Pragmatic trials for children with congenital heart disease - insights from the NITRIC Trial

NIH Pragmatic Trials, February 3rd

Luregn J Schlapbach, MD, PhD, FCICM, email: luregn.schlapbach@kispi.uzh.ch

on behalf of the NITRIC Study Group, the ANZICS Clinical Trials Group, and the ANZICS Paediatric Study Group

ANZICS Paediatric Study Group

COI & Funding

LJS:

- Funding from NHMRC, MRFF, SNF, PHRT/SPHN, Nomis Foundation, NIH

NITRIC trial:

- National Health and Medical Research Council, Australia
- HeartKids Foundation, Australia
- Children's Hospital Foundation, Brisbane, Australia
- Perth Children's Hospital Foundation, Australia
- Green Lane Research and Educational Fund, New Zealand
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- Health Research Council of New Zealand Fellowship to Paul Young
- The Operational Infrastructure Support Program, Victorian Government
- Dutch national Health Insurance Innovation Fund.

PICU TRIALS ARE DIFFICULT.

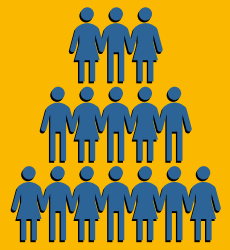
Heterogenous patient cohort

Complex consent

Low mortality

Lack of infrastructure

PICU TRIALS ARE POSSIBLE.



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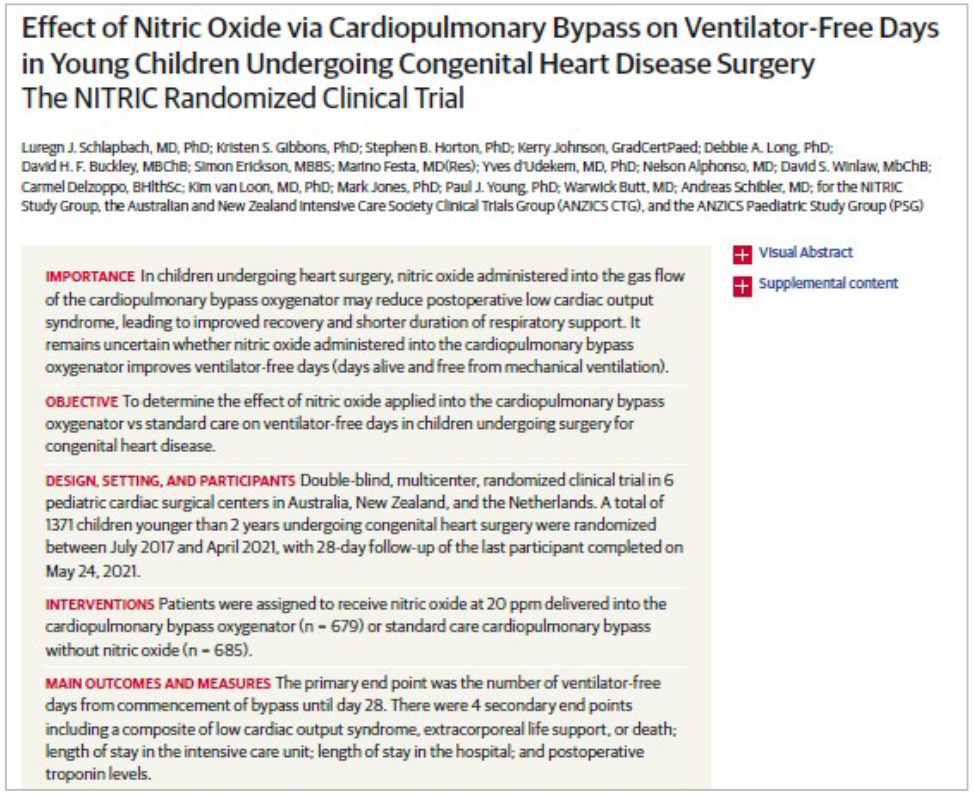

Effect of Nitric Oxide via Cardiopulmonary Bypass on Ventilator-Free Days in Young Children Undergoing Congenital Heart Disease Surgery
The NITRIC Randomized Clinical Trial

Luregn J. Schlapbach, MD, PhD; Kristen S. Gibbons, PhD; Stephen B. Horton, PhD; Kerry Johnson, GradCertPaed; Debbie A. Long, PhD; David H. F. Buckley, MBChB; Simon Erickson, MBBS; Marino Festa, MD(Res); Yves d'Udekem, MD, PhD; Nelson Alphonso, MD; David S. Winlaw, MbChB; Carmel Delzoppo, BHlthSc; Kim van Loon, MD, PhD; Mark Jones, PhD; Paul J. Young, PhD; Warwick Butt, MD; Andreas Schibler, MD; for the NITRIC Study Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), and the ANZICS Paediatric Study Group (PSG)

Visual Abstract
Supplemental content

IMPORTANCE In children undergoing heart surgery, nitric oxide administered into the gas flow of the cardiopulmonary bypass oxygenator may reduce postoperative low cardiac output syndrome, leading to improved recovery and shorter duration of respiratory support. It remains uncertain whether nitric oxide administered into the cardiopulmonary bypass oxygenator improves ventilator-free days (days alive and free from mechanical ventilation).

OBJECTIVE To determine the effect of nitric oxide applied into the cardiopulmonary bypass oxygenator vs standard care on ventilator-free days in children undergoing surgery for congenital heart disease.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, multicenter, randomized clinical trial in 6 pediatric cardiac surgical centers in Australia, New Zealand, and the Netherlands. A total of 1371 children younger than 2 years undergoing congenital heart surgery were randomized between July 2017 and April 2021, with 28-day follow-up of the last participant completed on May 24, 2021.

INTERVENTIONS Patients were assigned to receive nitric oxide at 20 ppm delivered into the cardiopulmonary bypass oxygenator (n = 679) or standard care cardiopulmonary bypass without nitric oxide (n = 685).

MAIN OUTCOMES AND MEASURES The primary end point was the number of ventilator-free days from commencement of bypass until day 28. There were 4 secondary end points including a composite of low cardiac output syndrome, extracorporeal life support, or death; length of stay in the intensive care unit; length of stay in the hospital; and postoperative troponin levels.

Luregn J. Schlapbach, MD, PhD; Kristen S. Gibbons, PhD; Stephen B. Horton, PhD; Kerry Johnson, GradCertPaed; Debbie A. Long, PhD; David H. F. Buckley, MBChB; Simon Erickson, MBBS; Marino Festa, MD(Res); Yves d'Udekem, MD, PhD; Nelson Alphonso, MD; David S. Winlaw, MbChB; Carmel Delzoppo, BHlthSc; Kim van Loon, MD, PhD; Mark Jones, PhD; Paul J. Young, PhD; Warwick Butt, MD; Andreas Schibler, MD; NITRIC Study Group, Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), ANZICS Paediatric Study Group (PSG)

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The NITRIC Randomized Clinical Trial

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ANZICS Paediatric Study Group

Content

- The NITRIC trial
- Critical Review of what we did
- Beyond NITRIC

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Acknowledgment of Country

We acknowledge the Traditional Owners and their custodianship of the land on which this trial was conducted.

We pay our respects to their Ancestors and their descendants, who continue cultural and spiritual connections to Country.

We recognise their valuable contributions to Australian and global society.

The burden of congenital heart disease

- About 1 in 100 newborn children (40,000 p.a. in the US)
- About 25% require surgery before age 2 years
- Most surgeries require cardiopulmonary bypass
- Mortality in pediatric heart centers 1-2%
- >1.5 million adult CHD survivors in the U.S.
- Annual inpatient costs due to CHD >$5.6 billion
- Risk for long-term cognitive, behavioral, and physical sequelae

Triedman JK, Newburger JW. Circulation. 2016;133(25):2716-2733
Virani SS, Alonso A, Aparicio HJ, et al; Circulation. 2021;143(8):e254-E743
Simeone RM, Oster ME, Cassell CH, et al. Birth Defects Res A Clin Mol Teratol. 2014;100(12):934-943;
Feldmann M, Bataillard C, Ehrler M, et al. Pediatrics. 2021;148(4):e2021050875.

Low cardiac output syndrome

- Cardiopulmonary bypass
- Surgical incision/trauma
- Reperfusion injury

→

- Complement & coagulation system activation
- Platelet + leukocyte activation
- Endothelial dysfunction
- Cytokine release (peak @ 6-12hrs)

Low cardiac output syndrome (LCOS) affects up to 26% of patients

Myocardial dysfunction with insufficient O_2 delivery to tissues

→delayed recovery, increased organ support (ventilation), worse short- and long-term outcomes

Hoffman TM, Wernovsky G, Atz AM, et al. Circulation. 2003;107(7):996-1002.
Levy JH, Tanaka KA. Ann Thorac Surg. 2003;75 (2):S715-S720.

Potential of Nitric Oxide to mitigate CPB-related side effects

- NO functions include endothelial regulation, inhibition of leukocyte adhesion & platelet activation, local vasodilatation
- CPB: - constitutive nitric oxide synthase (eNOS) downregulated
  - oxidative stress lowers NO levels
- In vitro and in vivo studies: NO administration attenuates myocardial injury during heart surgery

Jones SP, Bolli R. J Mol Cell Cardiol 2006;40:16–23.
Jones SP, Girod WG, Palazzo AJ, et al. Am J Physiol 1999;276:H1567–73.
Minamishima S, Kida K, Tokuda K, et al. Circulation 2011;124:1645–53.
Schulz R, Kelm M, Heusch G. Cardiovasc Res 2004;61:402–13.

Pilot data on NO during CPB in children

- **Checchia et al:** single center; n=16 patients with Tetralogy of Fallot randomized to 20ppm NO during CPB vs standard CPB
  - mechanical ventilation mean (SD) 8.4 (7.6) vs 16.3 (6.5) hours; P<.05
  - ICU LOS 53.8 (19.7) vs 79.4 (37.7) hours; P<.05
  - lower troponin and BNP in the NO arm

- **James et al:** single center; n=198 children with CHD surgery randomized to 20ppm NO during CPB vs standard CPB
  - LCOS 15 vs. 31 %, p = 0.007
  - effect on LCOS in younger patients and those with more complex surgery:
    < 6 wks 20 vs. 52 %; 6 wks – 2yrs 6 vs. 24 %; complex: 17% vs. 48%
  - ECMO 1% vs. 8%, p = 0.014
  - LCOS associated with duration of ventilation, ICU & hospital LOS

Checchia PA, Bronicki RA, Muenzer JT, et al. J Thorac Cardiovasc Surg. 2013; 146(3):530-536.
James C, Millar J, Horton S, Brizard C, Molesworth C, ButtW. Intensive Care Med. 2016;42(11):1744-1752.

Pilot

Table 2 Primary and secondary outcomes

	Nitric oxide ($n = 101$)	Control ($n = 97$)	p value
Primary outcome			
Incidence of low cardiac output syndrome (LCOS)	15 (15 %)	30 (31 %)	0.007
Secondary outcomes			
Duration of ventilation (h)	20.0 (10.0–63.0)	24.0 (12.0–89.0)	0.120
ICU stay (h)	48.0 (24.0–105.0)	72.0 (26.0–144.0)	0.111
Hospital stay (days)	9.0 (6.0–17.0)	12.0 (6.0–20.0)	0.164
Peritoneal dialysis (%)	23 (23 %)	24 (25 %)	0.745

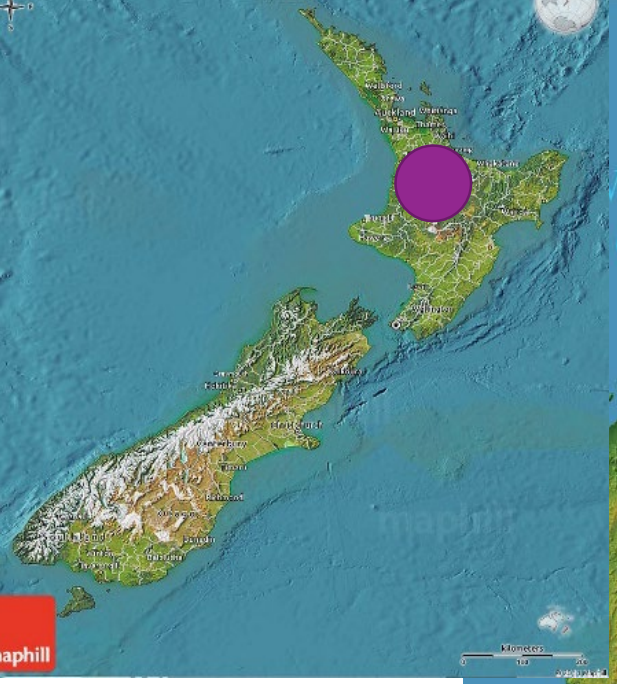
James C, Millar J, Horton S, Brizard C, Molesworth C, ButtW. Intensive Care Med. 2016;42(11):1744-1752.

Hypothesis

- **P:** In children undergoing surgery for congenital heart disease
- **I:** nitric oxide applied into the cardiopulmonary bypass oxygenator
- **C:** compared to standard care cardiopulmonary bypass (no NO)
- **O:** will result in more ventilator-free days

Study design

- investigator-initiated multicenter, randomized, double-blind, parallel-group trial
- Recruitment in 6 pediatric cardiac surgical centers in Australia, New Zealand, and The Netherlands
- Trial management by the Child Health Research Center at The University of Queensland; HREC approved by participating sites
- Endorsed by ANZICS CTG and ANZICS PSG
- Australian New Zealand Clinical Trials Registry ACTRN12617000821392




TIMOR SEA
ARAFURA SEA
Bathurst I
Darwin
Arnhem Land
GULF OF CARPENTARIA
Great
SOUTH PACIFIC OCEAN
INDIAN OCEAN
Kimberley Plateau
Cape York Peninsula
Cairns
Barrier
Barkly Tableland
Townsville
Tanami Desert
Great Sandy Desert
Reef
Great Dividing Range
Hamersley Range
Macdonnell Ranges
Alice Springs
Gibson Desert
Great Artesian Basin
Uluru (Ayers Rock)
Simpson Desert
Sunshine Coast
Great Victoria Desert
Strzelecki Desert
Nullarbor Plain
Hindes Ranges
Newcastle
Central Coast
Sydney
Wollongong
GREAT AUSTRALIAN BIGHT
Adelaide
Canberra
Kangaroo Island
Mt. Kosciuszko (2,228 m)
SOUTHERN OCEAN
TASMAN SEA
BASS STRAIT
INDIAN OCEAN
N
King Island
Flinders Island
Tasmania
Hobart
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Inclusion and Exclusion criteria

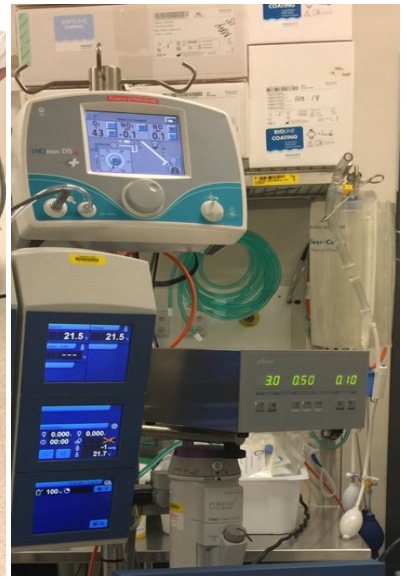
Inclusion criteria

- All infants and children <2 years of age undergoing open heart surgery on cardiopulmonary bypass.
- Elective cardiac surgery and consent of parents/guardian.

Exclusion criteria

- elevated PVR requiring drug treatment
- ECLS
- Chronic ventilator dependency
- Sepsis, ARDS, or high dose vasoactive drugs prior to surgery (inotrope score ≥15)
- Cardiac arrest within one week (7 days) prior to surgery
- Emergency cardiac surgery precluding informed consent
- Pre-existing methaemoglobinemia (MetHb>3%).

