

36ème Congrès Annuel de l'ADARPEF

In association with ESPA European Society for Paediatric Anaesthesiology

GAS Study: what we have learnt so far

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Istituto Giannina Gaslini

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BORDEAUX

In association with
ESPA EUROPEAN SOCIETY FOR PAEDIATRIC ANAESTHESIOLOGY



Istituto Giannina Gaslini



Disclosure

- No conflict of interest
- PI of the GAS Trial

G - General anaesthesia

A - Apoptosis – Apnoea

S - Spinal anaesthesia

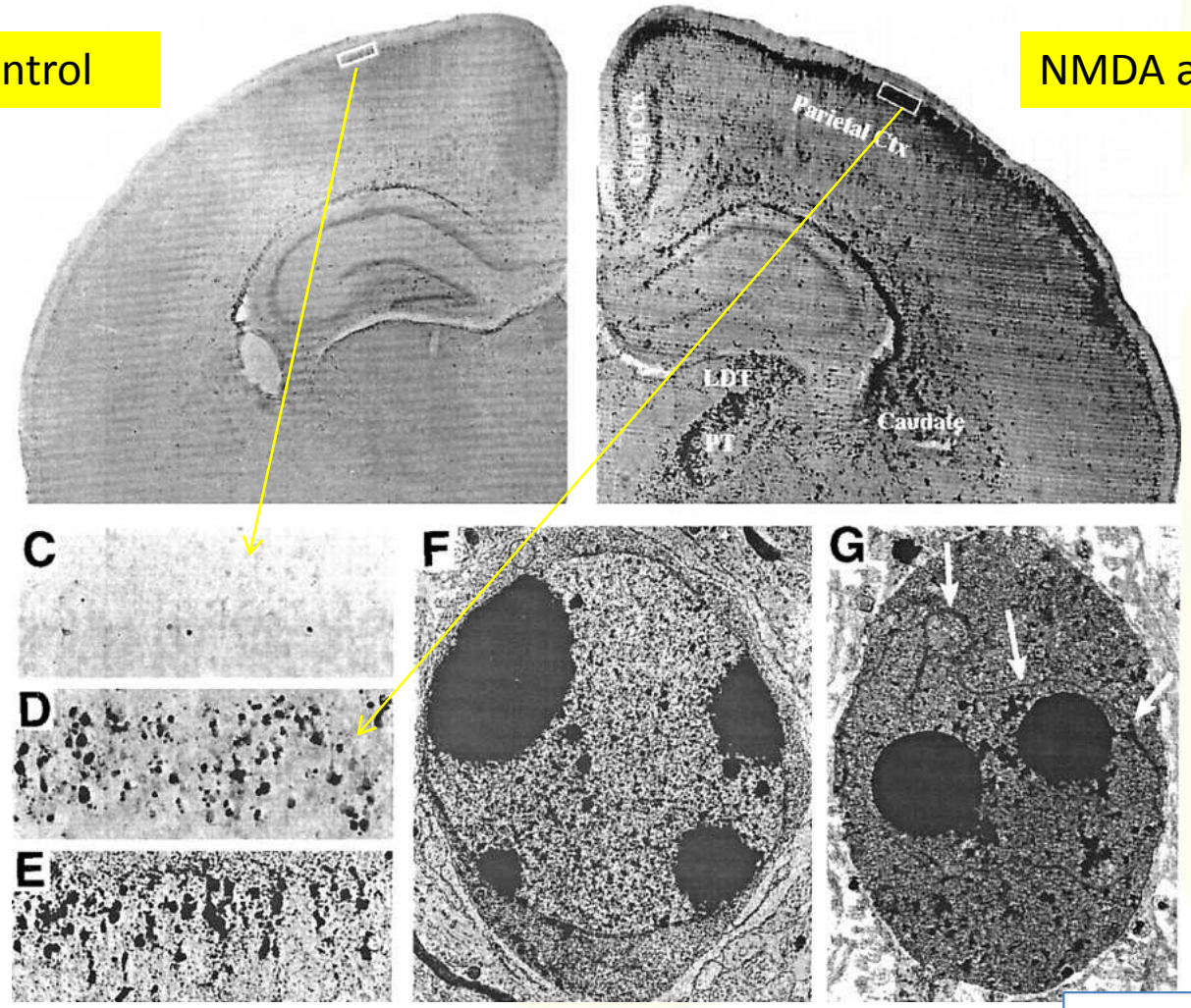
A multi-site RCT comparing regional and general anaesthesia on neurodevelopmental outcome and apnoea in neonates and infants

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Background

Control

NMDA antagonist



C Ikonomidou et al. Science 1999;283:70-74

Background

- **Animal Models**
  - General anaesthetics have a variety of effects on the developing brain in animal models
  - Effects are dose and age dependent
  - Evidence that early exposure is associated with long term neurodevelopmental changes in animals

- Mixed evidence in **cohort studies** for an association between surgery in early childhood and poor neurodevelopmental outcome
  - Confounding
  - Imprecise outcome measures
  - Mixed populations

Rationale of GAS Study

- **Spinal and GA** accepted techniques for infant inguinal hernia repair
- **Infants** probably most at risk
- Duration of anaesthesia for hernia repair is **short**, but most anaesthetics in children are short
- No reason to think that spinal anaesthesia is injurious

- **If we find equivalence then we can assume the majority of general anaesthetics in children are "safe"**



The GAS Study

Randomised, assessor-blinded, multi-site, equivalence trial

Primary aim

To determine whether different types of anaesthesia [regional *vs* general] given to infants, undergoing inguinal hernia repair result, in equivalent neurodevelopmental outcomes at 5 years of age.

