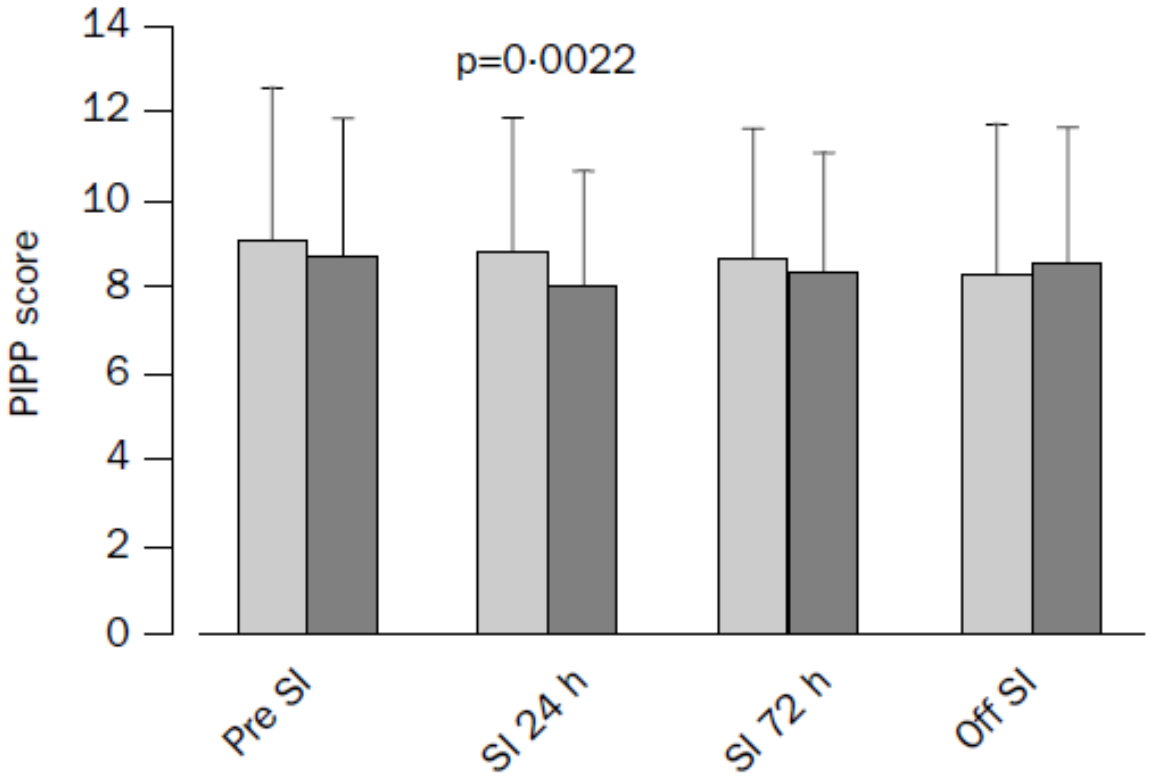

Figure 3: **Mean changes in heart rate, respiratory rate, and scores on the premature infant pain profile**
Error bars=SD. SI=study infusion; ET=endotracheal suctioning.

Lancet 2004; **363:** 1673–82

Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial

*K J S Anand, R Whit Hall, Nirmala Desai, Barbara Shephard, Lena L Bergqvist, Thomas E Young, Elaine M Boyle, Ricardo Carbajal, Vinod K Bhutani, Mary Beth Moore, Shari S Kronsberg, Bruce A Barton, for the NEOPAIN Trial Investigators Group**