Intervention



- NO connected to the gas inlet point of CPB oxygenator
- NO concentration @20ppm
- continuous sampling from start of CPB (cannulation) until decannulation
- Arterial blood gas pCO_2 targets as per local practice
- Mallinckrodt Pharmaceuticals and EKU Electronics provided NO delivery devices but had no involvement in design, conduct, analyses nor interpretation of the study

Controls and perioperative care

- No use of NO during CPB in controls

- All patients could receive inhalational NO during / after surgery if considered indicated by treating team
- No change in other perioperative care
- Pragmatic design: No prescription of pre-surgical, anaesthetic, surgical, perfusion, and ICU management (including respiratory management and weaning) procedures

Randomisation and blinding

- stratification variables: age group (<6 weeks vs ≥6 weeks), cardiac physiology (univentricular vs biventricular)
- REDCap trial database at The University of Queensland
- 1:1 randomization using permuted blocks (block sizes, 4, 6, 8, 10)
- Perfusionists performed randomization and were aware of allocation
- Intervention and control arm both had full NO on CPB delivery setup
- NO monitoring covered and only visible to perfusionist
- Surgical, anaesthetic, and PICU staff kept blinded

End Points

- **Primary:** ventilator-free days (VFD) from start of cardiopulmonary bypass to day 28; only invasive vent; zero value in children who died
- **Secondary:**
  - composite of LCOS*, ECMO (<48h), and/or mortality (≤28d)
  - ICU LOS and hospital LOS
  - postoperative troponin levels

  *lactate >4 mmol/L + avO_2 Extraction >35 and/or VISS ≥15; measured @0, 6, 12, 24, 48hrs
- **Exploratory:**
  - VISS, lactate, avO_2 Extraction, creatinine values @0, 6, 12, 24, 48hrs
  - AKI, RRT, iNO, PELOD-2

- **Ongoing investigations:**
  - serum cytokines and host transcriptomics pre/post CPB
  - healthcare costs
  - questionnaire-by-proxy follow-up @ 12 months

Sample size considerations

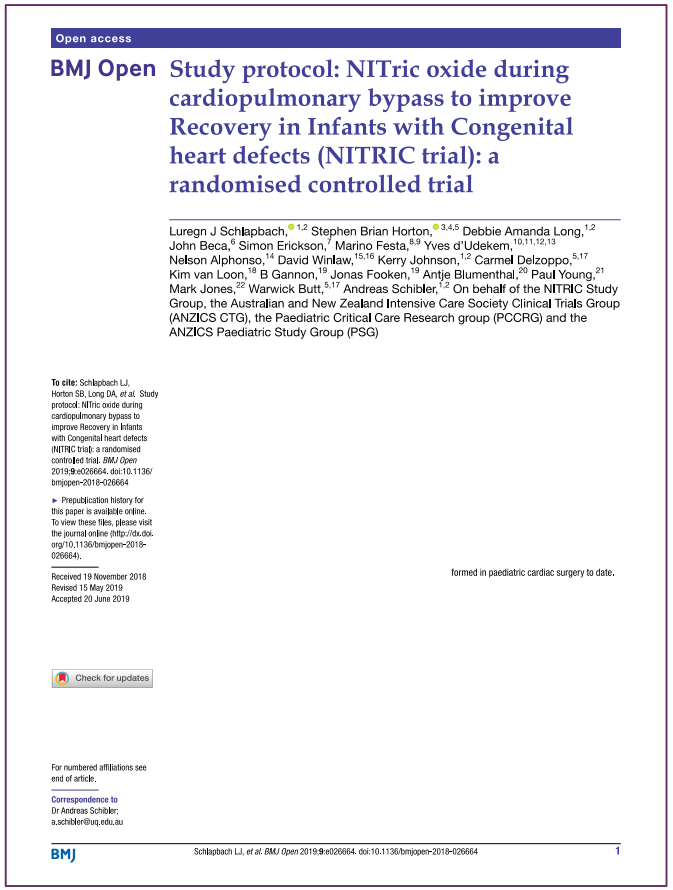
- Informed by Melbourne pilot (James et al. ICM 2016)
- Assuming mean (±SD) number of 22.5 ± 8.10 ventilator-free days in control arm
- power of 90% to detect a small effect size (Cohen's d = 0.2; absolute between-group difference of 1.66 ventilator-free days, i.e. 40 hours)
- 15% inflation to account for rank-based testing and 10% inflation to account for withdrawals and interim analyses
- two-sided type I error rate of 0.05
- N=1320 estimated

Statistical analysis plan

Protocol submitted Nov 19 2018, published Aug 15 2019:
Schlapbach LJ et al. BMJ Open 2019;9(8):e026664.

SAP submitted Aug 2020 published March 2021:
Gibbons KS et al. Crit Care Resusc 2021;23(1):47-58

Analysis code uploaded on GitHub Nov 26, 2021:
https://github.com/kgibbons44/NITRICAnalysis/



Open access

BMJ Open

Study protocol: NITric oxide during cardiopulmonary bypass to improve Recovery in Infants with Congenital heart defects (NITRIC trial): a randomised controlled trial

Luregn J Schlapbach,[1,2] Stephen Brian Horton,[3,4,5] Debbie Amanda Long,[1,2] John Beca,[6] Simon Erickson,[7] Marino Festa,[8,9] Yves d'Udekem,[10,11,12,13] Nelson Alphonso,[14] David Winlaw,[15,16] Kerry Johnson,[1,2] Carmel Delzoppo,[5,17] Kim van Loon,[18] B Gannon,[19] Jonas Fooken,[19] Antje Blumenthal,[20] Paul Young,[21] Mark Jones,[22] Warwick Butt,[5,17] Andreas Schibler,[1,2] On behalf of the NITRIC Study Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), the Paediatric Critical Care Research group (PCCRG) and the ANZICS Paediatric Study Group (PSG)

To cite: Schlapbach LJ, Horton SB, Long DA, *et al*. Study protocol: NITric oxide during cardiopulmonary bypass to improve Recovery in Infants with Congenital heart defects (NITRIC trial): a randomised controlled trial. *BMJ Open* 2019;**9**:e026664. doi:10.1136/bmjopen-2018-026664

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-026664).

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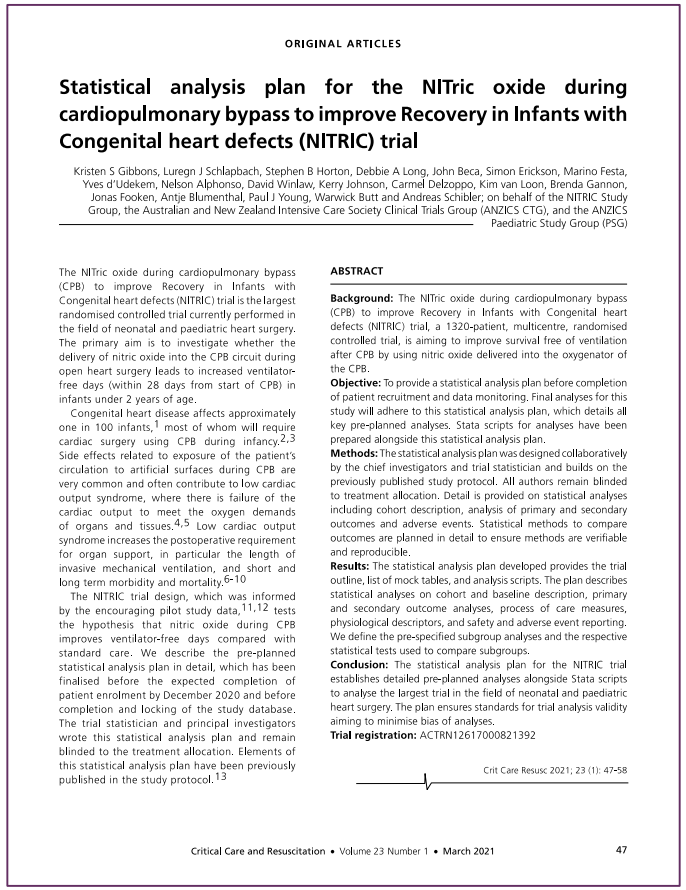
Check for updates

For numbered affiliations see end of article.

Correspondence to
Dr Andreas Schibler;
a.schibler@uq.edu.au

formed in paediatric cardiac surgery to date.



ORIGINAL ARTICLES

Statistical analysis plan for the NITric oxide during cardiopulmonary bypass to improve Recovery in Infants with Congenital heart defects (NITRIC) trial

Kristen S Gibbons, Luregn J Schlapbach, Stephen B Horton, Debbie A Long, John Beca, Simon Erickson, Marino Festa, Yves d'Udekem, Nelson Alphonso, David Winlaw, Kerry Johnson, Carmel Delzoppo, Kim van Loon, Brenda Gannon, Jonas Fooken, Antje Blumenthal, Paul J Young, Warwick Butt and Andreas Schibler; on behalf of the NITRIC Study Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), and the ANZICS Paediatric Study Group (PSG)

The NITric oxide during cardiopulmonary bypass (CPB) to improve Recovery in Infants with Congenital heart defects (NITRIC) trial is the largest randomised controlled trial currently performed in the field of neonatal and paediatric heart surgery. The primary aim is to investigate whether the delivery of nitric oxide into the CPB circuit during open heart surgery leads to increased ventilator-free days (within 28 days from start of CPB) in infants under 2 years of age.

Congenital heart disease affects approximately one in 100 infants,[1] most of whom will require cardiac surgery using CPB during infancy.[2,3] Side effects related to exposure of the patient's circulation to artificial surfaces during CPB are very common and often contribute to low cardiac output syndrome, where there is failure of the cardiac output to meet the oxygen demands of organs and tissues.[4,5] Low cardiac output syndrome increases the postoperative requirement for organ support, in particular the length of invasive mechanical ventilation, and short and long term morbidity and mortality.[6-10]

The NITRIC trial design, which was informed by the encouraging pilot study data,[11,12] tests the hypothesis that nitric oxide during CPB improves ventilator-free days compared with standard care. We describe the pre-planned statistical analysis plan in detail, which has been finalised before the expected completion of patient enrolment by December 2020 and before completion and locking of the study database. The trial statistician and principal investigators wrote this statistical analysis plan and remain blinded to the treatment allocation. Elements of this statistical analysis plan have been previously published in the study protocol.[13]

ABSTRACT

Background: The NITric oxide during cardiopulmonary bypass (CPB) to improve Recovery in Infants with Congenital heart defects (NITRIC) trial, a 1320-patient, multicentre, randomised controlled trial, is aiming to improve survival free of ventilation after CPB by using nitric oxide delivered into the oxygenator of the CPB.

Objective: To provide a statistical analysis plan before completion of patient recruitment and data monitoring. Final analyses for this study will adhere to this statistical analysis plan, which details all key pre-planned analyses. Stata scripts for analyses have been prepared alongside this statistical analysis plan.

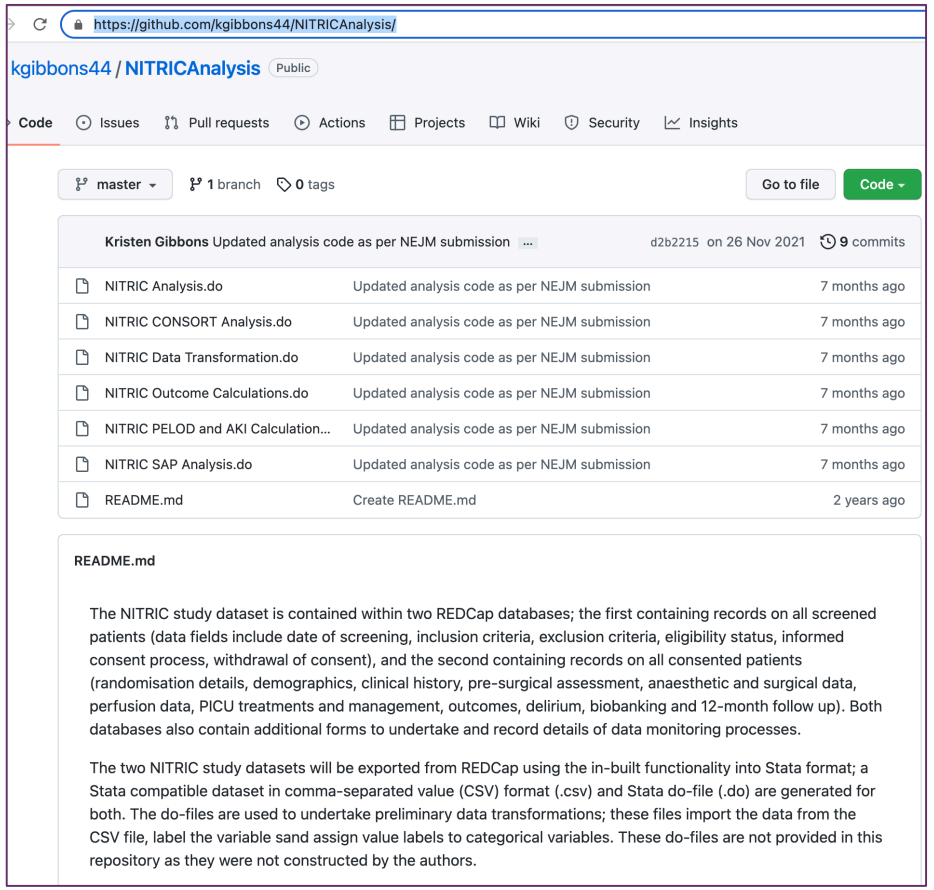
Methods: The statistical analysis plan was designed collaboratively by the chief investigators and trial statistician and builds on the previously published study protocol. All authors remain blinded to treatment allocation. Detail is provided on statistical analyses including cohort description, analysis of primary and secondary outcomes and adverse events. Statistical methods to compare outcomes are planned in detail to ensure methods are verifiable and reproducible.

Results: The statistical analysis plan developed provides the trial outline, list of mock tables, and analysis scripts. The plan describes statistical analyses on cohort and baseline description, primary and secondary outcome analyses, process of care measures, physiological descriptors, and safety and adverse event reporting. We define the pre-specified subgroup analyses and the respective statistical tests used to compare subgroups.

Conclusion: The statistical analysis plan for the NITRIC trial establishes detailed pre-planned analyses alongside Stata scripts to analyse the largest trial in the field of neonatal and paediatric heart surgery. The plan ensures standards for trial analysis validity aiming to minimise bias of analyses.

Trial registration: ACTRN12617000821392

Crit Care Resusc 2021; 23 (1): 47-58



https://github.com/kgibbons44/NITRICAnalysis/

kgibbons44 / NITRICAnalysis Public

Code Issues Pull requests Actions Projects Wiki Security Insights

master 1 branch 0 tags Go to file Code

Kristen Gibbons Updated analysis code as per NEJM submission ... d2b2215 on 26 Nov 2021 9 commits

NITRIC Analysis.do	Updated analysis code as per NEJM submission	7 months ago
NITRIC CONSORT Analysis.do	Updated analysis code as per NEJM submission	7 months ago
NITRIC Data Transformation.do	Updated analysis code as per NEJM submission	7 months ago
NITRIC Outcome Calculations.do	Updated analysis code as per NEJM submission	7 months ago
NITRIC PELOD and AKI Calculation...	Updated analysis code as per NEJM submission	7 months ago
NITRIC SAP Analysis.do	Updated analysis code as per NEJM submission	7 months ago
README.md	Create README.md	2 years ago

README.md

The NITRIC study dataset is contained within two REDCap databases; the first containing records on all screened patients (data fields include date of screening, inclusion criteria, exclusion criteria, eligibility status, informed consent process, withdrawal of consent), and the second containing records on all consented patients (randomisation details, demographics, clinical history, pre-surgical assessment, anaesthetic and surgical data, perfusion data, PICU treatments and management, outcomes, delirium, biobanking and 12-month follow up). Both databases also contain additional forms to undertake and record details of data monitoring processes.