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Participants

Inclusions

- Infants scheduled for hernia repair
- < 60 weeks post menstrual age

Exclusions

- Born < 26 weeks gestation
- Risk factors for poor neurodevelopmental outcome
- Previous exposure to GA in infancy or in utero
- Contraindications to awake regional or general anaesthesia



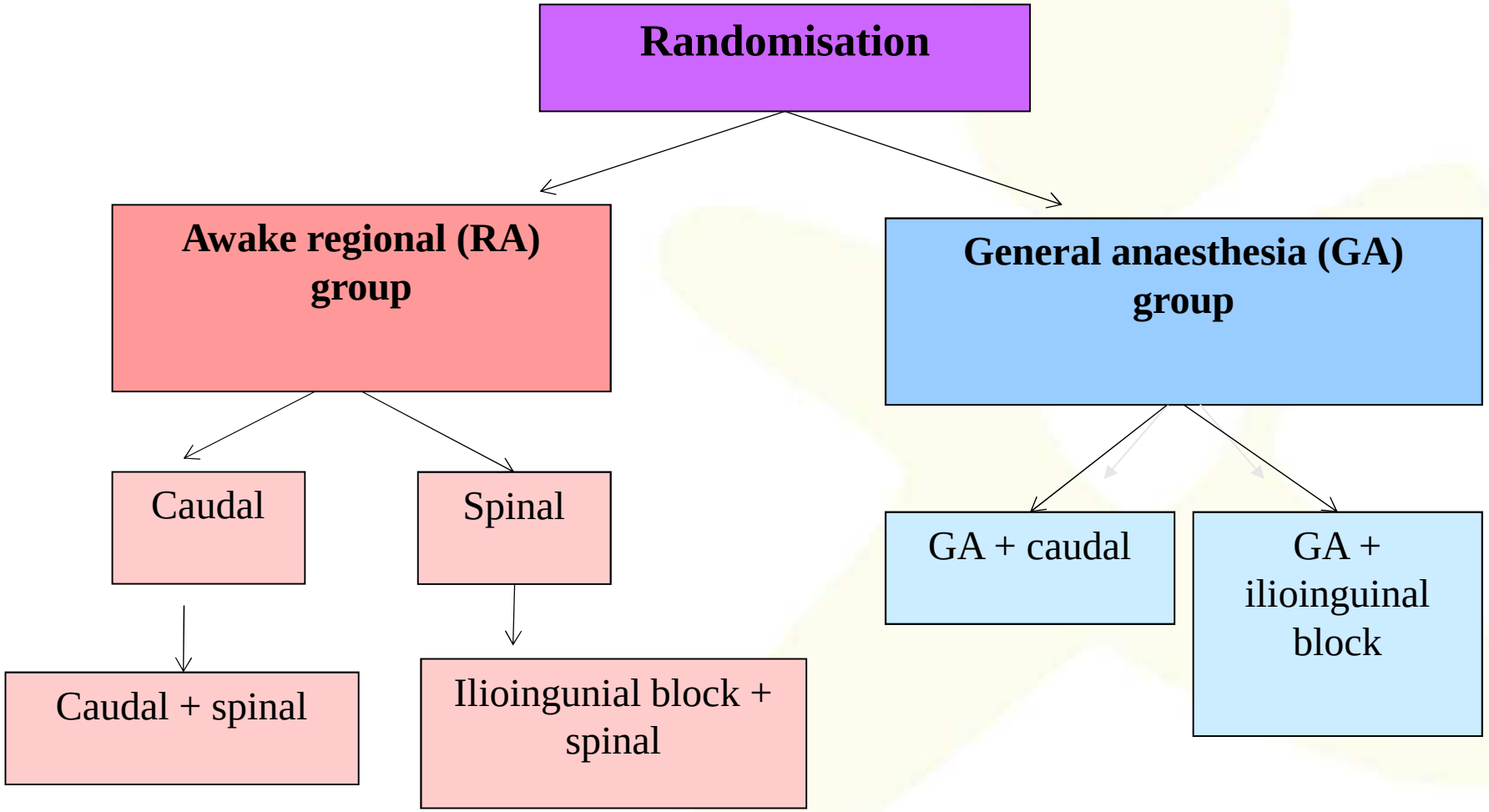
Sample size

- The sample size was based on WPPSI-III Full Scale IQ score.

- Assuming an expected difference of one standardised score point, and a 90% chance that a 95% confidence interval will exclude a difference of more than five points (the largest acceptable difference required to demonstrate equivalence), the trial would need **598 infants in total**.

- Enrolling approximately 720 participants would allow for a 10% loss to follow-up and 10% with a major protocol violation.

Web-based randomisation
Stratified by Site and Gestational Age at Birth



RA group

- Awake Spinal
  - Bupivacaine or levobupivacaine 0.5% 0.2 ml/kg (min 0.5 ml)
  - +/- caudal or ilioinguinal block
  - No sedation

or

- Awake Caudal
  - Bupivacaine 2.5mg/kg
  - No sedation

GA group

- Up to 8% Sevoflurane in oxygen/air
- No nitrous oxide, No opioids
- Facemask, LMA *or* ETT +/- NDNMB
- Mechanical or spontaneous ventilation
- Caudal *or* ilio-inguinal block

GAS Study - outcomes

- **Primary outcome**
  - WPPSI-III Full Scale IQ at 5 years
    - (data available by the end of 2017)

- Secondary outcomes
  - Neurodevelopmental measures at 2 years of age
  - Incidence of apnoea (GA *vs* RA)
  - Other outcomes relating to anaesthesia group
  - Surgical outcomes



