



Appendix

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Appendix to: Pham CT, Karnon JD, Middleton PF, et al. Randomised clinical trials in perinatal health care: a cost-effective investment. *Med J Aust* 2017; 207: 289-293. doi: 10.5694/mja16.01178.

Are randomised clinical trials in perinatal medicine a cost-effective investment?

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APPENDIX

Table A1. Study characteristics for all trials

Acronym (or truncated trial name)	Trial name	Main coordinating centre	Multi-centre centre	Population	Intervention (n)	Control (n)
Intervention superior to standard practice						
FIFI ¹	Father Infant Feeding Initiative: Increasing breastfeeding initiation and duration via education and social support for fathers (ACTRN12609000667213)	WA, Australia	Yes	Fathers intending to be involved and mothers intending to breastfeed	Antenatal education and postnatal support sessions for fathers (n=385)	Usual care (n=314)
Intervention superior to placebo						
HeLP-her ^{2,3}	Healthier lifestyles: Preventing excess weight gain and gestational diabetes in overweight and obese pregnancies: a research and education project (ACTRN12608000233325)	VIC, Australia	Yes	Women at 12-14 weeks' gestation at high risk for developing gestational diabetes	4-session lifestyle program (n=121)	Written health information only (n=107)
InFANT ^{4,5}	The Infant Feeding Activity and Nutrition Trial an early intervention to prevent childhood obesity: cluster-randomised controlled trial (ISRCTN81847050)	VIC, Australia	No	Primiparous women	6 dietitian delivered educational sessions (n=271)	Usual care (n=271)
MANGO ⁶	A randomised controlled trial of caseload midwifery (ACTRN12609000349246)	NSW, Australia	Yes	Women with a singleton pregnancy	Caseload midwifery care (n=871)	Standard care (n=877)
Analgesia after caesarean surgery ⁷	Ultrasound guided transverses abdominis plane (TAP) block for analgesia after caesarean surgery (ACTRN12608000540314)	QLD, Australia	No	Women who underwent elective caesarean section	Ultrasound guided transversus abdominis plane block with 20mL	Ultrasound guided transversus abdominis plane block with 20mL

Acronym (or truncated trial name)	Trial name	Main coordinating centre	Multi-centre	Population	Intervention (n)	Control (n)
				0.5% Ropivacaine (n=23)	saline (inactive placebo) (n=24)	
Sugar Babies ⁸	Sugar Babies study (ACTRN12608000623392)	Hamilton, New Zealand	No	Babies aged 35-42 weeks' gestation, <48 hours old, at risk of hypoglycaemia	40% dextrose gel (n=118)	2% carboxymethyl cellulose placebo gel (n=119)
Intervention comparable to standard practice						
Support for ongoing breastfeeding ⁹	Support for ongoing breastfeeding (ACTRN12608000361303)	NSW, Australia	Yes	Women breastfeeding up to 4 months	Motivational flowchart for practice nurses to support continuation of breastfeeding (n=154)	Standard treatment practice at child immunisation visits (n=176)
Effect of diet on gestational diabetes ¹⁰⁻¹²	Effect of different diets on gestational diabetes. Can a low glycemic index (GI) diet during pregnancy reduce prevalence of large for gestation age (LGA) amongst gravidae with gestational diabetes (GDM) - a randomised controlled trial (ACTRN12608000218392)	NSW, Australia	No	Women with gestational diabetes	Low glycaemic index diet (GI <50) until 36 weeks' gestation (n=50)	Wholegrain high fibre diet (GI ~60) until 36 weeks' gestation (n=49)
FLORIAN ¹³	In extremely low birth weight (ELBW) infants who require positive pressure at birth does the use of a respiratory Function Monitor reduce face mask leak and improve the target tidal volume in the first ten minutes of life? (ACTRN12608000357358)	VIC, Australia	No	Infants <32 weeks' gestation who needed positive pressure ventilation (PPV)	PPV with VISIBLE respiratory function monitor (n=26)	PPV with MASKED respiratory function monitor (n=23)
LIMIT ¹⁴⁻²⁰	Limiting weight gain in overweight and obese women during pregnancy to improve health outcomes: a randomised trial	SA, Australia	Yes	Pregnant women at 10-20 weeks' gestation with BMI	Dietary and lifestyle intervention (n=1,108)	Standard pregnancy care (n=1,104)