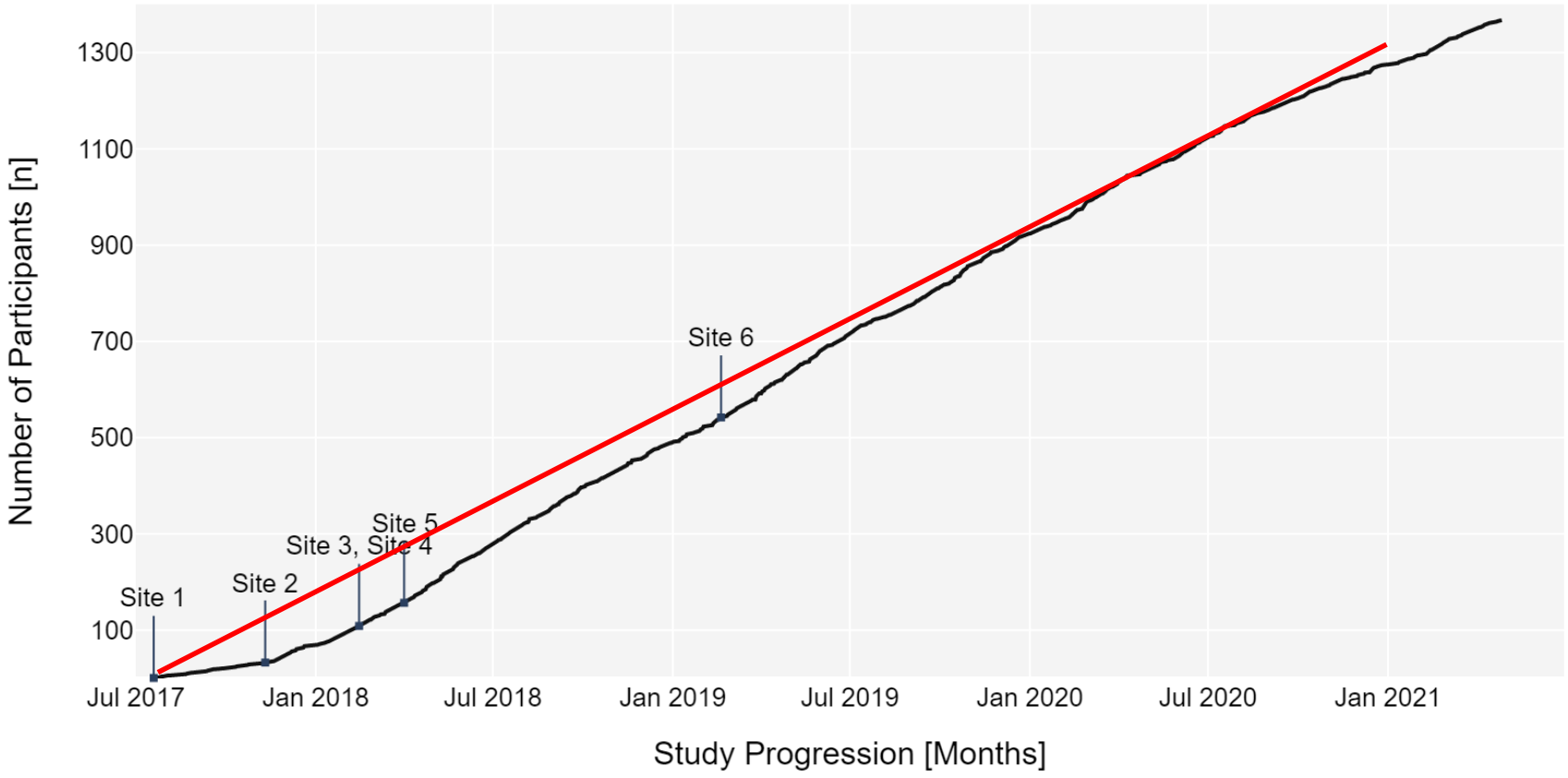
The two NITRIC study datasets will be exported from REDCap using the in-built functionality into Stata format; a Stata compatible dataset in comma-separated value (CSV) format (.csv) and Stata do-file (.do) are generated for both. The do-files are used to undertake preliminary data transformations; these files import the data from the CSV file, label the variable sand assign value labels to categorical variables. These do-files are not provided in this repository as they were not constructed by the authors.

ANZICS Paediatric Study Group

Statistical analysis plan

- interim analyses once 660 and 1000 patients had reached 28d (DSMB)
- Analyses on consented and randomised patients who received CPB
- Wilcoxon rank-sum test for unadjusted analysis
- differences between medians calculated using quantile regression after adjustment for stratification variables (age group, single ventricle physiology, and site)
- Pre-specified secondary analyses (considered exploratory)
  - secondary outcomes (regression models)
  - subgroup analyses on stratification subgroups
  - sensitivity analyses *a priori* adjusted for CPB duration, RACHS score, blood prime, sex, age, physiology, site

Recruitment July 2017 – April 2022



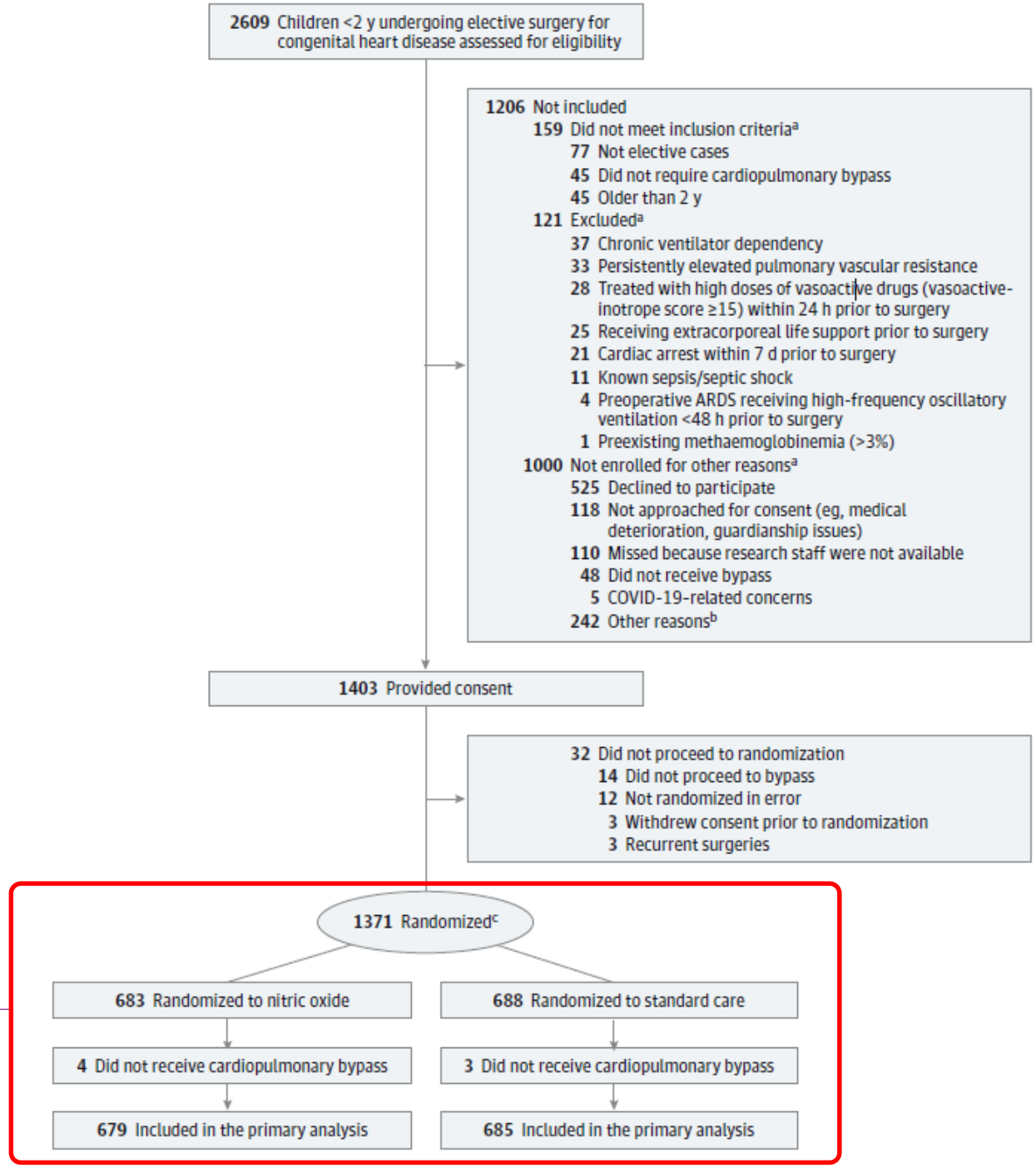
58% of eligible patients consented

71% of approached parents provided consent

ANZICS Paediatric Study Group

Recruitment

- 679 randomized to NO included
- 685 randomized to standard care included



Baseline characteristics

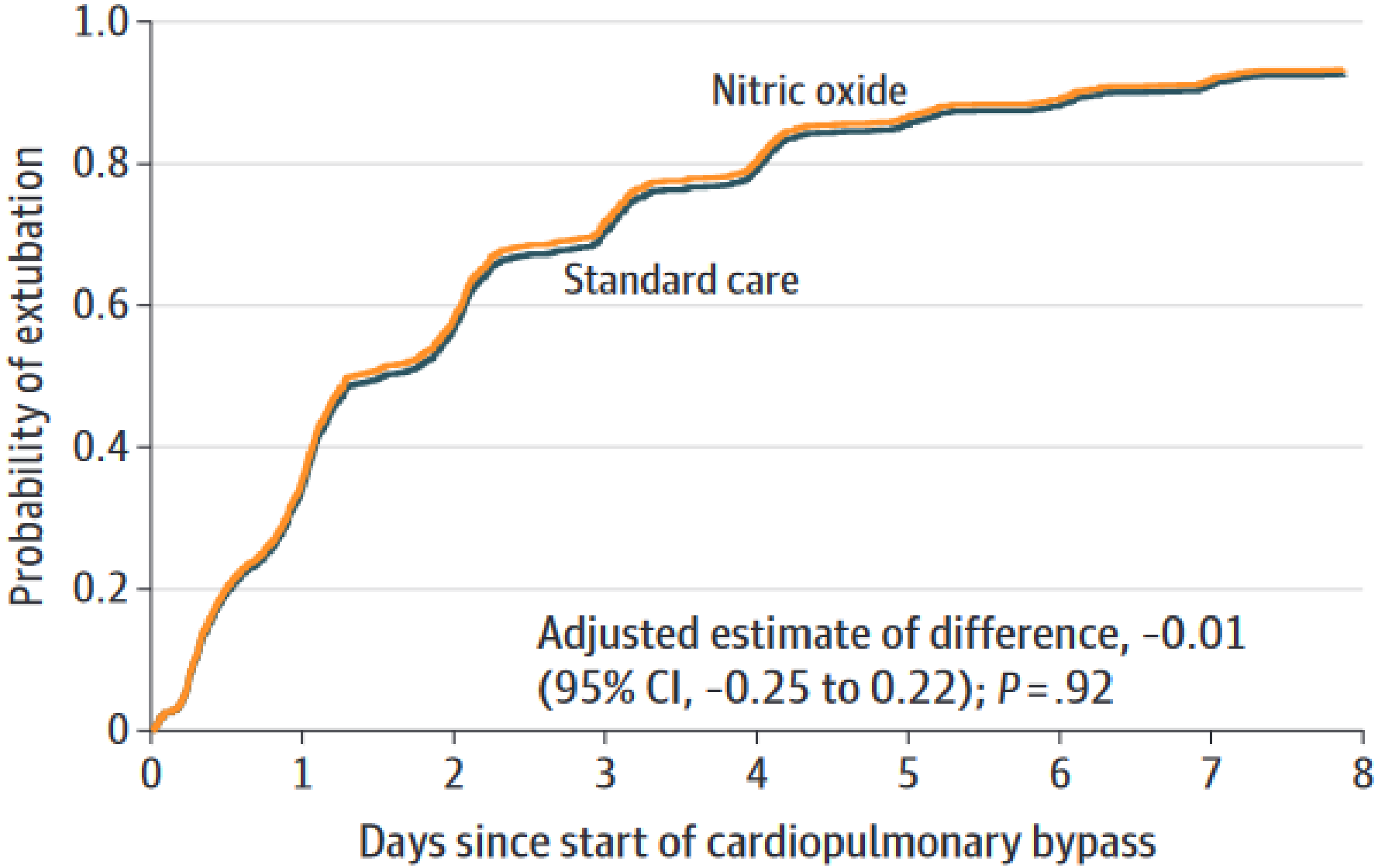
- Well balanced
- Median age 14 weeks
- VSD, TOF, ASD, TGA, HAA most common
- Median RACHS-2 2 (IQR 2,3)
- 20% in PICU before surgery
- 8% ventilated before surgery
- 18% congenital syndromes

Characteristic	Nitric Oxide N=679	Standard Care N=685
Age at randomisation (weeks)[a] *median (IQR)*	13.6 (2.3, 27.0)	14.2 (1.8, 30.6)
< 6 weeks *n (%)*	227 (33.4%)	232 (33.9%)
Weight (kg) *median (IQR)*	4.7 (3.5, 6.6)	4.8 (3.4, 7.0)
Female Sex *n (%)*	266 (39.2%)	317 (46.3%)
Congenital heart disease[a]		
Univentricular[a] *n (%)*	77 (11.3%)	76 (11.1%)
Biventricular[a] *n (%)*	602 (88.7%)	609 (88.9%)
Shunt lesions *n (%)*	454 (66.9%)	451 (65.8%)
VSD *n (%)*	271 (39.9%)	279 (40.7%)
TGA *n (%)*	105 (15.5%)	96 (14.0%)
ASD *n (%)*	102 (15.0%)	116 (16.9%)
AVSD *n (%)*	67 (9.9%)	56 (8.2%)
Right-sided obstructive lesions *n (%)*	196 (28.9%)	216 (31.5%)
Tetralogy of Fallot *n (%)*	105 (15.5%)	119 (17.4%)
Left-sided obstructive lesions *n (%)*	133 (19.6%)	153 (22.3%)
Hypoplastic aortic arch *n (%)*	70 (10.3%)	98 (14.3%)
HLHS *n (%)*	30 (4.4%)	32 (4.7%)
Various lesions *n (%)*	39 (5.7%)	32 (4.7%)
TAPVD *n (%)*	24 (3.5%)	18 (2.6%)
Pre-surgical ICU admission *n (%)*	142 (20.9%)	137 (20.0%)
Treatments prior to heart surgery		
Prostaglandin *n (%)*	132 (19.4%)	152 (22.2%)
Invasive ventilation *n (%)*	49 (7.2%)	56 (8.2%)
Inotropes *n (%)*	13 (1.9%)	13 (1.9%)
Comorbid congenital syndromes		
Congenital syndrome *n (%)*[d]	123 (18.1%)	120 (17.5%)

CPB procedures

Characteristic	Nitric Oxide N=679	Standard Care N=685	Unadjusted Estimate of Difference (95% CI)
Cardiopulmonary bypass characteristics			
Blood prime *n (%)*	679 (100%)	685 (100%)	-
CPB duration (min) *median (IQR)*	113 (71, 167)	114 (75, 166)	-1 (-11.6, 9.6)
Cross-clamp *n (%)*	641 (94.4%)	645 (94.2%)	0.2% (-2.2%, 2.7%)
Cross-clamp (min) *median (IQR)*	69 (44, 105)	71 (46, 107)	2 (-4.1, 8.1)
Deep hypothermic arrest *n (%)*	68 (10.0%)	60 (8.8%)	1.3% (-1.8%, 4.4%)
Duration of deep hypothermic arrest (min) *median (IQR)*	24 (7, 39)	12 (4, 36)	-12 (-25.3, -0.7)
Modified ultrafiltration used *n (%)*	598 (88.1%)	594 (86.7%)	1.4% (-2.2%, 4.9%)
Slow continuous ultrafiltration used *n (%)*	280 (41.2%)	292 (42.6%)	-1.4% (-6.6%, 3.8%)
Blood products received in theatre			
Red blood cells (mL/kg) *median (IQR)*	20.7 (11.7, 38.2)	18.1 (10.0, 33.8)	-2.5 (-6.3, 1.2)
Platelets (mL/kg) *median (IQR)*	16.1 (11.0, 21.3)	16.7 (11.9, 21.8)	0.6 (-0.8, 1.9)
Fresh frozen plasma (mL/kg) *median (IQR)*	52.1 (32.8, 78.7)	52.4 (27.2, 79.4)	-0.1 (8.3, -8.0)
Cryoprecipitate (mL/kg) *median (IQR)*	13.8 (10.0, 18.9)	13.5 (9.6, 19.5)	-0.3 (1.5, -1.0)
Drug treatments received in theatre			
Intravenous steroids *n (%)*	262 (38.6%)	257 (37.5%)	1.1% (-4.1%, 6.2%)
Inhaled Nitric Oxide *n (%)*	45 (6.6%)	41 (6.0%)	0.6% (-1.9%, 3.2%)
Administration of study drug (nitric oxide)			
Proportion of time spent on CPB with Nitric Oxide* *median (IQR)*	1.0 (1.0, 1.0)		