4023 screened

722 randomised

363 assigned RA

359 assigned GA

2 misrandomised

1 withdrew consent

361 ITT

358 ITT

74 protocol violations

2 protocol violations

287 APP

356 APP

45 LTFU, incomplete assessment

62 LTFU, incomplete assessment

238 complete assessment

294 complete assessment



Demographic data	RA Arm APP (N=287)	GA Arm APP (N=356)	RA Arm ITT (N=361)	GA Arm ITT (N=358)
Gender, Male	232 (81%)	304 (85%)	294 (82%)	306 (86%)
Chronological age at surgery (days)	68·9 (31)	71·1 (32)	70·1 (32)	71·0 (32)
Post menstrual age at surgery (days)	317·2 (32)	319·7 (32)	318·3 (33)	319·5 (32)
Weight of child at surgery (kg)	4·2 (1·1)	4·3 (1·1)	4·2 (1·1)	4·3 (1·1)
Mean (SD) Post menstrual age at birth (days)	248·2 (29)	248·6 (27)	248.3 (29)	248.6 (27)
Prematurity (Born < 37 weeks gestation)	160 (56%)	195 (55%)	198 (55%)	196 (55%)
Birth Weight (kg)	2·3 (0·9)	2·3 (0·9)	2·4 (0·9)	2·3 (0·9)
Z score for birth weight	-0.68 (1·3)	-0.69 (1·3)	-0.66 (1·2)	-0.69 (1·3)
Mode of delivery of birth				
Cephalic vaginal	135 (47%)	157 (44%)	169 (47%)	157 (44%)
Breech vaginal	1 (<1%)	6 (2%)	3 (1%)	6 (2%)
Compound vaginal	2 (1%)	4 (1%)	3 (1%)	4 (1%)
Caesarean section	149 (52%)	189 (53%)	185 (51%)	191 (53%)
Mother exposed to nitrous oxide during delivery	48 (18%)	62 (18%)	61 (18%)	62 (18%)
Maternal education				
Completed tertiary studies	150 (52%)	171 (48%)	181 (51%)	171 (48%)
Continuing tertiary studies	50 (17%)	67 (19%)	68 (19%)	67 (19%)
Completed year 11 or 12	62 (22%)	83 (23%)	77 (22%)	84 (24%)
Did not complete year 11	25 (9%)	33 (9%)	32 (9%)	34 (10%)



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Apnoea outcome

- Observation from leaving operating room to discharge, *or* 12 hours
  - **Early**: – up to 30 minutes
  - **Late**: – 30 minutes to 12 hours

- Significant apnoea:
  - Pause in breathing > 15 seconds, *or* pause > 10 seconds with SpO_2 <80% or bradycardia (20% decrease in heart rate).

GA *vs* RA: odds ratio for apnoea

	ITT		APP	
Any apnoea	1.55 (0.77-3.13),	P=0.22	2.11 (0.85-5.28),	P=0.11
Early apnoea	4.07 (1.37-12.06),	P=0.01	9.48 (1.72-52.39),	P=0.01
Late apnoea	0.87 (0.37-2.07),	P=0.76	0.93 (0.43-2.02),	P=0.86
Significant intervention	2.71 (1.37-5.36),	P=0.004	3.84 (1.54-9.58),	P=0.004



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Neurodevelopmental outcomes at 2 years of age

- Secondary outcomes
  - Bayley III at 2 years
  - MacArthur Bates at 2 years
  - Diagnosis of CP or other neurological or behavioural disorders

Bayley-III

- 5 scores
  - Cognitive
  - Motor
  - Language
  - Social/emotional
  - Adaptive behaviour

- Composite score normalised for each country
  - Mean 100
  - SD 15

Analysis

- Primary: As per protocol
- Secondary: Intention to treat

- Adjusted for gestational age at birth

- Multiple imputation
- Complete case



Results at 2 years	RA Arm APP (N=287)	GA Arm APP (N=356)	RA Arm ITT (N=361)	GA Arm ITT (N=358)
Corrected age at assessment (weeks)	108·9 (13·0)	108 (9·8)	108·7 (12·5)	108 (9·8)
Number of anaesthetics since				
1	34 (14%)	36 (12%)	42 (14%)	36 (12%)
2	5 (2%)	6 (2%)	6 (2%)	6 (2%)
>2	4 (2%)	4 (1%)	4 (1%)	4 (1%)
Child had a head injury that involved the loss of consciousness	7 (3%)	4 (1%)	7 (2%)	4 (1%)
Child has an acquired brain injury	1 (0%)	1 (0%)	1 (0%)	1 (0%)
Child had febrile seizures	8 (3%)	9 (3%)	10 (3%)	9 (3%)
Child had other seizures	1 (<1%)	4 (1%)	1 (<1%)	4 (1%)
The child has had an intervention for neurodevelopmental issues	46 (19%)	55 (18%)	54 (18%)	55 (18%)
Speech Therapy	22 (9%)	27 (9%)	28 (9%)	27 (9%)
Physiotherapy	22 (9%)	27 (9%)	26 (8%)	27 (9%)
Occupational Therapy	9 (4%)	12 (4%)	12 (4%)	12 (4%)
Psychology	1(<1%)	6 (2%)	1 (<1%)	6 (2%)
Developmental medicine/early intervention	8 (3%)	7 (2%)	9 (3%)	7 (2%)



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Number of anaesthetics since				
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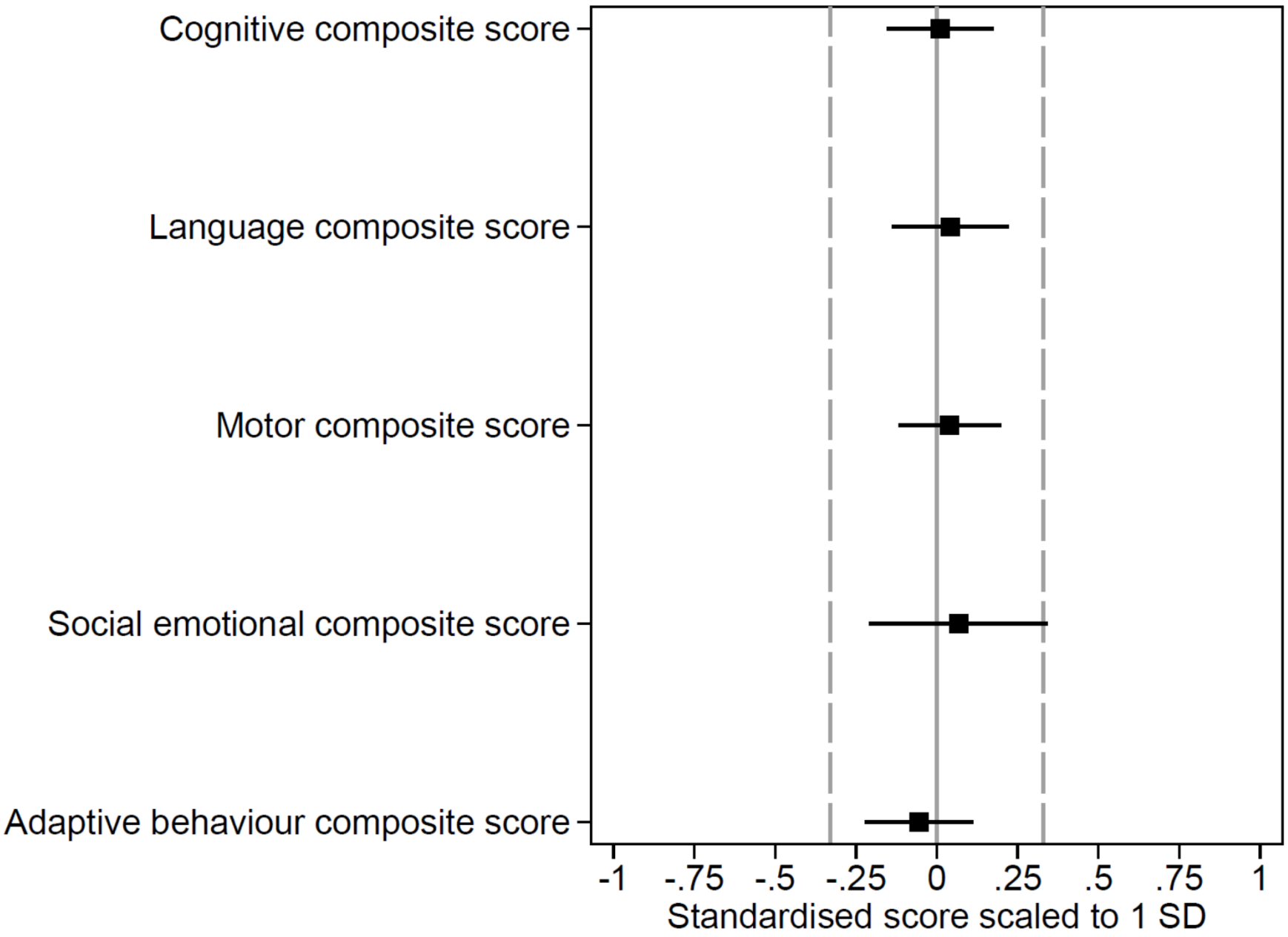