Acronym (or truncated trial name)	Trial name	Main coordinating centre	Multi-centre	Population	Intervention (n)	Control (n)
	(ACTRN12607000161426)			>25		
OPRA ^{21,22}	Outpatient cervical priming for induction of labour (ACTRN12608000249358)	SA, Australia	Yes	Women scheduled for induction of labour	Outpatient cervical ripening (411)	Inpatient cervical ripening (usual care) (n=416)
TIGGA ²³	Growth and nutritional status of infants fed formula based on goat milk or cow milk (ACTRN12608000047392)	SA, Australia	Yes	Infants at 37-42 weeks' gestation either formula-fed or breast-fed	Goatmilk formula (n=101)	Cow milk formula (n=99) or exclusive breastfeeding (human milk) (n=101)
WEAVE ²⁴	Women's Evaluation of Abuse and Violence Care in General Practice: a cluster randomised controlled trial (ACTRN12608000032358)	VIC, Australia	No	Familydoctors and female patients screening positive for intimate partner violence	Training of doctors to deliver a brief counselling intervention (n=137)	Standard care (n=135)
Excluded trials (patient recruitment problems)						
AC/VG Pmax Study ²⁵	Pressure limit selection during neonatal assist control volume guarantee ventilation: A randomised crossover trial (ACTRN12610000886088)	VIC, Australia	No	Infants up to 32 weeks' gestation with respiratory distress syndrome	Alternative peak inflation settings (n=22)	Standard NICU care (n=22)
Aminophylline in infants with bronchiolitis ²⁶	Randomised, double-blind, placebo-controlled trial of aminophylline in infants less than 12 months of age with bronchiolitis who require intensive care, to assess if aminophylline is superior to placebo in reducing the duration of ventilatory support (ACTRN12608000608369)	VIC, Australia	Yes	Infants aged <12 months with bronchiolitis	Aminophylline (n=23)	Placebo (n=22)
AC/VG Flow Study ²⁵	Ventilator circuit flow selection during neonatal assist control volume guarantee ventilation: a	VIC, Australia	No	Infants up to 32 weeks' gestation with	Alternative ventilator flow settings (n=22)	Standard NICU care (n=22)

Acronym (or truncated trial name)	Trial name	Main coordinating centre	Multi-centre	Population	Intervention (n)	Control (n)
	randomised crossover trial (ACTRN12610000885099)			respiratory distress syndrome		
AC/VG BUR Study ²⁷	Backup rate selection during neonatal assist control volume guarantee ventilation: a randomised crossover trial (ACTRN12610000884000)	VIC, Australia	No	Infants in the NICU	Alternative back-up rate settings (n=26)	Standard NICU care (n=26)
DETECT ^{28*}	Targeting of treatment of the patent ductus arteriosus using early echocardiography (ACTRN12608000295347)	NSW, Australia	Yes	Infants <29 weeks' gestation with large patent ductus arteriosus	Indomethacin (n=44)	No treatment or saline placebo (n=48)
Shift your Risk ²⁹	The feasibility and efficacy of an individualised approach to increase physical activity among women with previous gestational diabetes mellitus (ACTRN12608000280303)	QLD, Australia	No	Women with recent gestational diabetes	Supported care (increase physical activity) (n=15)	Usual care (n=13)
Excluded trials (no publications identified)						
Vitamin D supplementation	A randomised controlled trial on the effects of antenatal vitamin D supplementation to improve vitamin D levels in the maternal and cord blood at birth in vitamin D deficient pregnant women (ACTRN12609000142235)	VIC, Australia	No	Pregnant women at risk of vitamin D deficiency	Oral cholecalciferol during pregnancy (n=NR)	No treatment during pregnancy (n=NR)
CLOSURE†	Skin and subcutaneous fascia closure at caesarean section: a randomised controlled trial (ACTRN12608000143325)	SA, Australia	No	Women undergoing a caesarean section by transverse suprapubic incision	Absorbable OR Non-absorbable subcuticular suture material AND Closure OR Non-closure of	Participants randomised to receive 1 of the 4 currently used techniques listed in the intervention (2 x 2 factorial design)