Primary endpoint: VFD @ 28 days

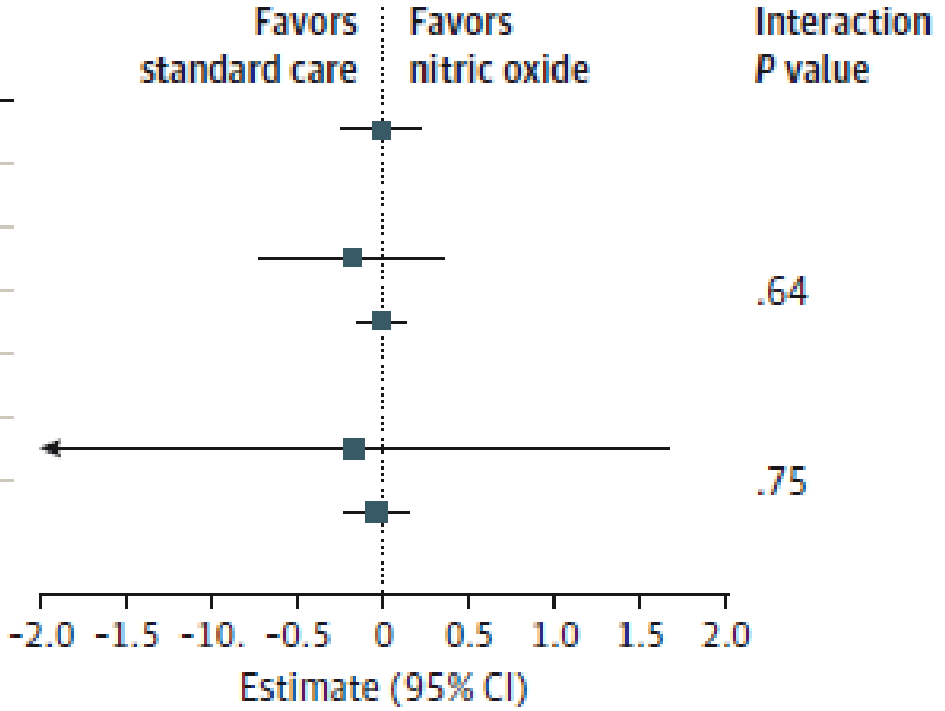


No. at risk

Standard care	685	166	57
Nitric oxide	679	148	62

Primary endpoint VFD – subgroup analyses

Group	Nitric oxide, No./total (%)	Standard care, No./total (%)	Estimate (95% CI)	Interaction *P* value
Overall[a]	679	685	-0.01 (-0.25 to 0.22)	
Age, wk[b]				
<6	227/459 (49.5)	232/459 (50.5)	-0.18 (-0.72 to 0.35)	.64
≥6	452/905 (49.9)	453/905 (50.1)	-0.01 (-0.15 to 0.13)	
Lesion[c]				
Univentricular	77/153 (50.3)	76/153 (49.7)	-0.17 (-2.01 to 1.67)	.75
Biventricular	601/1209 (49.7)	608/1209 (50.3)	-0.04 (-0.22 to 0.15)	



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Primary and secondary endpoints

Outcome	Nitric Oxide N=679	Standard Care N=685	Unadjusted Estimate of Difference (95% CI)	Adjusted Estimate of Difference (95% CI)[a]
Primary Outcome				
Ventilator-free days *median (IQR)*	26.6 (24.4, 27.4)	26.4 (24.0, 27.2)	0.18 (-0.11, 0.48)[b]	-0.012 (-0.25, 0.22)[c]
Secondary Outcomes				
Low cardiac output syndrome[d], need for extra corporeal life support or death *n (%)*	153 (22.5%)	143 (20.9%)	1.10 (0.85, 1.43)	1.12 (0.85, 1.47)
Length of stay in ICU (days) *median (IQR)*	3.0 (1.9, 5.9)	3.0 (1.9, 6.3)	0.98 (0.88, 1.10)	1.00 (0.90, 1.12)
Length of stay in hospital (days) *median (IQR)*	9.0 (6.0, 17.1)	9.1 (6.7, 17.8)	0.97 (0.87, 1.09)	0.97 (0.87, 1.09)
Troponin post-operatively[e] At ICU admission *median (IQR)*	9.67 (4.62, 22.98)	8.80 (4.16, 20.90)	0.90 (-0.59, 2.39)	1.21 (-1.66, 4.08)

Exploratory outcomes

	Nitric Oxide N=679	Standard Care N=685	Unadjusted Estimate of Difference (95% CI)	Adjusted Estimate of Difference (95% CI)[a]
Duration of time with open chest (hours) *median (IQR)*	44.2 (24.6, 89.6)	45.2 (26.0, 88.7)	-0.95 (-10.73, 8.84)	-0.17 (-13.01, 12.67)
Treated with inhaled Nitric Oxide post-operatively *n (%)*	80 (11.8%)	92 (13.4%)	0.86 (0.62, 1.19)	0.86 (0.62, 1.19)
Duration of inhaled Nitric Oxide (hours) *median (IQR)*	45 (20, 92)	45 (24, 89)	0 (-17.9, 17.9)	-3.6 (-25.2, 18.0)
Treated with kidney replacement post operatively *n (%)*	112 (16.5%)	119 (17.4%)	0.94 (0.71, 1.25)	0.94 (0.68, 1.30)
Duration of kidney replacement (hours) *median (IQR)*	28 (14, 68)	17 (18, 5[illegible])	1 (-8.2, 10.2)	0.5 (-10.6, 11.6)
PELOD-2 at ICU admission *mean (SD)*	7.7 (2.6)	7.4 (2.5)	0.3 (0.04, 0.57)	0.32 (0.073, 0.56)
PELOD-2 at 24 hours *mean (SD)*	2.4 (2.2)	2.4 (2.2)	0.022 (-0.21, 2.53)	0.024 (-0.20, 0.25)
PELOD-2 at 48 hours *mean (SD)*	1.9 (2.3)	1.9 (2.4)	0.00080 (-0.25, 0.25)	0.006 (-0.23, 0.25)
AKI @ ICU admission	150 (22.1%)	117 (17.1%)	1.38 (1.05, 1.80)	1.47 (1.10, 1.98)
AKI @ 24 hours	187 (27.5%)	162 (23.7%)	1.23 (0.96, 1.57)	1.25 (0.97, 1.60)
AKI @ 48 hours	129 (19.0%)	115 (16.8%)	1.16 (0.88, 1.53)	1.16 (0.88, 1.55)

No difference

Sensitivity analyses

adjusted for:

- treatment group, duration of CPB, surgical complexity (RACHS), blood prime, sex and strata variables as fixed effects
- site as a random effect

No difference

Outcome	Adjusted Estimate of Difference (95% CI)[a]
Primary Outcome	
Ventilator-free days	-0.022 (-0.24, 0.19)
Secondary Outcomes	
Duration of invasive ventilation (hours)	0.032 (-0.19, 0.24)
Low cardiac output syndrome[b], need for extra corporeal life support or death	1.12 (0.84, 1.50)
Low cardiac output syndrome	1.10 (0.82, 1.48)
Extra corporeal life support	1.40 (0.68, 2.87)
Death	1.16 (0.44, 3.06)
Length of stay in ICU (days)	1.01 (0.91, 1.13)
Length of stay in hospital (days)	0.98 (0.87, 1.10)
Troponin post-operatively*(µmol/L)*[c]	
At ICU admission	0.85 (-1.56, 3.27)
At 24 hours post-ICU admission	-0.15 (-0.95, 0.65)
Outcomes not Prespecified in the Formal Protocol	
Du[illegible]	2.38 (-8.60, 13.36)
[illegible]	0.86 (0.61, 1.21)
Duration of inhaled Nitric Oxide	-5.62 (-27.32, 16.08)
Treated with renal replacement post-operatively	0.93 (0.66, 1.32)
Duration of renal replacement	0.22 (-12.1, 12.5)
Organ dysfunction post-operatively (PELOD-2)[d]	
At ICU admission	0.33 (0.082, 0.57)
At 24 hours	0.033 (-0.19, 0.25)
At 48 hours	0.021 (-0.21, 0.25)
Creatinine post-operatively*(µmol/L)*[e]	
At ICU admission	1.38 (0.39, 2.38)
At 24 hours post-ICU admission	0.94 (-1.29, 3.17)
Acute kidney injury[f]	
At ICU admission	1.47 (1.09, 1.98)
At 24 hours	1.27 (0.98, 1.64)
At 48 hours	1.19 (0.89, 1.59)

Jenkins KJ, Gauvreau K, Newburger JW, et al. J Thorac Cardiovasc Surg. 2002;123(1):110-118.

Post hoc site-by-site analyses

Outcome	Nitric Oxide N=679	Standard Care N=685	Adjusted Estimate of Difference (95% CI)[a]
Primary Outcome: Ventilator-free days			
Site 1 *median (IQR)*	26.9 (24.9, 27.7) *(N=127)*	27.0 (23.8, 27.7) *(N=125)*	0.037 (-0.66, 0.73)
Site 2 *median (IQR)*	25.9 (24.0, 27.0) *(N=220)*	26.1 (24.0, 27.1) *(N=221)*	-0.14 (-0.55, 0.26)
Site 3 *median (IQR)*	26.8 (24.8, 27.1) *(N=55)*	26.1 (23.0, 27.0) *(N=57)*	0.043 (-0.98, 1.07)
Site 4 *median (IQR)*	26.[illegible] (24.9, 27.5) *([illegible]33)*	26.1 (25.0, 27.1) *(N=[illegible])*	-0.053 (-0.43, 0.32)
Site 5 *median (IQR)*	26.[illegible] (24[illegible]) *(N=102)*	26[illegible] (24[illegible]0, [illegible]7.5) *(N=104)*	0[illegible]98 (-0.42, 0.62)
Site 6 *median (IQR)*	26.8 (24.9, 27.7) *(N=42)*	26.9 (24.5, 27.6) *(N=40)*	0.38 (-0.51, 1.27)
Secondary Outcome: Low cardiac output syndrome[b], need for need for extra corporeal life support or death			
Site 1 *n (%)*	33 (26.0%)	36 (28.8%)	0.85 (0.46, 1.57)
Site 2 *n (%)*	51 (23.2%)	35 (15.8%)	1.69 (1.02, 2.79)
Site 3 *n (%)*	16 (29.1%)	24 (42.1%)	0.53 (0.23, 1.19)
Site 4 *n (%)*	23 (17.3%)	23 (16.7%)	1.06 (0.55, 2.01)
Site 5 *n (%)*	19 (18.6%)	17 (16.4%)	1.21 (0.57, 2.60)
Site 6 *n (%)*	11 (26.2%)	8 (20.0%)	1.47 (0.46, 4.71)

No difference

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Adverse events

11% of patients

1 intraoperative hypotension possibly related to NO on CPB

Adverse Event Type	Nitric Oxide N=104 Adverse Events	Standard Care N=107 Adverse Events
Cardiac	52 (50.0%)	43 (40.2%)
Gastrointestinal	3 (2.9%)	1 (0.9%)
General/administration site	8 (7.7%)	14 (13.1%)
Hepatobiliary	1 (1.0%)	0 (0%)
Infection/infestation	0 (0%)	1 (0.9%)
Injury/poison	7 (6.7%)	6 (5.6%)
Investigations	0 (0%)	1 (0.9%)
Metabolism/nutrition	1 (1.0%)	2 (1.9%)
Nervous system	7 (6.7%)	9 (8.4%)
Psychiatric	4 (3.9%)	4 (3.7%)
Renal/injury	2 (1.9%)	4 (3.7%)
Respiratory/thoracic/mediastinal	16 (15.4%)	17 (15.9%)
Vascular	2 (1.9%)	5 (4.7%)
Relatedness of Adverse Event to Study Drug		
Not related	80 (76.9%)	81 (75.7%)
Unlikely	23 (22.1%)	26 (24.3%)
Possibly	1 (1.0%)	0 (0%)
Probably	0 (0%)	0 (0%)
Definitely	0 (0%)	0 (%)

Content

- The NITRIC trial
- **Critical Review of what we did**
- Beyond NITRIC

Interpretation

- NO on CPB did not significantly affect VFD
- No evidence for benefit in any of the subgroups
- No signal for benefit in any of the secondary/exploratory outcomes
- Does not confirm findings from pediatric (n=16+198) and adult pilots
  - n=60 CAPD randomized to 40ppm on CPB (troponin and VIS decrease)
  - n=244 valve disease randomized to 80ppm on CPB and 24hrs iNO (less AKI)
- Largest RCT to date in CHD
- Awaiting cytokine, transcriptomic, and follow-up analyses

Kamenshchikov NO, Mandel IA, Podoksenov YK, et al. J Thorac Cardiovasc Surg. 2019;157(6):2328-2336.e1.
Lei C, Berra L, Rezoagli E, et al. Am J Respir Crit Care Med. 2018;198(10):1279-1287.

Strengths

- Blinding, size, balanced arms
- Pragmatic design
- reasonable consent rates; 85% consent for biobanking in 5/6 sites
- high compliance with study protocol
- heterogenous contemporary cohort
- full Stata code uploaded to Github before trial completion
- Overall outcomes comparable to recent CHD reports (18 deaths = 1.3%)

Nathan M, Levine JC, Van Rompay MI, et al; J AmColl Cardiol. 2021; 77(19):2382-2394.

Limitations

- No dose finding trial; no nitrosothiol compounds measured
- Perfusionists not blinded
- Open label iNO use allowed
- Choice of VFD as primary endpoint:
  - no weaning/extubation readiness protocol mandated
  - VFD may be influenced by staffing and practice rather than postop dysfunction
- Choice of LCOS for composite secondary endpoint

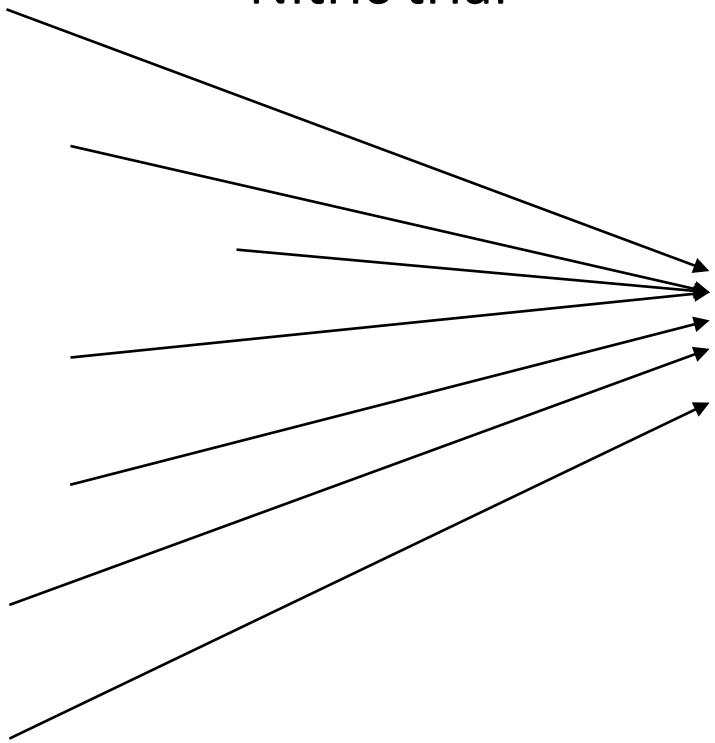
"Information is the resolution of uncertainty"