Composite scores - Results

	RA Arm APP	GA Arm APP	RA Arm ITT	GA Arm ITT
Cognitive, Composite Score	98·6 (14·2)	98·2 (14·7)	98·6 (14·2)	98·2 (14·6)
Language, Composite Score	94·6 (15·4)	94·0 (15·6)	94·9 (15·5)	94·0 (15·6)
Motor, Composite Score	98·3 (13·2)	97·9 (13·4)	98·9 (13·5)	97·8 (13·4)
Social Emotional, Composite Score	97·4 (19·0)	95·4 (18·3)	97·4 (19·2)	95·4 (18·3)
Adaptive Behaviour Composite Score	93·1 (15·6)	94·3 (14·7)	93·4 (16·1)	94·3 (14·7)
MacArthur Bates Percentile Score	32·4 (27·9)	34·7 (28·7)	33·6 (28·0)	34·7 (28·7)

Composite cognitive score RA *vs* GA

APP multiple imputation	0.169 (-2.30 to 2.64)
APP complete case	0.458 (-2.02 to 2.94)
ITT multiple imputation	0.256 (-2.06 to 2.57)
ITT complete case	0.430 (-1.90 to 2.76)


Cognitive composite score
Language composite score
Motor composite score
Social emotional composite score
Adaptive behaviour composite score
-1
-.75
-.5
-.25
0
.25
.5
.75
1
Standardised score scaled to 1 SD



Proportion below 1 and 2 SD

	RA Arm APP (N=238)	GA Arm APP (N=294)	RA Arm ITT (N=292)	GA Arm ITT (N=295)
One standard deviation below normal	27 (11%)	32 (11%)	32 (11%)	32 (11%)
Two standard deviations below normal	5 (2%)	7 (2%)	7 (2%)	7 (2%)

Risk ratios

		RR: RA/GA	95% CI for RR: RA/GA		P value
One SD below normal	APP	1·03	0·64	1·65	0·9073
	ITT	1·01	0·64	1·59	0·9663
Two SDs below normal	APP	0·87	0·28	2·71	0·8139
	ITT	1·00	0·36	2·82	0·9962



www.thelancet.com Published online October 25, 2015

Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial

*Andrew J Davidson, Nicola Disma, Jurgen C de Graaff, Davinia E Withington, Liam Dorris, Graham Bell, Robyn Stargatt, David C Bellinger, Tibor Schuster, Sarah J Arnup, Pollyanna Hardy, Rodney W Hunt, Michael J Takagi, Gaia Giribaldi, Penelope L Hartmann, Ida Salvo, Neil S Morton, Britta S von Ungern Sternberg, Bruno Guido Locatelli, Niall Wilton, Anne Lynn, Joss J Thomas, David Polaner, Oliver Bagshaw, Peter Szmuk, Anthony R Absalom, Geoff Frawley, Charles Berde, Gillian D Ormond, Jacki Marmor, Mary Ellen McCann, for the GAS consortium**

Conclusion

- Under just an hour of general anaesthesia in infancy does not cause a clinically-significant adverse neurodevelopmental outcome compared to awake regional anaesthesia, as measured at 2 years of age.



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GAS Study: what we I have learnt so far….