Acronym (or truncated trial name)	Trial name	Main coordinating centre	Multi-centre	Population	Intervention (n)	Control (n)
	subcutaneous fascia (n=NR)					
IDEAL	Dietary and Lifestyle advice for women with borderline gestational glucose intolerance (ACTRN12607000174482)	SA, Australia	Yes	Pregnant women with borderline gestational glucose intolerance	Dietary and lifestyle advice (n=NR)	Routine care (n=NR)
PRIME	The effect of midwife-led counselling on mental health outcomes for women experiencing a traumatic childbirth: a randomised controlled trial (ACTRN12610000098033)	QLD, Australia	Yes	Women reporting a distressing birth experience	Trauma focussed counselling (n=NR)	Parenting advice (n=NR)

NICU, neonatal intensive care unit; NR, not reported.

* Enrolment of participants also ceased early due to lack of availability of indomethacin; † Also did not reach full patient recruitment.

Table A2. Cost parameters for all trials

Acronym (or truncated trial name)	Funding source	Funding amount (AUD)	Primary outcome	Cost indicator	Cost of avoiding a primary outcome event (AUD)
Intervention superior to standard practice					
FIFI ¹	Healthway (#16175)	\$405,539 (\$340,653)	Any breastfeeding at 6 weeks	Cost of formula feeding per child for 6 weeks†	\$125 ³⁰
HeLP-her ^{2,3}	Jack Brockhoff Foundation and NHMRC postgraduate Scholarship (#519457)	\$1,785,714 (\$1,500,000; includes \$57,343 NHMRC scholarship)	Prevalence of gestational diabetes‡	Cost per woman for management of mild gestational diabetes	\$6,000 ³¹
InFANT ^{4,5}	NHMRC Primary Health Care Project Grant (#425801)	\$631,499 (\$530,459)	Non-core drink intake (e.g. fruit juice, soft drinks)
MANGO ⁶	NHMRC Project Grant (#510207)	\$718,073 (\$603,181)	Elective caesarean section	Cost of hospital stay per woman for caesarean section	\$9,500 ³²
Intervention superior to placebo					
Analgesia after caesarean surgery ⁷	ANZCA Novice Investigator Grant and Astra Zeneca	ANZCA: \$7,143 (\$6,000) Astra Zeneca: \$7,024 (\$5,900)	Morphine requirement in 24 hours
Sugar Babies ⁸	The Waikato Medical Research Foundation	\$53,792 (\$50,000 NZD)	Treatment failure (blood glucose concentration <2.6mmol/L after 2 doses of gel)	Cost per child for a 2-day stay in the NICU	\$8,000 ³³
Intervention comparable to standard practice					
Support for ongoing breastfeeding ⁹	University of New South Wales	\$159,524 (\$134,000)	Any breastfeeding at 4 months	N/A	N/A
Effect of diet on gestational diabetes ¹⁰⁻¹²	NHMRC Project Grant (#632889) and University of Sydney	NHMRC: \$422,281 (\$354,716)	Birthweight	N/A	N/A