PICU Trials are
difficult & expensive

Cardiac cases too
Hard to study at scale

No equipoise
to study

Never get consensus
on usual care



Clear result achieved in
relevant time frame at
modest cost

Courtesy of Mark Peters, GOSH

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Nitric N=1364

Top 5 individual patient randomised

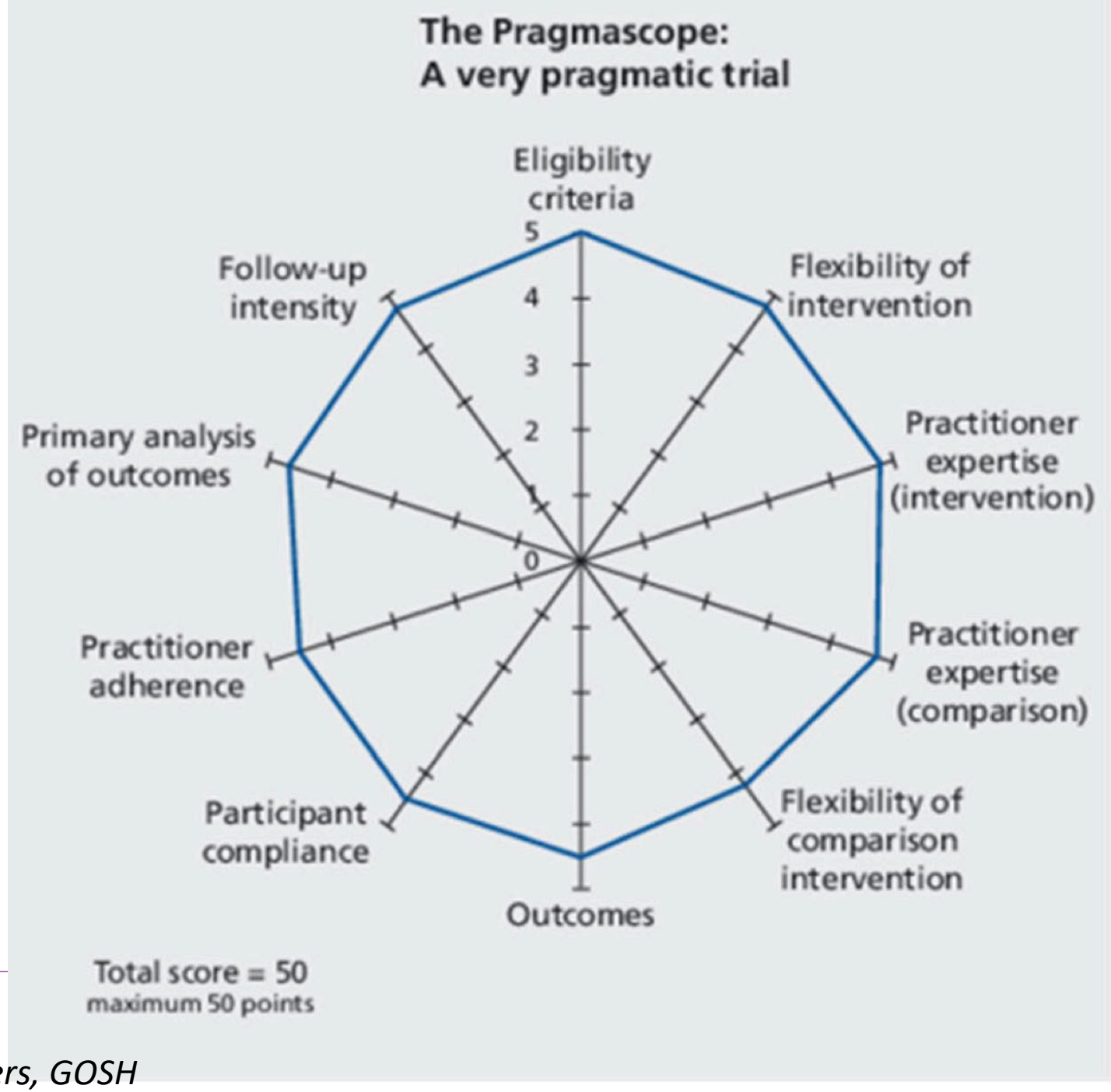
Intervention	Indication	Centres	Total Randomized	Year	
Reduced vs. extended-duration work schedules	Other	6	6577	2020	Link
Chlorhexidine vs. usual care	Infection-Prevention	1	4947	2013	Link
Protocolized sedation vs. usual care	CNS-Sedation/analgesia	31	2459	2015	Link
Antibiotic impregnated catheter or heparin impregnated catheter vs. standard catheter	Infection-Prevention	14	1859	2016	Link
Fresh blood transfusion vs. standard-issue transfusions	Heme-Anemia	50	1538	2019	Link
Late parenteral nutrition vs. early parenteral nutrition	GI-Nutrition	3	1440	2016	Link
Intensive insulin therapy vs. usual practice	Endocrine-Hyperglycemia	13	1369	2014	Link

Previous 1 Next

Sedation and Weaning in Childhood	18	8848

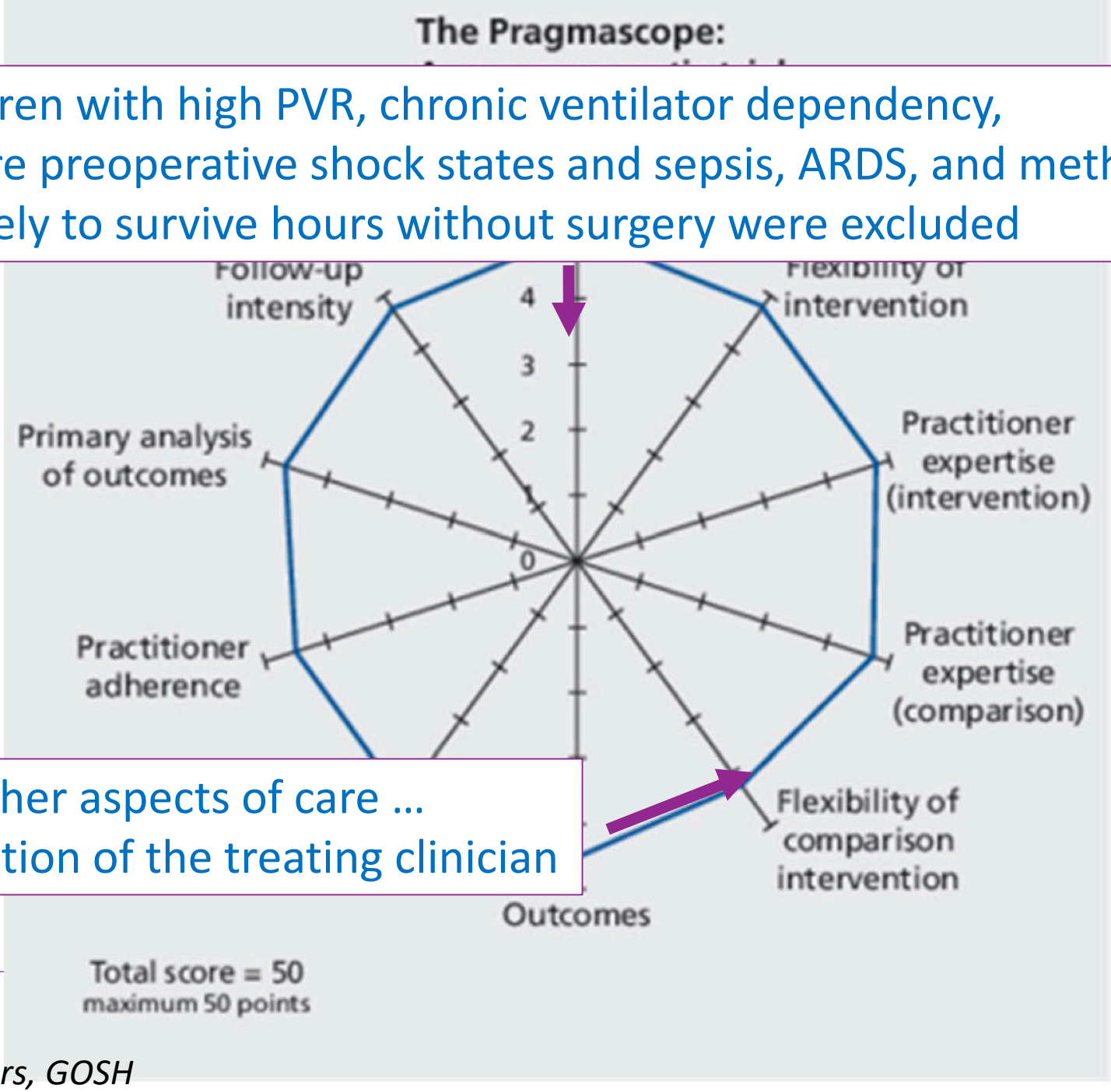
Courtesy of Mark Peters, GOSH

ANZICS Paediatric Study Group



Courtesy of Mark Peters, GOSH

Children with high PVR, chronic ventilator dependency, severe preoperative shock states and sepsis, ARDS, and methb or unlikely to survive hours without surgery were excluded



In both groups, other aspects of care …
were at the discretion of the treating clinician

Courtesy of Mark Peters, GOSH

Protocol deviations

Protocol Deviation Type	Nitric Oxide N=54 Deviations	Standard Care N=48 Deviations
Patient randomized but not eligible	6	1
Allocated to incorrect stratum (pathophysiology)	11	23
Allocated to incorrect stratum (age)	7	7
Protocol not followed	7	1
Intervention not delivered as per protocol	12	8
Blood collection not done as per protocol	6	1
Other	0	0
Other	5	7

Our own reflection on HOW we did it….

WELL DONE

- Strong multiprofessional involvement
- perfusionists, surgeons, PICU, nurse)
- Follow-up setup
- Biobanking in 70% of participants
- High data quality
- Dose based on strong pilot
- Population-based
- We didn’t stop early….

CAN BE DONE BETTER

- Minimal family/PPI involvement
- Minimal cardiology involvement
- Follow-on trial on xy not setup
- No funding to look at DNA
- Leverage from EHR (physiological response; fluids, sedation, echos etc)
- No dose finding
- no LMIC?
- We didn’t stop early….

Reproducibility

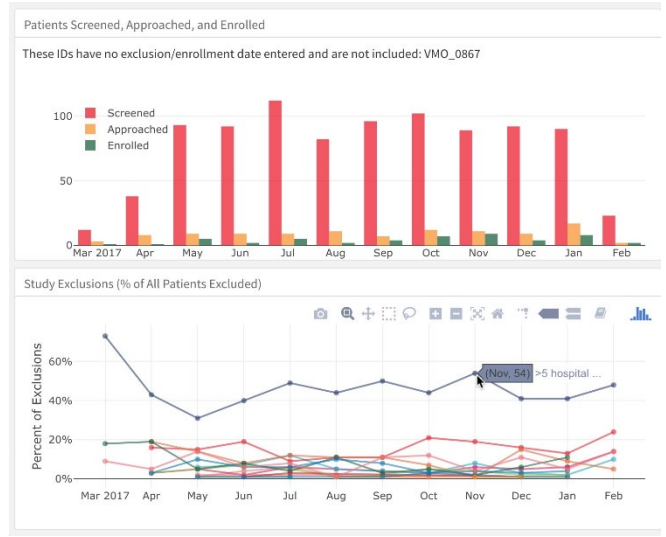
- Data collection forms (CRFs, eCRFs, databases)
- Statistical analysis plan + associated code to undertake analyses
- Risk assessment to inform the data monitoring plan
- Data and Safety Monitoring Boards

Monitoring

On-site Monitoring

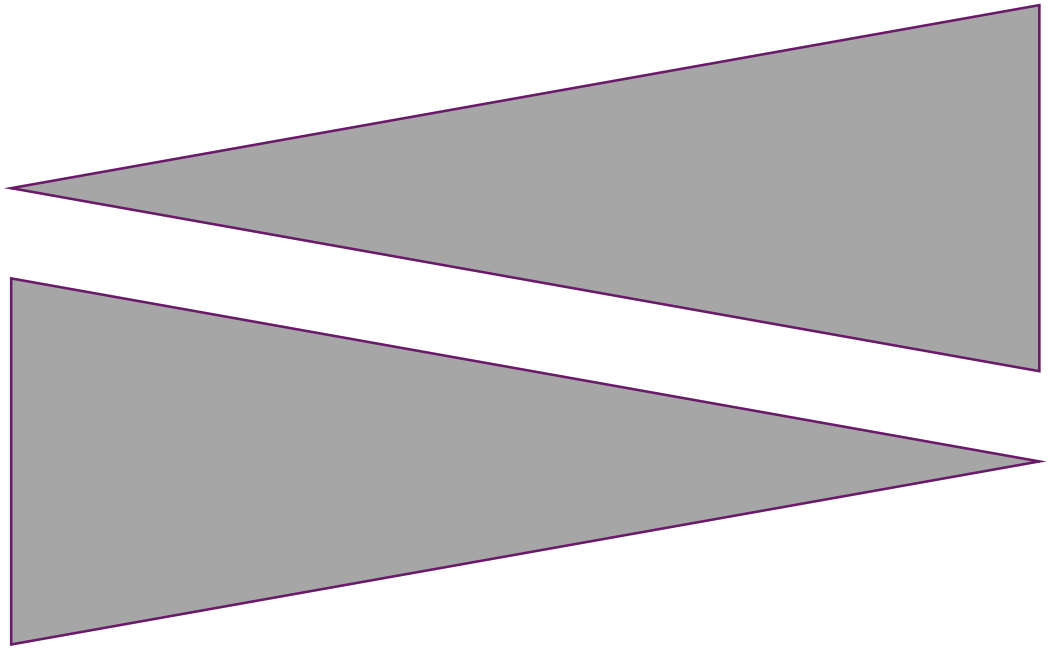
Remote Monitoring

Centralised Monitoring

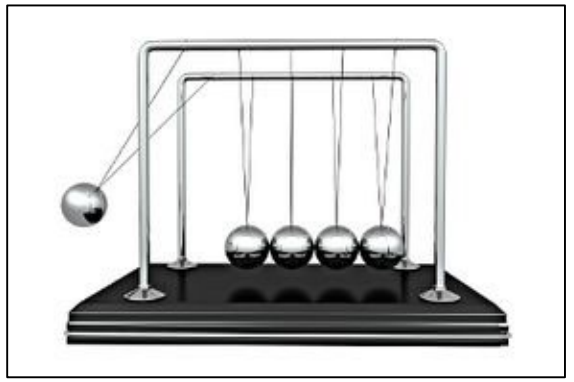


RCTs as a means to conduct an experiment in a non-experimental (clinical) environment

The real world



The perfect experiment

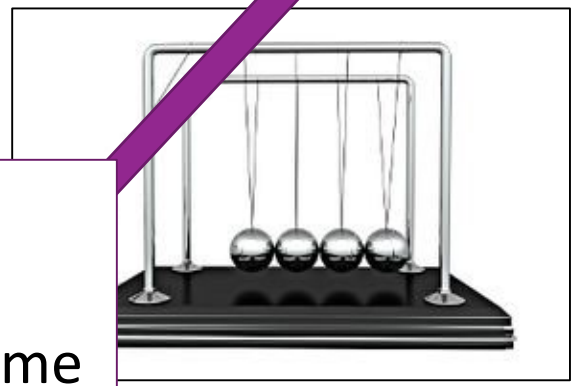


RCTs as a means to conduct an experiment in a non-experimental (clinical) environment

The real world

Randomization to ensure that real world intervention = control

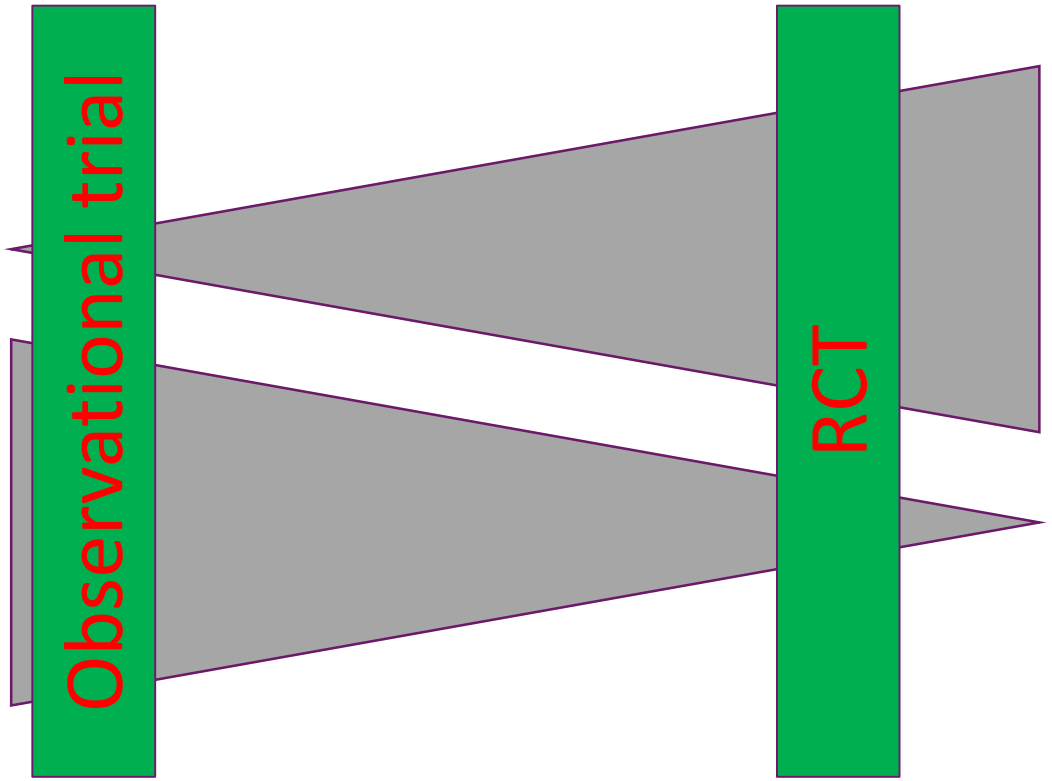
The perfect experiment



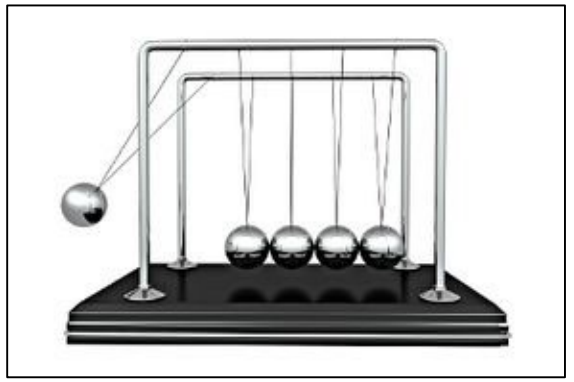
1 intervention to ensure that changes in outcome are likely related to the intervention