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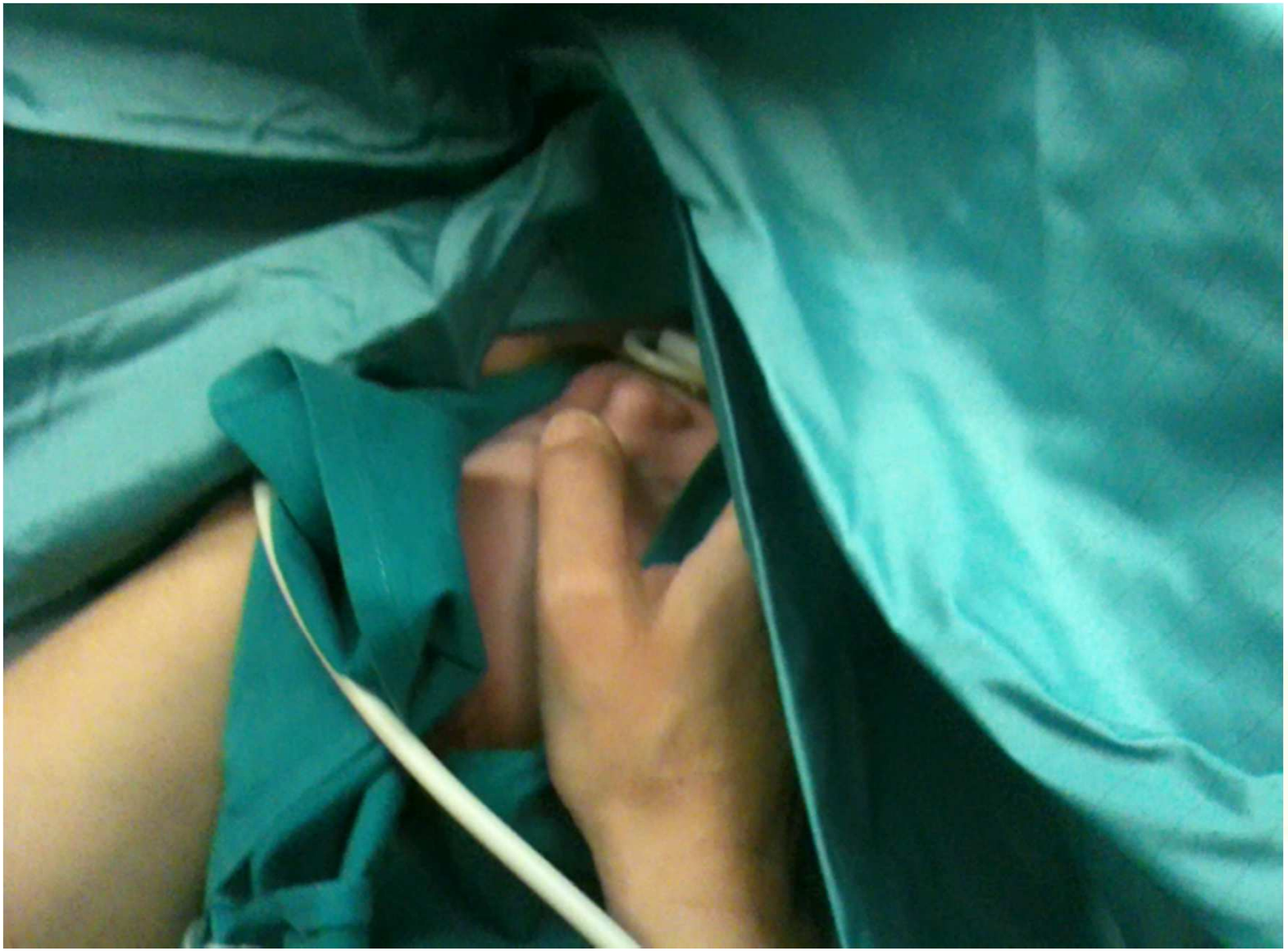
Lesson one – the risk of apnoea

- With modern anaesthesia, there is no evidence that awake regional anaesthesia reduces risk of apnoea
- Successful **RA reduces early apnoea**
- Spinal anaesthesia is a feasible alternative to GA
- **Prematurity is the major risk factor** of post-operative apnoea, and cardiorespiratory monitoring is strongly recommended.

THE WALL STREET JOURNAL.

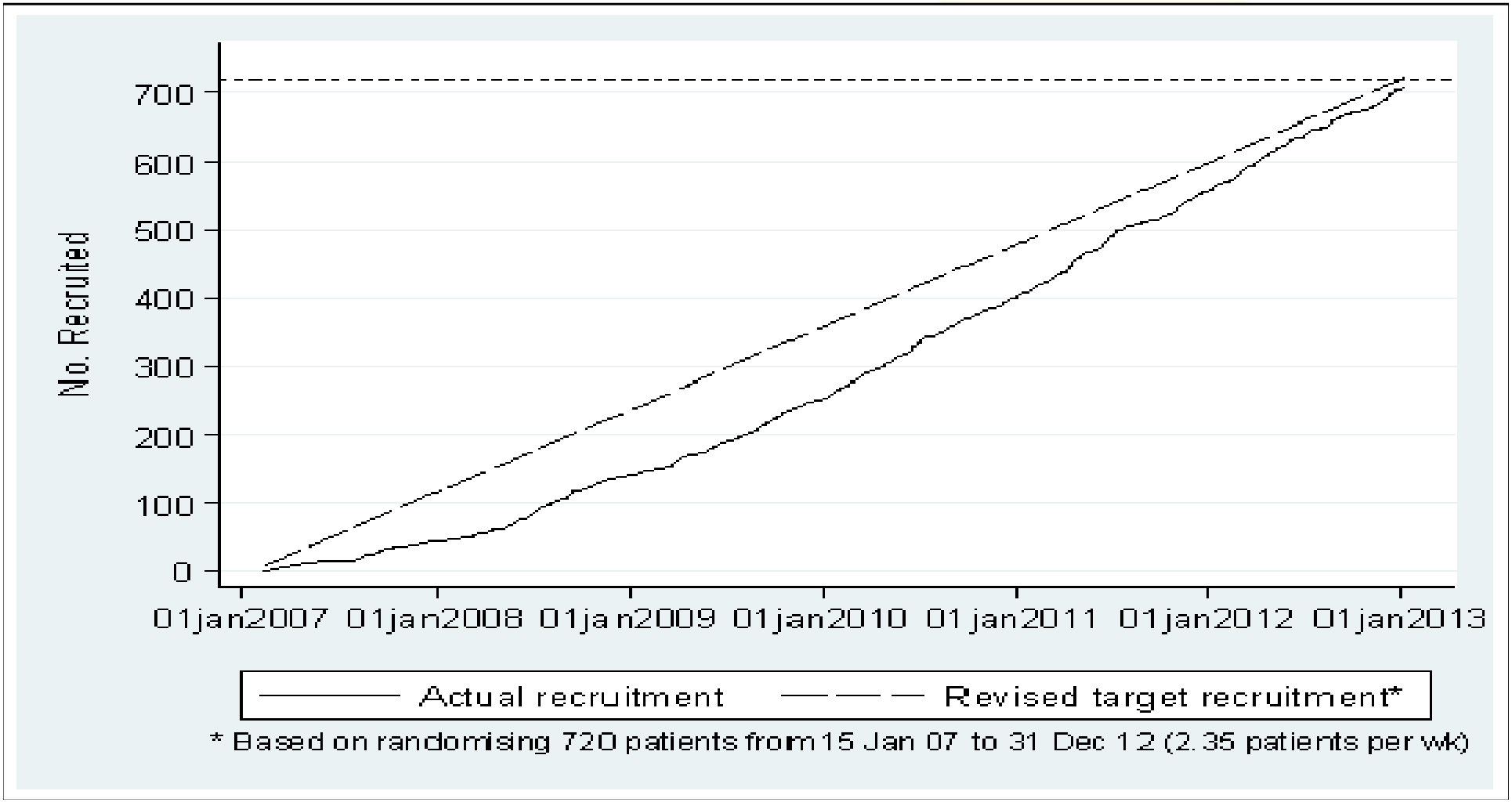
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A Less Risky Anesthesia for Babies