Acronym (or truncated trial name)	Funding source	Funding amount (AUD)	Primary outcome	Cost indicator	Cost of avoiding a primary outcome event (AUD)
FLORIAN ¹³	NHMRC Project Grant (#491103) and ARC Discovery Project (DP0664664)	Part of a larger NHMRC grant worth \$618,917 (\$519,890) Part of a larger ARC grant worth \$380,952 (\$320,000)	Percentage of mask leak with positive pressure ventilation during infant resuscitation	N/A	N/A
LIMIT ¹⁴⁻²⁰	NHMRC Project Grant (#519240)	\$1,835,052 (\$1,541,444)	Large for gestational age	N/A	N/A
OPRA ^{21,22}	NHMRC Project Grant (#519236)	\$728,110 (\$611,612)	Oxytocin use	N/A	N/A
TIGGA ²³	Dairy Goat Co-operative (NZ) Ltd	Not reported	Infant weight	N/A	N/A
WEAVE ²⁴	NHMRC Project Grant (#454532)	\$809,189 (\$679,719)	Quality of life	N/A	N/A
Excluded trials (patient recruitment problems)					
AC/VG Pmax Study ²⁵	5-year NHMRC Program Grant (2006-2010) (#491103)	Part of a larger NHMRC grant worth \$9,978,358 (\$8,381,821)	Number and duration of complete obstruction of endotracheal gas flow	N/A	N/A
Aminophylline in infants with bronchiolitis ²⁶	ANZICS Foundation	\$29,762 (\$25,000)	Respiratory support (nasal continuous positive airways pressure or mechanical ventilation)	N/A	N/A
AC/VG Flow Study ²⁵	5-year NHMRC Program Grant (2006-2010) (#491103)	Part of a larger NHMRC grant worth \$9,978,358 (\$8,381,821)	Number and duration of complete obstruction of endotracheal gas flow	N/A	N/A
AC/VG BUR	5-year NHMRC Program Grant	Part of a larger NHMRC	Proportion of triggered	N/A	N/A

Acronym (or truncated trial name)	Funding source	Funding amount (AUD)	Primary outcome	Cost indicator	Cost of avoiding a primary outcome event (AUD)
Study ²⁷	(2006-2010) (#491103)	grant worth \$9,978,358 (\$8,381,821)	inflations		
DETECT ²⁸	Self-funded / unfunded	-	Death and/or abnormal cranial ultrasound	N/A	N/A
Shift your Risk ²⁹	Diabetes Australia Research Trust	\$65,476 (\$55,000)	Change in physical activity	N/A	N/A
Excluded trials (no publications identified)					
Vitamin D supplementation	None listed	-	Incidence of vitamin D deficiency	N/A	N/A
CLOSURE	RANZCOG Research Fellowship	\$59,523 (\$50,000)	Wound infection at 30 days	N/A	N/A
IDEAL	NHMRC Project Grant (#1010292)	\$787,073 (\$661,141)	Incidence of large for gestational age infants	N/A	N/A
PRIME	NHMRC Project Grant (#481900)	\$802,668 (\$674,241)	Mental health outcomes (trauma and depression)	N/A	N/A

Ellipses indicate studies where costs savings could not be calculated due to use of surrogate primary outcome measures. NHMRC, National Health and Medical Research Council; ANZICS, Australian and New Zealand Intensive Care Society; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; N/A, not applicable.

*Funding amount adjusted to 2016, original funding amount granted in parentheses; †The number of formula cans required (based on the feeding guide provided) multiplied by the recommended retail price of 1 can of formula (\$25); ‡Secondary outcome reported as primary outcome was mean gestational weight gain.