RCTs as a means to conduct an experiment in a non-experimental (clinical) environment

The real world

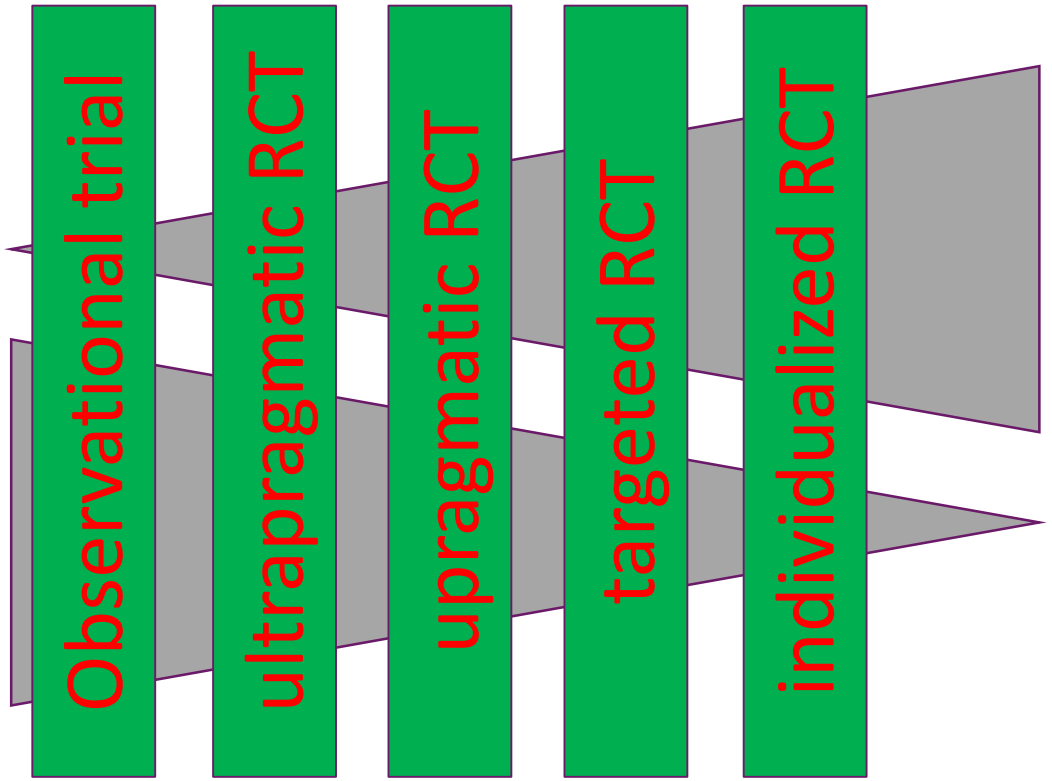


The perfect experiment

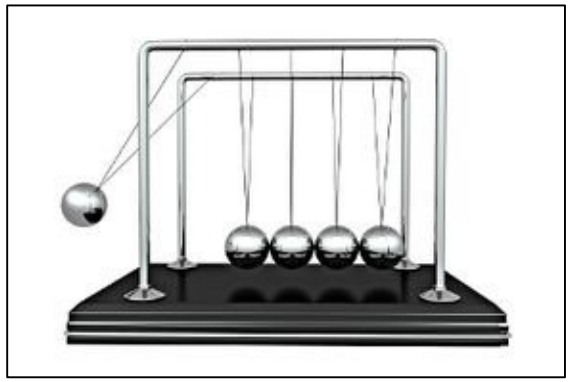


RCTs as a means to conduct an experiment in a non-experimental (clinical) environment

The real world

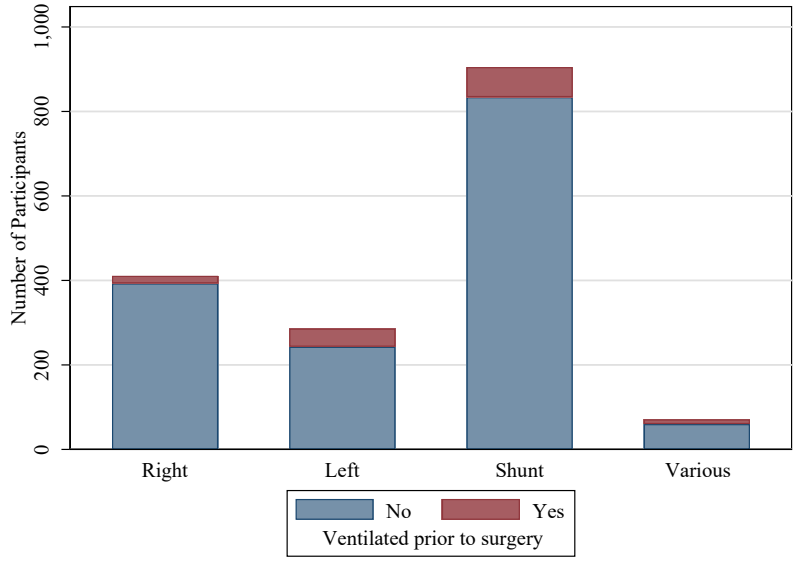


The perfect experiment

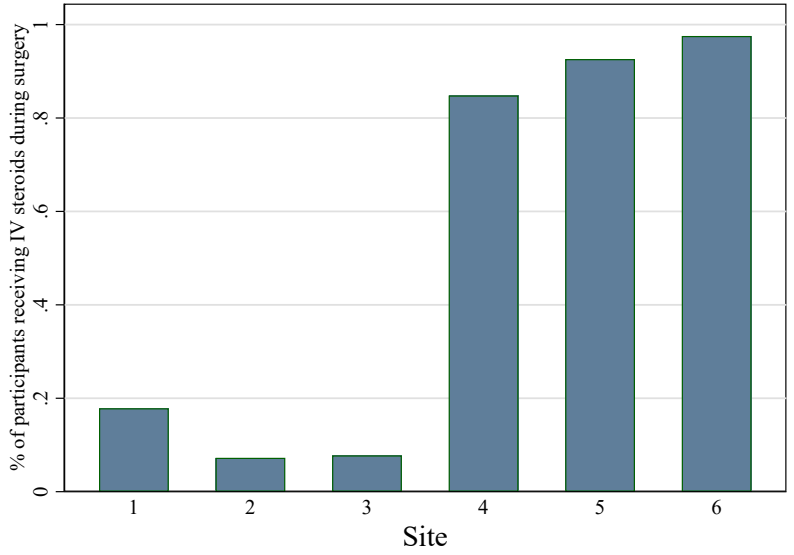


NITRIC – CPB during infancy

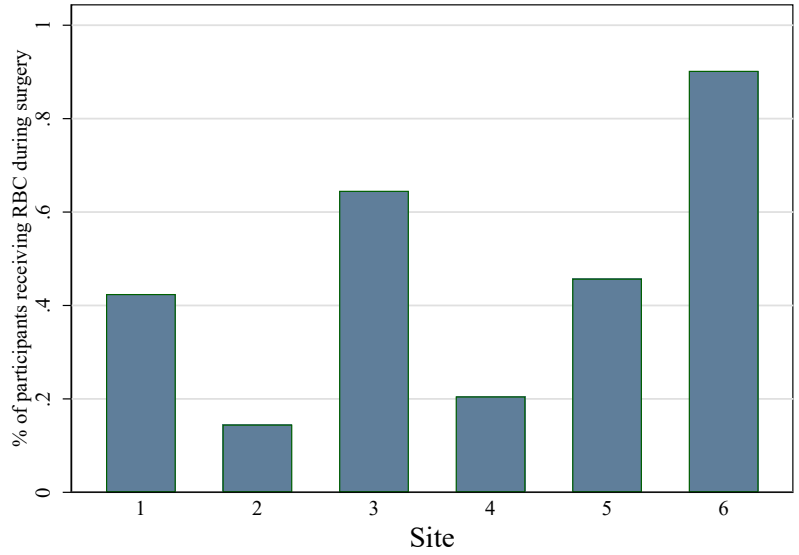
CHD lesion



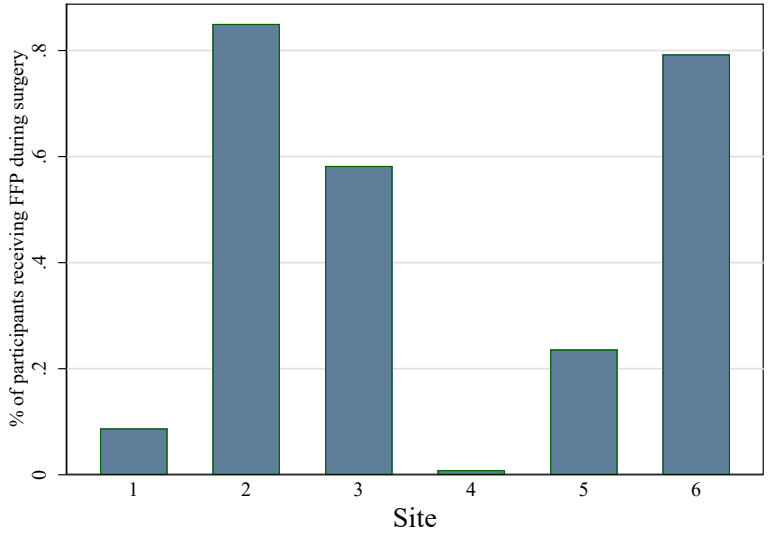
Steroids during CPB



RBC during CPB



FFP during CPB



The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Methylprednisolone for Heart Surgery in Infants — A Randomized, Controlled Trial

Hill KD et al. DOI: 10.1056/NEJMoa2212667

CLINICAL PROBLEM

For decades, infants undergoing congenital heart disease (CHD) surgery with cardiopulmonary bypass have received perioperative glucocorticoids to limit systemic inflammation, but evidence to support this practice is lacking.

CLINICAL TRIAL

Design: A prospective, multicenter, registry-based, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of perioperative methylprednisolone in infants undergoing elective CHD surgery with cardiopulmonary bypass.

Intervention: Infants younger than 1 year of age were assigned to receive prophylactic methylprednisolone (30 mg per kilogram of body weight) or placebo administered through the bypass pump prime. The primary outcome, assessed in 1200 infants, was a ranked composite of operative death, heart transplantation during hospitalization, any of 13 major complications, or postoperative length of stay. Individual components of the composite outcome were ranked into 97 levels of clinical prioritization — for example, death was ranked 97th (worst outcome), and heart transplantation during hospitalization was ranked 96th.

RESULTS

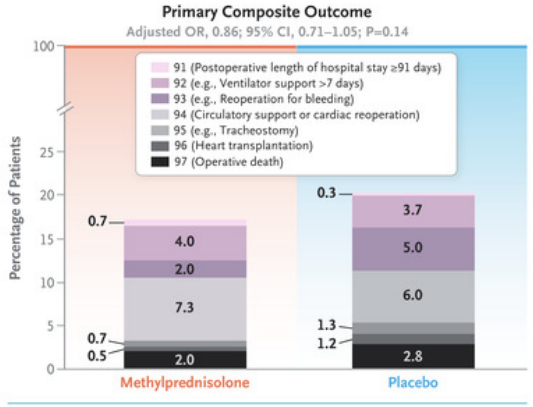
Efficacy: After adjustment for baseline characteristics, the results for the primary composite outcome did not differ significantly between the methylprednisolone group and the placebo group. Secondary analyses suggested a possible benefit with methylprednisolone.

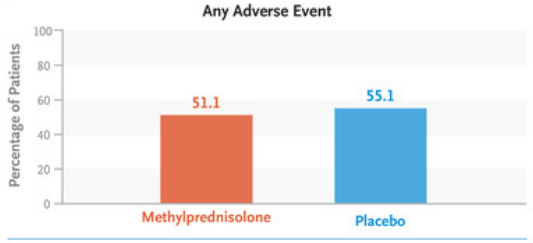
Safety: Methylprednisolone recipients were significantly more likely than placebo recipients to receive insulin for postoperative hyperglycemia. Incidences of other adverse events were generally similar in the two groups.

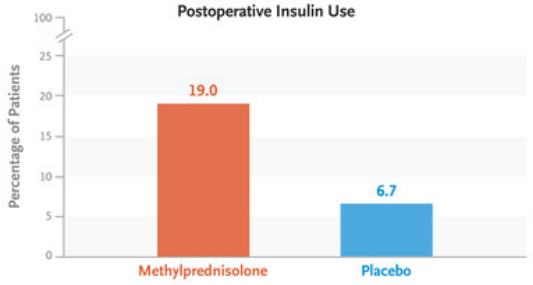
LIMITATIONS AND REMAINING QUESTIONS

- Registry data might not be as accurate as data collected prospectively as part of a trial and entered into a database.
- The use of postoperative glucocorticoids may have masked clinically significant results.

Links: Full Article | NEJM Quick Take







CONCLUSIONS

In infants undergoing CHD surgery with cardiopulmonary bypass, perioperative methylprednisolone did not reduce the likelihood of a worse outcome but was associated with an increased risk of postoperative hyperglycemia as compared with placebo.

- D: Double-blind placebo-controlled multicentre US
- P: < 1yrs undergoing CPB
- I: immunomodulation (30mg/kg methylpred into CPB)
- C: no methylpred (placebo)
- O: ranked composite death, tx, major complication, LOS

- Result: n=1200 patients
  aOR 0.86 (0.71 to 1.05; P = 0.14)
  win ratio 1.15 (1.00 to 1.32)

ANZICS Paediatric Study Group

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Methylprednisolone for Heart Surgery in Infants — A Randomized, Controlled Trial

CLINICAL PROBLEM

For decades, infants undergoing
(CHD) surgery with cardiopulmo
ceived perioperative glucocorticoi
inflammation, but evidence to su
lacking.

CLINICAL TRIAL

Design: A prospective, multicente
blind, randomized, placebo-contr
efficacy and safety of perioperati
infants undergoing elective CHD
monary bypass.

Intervention: Infants younger tha
signed to receive prophylactic me
per kilogram of body weight) or
through the bypass pump prime.
assessed in 1200 infants, was a r
erative death, heart transplantatio
tion, any of 13 major complicatio
length of stay. Individual compon
outcome were ranked into 97 leve
tion — for example, death was r
come), and heart transplantation
was ranked 96th.

RESULTS

Efficacy: After adjustment for bas
results for the primary composite
significantly between the methylp
the placebo group. Secondary ana
ble benefit with methylprednisolo

Safety: Methylprednisolone recipi
more likely than placebo recipien
postoperative hyperglycemia. Inci
events were generally similar in t

LIMITATIONS AND REMAINING QUES

- Registry data might not be as
ed prospectively as part of a trial and entered into a database.
- The use of postoperative glucocorticoids may have masked clinically significant results.

Links: Full Article | NEJM Quick Take

CONCLUSIONS

In infants undergoing CHD surgery with cardiopulmonary bypass, perioperative methylprednisolone did not reduce the likelihood of a worse outcome but was associated with an increased risk of postoperative hyperglycemia as compared with placebo.

Table 1. (Continued.)