Lancet 2004; **363:** 1673–82

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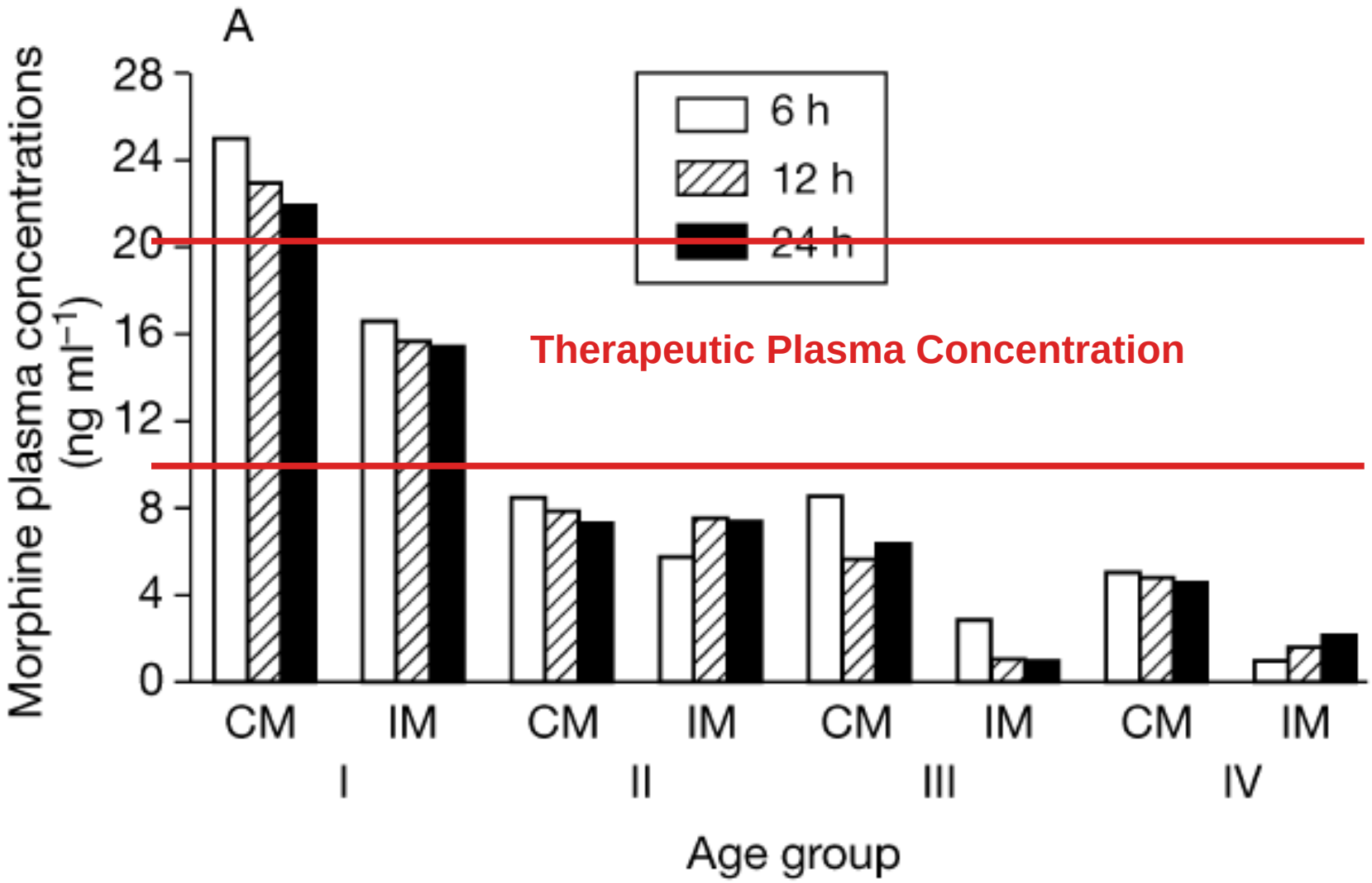
A
Morphine plasma concentrations (ng ml⁻¹)
28
24
20
16
12
8
4
0
6 h
12 h
24 h
Therapeutic Plasma Concentration
CM
IM
CM
IM
CM
IM
CM
IM
I
II
III
IV
Age group

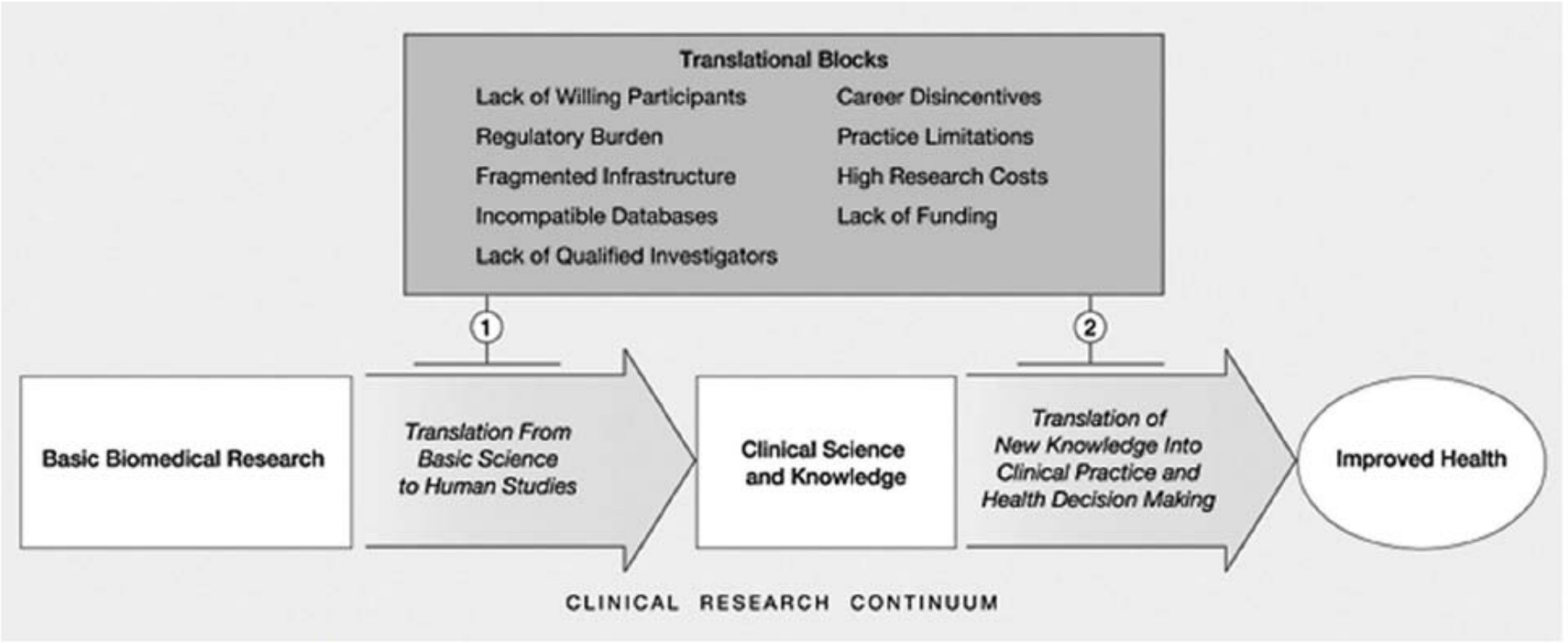

Figure 2. The two translational blocks in the clinical research continuum. Reproduced with permission from Sung et al (27).

Reade MC et al. Crit Care Med 2010;38:1882-1889
Sung NS et al. JAMA 2003;289:1278-1287

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Opioids for neonates receiving mechanical ventilation: a systematic review and meta-analysis

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