References for Appendix

1. Maycock B, Binns CW, Dhaliwal S, Tohotoa J, Hauck Y, Burns S, et al. Education and support for fathers improves breastfeeding rates: a randomized controlled trial. *Journal of Human Lactation*. 2013;29(4):484-90.
2. Harrison CL, Lombard CB, Strauss BJ, Teede HJ. Optimizing healthy gestational weight gain in women at high risk of gestational diabetes: a randomized controlled trial. *Obesity (Silver Spring)*. 2013;21(5):904-9.
3. Harrison CL, Lombard CB, Teede HJ. Limiting postpartum weight retention through early antenatal intervention: the HeLP-her randomised controlled trial. *The International Journal of Behavioural Nutrition and Physical Activity*. 2014;11:134.
4. Campbell KJ, Lioret S, McNaughton SA, Crawford DA, Salmon J, Ball K, et al. A parent-focused intervention to reduce infant obesity risk behaviors: a randomized trial. *Pediatrics*. 2013;131(4):652-60.
5. Cameron AJ, Ball K, Hesketh KD, McNaughton SA, Salmon J, Crawford DA, et al. Variation in outcomes of the Melbourne Infant, Feeding, Activity and Nutrition Trial (InFANT) Program according to maternal education and age. *Preventive Medicine*. 2014;58:58-63.
6. Tracy SK, Hartz DL, Tracy MB, Allen J, Forti A, Hall B, et al. Caseload midwifery care versus standard maternity care for women of any risk: M@NGO, a randomised controlled trial. *Lancet*. 2013;382(9906):1723-32.
7. Belavy D, Cowlishaw PJ, Howes M, Phillips F. Ultrasound-guided transversus abdominis plane block for analgesia after Caesarean delivery. *British Journal of Anaesthesia*. 2009;103(5):726-30.
8. Harris DL, Weston PJ, Signal M, Chase JG, Harding JE. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2013;382(9910):2077-83.
9. Elliott-Rudder M, Pilotto L, McIntyre E, Ramanathan S. Motivational interviewing improves exclusive breastfeeding in an Australian randomised controlled trial. *Acta Paediatrica*. 2014;103(1):e11-6.
10. Louie JC, Markovic TP, Perera N, Foote D, Petocz P, Ross GP, et al. A randomized controlled trial investigating the effects of a low-glycemic index diet on pregnancy outcomes in gestational diabetes mellitus. *Diabetes Care*. 2011;34(11):2341-6.
11. Louie JC, Markovic TP, Ross GP, Foote D, Brand-Miller JC. Effect of a low glycaemic index diet in gestational diabetes mellitus on post-natal outcomes after 3 months of birth: a pilot follow-up study. *Maternal and Child Nutrition*. 2015;11(3):409-14.
12. Markovic TP, Muirhead R, Overs S, Ross GP, Louie JC, Kizirian N, et al. Randomized Controlled Trial Investigating the Effects of a Low-Glycemic Index Diet on Pregnancy Outcomes in Women at High Risk of Gestational Diabetes Mellitus: The GI Baby 3 Study. *Diabetes Care*. 2016;39(1):31-8.
13. Schmolzer GM, Morley CJ, Wong C, Dawson JA, Kamlin CO, Donath SM, et al. Respiratory function monitor guidance of mask ventilation in the delivery room: a feasibility study. *The Journal of Pediatrics*. 2012;160(3):377-81 e2.