Lesson two – challenges of large a RCT

A 10-year trial

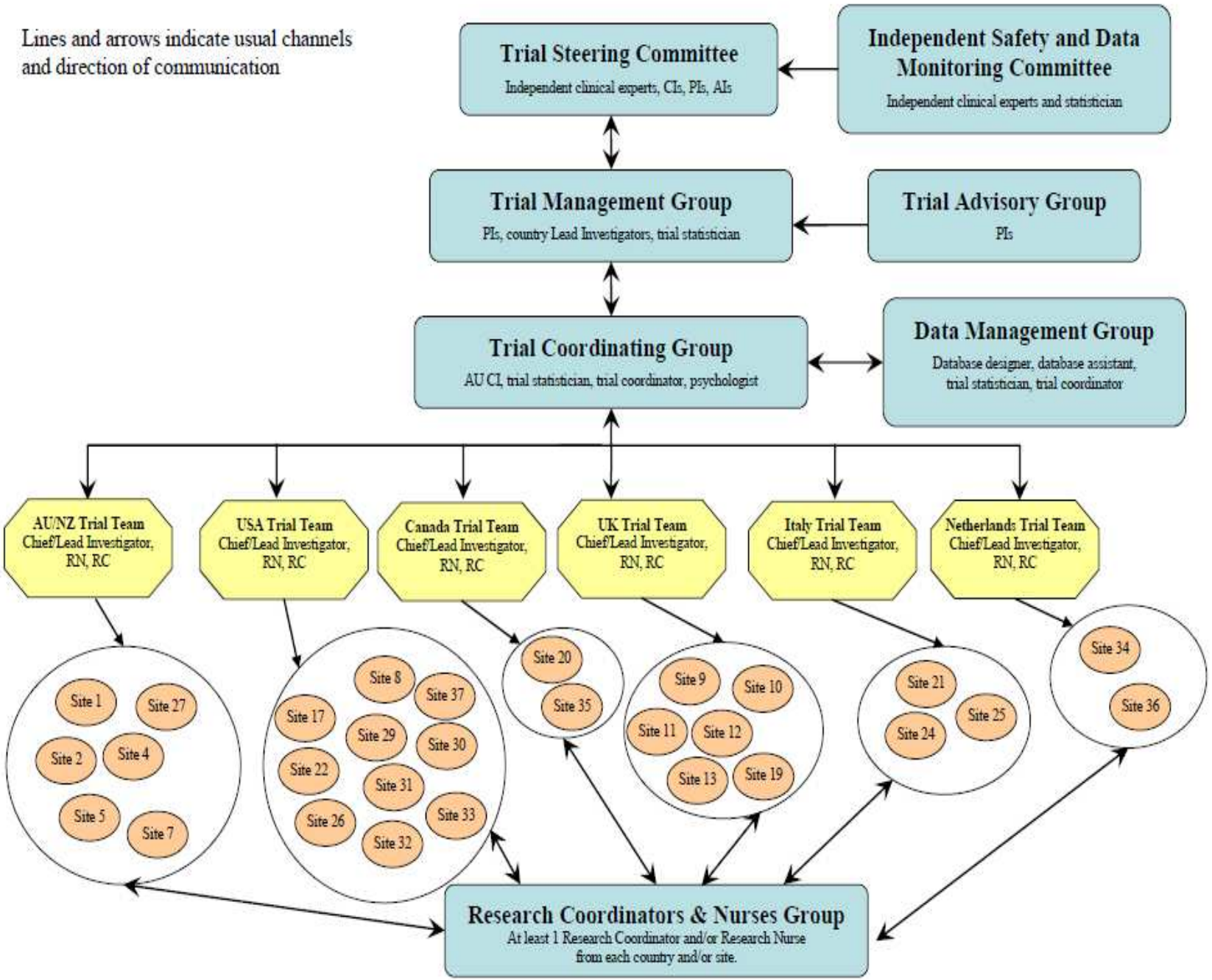


Ethic approval time in 2007-2008

- UK: 2½ years
- USA: 6-12 months *(3 years where funding needed)*
- The Netherlands 9 months
- NZ: 6 months
- Australia: 4-6 months
- Canada: 2-3 months
- Italy: 2-3 months



GAS – Organisational Structure





- Leadership
- Communication
- Maintaining enthusiasm
- Who needs to be paid
- Who is responsible for what
- Training of staff
- Phases of study

Principal Investigators

Expert Advisors

Coordinators

Site Leaders

Anaesthetists

Statisticians

Nurses

Database Managers

Data Managers

Data Entry

Psychologists

Paediatricians



- GAS Study was COSTLY
- Cannot start without funding
- Cannot get funding without evidence of feasibility
- Costs & funding structures vary enormously





Italian funding for GAS Study- GANTT diagram

Young Researchers Grant 2012-14

Clinical Trial Grant 2015-17

WPs	Sites	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Wp 1	1												
Wp 2	1												
Wp 2	2,3												
Wp 3	1,2,3												
Wp 4	1												
Wp 4	2,3												
Wp 5	1,2,3												
Wp 6	1												
Wp 6	2,3												
Wp 7	1,2,3												

Orange: recruitment

Yellow: 2-year follow-up

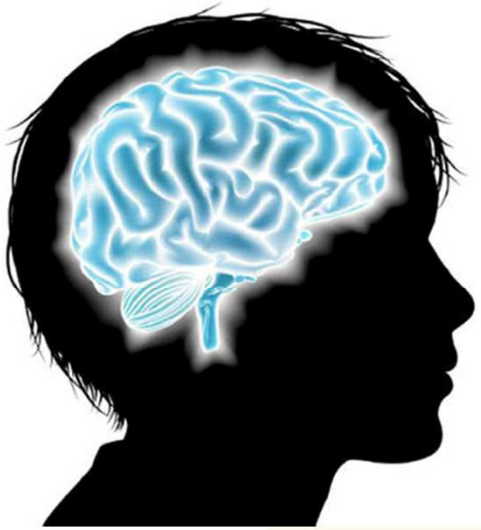
Blue: 5 year follow-up

Grey: data management and publications



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Lesson three – anaesthesia & neurotoxicity



BMJ O

February 2

: final

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Box 1 Top ten research priorities for Anaesthesia and Perioperative Care (May 2015)

What can we do to stop patients developing chronic pain after surgery?