Characteristic	Methylprednisolone (N = 599)	Placebo (N = 601)
Common primary procedures — no./total no. (%)		
Truncus arteriosus repair	4/599 (0.7)	8/600 (1.3)
Total anomalous pulmonary venous connection	21/599 (3.5)	14/600 (2.3)
Tetralogy of Fallot repair	70/599 (11.7)	74/600 (12.3)
Pulmonary atresia–VSD repair	7/599 (1.2)	15/600 (2.5)
Norwood procedure	45/599 (7.5)	48/600 (8.0)
Arterial switch operation	21/599 (3.5)	28/600 (4.7)
Coarctation of the aorta and aortic arch hypoplasia repair	47/599 (7.8)	45/600 (7.5)
Systemic to pulmonary artery shunt	11/599 (1.8)	19/600 (3.2)
VSD repair	96/599 (16.0)	80/600 (13.3)
Complete atrioventricular canal defect repair	80/599 (13.4)	62/600 (10.3)
Stage II single-ventricle palliation	44/599 (7.3)	56/600 (9.3)

ANZICS Paediatric Study Group

The NEW ENGLAND JOURNAL of MEDICINE

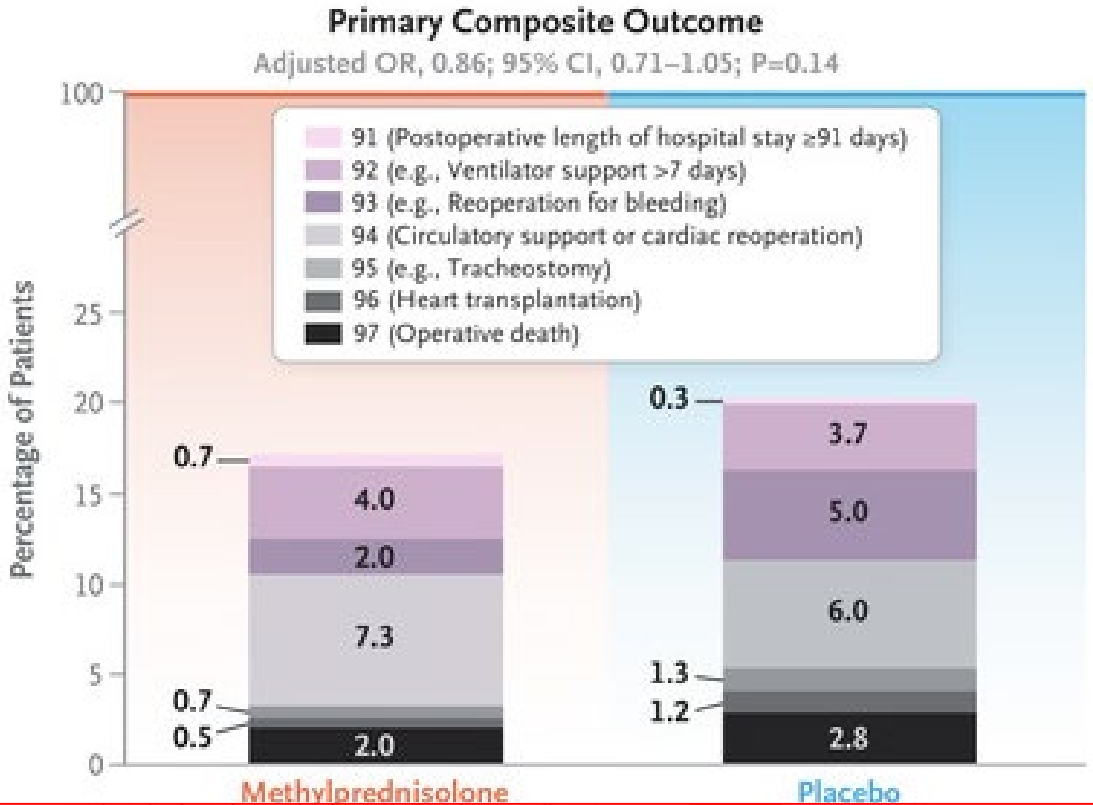
RESEARCH SUMMARY

Methylprednisolone for Heart Surgery in Infants — A Randomized, Controlled Trial

Hill KD et al. DOI: 10.1056/NEJMoa2212667

CLINICAL PROBLEM

Primary Composite Outcome



postoperative hyperglycemia. Incidences of other adverse events were generally similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- Registry data might not be as accurate as data collected prospectively as part of a trial and entered into a database.
- The use of postoperative glucocorticoids may have masked clinically significant results.

Links: Full Article | NEJM Quick Take

CONCLUSIONS

In infants undergoing CHD surgery with cardiopulmonary bypass, perioperative methylprednisolone did not reduce the likelihood of a worse outcome but was associated with an increased risk of postoperative hyperglycemia as compared with placebo.

Table 2. Components of the Primary End Point with Global Rank.

End-Point Event	Rank According to Level of Prioritization	Methylprednisolone (N=599)	Placebo (N=601)
		no. of infants (%)	
Operative death	97	12 (2.0)	17 (2.8)
Heart transplantation during hospitalization	96	3 (0.5)	7 (1.2)
Kidney failure with permanent dialysis, neurologic deficit persistent at discharge, or respiratory failure warranting tracheostomy	95	4 (0.7)	8 (1.3)
Postoperative mechanical circulatory support or unplanned cardiac reoperation, exclusive of reoperation for bleeding	94	44 (7.3)	36 (6.0)
Reoperation for bleeding, unplanned delayed sternal closure, or unplanned interventional cardiac catheterization after surgery	93	12 (2.0)	30 (5.0)
Postoperative cardiac arrest, multisystem organ failure, kidney failure with temporary dialysis, or mechanical ventilator support for more than 7 days	92	24 (4.0)	22 (3.7)
Postoperative length of hospital stay			
>90 days	91	4 (0.7)	2 (0.3)
81 to 90 days	81 to 90	0	1 (0.2)
71 to 80 days	71 to 80	0	0
61 to 70 days	61 to 70	2 (0.3)	5 (0.8)
51 to 60 days	51 to 60	5 (0.8)	3 (0.5)
41 to 50 days	41 to 50	6 (1.0)	7 (1.2)
31 to 40 days	31 to 40	14 (2.3)	18 (3.0)
21 to 30 days	21 to 30	44 (7.3)	46 (7.7)
11 to 20 days	11 to 20	115 (19.2)	112 (18.6)
0 to 10 days	0 to 10	310 (51.8)	287 (47.8)

ANZICS Paediatric Study Group

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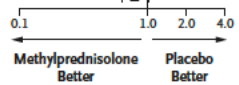
Subgroup	No. of Patients (%)	Adjusted Odds Ratio (95% CI)
Primary subgroups		
Age		
≤30 days	364 (30.3)	0.90 (0.64–1.27)
>30 days	836 (69.7)	0.86 (0.68–1.10)
STAT mortality category		
1, 2, or 3	969 (81.0)	0.75 (0.60–0.94)
4 or 5	228 (19.0)	1.18 (0.76–1.83)
Exploratory subgroups		
Duration of cardiopulmonary bypass		
60 min		0.93 (0.68–1.27)
120 min		0.85 (0.69–1.04)
180 min		0.77 (0.60–0.99)
Premature birth		
Yes	193 (16.1)	1.34 (0.81–2.22)
No	1004 (83.9)	0.80 (0.64–0.99)
Race		
White	853 (73.0)	1.17 (0.71–1.92)
Black	192 (16.4)	0.59 (0.31–1.10)
Other	123 (10.5)	0.84 (0.67–1.07)
Ethnic group		
Hispanic	143 (12.3)	1.27 (0.71–2.25)
Not Hispanic	1021 (87.7)	0.83 (0.67–1.03)
Sex		
Male	654 (54.5)	0.80 (0.61–1.04)
Female	545 (45.5)	0.95 (0.71–1.28)
Any preoperative risk factor		
Yes	435 (36.6)	0.81 (0.58–1.13)
No	753 (63.4)	0.86 (0.67–1.10)
Any noncardiac anatomical abnormality		
Yes	41 (3.4)	0.91 (0.25–3.28)
No	1158 (96.6)	0.85 (0.69–1.04)
Any syndrome or chromosomal abnormality		
Yes	383 (31.9)	1.00 (0.70–1.43)
No	816 (68.1)	0.80 (0.63–1.01)



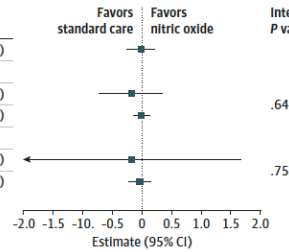
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Nitric Oxide via Cardiopulmonary Bypass on Ventilator-Free Days in Young Children Undergoing Congenital Heart Disease Surgery

The NITRIC Randomized Clinical Trial

Luregn J. Schlapbach, MD, PhD; Kristen S. Gibbons, PhD; Stephen B. Horton, PhD; Kerry Johnson, GradCertPaed; Debbie A. Long, PhD; David H. F. Buckley, MBChB; Simon Erickson, MBBS; Marino Festa, MD(Res); Yves d'Udekem, MD, PhD; Nelson Alphonso, MD; David S. Winlaw, MbChB; Carmel Delzoppo, BHlthSc; Kim van Loon, MD, PhD; Mark Jones, PhD; Paul J. Young, PhD; Warwick Butt, MD; Andreas Schibler, MD; for the NITRIC Study Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), and the ANZICS Paediatric Study Group (PSG)

Group	Nitric oxide, No./total (%)	Standard care, No./total (%)	Estimate (95% CI)	Interaction *P* value
Overall[a]	679	685	−0.01 (−0.25 to 0.22)	
Age, wk[b]				
<6	227/459 (49.5)	232/459 (50.5)	−0.18 (−0.72 to 0.35)	.64
≥6	452/905 (49.9)	453/905 (50.1)	−0.01 (−0.15 to 0.13)	
Lesion[c]				
Univentricular	77/153 (50.3)	76/153 (49.7)	−0.17 (−2.01 to 1.67)	.75
Biventricular	601/1209 (49.7)	608/1209 (50.3)	−0.04 (−0.22 to 0.15)	



ANZICS Paediatric Study Group

Pragmatic trials can be done - don’t STRESS too much?

STRESS

- Registry-based: STS-CHSD to collect patient and outcome information
- Blinded intervention administered by perfusionists
- 24 US CHD sites
- 1200 patients across CHD range
- 54 mo recruitment
- Total direct cost 3.2Mio USD

NITRIC

- All data manually collected and monitored, registry for QC
- Blinded intervention administered by perfusionists
- 6 CHD sites in 3 countries
- 1364 patients across CHD range
- 46 mo recruitment
- Total direct cost 2.2Mio AUD (ca. 1.5 Mio USD)

ANZICS Paediatric Study Group

Content

- The NITRIC trial
- Critical Review of what we did
- **Beyond NITRIC**

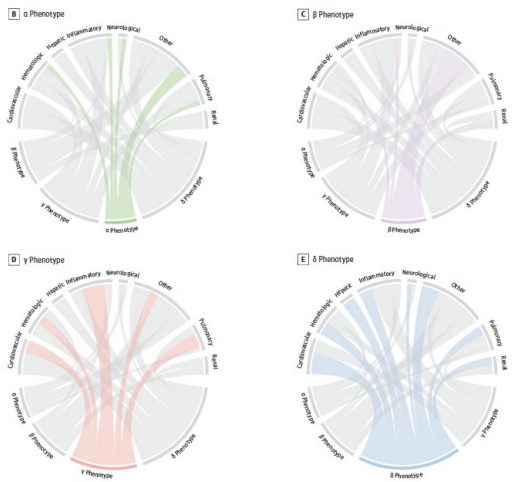
Recovery from CPB in 2022

- Mortality <2%
- Ventilation duration is <48h in most patients
- Optimization of CPB technique (MUF etc), less SIRS, less fluid overload?
- What is LCOS in 2022?
- Which children will develop LCOS?
- Biological phenotypes?
- Targeted interventions?

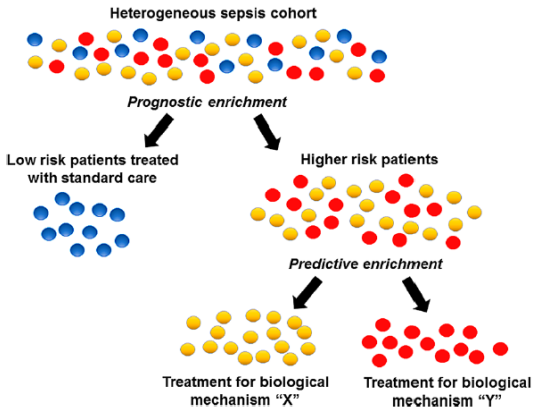
Targeting heterogeneity of disease

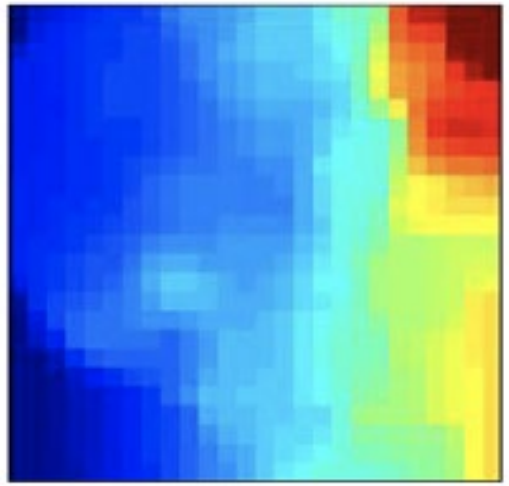
Eminence-based disease entities

Data-driven Phenotypes

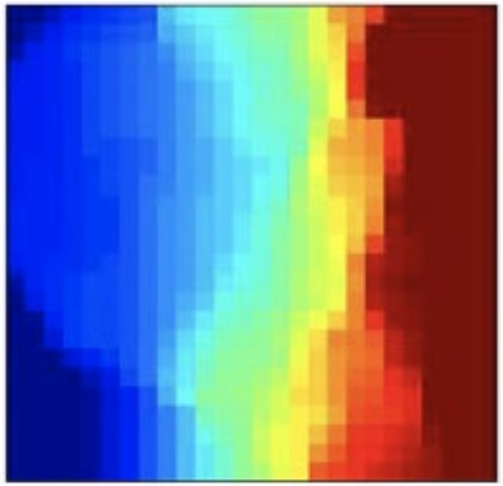


Personalized medicine



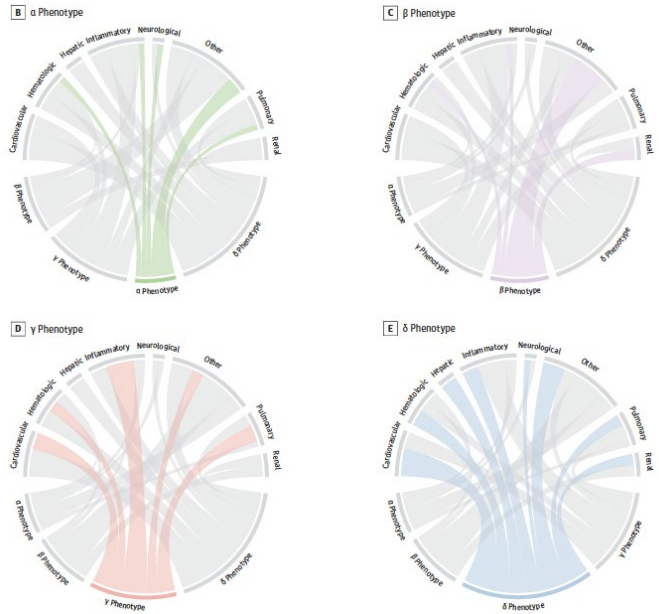


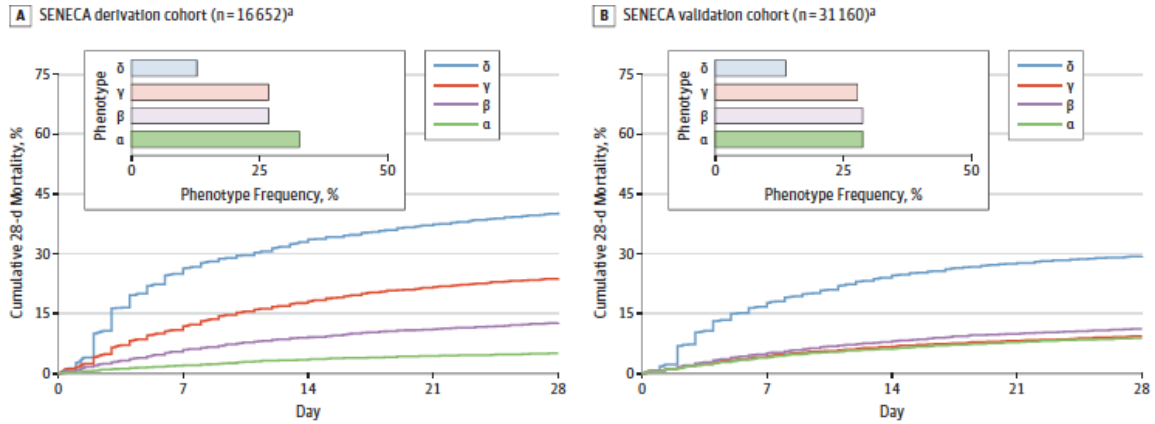
Subclass A



Subclass B

After adjusting for illness severity (PRISM score), presence of comorbidity, and age, adjunctive corticosteroids were independently associated with an increased risk of mortality in the subjects in subclass A (OR = 4.1; CI_{95} = 1.4–12.0; P = 0.011), but not the subjects in subclass B. When testing the interaction