14. Dodd JM, Turnbull D, McPhee AJ, Deussen AR, Grivell RM, Yelland LN, et al. Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. *British Medical Journal*. 2014;348:g1285.
15. Dodd JM, Cramp C, Sui Z, Yelland LN, Deussen AR, Grivell RM, et al. The effects of antenatal dietary and lifestyle advice for women who are overweight or obese on maternal diet and physical activity: the LIMIT randomised trial. *BMC Medicine*. 2014;12:161.
16. Dodd JM, McPhee AJ, Turnbull D, Yelland LN, Deussen AR, Grivell RM, et al. The effects of antenatal dietary and lifestyle advice for women who are overweight or obese on neonatal health outcomes: the LIMIT randomised trial. *BMC Medicine*. 2014;12:163.
17. Dodd JM, Ahmed S, Karon J, Umberger W, Deussen AR, Tran T, et al. The cost-effectiveness of providing antenatal lifestyle advice for women who are overweight or obese: the LIMIT randomised trial. *BMC Obesity*. 2015;2:14.
18. Dodd JM, Deussen AR, Mohamad I, Rifas-Shiman SL, Yelland LN, Louise J, et al. The effect of antenatal lifestyle advice for women who are overweight or obese on secondary measures of neonatal body composition: the LIMIT randomised trial. *BJOG: an International Journal of Obstetrics and Gynaecology*. 2016;123(2):244-53.
19. Dodd JM, Newman A, Moran LJ, Deussen AR, Grivell RM, Yelland LN, et al. The effect of antenatal dietary and lifestyle advice for women who are overweight or obese on emotional well-being: the LIMIT randomized trial. *Acta Obstetricia et Gynecologica Scandinavica*. 2016;95(3):309-18.
20. Grivell RM, Yelland LN, Deussen A, Crowther CA, Dodd JM. Antenatal dietary and lifestyle advice for women who are overweight or obese and the effect on fetal growth and adiposity: the LIMIT randomised trial. *BJOG: an International Journal of Obstetrics and Gynaecology*. 2016;123(2):233-43.
21. Wilkinson C, Bryce R, Adelson P, Turnbull D. A randomised controlled trial of outpatient compared with inpatient cervical ripening with prostaglandin E(2) (OPRA study). *BJOG: an International Journal of Obstetrics and Gynaecology*. 2015;122(1):94-104.
22. Adelson PL, Wedlock GR, Wilkinson CS, Howard K, Bryce RL, Turnbull DA. A cost analysis of inpatient compared with outpatient prostaglandin E2 cervical priming for induction of labour: results from the OPRA trial. *Australian Health Review*. 2013;37(4):467-73.
23. Zhou SJ, Sullivan T, Gibson RA, Lonnerdal B, Prosser CG, Lowry DJ, et al. Nutritional adequacy of goat milk infant formulas for term infants: a double-blind randomised controlled trial. *British Journal of Nutrition*. 2014;111(9):1641-51.
24. Hegarty K, O'Doherty L, Taft A, Chondros P, Brown S, Valpied J, et al. Screening and counselling in the primary care setting for women who have experienced intimate partner violence (WEAVE): a cluster randomised controlled trial. *Lancet*. 2013;382(9888):249-58.
25. Wheeler KI, Davis PG, Kamlin CO, Morley CJ. Assist control volume guarantee ventilation during surfactant administration. *Archives of Disease in Childhood Fetal and Neonatal Edition*. 2009;94(5):F336-8.
26. Turner A, Shann F, Delzoppo C, Henning R, Slater A, Beca J, et al. A multicentre, randomised, double-blind, placebo-controlled trial of aminophylline for bronchiolitis in infants admitted to intensive care. *Critical Care Resuscitation*. 2014;16(3):220-4.
27. Wheeler KI, Morley CJ, Hooper SB, Davis PG. Lower back-up rates improve ventilator triggering during assist-control ventilation: a randomized crossover trial. *Journal of Perinatology*. 2012;32(2):111-6.

28. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus. Archives of Disease in Childhood Fetal and Neonatal Edition. 2014;99(2):F99-F104.
29. McIntyre HD, Peacock A, Miller YD, Koh D, Marshall AL. Pilot study of an individualised early postpartum intervention to increase physical activity in women with previous gestational diabetes. International Journal of Endocrinology. 2012;2012:892019.
30. Aspen Nutritionals Australia Pty Ltd. Me and My Child: S-26 Gold Newborn. [May 2016]; Available from: <http://www.meandmychild.com.au/products/s-26-gold-newborn/>.
31. Moss JR, Crowther CA, Hiller JE, Willson KJ, Robinson JS. Costs and consequences of treatment for mild gestational diabetes mellitus – evaluation from the ACHOIS randomised trial. BMC Pregnancy and Childbirth. 2007;7:27.
32. Independent Hospital Pricing Authority. National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2012-2013, Round 17. Commonwealth of Australia; 2015 [May 2016]; Available from: [http://www.health.gov.au/internet/ihpa/publishing.nsf/Content/E941955AE78F18CACA257C160010C5F4/\\$File/NHCD%20Cost%20Report%202012-2013%20Round%2017.pdf](http://www.health.gov.au/internet/ihpa/publishing.nsf/Content/E941955AE78F18CACA257C160010C5F4/$File/NHCD%20Cost%20Report%202012-2013%20Round%2017.pdf).
33. The Royal Women's Hospital. Patient fees for patients who do not have a Medicare Card. [May 2016]; Available from: <https://www.thewomens.org.au/patients-visitors/patient-fees/>.