How can patient care around the time of emergency surgery be improved?

What long-term harm may result from anaesthesia, particularly following repeated anaesthetics?

What outcomes should we use to measure the 'success' of anaesthesia and perioperative care?

How can we improve recovery from surgery for elderly patients?

For which patients does regional (local) anaesthesia give better outcomes than general anaesthesia?

What are the effects of anaesthesia on the developing brain?

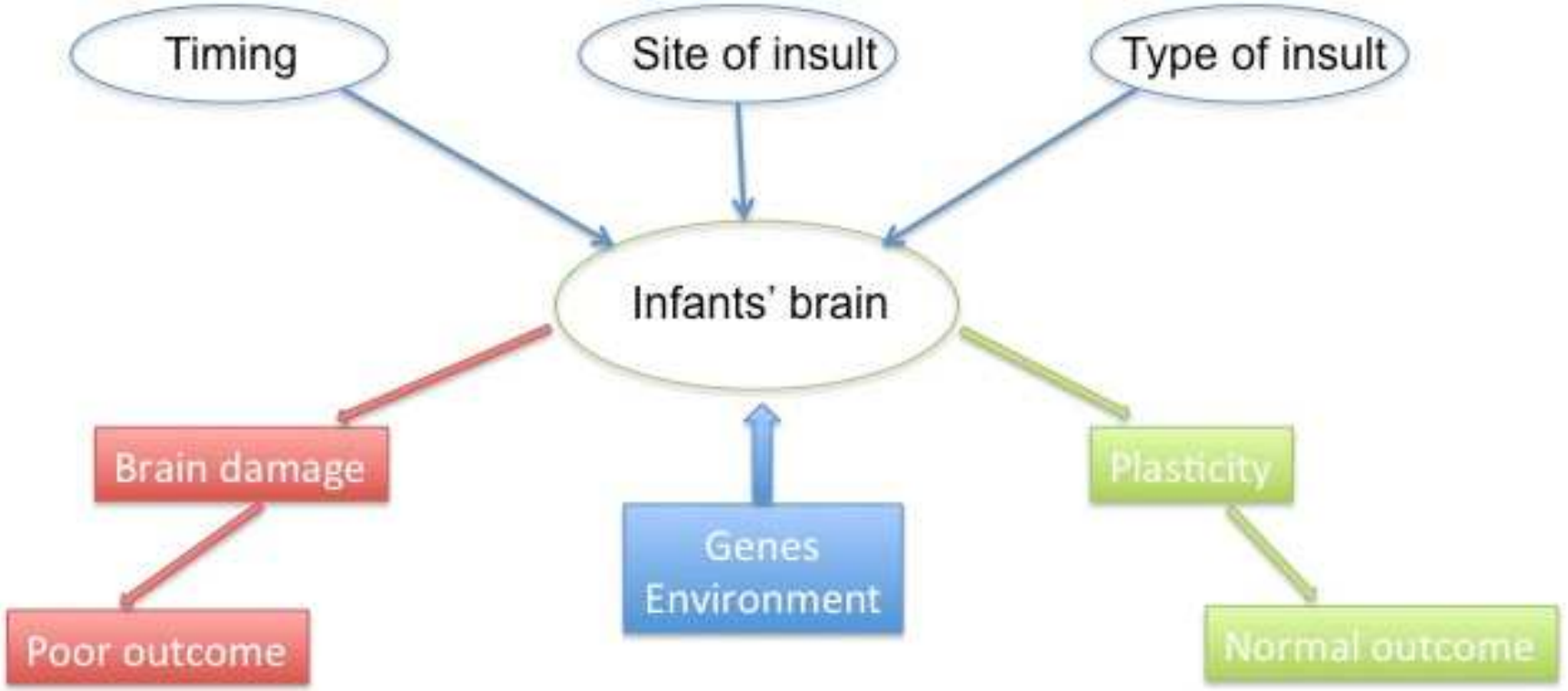
Do enhanced recovery programmes (fast-track surgery to speed up patient recovery) improve short and long-term outcomes?

How can preoperative exercise or fitness training, including physiotherapy, improve outcomes after surgery?

How can we improve communication between the teams looking after patients throughout their surgical journey?

Translating findings from animals to humans

Disma N, Hansen T. Minerva Anestesiologica 2016



SYSTEMATIC REVIEW

A systematic review of methodology applied during preclinical anesthetic neurotoxicity studies: important issues and lessons relevant to the design of future clinical research

Nicola Disma[1], Maria C. Mondardini[2], Niccolò Terrando[3], Anthony R. Absalom[4] & Federico Bilotta[5]

Andreas W. Loepke[1,2] & Laszlo Vutskits[3]

by definition, animal studies will never serve the same goals as human trials. While definitive answers regarding human applicability of anesthetic exposure early in life on long-term neurocognitive development will therefore have to come from clinical studies, properly assessed animal studies will contribute to advance patient safety and improve clinical outcomes by elucidating the phenomenon's mechanism, as envisioned by

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Anesthetic Neurotoxicity — Clinical Implications of Animal Models

Bob A. Rappaport, M.D., Santhanam Suresh, M.D., Sharon Hertz, M.D., Alex S. Evers, M.D., and Beverley A. Orser, M.D., Ph.D.

N ENGL J MED 372;9 NEJM.ORG FEBRUARY 26, 2015

brain. While we await clinical studies that can definitively determine whether anesthetics cause injury in humans, surgeons, anesthesiologists, and parents should consider carefully how urgently surgery is needed, particularly in children under 3 years of age.