ORIGINAL ARTICLE

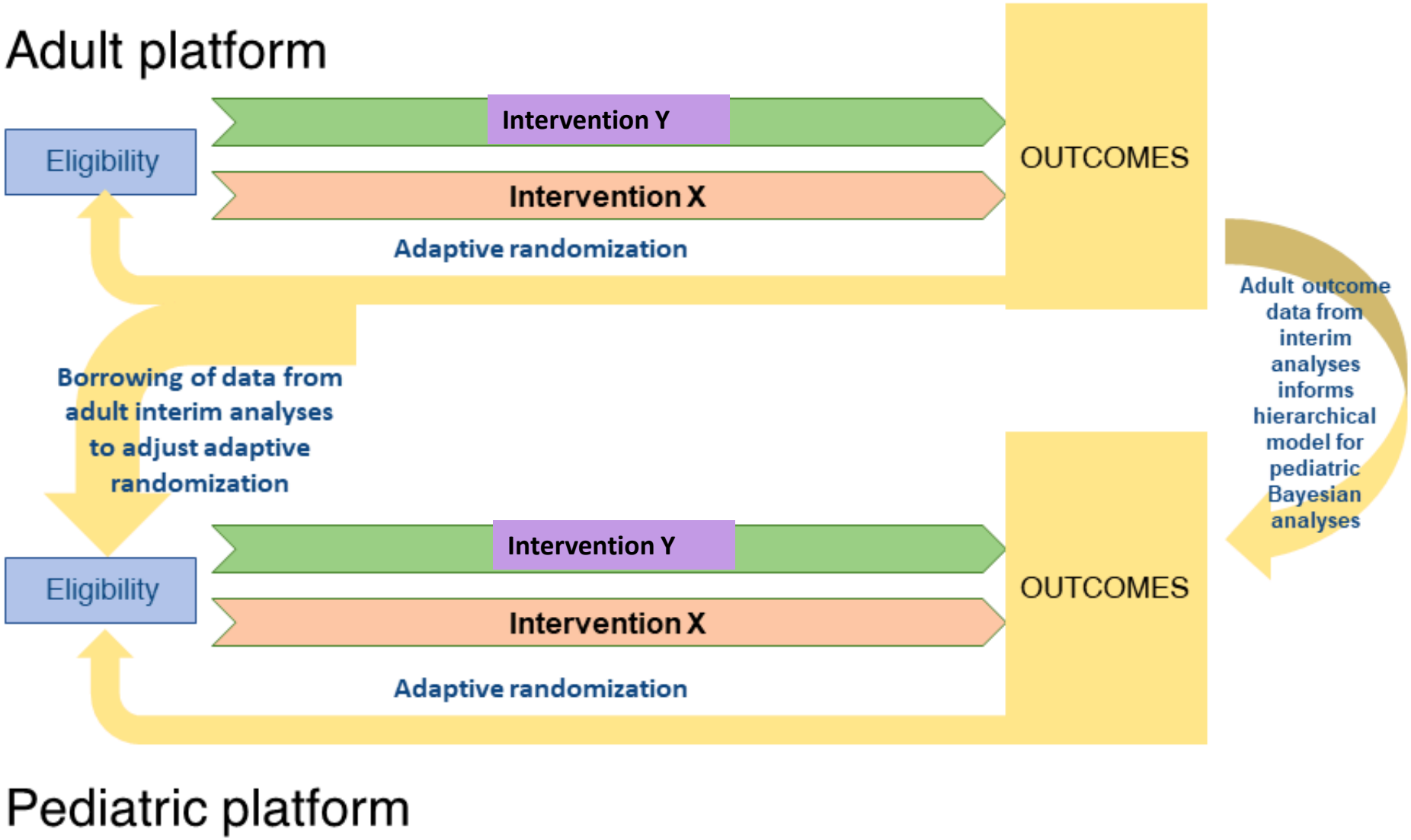
Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock

Hector R. Wong[1,2], Natalie Z. Cvijanovich[3], Nick Anas[4], Geoffrey L. Allen[5], Neal J. Thomas[6], Michael T. Bigham[7], Scott L. Weiss[8], Julie Fitzgerald[8], Paul A. Checchia[9], Keith Meyer[10], Thomas P. Shanley[11], Michael Quasney[11], Mark Hall[12], Rainer Gedeit[13], Robert J. Freishtat[14], Jeffrey Nowak[15], Raj S. Shekhar[16], Shira Gertz[17], Emily Dawson[18], Kelli Howard[1], Kelli Harmon[1], Eileen Beckman[1], Erin Frank[1], and Christopher J. Lindsell[19]

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS; Scott Berry, PhD; Gilles Clermont, MD, MSc; Gregory Cooper, MD, PhD; Hernando Gomez, MD, MPH; David T. Huang, MD, MPH; John A. Kellum, MD, FACP, MCCM; Qi Mi, PhD; Steven M. Opal, MD; Victor Talisa, MS; Tom van der Poll, MD, PhD; Shyam Visweswaran, MD, PhD; Yoram Vodovotz, PhD; Jeremy C. Weiss, MD, PhD; Donald M. Yealy, MD, FACEP; Sachin Yende, MD, MS; Derek C. Angus, MD, MPH


Adult platform
Eligibility
Intervention Y
Intervention X
Adaptive randomization
OUTCOMES
Adult outcome data from interim analyses informs hierarchical model for pediatric Bayesian analyses
Borrowing of data from adult interim analyses to adjust adaptive randomization
Eligibility
Intervention Y
Intervention X
Adaptive randomization
OUTCOMES
Pediatric platform

Step 1: Observational studies leveraging off “big data”

All patients – electronic health record/registry data (confounders, outcomes, etc)

Opinion

VIEWPOINT

Fusing Randomized Trials With Big Data
The Key to Self-learning Health Care Systems?

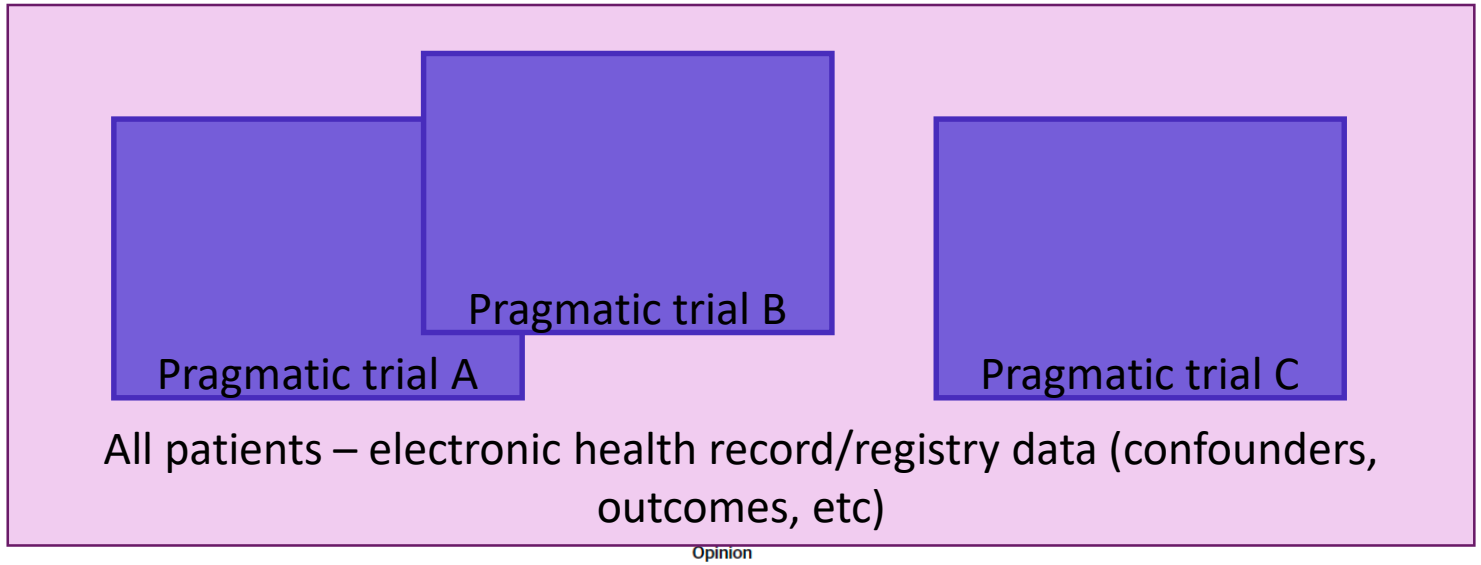
Derek C. Angus, MD, MPH
Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; and Associate Editor, *JAMA*.

Randomized clinical trials (RCTs) have revolutionized medicine by providing evidence on the efficacy and safety of drugs, devices, and procedures. Today, more than 40 000 RCTs are reported annually, their quality continues to increase, and oversight mechanisms ensure adequate protection of participants. However, RCTs have at least 4 related problems: (1) they are too expen-

access to massive amounts of data, the Achilles' heel is lack of causal inference. No matter how detailed the measurement and how sophisticated the adjustment for all known variables, big data cannot eliminate unmeasured factors coincident with a particular treatment assignment that could explain an apparent change in outcome.[2]

ANZICS Paediatric Study Group

Step 2: Nest pragmatic trials in large scale observational databases



VIEWPOINT

Fusing Randomized Trials With Big Data
The Key to Self-learning Health Care Systems?

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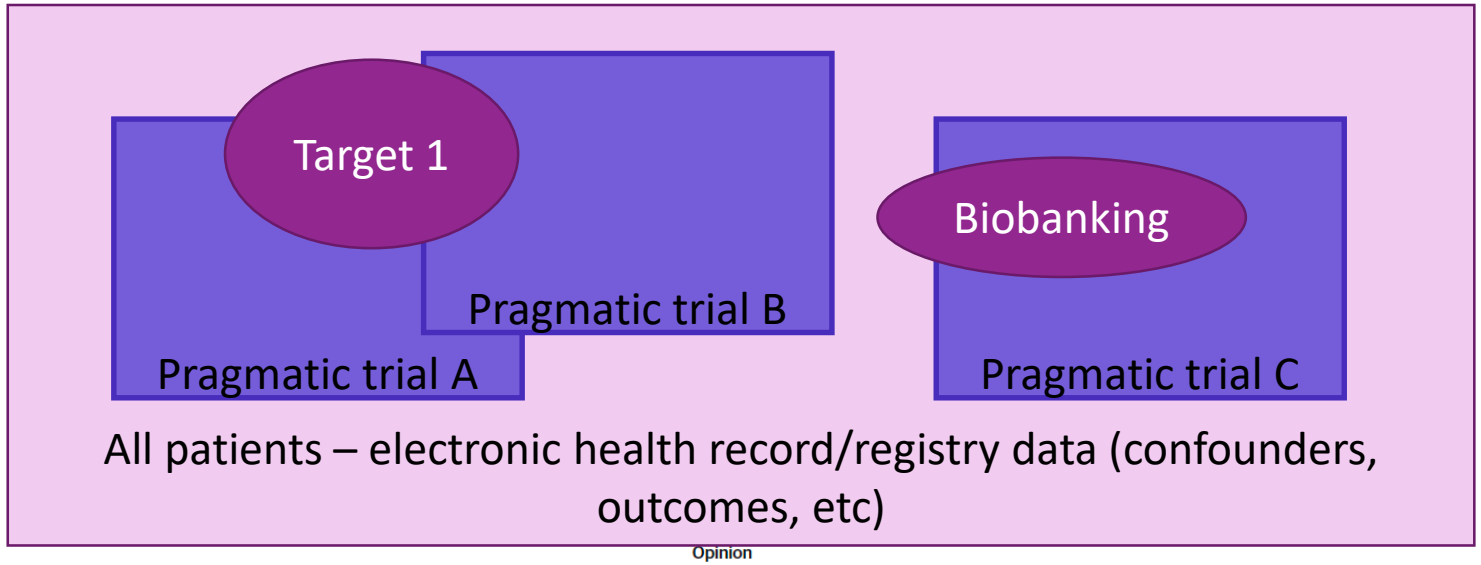
Step 3: Nest targeted & exploratory (omics etc) questions in pragmatic trials



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ANZICS Paediatric Study Group

Beyond NITRIC

Medical Research Future Fund

NITRIC RCT
(NHMRC funded)

MRFF Proposal

Clinical Cohort

N=1320 Infants < 2 Years of Age undergoing Heart Surgery on Cardiopulmonary Bypass

Pre Bypass RNA BioBanking

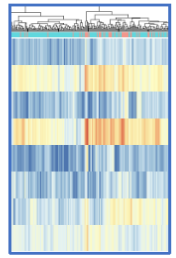
Study Intervention during Cardiopulmonary Bypass

Post Bypass RNA BioBanking

Postoperative Early Outcomes
- Low Cardiac Output Syndrome
- ECLS
- Death

Multi-omics
-Transcriptomics
-Metabolomics
-Proteomics

multi-omics



Outcome prediction

Long-term follow-up

2 years of Age: Parent completed Questionnaire

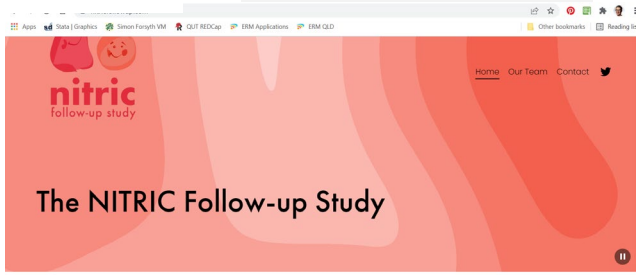
3 years of Age: Parent completed Questionnaire

4 years of Age: Parent completed Questionnaire

5 years of Age Face-to-face Neuropsychological Assessment

Consumer engagement & follow-up

NITRIC FU Video



Congenital heart defects (CHDs) are conditions that are present at birth and can affect the structure of a baby's heart and the way it works. They are the most common type of birth defect with over 1000 infants and children in Australia and New Zealand requiring heart surgery each year. As

Each year, over 1000 children with congenital heart disease (CHD) in Australia require heart surgery. The short and long-term outcomes of these children are primarily determined by pre-existing comorbidities and genetic factors, direct impact of the surgical intervention, the response to cardiopulmonary bypass (CPB), and the consequences thereof during their intensive care stay. Neurodevelopmental disabilities remain amongst the most common, and the most damaging, outcomes in children undergoing surgery for CHD.

Large longitudinal population-based studies assessing long-term outcome are lacking. One out of four infants undergoing heart surgery develop a harmful response to CPB, which leads to low cardiac output syndrome (LCOS). LCOS results in prolonged (multi-) organ dysfunction related to hypotension, organ hypoperfusion, renal failure, and brain ischemia. LCOS translates into adverse short-term outcomes (LCOS, need for extracorporeal life support (ECLS), and death), and determines adverse long-term outcomes manifesting into school age and beyond.

ANZICS Paediatric Study Group

https://www.picolo.org/research/nitric-follow-up

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Acknowledgements

A huge thanks to all the parents and children participating in this trial!!!!!!

We are most grateful for the medical, perfusion, nursing and research teams at all the study sites for their invaluable help conducting the study!

The NITRIC Study Group:

**Royal Children`s Hospital Melbourne:** Warwick Butt, Steve Horton, Carmen Delzoppo, Yves d`Uedekem, Johnny Millar, Kate Masterson
Perth Children`s Hospital: Simon Erickson, Sam Barr, David Andrews, Rae Kelly, Hannah Thompson, Kelly Holmes, Nigel Slade
Starship Children`s Hospital: David Buckley, John Beca, Claire Sherring, Taryn Evans, Shelley Coetzer, Claire Sherring
**Children`s Hospital at Westmead:** Marino Festa, Killian O`Shaugnessy, David Winlaw, Jennifer Darvas, Chong Tien Goh, Gail Harper
Queensland Children`s Hospital: Andreas Schibler, Luregn Schlapbach, Deborah Long, Kerry Johnson, Nelson Alphonso, Carla Zazulak, Ben Anderson
Utrecht Medical Center: Kim van der Loon, Annelies Hennink, Erik Koomen, Nicole van Belle-van Haaren, Bram van Wijk
ANZICS CTG: Paul Young
University of Queensland: Kristen Gibbons, Trang Pham, Endrias Ergetu, Renate LeMarsey, Antje Blumenthal, Mark Jones, Brenda Gannon, Jonathan Foken

DSMB: Tom Karl, MD, Philip Sargent, MD, Ben Gelbart, MBBS, Lahn Straney, PhD

ANZICS Clinical Trials Group

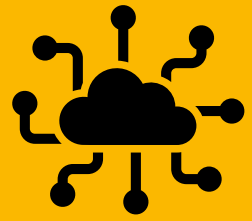
ANZICS Paediatric Study Group

PICU TRIALS ARE POSSIBLE.

Heterogenous patient cohort

Complex consent

Low mortality



Lack of infrastructure