What I have learned so far: conclusions

- The GAS trial was a great opportunity (research and life)
- Network is of paramount relevance
- Anaesthesia and neurocognitive outcome still in the top ten research priorities
- One trial cannot answer all the questions (multiple anaesthesia, long anaesthesia, etc.)
- If confirmed, GAS data at 5 years of age will provide incontrovertible evidence of safety, applicable to the majority of surgical procedures performed in infants and neonates



Sites involved

Australia and New Zealand :

- Royal Children's Hospital, Melbourne
- Monash Medical Centre, Melbourne
- Cabrini Hospital Melbourne
- Casey Hospital Melbourne
- Women's and Children's , Adelaide
- Princess Margaret Hospital, Perth
- Starship Children's Hospital, Auckland

USA:

- Children's Hospital, Boston
- Children's Memorial Hospital Chicago
- Dartmouth Hitchcock Medical Centre
- Vanderbilt Children's Hospital, Nashville
- The University of Iowa Hospital,
- Children's Medical Centre, Dallas
- Children's Hospital of Philadelphia
- Seattle Children's Hospital
- The Children's Hospital, Denver
- The University of Vermont/Fletcher Allen Health Care in Burlington, Vermont

UK :

- Royal Hospital for Sick Children, Glasgow
- Bristol Royal Hospital for Children
- Birmingham Children's Hospital NHS Trust
- Royal Belfast Hospital for Sick Children
- Royal Liverpool Children's NHS-Alder Hay Hospital
- Sheffield Children's Hospital

Italy:

- Gaslini Hospital for Children, Genoa
- Buzzi Children's Hospital, Milan
- Ospedali Riuniti, Bergamo

The Netherlands:

- Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands
- Universitair Medisch Centrum Groningen

Canada:

- Montreal Children's Hospital, Canada
- Centre de Recherche CHU Sainte-Justine, Canada



- **Mary Ellen McCann**
- **Nicola Disma**
- **Jurgen De Graaff**
- **Davinia Withington**
- **Liam Dorris**
- **Graham Bell**

- Robyn Stargatt
- David Bellinger
- Tibor Schuster
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- Pollyanna Hardy
- Rod Hunt
- Michael Takagi
- Gaia Giribaldi
- Penelope Hartmann

- Ida Salvo
- Neil Morten
- Britta von Ungern Sternberg
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- Anne Lynn
- Joss Thomas
- David Polaner
- Oliver Bagshaw
- Peter Szmuk
- Anthony Absalom
- Geoff Frawley
- Charles Berde
- Gillian Ormond
- Jacki Marmor
- **The GAS Consortium**



Trial steering committee

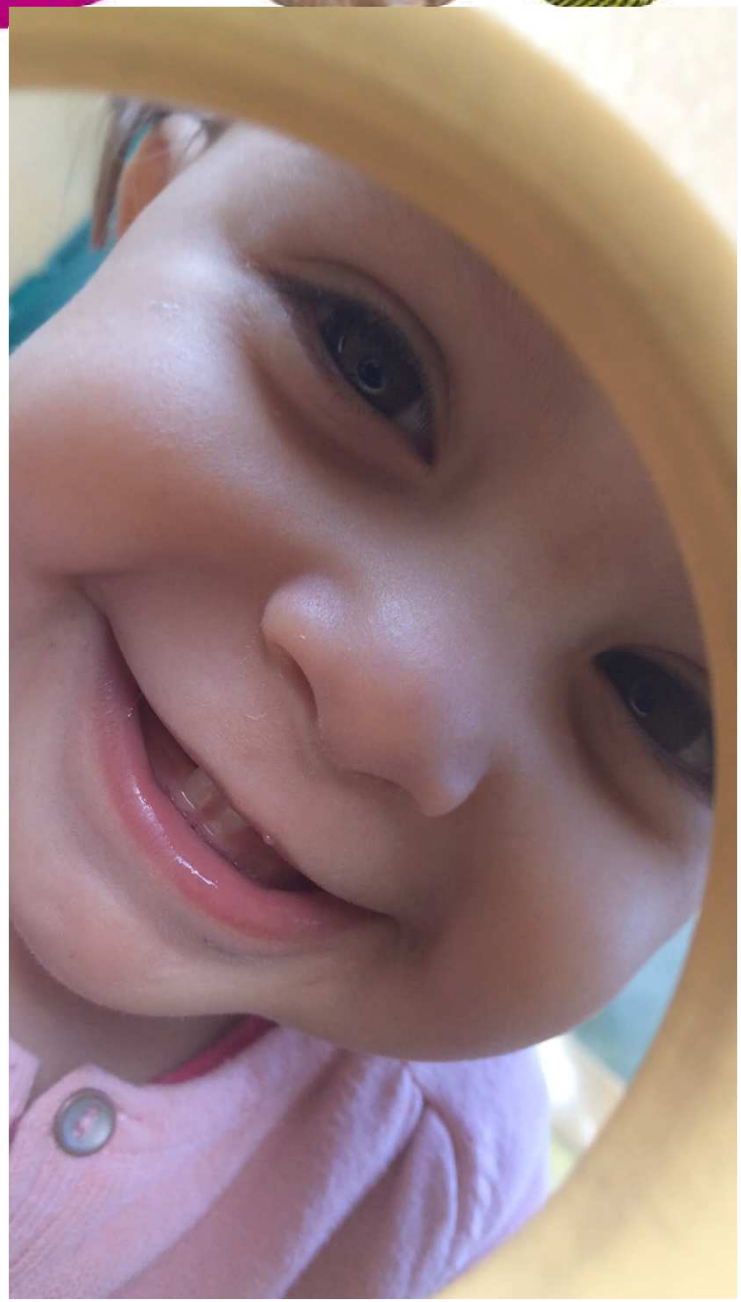
- Paul Myles
- Kate Leslie
- Neil McIntosh
- Andy Wolf
- John Carlin
- *Andrew Davidson*
- *Mary Ellen McCann*
- *Nicola Disma*
- *Davinia Withington*
- *Jurgen De Graaff*
- *Rod Hunt*
- *David Bellinger*
- *Charles Berde*

Data monitoring committee

- Jonathan de Lima
- Greg Hammer
- Val Gebski
- David Field
- Dick Tibboel



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Grazie per l'attenzione

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Authors of the GAS-Study. From left to right: Nicola Disma, Andrew Davidson and Jurgen de Graaff